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No. 351

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *PARA*-CHLOROANILINE HYDROCHLORIDE

(CAS NO. 20265-96-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *PARA*-CHLOROANILINE HYDROCHLORIDE

(CAS NO. 20265-96-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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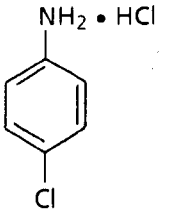

p-CHLOROANILINE HYDROCHLORIDE

CAS No. 20265-96-7

$C_6H_6NCl \cdot HCl$ Molecular weight 164.1

Synonyms: 1-amino-4-chlorobenzene hydrochloride; 4-chlorophenylamine hydrochloride; 4-chlorobenzenamine hydrochloride

ABSTRACT

p-Chloroaniline has a large production volume and is used as a dye intermediate. Toxicology and carcinogenesis studies of *p*-chloroaniline (greater than 99% pure) were conducted by administering *p*-chloroaniline hydrochloride in water by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 13 weeks, or 2 years. Vehicle controls were given deionized water by gavage. All doses were calculated as *p*-chloroaniline; the chemical was administered as the hydrochloride after dissolution in water containing molar equivalents of hydrochloric acid. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse L5178Y lymphoma cells, and Chinese hamster ovary (CHO) cells. Hematologic parameters were measured at the end of the 13-week studies and at 6, 12, 18, and 24 months in the 2-year studies. Supplemental studies of the distribution and disposition of *p*-chloroaniline were conducted in male F344 rats.

Sixteen-Day and Thirteen-Week Studies: In the 16-day studies, male and female rats and mice received 25, 50, 100, 200, or 400 mg/kg of body weight. The vehicle controls received deionized water. All rats and mice that received 200 or 400 mg/kg died during the first 6 days of the studies. Some deaths occurred in each of the lower dose groups of mice. Splenic enlargement was observed at necropsy in rats administered 25, 50, or 100 mg/kg. Congestion of the spleen and hemosiderin deposition in the renal cortical tubular epithelial cells were observed at 100 mg/kg in male and female rats. Compound-related lesions in mice included hemosiderosis of the liver Kupffer cells and congestion of the spleen.

In the 13-week studies, 10 rats of each sex were administered doses of 0, 5, 10, 20, 40, or 80 mg/kg. All male rats lived to the end of the 13-week studies. One of 10 female rats that received 80 mg/kg died from unknown causes. The final mean body weights of rats that received 80 mg/kg were 16% lower than that of vehicle controls for males and 4% lower for females. In the 13-week studies in mice, 10 animals of each sex were administered doses of 0, 7.5, 15, 30, 60, or 120 mg/kg. Deaths in mice were not related to *p*-chloroaniline hydrochloride administration. The final mean body weights of dosed and vehicle control mice were similar. In both rats and mice, no chemically related effects on organ weights were observed at necropsy, except for the spleen, which was enlarged as a function of increasing dose. Methemoglobin was increased in dosed groups and resulted in a secondary anemia, the severity of which was dose related. Compound-related lesions observed histologically, including pigmentation (hemosiderin) in the kidney, spleen, and liver and hematopoiesis in the liver and spleen, reflected the response to the hemolytic anemia and methemoglobinemia induced by *p*-chloroaniline hydrochloride.

Based on these results, groups of 50 rats of each sex were administered 2, 6, or 18 mg/kg *p*-chloroaniline hydrochloride in water by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 3, 10, or 30 mg/kg on the same schedule.

Metabolism and Disposition Studies in Rats: The metabolism and disposition studies in F344/N rats showed that metabolic and excretory pathways were not saturated by *p*-chloroaniline administered orally at doses ranging from 0.3 to 30 mg/kg. *p*-Chloroaniline was rapidly metabolized and excreted primarily in urine with a half-life of approximately 2 hours.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed rats were generally within 5% of those of vehicle controls throughout the studies. The survival of the low and mid dose groups of male rats and of the low and high dose groups of female rats was significantly greater than that of the vehicle controls (male: vehicle control, 18/49; low dose, 32/50; mid dose, 32/50; high dose, 21/50; female: 27/50; 39/50; 36/50; 37/50). The increased survival was attributed to the decreased incidences of mononuclear cell leukemia. Mean body weights of high dose male and female mice were generally within 5% of those of vehicle controls throughout the studies. The survival of the mid dose group of male mice was lower than that of the vehicle controls after week 99 (male: 43/50; 36/50; 29/50; 35/50; female: 39/50; 42/50; 44/50; 41/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Fibrosis of the spleen was increased in dosed male and high dose female rats (male: vehicle control, 3/49; low dose, 11/50; mid dose, 12/50; high dose, 41/50; female: 1/50; 2/50; 3/50; 42/50). Cellular infiltration of lipocytes (fatty metaplasia) was observed in the spleen at increased incidences in high dose rats (male: 0/49; 0/50; 0/50; 24/50; female: 0/50; 0/50; 0/50; 11/50). The incidence of uncommon sarcomas of the spleen in high dose male rats was significantly greater than that in the vehicle controls (fibrosarcomas, osteosarcomas, or hemangiosarcomas, combined: 0/49; 1/50; 3/50; 38/50). Many of these tumors metastasized to one or more sites. In female rats, one fibrosarcoma of the spleen was found in a mid dose animal, and one osteosarcoma of the spleen was found in a high dose animal. The historical incidence of splenic connective tissue sarcomas (all types) in water gavage vehicle controls is 1/298 (0.3%) for male rats and 0/297 for female rats. The historical incidence of hemangiosarcomas in water gavage controls is 0/300 for male rats and 1/297 (0.3%) for female rats.

Adrenal medullary hyperplasia was observed at an increased incidence in high dose female rats (4/50; 4/50; 7/50; 24/50). Marginally increased incidences of pheochromocytomas were seen in high dose male (13/49; 14/48; 15/48; 26/49) and female (2/50; 3/50; 1/50; 6/50) rats. The historical incidence of pheochromocytomas in water gavage vehicle control male F344/N rats is 121/299 (40% ± 16%); the historical incidence in water gavage vehicle control female F344/N rats is 20/295 (7% ± 2%).

The incidences of mononuclear cell leukemia in dosed male and female rats were lower than those in vehicle controls (male: 21/49; 3/50; 2/50; 3/50; female: 10/50; 2/50; 1/50; 1/50). The incidences of malignant lymphomas in dosed male and female mice were lower than those in vehicle controls (male: 10/50; 3/49; 9/50; 3/50; female: 19/50; 12/50; 5/50; 10/50).

Hematologic and methemoglobin measurements were made on blood samples collected from 15 randomly selected male and female rats per dose group at 6, 12, 18, and 24 months. In general, the high dose group at various intervals showed mild hemolytic anemia and dose-related increases in methemoglobin.

In rats, compound-related nonneoplastic lesions were seen histopathologically in the bone marrow, spleen, and liver. These lesions included bone marrow hyperplasia, hepatic hemosiderosis, and splenic fibrosis and suggest compound-related effects on the hematopoietic system in general, the erythropoietic system specifically, and mesenchymal cells in the spleen.

In male mice, the incidence of hemangiosarcomas of the liver or spleen in high dose male mice was greater than that in the vehicle controls (4/50; 4/49; 1/50; 10/50). The historical incidence of hemangiomas or hemangiosarcomas at all sites (combined) in water gavage vehicle control male $B6C3F_1$ mice is 11/350 (3% ± 3%).

The incidences of hepatocellular adenomas or carcinomas (combined) were increased in dosed male mice (11/50; 21/49; 20/50; 21/50), primarily due to increased incidences of hepatocellular carcinomas (3/50; 7/49; 11/50; 17/50). Hepatocellular carcinomas metastasized to the lung in 1/50 vehicle control, 1/49 low dose, 2/50 mid dose, and 9/50 high dose male mice. The historical incidence of hepatocellular neoplasms in water gavage vehicle controls is 106/347 (31% ± 6%).

Genetic Toxicology: *p*-Chloroaniline was mutagenic in *S. typhimurium* strains TA98 and TA100 in the presence of exogenous metabolic activation; no increase in revertant colonies was observed in strains TA97, TA1535, or TA1537. *p*-Chloroaniline induced trifluorothymidine (Tft) resistance in mouse L5178Y lymphoma cells with and without metabolic activation. In cultured CHO cells, treatment with *p*-chloroaniline produced significant increases in sister chromatid exchanges (SCEs) both with and without metabolic activation (S9); chromosomal aberrations were significantly increased only in the presence of S9.

Audit: The data, documents, and pathology materials from the 2-year studies of *p*-chloroaniline have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year water gavage studies, there was *clear evidence of carcinogenic activity** of *p*-chloroaniline hydrochloride for male F344/N rats, as indicated by increased incidences of uncommon sarcomas of the spleen. Pheochromocytomas of the adrenal gland may also have been associated with chemical administration. There was *equivocal evidence of carcinogenic activity* of *p*-chloroaniline hydrochloride for female F344/N rats, as indicated by the presence of uncommon sarcomas of the spleen in one mid and one high dose animal and the increased incidence of pheochromocytomas of the adrenal gland. There was *some evidence of carcinogenic activity* of *p*-chloroaniline hydrochloride for male $B6C3F_1$ mice, as indicated by increased incidences of hepatocellular neoplasms and of hemangiosarcomas of the liver or spleen. There was *no evidence of carcinogenic activity* of *p*-chloroaniline hydrochloride for female $B6C3F_1$ mice administered 3, 10, or 30 mg/kg by gavage for 2 years.

The incidences of mononuclear cell leukemia in male and female rats and of malignant lymphomas in male and female mice were decreased by administration of *p*-chloroaniline hydrochloride. Compound-related splenic fibrosis was present in male and female rats.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE AND GENETIC TOXICOLOGY STUDIES OF *p*-CHLOROANILINE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
2, 6, or 18 mg/kg *p*-chloroaniline in acidified water, 5 d/wk; vehicle controls received deionized water	2, 6, or 18 mg/kg *p*-chloroaniline in acidified water, 5 d/wk; vehicle controls received deionized water	3, 10, or 30 mg/kg *p*-chloroaniline in acidified water, 5 d/wk; vehicle controls received deionized water	3, 10, or 30 mg/kg *p*-chloroaniline in acidified water, 5 d/wk; vehicle controls received deionized water
Body weights in the 2-year study			
Dosed groups within 5% of vehicle controls	Dosed groups within 5% of vehicle controls	Dosed groups within 5% of vehicle controls	Dosed groups within 5% of vehicle controls
Survival rates in the 2-year study			
18/49; 32/50; 32/50; 21/50	27/50; 39/50; 36/50; 37/50	43/50; 36/50; 29/50; 35/50	39/50; 42/50; 44/50; 41/50
Nonneoplastic effects			
Fibrosis of the spleen (3/49; 11/50; 12/50; 41/50)	Fibrosis of the spleen (1/50; 2/50; 3/50; 42/50)		
Neoplastic effects			
Sarcomas of the spleen (0/49; 1/50; 3/50; 38/50); pheochromocytomas of the adrenal gland (13/49; 14/48; 15/48; 26/49)	Sarcomas of the spleen (0/50; 0/50; 1/50; 1/50); pheochromocytomas of the adrenal gland (2/50; 3/50; 1/50; 6/50)	Hepatocellular adenomas or carcinomas (combined) (11/50; 21/49; 20/50; 21/50); hemangiosarcomas (4/50; 4/49; 1/50; 10/50)	None
Level of evidence of carcinogenic activity			
Clear evidence	Equivocal evidence	Some evidence	No evidence
Other considerations			
Decreased incidences of leukemia (21/49; 3/50; 2/50; 3/50)	Decreased incidences of leukemia (10/50; 2/50; 1/50; 1/50)	Decreased incidences of lymphomas (10/50; 3/49; 9/50; 3/50)	Decreased incidences of lymphomas (19/50; 12/50; 5/50; 10/50)
Genetic toxicology			
Salmonella (gene mutation): Positive with S9; negative without S9	**Mouse L5178Y/TK$^{+/-}$ (Tft resistance)**: Positive with and without S9	**CHO Cells in Vitro — SCE**: Positive with and without S9	**CHO Cells in Vitro — Aberration**: Positive with S9; negative without S9

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either 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 chemically 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 chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically 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. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (*same lesion in another sex or species*);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The 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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of *p*-Chloroaniline Hydrochloride is based on 13-week studies that began in March 1981 and ended in June 1981 and on 2-year studies that began in January 1982 and ended in January 1984 at Battelle Columbus Laboratories (Columbus, Ohio).

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The members of the Peer Review Panel who evaluated the draft Technical Report on *p*-chloroaniline hydrochloride on April 18, 1988, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

On April 18, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of *p*-chloroaniline hydrochloride received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina.

Dr. R.S. Chhabra, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male rats, equivocal evidence of carcinogenic activity for female rats, some evidence of carcinogenic activity for male mice, no evidence of carcinogenic activity for female mice).

Dr. Sivak, a principal reviewer, agreed with the conclusions. However, he suggested that the unusually low hepatic tumor incidence in vehicle control male mice, coupled with a tumor yield in high dose male mice not much above the historical control range, might be mentioned. Dr. Chhabra agreed and pointed out that the effects were mainly due to carcinomas and, further, that there was considerable metastasis of these tumors to the lung (1/50, vehicle controls vs. 9/50, high dose). Dr. Sivak stated that inclusion of pharmacokinetic data indicating that saturation was not reached, even at the highest dose, was an important addition to the data base. He suggested deleting the speculation that increased sensitivity to aniline toxicity was based on differences in a single erythrocyte enzyme, and Dr. Chhabra agreed.

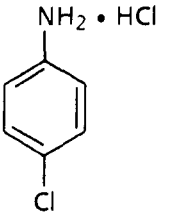
Dr. Hughes, the second principal reviewer, agreed with the conclusions. He requested an explanation for poor survival in male and female vehicle control rats compared with that in dosed groups. Dr. Chhabra noted that there appeared to be a correlation with a marked negative trend for mononuclear cell leukemia. Dr. Hughes thought that the addition of structure-activity data on genetic toxicity, carcinogenicity, and other effects for the aniline compounds was useful.

Dr. Gallo, the third principal reviewer, agreed with the conclusions, although he argued that if rarity of the tumors is the criterion for the level of evidence, then the level in female rats should be the same as that in male rats. Dr. J. Haseman, NIEHS, said that to his knowledge, the Program had never made a call above equivocal evidence based on a single tumor, regardless of rarity. Dr. Gallo commented that there were marked increases in methemoglobinemia for both rats and mice in the 13-week studies, even at the lowest doses, and suggested that chronic methemoglobinemia could be an appropriate criterion for dose selection for this type of compound.

In response to inquiries as to why the 1979 NCI studies (NCI Technical Report No. 189) were repeated, Dr. Chhabra said *p*-chloroaniline was considered to be a good candidate for restudy because the findings from the NCI studies were unclear as to carcinogenicity and because of the nature of the chemical and the degree of industrial exposure of humans. Dr. J. Huff, NIEHS, added that three of the four previous studies were equivocal, the duration of exposure was only 18 months, and the gavage route was used in the current studies.

Dr. Sivak moved that the Technical Report on *p*-chloroaniline hydrochloride be accepted with the revisions discussed and with the conclusions as written: for male rats, clear evidence of carcinogenic activity; for female rats, equivocal evidence of carcinogenic activity; for male mice, some evidence of carcinogenic activity; and for female mice, no evidence of carcinogenic activity. Dr. Hughes seconded the motion, which was approved by eight members, with one abstention (Dr. Ashby).

I. INTRODUCTION



p-CHLOROANILINE HYDROCHLORIDE

CAS No. 20265-96-7

$C_6H_6NCl \cdot HCl$ Molecular weight 164.1

Synonyms: 1-amino-4-chlorobenzene hydrochloride; 4-chlorophenylamine hydrochloride; 4-chlorobenzenamine hydrochloride

Physical and Chemical Properties

p-Chloroaniline forms colorless orthorhombic crystals and has a melting point of 72.5° C and a boiling point of 232° C. It is soluble in hot water and freely soluble in alcohol, ether, acetone, and carbon disulfide (Merck, 1983). *p*-Chloroaniline (99% pure) was used to prepare *p*-chloroaniline hydrochloride solutions for administration to animals.

Use, Production, and Exposure

p-Chloroaniline is an aromatic amine widely used in the dye, chemical, textile, rubber, and other industries (Beard and Noe, 1981). *p*-Chloroaniline is used as an intermediate in the manufacture of more than 10 dyes and pigments (Colour Index, 1956) and has been detected as a degradation product in some pharmaceutical preparations (Ciarlone et al., 1976). In rats, *p*-chloroaniline is one of the metabolites of the urea herbicides monuron, buturon, and monolinuron (Ernst, 1969; Hargesheimer et al., 1981). Monuron is carcinogenic in male rats, causing increased incidences of tubular cell adenocarcinomas of the kidney, tubular cell adenomas of the kidney, and neoplastic lesions of the liver (NTP, 1988). *p*-Chloroaniline has also been identified as a degradation product of 4,4'-dichloro-3-(trifluoromethyl)carbanilide, an active component of deodorant bars (Demers and Yates, 1977).

Specific production data for *p*-chloroaniline are not available; however, the Toxic Substance Control Act (TSCA) Inventory listed two companies that manufactured *p*-chloroaniline in 1977 (USEPA, 1978). One company reported that it produced between 100,000 pounds and 1,000,000 pounds; the other company did not report its production volume in the nonconfidential portion of the TSCA inventory. Four companies were reported to import *p*-chloroaniline in 1977. Of these four, two reported a combined import volume of between 10,000 and 101,000 pounds; the other two companies did not report import volumes.

No data are available on the number of workers exposed to this chemical, but the use pattern of *p*-chloroaniline suggests an exposure potential to workers in the dye, agricultural, and chemical industries. It is also a potential food contaminant because of its release as a metabolic degradation product from herbicides used in agriculture. Aromatic organochlorine compounds are known to be persistent in the aquatic environment. Schauerte et al. (1982) studied the long-term fate of hexachlorobenzene, pentachlorobenzene, and *p*-chloroaniline in small experimental ponds in southern Germany. The chemicals, with added ^{14}C-labeled tracers, were applied to the ponds for 4-6 weeks in amounts sufficient to maintain an average concentration of 50 µg/liter. Chemical residue concentrations were determined in water, sediment, flora, and fauna up

to 166 weeks after application. Residues of these compounds were initially present in the biota at relatively high concentrations; concentrations of residue slowly built up and then declined in the sediment. Suss et al. (1978) studied the degradation of aniline, *p*-chloroaniline, and 3,4-dichloroaniline in four different soil types in the laboratory and reported low degradation rates and strong adsorption for the chloroanilines, suggesting accumulation in the soil. However, according to Freitag et al. (1984), laboratory soil mobility studies, which normally have much higher leaching rates and shorter time spans than those conducted under environmental conditions, are not suitable for predicting the long-term behavior of *p*-chloroaniline.

Absorption, Distribution, Metabolism, and Excretion

p-Chloroaniline is readily absorbed through skin and from the gastrointestinal tract after oral administration. It causes more intense methemoglobinemia after dermal exposure than after oral exposure, suggesting greater or more rapid hepatic metabolism following absorption from the gastrointestinal tract (Gosselin et al., 1984). Distribution and excretion studies of [^{14}C]*p*-chloroaniline hydrochloride in rats showed that *p*-chloroaniline is excreted rapidly after oral administration at 0.3, 3.0, or 30 mg/kg (Perry et al., 1981a,b; Appendix H). Within 24 hours, 81% of the administered dose appeared in urine and 10% in feces. An average of 98% of the dose was recovered in excreta (87% in urine, 11% in feces) 7 days after administration. At day 7, essentially all of the remaining radioactivity was located in the erythrocytes. The preliminary results from a single intravenous dose (3 mg/kg) also revealed an accumulation of *p*-chloroaniline-derived radioactivity in erythrocytes. The ratio of concentration of *p*-chloroaniline in erythrocytes to that in plasma increased with time and was 2:1 at 2 hours, 20:1 at 12 hours, and 74:1 at 2 days. These studies also revealed that *p*-chloroaniline administered to F344 rats by intravenous injection was rapidly *N*-acetylated to *p*-chloroacetanilide as the first step in metabolism and excretion. The absence of any *p*-chloroacetanilide in urine indicated further metabolism before excretion.

Concurrent disposition studies in mongrel dogs and in A/J and Swiss Webster mice also were performed by Perry et al. (1981a,b). Dogs administered 3 mg/kg [^{14}C]*p*-chloroaniline by intravenous injection excreted 93% of the radioactivity in urine and 3% in feces within 2 days, whereas mice of both strains eliminated 75% in urine and 10% in feces in a similar time period; recovery of mouse urine was probably not complete. For all species, the disappearance of total radioactivity from whole blood displayed two-phase decay kinetics, but the rates were substantially different. The initial decay constants in both strains of mice were 10 times greater than those in dogs and rats, and the terminal rates were greater by a factor of 2 to 4. The half-life of the radioactivity in plasma was similar in F344 rats and dogs. Dogs and rats rapidly eliminated the parent compound in a manner best described by biexponential decay kinetics, with a half-life of less than 10 minutes for the first phase and 1.5-4.6 hours for the second phase. The parent compound could not be detected after 4 hours in dogs and rats or after 1 hour in mice. *p*-Chloroaniline clearance by mice was too rapid to permit calculation of the kinetic parameters.

The biologic activity, including mutagenicity and carcinogenicity, of a number of aromatic amines may be due to their *N*-hydroxy metabolites (Poirier and Weisburger, 1972; Weisburger and Weisburger, 1973; Selkirk, 1980). A number of in vitro studies have shown *N*-oxidation of *p*-chloroaniline by the hepatic microsomal cytochrome P450 system (Smith and Gorrod, 1978; Liu and Franklin, 1984; Hlavica, 1984). *N*-oxidation of *p*-chloroaniline during lipid peroxidation promoted by various mechanisms in rabbit liver microsomal preparations was also reported (Golly et al., 1984). In addition, based on in vitro studies of the *N*-oxidation of *p*-chloroaniline by rabbit hemoglobin, Golly and Hlavica (1983) proposed that erythrocytes may be a site of bioactivation of aromatic amines. This proposal of a reactive intermediate produced by, and reacting with, erythrocytes would be consistent with the observed persistence of *p*-chloroaniline-derived radioactivity in erythrocytes by Perry et al. (1981a,b). However, this conclusion has not been confirmed because it was not possible to extract the *p*-chloroaniline-derived radioactivity from erythrocytes. Microbial oxidation of

p-chloroaniline was shown by Kaufman et al. (1973); Corbett et al. (1980) demonstrated the *N*-oxidizing action of the fungal enzyme chloride peroxidase in vitro.

Genetic Toxicology

p-Chloroaniline has been tested for mutagenicity by numerous laboratories in bacterial assays with *Escherichia coli* and *Salmonella typhimurium*. Test results reported in the literature were generally negative (Garner and Nutman, 1977; Pai et al., 1978; Rosenkranz and Poirier, 1979; Seuferer et al., 1979; Gilbert et al., 1980; Zimmer et al., 1980; Thompson et al., 1983) with two exceptions: a positive response for gene mutation in *S. typhimurium* strain TA98 in the presence of S9 metabolic activation (Dunkel et al., 1985) and the observation of growth inhibition due to DNA damage in *E. coli* polA$^+$/polA$^-$ (Rosenkranz and Poirier, 1979). *p*-Chloroaniline was tested for mutagenicity in *S. typhimurium* for the NTP by three independent laboratories. Mutagenic activity was observed by two laboratories in strain TA98 in the presence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster S9, and one laboratory noted an increase in revertant colonies in strain TA100 in the presence of hamster S9 only. No mutagenic activity was reported in strains TA97, TA1535, or TA1537 (Mortelmans et al., 1986; Table 27). Several of the negative studies that were reported in the literature tested *p*-chloroaniline within dose ranges similar to those used by the NTP laboratories (1,000-2,000 µg/plate).

In addition to the bacterial assays, gene mutation was also reported in *Aspergillus nidulans* after administration of 200 µg/ml *p*-chloroaniline in the absence of exogenous metabolic activation (Prasad, 1970) and in cultured mouse L5178Y lymphoma cells both with and without Aroclor 1254-induced male F344 rat liver S9 (Myhr and Caspary, 1989; Table 28).

Treatment of primary hepatocyte cultures from adult male F344 rats with 20 µg/ml *p*-chloroaniline was reported to induce unscheduled DNA synthesis (UDS) (Williams et al., 1982); another such investigation detected no induction of UDS at doses of 6.35 µg/ml and lower and found toxicity at all doses greater than 10 µg/ml (Thompson et al., 1983). Therefore, it may be that only doses within a narrow range close to toxic levels elicit a positive response in this assay.

The NTP tested several structural analogs of *p*-chloroaniline for mutagenic activity, including aniline, *o*- and *m*-chloroaniline, and *p*-bromoaniline. All these compounds produced a negative response in the Salmonella gene mutation assay (Haworth et al., 1983; Zeiger et al., 1987). Aniline and *m*-chloroaniline induced SCEs in cultured CHO cells with and without S9 from Aroclor 1254-induced male Sprague Dawley rat liver; both compounds also induced chromosomal aberrations in this test system, but aniline required the addition of S9 for a positive response (Galloway et al., 1987). Aniline induced trifluorothymidine (Tft) resistance in mouse L5178Y lymphoma cells with and without Aroclor 1254-induced male F344 rat liver S9 (Myhr and Caspary, 1989; Mitchell et al., 1989). Published reports on the absence of mutagenic activity of aniline, *p*-bromoaniline, and *m*-chloroaniline in bacteria support the NTP results (Garner and Nutman, 1977; Simmon, 1979; Chung et al., 1981; De Flora, 1981; Probst et al., 1981; Ashby et al., 1983; Thompson et al., 1983). Although *o*-chloroaniline was reported to be nonmutagenic in Salmonella, it was observed to produce growth inhibition due to DNA damage in *E. coli* strain polA$^+$/polA$^-$, with and without S9 activation (Rosenkranz and Poirier, 1979; Rosenkranz and Leifer, 1980). The only reported genetic effects of aniline exposure were the induction of SCEs in vitro (Wilmer et al., 1981; Tohda et al., 1983) and in vivo (Parodi et al., 1983) and DNA damage as determined by alkaline elution sedimentation in liver and kidney cells of Sprague Dawley rats administered 420 mg/kg aniline; no DNA damage was observed in the spleen cells of these rats (Parodi et al., 1982a,b). Swiss mice administered identical doses of aniline showed no liver, kidney, or bone marrow DNA damage (Parodi et al., 1982a). No induction of UDS was observed in primary hepatocyte cultures from F344 rats, DS-1 mice, or Syrian golden hamsters; the cultures contained 1×10^{-3} or 1×10^{-5} M aniline (Williams, 1981; McQueen et al., 1981).

Mutagenicity information is available on *p*-aminophenol, one of the purported metabolites of *p*-chloroaniline (Ichikawa et al., 1969). Although *p*-aminophenol is not generally observed to be mutagenic in Salmonella (NTP unpublished results; Garner and Nutman, 1977; Degawa et al., 1979; Thompson et al., 1983), there is one report of a positive response in the absence of S9 in *S. typhimurium* strain TA1535 (Wild et al., 1980). In addition, induction of Tft resistance in mouse L5178Y lymphoma cells has been reported (Amacher and Turner, 1982; Oberly et al., 1984) as well as in vivo induction of chromosomal aberrations (Mitra and Manna, 1971), micronuclei (Wild et al., 1980), and sperm head abnormalities (Topham, 1980). Treatment of human EBV-transformed lymphoblastoid cells with *p*-aminophenol resulted in inhibition of DNA synthesis presumably through alterations of the DNA superstructure as noted by changes in the sedimentation rate of DNA extracts from treated cells (Hayward et al., 1982). SCE induction in human lymphocytes was reported after exposure to *p*-aminophenol (Takehisa and Kanaya, 1982).

Toxicity and Carcinogenicity

The dominant toxic effect of aromatic amines is methemoglobin formation (Beard and Noe, 1981). Specific information on *p*-chloroaniline toxicity in humans is limited. Short-term exposure to *p*-chloroaniline produces cyanosis, a manifestation of methemoglobin formation that could develop with or without loss of hemoglobin. Medical intervention is required when methemoglobin levels are at or above 10% in the blood of humans. Long-term exposure could produce reversible anemia (Linch, 1974). *p*-Chloroaniline administered dermally induces more intense methemoglobin formation than when administered orally (Gosselin et al., 1984). A threshold limit value for aniline and its homologs has been set at 2 ppm for dermal exposure (ACGIH, 1988-89). McLean et al. (1969) studied methemoglobin formation in cats by a number of substituted anilines including *p*-chloroaniline. These studies showed that chloro- and bromoanilines, especially the 3- and 4-halo compounds, tend to produce a long-lasting methemoglobin response. The oral LD_{50} value in rats for *p*-chloroaniline was reported to be 310 mg/kg, and the dermal LD_{50} value in rabbits was reported to be 360 mg/kg (Smyth et al., 1962).

Aniline hydrochloride was carcinogenic for male F344/N rats (NCI, 1978a; Gralla et al., 1979). Azobenzene (NCI, 1979a), D & C Red No. 9 (NTP, 1982a), dapsone (NCI, 1977a), and *o*-toluidine hydrochloride (NCI, 1979b), all structurally related to aniline, are carcinogens in rats. Carcinogenesis studies on *p*-chloroaniline in feed were conducted by the National Cancer Institute in F344/N rats and $B6C3F_1$ mice of each sex (NCI, 1979c). The dietary concentrations were 250 and 500 ppm for rats and 2,500 and 5,000 ppm for mice. The duration of compound administration was 78 weeks, followed by an observation period of 24 weeks for rats and 13 weeks for mice. Mesenchymal neoplasms (including six fibromas, one sarcoma, one fibrosarcoma, one osteosarcoma, and one hemangiosarcoma) in the spleen of male rats (vehicle control, 0/20; low dose, 0/49; high dose, 10/49) and hemangiomatous neoplasms in mice (male: 2/20; 10/50; 14/50; female: 0/18; 3/49; 8/42) may have been related to *p*-chloroaniline administration. However, the conclusions of the studies given in the Technical Report were that "sufficient evidence was not found to establish the carcinogenicity of *p*-chloroaniline for F344/N rats and $B6C3F_1$ mice."

p-Chloroaniline is 1 of 17 compounds with a chloroaniline moiety which have been evaluated or are under evaluation by the NCI/NTP (Table 1). Six of the nine compounds evaluated to date were found to be carcinogenic, whereas the results of the original *p*-chloroaniline carcinogenesis studies were considered equivocal. 2-Chloro-*p*-phenylenediamine sulfate (NCI, 1978b) and 3-chloro-*p*-toluidine (NCI, 1978c) were determined not to be carcinogenic in rats or mice.

No epidemiologic study of *p*-chloroaniline carcinogenicity was available in the literature. However, an epidemiologic study on an analog, 4-chloro-2-methylaniline, indicated the possibility of bladder cancer in exposed workers (USEPA, 1986). Other structurally related chemicals such as 4,4'-methylene bis(2-methylaniline) and toluidine were reported to be

TABLE 1. NCI/NTP STUDIES OF CHEMICALS CONTAINING CHLOROANILINE MOIETIES

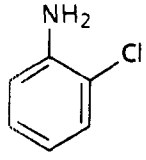
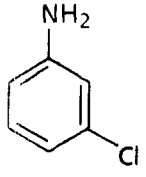
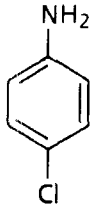
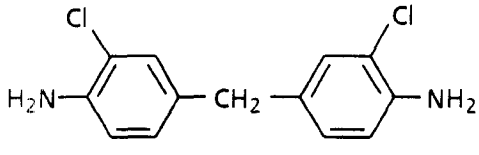
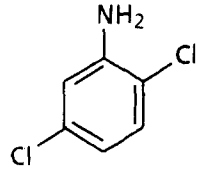
Structure	Chemical	CAS Number	NTP Testing Status: Genetic Toxicity	NTP Testing Status: Carcinogenicity and Other
	o-Chloroaniline	95-51-2	Negative in Salmonella (Zeiger et al., 1987)	Not evaluated for carcinogenicity
	*m*-Chloroaniline	108-42-9	Negative in Salmonella (Zeiger et al., 1987); positive for chromosomal aberrations and SCE in CHO cells	Not evaluated for carcinogenicity
	*p*-Chloroaniline	106-47-8	Positive in Salmonella (Mortelmans et al., 1986); positive in mouse lymphoma cells (Mitchell et al., 1989; Myhr and Caspary, 1989); positive for chromosomal aberrations and SCE in CHO cells; negative in BALB/c-3T3 transformation assay; positive in Fischer cell/Rauscher leukemia virus transformation assay; positive for UDS in primary rat hepatocytes	Equivocal results in feed studies in rats and mice (NCI, 1979c)
	4,4'-Methylene bis(*o*-chloroaniline)	101-14-4	Positive in Salmonella (Haworth et al., 1983); positive in mouse lymphoma cells (Mitchell et al., 1989; Myhr and Caspary, 1989); negative for chromosomal aberrations; positive for SCE in CHO cells (Galloway et al., 1985); positive in BALB/c-3T3 transformation assay; positive in Fischer cell/Rauscher leukemia virus transformation assay; positive for UDS in primary rat hepatocytes; on test in Drosophila	Determined by IARC to have sufficient evidence of carcinogenicity in animals (IARC, 1974); nominated for reproductive effects study
	2,5-Dichloroaniline	95-82-9	Negative in Salmonella	Not evaluated for carcinogenicity

TABLE 1. *NCI/NTP* STUDIES OF CHEMICALS CONTAINING CHLOROANILINE MOIETIES (Continued)

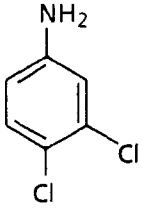
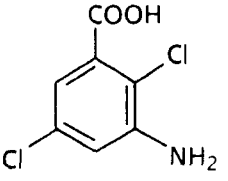
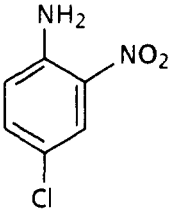
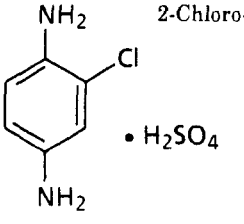
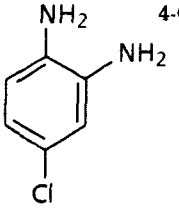
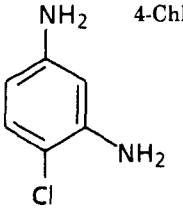
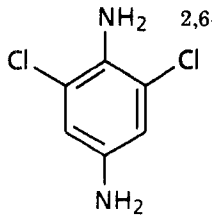
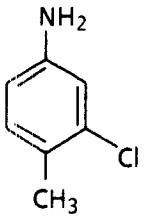
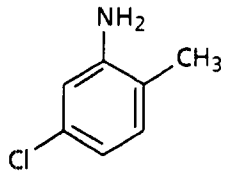
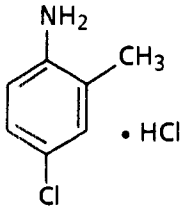
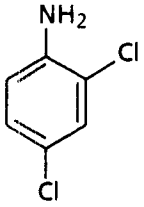
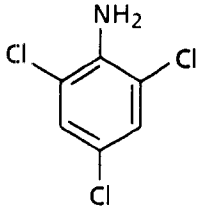
Structure	Chemical	CAS Number	NTP Testing Status	
			Genetic Toxicity	Carcinogenicity and Other
	3,4-Dichloroaniline	95-76-1	Negative for Salmonella	Not evaluated for carcinogenicity
	Chloramben	133-90-4	Positive in Salmonella (Haworth et al., 1983); positive for chromosomal aberrations and SCE in CHO cells; equivocal for sex-linked recessive lethals in Drosophila (Valencia et al., 1985)	Positive in feed studies; hepatocellular carcinomas in female mice (NCI, 1977b)
	4-Chloro-*o*-nitroaniline	89-63-4	Positive in Salmonella (Haworth et al., 1983); positive for chromosomal aberrations, weakly positive for SCE in CHO cells; positive in mouse lymphoma assay (Galloway et al., 1987)	Short-term gavage studies in rats and mice; chemical disposition studies in rats; on test in sperm morphology and vaginal cytologic assays
	2-Chloro-*p*-phenylenediamine sulfate	61702-44-1	Positive in Salmonella (Haworth et al., 1983); positive for chromosomal aberrations and for SCE in CHO cells	Negative in feed studies in rats and mice (NCI, 1978b)
	4-Chloro-*o*-phenylenediamine	95-83-0	Positive in Salmonella (Zeiger et al., 1988; Dunkel et al., 1985); positive for chromosomal aberrations and for SCE in CHO cells	Positive in feed studies; neoplasms of urinary bladder and forestomach in rats of each sex; hepatocellular carcinomas in mice of each sex (NCI, 1978d)
	4-Chloro-*m*-phenylenediamine	5131-60-2	Positive in Salmonella (Haworth et al., 1983; Dunkel et al., 1985); positive for chromosomal aberrations and SCE in CHO cells	Positive in feed studies; adrenal gland pheochromocytomas in male rats; hepatocellular neoplasms in female mice (NCI, 1978e)

TABLE 1. NCI/NTP STUDIES OF CHEMICALS CONTAINING CHLOROANILINE MOIETIES (Continued)

Structure	Chemical	CAS Number	NTP Testing Status: Genetic Toxicity	NTP Testing Status: Carcinogenicity and Other
	2,6-Dichloro-*p*-phenylene-diamine	609-20-1	Positive in Salmonella (Mortelmans et al., 1986); positive in mouse lymphoma cells; positive for chromosomal aberrations and for SCE in CHO cells	Positive in feed studies; hepatocellular adenomas or carcinomas (combined) in mice of each sex; hepatocellular adenomas in male mice (NTP, 1982b); on test for chemical disposition
	3-Chloro-*p*-toluidine	95-74-9	Negative in Salmonella (Haworth et al., 1983); positive for chromosomal aberrations and SCE in CHO cells	Negative in feed studies in rats and mice (NCI, 1978c)
	5-Chloro-*o*-toluidine	95-79-4	Negative in Salmonella (Haworth et al., 1983); negative in mouse lymphoma cells; negative in in vitro cytogenetics (Galloway et al., 1987)	Positive in feed studies; hemangiosarcomas and hepatocellular carcinomas in mice of each sex; not carcinogenic in rats (NCI, 1979d)
	4-Chloro-*o*-toluidine hydrochloride	3165-93-3	Negative in Salmonella (Haworth et al., 1983); positive in mouse lymphoma cells; positive for chromosomal aberrations and for SCE in CHO cells (Galloway et al., 1987)	Positive in feed studies; hemangiosarcomas and hemangiomas in mice of each sex; not carcinogenic in rats (NCI, 1979e)
	2,4-Dichloroaniline	554-00-7	Negative in Salmonella	Not evaluated for carcinogenicity
	2,4,6-Trichloroaniline	634-93-5	On test in Salmonella	Not evaluated for carcinogenicity

associated with increased deaths from urinary bladder cancer in dyestuff factory workers in northern Italy (Rubino et al., 1982; Lamb et al., 1986).

Study Rationale

In a previous *p*-chloroaniline study, rare splenic neoplasms were found in dosed male rats; however, the number of neoplasms was considered to be insufficient to establish clearly the carcinogenicity of *p*-chloroaniline (NCI, 1979c). *p*-Chloroaniline is unstable in feed, and the animals may have received the chemical at less than the targeted dietary concentration. Thus, the study is considered to be inadequate for determining carcinogenicity.

The widespread exposure of workers to *p*-chloroaniline in the dye, chemical, and pharmaceutical manufacturing industries and the structural resemblance of *p*-chloroaniline to known carcinogens were the rationale for reevaluating this chemical for toxicity and carcinogenicity in laboratory animals. The studies described in this report were conducted in F344/N rats and B6C3F$_1$ mice of each sex at three doses. The gavage route with a water vehicle was selected because the chemical was found to be unstable in feed.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *p*-CHLOROANILINE

PREPARATION AND CHARACTERIZATION OF *p*-CHLOROANILINE HYDROCHLORIDE DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

GENETIC TOXICOLOGY

PROCUREMENT AND CHARACTERIZATION OF *p*-CHLOROANILINE

p-Chloroaniline (S2 flaked, technical grade) was obtained in one lot (lot no. 127) from E.I. DuPont de Nemours and Company, Inc. (Wilmington, Delaware). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on the analyses performed in support of the *p*-chloroaniline studies are on file at the National Institute of Environmental Health Sciences. Lot no. 127 was identified as *p*-chloroaniline by infrared (Figure 1), ultraviolet/visible, and nuclear magnetic resonance spectra (Figure 2), which were consistent with those expected for the structure and the spectra in the literature (Sadtler Standard Spectra).

Purity was determined by elemental analysis, Karl Fischer water analysis, titration of the amine component with perchloric acid, thin-layer chromatography, and gas chromatography. Cumulative data indicated that lot no. 127 was 99.1% pure. Results of elemental analysis of lot no. 127 were in agreement with theoretical values for carbon, hydrogen, chlorine, and nitrogen. Water content was 0.020% by Karl Fischer titration. Titration of the amine group in glacial acetic acid with perchloric acid indicated a purity of 98.8%. Thin-layer chromatography with two different solvent systems (chloroform:methanol:acetic acid, 95:4:1, or diethylamine) showed a single spot. Gas chromatography performed with a 10% Carbowax 20M column indicated one impurity after the major peak with an area 0.14% that of the major peak and three other impurities, two before and one after the major peak, with individual peak areas less than 0.1% that of the major peak. A second gas chromatographic system with a 3% SP2100(DB) column indicated one impurity after the major peak with an area 0.13% that of the major peak and a group of unresolved impurities after the major peak, with a total area 0.15% that of the major peak.

PREPARATION AND CHARACTERIZATION OF *p*-CHLOROANILINE HYDROCHLORIDE DOSE MIXTURES

All dose mixtures administered to animals in these studies were prepared from weighed quantities of *p*-chloroaniline dissolved in water containing hydrochloric acid; all doses refer to the *p*-chloroaniline content of the solution. *p*-Chloroaniline and molar equivalents of 1.0 N hydrochloric acid were mixed together in a calibrated container (Table 2). The resulting *p*-chloroaniline hydrochloride solutions were diluted to the appropriate concentration with deionized water and had a pH of approximately 2. The solutions were refrigerated for 1 day and filtered through filter paper to remove precipitate. The stability of *p*-chloroaniline hydrochloride in water gavage solutions (5 mg/ml as *p*-chloroaniline) was determined by gas chromatography with a 3% SP2401 on 100/200 mesh Supelcoport packed column after dilutions with methanol and additions of biphenyl as an internal reference. The chemical was found to be stable in water for at least 14 days at room temperature. For the 16-day and 13-week studies, dose mixtures were prepared at weekly intervals, placed in foil-wrapped containers, and refrigerated until the day of dosing. For the 2-year studies, the filtrates were stored in amber bottles at 5° C and were used as the stock solutions or as the dose mixtures for the highest dose groups of rats and mice.

Periodic analysis of formulated *p*-chloroaniline hydrochloride in water dose mixtures by ultraviolet spectroscopy at 216 nm was conducted at the study and analytical chemistry laboratories. The study laboratory analyzed dose mixtures by ultraviolet spectroscopy two times during the 13-week studies (Table 3). During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. The number of times that concentrations were not within specifications can be extrapolated to indicate the frequency with which mixtures were formulated

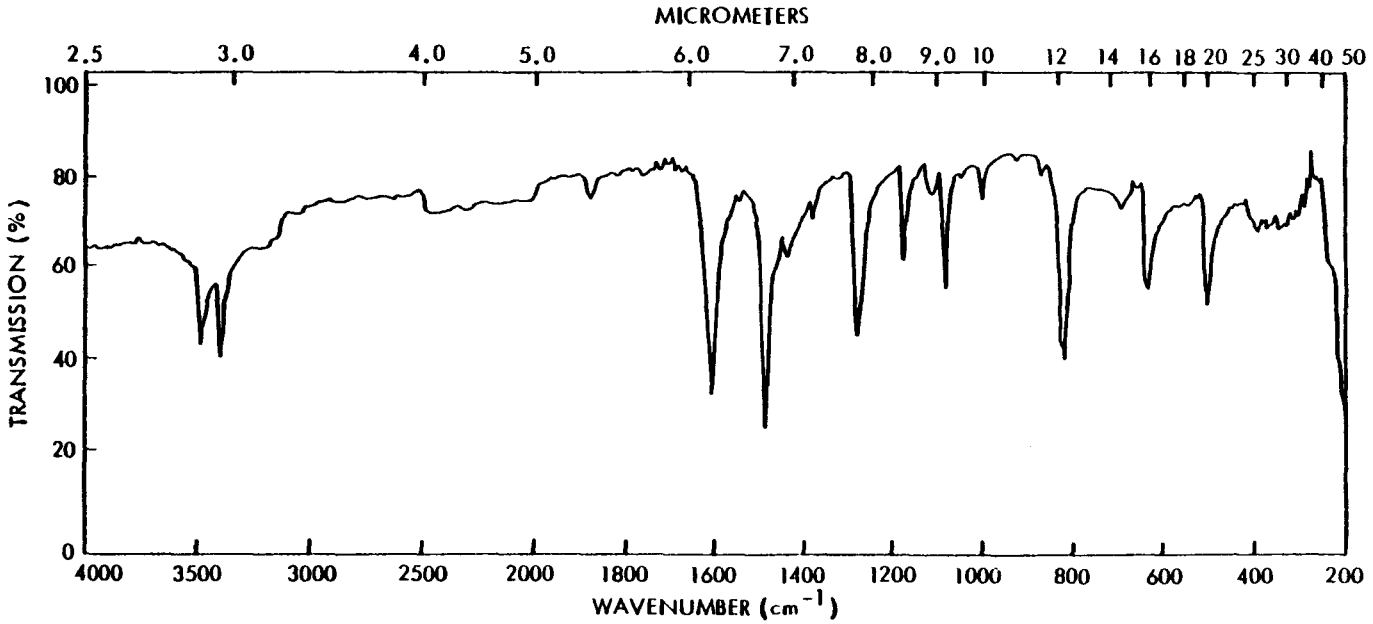


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF *p*-CHLOROANILINE (LOT NO. 127)

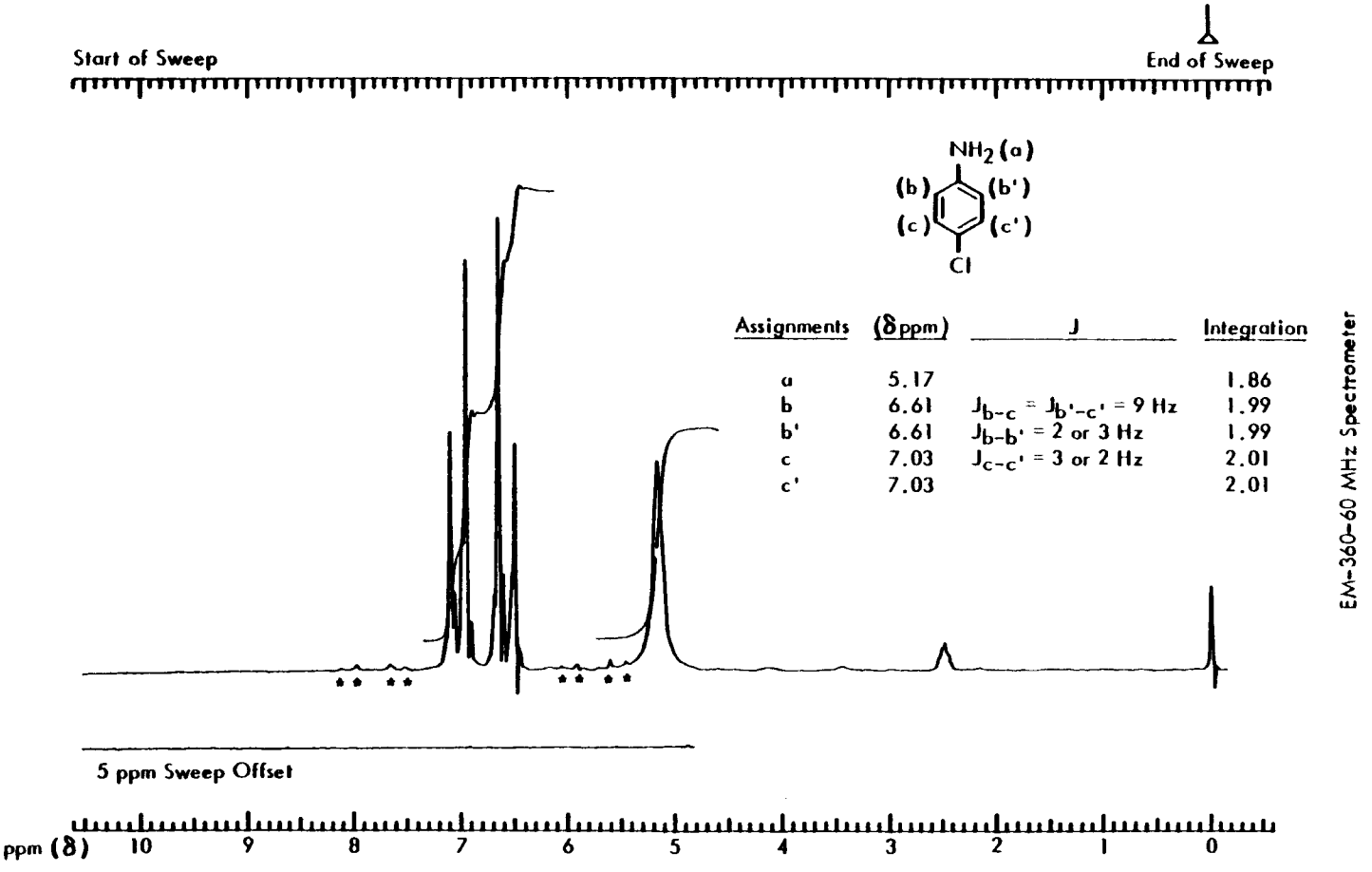


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF *p*-CHLOROANILINE (LOT NO. 127)

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Weighed portions of *p*-chloroaniline mixed with molar equivalents of 1.0 N hydrochloric acid. Resulting solution further diluted to appropriate concentration with deionized water. Solution allowed to stand 1 d and then filtered through filter paper. Serial dilutions made with deionized water to obtain lower dose mixtures	Same as 16-d studies	Same as 16-d studies
Maximum Storage Time		
2 wk	2 wk	2 wk
Storage Conditions		
5° C in foil-wrapped containers	5° C in foil-wrapped containers	5° C in amber glass containers

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Date Mixed	Concentration of *p*-Chloroaniline in Aqueous Hydrochloric Acid (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
3/25/81	1	1.09	109
	1.5	1.4	93
	2	2.0	100
	3	2.8	93
	4	4.2	105
	6	5.6	93
	8	8.5	106
	12	10.9	91
	16	17.1	107
	24	22.2	92
5/12/81	1	1	100
	2	1.8	90
	4	3.9	98
	8	8.6	108
	16	17.6	110
5/12/81	1.5	1.0	67
	3	2.8	93
	6	6.3	105
	12	13.0	108
	24	25.7	107
5/19/81	1.5	(b) 1.4	93
	3	(c) 3.1	103
	6	(c) 6.4	107
	12	(c) 13.0	108
	24	(c) 26.0	108

(a) Results of duplicate analysis; concentrations expressed as milligrams per milliliter *p*-chloroaniline; the hydrochloride was formed during dose preparation.
(b) Remix of dose mixture of 5/12/81 which was out of specifications
(c) Remix of dose mixture of 5/12/81

within the specified ±10% of the target concentrations. For the 2-year *p*-chloroaniline hydrochloride studies, 72/72 dose mixtures were formulated within ±10% of the target concentrations, and it is therefore estimated that 100% of the dose mixtures were properly prepared (Table 4). Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table 5).

TABLE 4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Date Mixed	Concentration of *p*-Chloroaniline in Aqueous Hydrochloric Acid for Target Concentration (mg/ml) (a)					
	0.4	0.6	1.2	2.0	3.6	6.0
01/20/82	0.37	--	1.25	--	3.70	--
02/03/82	--	0.61	--	1.86	--	5.98
06/10/82	0.40	0.57	1.19	2.03	3.56	6.09
08/11/82	0.37	0.60	1.11	1.97	3.61	6.08
10/14/82	0.37	0.66	1.12	1.95	3.65	6.00
12/08/82	--	0.59	--	2.02	--	6.13
12/09/82	0.39	--	1.15	--	3.66	--
02/09/83	0.39	0.58	1.17	2.06	3.54	6.08
03/30/83	0.44	0.57	1.27	2.09	3.49	5.79
06/15/83	0.39	--	1.18	--	3.59	--
06/16/83	--	0.60	--	1.99	--	5.96
07/27/83	0.41	0.60	1.20	1.93	3.54	5.83
09/21/83	0.36	0.55	1.17	2.02	3.56	5.90
11/17/83	0.37	0.57	1.16	2.03	3.50	5.92
01/11/84	0.39	0.62	1.21	2.01	3.62	5.83
Mean (mg/ml)	0.39	0.59	1.18	2.00	3.58	5.97
Standard deviation	0.022	0.029	0.047	0.062	0.065	0.114
Coefficient of variation (percent)	5.9	4.9	4.0	3.1	1.8	1.9
Range (mg/ml)	0.36-0.44	0.55-0.66	1.11-1.27	1.86-2.09	3.49-3.70	5.79-6.13
Number of samples	12	12	12	12	12	12

(a) Results of duplicate analysis; concentrations expressed as milligrams per milliliter *p*-chloroaniline; the hydrochloride was formed during dose preparation.

TABLE 5. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
01/20/82	1.2	1.25	1.18
08/11/82	0.6	0.60	0.655
02/09/83	3.6	3.54	3.50
09/21/83	6.0	5.90	5.99

(a) Results of duplicate analysis; concentrations expressed as milligrams per milliliter *p*-chloroaniline; the hydrochloride was formed during dose preparation.
(b) Results of triplicate analysis

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 14 days (rats) or 15 days (mice) before the studies began. The rats were approximately 7 weeks old when placed on study, and the mice were 8 weeks old.

Groups of five rats and mice of each sex were administered 25, 50, 100, 200, or 400 mg/kg *p*-chloroaniline by gavage in aqueous hydrochloric acid, 5 days per week for a total of 12 doses over 16 days. Vehicle controls received deionized water by gavage.

Animals were housed five per cage. Water and feed were available ad libitum. Rats and mice were observed twice per day. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 6.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of *p*-chloroaniline hydrochloride and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and 6-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries, observed for 19 days, distributed to weight classes, and assigned to dose groups according to a table of random numbers. Rats were approximately 7 weeks old when placed on study, and mice were 9 weeks old.

Groups of 10 rats of each sex were administered 5, 10, 20, 40, or 80 mg/kg *p*-chloroaniline by gavage in water acidified with hydrochloric acid, 5 days per week for 13 weeks for a total of 64 or 65 doses. Groups of 10 mice of each sex were administered 7.5, 15, 30, 60, or 120 mg/kg on the same schedule for a total of 66 or 67 doses. Vehicle controls received deionized water by gavage.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded once per week. Further experimental details are summarized in Table 6.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 6.

On the day of necropsy, blood was taken for hematologic and methemoglobin determinations from the vena cava of pentobarbital-anesthetized rats or from the retro-orbital sinus of unanesthetized mice. Blood was collected in Becton-Dickinson® microtainers containing sodium EDTA. Hematologic analyses were performed with an Ortho ELT-8 Hematology Analyzer. The methemoglobin concentration was determined by the method of Evelyn and Malloy (1938).

TWO-YEAR STUDIES

Study Design

Groups of 49 or 50 rats of each sex were administered 2, 6, or 18 mg/kg *p*-chloroaniline by gavage in aqueous hydrochloric acid, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 3, 10, or 30 mg/kg on the same schedule. Vehicle controls received deionized water by gavage.

Source and Specifications of Animals

The male and female F344/N rats used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories, and the B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced at Frederick Cancer Research Center. Breeding stock for the foundation colonies at the production facilities originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rodents were shipped to the study laboratory at 5-6 weeks of age. Rats were quarantined at the study laboratory for 20 days and

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	49 or 50 males and 50 females of each species
Doses		
25, 50, 100, 200, or 400 mg/kg *p*-chloroaniline by gavage in aqueous hydrochloric acid (molar equivalents); dose vol--5 ml/kg; vehicle controls received deionized water by gavage	Rats--5, 10, 20, 40, or 80 mg/kg *p*-chloroaniline by gavage in aqueous hydrochloric acid (molar equivalents); mice--7.5, 15, 30, 60, or 120 mg/kg; dose vol--5 ml/kg; vehicle controls received deionized water by gavage	Rats--2, 6, or 18 mg/kg *p*-chloroaniline by gavage in aqueous hydrochloric acid (molar equivalents); mice--3, 10, or 30 mg/kg; dose vol--5 ml/kg; vehicle controls received deionized water by gavage
Date of First Dose		
Rats--2/3/81; mice--2/4/81	3/30/81	Rats--1/25/82; mice--2/8/82
Date of Last Dose		
Rats--2/18/81; mice--2/19/81	Rats--male: 6/26/81; female: 6/29/81; mice--male: 6/30/81; female: 7/1/81	Rats--1/13/84; mice--1/27/84
Duration of Dosing		
12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed 1 × wk for 13 wk and then 1 × mo
Necropsy, Histologic Examinations, and Supplemental Studies		
Necropsy performed on all animals; histologic exams performed on 2 males and 2 females in the vehicle control and 100 mg/kg groups. Tissues examined include: adrenal glands, bone marrow, brain, colon, esophagus, gallbladder (mice), heart, jejunum, kidneys, liver, lungs and mainstem bronchi, mandibular lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, regional lymph nodes, salivary glands, seminal vesicles (mice), skin, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Spleen examined from 2 males and 2 females in the 25 mg/kg groups	Necropsy and histologic exams performed on all vehicle control and high dose animals; the following tissues were examined: adrenal glands, bone marrow, brain, colon, duodenum, esophagus, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mandibular lymph nodes, nasal cavity, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, rectum, regional lymph nodes (rats), salivary glands, skin, spleen, stomach, thymus, thyroid gland, tissue masses (rats), trachea, and urinary bladder. Tissues examined in the lower dose groups include: adrenal glands (mice), bone marrow, kidneys, liver, lungs and bronchi (mice), nasal cavity (rats), spleen (rats), and stomach (mice). Organ weights obtained at necropsy include brain, heart, liver, lungs, right kidney, spleen, testes, and thymus; hematologic and methemoglobin determinations performed	Necropsy performed on all animals; histologic exams performed on all vehicle control and high dose animals and on all animals dying before the end of the studies. Tissues examined include: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, regional lymph nodes, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae or vertebrae or femur including marrow, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Tissues examined in the lower dose groups include: adrenal glands, bone, bone marrow, kidneys, liver, spleen, and testes for rats and liver and spleen for mice. Hematologic and methemoglobin determinations performed for rats at 6, 12, 18, and 24 mo
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animal Source Charles River Breeding Laboratories (Kingston, NY)	Harlan Industries (Indianapolis, IN)	Rats--Charles River Breeding Laboratories (Kingston, NY); mice--Frederick Cancer Research Center (Frederick, MD)
Study Laboratory Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification Toe mark	Toe mark	Toe clip and ear mark
Time Held Before Study Rats--14 d; mice--15 d	19 d	Rats--20 d; mice--12 d
Age When Placed on Study Rats--7 wk; mice--8 wk	Rats--7 wk; mice--9 wk	Rats--8 wk; mice--7 wk
Age When Killed Rats--9 wk; mice--10 wk	Rats--20 wk; mice--22 wk	Rats--112 wk; mice--111 wk
Necropsy Dates Rats--2/19/81; mice--2/20/81	Rats--male: 6/29/81; female: 6/30/81; mice--male: 7/1/81; female: 7/2/81	Rats--1/24/84-1/27/84; mice--2/6/84-2/10/84
Method of Animal Distribution Animals distributed to weight classes and assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as 16-d studies	Same as 16-d studies
Feed NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies
Bedding Absorb-dri hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Same as 16-d studies	Same as 16-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 16-d studies
Cage Filters Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies
Animals per Cage 5	5	5
Chemicals on Study in the Same Room None	None	None

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animal Room Environment		
Temp--70°-74° F; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as 16-d studies	Temp--64°-82° F; hum--24%-75%; fluorescent light 12 h/d; at least 15 room air changes/h

mice for 12 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 7-8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Cages and racks were rotated. Further details of animal maintenance are given in Table 6.

Clinical Examinations and Pathology

Blood samples for hematologic and methemoglobin determinations were collected in Vacutainers® containing EDTA by retro-orbital puncture from 15 randomly selected rats from each group at 6, 12, 18, and 24 months. Rats were dosed for 2 consecutive days before blood collection except at 24 months when collection was performed 11-14 days after administration of the last dose. Hematologic analyses were performed with an Ortho ELT-8 Hematology Analyzer; methemoglobin concentration was determined by the method of Evelyn and Malloy (1938).

All animals were observed two times per day. Clinical signs were recorded once per week for 13 weeks and then at least once per month. Individual body weights were recorded once per week for the first 13 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 6) were performed on all high dose and vehicle control animals and on lower dose animals dying before the end of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose groups were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the 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

quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

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 to be missing or dead from other than natural causes; 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 for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic 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 could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: The majority of tumors in this study 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 vehicle control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the

appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with vehicle 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 data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983) and Mortelmans et al. (1986). Chemicals were sent to three different laboratories as coded aliquots from Radian Corporation (Austin, Texas). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, TA1535, and/or 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° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in a series (four strains used) or in a hierarchy (initial testing in TA98 and TA100; if results were negative, then the chemical was tested further in additional strains). If all results were negative, the chemical was retested in all strains with a different concentration of S9.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, Texas). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 1 mg/ml. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were

replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells ($TK^{+/+}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was initially performed without S9; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations 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 (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more 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 the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 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 chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 first-division metaphase cells were scored at each dose for the chromosomal aberration 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. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Hematology at Six, Twelve, Eighteen, and Twenty-Four Months

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

SIXTEEN-DAY STUDIES

All rats that received 200 or 400 mg/kg *p*-chloroaniline hydrochloride died within 5 days (Table 7). The final mean body weights of rats that received 100 mg/kg were 19% lower than that of vehicle controls for males and 5% lower for females. Compound-related clinical signs included blue extremities and eyes, indicative of cyanosis. Rats that received 200 or 400 mg/kg were lethargic, and rats that received 25 or 50 mg/kg had labored breathing. Splenic enlargement was observed at 25, 50, and 100 mg/kg. Sinusoidal congestion of the spleen and hemosiderin deposition in the renal cortical tubular epithelial cells were observed in 2/2 males and 2/2 females that received 100 mg/kg.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Dose (a) (mg/kg)	Survival (b)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (c)	Final	Change (d)	
MALE					
0	5/5	125	209	+84	
25	5/5	124	199	+75	95.2
50	5/5	123	196	+73	93.8
100	5/5	125	169	+44	80.9
200	(e) 0/5	124	(f)	(f)	(f)
400	(g) 0/5	124	(f)	(f)	(f)
FEMALE					
0	5/5	105	132	+27	
25	5/5	105	131	+26	99.2
50	5/5	104	133	+29	100.8
100	5/5	105	125	+20	94.7
200	(e) 0/5	104	(f)	(f)	(f)
400	(h) 0/5	103	(f)	(f)	(f)

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Number surviving/number initially in group
(c) Initial group mean body weight
(d) Mean body weight change of the group
(e) Day of death: 4,4,4,4,5
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 2,2,2,3,3
(h) Day of death: 2,2,3,3,3

THIRTEEN-WEEK STUDIES

All male rats lived to the end of the studies (Table 8). One of 10 female rats that received 80 mg/kg died before the end of the studies. The final mean body weights of rats that received 80 mg/kg were 16% lower than that of vehicle controls for males and 4% lower for females. The weights of brain, liver, thymus, kidney, heart, lung, and testis for dosed groups were comparable to those of vehicle controls, except that the brain and lung weights of male rats at 80 mg/kg were significantly lower than those of vehicle controls and the heart and kidney weights of female rats were significantly greater than those of vehicle controls (Table F1). Spleen weights were increased in dosed groups, and a clear dose-response relationship was observed (Figure 3; Table F1). Spleen weights were not recorded for male vehicle controls, but the spleens of untreated animals of comparable age weigh 0.678-0.848 g (NTP data base). The hematocrit value, the hemoglobin concentration, and the erythrocyte count for all dosed groups of rats were significantly lower than those for vehicle controls (Table 9; Figures 4 and 5). The methemoglobin concentrations for all dosed groups of rats were significantly greater than those for vehicle controls. Blood samples for hematologic analysis were taken 72 (male) or 24 (female) hours after administration of the final dose.

This time difference probably contributed to the lower methemoglobin concentrations observed for males compared with those for females. Compound-related increases were seen for the number of segmented neutrophils, the mean corpuscular hemoglobin, the mean corpuscular hemoglobin concentration, the mean corpuscular volume, and the numbers of nucleated and polychromatophilic erythrocytes. The leukocyte count and lymphocyte count were significantly increased for male rats at 40 mg/kg (but not at 80 mg/kg) and for all dosed groups of female rats.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Dose (a) (mg/kg)	Survival (b)	Mean Body Weights (grams) Initial (c)	Final	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	140 ± 3	334 ± 9	+194 ± 7	
5	10/10	135 ± 3	338 ± 6	+203 ± 5	101
10	10/10	137 ± 2	345 ± 4	+208 ± 4	103
20	10/10	135 ± 2	338 ± 4	+203 ± 4	101
40	10/10	137 ± 3	325 ± 8	+188 ± 5	97
80	10/10	136 ± 3	280 ± 9	+144 ± 8	84
FEMALE					
0	10/10	110 ± 2	197 ± 2	+87 ± 2	
5	10/10	109 ± 2	199 ± 3	+90 ± 2	101
10	10/10	111 ± 2	197 ± 3	+86 ± 3	100
20	10/10	109 ± 2	194 ± 2	+85 ± 2	98
40	10/10	107 ± 2	192 ± 3	+85 ± 3	97
80	(e) 9/10	104 ± 2	189 ± 3	+84 ± 3	96

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Number surviving/number initially in group
(c) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(d) Mean body weight change of the survivors ± standard error of the mean
(e) Week of death: 3

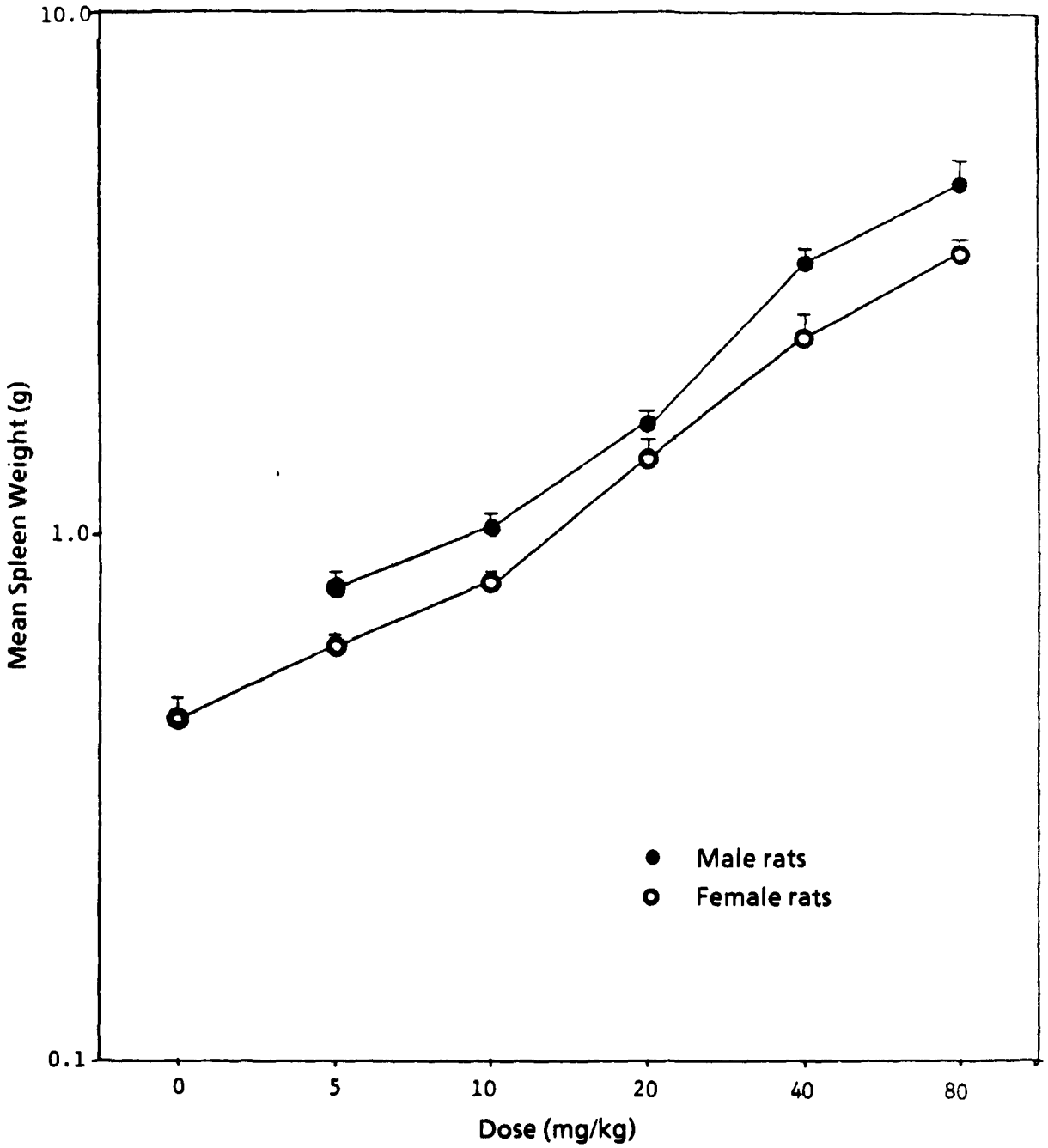


FIGURE 3. SPLEEN WEIGHTS (MEAN AND STANDARD DEVIATION) OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

TABLE 9. ANALYSIS OF HEMATOLOGIC DATA FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg
MALE						
Number examined	10	10	9	10	10	10
Leukocytes (1,000/mm^3)	5.49 ± 0.222	6.28 ± 0.227	6.60 ± 0.197	6.55 ± 0.109	(b) 12.55 ± 0.816	(b) 3.47 ± 0.231
Lymphocytes (1,000/mm^3)	4.64 ± 0.274	5.36 ± 0.221	5.38 ± 0.132	5.50 ± 0.119	(b) 10.34 ± 0.638	(b) 2.76 ± 0.167
Segmented neutrophils (1,000/mm^3)	0.74 ± 0.096	0.86 ± 0.072	1.19 ± 0.140	1.00 ± 0.078	(b) 2.07 ± 0.328	0.66 ± 0.094
Monocytes (1,000/mm^3)	0.06 ± 0.021	0.01 ± 0.008	0.00 ± 0.000	0.01 ± 0.007	0.08 ± 0.032	0.04 ± 0.019
Eosinophils (1,000/mm^3)	0.05 ± 0.015	0.04 ± 0.016	0.03 ± 0.016	0.05 ± 0.020	0.06 ± 0.023	0.01 ± 0.007
Hematocrit (percent)	45.5 ± 0.43	(b) 42.8 ± 0.49	(b) 42.4 ± 0.24	(b) 42.7 ± 0.37	(b) 39.4 ± 0.31	(b) 36.5 ± 0.43
Hemoglobin (g/dl)	15.5 ± 0.11	(b) 14.7 ± 0.17	(b) 14.6 ± 0.10	(b) 15.1 ± 0.13	(b) 14.2 ± 0.13	(b) 13.4 ± 0.16
MCH (pg)	16.9 ± 0.06	17.0 ± 0.10	(b) 17.9 ± 0.12	(b) 20.1 ± 0.12	(b) 23.5 ± 0.15	(b) 27.3 ± 0.14
MCHC (g/dl)	34.0 ± 0.10	34.3 ± 0.19	(b) 34.5 ± 0.14	(b) 35.3 ± 0.14	(b) 35.9 ± 0.16	(b) 36.6 ± 0.13
MCV (cubic microns)	50.1 ± 0.18	49.4 ± 0.16	(b) 51.8 ± 0.28	(b) 56.9 ± 0.28	(b) 65.1 ± 0.41	(b) 74.7 ± 0.40
Methemoglobin (percent of hemoglobin)	0.08 ± 0.035	(c) 0.59 ± 0.098	(c) 0.70 ± 0.241	(c) 0.68 ± 0.195	(c) 0.68 ± 0.186	(b) 0.86 ± 0.155
Nucleated erythrocytes (1,000/mm^3)	0.00 ± 0.000	1.70 ± 0.496	(c) 3.44 ± 0.603	(c) 2.90 ± 0.458	(b) 8.70 ± 1.359	(b) 23.80 ± 1.590
Erythrocytes (10^6/mm^3)	9.14 ± 0.056	(b) 8.68 ± 0.096	(b) 8.18 ± 0.035	(b) 7.48 ± 0.061	(b) 6.07 ± 0.063	(b) 4.90 ± 0.069
FEMALE						
Number examined	10	10	10	10	10	9
Leukocytes (1,000/mm^3)	4.57 ± 0.321	(c) 6.04 ± 0.221	(b) 8.09 ± 0.278	(b) 9.70 ± 0.550	(b) 10.26 ± 0.781	(b) 6.49 ± 0.391
Lymphocytes (1,000/mm^3)	3.84 ± 0.270	(c) 5.14 ± 0.232	(b) 6.81 ± 0.228	(b) 7.99 ± 0.479	(b) 7.93 ± 0.647	(b) 5.13 ± 0.332
Segmented neutrophils (1,000/mm^3)	0.68 ± 0.081	0.86 ± 0.075	(c) 1.17 ± 0.138	(b) 1.64 ± 0.244	(b) 2.26 ± 0.241	(b) 1.33 ± 0.148
Eosinophils (1,000/mm^3)	0.05 ± 0.016	0.04 ± 0.015	0.10 ± 0.028	0.06 ± 0.033	0.06 ± 0.028	0.03 ± 0.015
Hematocrit (percent)	45.7 ± 0.26	(b) 43.8 ± 0.29	(b) 43.3 ± 0.40	(b) 42.5 ± 0.34	(b) 39.8 ± 0.63	(b) 36.3 ± 0.47
Hemoglobin (g/dl)	15.1 ± 0.11	(b) 14.4 ± 0.11	(b) 14.3 ± 0.14	(b) 14.8 ± 0.16	(b) 13.7 ± 0.24	(b) 13.0 ± 0.12
MCH (pg)	18.1 ± 0.08	18.5 ± 0.06	(b) 19.6 ± 0.09	(b) 22.8 ± 0.17	(b) 24.0 ± 0.22	(b) 25.8 ± 0.21
MCHC (g/dl)	33.1 ± 0.12	32.8 ± 0.13	33.2 ± 0.27	(b) 35.0 ± 0.17	(b) 34.3 ± 0.22	(b) 35.7 ± 0.31
MCV (cubic microns)	55.0 ± 0.00	(b) 56.3 ± 0.15	(b) 59.3 ± 0.15	(b) 65.1 ± 0.23	(b) 69.9 ± 0.28	(b) 72.2 ± 0.22
Methemoglobin (percent of hemoglobin)	0.46 ± 0.126	(b) 1.35 ± 0.146	(b) 1.85 ± 0.178	(b) 1.73 ± 0.213	(b) 2.40 ± 0.154	(b) 3.68 ± 0.448
Nucleated erythrocytes (1,000/mm^3)	1.40 ± 0.542	3.10 ± 0.605	4.40 ± 0.618	(c) 7.90 ± 1.048	(b) 22.60 ± 3.622	(b) 24.44 ± 1.676
Erythrocytes (10^6/mm^3)	8.33 ± 0.049	(b) 7.77 ± 0.048	(b) 7.27 ± 0.082	(b) 6.49 ± 0.060	(b) 5.69 ± 0.085	(b) 5.06 ± 0.060

(a) Mean ± standard error. MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; P values are vs. the vehicle controls; Dunnett's test was used when a nonsignificant result was obtained by the Jonckheere test; otherwise Williams' test was used (Dunnett, 1980; Jonckheere, 1954; Williams, 1971, 1972); doses calculated as *p*-chloroaniline.

(b) $P < 0.01$ vs. vehicle controls

(c) $P < 0.05$ vs. vehicle controls

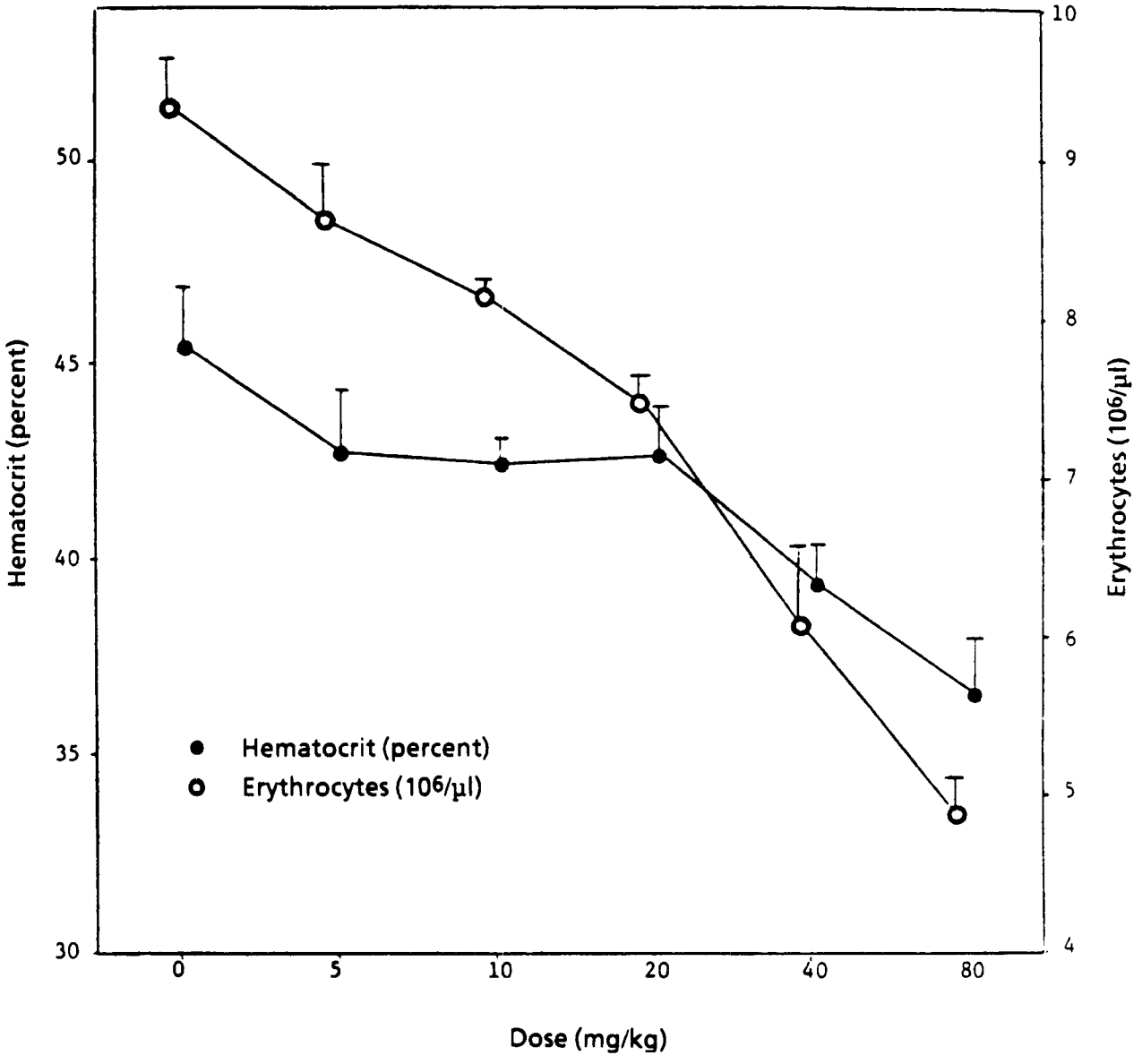


FIGURE 4. PERCENTAGE HEMATOCRIT AND ERYTHROCYTE COUNT (AND STANDARD DEVIATION) FOR MALE RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

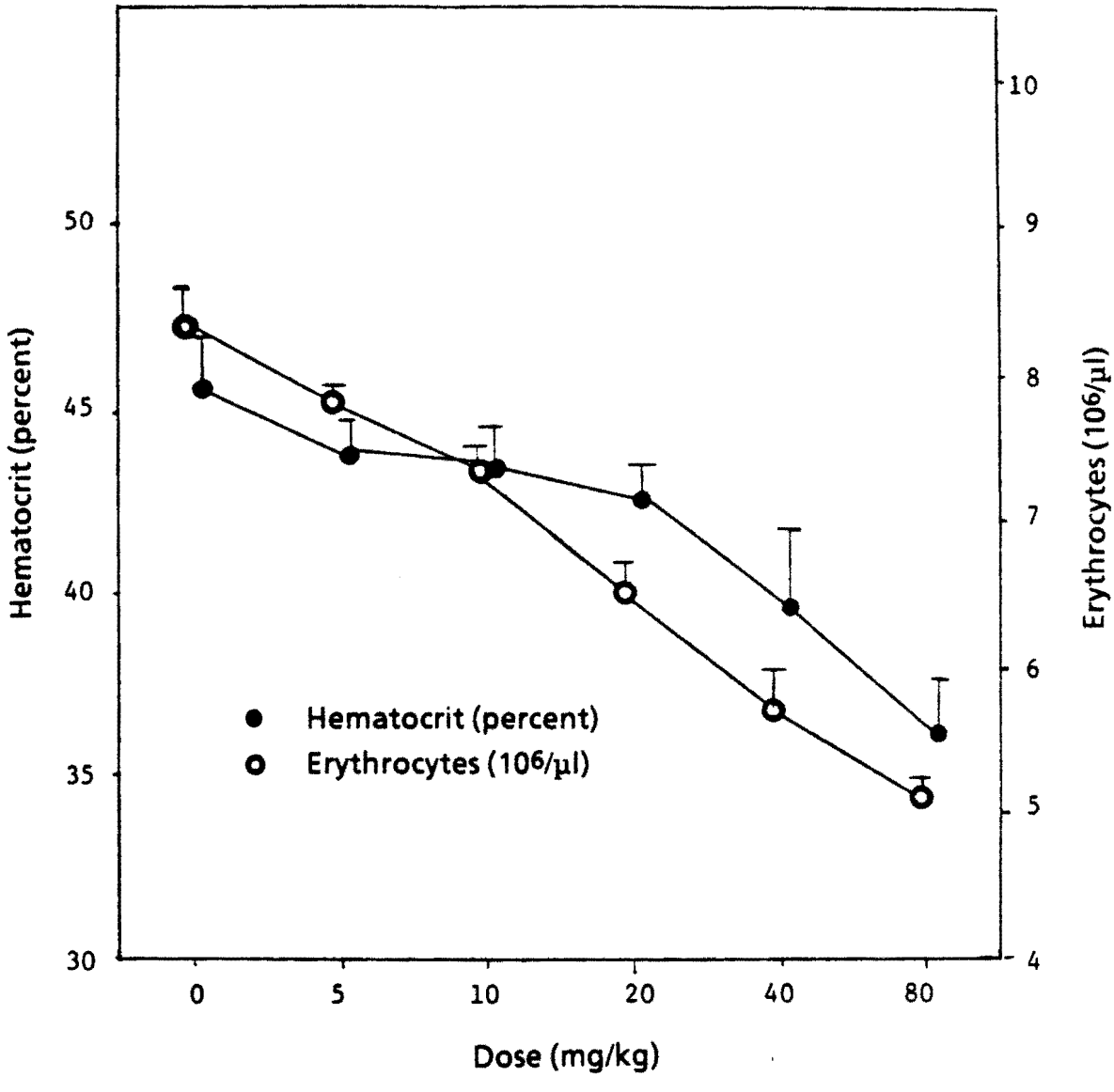


FIGURE 5. PERCENTAGE HEMATOCRIT AND ERYTHROCYTE COUNT (AND STANDARD DEVIATION) FOR FEMALE RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

Compound-related lesions included bone marrow hyperplasia (severe at 80 mg/kg and minimal at 5 mg/kg), pigmentation (hemosiderin) of the kidney, spleen, and Kupffer cells of the liver, hematopoiesis of the liver and spleen, and splenic congestion, which are attributable to increased erythrocyte destruction secondary to methemoglobin formation (Table 10).

TABLE 10. NUMBER OF RATS WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

Site/Lesion	Dose (mg/kg) 0	5	10	20	40	80
MALE						
Femoral bone marrow						
Hyperplasia	0	10	10	10	10	10
Kidney						
Hemosiderosis	0	5	10	10	10	10
Liver						
Hemosiderosis of Kupffer cells	0	0	0	3	5	10
Hematopoiesis	0	0	1	2	4	7
Spleen						
Hematopoiesis	0	3	10	10	10	10
Hemosiderosis	0	10	9	9	4	10
Congestion	0	10	10	10	10	10
FEMALE						
Femoral bone marrow						
Hyperplasia	0	9	10	10	10	10
Kidney						
Hemosiderosis	0	2	7	10	10	10
Liver						
Hemosiderosis of Kupffer cells	0	0	2	6	9	10
Hematopoiesis	0	0	0	0	3	2
Spleen						
Hematopoiesis	0	0	4	1	10	5
Hemosiderosis	0	10	10	8	10	9
Congestion	0	10	10	9	10	10

(a) Ten animals in each group examined; all doses calculated as milligrams *p*-chloroaniline per kilogram body weight.

Dose Selection Rationale: Major compound-related effects observed in rats were hemolytic anemia, methemoglobinemia, and splenomegaly. The hemolytic anemia and splenomegaly responses were dose related. Methemoglobin levels were approximately 1%-4% in the highest dose groups and slightly lower in the other dose groups. It was judged that doses higher than 20 mg/kg for the 2-year studies might produce severe anemia in animals because hematocrit and erythrocyte values were reduced substantially in the 13-week studies at doses of 40 and 80 mg/kg. Furthermore, the magnitude of splenomegaly was considered to be too great to permit selection of doses higher than 20 mg/kg. Therefore, 18 mg/kg was selected as the high dose and 2 and 6 mg/kg, as the low and mid doses, respectively. This dose regimen was expected to achieve a no-effect level at the low dose and to produce some effects on the hematopoietic system at the mid dose in the 2-year studies.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The mean body weights of high dose female rats were 4%-6% lower than those of vehicle controls after week 70 (Table 11 and Figure 6). Mean body weights of dosed male rats were generally within 5% of those of vehicle controls throughout the studies. Mid and high dose male rats and high dose female rats had blue extremities indicative of cyanosis.

TABLE 11. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. Weighed	2 mg/kg Av. Wt. (grams)	2 mg/kg Wt. (percent of veh. controls)	2 mg/kg No. Weighed	6 mg/kg Av. Wt. (grams)	6 mg/kg Wt. (percent of veh. controls)	6 mg/kg No. Weighed	18 mg/kg Av. Wt. (grams)	18 mg/kg Wt. (percent of veh. controls)	18 mg/kg No. Weighed
MALE											
0	135	49	131	97	50	134	99	50	134	99	50
1	170	49	166	98	50	168	99	50	166	98	50
2	203	49	200	99	50	202	100	50	203	100	50
3	232	49	229	99	50	229	99	50	232	100	50
4	241	49	238	99	50	248	103	50	255	106	50
5	265	49	258	97	50	263	99	50	269	102	50
6	279	49	275	99	50	275	99	50	284	102	50
7	295	49	289	98	50	289	98	50	293	99	50
8	305	49	304	100	50	307	101	50	307	101	50
9	316	49	315	100	50	313	99	50	315	100	50
10	330	49	325	98	50	319	97	50	324	98	50
11	337	48	334	99	50	326	97	50	331	98	50
12	346	48	344	99	50	338	98	50	341	99	50
13	354	48	352	99	50	348	98	50	348	98	50
17	375	48	373	99	50	371	99	50	371	99	50
22	397	(a) 47	395	99	50	392	99	(a) 39	387	97	(a) 35
26	411	48	413	100	50	404	98	50	403	98	50
30	429	48	429	100	50	418	97	50	417	97	50
34	440	48	437	99	50	427	97	50	425	97	50
38	448	48	447	100	50	440	98	50	436	97	50
42	454	47	449	99	50	446	98	50	440	97	(a) 45
46	462	47	456	99	50	454	98	50	446	97	50
50	474	46	466	98	50	458	97	49	453	96	50
54	467	46	468	100	50	460	99	48	443	95	50
55	471	46	473	100	50	466	99	48	451	96	50
58	472	46	484	103	50	474	100	48	464	98	50
62	489	(a) 41	484	99	(a) 45	478	98	48	468	96	(a) 44
66	493	45	492	100	50	486	99	48	475	96	49
70	492	44	488	99	49	482	98	46	467	95	(a) 47
74	484	43	484	100	49	475	98	45	461	95	47
78	479	42	480	100	48	476	99	(a) 39	458	96	45
82	474	40	474	100	47	467	99	42	461	97	44
86	478	38	473	99	47	469	98	39	460	96	43
90	469	36	470	100	46	467	100	39	460	98	39
94	456	31	460	101	42	461	101	39	458	100	39
98	455	26	474	104	37	456	100	39	456	100	32
102	442	21	462	105	35	453	102	37	462	105	28
FEMALE											
0	108	50	109	101	50	108	100	50	109	101	50
1	128	50	128	100	50	128	100	50	124	97	50
2	138	50	138	100	50	140	101	50	137	99	50
3	150	50	151	101	50	154	103	50	150	100	50
4	156	50	160	103	50	149	96	50	148	95	50
5	165	50	168	102	50	167	101	50	166	101	50
6	169	50	175	104	50	172	102	50	170	101	50
7	173	50	179	103	50	179	103	50	178	103	50
8	181	50	185	102	50	185	102	50	182	101	50
9	184	50	188	102	50	189	103	50	188	102	50
10	186	50	191	103	50	192	103	50	189	102	50
11	188	50	193	103	50	195	104	50	193	103	50
12	190	49	195	103	50	198	104	50	195	103	50
13	192	49	198	103	50	200	104	50	200	104	50
17	200	49	206	103	50	207	104	50	206	103	50
22	207	(a) 47	217	105	(a) 48	214	103	(a) 46	212	102	(a) 48
26	211	49	220	104	49	218	103	50	214	101	50
30	224	47	229	102	49	230	103	50	225	100	50
34	226	46	231	102	49	233	103	50	229	101	50
38	231	46	237	103	49	241	104	50	236	102	50
42	234	46	241	103	49	244	104	50	240	103	50
46	238	46	245	103	49	245	103	50	239	100	50
50	249	46	258	104	49	258	104	49	247	99	50
54	256	45	264	103	49	261	102	49	249	97	(a) 46
58	260	44	274	105	49	272	105	49	260	100	50
62	276	44	286	104	48	286	104	49	272	99	(a) 47
66	287	44	298	104	48	297	103	49	275	96	50
70	292	43	305	104	48	300	103	49	282	97	50
74	292	43	303	104	48	303	104	49	279	96	49
78	299	40	308	103	48	304	102	47	284	95	47
82	299	38	305	102	48	302	101	46	283	95	46
86	309	38	320	104	48	317	103	43	294	95	44
90	309	35	314	102	45	317	103	41	291	94	42
94	316	33	322	102	45	327	103	40	301	95	41
98	324	31	332	102	44	332	102	39	303	94	40
102	323	30	333	103	42	334	103	38	310	96	37

(a) The number of animals weighed was lower than the number of animals surviving.

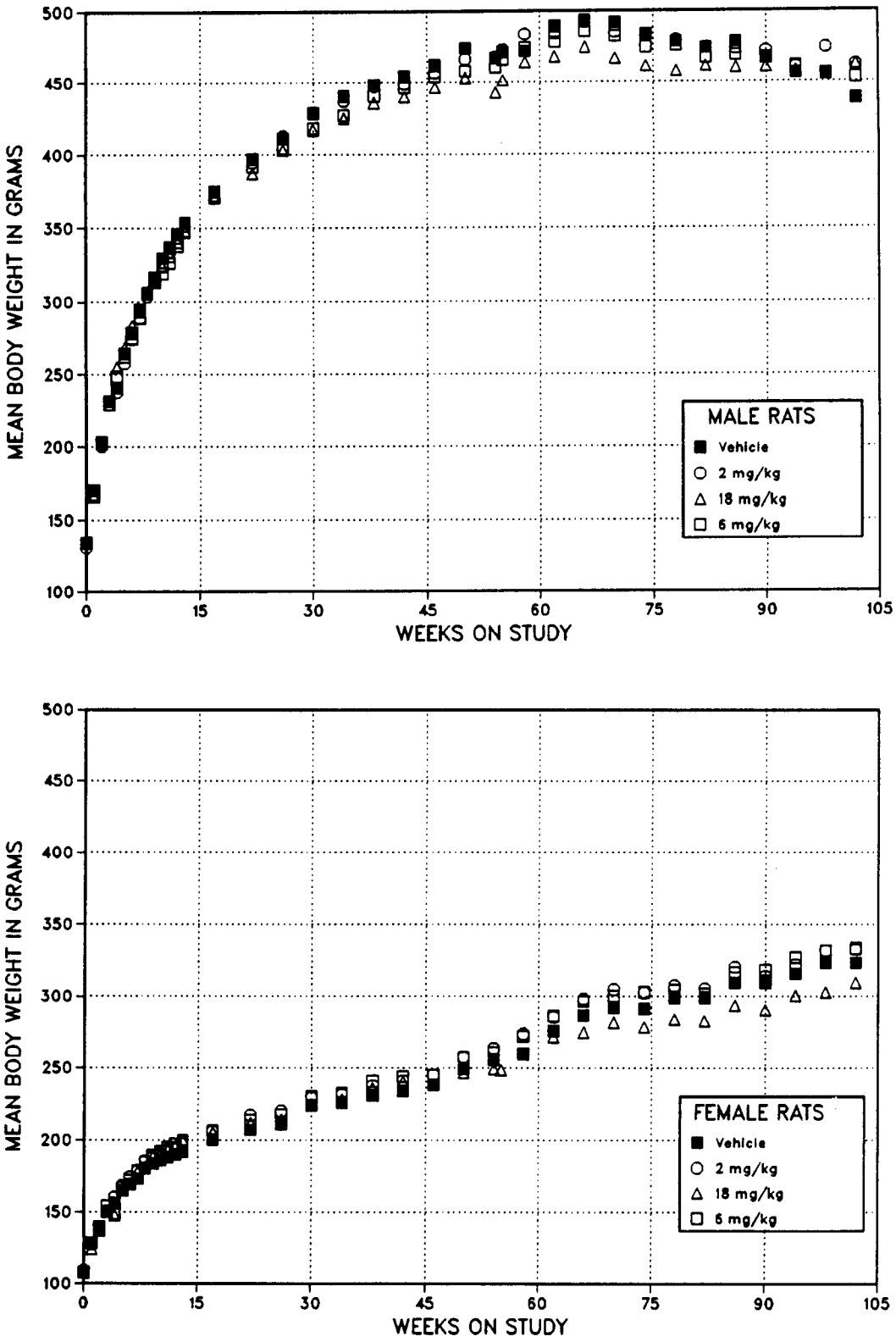


FIGURE 6. GROWTH CURVES FOR RATS ADMINISTERED *p*-CHLOROANILINE HYDROCHLORIDE BY GAVAGE FOR TWO YEARS

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

Survival

Estimates of the probabilities of survival for male and female rats administered *p*-chloroaniline hydrochloride at the doses used in these studies and for vehicle controls are shown in Table 12 and in the Kaplan and Meier curves in Figure 7. The survival of the low and mid dose groups of male rats was significantly greater than that of the vehicle controls after week 94. The survival of the high dose group of female rats was significantly greater than that of the vehicle controls at the end of the study; the survival of the low dose female group was significantly greater than that of the vehicle controls after week 77.

Hematology at Six, Twelve, Eighteen, and Twenty-Four Months

Hematologic changes at 6 months for male and female rats included decreases in hemoglobin concentration, erythrocyte count, and hematocrit value and increases in mean corpuscular volume, nucleated erythrocytes, and mean corpuscular hemoglobin (Tables 13 and 14). These changes, which were mild in the mid dose groups and moderate in the high dose groups, are consistent with a regenerative response (increases in mean corpuscular hemoglobin, nucleated erythrocytes, and mean corpuscular volume) secondary to a decreased erythrocyte mass (decrease in erythrocyte count, hematocrit value, and hemoglobin concentration). The increases in methemoglobin concentrations in the dosed groups indicate a hemolytic mechanism through the oxidation and subsequent denaturation of hemoglobin as the cause of the regenerative anemia. The increase in methemoglobin was more pronounced in high dose male rats (approximately sevenfold that of vehicle controls) compared with that in the high dose female rats (approximately twofold that of vehicle controls); however, the regenerative response, as measured by nucleated erythrocyte count and mean corpuscular volume, was greater in female rats.

TABLE 12. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
MALE (b)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (c)	31	18	16	28
Accidentally killed	0	0	2	1
Animals missexed	1	0	0	0
Killed at termination	18	32	32	20
Died during termination period	0	0	0	1
Survival P values (d)	0.793	0.007	0.005	0.367
FEMALE (b)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (c)	23	11	14	13
Killed at termination	27	39	36	37
Survival P values (d)	0.244	0.011	0.075	0.043

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) First day of termination period: 730 (week 105)
(c) Includes animals killed in a moribund condition
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

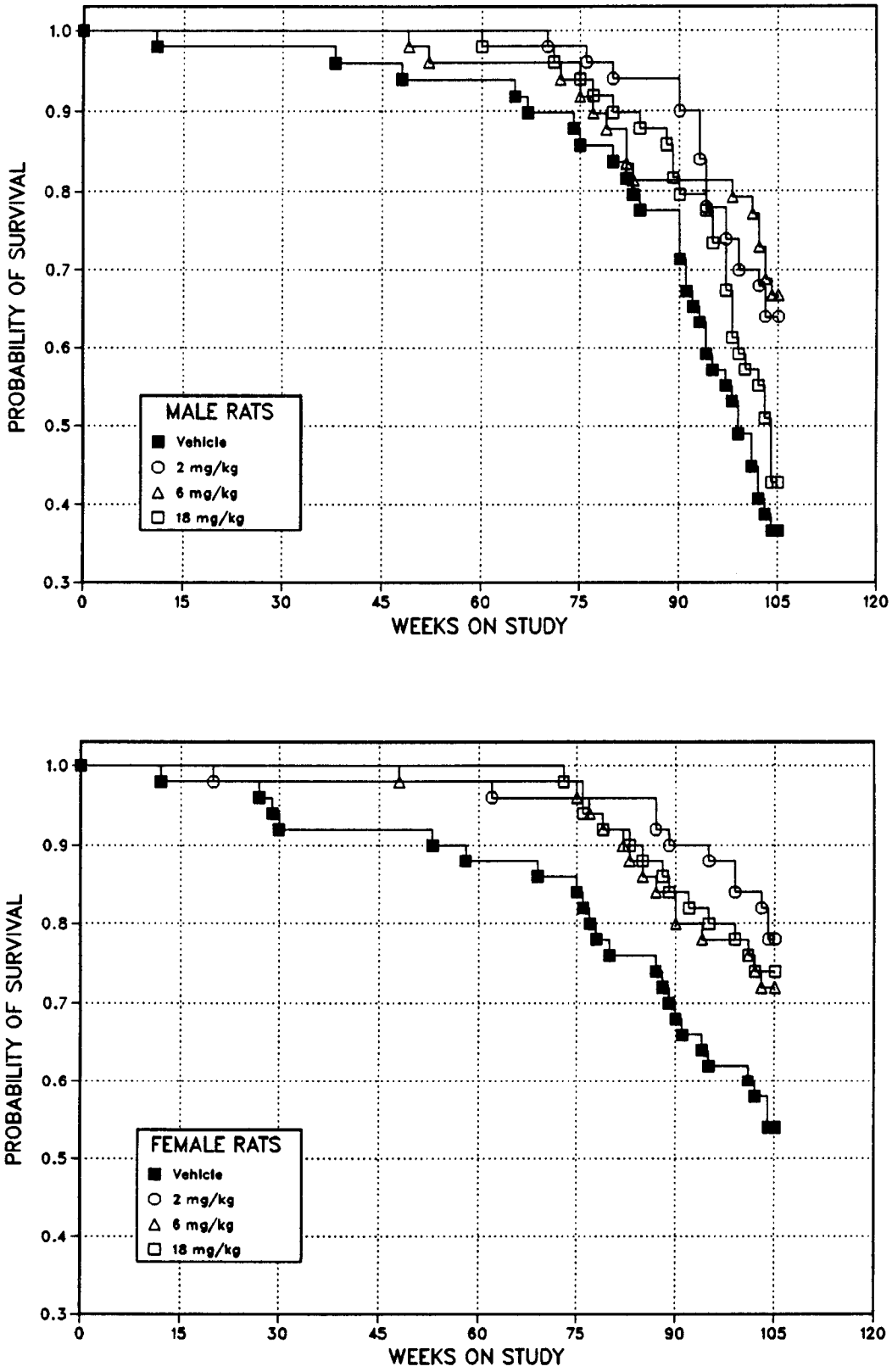


FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED *p*-CHLOROANILINE HYDROCHLORIDE BY GAVAGE FOR TWO YEARS

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

TABLE 13. HEMATOLOGY FOR MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

Analysis	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
6 Months				
Number examined (b)	13	12	12	13
Hemoglobin (g/dl)	15.3 ± 0.21	15.2 ± 0.27	(c) 14.6 ± 0.14	(c) 14.7 ± 0.14
Hematocrit (percent)	45 ± 0.5	44 ± 1.1	(d) 42 ± 0.5	(d) 41 ± 0.4
Leukocytes (10^3/mm^3)	6.0 ± 0.37	5.9 ± 0.36	7.1 ± 0.38	6.7 ± 0.21
Erythrocytes (10^6/mm^3)	9.34 ± 0.102	9.10 ± 0.190	(d) 8.61 ± 0.094	(d) 7.58 ± 0.058
Mean corpuscular volume (μ^3)	48 ± 0.2	(c) 49 ± 0.2	(d) 50 ± 0.3	(d) 54 ± 0.2
Bands (percent)	0 ± 0.0 (14)	0 ± 0.0	0 ± 0.0	0 ± 0.0
Segmented neutrophils (percent)	22 ± 1.7 (14)	24 ± 2.0	18 ± 1.9	18 ± 1.4
Eosinophils (percent)	1 ± 0.3 (14)	1 ± 0.4	1 ± 0.5	1 ± 0.4
Lymphocytes (percent)	77 ± 1.7 (14)	74 ± 1.8	80 ± 2.1	80 ± 1.4
Monocytes (percent)	0 ± 0.0 (14)	0 ± 0.1	0 ± 0.3	(d) 1 ± 0.4
Nucleated erythrocytes (per 100 leukocytes)	1 ± 0.3 (14)	1 ± 0.5	2 ± 0.4	(d) 4 ± 0.3
Mean corpuscular hemoglobin (pg)	16.4 ± 0.09	16.7 ± 0.14	(d) 16.9 ± 0.10	(d) 19.4 ± 0.10
Mean corpuscular hemoglobin concentration (percent)	34.4 ± 0.16	34.2 ± 0.36	34.3 ± 0.29	(d) 36.0 ± 0.19
Methemoglobin (percent of hemoglobin)	0.26 ± 0.111	(c) 0.79 ± 0.151	(d) 0.89 ± 0.178	(d) 1.97 ± 0.170
12 Months				
Number examined	14	15	15	15
Hemoglobin (g/dl)	14.3 ± 0.28	14.5 ± 0.16	13.9 ± 0.28	14.4 ± 0.18
Hematocrit (percent)	42 ± 0.9	43 ± 0.5	42 ± 0.1	43 ± 0.5
Leukocytes (10^3/mm^3)	5.0 ± 0.27	6.0 ± 0.24	(d) 7.0 ± 0.58	(d) 8.6 ± 0.56
Erythrocytes (10^6/mm^3)	8.91 ± 0.183	9.04 ± 0.104	8.57 ± 0.192	(c) 8.38 ± 0.103
Mean corpuscular volume (μ^3)	48 ± 0.3	47 ± 0.2	(d) 49 ± 0.3	(d) 51 ± 0.2
Bands (percent)	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Segmented neutrophils (percent)	26 ± 1.8	27 ± 1.8	30 ± 3.0	(d) 42 ± 2.9
Eosinophils (percent)	1 ± 0.3	1 ± 0.3	1 ± 0.3	(c) 0 ± 0.1
Lymphocytes (percent)	73 ± 2.0	72 ± 1.9	69 ± 3.0	(d) 58 ± 2.8
Monocytes (percent)	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Nucleated erythrocytes (per 100 leukocytes)	1 ± 0.2	1 ± 0.3	2 ± 0.5	(d) 3 ± 0.4
Mean corpuscular hemoglobin (pg)	16.1 ± 0.15	16.0 ± 0.09	16.2 ± 0.12	(d) 17.2 ± 0.09
Mean corpuscular hemoglobin concentration (percent)	33.7 ± 0.29	33.9 ± 0.15	33.3 ± 0.17	33.4 ± 0.14
Reticulocytes (percent of erythrocytes)	0.8 ± 0.05	(c) 1.3 ± 0.18	(c) 1.5 ± 0.20	(c) 1.4 ± 0.19
Methemoglobin (percent of hemoglobin)	0.28 ± 0.056	0.41 ± 0.090	(d) 1.08 ± 0.122	(d) 1.18 ± 0.167
18 Months				
Number examined	13	15	13	13
Hemoglobin (g/dl)	14.4 ± 0.19	13.8 ± 0.42	13.9 ± 0.24	13.7 ± 0.47
Hematocrit (percent)	47 ± 0.7	46 ± 1.3	45 ± 0.8	(c) 43 ± 1.3
Leukocytes (10^3/mm^3)	5.2 ± 0.31	4.4 ± 0.21	5.0 ± 0.35	(d) 8.4 ± 0.72
Erythrocytes (10^6/mm^3)	8.92 ± 0.106	8.89 ± 0.177	8.47 ± 0.167	(d) 7.32 ± 0.206
Mean corpuscular volume (μ^3)	53 ± 0.6	51 ± 0.9	54 ± 0.5	(d) 58 ± 0.5
Bands (percent)	0 ± 0.0	0 ± 0.1	0 ± 0.2	0 ± 0.2
Segmented neutrophils (percent)	43 ± 2.2	36 ± 2.5	43 ± 2.7	(c) 53 ± 3.4
Eosinophils (percent)	1 ± 0.6	2 ± 0.4	2 ± 0.2	1 ± 0.2
Lymphocytes (percent)	56 ± 2.4	61 ± 2.4	55 ± 2.7	(d) 45 ± 3.3
Monocytes (percent)	0 ± 0.2	(c) 1 ± 0.2	0 ± 0.0	0 ± 0.0
Nucleated erythrocytes (per 100 leukocytes)	1 ± 0.3	1 ± 0.4	2 ± 0.4	(d) 5 ± 1.5
Mean corpuscular hemoglobin (pg)	16.1 ± 0.17	15.5 ± 0.26	16.4 ± 0.18	(d) 18.7 ± 0.36
Mean corpuscular hemoglobin concentration (percent)	30.5 ± 0.40	30.3 ± 0.19	30.7 ± 0.11	(d) 32.1 ± 0.44
Reticulocytes (percent of erythrocytes)	2.0 ± 0.12	(c) 3.2 ± 0.43	(c) 3.2 ± 0.19	(d) 6.4 ± 0.54
Methemoglobin (percent of hemoglobin)	1.04 ± 0.056	(d) 1.96 ± 0.130	(d) 2.37 ± 0.245	(d) 4.09 ± 0.248

TABLE 13. HEMATOLOGY FOR MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

Analysis	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
24 Months (e)				
Number examined (b)	15	15	15	15
Hemoglobin (g/dl)	14.1 ± 0.41	14.0 ± 0.33	13.9 ± 0.48	13.8 ± 0.71
Hematocrit (percent)	42 ± 1.1	42 ± 0.9	42 ± 1.4	40 ± 2.1
Leukocytes (10^3/mm^3)	6.9 ± 1.07	(f) 5.4 ± 0.34 (14)	6.1 ± 0.96	8.8 ± 0.97
Erythrocytes (10^6/mm^3)	7.82 ± 0.268	8.07 ± 0.179	8.08 ± 0.262	7.54 ± 0.402
Mean corpuscular volume (μ^3)	54 ± 0.7	52 ± 0.5	52 ± 0.5	54 ± 0.6
Bands (percent)	1 ± 0.2	0 ± 0.1	0 ± 0.2	1 ± 0.7
Segmented neutrophils (percent)	55 ± 3.2	49 ± 3.8	57 ± 2.9	63 ± 1.8
Eosinophils (percent)	1 ± 0.2	2 ± 0.4	1 ± 0.4	1 ± 0.3
Lymphocytes (percent)	44 ± 3.2	48 ± 4.0	41 ± 3.0	(c) 34 ± 1.9
Monocytes (percent)	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.0
Nucleated erythrocytes (per 100 leukocytes)	3 ± 0.7	1 ± 0.2	1 ± 0.4	5 ± 1.1
Mean corpuscular hemoglobin (pg)	18.1 ± 0.22	(c) 17.3 ± 0.20	(d) 17.2 ± 0.20	18.4 ± 0.19
Mean corpuscular hemoglobin concentration (percent)	33.6 ± 0.21	33.2 ± 0.27	33.2 ± 0.23	34.1 ± 0.27
Platelets (× 10^3/mm^3)	408 ± 28.3	(c) 486 ± 20.6	(c) 490 ± 23.8	(d) 609 ± 33.5
Reticulocytes (percent of eythrocytes)	3.4 ± 0.61	3.0 ± 0.44	3.2 ± 0.32	4.2 ± 0.66
Methemoglobin (percent of hemoglobin)	1.56 ± 1.333	1.79 ± 0.136	(d) 2.16 ± 0.101	(d) 2.17 ± 0.195

(a) Mean ± standard error; P values vs. the vehicle controls by Williams' test (Williams, 1971, 1972); doses calculated as *p*-chloroaniline.
(b) Unless otherwise specified by a number in parentheses
(c) $P<0.05$
(d) $P<0.01$
(e) Blood taken for analysis 11-14 days after the last dose was administered
(f) One value of 128.2 excluded

TABLE 14. HEMATOLOGY FOR FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

Analysis	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
6 Months				
Number examined	15	15	15	15
Hemoglobin	14.8 ± 0.24	14.3 ± 0.18	(b) 13.9 ± 0.12	(b) 13.2 ± 0.32
Hematocrit (percent)	45 ± 0.6	(c) 43 ± 0.6	(c) 43 ± 0.3	(b) 40 ± 0.8
Leukocytes (10^3/mm^3)	4.1 ± 0.32	3.9 ± 0.18	4.6 ± 0.19	3.8 ± 0.19
Erythrocytes (10^6/mm^3)	8.54 ± 0.123	(b) 8.08 ± 0.113	(b) 7.60 ± 0.057	(b) 6.49 ± 0.121
Mean corpuscular volume (μ^3)	53 ± 0.2	(b) 54 ± 0.1	(b) 56 ± 0.2	(b) 61 ± 0.2
Bands (percent)	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.0
Segmented neutrophils (percent)	13 ± 1.6	15 ± 1.5	15 ± 1.4	(b) 19 ± 1.4
Eosinophils (percent)	1 ± 0.2	1 ± 0.3	1 ± 0.2	1 ± 0.2
Lymphocytes (percent)	86 ± 1.7	84 ± 1.6	84 ± 1.3	(b) 80 ± 1.4
Monocytes (percent)	1 ± 0.2	0 ± 0.2	1 ± 0.2	1 ± 0.2
Nucleated erythrocytes (per 100 leukocytes)	2 ± 0.4	2 ± 0.5	(c) 5 ± 0.8	(b) 12 ± 1.4
Mean corpuscular hemoglobin (pg)	17.3 ± 0.13	(c) 17.7 ± 0.09	(b) 18.3 ± 0.07	(b) 20.3 ± 0.19
Mean corpuscular hemoglobin concentration (percent)	32.6 ± 0.22	33.1 ± 0.15	32.7 ± 0.12	33.2 ± 0.32
Methemoglobin (percent of hemoglobin)	0.20 ± 0.108	0.63 ± 0.322	0.07 ± 0.029	0.45 ± 0.136
12 Months				
Number examined	12	15	14	15
Hemoglobin (g/dl)	14.8 ± 0.31	14.5 ± 0.19	13.8 ± 0.36	14.8 ± 0.30
Hematocrit (percent)	45 ± 1.1	44 ± 0.9	42 ± 1.1	47 ± 1.1
Leukocytes (10^3/mm^3)	3.0 ± 0.17	3.0 ± 0.17	3.5 ± 0.39	(b) 4.7 ± 0.44
Erythrocytes (10^6/mm^3)	8.41 ± 0.197	8.13 ± 0.166	7.62 ± 0.202	8.17 ± 0.173
Mean corpuscular volume (μ^3)	54 ± 0.2	54 ± 0.2	(b) 55 ± 0.3	(b) 57 ± 0.2
Bands (percent)	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.1
Segmented neutrophils (percent)	24 ± 1.7	28 ± 2.6	(c) 32 ± 2.5	(c) 30 ± 0.9
Eosinophils (percent)	2 ± 0.5	1 ± 0.3	1 ± 0.3	1 ± 0.3
Lymphocytes (percent)	74 ± 1.9	71 ± 2.5	(c) 66 ± 2.3	(c) 69 ± 1.0
Monocytes (percent)	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.0
Nucleated erythrocytes (per 100 leukocytes)	1 ± 0.5	2 ± 0.3	(b) 3 ± 0.6	(b) 5 ± 0.4
Mean corpuscular hemoglobin (pg)	17.6 ± 0.16	17.9 ± 0.21	18.1 ± 0.10	18.2 ± 0.34
Mean corpuscular hemoglobin concentration (percent)	32.6 ± 0.29	33.4 ± 0.42	32.9 ± 0.24	31.9 ± 0.62
Reticulocytes (percent of erythrocytes)	1.5 ± 0.10	1.6 ± 0.12	(b) 2.6 ± 0.15	(b) 2.7 ± 0.21
Methemoglobin (percent of hemoglobin)	0.47 ± 0.108	0.34 ± 0.069	(b) 1.16 ± 0.123	(b) 1.82 ± 0.122
18 Months				
Number examined	12	15	14	14
Hemoglobin (g/dl)	14.6 ± 0.27	14.1 ± 0.18	(b) 13.5 ± 0.23	(b) 13.5 ± 0.24
Hematocrit (percent)	47 ± 0.7	46 ± 0.6	(b) 44 ± 0.7	(b) 44 ± 0.7
Leukocytes (10^3/mm^3)	2.5 ± 0.21	2.9 ± 0.13	(c) 3.2 ± 0.24	(b) 3.8 ± 0.26
Erythrocytes (10^6/mm^3)	8.30 ± 0.122	8.00 ± 0.104	(b) 7.35 ± 0.119	(b) 6.80 ± 0.075
Mean corpuscular volume (μ^3)	57 ± 0.4	57 ± 0.3	(b) 59 ± 0.4	(b) 66 ± 0.4
Bands (percent)	0 ± 0.0	0 ± 0.1	0 ± 0.1	0 ± 0.1
Segmented neutrophils (percent)	35 ± 1.3	37 ± 1.8	36 ± 2.3	33 ± 2.3
Eosinophils (percent)	2 ± 0.5	(c) 1 ± 0.3	1 ± 0.3	1 ± 0.1
Lymphocytes (percent)	64 ± 1.7	62 ± 1.8	62 ± 2.3	66 ± 2.4
Monocytes (percent)	0 ± 0.1	0 ± 0.1	0 ± 0.0	0 ± 0.1
Nucleated erythrocytes (per 100 leukocytes)	2 ± 0.5	3 ± 0.9	(c) 6 ± 0.9	(b) 10 ± 1.7
Mean corpuscular hemoglobin (pg)	17.5 ± 0.17	17.6 ± 0.12	(b) 18.3 ± 0.16	(b) 19.9 ± 0.24
Mean corpuscular hemoglobin concentration (percent)	30.7 ± 0.26	30.7 ± 0.12	30.8 ± 0.22	30.4 ± 0.26
Reticulocytes (percent of erythrocytes)	2.5 ± 0.10	2.9 ± 0.21	(b) 5.3 ± 0.25	(b) 8.4 ± 0.47
Methemoglobin (percent of hemoglobin)	0.75 ± 0.082	(b) 1.42 ± 0.106	(b) 2.52 ± 0.178	(b) 3.41 ± 0.156

TABLE 14. HEMATOLOGY FOR FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

Analysis	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
24 Months (d)				
Number examined	15	15	15	15
Hemoglobin (g/dl)	13.2 ± 0.41	13.2 ± 0.43	13.8 ± 0.16	14.1 ± 0.54
Hematocrit (percent)	39 ± 1.1	40 ± 1.6	41 ± 0.5	41 ± 1.6
Leukocytes (10^3/mm^3)	3.4 ± 0.34	3.5 ± 0.33	4.1 ± 0.46	4.3 ± 0.57
Erythrocytes (10^6/mm^3)	7.12 ± 0.248	7.22 ± 0.226	7.33 ± 0.162	7.10 ± 0.184
Mean corpuscular volume (μ^3)	55 ± 0.6	54 ± 0.3	55 ± 0.7	(b) 58 ± 1.1
Bands	2 ± 1.0	1 ± 0.5	1 ± 0.3	1 ± 0.3
Segmented neutrophils (percent)	46 ± 2.6	48 ± 2.2	47 ± 3.7	53 ± 3.2
Eosinophils (percent)	2 ± 0.4	2 ± 0.5	2 ± 0.4	1 ± 0.3
Lymphocytes (percent)	50 ± 2.8	48 ± 2.3	50 ± 3.8	44 ± 3.1
Monocytes (percent)	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.1
Nucleated erythrocytes (per 100 leukocytes)	2 ± 0.5	1 ± 0.2	1 ± 0.3	2 ± 0.5
Mean corpuscular hemoglobin (pg)	18.5 ± 0.19	18.3 ± 0.12	18.7 ± 0.23	(b) 19.7 ± 0.40
Mean corpuscular hemoglobin concentration (percent)	33.6 ± 0.23	34.1 ± 0.25	33.9 ± 0.16	34.2 ± 0.21
Platelets (10^3/mm^3)	382 ± 35.6	426 ± 14.8	396 ± 17.7	320 ± 42.3
Reticulocytes (percent of erythrocytes)	2.5 ± 0.65	2.7 ± 0.84	2.1 ± 0.20	5.1 ± 2.32
Methemoglobin (percent of hemoglobin)	1.67 ± 0.099	1.97 ± 0.099	(c) 2.03 ± 0.167	(c) 1.91 ± 0.149

(a) Mean ± standard error; P values vs. the vehicle controls by Williams' test (Williams, 1971, 1972); doses calculated as *p*-chloroaniline.
(b) $P<0.01$
(c) $P<0.05$
(d) Blood taken for analysis 11-14 days after the last dose was administered

At 12 months, dose-related changes in the erythron were minimal to mild. Mild increases in mean corpuscular volume, nucleated erythrocytes, mean corpuscular hemoglobin, and methemoglobin were detected. At 18 months, however, changes in the erythrocyte mass and in methemoglobin concentrations were similar to those detected at 6 months. Approximately twofold to fourfold increases in methemoglobin concentrations in mid and high dose male and female rats were associated with hematologic evidence of regenerative anemia. At 24 months, results of methemoglobin and hematologic analyses were essentially unremarkable. Because these animals had not been dosed for 11-14 days before the collection of the samples, these data suggest that the direct hematologic effects of *p*-chloroaniline hydrochloride are transient.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the spleen, adrenal gland, testis, bone marrow, liver, hematopoietic system, and anterior pituitary gland.

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 control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

Spleen: The incidences of proliferative mesenchymal lesions, which varied from nonneoplastic fibrous connective tissue (fibrosis) to highly malignant sarcomas, were increased in the spleen of dosed rats. The incidences of splenic fibrosis were increased in dosed males and females, whereas the incidences of sarcomas (fibrosarcomas, osteosarcomas, and hemangiosarcomas) were increased in males (Table 15). Many of the splenic sarcomas metastasized to one or more sites. Cellular infiltration of lipocytes (fatty metaplasia) was observed in high dose rats (male: vehicle control, 0/49; low dose, 0/50; mid dose, 0/50; high dose, 24/50; female: 0/50; 0/50; 0/50; 11/50). A fibrosarcoma was observed in one mid dose female rat, and an osteosarcoma was observed in one high dose female rat.

Fibrosis consisted of focal or diffuse proliferation of bundles of dense collagen intermixed with mildly to moderately pleomorphic fibroblasts. Fibrosis usually affected the splenic red pulp, where it replaced the splenic parenchyma, but in some animals fibrosis occurred in the splenic capsule with the formation of cysts on the capsular surface. In two high dose males, the fibrous tissue formed well-demarcated expansile lesions that were diagnosed as fibromas. Sarcomas were poorly demarcated, expansile, and invasive lesions; in some cases, fibrosis and sarcomas were present in the same spleen. Fibrosarcomas had a typical morphology consisting of irregular, interlacing bundles of collagen mixed with spindle cells having highly pleomorphic, anaplastic nuclei. Many of the neoplasms with features of fibrosarcomas also contained either areas of osteoid formation or cavernous or sinusoidal vascular spaces; these neoplasms were diagnosed as osteosarcomas or hemangiosarcomas, respectively. Cellular infiltration of lipocytes was seen concurrently with fibrosis or sarcomas and consisted of a few to several clumped and/or scattered, variably sized adipose cells within the areas of fibrosis or neoplasia. This change appeared to represent metaplasia of the proliferating fibrous tissue elements to adipose cells (fatty metaplasia).

Adrenal Gland: Medullary hyperplasia was observed at an increased incidence in high dose female rats; pheochromocytomas were also observed in vehicle control and dosed females (Table 16). Pheochromocytomas or malignant pheochromocytomas (combined) in male rats occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls.

TABLE 15. SPLENIC FIBROSIS AND PRIMARY SARCOMAS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
MALE				
Fibrosis				
Overall Rates	3/49 (6%)	11/50 (22%)	12/50 (24%)	41/50 (82%)
Fibroma				
Overall Rates	0/49 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Fibrosarcoma (b)				
Overall Rates	0/49 (0%)	1/50 (2%)	2/50 (4%)	17/50 (34%)
Adjusted Rates	0.0%	2.7%	5.7%	47.1%
Terminal Rates	0/18 (0%)	0/32 (0%)	1/32 (3%)	5/21 (24%)
Day of First Observation		687	702	522
Life Table Tests	P<0.001	P=0.570	P=0.364	P<0.001
Logistic Regression Tests	P<0.001	P=0.523	P=0.293	P<0.001
Osteosarcoma (b)				
Overall Rates	0/49 (0%)	0/50 (0%)	1/50 (2%)	19/50 (38%)
Adjusted Rates	0.0%	0.0%	3.1%	62.8%
Terminal Rates	0/18 (0%)	0/32 (0%)	1/32 (3%)	11/21 (52%)
Day of First Observation			730	495
Life Table Tests	P<0.001	(c)	P=0.615	P<0.001
Logistic Regression Tests	P<0.001	(c)	P=0.615	P<0.001
Hemangiosarcoma (d)				
Overall Rates	0/49 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	0.0%	12.0%
Terminal Rates	0/18 (0%)	0/32 (0%)	0/32 (0%)	0/21 (0%)
Day of First Observation				618
Life Table Tests	P=0.002	(c)	(c)	P=0.095
Logistic Regression Tests	P=0.002	(c)	(c)	P=0.068
Fibrosarcoma, Osteosarcoma, or Hemangiosarcoma				
Overall Rates	0/49 (0%)	1/50 (2%)	3/50 (6%)	38/50 (76%)
Adjusted Rates	0.0%	2.7%	8.7%	87.9%
Terminal Rates	0/18 (0%)	0/32 (0%)	2/32 (6%)	16/21 (76%)
Day of First Observation		687	702	494
Life Table Tests	P<0.001	P=0.570	P=0.236	P<0.001
Logistic Regression Tests	P<0.001	P=0.485	P=0.140	P<0.001
FEMALE (e)				
Fibrosis				
Overall Rates	1/50 (2%)	2/50 (4%)	3/50 (6%)	42/50 (84%)
Fibrosarcoma				
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Osteosarcoma				
Overall Rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes); all doses calculated as milligrams *p*-chloroaniline per kilogram body weight.
(b) Historical incidence of all sarcomas in water gavage vehicle controls (mean ± SD): 1/298 (0.3% ± 0.8%); historical incidence in untreated controls in NTP studies: 8/1,906 (0.4% ± 0.8%); no benign tumors, fibrosarcomas, or osteosarcomas have been observed in untreated controls.
(c) No P value is reported because no tumors were observed in the vehicle control and dosed groups.
(d) Historical incidence of hemangiomas or hemangiosarcomas (combined, for all organs) in water gavage vehicle controls (mean ± SD): 2/300 (0.7% ± 2%); historical incidence in untreated controls in NTP studies: 12/1,936 (0.6% ± 1%)
(e) Historical incidence of sarcomas in water gavage vehicle controls: 0/297; historical incidence of sarcomas in untreated controls in NTP studies: 1/1,961 (mean ± SD) (0.05% ± 0.4%); no fibrosarcomas or osteosarcomas have been observed.

TABLE 16. ADRENAL MEDULLARY LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
MALE				
Hyperplasia				
Overall Rates	15/49 (31%)	21/48 (44%)	15/48 (31%)	17/49 (35%)
Pheochromocytoma				
Overall Rates	13/49 (27%)	14/48 (29%)	14/48 (29%)	25/49 (51%)
Adjusted Rates	53.8%	40.3%	40.7%	79.5%
Terminal Rates	8/18 (44%)	11/31 (35%)	12/32 (38%)	15/21 (71%)
Day of First Observation	633	651	476	618
Life Table Tests	P<0.001	P=0.158N	P=0.134N	P=0.061
Logistic Regression Tests	P=0.003	P=0.358N	P=0.504N	P=0.028
Malignant Pheochromocytoma				
Overall Rates	1/49 (2%)	0/48 (0%)	1/48 (2%)	1/49 (2%)
Pheochromocytoma or Malignant Pheochromocytoma (b)				
Overall Rates	13/49 (27%)	14/48 (29%)	15/48 (31%)	26/49 (53%)
Adjusted Rates	53.8%	40.3%	43.6%	82.9%
Terminal Rates	8/18 (44%)	11/31 (35%)	13/32 (41%)	16/21 (76%)
Day of First Observation	633	651	476	618
Life Table Tests	P<0.001	P=0.158N	P=0.175N	P=0.041
Logistic Regression Tests	P=0.001	P=0.358N	P=0.586N	P=0.017
FEMALE				
Hyperplasia				
Overall Rates	4/50 (8%)	4/50 (8%)	7/50 (14%)	24/50 (48%)
Pheochromocytoma (c)				
Overall Rates	2/50 (4%)	3/50 (6%)	1/50 (2%)	6/50 (12%)
Adjusted Rates	6.2%	7.7%	2.8%	16.2%
Terminal Rates	1/27 (4%)	3/39 (8%)	1/36 (3%)	6/37 (16%)
Day of First Observation	557	729	729	729
Life Table Tests	P=0.091	P=0.650	P=0.415N	P=0.248
Logistic Regression Tests	P=0.077	P=0.553	P=0.488N	P=0.192

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Historical incidence in water gavage vehicle controls (mean ± SD): 121/299 (40% ± 16%); historical incidence in untreated controls in NTP studies: 489/1,915 (26% ± 14%)
(c) Historical incidence of pheochromocytomas or malignant pheochromocytomas (combined) in water gavage vehicle controls (mean ± SD): 20/295 (7% ± 2%); historical incidence in untreated controls in NTP studies: 99/1,968 (5% ± 4%)

Testis: The incidences of interstitial cell adenomas in the dosed groups of male rats were greater than that in the vehicle controls (vehicle control, 36/49; low dose, 44/46; mid dose, 44/50; high dose, 46/50). These marginal increases were not considered to be related to chemical exposure.

Bone Marrow: Femoral hyperplasia was observed at increased incidences in high dose male and mid and high dose female rats (male: vehicle control, 26/49; low dose, 36/50; mid dose, 35/49; high dose, 46/50; female: 11/50; 12/48; 21/50; 37/47). Femoral reticular cell hyperplasia was observed at increased incidences in mid and high dose female rats (male: 0/49; 0/50; 3/49; 0/50; female: 1/50; 2/48; 7/50; 7/47).

Liver: Hemosiderin pigmentation was observed at an increased incidence in high dose male rats (male: vehicle control, 1/49; low dose, 0/50; mid dose, 0/49; high dose, 26/49; female: 0/50; 0/50; 0/50; 1/50).

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with significant negative trends; the incidences in the dosed groups were significantly lower than those in the vehicle controls (Table 17).

Anterior Pituitary Gland: Cysts of the pars distalis were observed at increased incidences in female rats (male: vehicle control, 3/47; low dose, 0/18; mid dose, 0/19; high dose, 1/46; female: 2/50; 3/33; 7/35; 12/50). The incidence of adenomas in high dose male rats was significantly lower than that in vehicle controls (20/47; 13/18; 11/19; 11/46; P=0.027).

TABLE 17. MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
MALE (b)				
Overall Rates	21/49 (43%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates	59.7%	8.7%	5.2%	9.8%
Terminal Rates	5/18 (28%)	2/32 (6%)	1/32 (3%)	1/21 (5%)
Day of First Observation	466	674	498	615
Life Table Tests	P=0.001N	P<0.001N	P<0.001N	P<0.001N
Logistic Regression Tests	P<0.001N	P<0.001N	P<0.001N	P<0.001N
FEMALE (c)				
Overall Rates	10/50 (20%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted Rates	27.2%	4.6%	2.6%	2.7%
Terminal Rates	2/27 (7%)	0/39 (0%)	0/36 (0%)	1/37 (3%)
Day of First Observation	529	617	711	729
Life Table Tests	P=0.010N	P=0.005N	P=0.003N	P=0.002N
Logistic Regression Tests	P=0.013N	P=0.015N	P=0.004N	P=0.004N

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Historical incidence of leukemia in water gavage vehicle controls at study laboratory (mean ± SD): 120/300 (40% ± 16%); historical incidence in untreated controls in NTP studies: 636/1,936 (33% ± 15%)
(c) Historical incidence of leukemia in water gavage vehicle controls at study laboratory (mean ± SD): 75/299 (25% ± 15%); historical incidence in untreated controls in NTP studies: 383/1,983 (19% ± 7%)

SIXTEEN-DAY STUDIES

Deaths occurred in all dosed groups (Table 18). The final mean body weights of dosed and vehicle control mice were comparable. Cyanosis was indicated by the bluish extremities of dosed mice. Compound-related lesions at 100 mg/kg included diffuse hemosiderosis of the liver Kupffer cells and diffuse congestion of the spleen in 2/2 males and 2/2 females.

TABLE 18. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Dose (a) (mg/kg)	Survival (b)	Mean Body Weights (grams) Initial (c)	Final	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	24.4	27.0	+2.6	
25	(e) 4/5	24.2	28.2	+4.0	104.4
50	(f) 4/5	22.8	27.7	+4.9	102.6
100	(g) 4/5	24.2	27.7	+3.5	102.6
200	(h) 0/5	24.0	(i)	(i)	(i)
400	(j) 0/5	18.8	(i)	(i)	(i)
FEMALE					
0	5/5	18.4	20.4	+2.0	
25	(k) 3/5	18.4	21.0	+2.6	102.9
50	(l) 4/5	17.6	21.0	+3.4	102.9
100	(m) 3/5	18.0	21.3	+3.3	104.4
200	(j) 0/5	14.0	(i)	(i)	(i)
400	(n) 0/5	13.8	(i)	(i)	(i)

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Number surviving/number initially in group; laboratory report states that three of the deaths were probably gavage related.
(c) Initial group mean body weight
(d) Mean body weight change of the survivors
(e) Day of death: 16
(f) Day of death: 7
(g) Day of death: 3
(h) Day of death: 3,3,4,4,6
(i) No data are reported due to the 100% mortality in this group.
(j) Day of death: 2,2,2,2,3
(k) Day of death: 2,8
(l) Day of death: 5
(m) Day of death: 7,8
(n) Day of death: all 2

THIRTEEN-WEEK STUDIES

Two male mice that received 120 mg/kg, three female mice that received 60 mg/kg, one female mouse that received 30 mg/kg, and one female vehicle control mouse died before the end of the studies (Table 19). Deaths were attributed to pneumonia. The pneumonia was generally confined to the terminal bronchioles and surrounding alveoli and was characterized by necrosis of bronchiolar and alveolar epithelium, suppurative inflammation, fibrosis, and varying degrees of hyperplasia of the remaining epithelium, sometimes leading to bronchiolization of alveoli. Epithelial cells in one affected animal contained intracytoplasmic inclusions. The mice were positive for Sendai titer, and the appearance of the pneumonia was compatible with Sendai virus infection. The final mean body weights of dosed and vehicle control mice were similar. The heart weights of male mice at 30 mg/kg or more, the lung weights of male mice at 60 and 120 mg/kg, the spleen weights of all groups of dosed male mice, and the spleen weights of female mice at 30 mg/kg or more were significantly greater than those of vehicle controls (Figure 8; Table F2). The hematocrit value and the erythrocyte count for almost all dosed groups of mice were significantly lower than those for vehicle controls (Table 20; Figures 9 and 10). The methemoglobin concentration for all groups of male mice and female mice dosed at 15 mg/kg or more was significantly greater than those for vehicle controls. Compound-related increases were seen for the hemoglobin concentration, the number of segmented neutrophils (females only), the mean corpuscular hemoglobin, the mean corpuscular hemoglobin concentration, the mean corpuscular volume, and the number of nucleated erythrocytes. Erythrocytes from male and female mice in the mid (30 mg/kg) and high (120 mg/kg) dose groups had moderate to marked numbers of Heinz bodies (inclusions of denatured hemoglobin). Related findings included moderate to marked polychromasia and poikilocytosis (presence of erythrocytes with abnormal shapes).

TABLE 19. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Dose (a) (mg/kg)	Survival (b)	Mean Body Weights (grams) Initial (c)	Final	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	23.2 ± 0.5	31.9 ± 1.3	+8.7 ± 1.2	
7.5	10/10	23.5 ± 0.5	33.3 ± 1.0	+9.8 ± 0.9	104.4
15	10/10	24.3 ± 0.5	32.4 ± 1.0	+8.1 ± 0.8	101.6
30	10/10	23.1 ± 0.6	33.6 ± 0.6	+10.5 ± 0.6	105.3
60	10/10	23.3 ± 0.4	32.5 ± 0.7	+9.2 ± 0.5	101.9
120	(e) 8/10	23.7 ± 0.5	31.8 ± 1.0	+8.4 ± 0.9	99.7
FEMALE					
0	(f) 9/10	18.6 ± 0.2	26.6 ± 0.5	+7.9 ± 0.4	
7.5	10/10	18.2 ± 0.2	25.7 ± 0.4	+7.5 ± 0.4	96.6
15	10/10	19.1 ± 0.3	25.3 ± 0.7	+6.2 ± 0.5	95.1
30	(g) 9/10	18.1 ± 0.2	25.2 ± 0.7	+7.1 ± 0.7	94.7
60	(f) 7/10	18.2 ± 0.3	25.9 ± 0.7	+7.4 ± 0.5	97.4
120	10/10	18.7 ± 0.3	26.1 ± 0.4	+7.4 ± 0.2	98.1

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Number surviving/number initially in group
(c) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(d) Mean body weight change of the survivors ± standard error of the mean
(e) Week of death: 2,3
(f) Week of death: all 2
(g) Week of death: 6

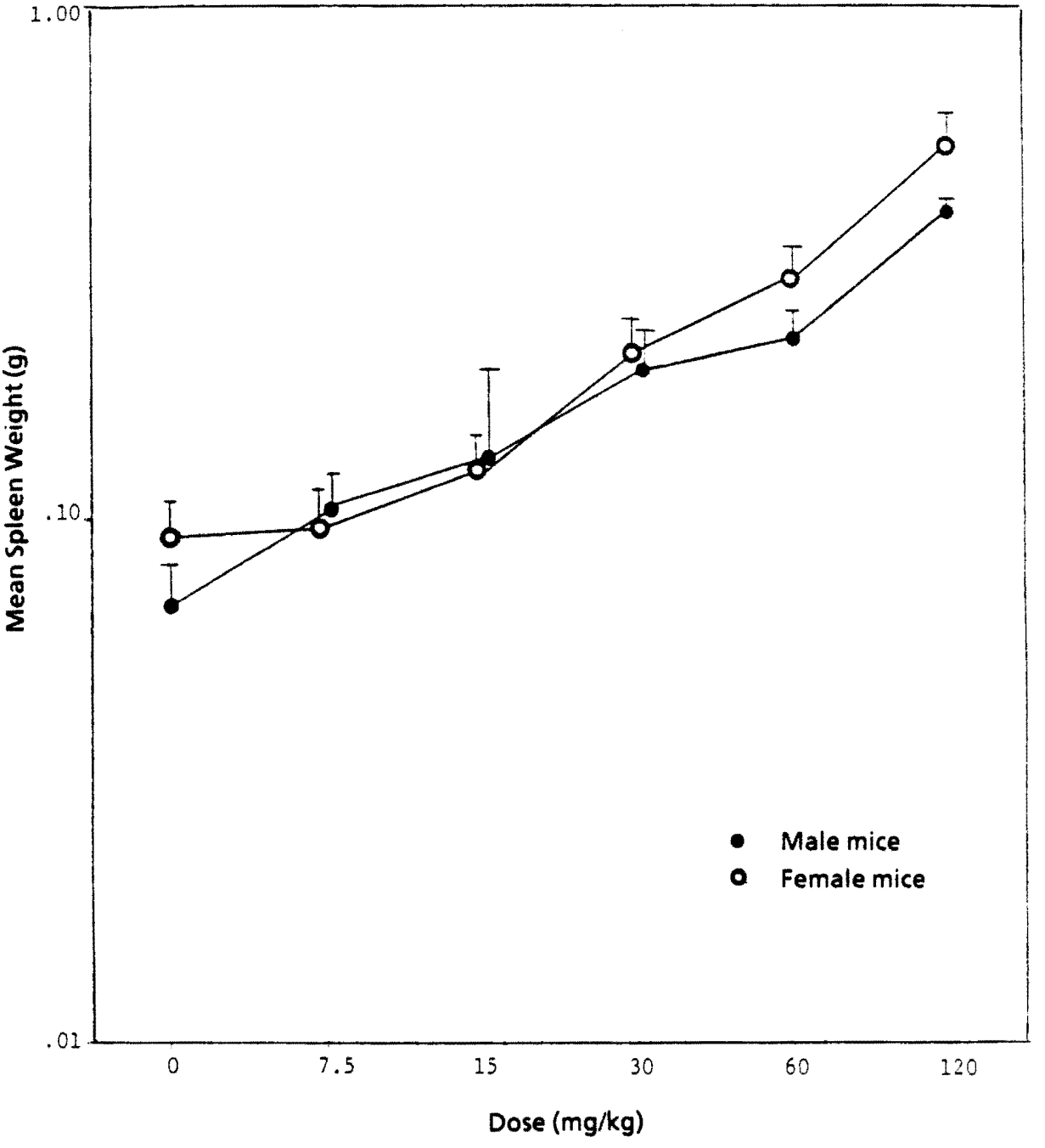


FIGURE 8. SPLEEN WEIGHTS (MEAN AND STANDARD DEVIATION) OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

TABLE 20. HEMATOLOGY FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
MALE						
No. examined	10	10	10	10	10	8
Leukocytes (1,000/mm^3)	8.27 ± 0.516	6.92 ± 0.533	(b) 5.44 ± 0.697	7.15 ± 0.747	9.26 ± 0.795	8.99 ± 1.284
Lymphocytes (1,000/mm^3)	6.01 ± 0.349	(b) 3.76 ± 0.209	(b) 3.83 ± 0.686	4.90 ± 0.696	6.06 ± 0.751	5.54 ± 0.711
Segmented neutrophils (1,000/mm^3)	2.07 ± 0.331	3.07 ± 0.613	1.46 ± 0.341	2.07 ± 0.293	3.10 ± 0.496	3.35 ± 1.005
Monocytes (1,000/mm^3)	0.01 ± 0.009	0.04 ± 0.020	0.03 ± 0.017	0.04 ± 0.015	0.03 ± 0.015	0.02 ± 0.021
Eosinophils (1,000/mm^3)	0.18 ± 0.055	0.05 ± 0.022	0.11 ± 0.026	0.15 ± 0.047	0.06 ± 0.023	0.08 ± 0.032
Hematocrit (percent)	48.70 ± 0.400	46.90 ± 0.530	(c) 45.50 ± 1.340	(c) 43.80 ± 0.530	(c) 40.40 ± 0.400	(c) 32.63 ± 0.820
Hemoglobin (g/dl)	16.7 ± 0.10	15.9 ± 0.15	16.1 ± 0.61	16.3 ± 0.28	(b) 18.4 ± 0.24	(b) 17.2 ± 0.31
MCH (pg)	15.7 ± 0.04	15.5 ± 0.18	(b) 16.5 ± 0.25	(c) 17.6 ± 0.25	(c) 20.9 ± 0.29	(c) 25.1 ± 0.21
MCHC (g/dl)	34.2 ± 0.09	34.0 ± 0.15	35.4 ± 0.53	(c) 37.3 ± 0.39	(c) 45.3 ± 0.71	(c) 52.6 ± 0.65
MCV (cubic microns)	45.7 ± 0.15	45.9 ± 0.69	46.5 ± 0.48	47.2 ± 0.44	46.3 ± 0.30	(c) 47.9 ± 0.44
Methemoglobin (percent of hemoglobin)	0.63 ± 0.075	(c) 1.72 ± 0.194	(c) 1.77 ± 0.140	(c) 2.36 ± 0.174	(c) 2.84 ± 0.388	(c) 3.80 ± 0.201
Nucleated erythrocytes (1,000/mm^3)	0.00 ± 0.000	0.00 ± 0.000	0.20 ± 0.200	0.30 ± 0.153	0.50 ± 0.307	(c) 3.13 ± 0.833
Erythrocytes (10^6/mm^3)	10.66 ± 0.070	10.24 ± 0.130	(c) 9.79 ± 0.350	(c) 9.26 ± 0.100	(c) 8.78 ± 0.090	(c) 6.86 ± 0.160
FEMALE						
No. examined	9	10	10	9	7	10
Leukocytes (1,000/mm^3)	6.13 ± 0.681	5.10 ± 0.428	6.48 ± 0.334	7.39 ± 0.644	9.37 ± 0.929	7.13 ± 1.022
Lymphocytes (1,000/mm^3)	4.87 ± 0.553	4.16 ± 0.332	5.06 ± 0.236	5.70 ± 0.522	7.36 ± 0.870	5.23 ± 0.935
Segmented neutrophils (1,000/mm^3)	1.13 ± 0.190	0.83 ± 0.146	1.30 ± 0.184	1.60 ± 0.214	(b) 1.89 ± 0.238	(b) 1.75 ± 0.149
Monocytes (1,000/mm^3)	0.04 ± 0.012	0.01 ± 0.007	0.00 ± 0.000	0.00 ± 0.000	0.08 ± 0.038	0.05 ± 0.031
Eosinophils (1,000/mm^3)	0.09 ± 0.038	0.10 ± 0.025	0.12 ± 0.029	0.08 ± 0.025	0.05 ± 0.030	0.11 ± 0.028
Hematocrit (percent)	49.78 ± 0.720	(b) 47.30 ± 0.750	(b) 47.20 ± 0.470	(c) 45.67 ± 0.530	(c) 41.43 ± 1.460	(c) 35.40 ± 0.650
Hemoglobin (g/dl)	16.8 ± 0.22	16.1 ± 0.22	16.6 ± 0.17	17.1 ± 0.22	(c) 19.6 ± 0.56	(c) 18.1 ± 0.22
MCH (pg)	15.7 ± 0.07	15.7 ± 0.08	16.3 ± 0.13	(c) 17.8 ± 0.17	(c) 22.0 ± 0.59	(c) 25.0 ± 0.43
MCHC (g/dl)	33.9 ± 0.16	34.1 ± 0.13	35.1 ± 0.19	(c) 37.5 ± 0.36	(c) 47.2 ± 1.12	(c) 51.3 ± 0.80
MCV (cubic microns)	46.3 ± 0.33	46.0 ± 0.26	46.4 ± 0.37	47.6 ± 0.24	46.9 ± 0.63	(c) 48.8 ± 0.44
Methemoglobin (percent of hemoglobin)	0.29 ± 0.071	0.30 ± 0.112	(c) 1.65 ± 0.189	(c) 2.88 ± 0.360	(c) 3.22 ± 0.146	(c) 3.32 ± 0.257
Nucleated erythrocytes (1,000/mm^3)	0.22 ± 0.147	0.00 ± 0.000	0.10 ± 0.100	0.00 ± 0.000	0.86 ± 0.404	(c) 5.80 ± 1.218
Erythrocytes (10^6/mm^3)	10.69 ± 0.150	10.30 ± 0.160	(b) 10.18 ± 0.150	(c) 9.63 ± 0.100	(c) 8.93 ± 0.330	(c) 7.26 ± 0.150

(a) Mean ± standard error. MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; P values are vs. the vehicle controls; Dunnett's test was used when a nonsignificant result was obtained by the Jonckheere trend test; otherwise Williams' test was used (Dunnett, 1980; Jonckheere, 1954; Williams, 1971, 1972); doses calculated as *p*-chloroaniline.

(b) $P<0.05$ vs. vehicle controls

(c) $P<0.01$ vs. vehicle controls

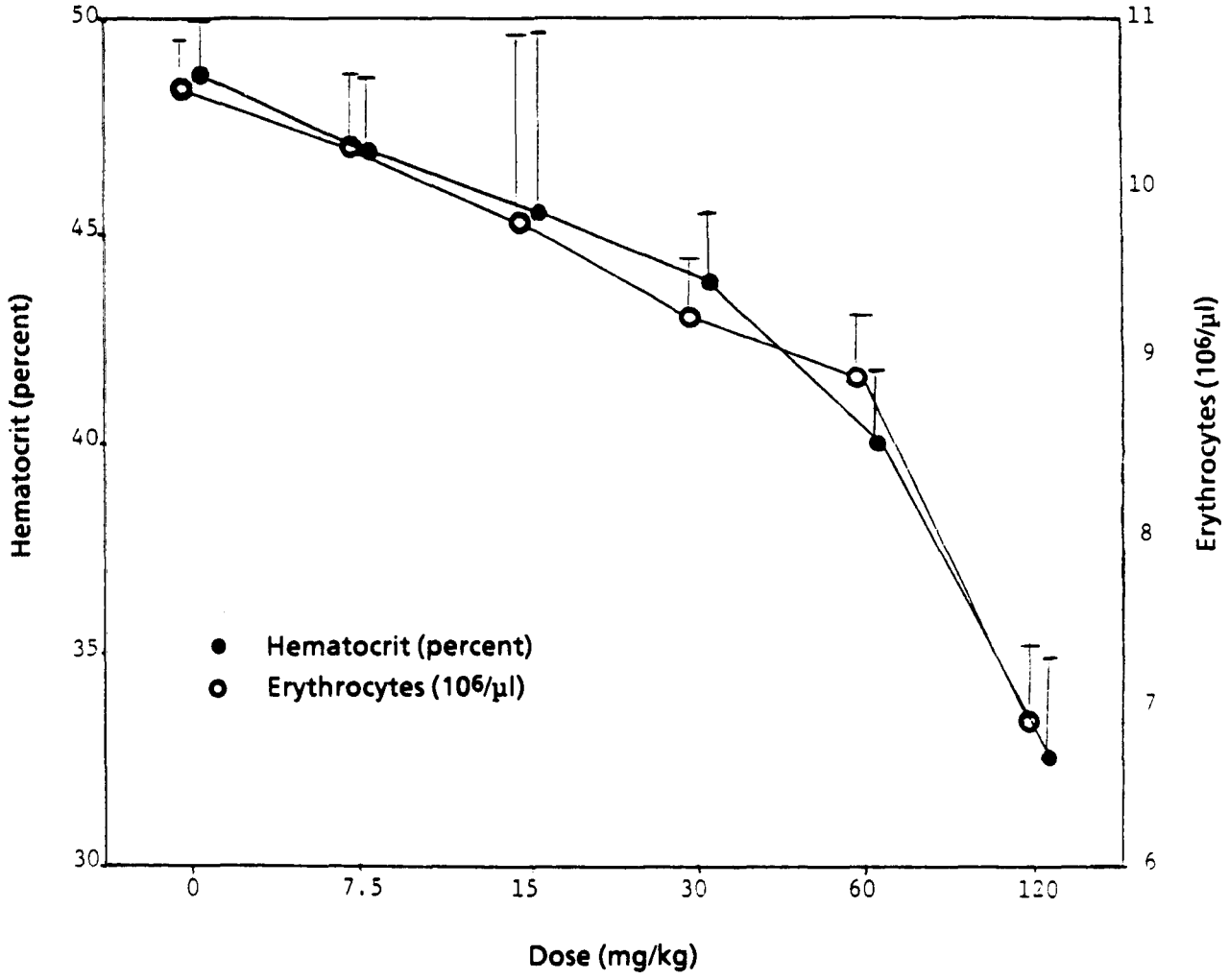


FIGURE 9. PERCENTAGE HEMATOCRIT AND ERYTHROCYTE COUNT (AND STANDARD DEVIATION) FOR MALE MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

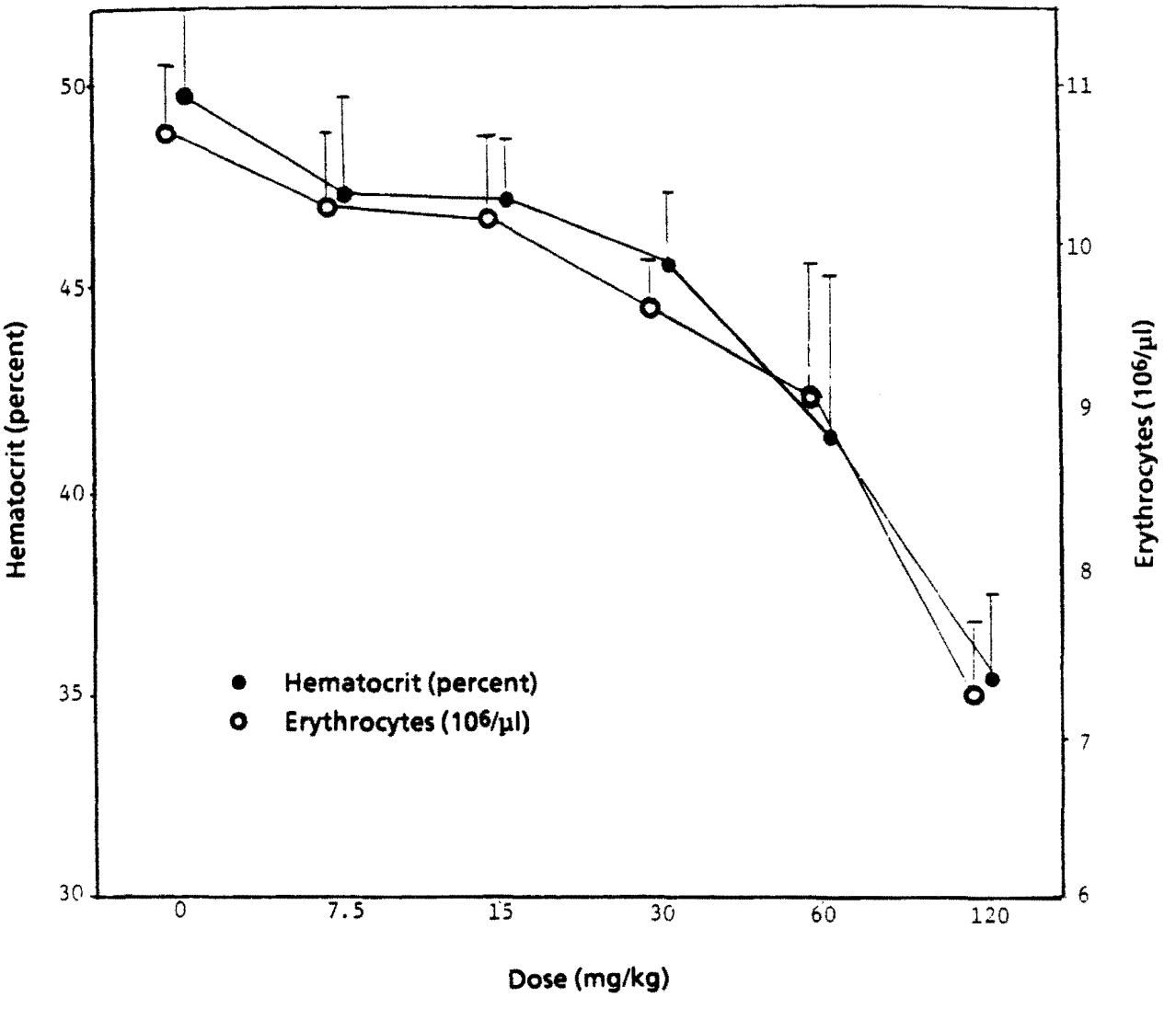


FIGURE 10. PERCENTAGE HEMATOCRIT AND ERYTHROCYTE COUNT (AND STANDARD DEVIATION) FOR FEMALE MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

Compound-related effects in the 13-week studies included increased incidences of pigmentation (hemosiderin) of the kidney and Kupffer cells of the liver and hematopoiesis of the spleen (Table 21). The severity of the hematopoiesis increased as the dose increased.

Dose Selection Rationale: Major compound-related effects observed in mice were hemolytic anemia, methemoglobinemia, and splenomegaly. The hemolytic anemia and splenomegaly responses were dose related. Methemoglobin levels ranged from 0.3% to 3.8% in dosed groups compared with 0.3% to 0.6% in vehicle controls. It was judged that doses higher than 30 mg/kg for the 2-year studies might produce severe anemia in animals because hematocrit and erythrocyte values were reduced substantially in the 13-week studies at doses of 60 and 120 mg/kg. Furthermore, the magnitude of splenomegaly was thought to be too great for selection of doses higher than 30 mg/kg. Based on this information, 30 mg/kg was selected as the high dose and 3 and 10 mg/kg as the low and mid doses, respectively. This dose regimen was expected to achieve a no-effect level at the low dose and some effects on the hematopoietic system at the mid dose in the 2-year studies.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male and female mice were generally within 5% of those of vehicle controls throughout the studies (Table 22 and Figure 11). No compound-related clinical signs were observed.

TABLE 21. NUMBER OF MICE WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

Site/Lesion	Dose (mg/kg) 0	7.5	15	30	60	120
MALE						
Kidney						
Hemosiderosis	0	0	0	0	0	9
Liver						
Hemosiderosis of Kupffer cells	0	0	0	2	10	9
Spleen						
Hematopoiesis	0	8	10	10	10	8
FEMALE						
Kidney						
Hemosiderosis	0	0	0	0	4	10
Liver						
Hemosiderosis of Kupffer cells	0	0	0	0	7	10
Spleen						
Hematopoiesis	2	9	10	9	8	10

(a) Ten animals in each group examined; all doses calculated as milligrams *p*-chloroaniline per kilogram body weight.

TABLE 22. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

Weeks on Study	Vehicle Control		3 mg/kg			10 mg/kg			30 mg/kg		
	Av. Wt. (grams)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed
MALE											
1	21.9	50	21.8	99.5	50	22.5	102.7	50	21.6	98.6	50
2	23.3	50	23.8	102.1	50	24.0	103.0	50	23.7	101.7	50
3	24.0	50	24.9	103.8	50	25.1	104.6	50	24.8	103.3	50
4	25.5	50	26.2	102.7	50	26.7	104.7	50	26.6	104.3	50
5	27.7	50	27.6	99.6	50	28.4	102.5	50	28.0	101.1	50
6	28.6	50	28.0	97.9	50	29.0	101.4	50	28.2	98.6	50
7	28.5	50	28.6	100.4	50	29.7	104.2	50	28.6	100.4	50
8	28.9	50	29.6	102.4	50	30.5	105.5	50	29.3	101.4	50
9	30.2	50	30.9	102.3	50	31.2	103.3	50	29.9	99.0	50
10	30.3	50	29.4	97.0	50	30.2	99.7	50	28.8	95.0	50
11	31.2	50	31.6	101.3	50	31.9	102.2	50	31.0	99.4	50
12	31.0	50	30.6	98.7	50	32.3	104.2	50	31.8	102.6	50
13	32.0	50	31.4	98.1	50	31.7	99.1	50	31.7	99.1	50
17	33.5	50	34.3	102.4	50	34.3	102.4	50	33.1	98.8	50
22	35.2	50	34.9	99.1	49	35.1	99.7	50	35.2	100.0	50
26	35.7	50	35.3	98.9	49	36.2	101.4	50	35.9	100.6	50
30	37.5	50	36.7	97.9	49	37.9	101.1	50	37.0	98.7	50
34	38.7	50	37.3	96.4	49	38.6	99.7	50	38.2	98.7	50
38	42.8	50	41.3	96.5	48	42.8	100.0	50	42.2	98.6	50
42	44.4	50	43.4	97.7	48	44.7	100.7	50	44.1	99.3	50
46	43.7	50	42.5	97.3	48	43.8	100.2	50	42.0	96.1	50
50	41.6	50	37.8	90.9	48	41.5	99.8	50	41.7	100.2	50
54	42.9	50	40.9	95.3	48	42.8	99.8	50	42.9	100.0	50
58	43.1	50	42.8	99.3	47	44.5	103.2	49	44.2	102.6	49
62	45.0	50	43.8	97.3	47	44.0	97.8	48	44.9	99.8	49
66	45.1	50	43.9	97.3	46	44.4	98.4	(a) 28	45.5	100.9	49
70	44.8	50	43.8	97.8	45	43.9	98.0	47	44.6	99.6	49
74	44.9	48	43.0	95.8	45	43.2	96.2	45	45.6	101.6	47
78	44.9	47	43.6	97.1	45	43.8	97.6	44	44.6	99.3	46
82	45.4	47	43.9	96.7	45	44.6	98.2	(a) 38	45.3	99.8	(a) 44
86	45.6	46	43.5	95.4	45	44.4	97.4	43	44.8	98.2	46
90	44.3	46	43.1	97.3	45	43.4	98.0	43	44.0	99.3	45
94	44.9	(a) 44	42.6	94.9	(a) 43	42.5	94.7	(a) 40	43.1	96.0	(a) 41
98	44.2	43	42.6	96.4	40	42.8	96.8	34	42.4	95.9	(a) 41
102	42.9	43	42.2	98.4	37	41.8	97.4	30	41.1	95.8	37
FEMALE											
1	16.8	50	16.3	97.0	50	17.1	101.8	50	17.3	103.0	50
2	17.1	49	17.9	104.7	47	18.2	106.4	50	18.3	107.0	50
3	19.1	49	18.7	97.9	47	19.3	101.0	50	19.5	102.1	50
4	20.0	49	19.9	99.5	47	20.4	102.0	50	20.7	103.5	50
5	20.6	49	21.3	103.4	47	21.5	104.4	50	21.5	104.4	50
6	21.2	49	21.6	101.9	47	21.9	103.3	50	21.5	101.4	50
7	22.0	49	22.2	100.9	47	22.1	100.5	50	21.9	99.5	50
8	22.2	49	22.6	101.8	47	22.9	103.2	50	23.1	104.1	50
9	23.2	49	23.2	100.0	47	23.7	102.2	50	23.8	102.6	50
10	22.7	49	22.7	100.0	47	22.6	99.6	50	24.5	107.9	50
11	23.4	49	23.6	100.9	47	23.4	100.0	50	23.4	100.0	50
12	23.6	49	23.6	100.0	47	23.9	101.3	50	23.7	100.4	50
13	24.0	49	23.7	98.8	47	24.2	100.8	50	24.6	102.5	50
17	25.4	49	25.2	99.2	47	25.5	100.4	50	25.9	102.0	50
22	26.7	48	26.7	100.0	47	27.2	101.9	50	27.2	101.9	50
26	28.1	48	27.7	98.6	47	27.7	98.6	50	28.2	100.4	50
30	28.5	48	28.2	98.9	47	28.9	101.4	50	29.4	103.2	50
34	30.5	48	29.6	97.0	47	29.8	97.7	50	29.3	96.1	50
38	31.7	48	31.5	99.4	47	32.5	102.5	50	31.8	100.3	50
42	33.4	48	32.9	98.5	47	34.0	101.8	50	32.9	98.5	50
46	33.7	48	33.8	100.3	47	34.4	102.1	50	33.0	97.9	50
50	34.7	48	34.3	98.8	47	34.4	99.1	50	33.4	96.3	50
54	36.2	48	35.2	97.2	47	35.3	97.5	50	35.5	98.1	50
58	36.9	48	36.8	99.7	47	37.2	100.8	50	36.8	99.7	50
62	39.0	48	37.9	97.2	47	39.5	101.3	50	38.0	97.4	50
66	40.7	48	39.1	96.1	46	40.4	99.3	50	38.6	94.8	49
70	41.0	47	39.9	97.3	46	41.3	100.7	50	39.0	95.1	49
74	40.9	47	38.8	94.9	46	41.8	102.2	50	39.7	97.1	49
78	40.1	46	39.5	98.5	45	41.5	103.5	48	40.3	100.5	49
82	41.8	(a) 45	41.5	99.3	45	42.0	100.5	(a) 46	41.5	99.3	(a) 47
86	42.3	46	42.3	100.0	45	42.9	101.4	48	42.2	99.8	48
90	43.1	46	42.6	98.8	45	43.1	100.0	47	41.3	95.8	46
94	43.4	46	42.6	98.2	(a) 43	43.6	100.5	47	41.8	96.3	45
98	44.2	44	44.0	99.5	44	45.2	102.3	44	43.1	97.5	44
102	44.4	42	43.9	98.9	43	45.2	101.8	44	43.5	98.0	42

(a) The number of animals weighed was lower than the number of animals surviving.

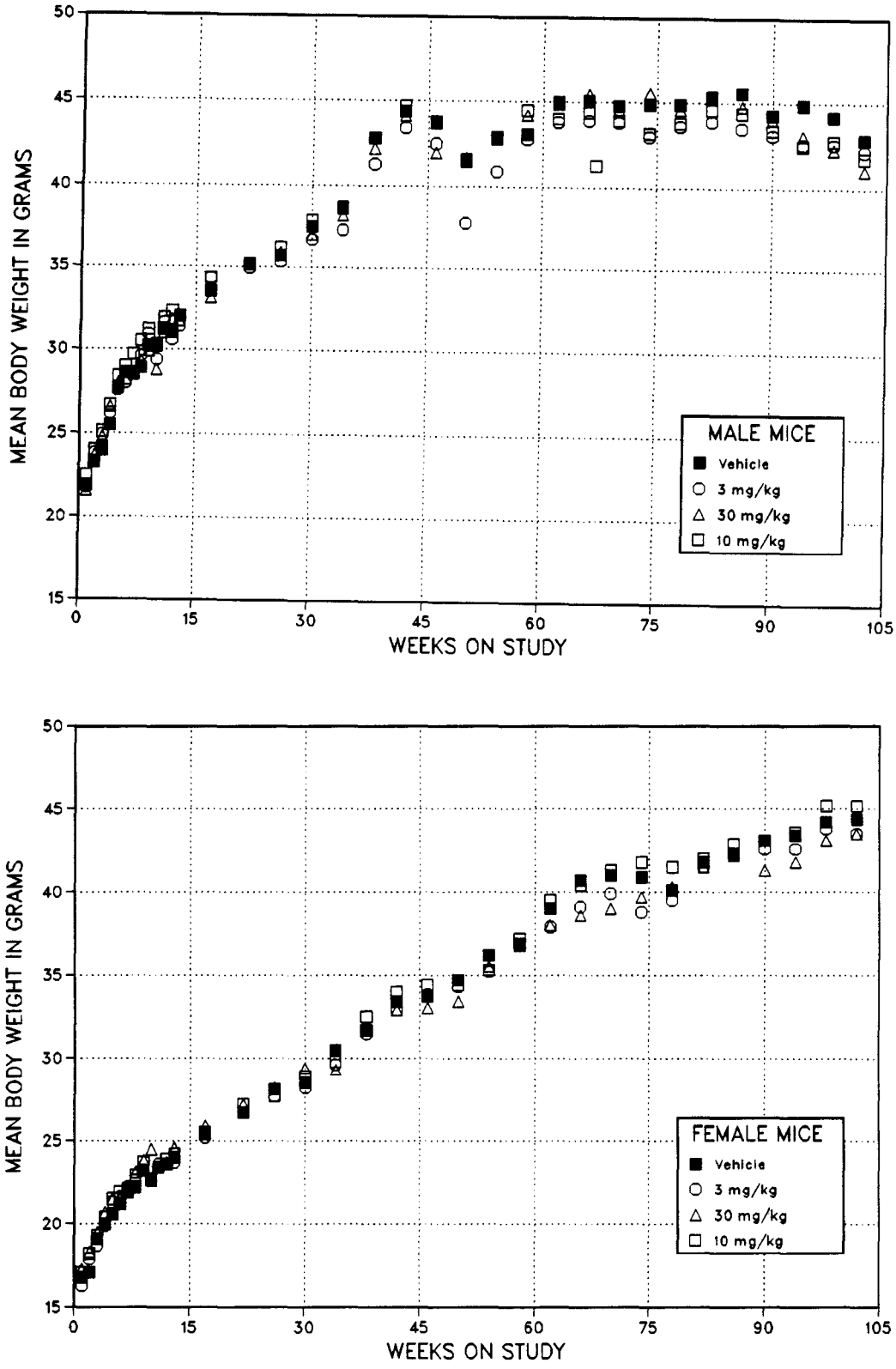


FIGURE 11. GROWTH CURVES FOR MICE ADMINISTERED *p*-CHLOROANILINE HYDROCHLORIDE BY GAVAGE FOR TWO YEARS

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

Survival

Estimates of the probabilities of survival for male and female mice administered *p*-chloroaniline hydrochloride at the doses used in these studies and for vehicle controls are shown in Table 23 and in the Kaplan and Meier curves in Figure 12. The survival of the mid dose group of male mice was significantly lower than that of the vehicle controls after week 99. No other significant differences in survival were observed between any groups of males or females.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, circulatory system, hematopoietic system, and kidney.

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 control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 23. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
MALE (b)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (c)	7	13	21	15
Animals missing	0	1	0	0
Killed at termination	43	36	29	35
Survival P values (d)	0.295	0.211	0.005	0.110
FEMALE (b)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (c)	10	5	6	9
Accidentally killed	1	3	0	0
Killed at termination	39	42	44	41
Survival P values (d)	0.875	0.298	0.408	0.966

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) First day of termination period: 728 (week 104)
(c) Includes animals killed in a moribund condition
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

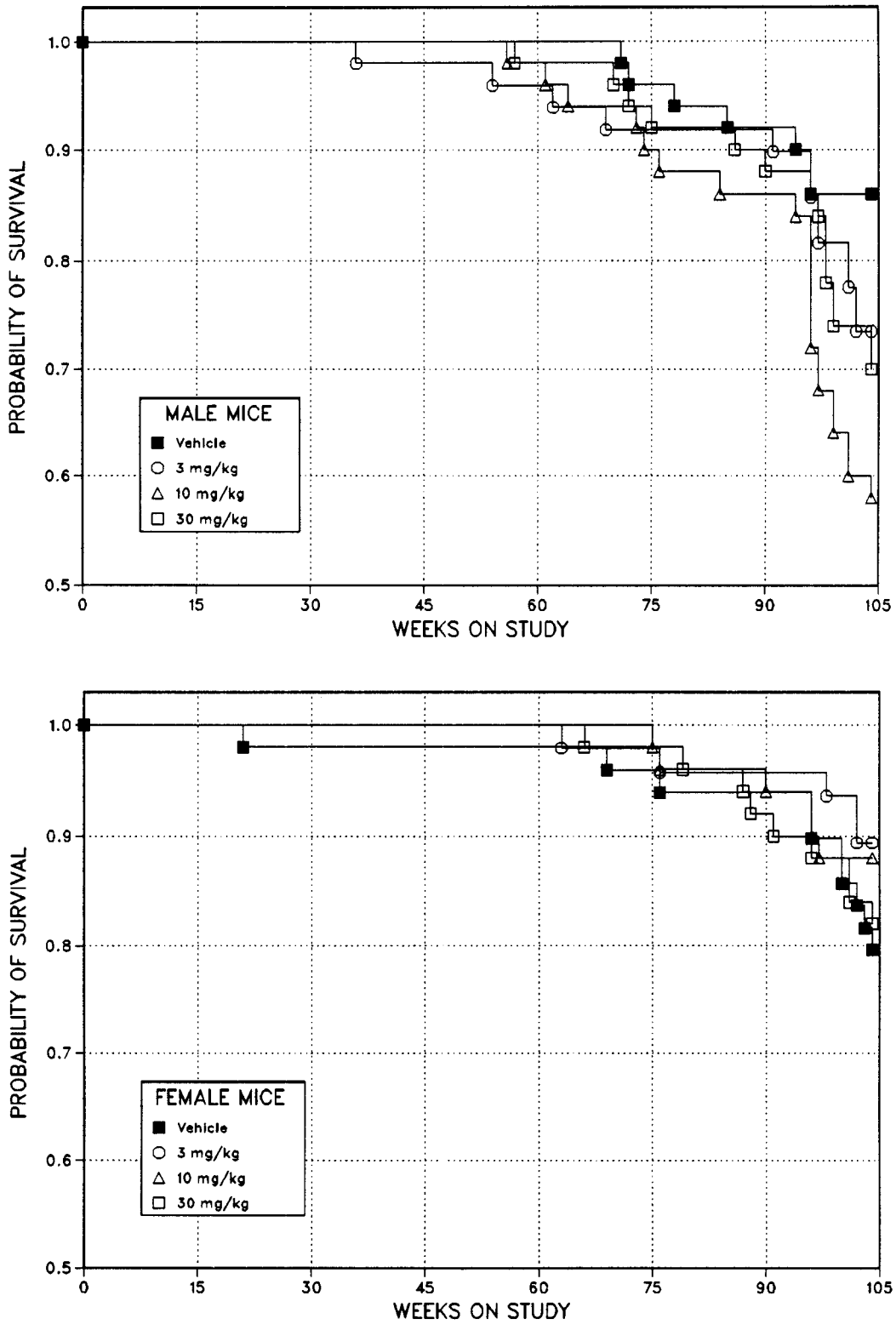


FIGURE 12. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED *p*-CHLOROANILINE HYDROCHLORIDE BY GAVAGE FOR TWO YEARS

(all doses calculated as milligrams *p*-chloroaniline per kilogram body weight)

Liver: Pigmentation (hemosiderin) of the Kupffer cells was observed in high dose mice (male: vehicle control, 0/50; low dose, 0/49; mid dose, 0/50; high dose, 50/50; female: 0/50; 0/50; 1/50; 46/50). Hepatocellular adenomas in male mice occurred with a significant negative trend, and hepatocellular carcinomas in male mice occurred with a significant positive trend (Table 24). The incidences of hepatocellular carcinomas in mid and high dose males and of hepatocellular adenomas or carcinomas (combined) in low, mid, and high dose males were significantly greater than those in vehicle controls. Hepatocellular carcinomas metastasized to the lung in 1/50 vehicle control, 1/49 low dose, 2/50 mid dose, and 9/50 high dose male mice. Hepatocellular adenomas or carcinomas (combined) were observed in 6/50 vehicle control, 9/50 low dose, 8/50 mid dose, and 11/50 high dose female mice.

TABLE 24. HEPATOCELLULAR TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Adenoma (b)				
Overall Rates	9/50 (18%)	15/49 (31%)	10/50 (20%)	4/50 (8%)
Adjusted Rates	20.9%	36.0%	29.1%	11.4%
Terminal Rates	9/43 (21%)	10/36 (28%)	7/29 (24%)	4/35 (11%)
Day of First Observation	728	432	443	728
Life Table Tests	P=0.044N	P=0.060	P=0.205	P=0.209N
Logistic Regression Tests	P=0.020N	P=0.097	P=0.478	P=0.209N
Carcinoma (c)				
Overall Rates	3/50 (6%)	7/49 (14%)	11/50 (22%)	17/50 (34%)
Adjusted Rates	7.0%	16.3%	25.9%	37.9%
Terminal Rates	3/43 (7%)	2/36 (6%)	1/29 (3%)	8/35 (23%)
Day of First Observation	728	637	514	490
Life Table Tests	P<0.001	P=0.127	P=0.011	P<0.001
Logistic Regression Tests	P<0.001	P=0.149	P=0.034	P<0.001
Metastatic to Lung	1/50	1/49	2/50	9/50
Adenoma or Carcinoma (d)				
Overall Rates	11/50 (22%)	21/49 (43%)	20/50 (40%)	21/50 (42%)
Adjusted Rates	25.6%	46.4%	47.0%	47.1%
Terminal Rates	11/43 (26%)	12/36 (33%)	8/29 (28%)	12/35 (34%)
Day of First Observation	728	432	443	490
Life Table Tests	P=0.081	P=0.012	P=0.007	P=0.010
Logistic Regression Tests	P=0.117	P=0.019	P=0.045	P=0.027

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table C3 (footnotes); all doses calculated as milligrams *p*-chloroaniline per kilogram body weight.
(b) Historical incidence in water gavage vehicle controls (mean ± SD): 54/347 (16% ± 4%); historical incidence in untreated controls in NTP studies: 259/2,032 (13% ± 7%)
(c) Historical incidence in water gavage vehicle controls (mean ± SD): 56/347 (16% ± 8%); historical incidence in untreated controls in NTP studies: 379/2,032 (19% ± 7%)
(d) Historical incidence in water gavage vehicle controls (mean ± SD): 106/347 (31% ± 6%); historical incidence in untreated controls in NTP studies: 609/2,032 (30% ± 8%)

Circulatory System: The incidence of hemangiosarcomas in high dose male mice was marginally increased relative to that in vehicle controls (Table 25). Nearly all of the hemangiosarcomas occurred in the liver or spleen (liver: vehicle control, 2/50; low dose, 2/49; mid dose, 1/50; high dose, 6/50; spleen: 3/50; 2/49; 0/50; 5/50). One vehicle control male mouse and three high dose male mice had liver neoplasms with characteristics of hepatocellular carcinomas but which also contained vascular elements similar to those of hemangiosarcomas; both hepatocellular carcinomas and hepatic hemangiosarcomas were diagnosed in each of these animals. However, it is not uncommon for hepatocellular carcinomas to contain prominent, dilated, vascular spaces or areas of necrosis and hemorrhage with reactive endothelial cells and fibroblasts that resemble a vascular neoplasm. For these lesions, it is difficult to determine if two distinctly different primary neoplasms are present.

TABLE 25. HEMANGIOSARCOMAS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Liver				
Overall Rates	2/50 (4%)	2/50 (4%)	1/50 (2%)	6/50 (12%)
Spleen				
Overall Rates	3/50 (6%)	2/50 (4%)	0/50 (0%)	5/50 (10%)
All Sites (b)				
Overall Rates	4/50 (8%)	4/49 (8%)	1/50 (2%)	10/50 (20%)
Adjusted Rates	9.3%	9.7%	3.4%	23.9%
Terminal Rates	4/43 (9%)	2/36 (6%)	1/29 (3%)	5/35 (14%)
Day of First Observation	728	479	728	399
Life Table Tests	P=0.011	P=0.560	P=0.315N	P=0.047
Logistic Regression Tests	P=0.014	P=0.639N	P=0.313N	P=0.083

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Historical incidence of hemangiomas or hemangiosarcomas (combined) in water gavage vehicle controls (mean ± SD): 11/350 (3% ± 3%); historical incidence in untreated controls in NTP studies: 98/2,040 (5% ± 4%)

Hematopoietic System: Proliferation of hematopoietic cells in the liver was observed at increased incidences in dosed female mice (male: vehicle control, 7/50; low dose, 4/49; mid dose, 7/50; high dose, 5/50; female: 15/50; 29/50; 24/50; 31/50). The incidences of malignant lymphomas in low and high dose males and in mid and high dose females were significantly lower than those in vehicle controls (Table 26).

Kidney: Multifocal renal tubular pigmentation (hemosiderin) was observed in high dose female mice (male: vehicle control, 0/50; low dose, 0/6; mid dose, 0/10; high dose, 4/49; female: 0/50; 0/7; 0/4; 38/49).

TABLE 26. MALIGNANT LYMPHOMAS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
MALE (b)				
Overall Rates	10/50 (20%)	3/49 (6%)	9/50 (18%)	3/50 (6%)
Adjusted Rates	21.6%	7.7%	23.9%	8.0%
Terminal Rates	7/43 (16%)	1/36 (3%)	4/29 (14%)	2/35 (6%)
Day of First Observation	496	674	423	682
Life Table Tests	P=0.149N	P=0.072N	P=0.443	P=0.074N
Logistic Regression Tests	P=0.095N	P=0.037N	P=0.397N	P=0.034N
FEMALE (c)				
Overall Rates	19/50 (38%)	12/50 (24%)	5/50 (10%)	10/50 (20%)
Adjusted Rates	41.3%	27.8%	10.3%	23.0%
Terminal Rates	12/39 (31%)	11/42 (26%)	2/44 (5%)	8/41 (20%)
Day of First Observation	666	528	521	609
Life Table Tests	P=0.082N	P=0.083N	P=0.001N	P=0.041N
Logistic Regression Tests	P=0.071N	P=0.104N	P=0.001N	P=0.032N

(a) All doses calculated as milligrams *p*-chloroaniline per kilogram body weight
(b) Historical incidence of lymphomas or leukemia (combined) in water gavage vehicle controls (mean ± SD): 42/350 (12% ± 6%); historical incidence in untreated controls in NTP studies: 252/2,040 (12% ± 7%)
(c) Historical incidence of lymphomas or leukemia (combined) in water gavage vehicle controls (mean ± SD): 122/350 (35% ± 10%); historical incidence in untreated controls in NTP studies: 636/2,040 (31% ± 13%)

Mutagenic activity for *p*-chloroaniline was observed by two laboratories in strain TA98 in the presence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster S9, and one laboratory noted an increase in revertant colonies in strain TA100 in the presence of hamster S9 only (Table 27). No mutagenic activity was reported in strains TA97, TA1535, or TA1537. Trifluorothymidine resistance was observed in cultured mouse L5178Y lymphoma cells both with and without Aroclor 1254-induced male F344 rat liver S9 (Table 28). *p*-Chloroaniline induced sister chromatid exchanges (SCEs) both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9; tests performed at Environmental Health Research and Testing (EHRT) found an increase in SCEs only in the absence of S9 (Table 29). Chromosomal aberration studies conducted at Litton Bionetics, Inc. (LBI), showed a significant increase in aberrations in the presence of S9 (Table 30). No significant increase in aberrations in either the presence or absence of S9 was observed in a study conducted by EHRT; however, the maximum doses of *p*-chloroaniline used in this study were lower than the doses that produced positive responses in the LBI study.

TABLE 27. MUTAGENICITY OF *p*-CHLOROANILINE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)		
Study performed at SRI International				
		−S9	+S9 (hamster)	+S9 (rat)
TA100	0	131 ± 8.3	169 ± 9.5	172 ± 5.3
	33	128 ± 9.5	158 ± 10.1	164 ± 2.2
	100	124 ± 12.5	151 ± 6.1	161 ± 12.0
	333	113 ± 11.9	148 ± 5.2	163 ± 10.8
	1,000	120 ± 3.5	170 ± 9.8	173 ± 7.6
	1,666	Toxic	160 ± 6.4	155 ± 3.7
Trial summary		Negative	Negative	Negative
Positive control (c)		510 ± 11.1	2,285 ± 42.7	1,053 ± 75.0
TA1535	0	23 ± 1.8	5 ± 0.9	8 ± 0.6
	33	18 ± 2.9	11 ± 1.5	10 ± 0.6
	100	16 ± 0.9	9 ± 1.5	8 ± 1.5
	333	22 ± 1.3	8 ± 1.3	10 ± 1.2
	1,000	22 ± 2.6	11 ± 3.1	10 ± 2.1
	1,666	(d) 0 ± 0.0	11 ± 1.0	9 ± 2.3
Trial summary		Negative	Negative	Negative
Positive control (c)		451 ± 26.8	600 ± 17.8	232 ± 9.2
TA97	0	166 ± 7.7	178 ± 10.7	193 ± 5.1
	33	173 ± 10.7	171 ± 17.2	207 ± 3.1
	100	170 ± 4.7	186 ± 12.7	190 ± 12.2
	333	162 ± 6.0	206 ± 10.3	205 ± 2.9
	1,000	126 ± 6.4	202 ± 28.4	203 ± 3.7
	1,666	Toxic	185 ± 1.2	(d) 95 ± 5.0
Trial summary		Negative	Negative	Negative
Positive control (c)		1,615 ± 55.6	1,466 ± 12.8	1,235 ± 24.1

		−S9	+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 1	Trial 2	Trial 1	Trial 2
TA98	0	21 ± 1.5	24 ± 2.1	36 ± 1.5	28 ± 1.7	27 ± 2.6
	33	23 ± 1.7	36 ± 4.0	39 ± 1.8	30 ± 2.3	31 ± 3.8
	100	23 ± 0.9	38 ± 7.2	34 ± 3.2	41 ± 5.2	35 ± 4.3
	333	22 ± 3.8	53 ± 6.7	44 ± 3.1	56 ± 8.4	49 ± 5.1
	666	--	--	76 ± 3.2	--	65 ± 5.5
	1,000	24 ± 1.7	93 ± 1.9	69 ± 2.9	80 ± 2.4	88 ± 6.9
	1,666	Toxic	83 ± 7.0	--	55 ± 8.1	--
Trial summary		Negative	Positive	Positive	Positive	Positive
Positive control (c)		1,626 ± 93.3	1,660 ± 60.2	829 ± 83.6	690 ± 49.7	248 ± 20.6

TABLE 27. MUTAGENICITY OF *p*-CHLOROANILINE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)				
Study performed at Microbiological Associates						
		−S9	+S9 (hamster)			
			5%	10%	30%	30%
TA100	0	99 ± 4.7	92 ± 3.2	86 ± 3.3	109 ± 4.4	114 ± 11.1
	33	103 ± 2.6	83 ± 4.4	94 ± 4.9	144 ± 3.3	115 ± 0.7
	100	97 ± 2.9	92 ± 5.2	97 ± 3.2	142 ± 0.0	134 ± 8.9
	333	102 ± 0.9	83 ± 6.1	100 ± 7.9	149 ± 25.7	160 ± 10.8
	1,000	(d) 90 ± 1.3	96 ± 9.2	106 ± 3.2	178 ± 5.5	174 ± 12.2
	1,500	--	(d) 57 ± 13.0	(d) 85 ± 7.5	--	(d) 158 ± 8.8
	2,000	(d) 33 ± 18.0	--	--	(d) 100 ± 47.7	--
Trial summary		Negative	Negative	Negative	Equivocal	Weakly positive
Positive control (c)		453 ± 2.0	1,714 ± 97.5	904 ± 8.4	493 ± 14.6	505 ± 36.9
			+S9 (rat)			
			5%	10%	30%	30%
TA100	0		87 ± 3.8	98 ± 9.7	130 ± 2.1	121 ± 0.3
	33		98 ± 5.0	99 ± 3.5	136 ± 7.8	102 ± 7.0
	100		84 ± 6.4	99 ± 4.9	144 ± 7.2	107 ± 2.3
	333		93 ± 0.3	99 ± 9.0	146 ± 19.8	111 ± 3.5
	1,000		105 ± 1.2	107 ± 3.2	162 ± 8.6	130 ± 6.1
	1,500		(d) 69 ± 2.3	(d) 78 ± 1.5	--	(d) 129 ± 2.7
	2,000		--	--	(d) 98 ± 15.3	--
Trial summary			Negative	Negative	Negative	Negative
Positive control (c)			1,043 ± 29.3	993 ± 84.3	729 ± 7.1	859 ± 3.3
		−S9	+S9 (hamster)			
			5%	10%	30%	30%	30%
TA98	0	38 ± 5.8	26 ± 1.7	29 ± 2.0	55 ± 2.3	26 ± 1.8	24 ± 0.6
	33	39 ± 1.2	35 ± 1.9	27 ± 2.5	49 ± 5.2	25 ± 1.8	23 ± 1.9
	100	37 ± 6.5	26 ± 3.0	28 ± 2.2	57 ± 1.8	24 ± 1.0	29 ± 1.8
	333	37 ± 8.4	39 ± 1.9	47 ± 3.8	63 ± 3.5	44 ± 2.4	30 ± 1.9
	1,000	26 ± 0.6	50 ± 2.8	73 ± 6.4	(d) 90 ± 7.1	42 ± 6.2	66 ± 4.4
	1,500	--	(d) 32 ± 3.0	(d) 61 ± 3.8	--	(d) 60 ± 7.5	(d) 57 ± 1.5
	2,000	(d) 8 ± 2.0	--	--	(d) 21 ± 11.1	--	--
Trial summary		Negative	Weakly positive	Positive	Equivocal	Weakly positive	Weakly positive
Positive control (d)		205 ± 12.8	107 ± 12.0	77 ± 7.9	111 ± 5.7	142 ± 5.5	70 ± 4.0
			+S9 (rat)			
			5%	10%	30%	30%	30%
TA98	0		23 ± 5.3	26 ± 1.5	51 ± 3.5	30 ± 3.2	27 ± 2.9
	33		29 ± 2.7	31 ± 1.5	54 ± 0.6	28 ± 1.8	26 ± 2.1
	100		31 ± 3.8	31 ± 5.6	53 ± 1.7	33 ± 5.6	21 ± 2.3
	333		45 ± 2.8	41 ± 2.5	66 ± 4.7	42 ± 0.6	30 ± 2.1
	1,000		63 ± 6.5	71 ± 4.5	86 ± 1.5	81 ± 6.6	50 ± 5.3
	1,500		(d) 30 ± 2.1	(d) 46 ± 3.5	--	(d) 83 ± 9.7	(d) 51 ± 3.1
	2,000		--	--	(d) 12 ± 12.0	--	--
Trial summary			Positive	Positive	Equivocal	Positive	Positive
Positive control (d)			382 ± 4.9	316 ± 25.1	169 ± 16.3	169 ± 17.2	171 ± 5.2

TABLE 27. MUTAGENICITY OF *p*-CHLOROANILINE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)		
Study performed at Case Western Reserve University				
		−S9	+S9 (hamster)	+S9 (rat)
TA100	0	97 ± 6.8	122 ± 11.6	121 ± 6.8
	10	104 ± 8.0	165 ± 9.6	125 ± 5.1
	33	94 ± 5.0	166 ± 13.9	143 ± 5.7
	100	107 ± 6.4	157 ± 11.2	146 ± 4.2
	333	90 ± 4.7	150 ± 9.5	143 ± 12.1
	1,000	93 ± 4.5	130 ± 13.9	135 ± 3.2
	3,333	--	--	--
Trial summary		Negative	Negative	Negative
Positive control (c)		459 ± 23.9	1,818 ± 296.3	1,057 ± 174.4
TA1535	0	6 ± 0.9	6 ± 3.0	6 ± 2.1
	10	--	4 ± 0.7	2 ± 0.6
	33	5 ± 1.9	5 ± 0.7	4 ± 0.3
	100	4 ± 1.2	3 ± 0.7	2 ± 0.7
	333	5 ± 2.3	4 ± 1.2	7 ± 1.3
	1,000	6 ± 1.5	3 ± 0.9	7 ± 2.6
	3,333	1 ± 1.3	--	--
Trial summary		Negative	Negative	Negative
Positive control (c)		212 ± 33.8	30 ± 3.7	38 ± 2.1
TA1537	0	2 ± 1.2	6 ± 1.2	6 ± 0.0
	10	--	6 ± 0.6	10 ± 2.0
	33	3 ± 0.9	7 ± 0.7	8 ± 0.9
	100	2 ± 0.3	6 ± 0.7	9 ± 0.9
	333	3 ± 1.3	3 ± 1.9	10 ± 1.5
	1,000	2 ± 0.3	4 ± 1.7	5 ± 1.5
	3,333	Toxic	--	--
Trial summary		Negative	Negative	Negative
Positive control (c)		398 ± 32.0	107 ± 1.8	109 ± 2.3
TA98	0	15 ± 2.3	19 ± 0.6	22 ± 1.2
	10	14 ± 3.2	25 ± 2.9	--
	33	8 ± 1.2	21 ± 3.0	23 ± 2.6
	100	13 ± 1.2	25 ± 3.8	25 ± 2.0
	333	13 ± 2.4	21 ± 3.5	30 ± 2.2
	1,000	10 ± 1.7	17 ± 3.6	24 ± 0.9
	3,333	--	--	8 ± 5.8
Trial summary		Negative	Negative	Negative
Positive control (c)		278 ± 25.4	984 ± 100.2	626 ± 139.2

(a) The detailed protocol is presented by Mortelmans et al. (1986). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA97 and TA1537.
(d) Slight toxicity

TABLE 28. MUTAGENICITY OF *p*-CHLOROANILINE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Study performed at Inveresk Research International					
-S9					
Ethanol (d)		77.8 ± 2.8	99.8 ± 1.8	180.5 ± 15.7	77.3 ± 6.0
p-Chloroaniline	50	54.0 ± 6.7	62.3 ± 4.3	232.0 ± 18.1	(e) 145.0 ± 7.8
	100	67.0 ± 3.5	56.3 ± 1.7	333.3 ± 22.8	(e) 166.3 ± 11.0
	200	65.7 ± 5.6	39.7 ± 3.8	330.0 ± 36.2	(e) 170.3 ± 24.8
	400	58.3 ± 0.9	12.3 ± 1.2	452.0 ± 20.5	(e) 260.0 ± 11.7
	600	Lethal	--	--	--
Ethyl methanesulfonate (f)	250	74.0 ± 0.0	94.5 ± 5.5	660.5 ± 81.5	(e) 296.5 ± 36.5
+S9 (g)					
Trial 1					
Methanol (d)		83.0 ± 8.4	100.0 ± 1.9	144.0 ± 11.8	58.3 ± 1.7
p-Chloroaniline (f)	25	63.5 ± 4.5	62.5 ± 2.5	594.0 ± 5.0	(e) 314.0 ± 25.0
	50	70.0 ± 15.0	44.0 ± 8.0	637.0 ± 38.0	(e) 315.0 ± 50.0
	100	49.5 ± 2.5	14.5 ± 3.5	926.5 ± 23.5	(e) 627.0 ± 54.0
	200	Lethal	--	--	--
Methylcholanthrene (f)	2.5	45.0 ± 3.0	20.0 ± 1.0	884.5 ± 41.5	667.0 ± 77.0
Trial 2					
Methanol (d)		59.3 ± 3.4	100.0 ± 9.7	139.5 ± 6.6	79.0 ± 5.1
p-Chloroaniline (f)	9.375	52.0 ± 7.0	59.5 ± 4.5	205.5 ± 10.5	(e) 132.5 ± 11.5
	18.75	44.0 ± 3.0	49.0 ± 2.0	215.5 ± 13.5	(e) 165.5 ± 21.5
	37.5	50.0 ± 11.0	30.0 ± 4.0	472.0 ± 88.0	(e) 318.0 ± 14.0
	75	31.5 ± 0.5	7.5 ± 0.5	402.5 ± 67.5	(e) 427.0 ± 78.0
	150	Lethal	--	--	--
Methylcholanthrene (f)	2.5	31.5 ± 2.5	25.5 ± 4.5	413.0 ± 11.0	441.5 ± 25.5
Study performed at Litton Bionetics, Inc.					
-S9					
Trial 1					
Dimethyl sulfoxide (d)		83.0 ± 9.0	100.0 ± 9.0	98.8 ± 4.7	40.8 ± 4.4
p-Chloroaniline	(h) 31.3	115	117	81	24
	(f) 62.5	82.5 ± 2.5	88.5 ± 2.5	90.5 ± 17.5	36.0 ± 6.0
	(h) 125	78	82	87	37
	(f) 250	89.0 ± 14.0	62.0 ± 9.0	134.0 ± 7.0	51.0 ± 5.0
	(f) 375	88.5 ± 20.5	19.0 ± 5.0	199.0 ± 3.0	(e) 80.0 ± 20.0
	(i) 500	81	12	244	100
	1,000	Lethal	--	--	--
Ethyl methanesulfonate (f)	500	49.5 ± 2.5	37.0 ± 0.0	952.0 ± 31.0	(e) 645.0 ± 13.0

TABLE 28. MUTAGENICITY OF *p*-CHLOROANILINE IN MOUSE L5178Y LYMPHOMA CELLS
(Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
−S9 (Continued)					
Trial 2					
Dimethyl sulfoxide (d)		86.3 ± 4.0	100.0 ± 5.7	40.3 ± 5.3	15.8 ± 2.1
p-Chloroaniline	(f) 200	46.0 ± 8.0	48.0 ± 2.0	26.5 ± 6.5	19.0 ± 1.0
	300	52.0 ± 5.5	28.7 ± 6.3	37.0 ± 7.4	24.0 ± 4.2
	400	58.0 ± 10.4	16.0 ± 6.2	39.0 ± 5.3	22.7 ± 1.7
	450	74.3 ± 10.2	25.7 ± 2.7	60.0 ± 11.5	(e) 26.3 ± 1.7
	500	88.7 ± 6.6	18.0 ± 2.1	67.0 ± 5.0	(e) 25.3 ± 1.2
	550	75.0 ± 10.5	14.3 ± 3.9	61.3 ± 10.5	(e) 27.3 ± 1.9
Ethyl methanesulfonate	500	34.0 ± 6.0	26.3 ± 1.2	379.3 ± 53.1	(e) 378.3 ± 21.5
Trial 3					
Dimethyl sulfoxide (d)		65.8 ± 1.3	100.0 ± 5.0	30.3 ± 3.3	15.5 ± 1.7
p-Chloroaniline	100	48.0 ± 3.1	49.7 ± 2.2	49.7 ± 4.3	(e) 34.7 ± 1.8
	200	43.7 ± 2.6	32.3 ± 3.4	41.0 ± 3.0	(e) 31.7 ± 1.2
	300	29.7 ± 0.7	10.7 ± 1.3	28.0 ± 2.3	(e) 31.7 ± 2.7
	(j) 400	35.5 ± 6.5	5.0 ± 0.0	35.5 ± 4.5	(e) 35.0 ± 10.0
	(k) 500	50	6	43	29
	(k) 550	38	4	30	26
	600	Lethal	--	--	--
Ethyl methanesulfonate (f)	500	16.0 ± 3.0	11.0 ± 1.0	500.5 ± 34.5	(e) 1,075.0 ± 120.0
+S9 (g)					
Trial 1					
Dimethyl sulfoxide (d)		76.8 ± 4.5	99.8 ± 4.3	84.5 ± 7.7	36.5 ± 1.3
p-Chloroaniline (f)	7.8	65.0 ± 3.0	67.0 ± 2.0	106.5 ± 6.5	55.0 ± 6.0
	15.6	74.0 ± 4.0	55.5 ± 7.5	144.5 ± 0.5	(e) 65.5 ± 3.5
	31.3	67.0 ± 16.0	43.0 ± 8.0	122.5 ± 8.5	(e) 63.5 ± 10.5
	62.5	74.0 ± 8.0	30.5 ± 2.5	174.0 ± 42.0	(e) 77.0 ± 11.0
	125	61.5 ± 1.5	21.0 ± 0.0	188.5 ± 0.5	(e) 102.5 ± 3.5
Methylcholanthrene (f)	5	38.0 ± 1.0	19.5 ± 1.5	396.5 ± 24.5	(e) 353.0 ± 31.0
Trial 2					
Dimethyl sulfoxide (d)		80.5 ± 3.5	100.0 ± 4.5	108.8 ± 7.4	45.0 ± 1.2
p-Chloroaniline (f)	31.3	79.0 ± 6.0	37.0 ± 3.0	122.0 ± 18.0	51.0 ± 4.0
	62.5	75.0 ± 3.0	26.5 ± 3.5	151.0 ± 21.0	68.0 ± 12.0
	83.4	78.5 ± 8.5	21.0 ± 0.0	151.5 ± 11.5	64.5 ± 1.5
	125	72.5 ± 6.5	16.0 ± 1.0	190.0 ± 16.0	(e) 87.5 ± 0.5
	166.7	75.0 ± 8.0	15.0 ± 0.0	152.5 ± 33.5	67.0 ± 8.0
Methylcholanthrene (f)	5	48.0 ± 7.0	26.5 ± 2.5	347.5 ± 30.5	(e) 244.0 ± 16.0

TABLE 28. MUTAGENICITY OF *p*-CHLOROANILINE IN MOUSE L5178Y LYMPHOMA CELLS
(Continued)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
+ S9 (g) (Continued)					
Trial 3					
Dimethyl sulfoxide (d)		87.8 ± 6.4	100.0 ± 7.2	57.0 ± 5.8	21.8 ± 1.1
p-Chloroaniline	75	83.0 ± 1.5	35.0 ± 2.6	95.7 ± 3.2	(e) 38.7 ± 2.2
	100	74.7 ± 4.9	29.0 ± 2.3	90.7 ± 11.2	(e) 40.7 ± 4.3
	125	83.3 ± 3.8	29.0 ± 1.2	136.7 ± 12.7	(e) 54.7 ± 2.7
	150	88.3 ± 1.7	23.3 ± 0.9	132.7 ± 4.9	(e) 50.0 ± 2.6
	166.7	76.0 ± 5.5	15.3 ± 1.2	114.7 ± 10.8	(e) 50.3 ± 3.3
	200	65.7 ± 3.9	17.0 ± 1.2	118.7 ± 9.9	(e) 60.7 ± 4.8
Methylcholanthrene	5	52.0 ± 2.5	39.7 ± 3.2	291.3 ± 23.8	(e) 187.0 ± 19.5

(a) The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; the average for the three tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Data presented are the average of four tests.
(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(f) Data presented are the average of two tests.
(g) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.
(h) Data presented are for one test.
(i) Data presented are for one test. The dose in one test was lethal.
(j) Data presented are the average of two tests. The dose in one test was lethal.
(k) Data presented are for one test. The dose in two tests was lethal.

TABLE 29. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *p*-CHLOROANILINE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
Study performed at Litton Bionetics, Inc.								
-S9 (c)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,048	449	0.43	9.0	25.5	--
p-Chloroaniline	16.7	50	1,039	589	0.57	11.8	25.5	131.1
	50	50	1,043	586	0.56	11.7	25.5	130.0
	167	50	1,044	773	0.74	15.5	(d) 33.5	172.2
	500	0						
Mitomycin C	0.001	50	1,050	692	0.66	13.8	25.5	153.3
	0.01	5	105	259	2.47	51.8	25.5	575.6
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,046	497	0.48	9.9	25.8	--
p-Chloroaniline	150	50	1,050	769	0.73	15.4	(d) 35.3	155.6
	175	50	1,043	736	0.71	14.7	(d) 35.3	148.5
	200	50	1,047	843	0.81	16.9	(d) 35.3	170.7
Mitomycin C	0.001	50	1,049	695	0.66	13.9	25.8	140.4
	0.01	5	105	302	2.88	60.4	25.8	610.1
+S9 (e) Summary: Positive								
Dimethyl sulfoxide		50	1,048	478	0.46	9.6	25.8	--
p-Chloroaniline	900	50	1,043	656	0.63	13.1	25.8	136.5
	1,000	50	1,036	823	0.79	16.5	(d) 35.3	171.9
	1,100	50	1,043	794	0.76	15.9	(d) 35.3	165.6
	1,200	0						
Cyclophosphamide	0.35	50	1,046	725	0.69	14.5	25.8	151.0
	2	5	104	210	2.02	42.0	25.8	437.5
Study performed at Environmental Health Research & Testing, Inc.								
-S9 (c)								
Trial 1--Summary: Equivocal								
Dimethyl sulfoxide		50	1,046	432	0.41	8.6	26.0	--
p-Chloroaniline	0.5	50	1,041	437	0.42	8.7	26.0	101.2
	1.6	50	1,041	406	0.39	8.1	26.0	94.2
	5	50	1,037	405	0.39	8.1	26.0	94.2
	16	50	1,035	495	0.48	9.9	26.0	115.1
	50	50	1,046	443	0.42	8.9	26.0	103.5
	160	50	1,041	524	0.50	10.5	26.0	122.1
	500	0					26.0	
Mitomycin C	0.005	50	1,047	1,399	1.34	28.0	26.0	325.6
	0.01	50	1,033	1,964	1.90	39.3	26.0	457.0

TABLE 29. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *p*-CHLOROANILINE (Continued)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (Continued)								
Trial 2--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,042	431	0.41	8.6	28.0	--
p-Chloroaniline	50	50	1,043	453	0.43	9.1	28.0	105.8
	100	50	1,050	521	0.50	10.4	28.0	120.9
	200	50	1,042	550	0.53	11.0	28.0	127.9
	300	0						
	400	0						
	500	0						
Mitomycin C	0.005	50	1,034	1,246	1.21	24.9	28.0	289.5
	0.01	50	1,040	1,912	1.84	38.2	28.0	444.2
Trial 3--Summary: Positive								
Dimethyl sulfoxide		50	1,042	431	0.41	8.6	28.0	--
p-Chloroaniline	50	50	1,025	504	0.49	10.1	(d) 37.0	117.4
	100	50	1,036	503	0.49	10.1	(d) 37.0	117.4
	200	50	1,029	582	0.57	11.6	(d) 37.0	134.9
	300	50	1,029	604	0.59	12.1	(d) 37.0	140.7
	400	0						
	500	0						
Mitomycin C	0.005	50	1,034	1,246	1.21	24.9	28.0	289.5
	0.01	50	1,040	1,912	1.84	38.2	28.0	444.2
+S9 (e)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,047	410	0.39	8.2	26.0	--
p-Chloroaniline	1.6	50	1,047	467	0.45	9.3	26.0	113.4
	5	50	1,043	447	0.43	8.9	26.0	108.5
	16	50	1,046	453	0.43	9.1	26.0	111.0
	50	50	1,045	479	0.46	9.6	26.0	117.1
	160	50	1,045	469	0.45	9.4	26.0	114.6
	500	50	1,043	472	0.45	9.4	26.0	114.6
	1,600	0					26.0	
Cyclophosphamide	1.5	50	1,044	1,593	1.53	31.9	26.0	389.0
Trial 2--Summary: Equivocal								
Dimethyl sulfoxide		50	1,034	434	0.42	8.7	26.0	--
p-Chloroaniline	100	50	1,033	492	0.48	9.8	26.0	112.6
	200	50	1,029	521	0.51	10.4	26.0	119.5
	300	50	1,038	476	0.46	9.5	26.0	109.2
	400	50	1,033	465	0.45	9.3	26.0	106.9
	500	50	1,031	482	0.47	9.6	26.0	110.3
	600	50	1,036	480	0.46	9.6	26.0	110.3
Cyclophosphamide	1.5	50	1,035	1,918	1.85	38.4	26.0	441.4
	2	50	1,038	2,959	2.85	59.2	26.0	680.5

TABLE 29. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *p*-CHLOROANILINE (Continued)

(a) SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE 30. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY *p*-CHLOROANILINE (a)

	−S9 (b)					+S9 (c)			
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Study performed at Litton Bionetics, Inc. (d)									
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	4	0.04	3.0		100	4	0.04	4.0
p-Chloroaniline					*p*-Chloroaniline				
400	100	19	0.19	10.0	800	100	5	0.05	5.0
450	100	8	0.08	7.0	900	100	27	0.27	21.0
500	100	2	0.02	2.0	1,000	50	35	0.70	38.0
600	0								
	Summary: Negative					Summary: Positive			
Mitomycin C					Cyclophosphamide				
0.062	50	52	1.04	58.0	10	50	19	0.38	24.0
Study performed at Environmental Health Research & Testing, Inc.									
Trial 1 (e)									
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.00	0.0		100	0	0.00	0.0
p-Chloroaniline					*p*-Chloroaniline				
30	100	0	0.00	0.0	1.6	100	0	0.00	0.0
100	100	0	0.00	0.0	5	100	0	0.00	0.0
160	100	1	0.01	1.0	16	100	0	0.00	0.0
300	100	0	0.00	0.0	50	100	0	0.00	0.0
400	100	0	0.00	0.0	160	100	0	0.00	0.0
500	100	3	0.03	3.0	500	100	0	0.00	0.0
600	0				800	0			
	Summary: Negative					Summary: Negative			
Mitomycin C					Cyclophosphamide				
0.25	100	26	0.26	24.0	50	100	125	1.25	59.0
0.5	100	42	0.42	33.0					
Trial 2 (f)									
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.00	0.0		100	0	0.00	0.0
p-Chloroaniline					*p*-Chloroaniline				
100	100	0	0.00	0.0	100	100	0	0.00	0.0
200	100	0	0.00	0.0	200	100	0	0.00	0.0
300	100	2	0.02	2.0	300	100	0	0.00	0.0
400	100	0	0.00	0.0	400	100	0	0.00	0.0
500	100	4	0.04	4.0	500	100	0	0.00	0.0
550	100	6	0.06	6.0	550	100	3	0.03	3.0
					600	100	0	0.00	0.0
	Summary: Weakly positive					Summary: Negative			
Mitomycin C					Cyclophosphamide				
0.5	100	58	0.58	39.0	50	100	115	1.15	61.0

TABLE 30. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY *p*-CHLOROANILINE (Continued)

(a) Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Harvest time, 23.0 hours; because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.
(e) Harvest time, 12.0 hours
(f) Harvest time, 13.0 hours

IV. DISCUSSION AND CONCLUSIONS

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IV. DISCUSSION AND CONCLUSIONS

Toxicity

The current *p*-chloroaniline hydrochloride 13-week studies in rats and mice revealed that the hematopoietic system was the major target of *p*-chloroaniline hydrochloride toxicity. Methemoglobin formation and the accompanying hemolytic anemia, extramedullary hematopoiesis, and splenomegaly were indicative of erythrocyte toxicity induced by *p*-chloroaniline hydrochloride. In the 2-year studies, results of hematologic analyses in rats and the occurrence of nonneoplastic lesions in the spleen and liver in both rats and mice and the kidney in mice showed that the hematopoietic system was also affected by long-term administration of *p*-chloroaniline hydrochloride. Erythrocyte toxicity as expressed by methemoglobin formation is the dominant toxic effect seen in laboratory animals and humans exposed to a number of amino and nitro aromatic compounds (Beard and Noe, 1981; Beutler, 1985). Methemoglobin formation in eythrocytes results from the change of heme iron from the ferrous to ferric state. The brown pigment formed is called methemoglobin, a derivative of hemoglobin that is physiologically inactive. Acute methemoglobinemia may be life threatening when the level of methemoglobin exceeds half of the total circulating hemoglobin (Beutler, 1972).

Short-term exposure of humans to *p*-chloroaniline produces cyanosis, a manifestation of methemoglobin formation. Long-term exposure may result in reversible anemia (Linch, 1974). The methemoglobin can be reduced to hemoglobin in mammalian species by a NADH-dependent methemoglobin reductase located in the erythrocytes. A tenfold difference exists in the activity of this enzyme among various species. Enzymic activity in rat and mouse erythrocytes is 5 and 10 times higher, respectively, than that in human erythrocytes (Smith, 1986), suggesting that humans are more susceptible to this particular toxic effect of aniline and its homologs. The formation of methemoglobin by aromatic nitro and amino compounds, mechanism(s) of formation, and toxicologic implications have been reviewed extensively (Kiese, 1966; Beard and Noe, 1981). There is convincing evidence that an *N*-hydroxy metabolite is the reactive species responsible for this toxic effect (Selkirk, 1980; Weisburger, 1983). The *p*-chloroaniline hydrochloride-induced erythrocyte toxicity seen in the current studies also could be due to an *N*-hydroxy derivative, since *p*-chloroaniline was shown to be metabolized to its *N*-hydroxy derivative by the hepatic microsomal mono-oxygenase system of guinea pigs, rabbits, hamsters, mice, and rats (Smith and Gorrod, 1978; Uehleke and Hellmer, 1971). According to Bus and Popp (1987), the *N*-oxidation pathway of aniline, an analog of *p*-chloroaniline, is inconsequential for rat liver, as liver rapidly reduces *N*-oxidized metabolites back to the parent compound. On the contrary, the small amount of *N*-phenylhydroxylamine taken up by the erythrocytes is rapidly oxidized by oxyhemoglobin to nitrosobenzene, with concurrent formation of methemoglobin. The metabolism and pattern of erythrocyte toxicity of *p*-chloroaniline hydrochloride suggest that the mechanisms of methemoglobin formation by aniline and its analog *p*-chloroaniline have common characteristics.

In the 13-week studies, a dose-related increase in splenic weights was observed for both rats and mice. A similar enlargement in the spleen was seen in rats dosed with aniline (Gralla et al. 1979). Bus (1983) suggested that splenic weight increases in aniline-dosed rats were due to excessive deposition of damaged erythrocytes as a result of aniline toxicity and thus that splenomegaly is a secondary effect of erythrocyte toxicity. Results of the current studies support this contention, as rats and mice in the 13-week *p*-chloroaniline hydrochloride studies did not show any degenerative changes in the spleen. The increases in spleen weight were probably a result of increased vascular engorgement in response to methemoglobinemia.

Carcinogenicity

Recent carbon-13 nuclear magnetic resonance studies on relationships between chemical structure and carcinogenicity of chlorinated monocyclic aromatic compounds predicted that *p*-chloroaniline would be carcinogenic (Sakamoto and Watanabe, 1986). The results of previous 2-year studies on *p*-chloroaniline were strongly suggestive of carcinogenicity because several rare fibromas and sarcomas of the spleen were found in exposed male rats (NCI, 1979c). The results

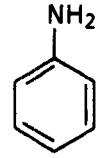
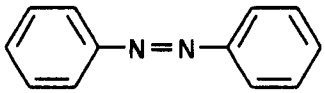
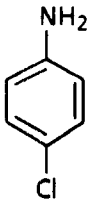
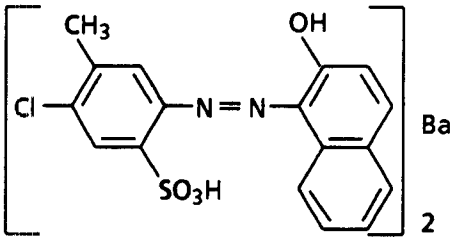
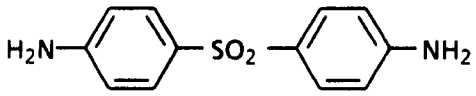
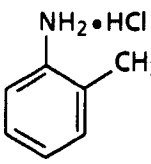
from those studies have been substantiated by results from the current studies, which show that *p*-chloroaniline hydrochloride is carcinogenic for male rats, based on the increased incidence of splenic sarcomas in high dose male rats (see Table 15). The possibility exists that in the first set of studies *p*-chloroaniline was administered to animals at less than target concentrations due to the instability of the chemical in feed. The target concentrations in feed for that study were approximately equivalent to 15 and 30 mg/kg body weight of rats, compared with 2, 6, and 18 mg/kg in the current gavage studies. The different modes of oral administration (single dose per day by gavage and continuous dosing by feed) could possibly have resulted in differences in pharmacokinetics and might have been responsible for quantitative differences seen between the results of these two studies. The dose response for splenic tumors in male rats in the current studies was nonlinear with increases in dose; although the high dose was 3 times the mid dose, the incidence of sarcomas in the high dose group was 12 times that in the mid dose group. The doses used in these studies apparently did not saturate the metabolic and excretory pathways, as evidenced by disposition studies on *p*-chloroaniline and *p*-chloroaniline hydrochloride conducted by the NTP (Appendix H).

Other structurally related aniline compounds seem to exhibit nonlinear responses for the occurrence of splenic tumors in male rats (Table 31). The carcinogenesis study conducted by the Chemical Industry Institute of Toxicology (CIIT) on aniline hydrochloride administered to male rats at 0, 10, 30, or 100 mg/kg body weight (0, 200, 600, or 2,000 ppm) in feed also showed a similar type of nonlinearity in tumor response (Bus and Popp, 1987). In that study, an apparent no-observable-effect level of 10 mg/kg aniline was found, whereas in the current studies with *p*-chloroaniline hydrochloride, no apparent no-observable-effect level for splenic tumors in male rats was reached. The female rats were less sensitive than the males to *p*-chloroaniline hydrochloride induction of splenic neoplasms, since neoplasms were seen in only one mid dose and one high dose female rat in the NTP studies. Table 31 shows that similar sex differences in the incidences of splenic tumors were seen with other aniline compounds, except for azobenzene and *o*-toluidine hydrochloride studies in which female rats were equally sensitive. In the current studies, the incidences of splenic fibrosis in high dose male and female rats were 41/50 and 42/50, respectively. Fibrosis of the spleen is a potential preneoplastic lesion that may progress to fibrosarcomas (Goodman et al., 1984).

The incidence of adrenal gland pheochromocytomas in male rats occurred with a positive trend (see Table 16). Medullary hyperplasia was observed at an increased incidence in high dose female rats; pheochromocytomas were seen in 2/50 vehicle control and 10/150 dosed females. Examination of Table 31 shows that aniline hydrochloride was the only structurally related chemical studied by the NCI/NTP that clearly caused an increase in the incidences of these neoplasms in dosed male rats and, to a lesser extent, in females. The incidences of adrenal gland tumors in the current studies may have been related to *p*-chloroaniline administration.

For mice, the body weights and survival in the current 2-year studies were in general not affected by the administration of *p*-chloroaniline hydrochloride. No splenic fibrosarcomas or osteosarcomas were observed in mice of either sex. The species differences between rats and mice in aromatic amine-induced neoplasms were reviewed by Weisburger (1983). None of the aromatic amines studied for carcinogenic potential by the NCI/NTP caused increased incidences of splenic tumors in mice. However, induction of liver tumors by those chemicals was frequently observed in mice. The tumor incidences in mice administered *p*-chloroaniline hydrochloride in the current studies followed the pattern reported by Weisburger (1983), with the incidences of hepatocellular carcinomas being increased in dosed male mice. Even though the incidence of hepatocellular carcinomas in vehicle controls is much lower than that in historical water gavage controls (6% versus 16%), the strong dose-response relationship and the metastasis to the lung of the carcinomas are additional evidence for a chemically related effect. Also, there was a marginal increase in the incidence of hemangiosarcomas in the liver in high dose male mice. The significance of the increased incidences of neoplasms in dosed male mice was further

TABLE 31. INCIDENCES OF SPLEEN AND ADRENAL GLAND NEOPLASMS IN RATS INDUCED BY ANILINE HYDROCHLORIDE AND STRUCTURALLY RELATED CHEMICALS STUDIED BY THE NCI/NTP

Structure/Chemical CAS Number (Reference)	Concentration in Feed (ppm)	Spleen				Adrenal Gland	
		Sarcomas (a)		Hemangiosarcomas or Angiosarcomas		Pheochromocytomas	
		Male	Female	Male	Female	Male	Female
 Aniline hydrochloride CAS No. 142-04-1 (NCI TR 130, 1978a)	0	0/25	0/23	0/25	0/23	2/24	1/24
	3,000	7/50	0/50	19/50	1/50	6/50	0/50
	6,000	9/46	3/50	20/46	3/50	12/44	5/48
Azobenzene CAS No. 103-33-3 (NCI TR 154, 1979a) 	0	0/20	0/20	0/20	0/20	1/20	0/20
	200	4/49	3/50	1/49	1/50	1/49	0/50
	400	10/49	12/50	4/49	4/50	1/50	1/50
 *p*-Chloroaniline CAS No. 106-47-8 (NCI TR 189, 1979c)	0	0/20	(b) --	0/20	0/20	3/19	--
	250	0/49	--	0/49	0/48	4/46	--
	500	3/49	--	1/49	1/50	3/49	--
Current studies on *p*-chloroaniline hydrochloride (c)	0 mg/kg	0/49	0/50	0/50	--	13/49	2/50
	2 mg/kg	1/50	0/50	0/50	--	14/48	3/50
	6 mg/kg	3/50	1/50	0/50	--	15/48	1/50
	18 mg/kg	36/50	1/50	4/50	--	26/49	6/50
D & C Red No. 9 CAS No. 5160-02-1 (NTP TR 225, 1982a) 	0	0/50	--	--	--	17/48	3/48
	1,000	0/50	--	--	--	14/50	4/49
	3,000	26/48	--	--	--	14/48	5/50
Dapsone CAS No. 80-08-0 (NCI TR 20, 1977a) 	0	0/14	--	--	--	--	--
	600	0/34	--	--	--	--	--
	1,200	6/32	--	--	--	--	--
 *o*-Toluidine hydrochloride CAS No. 142-04-1 (NCI TR 153, 1979b)	0	0/20	0/20	0/20	0/20	0/20	0/20
	3,000	1/49	2/49	7/49	7/49	3/50	4/49
	6,000	4/42	4/49	0/42	9/49	2/49	2/49

(a) Includes fibrosarcomas, osteosarcomas, and sarcomas, NOS
(b) -- denotes no tumors reported
(c) Gavage studies in water

supported by the apparent reduction in the latency period for liver neoplasms. The first day of observation of these neoplasms in vehicle controls was 728; in dosed groups, it ranged from day 432 to day 490. Table 32 gives the incidence of hepatocellular neoplasms in mice dosed with those aniline compounds shown to also cause splenic neoplasms in male rats. Administration of all the aniline compounds listed seemed to result in some increase in the incidences of hepatocellular neoplasms in male or female mice.

In the current studies, *p*-chloroaniline hydrochloride was carcinogenic for rats and mice, but the sites of compound-related neoplasia were different. The species differences between rats and mice with regard to splenic and liver neoplasms could be due to differences in metabolism and disposition of *p*-chloroaniline. Perry et al. (1981a) studied the disposition of ^{14}C-labeled *p*-chloroaniline or *p*-chloroaniline hydrochloride in F344 rats, mongrel dogs, and A/J and Swiss Webster mice. They showed that the initial decay constants for *p*-chloroaniline clearance from whole blood in both strains of mice were 10 times greater than those in dogs and rats. The *p*-chloroaniline clearance in mice was too rapid to permit calculation of kinetic parameters.

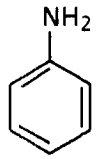
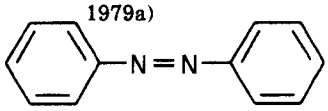
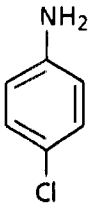
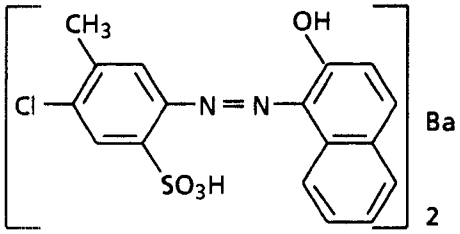
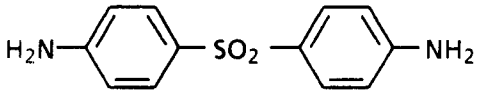
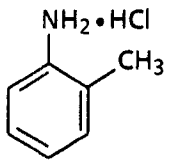
The differences in the metabolism and disposition of aniline have also been suggested as the reason for differences in the carcinogenicity of aniline in rats and mice. The larger concentrations of the putative reactive metabolite *N*-phenylhydroxylamine in rats were considered to be responsible for the production of splenic tumors in rats (McCarthy et al., 1985). If excessive methemoglobin formation in dosed animals and the subsequent progression to splenic sarcomas constitute one of the mechanisms of action of aniline compounds, then methemoglobin reductase activity or diaphorase activity, which is two times greater in mice than in rats, may be another reason for a species difference.

Decreases were seen in the incidences of certain neoplasms in *p*-chloroaniline hydrochloride-dosed animals and were considered related to chemical administration. The incidences of mononuclear cell leukemia in rats and malignant lymphomas in mice were decreased in dosed animals of each sex. Such decreases were not seen in animals exposed to other aniline compounds listed in Table 31.

Possible Mechanisms of Splenic Toxicity and Carcinogenicity

The unusual and rare tumors of the spleen induced in F344 rats by a number of structurally related aniline compounds led some workers to study the pathogenesis of splenic lesions and to perform disposition studies of ^{14}C-labeled aniline to explain the possible mechanism(s) of action of these chemicals. Goodman et al. (1984) studied splenic lesions from male rats in the NCI/NTP studies listed in Table 31 and proposed that fibrosis of the splenic parenchyma was a potential preneoplastic lesion. They postulated that methemoglobin bound with aniline compounds or their reactive metabolites is broken down in the red pulp of the spleen and reactive metabolites are released which bind to splenic mesenchymal tissues, resulting in fibrosis that progresses to formation of splenic tumors. Weinberger et al. (1985) proposed a similar hypothesis with their detailed analysis of splenic tumors in NCI/NTP studies on D & C Red No. 9 (NTP, 1982a) and aniline hydrochloride (NCI, 1978a). Bus and Popp (1987) reviewed splenic tumors caused by administration of the chemicals listed in Table 31, CIIT-sponsored aniline carcinogenesis studies in rats, and their own disposition studies on ^{14}C-labeled aniline in rats and mice. They proposed several possible mechanisms for splenic-directed toxicity of aniline compounds. The scheme proposed for these possible mechanisms is reproduced in Figure 13. According to this scheme, the occurrence of splenic tumors in rats may be the result of erythrocyte toxicity. The authors suggest that there is strong evidence for the nongenetic mechanism in the formation of splenic tumors. However, there is a possibility that a direct-acting genotoxic mechanism is involved in the induction of the neoplasms, as shown by McCarthy et al. (1985), who found that in rats and mice, [^{14}C]aniline binds to a greater extent to the kidney, small intestine, large intestine, and spleen than to other tissues. Protein and RNA were major macromolecular targets for [^{14}C]aniline binding; DNA binding occurred to a lesser extent. The possibility for

TABLE 32. INCIDENCES OF LIVER NEOPLASMS IN MICE INDUCED BY ANILINE HYDROCHLORIDE AND STRUCTURALLY RELATED CHEMICALS STUDIED BY THE NCI/NTP

Structure/Chemical CAS Number (Reference)	Concentration in Feed (ppm)	Hepatocellular Adenomas or Carcinomas (a) Male	Female
 Aniline hydrochloride CAS No. 142-04-1 (NCI TR 130, 1978a)	0	12/39	1/46
	6,000	9/49	5/48
	12,000	7/49	5/48
Azobenzene CAS No. 103-33-3 (NCI TR 154, 1979a) 	0	9/20	
	200	18/49	
	400	2/48	
	0		0/20
	208		2/47
	545		0/36
 *p*-Chloroaniline CAS No. 106-47-8 (NCI TR 189, 1979c)	0	3/19	0/18
	2,500	7/49	1/49
	5,000	2/49	6/41
Current studies on *p*-chloroaniline hydrochloride (c)	0 mg/kg	11/50	6/50
	3 mg/kg	21/49	9/50
	10 mg/kg	20/50	8/50
	30 mg/kg	21/50	11/50
D & C Red No. 9 CAS No. 5160-02-1 (NTP TR 225, 1982a) 	0	8/50	5/50
	1,000	13/50	3/50
	2,000	15/50	6/49
Dapsone CAS No. 80-08-0 (NCI TR 20, 1977a) 	0	0/11	(b) --
	500	6/33	--
	1,000	2/31	--
 *o*-Toluidine hydrochloride CAS No. 636-21-5 (NCI TR 153, 1979b)	0	6/19	0/20
	1,000	19/50	4/49
	3,000	14/50	13/50

(a) Includes neoplastic nodules, hepatocellular adenomas, and hepatocellular carcinomas
(b) -- denotes no tumors reported
(c) Gavage studies in water

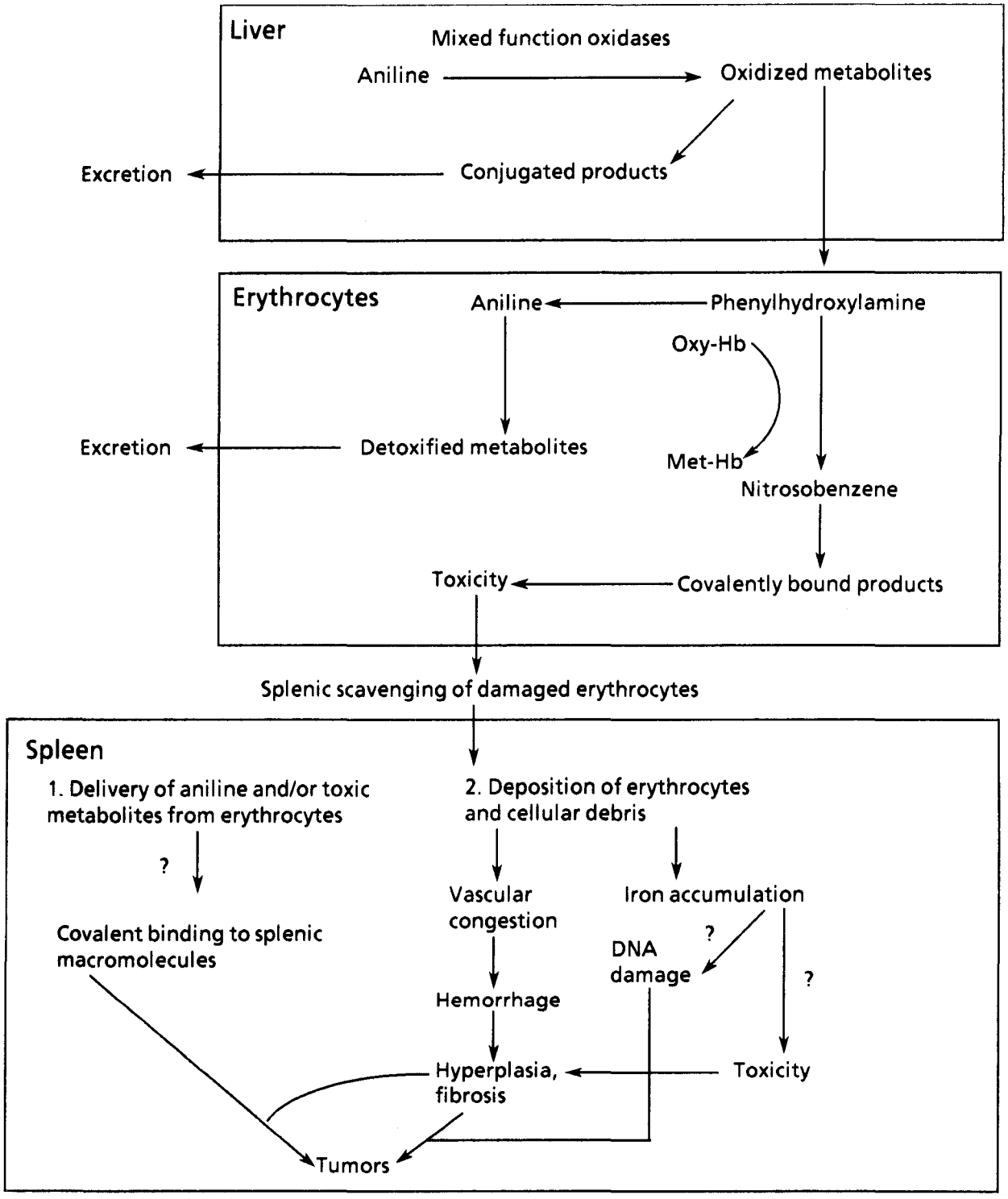


FIGURE 13. PROPOSED MECHANISTIC SCHEME FOR THE SPLEEN-DIRECTED TOXICITY OF ANILINE AND STRUCTURALLY RELATED COMPOUNDS

(Taken from Bus and Popp, 1987)

involvement of genotoxic mechanisms is further supported by Parodi et al. (1982a,b), who showed that aniline induces DNA damage in vivo in the liver and kidney of rats. Also, aniline was clearly positive in induction of sister chromatid exchanges (SCEs) in vivo in male Swiss mice. The damage to DNA seen in the liver, kidney, and bone marrow was absent in male Swiss mice.

The patterns of *p*-chloroaniline hydrochloride-induced splenic toxicity and carcinogenicity and results of disposition studies suggest that the mechanism(s) of *p*-chloroaniline hydrochloride toxicity and carcinogenicity could likely follow the scheme proposed by Bus and Popp (1987). However, whether the mechanism of carcinogenesis is mediated through genotoxic or nongenotoxic events is unresolved. *p*-Chloroaniline is clearly genotoxic in vitro. In the Salmonella assay and the test for chromosomal aberrations in Chinese hamster ovary cells, *p*-chloroaniline was mutagenic only in the presence of S9 metabolizing enzymes. *p*-Chloroaniline also increased the fraction of cultured mouse lymphoma cells exhibiting trifluorothymidine resistance and the frequency of SCEs in Chinese hamster ovary cells, both in the presence and absence of S9. Thus, the in vitro genotoxic activity of *p*-chloroaniline appears to be dependent on metabolism for its full expression. Experimental evidence indicates that *p*-chloroaniline undergoes oxidative transformations as a reactive amine, with the probable formation of electrophilic intermediates that could be stablized by the chlorine. For example, *p*-chloro-*N*-hydroxyaniline (Von Jagow et al., 1966), which may be formed through a nitronium ion intermediate in the presence of oxidative enzymes, and *p*-aminophenol (Ichikawa et al., 1969), which may be formed via an arene oxide intermediate possibly in the absence of metabolizing enzymes, have been reported as metabolites of *p*-chloroaniline in the rabbit. Both of these intermediates are potential electrophiles and could covalently bind macromolecules.

Audit

The experimental and tabulated data for the NTP Technical Report on *p*-chloroaniline hydrochloride were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix I, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions

Under the conditions of these 2-year water gavage studies, there was *clear evidence of carcinogenic activity** of *p*-chloroaniline hydrochloride for male F344/N rats, as indicated by increased incidences of uncommon sarcomas of the spleen. Pheochromocytomas of the adrenal gland may also have been associated with chemical administration. There was *equivocal evidence of carcinogenic activity* of *p*-chloroaniline hydrochloride for female F344/N rats, as indicated by the presence of uncommon sarcomas of the spleen in one mid and one high dose animal and the increased incidence of pheochromocytomas of the adrenal gland. There was *some evidence of carcinogenic activity* of *p*-chloroaniline hydrochloride for male B6C3F_1 mice, as indicated by increased incidences of hepatocellular neoplasms and of hemangiosarcomas of the liver or spleen. There was *no evidence of carcinogenic activity* of *p*-chloroaniline hydrochloride for female B6C3F_1 mice administered 3, 10, or 30 mg/kg by gavage for 2 years.

The incidences of mononuclear cell leukemia in male and female rats and of malignant lymphomas in male and female mice were decreased by administration of *p*-chloroaniline hydrochloride. Compound-related splenic fibrosis was present in male and female rats.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

V. REFERENCES

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1. Amacher, D.E.; Turner, G.N. (1982) Mutagenic evaluation of carcinogens and non-carcinogens in the L5178Y/TK assay utilizing postmitochondrial fractions (S9) from normal rat liver. Mutat. Res. 97:49-65.

2. American Conference of Governmental Industrial Hygienists (ACGIH) (1988-89) Aniline and its homologs. Threshold Limit Values and Biological Exposure Indices for 1988-1989, p. 11.

3. Ames, B.N.; McCann, J.; Yamasaki, E. (1975) Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res. 31:347-364.

4. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

5. Ashby, J.; Lefevre, P.A; Callander, R.D. (1983) The possible role of azoreduction in the bacterial mutagenicity of 4-dimethylaminoazobenzene (DAB) and 2 of its analogs (6BT and 5I). Mutat. Res. 116:271-279.

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

7. Beutler, E. (1972) Methemoglobinemia and sulfhemoglobinemia. Williams, W.J., Ed.: Hematology. City: McGraw-Hill, pp. 409-412.

8 Beutler, E. (1985) Chemical toxicity of the erythrocyte. Irons, R.D., Ed.: Toxicology of the Blood and Bone Marrow. New York: Raven Press, p. 39.

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

10. Bus, J.S. (1983) Aniline and nitrobenzene: Erythrocyte and spleen toxicity. CIIT Activities 3:1,6.

11. Bus, J.S.; Popp, J.A. (1987) Perspectives on the mechanism of action of the splenic toxicity of aniline and structurally-related compounds. Food Chem. Toxicol. 25:619-626.

12. Chung, K.-T.; Fulk, G.E.; Andrews, A.W. (1981) Mutagenicity testing of some commonly used dyes. Appl. Environ. Microbiol. 42:641-648.

13. Ciarlone, A.E.; Gangarosa, L.P.; Fong, B.C. (1976) Detection of *p*-chloroaniline in chlorhexidine solutions using thin-layer chromatography. J. Dent. Res. 55:918-.

14. Clive, D.; Johnson, K.O.; Spector, J.F.S.; Batson, A.G.; Brown, M.M.M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

15. The Colour Index (1956) 2nd ed. Bradford, England: The Society of Dyers and Colourists.

16. Corbett, M.D.; Chipko, B.R.; Batchelor, A.O. (1980) The action of chloride peroxidase on 4-chloroaniline. *N*-Oxidation and ring halogenation. Biochem. J. 187:893-903.

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

18. De Flora, S. (1981) Study of 106 organic and inorganic compounds in the *Salmonella*/microsome test. Carcinogenesis 2:283-298.

19. Degawa, M.; Shoji, Y.; Masuko, K.; Hashimoto, Y. (1979) Mutagenicity of metabolites of carcinogenic aminoazo dyes. Cancer Lett. 8:71-76.

20. Demers, F.X.; Yates, R.L. (1977) Antimicrobials: Identification of 3,4,4'-trichlorocarbanilide and 4,4'-dichloro-3-(trifluoromethyl)carbanilide in deodorant bars. J. Soc. Cosmet. Chem. 28:659-666.

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

22. Dinse, G.E.; Lagakos, S.W. (1983) Regression analysis of tumour prevalence data. J. R. Stat. Soc. C32:236-248.

23. Dunkel, V.C.; Zeiger, E.; Brusick, D.; McCoy, E.; McGregor, D.; Mortelmans, K.; Rosenkranz, H.S.; Simmon, V.F. (1985) Reproducibility of microbial mutagenicity assays. II. Testing of carcinogens and noncarcinogens in *Salmonella typhimurium* and *Escherichia coli*. Environ. Mutagen. 7(Suppl. 5):1-248.

24. Dunnett, C.W. (1980) Pairwise multiple comparisons in the unequal variance case. J. Am. Stat. Assoc. 75:796-800.

25. Ernst, W. (1969) Metabolism of substituted dinitrophenols and ureas in mammals and methods for the isolation and identification of metabolites. J. S. Afr. Chem. Inst. 22:S79-S88.

26. Evelyn, K.A.; Malloy, H.T. (1938) Microdetermination of oxyhemoglobin, methemoglobin and sulfhemoglobin in a single sample of blood. J. Biol. Chem. 126:655.

27. Freitag, D.; Scheunert, I.; Klein, W.; Korte, F. (1984) Long-term fate of 4-chloroaniline-^{14}C in soil and plants under outdoor conditions. A contribution to terrestrial ecotoxicology of chemicals. J. Agric. Food Chem. 32:203-207.

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

29. Galloway, S.M.; Armstrong, M.J.; Reuben, C.; Colman, S.; Brown, B.; Cannon, C.; Bloom, A.D.; Nakamura, F.; Ahmed, M.; Duk, S.; Rimpo, J.; Margolin, B.H.; Resnick, M.A.; Anderson, B.; Zeiger, E. (1987) Chromosome aberration and sister chromatid exchange tests in vitro in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ. Molec. Mutagen. 10(Suppl. 10):1-175.

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

31. Gart, J.J.; Chu, K.C.; Tarone, R.E. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62:957-974.

32. Gibaldi, M.; Perrier, D. (1975) Pharmacokinetics. New York: M. Dekker.

33. Gilbert, P.; Saint-Ruf, G.; Poncelet, F.; Mercier, M. (1980) Genetic effects of chlorinated anilines and azobenzenes on *Salmonella typhimurium*. Arch. Environ. Contam. Toxicol. 9:533-541.

34. Golly, I.; Hlavica, P. (1983) The role of hemoglobin in the N-oxidation of 4-chloroaniline. Biochim. Biophys. Acta 760:69-76.

35. Golly, I.; Hlavica, P.; Wolf, J. (1984) The role of lipid peroxidation in the *N*-oxidation of 4-chloroaniline. Biochem. J. 224:415-421.

36. Goodman, D.G.; Ward, J.M.; Reichardt, W.D. (1984) Splenic fibrosis and sarcomas in F344 rats fed diets containing aniline hydrochloride, *p*-chloroaniline, azobenzene, *o*-toluidine hydrochloride, 4,4'-sulfonyldianiline, or D & C Red No. 9. J. Natl. Cancer Inst. 73:265-273.

37. Gosselin, R.E.; Smith, R.P.; Hodge, H.C.; Braddock, J.E. (1984) Clinical Toxicology of Commercial Products, 5th ed. Baltimore: Williams & Wilkins, p. II-208.

38. Gralla, E.J.; Bus, J.S.; Reno, F.; Cushman, J.R.; Ulland, B.N. (1979) Studies of aniline HCl in rats. Toxicol. Appl. Pharmacol. 48:A97.

39. Hargesheimer, E.E.; Coutts, R.T.; Pasutto, F.M. (1981) Gas-liquid chromatographic determination of aniline metabolites of substituted urea and carbamate herbicides in aqueous solution. J. Assoc. Off. Anal. Chem. 64:833-840.

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

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

V. REFERENCES

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

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

44. Hayward, N.K.; Lavin, M.F.; Craswell, P.W. (1982) Inhibition of DNA synthesis and alteration to DNA structure by the phenacetin analog p-aminophenol. Biochem. Pharmacol. 31:1425-1429.

45. Hlavica, P. (1984) On the function of cytochrome b_5 in the cytochrome *P*-450-dependent oxygenase system. Arch. Biochem. Biophys. 228:600-608.

46. Ichikawa, Y.; Yamano, T.; Fujishima, H. (1969) Relationship between the interconversion of cytochrome P-450 and P-420 and its activities in hydroxylations and demethylations by P-450 oxidase systems. Biochim. Biophys. Acta 171:32-36.

47. International Agency for Research on Cancer (IARC) (1974) IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents, Vol. 4. Lyon, France: World Health Organization, IARC, pp. 65-77.

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

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

50. Kaufman, D.D.; Plimmer, J.R.; Klingebiel, U.I. (1973) Microbial oxidation of 4-chloroaniline. J. Agr. Food Chem. 21:127-132.

51. Kiese, M. (1966) The biochemical production of ferrihemoglobin-forming derivatives from aromatic amines, and mechanisms of ferrihemoglobin formation. Pharmacol. Rev. 18:1091-1161.

52. Lamb, J.C.; Huff, J.E.; Haseman, J.K.; Murthy, A.S.K.; Lilja, H. (1986) Carcinogenesis studies of 4,4′-methylenedianiline dihydrochloride given in drinking water to F344/N rats and B6C3F_1 mice. J. Toxicol. Environ. Health 18:325-337.

53. Linch, A.L. (1974) Biological monitoring for industrial exposure to cyanogenic aromatic nitro and amino compounds. Am. Ind. Hyg. Assoc. J. 7:426-432.

54. Liu, Z.; Franklin, M.R. (1984) Cytochrome P-450 metabolic--Intermediate complex formation from p-aminobenzoic acid esters and other arylamines. Eur. J. Drug Metab. Pharmacokinet. 9:155-159.

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

56. Matthews, H.B.; Anderson, M.W. (1975) The distribution and excretion of 2,4,5,2′,5′-pentachlorobiphenyl in the rat. Drug Metab. Dispos. 3:211.

57. McCarthy, D.J.; Waud, W.R.; Struck, R.F.; Hill, D.L. (1985) Disposition and metabolism of aniline in Fischer 344 rats and C57BL/6 × C3H F_1 mice. Cancer Res. 45:174-180.

58. McConnell, E.E. (1983a) Pathology requirements for rodent two-year studies. I. A review of current procedures. Toxicol. Pathol. 11:60-64.

59. McConnell, E.E. (1983b) Pathology requirements for rodent two-year studies. II. Alternative approaches. Toxicol. Pathol. 11:65-76.

60. McConnell, E.E.; Solleveld, H.A.; Swenberg, J.A.; Boorman, G.A. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76:283-289.

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

62. McLean, S.; Starmer, G.A.; Thomas, J. (1969) Methaemoglobin formation by aromatic amines. J. Pharm. Pharmacol. 21:441-450.

63. McQueen, C.A.; Maslansky, C.J.; Crescenzi, S.B.; Williams, G.M. (1981) Genotoxicity of 4,4'-methylenebis-2-chloroaniline in rat, mouse, and hamster hepatocytes. Toxicol. Appl. Pharmacol. 58:231-235.

64. The Merck Index (1983) 10th ed. Rahway, NJ: Merck & Co., Inc., p. 297.

65. Metzler, C.M. (1969) A User's Manual for NON-LIN. Technical Report No. 7297/69/7292/005. Kalamazoo, MI: Upjohn Co.

66. Miller, M.J.; Carter, L.E.; Sipes, I.G. (1982) Pharmacokinetics of acrylamide in Fischer-344 rats. Toxicol. Appl. Pharmacol. 63:36-44.

67. Mitchell, A.D.; Rudd, C.J.; Caspary, W.J. (1989) Evaluation of the L5178Y mouse lymphoma cell mutagenesis system: Results of assays of 63 coded chemicals tested at SRI International. Environ. Mutagen. (in press).

68. Mitra, A.B.; Manna, G.K. (1971) Effect of some phenolic compounds on chromosomes of bone marrow cells of mice. Indian J. Med. Res. 59:1442-1447.

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

70. Myhr, B.C.; Caspary, W.J. (1989) Evaluation of the L5178Y mouse lymphoma cell mutagenesis system: Results of assays of 63 coded chemicals tested at Litton Bionetics, Inc. Environ. Mutagen. (in press).

71. Myhr, B.C.; Bowers, L.; Caspary, W.J. (1985) Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. Prog. Mutat. Res. 5:555-568.

72. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Technical Report No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 65 p.

73. National Cancer Institute (NCI) (1977a) Bioassay of Dapsone for Possible Carcinogenicity. NCI Technical Report No. 20. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 97 p.

74. National Cancer Institute (NCI) (1977b) Bioassay of Chloramben for Possible Carcinogenicity. NCI Technical Report No. 25. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 90 p.

75. National Cancer Institute (NCI) (1978a) Bioassay of Aniline Hydrochloride for Possible Carcinogenicity. NCI Technical Report No. 130. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 95 p.

76. National Cancer Institute (NCI) (1978b) Bioassay of 2-Chloro-p-phenylenediamine Sulfate for Possible Carcinogenicity. NCI Technical Report No. 113. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 87 p.

77. National Cancer Institute (NCI) (1978c) Bioassay of 3-Chloro-p-toluidine for Possible Carcinogenicity. NCI Technical Report No. 145. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 81 p.

78. National Cancer Institute (NCI) (1978d) Bioassay of 4-Chloro-o-phenylenediamine for Possible Carcinogenicity. NCI Technical Report No. 63. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 52 p.

79. National Cancer Institute (NCI) (1978e) Bioassay of 4-Chloro-m-phenylenediamine for Possible Carcinogenicity. NCI Technical Report No. 85. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 46 p.

80. National Cancer Institute (NCI) (1979a) Bioassay of Azobenzene for Possible Carcinogenicity. NCI Technical Report No. 154. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 112 p.

81. National Cancer Institute (NCI) (1979b) Bioassay of o-Toluidine Hydrochloride for Possible Carcinogenicity. NCI Technical Report No. 153. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 131 p.

82. National Cancer Institute (NCI) (1979c) Bioassay of p-Chloroaniline for Possible Carcinogenicity. NCI Technical Report No. 189. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 53 p.

83. National Cancer Institute (NCI) (1979d) Bioassay of 5-Chloro-o-toluidine for Possible Carcinogenicity. NCI Technical Report No. 187. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 44 p.

84. National Cancer Institute (NCI) (1979e) Bioassay of 4-Chloro-o-toluidine Hydrochloride for Possible Carcinogenicity. NCI Technical Report No. 165. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 104 p.

85. National Institutes of Health (NIH) (1978) Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

86. National Toxicology Program (NTP) (1982a) Carcinogenesis Bioassay of D & C Red No. 9 in F344 Rats and B6C3F$_1$ Mice. NTP Technical Report No. 225. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. 168 p.

87. National Toxicology Program (NTP) (1982b) Carcinogenesis Bioassay of 2,6-Dichloro-p-phenylenediamine in F344 Rats and B6C3F$_1$ Mice. NTP Technical Report No. 219. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. 121 p.

88. National Toxicology Program (NTP) (1988) Toxicology and Carcinogenesis Studies of Monuron in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 266. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 166 p.

89. Oberly, T.J.; Bewsey, B.J.; Probst, G.S. (1984) An evaluation of the L5178Y TK$^{+/-}$ mouse lymphoma forward mutation assay using 42 chemicals. Mutat. Res. 125:291-306.

90. Pai, V.; Bloomfield, S.F.; Jones, J.; Gorrod, J.W. (1978) Mutagenicity testing of nitrogenous compounds and their N-oxidized products using *trp*$^+$ reversion in *E. coli*. Biol. Oxid. Nitrogen, 2nd Int. Symp. Proc., 1977, pp. 375-382.

91. Parodi, S.; Pala, M.; Russo, P.; Zunino, A.; Balbi, C.; Albini, A.; Valerio, F.; Cimberle, M.R.; Santi, L. (1982a) DNA damage in liver, kidney, bone marrow, and spleen of rats and mice treated with commercial and purified aniline as determined by alkaline elution assay and sister chromatid exchange induction. Cancer Res. 42:2277-2283.

92. Parodi, S.; Taningher, M.; Boero, P.; Santi, L. (1982b) Quantitative correlations amongst alkaline DNA fragmentation, DNA covalent binding, mutagenicity in the Ames test, and carcinogenicity, for 21 compounds. Mutat. Res. 93:1-24.

93. Parodi, S.; Zunino, A.; Ottagio, L.; De Ferrari, M.; Santi, L. (1983) Lack of correlation between the capability of inducing sister-chromatid exchanges *in vivo* and carcinogenic potency, for 16 aromatic amines and azo derivatives. Mutat. Res. 108:225-238.

94. Perry, D.F.; Carter, D.E.; Sipes, I.G. (1981a) Distribution and disposition of p-chloroaniline in Fischer-344 rats. Presented at Society of Toxicology 20th Annual Meeting, San Diego, CA.

95. Perry, D.F.; Carter, D.E.; Sipes, I.G. (1981b) Distribution and excretion of ^{14}C-parachloroaniline in the rat. Toxicologist 1:14.

96. Poirier, L.A.; Weisburger, J.H. (1972) *N*-Hydroxylation and carcinogenesis. Fifth International Congress on Pharmacology. Symposium: Mechanisms of Toxicity by Therapeutic and Environmental Agents, pp. 208-209.

97. Prasad, I. (1970) Mutagenic effects of the herbicide 3',4'-dichloropropionanilide and its degradation products. Can. J. Microbiol. 16: 369-372.

98. Probst, G.S.; McMahon, R.E.; Hill, L.E.; Thompson, C.Z.; Epp, J.K.; Neal, S.B. (1981) Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: Comparison with bacterial mutagenicity using 218 compounds. Environ. Mutagen. 3:11-32.

99. Rosenkranz, H.S.; Leifer, Z. (1980) Determining the DNA-modifying activity of chemicals using DNA polymerase-deficient *Escherichia coli*. Chemical Mutagens: Principles and Methods for Their Detection, 6th ed. New York: Plenum Press, pp. 109-147.

100. Rosenkranz, H.S.; Poirier, L.A. (1979) Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J. Natl. Cancer Inst. 67:873-892.

101. Rubino, G.F.; Scansetti, G.; Piolatto, G.; Pira, E. (1982) The carcinogenic effect of aromatic amines: An epidemiological study on the role of *o*-toluidine and 4,4'-methylene bis (2-methylaniline) in inducing bladder cancer in man. Environ. Res. 27:241-254.

102. Sadtler Standard Spectra. IR No. 1317; NMR No. 10490M. Philadelphia: Sadtler Research Laboratories.

103. Sakamoto, Y.; Watanabe, S. (1986) On the relationship between the chemical structure and the carcinogenicity of polycyclic and chlorinated monocyclic aromatic compounds as studied by means of ^{13}C NMR. Bull. Chem. Soc. Jpn. 59:3033-3038.

104. Schauerte, W.; Lay, J.P.; Klein, W.; Korte, F. (1982) Long-term fate of organochlorine xenobiotics in aquatic ecosystems. Distribution, residual behavior, and metabolism of hexachlorobenzene, pentachloronitrobenzene, and 4-chloroaniline in small experimental ponds. Ecotoxicol. Environ. Safety 6:560-569.

105. Selkirk, J.K. (1980) Chemical carcinogenesis: A brief overview of the mechanism of action of polycyclic hydrocarbons, aromatic amines, nitrosamines, and aflatoxins. Carcinogenesis 5:1-31.

106. Seuferer, S.L.; Braymer, H.D.; Dunn, J.J. (1979) Metabolism of diflubenzuron by soil microorganisms and mutagenicity of the metabolites. Pestic. Biochem. Physiol. 10:174-180.

107. Shapiro, S.L.; Ross, I.M.; Freedman, L. (1959) α-Hydroxyamides and related compounds. J. Am. Chem. Soc. 81:6322.

108. Simmon, V.F. (1979) *In vitro* mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium*. J. Natl. Cancer Inst. 62:893-899.

109. Smith, M.R.; Gorrod, J.W. (1978) The microsomal N-oxidation of some primary aromatic amines. Gorrod, J.W., Ed.: Biological Oxidation of Nitrogen. Elsevier/North-Holland Biomedical Press, pp. 65-70.

110. Smith, R.P. (1986) Toxic responses of the blood. Klaassen, C.D.; Amdur, M. O.; Doull, J., Eds.: *Casarett and Doull's* Toxicology. The Basic Science of Poisons, 3rd ed. New York: Macmillan Publishing Co., pp. 223.

111. Smyth, H.F., Jr.; Carpenter, C.P.; Weil, C.S.; Pozzani, U.C.; Striegel, J.A. (1962) Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

112. Suss, A.; Fuchsbichler, G.; Eben, C. (1978) Abbau von Anilin, 4-Chloranilin und 3,4-Dichloranilin in verschiedenen Boden. Z. Pflanzenernaehr. Bodenkd. 141:57-66.

113. Takehisa, S.; Kanaya, N. (1982) SCE induction in human lymphocytes by combined treatment with aniline and norharman. Mutat. Res. 101:165-172.

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

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

116. Tohda, H.; Tada, M.; Sugawara, R.; Oikawa, A. (1983) Actions of amino-beta-carbolines on induction of sister-chromatid exchanges. Mutat. Res. 116:137-147.

117. Topham, J.C. (1980) The detection of carcinogen-induced sperm head abnormalities in mice. Mutat. Res. 69:149-155.

118. Uehleke, H.; Hellmer, K.H.. (1971) Competitive inhibition of the microsomal N-hydroxylation of 4-chloroaniline by metyrapone and cyclohexane. N. S. Arch. Pharmakol. 268:242-246.

119. U.S. Environmental Protection Agency (USEPA) (1978) 4-Chloro-2-methylaniline. TSCA Inventory.

120. U.S. Environmental Protection Agency (USEPA) (1986) 4-Chloro-2-methylaniline. TSCA Inventory.

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

122. Von Jagow, R.; Kiese, M.; Renner, G. (1966) Urinary excretion of N-hydroxy derivatives of some aromatic amines by rabbits, guinea pigs, and dogs. Biochem. Pharmacol. 15:1899-1910.

123. Weinberger, M.A.; Albert, R.H.; Montgomery, S.B. (1985) Splenotoxicity associated with splenic sarcomas in rats fed high doses of D & C Red No. 9 or aniline hydrochloride. J. Natl. Cancer Inst. 75:681-690.

124. Weisburger, E.K. (1983) Species differences in response to aromatic amines. USEPA Research Division. PB83-NO220137. Langenbach, R.; Nesnow, S.; Rice, J., Eds.: Organ and Species Specificity in Chemical Carcinogenesis, pp. 23-47.

125. Weisburger, J.H.; Weisburger, E.K. (1973) Biochemical formation and pharmacological, toxicological, and pathological properties of hydroxylamines and hydroxamic acids. Pharmacol. Rev. 25:1-66.

126. Wild, D.; Eckhardt, K.; Gocke, E.; King, M.T. (1980) Comparative results of short-term *in vitro* and *in vivo* mutagenicity tests obtained with selected environmental chemicals. Short-Term Test Syst. Detect. Carcinog. Proc. Symp., pp. 170-178.

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

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

129. Williams, G.M. (1981) Mammalian culture systems for the study of genetic effects of N-substituted aryl compounds. Natl. Cancer Inst. Monogr. 58:237-242.

130. Williams, G.M.; Laspia, M.F.; Dunkel, V.C. (1982) Reliability of the hepatocyte primary culture/DNA repair test in testing of coded carcinogens and noncarcinogens. Mutat. Res. 97:359-370.

131. Wilmer, J.L.; Kligerman, A.D.; Erexson, G.L. (1981) Sister chromatid exchange induction and cell cycle inhibition by aniline and its metabolites in human fibroblasts. Environ. Mutagen. 3:627-638.

132. Zeiger, E.; Anderson, B.; Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W. (1987) Salmonella mutagenicity tests. III. Results from the testing of 255 chemicals. Environ. Mutagen. 9(Suppl. 9):1-110.

133. Zeiger, E.; Anderson, B.; Haworth, S.; Lawlor, T.; Mortelmans, K. (1988) *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. Environ. Molec. Mutagen. 11(Suppl. 12):1-158.

134. Zimmer, D.; Mazurek, J.; Petzold, G.; Bhuyan, B.K. (1980) Bacterial mutagenicity and mammalian cell DNA damage by several substituted anilines. Mutat. Res. 77:317-326.

APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	49	50	50	50
ALIMENTARY SYSTEM				
Intestine large, cecum	(46)	*(50)	*(50)	(44)
Colon, rectum, osteosarcoma, metastatic, spleen				1 (2%)
Intestine large, rectum	(47)	*(50)	*(50)	(44)
Mesothelioma malignant	1 (2%)			
Intestine small, duodenum	(48)	*(50)	*(50)	(46)
Fibrosarcoma, metastatic, spleen				2 (4%)
Osteosarcoma, metastatic, spleen				3 (7%)
Ileum, jejunum, osteosarcoma, metastatic, spleen				1 (2%)
Intestine small, jejunum	(46)	*(50)	*(50)	(41)
Adenocarcinoma		1 (2%)		
Osteosarcoma, metastatic, spleen				1 (2%)
Polyp adenomatous			1 (2%)	
Liver	(49)	(50)	(49)	(49)
Fibrosarcoma, metastatic, spleen				4 (8%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)	
Hepatocellular carcinoma, multiple			1 (2%)	
Leukemia mononuclear	21 (43%)	3 (6%)	2 (4%)	3 (6%)
Mesothelioma malignant		1 (2%)		
Neoplastic nodule		5 (10%)	3 (6%)	
Osteosarcoma, metastatic, spleen				8 (16%)
Mesentery	*(49)	*(50)	*(50)	*(50)
Fibrosarcoma, metastatic, spleen			1 (2%)	9 (18%)
Leukemia mononuclear	8 (16%)			2 (4%)
Mesothelioma malignant	1 (2%)	2 (4%)		2 (4%)
Osteosarcoma, metastatic, spleen				11 (22%)
Pheochromocytoma malignant, metastatic, adrenal gland			1 (2%)	
Sarcoma		1 (2%)		
Pancreas	(48)	*(50)	*(50)	(47)
Fibrosarcoma, metastatic, spleen			1 (2%)	6 (13%)
Leukemia mononuclear	4 (8%)	1 (2%)		
Mesothelioma malignant	1 (2%)	2 (4%)		1 (2%)
Osteosarcoma, metastatic, spleen				10 (21%)
Acinus, adenoma	1 (2%)			
Salivary glands	(49)	*(50)	*(50)	(49)
Leukemia mononuclear	1 (2%)			
Stomach, forestomach	(47)	*(50)	*(50)	(46)
Leukemia mononuclear	1 (2%)			
Osteosarcoma, metastatic, spleen				1 (2%)
Glandular, osteosarcoma, metastatic, spleen				1 (2%)
Stomach, glandular	(48)	*(50)	*(50)	(45)
Fibrosarcoma, metastatic, spleen				1 (2%)
Leukemia mononuclear	1 (2%)			
Osteosarcoma, metastatic, spleen				1 (2%)
Tongue	*(49)	*(50)	*(50)	*(50)
Papilloma squamous	2 (4%)	1 (2%)		1 (2%)
Tooth	*(49)	*(50)	*(50)	*(50)
Gingiva, squamous cell carcinoma				1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
CARDIOVASCULAR SYSTEM				
Blood vessel	*(49)	*(50)	*(50)	*(50)
Pulmonary artery, fibrosarcoma, metastatic, spleen				1 (2%)
Heart	(49)	*(50)	*(50)	(50)
Leukemia mononuclear	3 (6%)		1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(49)	(49)	(49)	(49)
Adenoma	1 (2%)			
Leukemia mononuclear	14 (29%)	1 (2%)	1 (2%)	1 (2%)
Capsule, fibrosarcoma, metastatic, spleen				1 (2%)
Capsule, osteosarcoma, metastatic, spleen				1 (2%)
Medulla, fibrosarcoma, metastatic, spleen				1 (2%)
Adrenal gland, medulla	(49)	(48)	(48)	(48)
Leukemia mononuclear	14 (29%)	1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma malignant	1 (2%)		1 (2%)	1 (2%)
Pheochromocytoma benign	10 (20%)	12 (25%)	9 (19%)	13 (27%)
Bilateral, pheochromocytoma benign	3 (6%)	2 (4%)	5 (10%)	12 (25%)
Islets, pancreatic	(48)	*(50)	*(50)	(46)
Adenoma	3 (6%)			1 (2%)
Carcinoma				1 (2%)
Fibrosarcoma, metastatic, spleen				4 (9%)
Osteosarcoma, metastatic, spleen				7 (15%)
Parathyroid gland	(48)	*(50)	*(50)	(45)
Adenoma		1 (2%)		1 (2%)
Leukemia mononuclear	1 (2%)			
Pituitary gland	(47)	*(50)	*(50)	(46)
Leukemia mononuclear	1 (2%)			
Pars distalis, adenoma	19 (40%)	13 (26%)	11 (22%)	10 (22%)
Pars distalis, adenoma, multiple	1 (2%)			1 (2%)
Pars distalis, carcinoma			1 (2%)	
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(48)	*(50)	*(50)	(45)
Leukemia mononuclear	2 (4%)			
C-cell, adenoma	8 (17%)	2 (4%)		9 (20%)
C-cell, adenoma, multiple	1 (2%)			
C-cell, carcinoma	1 (2%)	1 (2%)		1 (2%)
Follicular cell, adenocarcinoma		1 (2%)		
Follicular cell, adenoma		1 (2%)		
GENERAL BODY SYSTEM				
Tissue, NOS	*(49)	*(50)	*(50)	*(50)
Osteosarcoma, metastatic, spleen				1 (2%)
GENITAL SYSTEM				
Epididymis	(49)	*(50)	*(50)	(50)
Fibrosarcoma, metastatic, spleen				2 (4%)
Leukemia mononuclear	1 (2%)			
Mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)	
Osteosarcoma, metastatic, spleen				3 (6%)
Sarcoma				1 (2%)
Bilateral, mesothelioma malignant		1 (2%)		1 (2%)
Bilateral, osteosarcoma, metastatic, spleen				1 (2%)
Penis	*(49)	*(50)	*(50)	*(50)
Leukemia mononuclear			1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
GENITAL SYSTEM (Continued)				
Preputial gland	(46)	*(50)	*(50)	(48)
Adenocarcinoma				1 (2%)
Adenoma	1 (2%)	7 (14%)	4 (8%)	2 (4%)
Leukemia mononuclear	1 (2%)			
Prostate	(49)	*(50)	*(50)	(48)
Fibrosarcoma, metastatic, spleen				1 (2%)
Leukemia mononuclear	1 (2%)			
Osteosarcoma, metastatic, spleen				3 (6%)
Seminal vesicle	*(49)	*(50)	*(50)	*(50)
Osteosarcoma, metastatic, spleen				2 (4%)
Testes	(49)	*(50)	*(50)	(50)
Mesothelioma malignant	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Osteosarcoma, metastatic, spleen				3 (6%)
Bilateral, mesothelioma malignant		1 (2%)		
Bilateral, interstitial cell, adenoma	25 (51%)	38 (76%)	33 (66%)	40 (80%)
Interstitial cell, adenoma	11 (22%)	6 (12%)	11 (22%)	6 (12%)
HEMATOPOIETIC SYSTEM				
Blood	*(49)	*(50)	*(50)	*(50)
Leukemia mononuclear	19 (39%)	3 (6%)	1 (2%)	3 (6%)
Bone marrow	(49)	(50)	(49)	(50)
Leukemia mononuclear			1 (2%)	
Osteosarcoma, metastatic, spleen				1 (2%)
Femoral, leukemia mononuclear	6 (12%)		1 (2%)	
Lymph node	(49)	*(50)	*(50)	(49)
Axillary, leukemia mononuclear	1 (2%)			
Deep cervical, leukemia mononuclear	1 (2%)			
Inguinal, leukemia mononuclear	4 (8%)			
Lumbar, leukemia mononuclear	1 (2%)			
Mediastinal, fibrosarcoma, metastatic, spleen				2 (4%)
Mediastinal, leukemia mononuclear	16 (33%)		1 (2%)	3 (6%)
Mediastinal, osteosarcoma, metastatic, spleen				6 (12%)
Mediastinal, pancreatic, fibrosarcoma, metastatic, spleen				1 (2%)
Pancreatic, leukemia mononuclear	1 (2%)	1 (2%)		
Pancreatic, mesothelioma malignant				1 (2%)
Renal, leukemia mononuclear	1 (2%)			1 (2%)
Lymph node, mandibular	(48)	*(50)	*(50)	(48)
Leukemia mononuclear	17 (35%)	1 (2%)	1 (2%)	3 (6%)
Lymph node, mesenteric	(10)	*(50)	*(50)	(10)
Leukemia mononuclear	7 (70%)	1 (2%)		3 (30%)
Mediastinal, osteosarcoma, metastatic, spleen				1 (10%)
Pancreatic, fibrosarcoma, metastatic, spleen				1 (10%)
Spleen	(49)	(50)	(50)	(50)
Fibroma				2 (4%)
Fibrosarcoma		1 (2%)	2 (4%)	17 (34%)
Hemangiosarcoma				4 (8%)
Leukemia mononuclear	21 (43%)	3 (6%)	2 (4%)	3 (6%)
Mesothelioma malignant	1 (2%)	2 (4%)		1 (2%)
Osteosarcoma			1 (2%)	19 (38%)
Thymus	(43)	*(50)	*(50)	(36)
Leukemia mononuclear	8 (19%)		1 (2%)	2 (6%)
Osteosarcoma, metastatic, spleen				1 (3%)
Thymoma benign		1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
INTEGUMENTARY SYSTEM				
Mammary gland	(32)	*(50)	*(50)	(36)
Fibroadenoma	1 (3%)	2 (4%)	3 (6%)	3 (8%)
Skin	(47)	*(50)	*(50)	(49)
Basal cell adenoma		1 (2%)		
Basosquamous tumor benign	1 (2%)	1 (2%)		
Keratoacanthoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Leukemia mononuclear	1 (2%)			
Papilloma squamous			1 (2%)	
Squamous cell carcinoma		1 (2%)		
Sebaceous gland, adenoma			1 (2%)	
Subcutaneous tissue, fibroma	3 (6%)	2 (4%)	1 (2%)	4 (8%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM				
Bone	(48)	*(50)	*(50)	(50)
Cranium, osteosarcoma		1 (2%)		
Rib, osteosarcoma	1 (2%)			
Skeletal muscle	*(49)	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)			
Osteosarcoma, metastatic, bone	1 (2%)	1 (2%)		
Osteosarcoma, metastatic, spleen				2 (4%)
Diaphragm, fibrosarcoma, metastatic, spleen				3 (6%)
Diaphragm, mesothelioma malignant	1 (2%)			
Diaphragm, osteosarcoma, metastatic, spleen				2 (4%)
NERVOUS SYSTEM				
Brain	(49)	*(50)	*(50)	(50)
Astrocytoma benign	1 (2%)			
Ependymoma malignant	1 (2%)			
Leukemia mononuclear	1 (2%)			
Cerebellum, meningioma malignant			1 (2%)	
RESPIRATORY SYSTEM				
Lung	(49)	*(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Fibrosarcoma, metastatic, spleen				5 (10%)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Leukemia mononuclear	20 (41%)		1 (2%)	3 (6%)
Osteosarcoma, metastatic, bone		1 (2%)		
Osteosarcoma, metastatic, spleen				3 (6%)
Squamous cell carcinoma			1 (2%)	
Nose	*(49)	*(50)	*(50)	(46)
Leukemia mononuclear	1 (2%)			
Polyp	1 (2%)			
Nasolacrimal duct, squamous cell carcinoma				1 (2%)
SPECIAL SENSES SYSTEM				
Eye	*(49)	*(50)	*(50)	*(50)
Bilateral, leukemia mononuclear	1 (2%)			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
URINARY SYSTEM				
Kidney	(48)	(50)	(49)	(50)
Fibrosarcoma, metastatic, spleen			1 (2%)	3 (6%)
Leukemia mononuclear	18 (38%)	2 (4%)	1 (2%)	3 (6%)
Mesothelioma malignant	1 (2%)			
Osteosarcoma, metastatic, bone		1 (2%)		
Osteosarcoma, metastatic, spleen				6 (12%)
Renal tubule, adenoma				1 (2%)
Ureter	*(49)	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)			
Urethra	*(49)	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)			
Urinary bladder	(47)	*(50)	*(50)	(46)
Fibrosarcoma, metastatic, spleen				2 (4%)
Leukemia mononuclear	1 (2%)			
Mesothelioma malignant	1 (2%)			
Osteosarcoma, metastatic, spleen				1 (2%)
Papilloma			1 (2%)	
SYSTEMIC LESIONS				
Multiple organs	*(49)	*(50)	*(50)	*(50)
Leukemia mononuclear	21 (43%)	3 (6%)	2 (4%)	3 (6%)
Mesothelioma malignant	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Hemangiosarcoma				4 (8%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	49	50	50	50
Dead	5	5	9	18
Terminal sacrifice	18	32	32	20
Dosing accident			2	1
Moribund	26	13	7	11
TUMOR SUMMARY				
Total animals with primary neoplasms **	46	49	49	49
Total primary neoplasms	125	112	98	159
Total animals with benign neoplasms	44	49	47	47
Total benign neoplasms	97	96	85	107
Total animals with malignant neoplasms	28	14	12	43
Total malignant neoplasms	28	16	13	52
Total animals with secondary neoplasms ***	1	1	2	23
Total secondary neoplasms	2	3	4	132

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: VEHICLE CONTROL

WEEKS ON STUDY	011	038	048	065	067	074	075	080	082	083	084	090	090	090	091	091	092	093	094	094	095	097	098	099	099
CARCASS ID	382	352	381	334	342	401	321	384	341	372	404	324	375	365	325	331	444	395	333	351	354	391	403	374	393
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																	X								
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear					X			X			X					X		X	X	X	X	X	X	X
Mesentery		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X	X		X	X		X	
Mesothelioma malignant																	X								
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+
Leukemia mononuclear																X			X			X			
Mesothelioma malignant																	X								
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Tongue																	+								
Papilloma squamous																	X								
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X			X	X					
Osteosarcoma, metastatic, bone													X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Leukemia mononuclear								X			X							X	X	X	X	X	X	X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X							X	X	X	X	X	X	X
Pheochromocytoma malignant																									
Pheochromocytoma benign																X				X	X				
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	-	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Pituitary gland	+	+	+	+	+	+	+	+	+	+	-	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear											X														
Pars distalis, adenoma				X		X	X					X		X	X			X				X	X		
Pars distalis, adenoma, multiple																									
Pars intermedia, adenoma															X										
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X			X						
C-cell, adenoma								X																	
C-cell, adenoma, multiple																									
C-cell, carcinoma												X													
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Mesothelioma malignant																	X								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear																			X						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Seminal vesicle		+	+	+	+	+	+		+	+	+		+		+	+	+		M	+		+		+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																	X								
Bilateral, interstitial cell, adenoma												X					X			X	X	X	X	X	X
Interstitial cell, adenoma					X			X	X		X		X	X		X		X							

+: Tissue examined microscopically
: Not examined
-: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (*Continued*)

WEEKS ON STUDY	101	101	102	102	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	39 2	40 2	38 3	31 2	33 2	40 5	31 1	32 3	36 3	31 5	34 3	35 3	36 1	36 4	39 4	31 3	31 4	32 2	37 1	38 5	33 5	34 5	36 2	37 3	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mesothelioma malignant																									1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																X									1
Leukemia mononuclear	X		X		X	X			X					X	X		X				X				21
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear			X											X	X										8
Mesothelioma malignant																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear														X											4
Mesothelioma malignant																									1
Acinus, adenoma															X										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																									1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																									1
Tongue					+																				2
Papilloma squamous					X																				2
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																									3
Osteosarcoma, metastatic, bone																									1
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									1
Leukemia mononuclear	X		X			X									X										14
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X		X			X									X										14
Pheochromocytoma malignant		X																							1
Pheochromocytoma benign	X	X					X		X				X	X						X					10
Bilateral, pheochromocytoma benign																X					X		X		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma										X		X													3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																									1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																									1
Pars distalis, adenoma			X	X	X	X		X		X		X							X		X		X		19
Pars distalis, adenoma, multiple													X												1
Pars intermedia, adenoma																									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																									2
C-cell, adenoma						X	X			X						X		X		X				X	8
C-cell, adenoma, multiple													X												1
C-cell, carcinoma																									1
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																									1
Mesothelioma malignant																									1
Preputial gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	46
Adenoma														X											1
Leukemia mononuclear																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																									1
Seminal vesicle	+			+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	36
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant																									1
Bilateral, interstitial cell, adenoma		X	X				X	X	X	X	X			X	X	X	X	X	X	X		X	X	X	25
Interstitial cell, adenoma					X	X							X												11

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	011	038	048	065	067	074	075	080	082	083	084	090	090	090	091	091	092	093	094	094	095	097	098	099	099
CARCASS ID	382	352	381	334	342	401	321	384	341	372	404	324	375	365	325	331	444	395	333	351	354	391	403	374	393
HEMATOPOIETIC SYSTEM																									
Blood		+	+			+	+	+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X					X		X	X	X	X	X	X	X	X
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear					X											X			X		X			X	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, leukemia mononuclear																			X						
Deep cervical, leukemia mononuclear																			X						
Inguinal, leukemia mononuclear								X											X						
Lumbar, leukemia mononuclear																			X						
Mediastinal, leukemia mononuclear					X			X			X					X		X	X	X	X	X		X	X	X
Pancreatic, leukemia mononuclear																		X							
Renal, leukemia mononuclear																			X						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Leukemia mononuclear					X			X			X					X		X	X	X		X	X	X	X
Lymph node, mesenteric					+														+					+	
Leukemia mononuclear					X														X					X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X			X					X		X	X	X	X	X	X	X	X
Mesothelioma malignant																	X								
Thymus	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+
Leukemia mononuclear					X			X			X								X					X	
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+
Fibroadenoma												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																				X					
Keratoacanthoma																									
Leukemia mononuclear																			X						
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, osteosarcoma														X											
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Osteosarcoma, metastatic, bone														X											
Diaphragm, mesothelioma malignant																	X								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																									
Ependymoma malignant			X																						
Leukemia mononuclear																			X						
Peripheral nerve										+															
Spinal cord			+	+						+													+		
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear					X			X			X					X		X	X	X	X	X	X	X	X
Nose	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Polyp																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye											+								+					+	
Bilateral, leukemia mononuclear																			X						
Harderian gland	+	+	+	+	+	+	+	+		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+
Leukemia mononuclear					X			X			X					X		X	X	X	X	X	X	X	X
Mesothelioma malignant																	X								
Ureter	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		−	−	+	+	+
Leukemia mononuclear																			X						
Urethra		+					+								+		+	+	+	+		+			
Leukemia mononuclear																			X						
Urinary bladder	A	+	+	+	−	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Leukemia mononuclear																			X						
Mesothelioma malignant																	X								

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	101	101	102	102	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	39 2	40 2	38 3	31 2	33 2	40 5	31 1	32 3	36 3	31 5	34 3	35 3	36 1	36 4	39 4	31 3	31 4	32 2	37 1	38 5	33 5	34 5	36 2	37 3	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																									
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Leukemia mononuclear	X		X		X	X			X					X	X		X								19
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, leukemia mononuclear	X																								6
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Axillary, leukemia mononuclear																									1
Deep cervical, leukemia mononuclear																									1
Inguinal, leukemia mononuclear			X											X											4
Lumbar, leukemia mononuclear																									1
Mediastinal, leukemia mononuclear	X		X			X			X					X											16
Pancreatic, leukemia mononuclear																									1
Renal, leukemia mononuclear																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear	X		X			X			X					X	X										17
Lymph node, mesenteric	+		+			+	+	+							+				+						10
Leukemia mononuclear	X		X			X									X										7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X		X		X	X			X					X	X		X				X				21
Mesothelioma malignant																									1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	43
Leukemia mononuclear	X		X			X																			8
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	M	M	+	M	M	M	M	M	+	+	+	M	+	+	+	+	M	+	+	32
Fibroadenoma																									1
Skin	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Basosquamous tumor benign																									1
Keratoacanthoma			X					X																	2
Leukemia mononuclear																									1
Subcutaneous tissue, fibroma			X											X											3
Subcutaneous tissue, fibrosarcoma																								X	1
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Rib, osteosarcoma																									1
Skeletal muscle	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Leukemia mononuclear																									1
Osteosarcoma, metastatic, bone																									1
Diaphragm, mesothelioma malignant																									1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma benign							X																		1
Ependymoma malignant																									1
Leukemia mononuclear																									1
Peripheral nerve																									1
Spinal cord																									4
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																			X						1
Leukemia mononuclear	X		X			X			X					X	X		X				X				20
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																									1
Polyp													X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																									
Eye						+								+		+								+	7
Bilateral, leukemia mononuclear																									1
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear	X		X			X			X						X						X				18
Mesothelioma malignant																									1
Ureter	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																									1
Urethra	+	+	+	+			+	+		+						+	+	+		+	+	+			21
Leukemia mononuclear																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																									1
Mesothelioma malignant																									1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: LOW DOSE

WEEKS ON STUDY	070	076	080	090	090	093	093	093	094	094	094	097	097	099	099	102	103	103	105	105	105	105	105	105	105
CARCASS ID	225	271	234	264	283	223	251	282	265	274	292	244	302	233	224	304	215	213	221	242	262	263	275	293	212
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+																				
Intestine large	+	+	+	+	+														●						
Intestine large, cecum	+	+	+	+	+																				
Intestine large, colon	+	+	+	+	+																				
Intestine large, rectum	+	+	+	+	+																				
Intestine small	+	+	+	+	+		+																		
Intestine small, duodenum	+	+	+	+	+																				
Intestine small, ileum	+	+	+	+	+																				
Intestine small, jejunum	+	+	+	+	+		●																		
Adenocarcinoma							X																		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear													X						X						
Mesothelioma malignant																X									
Neoplastic nodule																					X				X
Mesentery	+	+	+	+	+		+	+								+									
Mesothelioma malignant								X								X									
Sarcoma																									
Pancreas	M	+	+	+	+			+					●			+									
Leukemia mononuclear													X												
Mesothelioma malignant								X								X									
Salivary glands	+	+	+	+	+			+																	
Stomach	+	+	+	+	+						+														
Stomach, forestomach	+	+	+	+	+						+														
Stomach, glandular	+	+	+	+	+						+														
Tongue																									
Papilloma squamous																									
Tooth	+	+	+	+	+																				
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+													+							
Heart	+	+	+	+	+			+							+	+	+	+			+				+
ENDOCRINE SYSTEM																									
Adrenal gland	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Adrenal gland, medulla	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Pheochromocytoma benign						X							X		X								X	X	X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	M	+	+	+	+																				
Parathyroid gland	+	+	+	+	+													+	+						
Adenoma		X																							
Pituitary gland	+	+	+	+	M				+		+					+	+						+	+	+
Pars distalis, adenoma	X								X		X					X	X						X	X	X
Thyroid gland	+	+	+	+	+													A	+						
C-cell, adenoma																			X						
C-cell, carcinoma																									
Follicular cell, adenocarcinoma	X																								
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+		+								+	+			+		+				+
Mesothelioma malignant																X									
Bilateral, mesothelioma malignant																									
Preputial gland	+	+	+	+	+	+				+		+		+			+								
Adenoma				X		X				X		X		X											
Prostate	+	+	+	+	+											+									
Seminal vesicle			+		+											+									
Testes	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+		+	+	+	+	+	+	+	+
Mesothelioma malignant								X								X									
Bilateral, mesothelioma malignant																									
Bilateral, interstitial cell, adenoma					X		X	X		X		X	X	X	X	X		X	X	X	X	X	X	X	X
Interstitial cell, adenoma			X	X		X			X																

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	231	252	284	285	295	305	232	241	243	254	261	272	273	291	303	211	214	222	235	245	253	255	281	294	301	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										5
Intestine large																								+		7
Intestine large, cecum																										5
Intestine large, colon																										5
Intestine large, rectum																										5
Intestine small																										6
Intestine small, duodenum																										5
Intestine small, ileum																										5
Intestine small, jejunum																										6
Adenocarcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma														X												1
Leukemia mononuclear														X												3
Mesothelioma malignant																										1
Neoplastic nodule									X				X						X							5
Mesentery		+				+														+						11
Mesothelioma malignant																										2
Sarcoma						X																				1
Pancreas												+														8
Leukemia mononuclear																										1
Mesothelioma malignant																										2
Salivary glands																										6
Stomach																										6
Stomach, forestomach																										6
Stomach, glandular																										6
Tongue																						+				1
Papilloma squamous																						X				1
Tooth																										5
CARDIOVASCULAR SYSTEM																										
Blood vessel								+								+										8
Heart	+				+					+	+		+											+		18
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Pheochromocytoma benign	X							X				X						X	X						X	12
Bilateral, pheochromocytoma benign																				X				X		2
Islets, pancreatic																										4
Parathyroid gland																										7
Adenoma																										1
Pituitary gland		+		+	+						+				+					+		+				18
Pars distalis, adenoma		X			X						X				X					X						13
Thyroid gland																			+						+	8
C-cell, adenoma																			X							2
C-cell, carcinoma																									X	1
Follicular cell, adenocarcinoma																										1
Follicular cell, adenoma																			X							1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis		+		+		+			+			+			+	+		+				+				20
Mesothelioma malignant																										1
Bilateral, mesothelioma malignant						X																				1
Preputial gland							+																	+		12
Adenoma							X																	X		7
Prostate																										6
Seminal vesicle																										3
Testes	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Mesothelioma malignant																										2
Bilateral, mesothelioma malignant						X																				1
Bilateral, interstitial cell, adenoma	X	X	X	X		X		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	38
Interstitial cell, adenoma					X		X																			6

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	070	076	080	090	090	093	093	093	094	094	094	097	097	099	099	102	103	103	105	105	105	105	105	105	105
CARCASS ID	225	271	234	264	283	223	251	282	265	274	292	244	302	233	224	304	115	213	211	242	262	263	275	293	212
HEMATOPOIETIC SYSTEM																									
Blood	+	+	+	+	+			+	+	+	+	+	+		+	+			+	+	+	+	+	+	+
Leukemia mononuclear													X						X						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+		+	+					+	+	+				+						
Pancreatic, leukemia mononuclear													X												
Lymph node, mandibular		+	+	+	+			+							+				+						
Leukemia mononuclear																			X						
Lymph node, mesenteric	+		+				+																		
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma														X											
Leukemia mononuclear													X						X						
Mesothelioma malignant								X								X									
Thymus	+	M	+	M	+																				
Thymoma benign																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	M													+							
Fibroadenoma																									
Skin	+	+	+	+	+					+		+		+	+	+	+			+			+		
Basal cell adenoma																							X		
Basosquamous tumor benign																				X					
Keratoacanthoma																									
Squamous cell carcinoma															X										
Subcutaneous tissue, fibroma				X																					
Subcutaneous tissue, fibrosarcoma										X		X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteosarcoma		X																							
Skeletal muscle	+	+	+	+	+											+									
Osteosarcoma, metastatic, bone		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+																				
Peripheral nerve	+																								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+		+	+																	
Osteosarcoma, metastatic, bone		X																							
Nose	+	+	+	+	+																				
Trachea	+	+	+	+	+																				
SPECIAL SENSES SYSTEM																									
Eye								+										+				+			+
Harderian gland	+			+																					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X						X						
Osteosarcoma, metastatic, bone		X																							
Ureter	+	+	+	+	+		+				+					+			+			+		+	+
Urethra	+	+														+									
Urinary bladder	+	+	+	+	+											+									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	231	252	284	285	295	305	232	241	243	254	261	272	273	291	303	211	214	222	235	245	253	255	281	294	301	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear														X												3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+					+						+		+				+						16
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular																										7
Leukemia mononuclear																										1
Lymph node, mesenteric														+						+						5
Leukemia mononuclear														X												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Leukemia mononuclear														X												3
Mesothelioma malignant																										2
Thymus								+								+										5
Thymoma benign								X																		1
INTEGUMENTARY SYSTEM																										
Mammary gland							+									+										6
Fibroadenoma							X									X										2
Skin			+				+					+				+								+		18
Basal cell adenoma																										1
Basosquamous tumor benign																										1
Keratoacanthoma			X																							1
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma												X														2
Subcutaneous tissue, fibrosarcoma																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteosarcoma																										1
Skeletal muscle																										6
Osteosarcoma, metastatic, bone																										1
NERVOUS SYSTEM																										
Brain																										5
Peripheral nerve																										1
RESPIRATORY SYSTEM																										
Lung																										7
Osteosarcoma, metastatic, bone																										1
Nose																										5
Trachea																										5
SPECIAL SENSES SYSTEM																										
Eye	+		+	+							+		+			+								+		11
Harderian gland					+								+													4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Osteosarcoma, metastatic, bone																										1
Ureter	+	+			+			+	+		+					+		+	+	+				+	+	24
Urethra																										3
Urinary bladder																				+						7

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: MID DOSE

WEEKS ON STUDY	049	052	068	068	072	075	077	079	082	082	083	098	101	102	102	103	103	104	105	105	105	105	105	105	105
CARCASS ID	201	111	132	203	205	154	153	131	193	155	164	165	173	133	195	112	171	135	113	115	122	125	134	141	144
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+							+							
Intestine large	+	+	+	+	+	+	+	+	+	+	+														
Intestine large, cecum	A	+	A	A	+	M	A	+	A	+	+														
Intestine large, colon	+	+	A	+	+	+	A	+	+	+	+														
Intestine large, rectum	+	M	+	+	+	+	+	A	A	+	+														
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+													
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+														
Intestine small, ileum	+	+	A	A	+	+	A	+	A	+	A														
Intestine small, jejunum	+	+	+	A	+	+	A	A	A	+	+	+													
Polyp adenomatous												X													
Liver	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																X									
Hepatocellular carcinoma, multiple																									
Leukemia mononuclear					X																				
Neoplastic nodule																									
Mesentery	+	+		+	+	+		+	+	+	+		+			+									
Fibrosarcoma, metastatic, spleen													X												
Pheochromocytoma malignant, metastatic, adrenal gland						X																			
Pancreas	+	+	A	+	+	+	+	+	+	+	+		+			+									
Fibrosarcoma, metastatic, spleen													X												
Salivary glands	+	+	A	+	+	+	+	+	+	+	+							+							
Stomach	+	+	A	+	+	+	+	+	+	+	+					+									
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+					+									
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+					+									
Tooth	+	+	+	+	+	+	+	+	+																
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+							+							
Heart	+	+	+	+	+	+	+	+	+	+	+					+	+	+		+					
Leukemia mononuclear					X																				
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	A	+	+		+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Pheochromocytoma malignant																									
Pheochromocytoma benign			X															X		X			X	X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+														
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+														
Pituitary gland	+	+	A	+	+	+	+	+	+	+	+			+	+	+	+			+		+			
Pars distalis, adenoma					X		X			X	X				X	X	X			X		X			
Pars distalis, carcinoma														X											
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+														
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+				+	+	+			+					
Mesothelioma malignant																X									
Penis					+																				
Leukemia mononuclear					X																				
Preputial gland	+	+	+	+	+	+	+	+	M	+	+								+			+			
Adenoma																			X			X			
Prostate	+	+	+	+	+	+	+	+	+	+	+		+							+					
Seminal vesicle				+	+				+		+		+												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																X									
Bilateral, interstitial cell, adenoma												X	X			X	X	X		X	X	X	X	X	
Interstitial cell, adenoma				X		X			X	X	X			X	X				X						X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	185	202	114	121	163	174	142	143	151	152	175	182	194	123	124	145	161	162	172	181	183	184	191	192	204	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus							+																			13
Intestine large											+															12
Intestine large, cecum											+															6
Intestine large, colon																										9
Intestine large, rectum																										8
Intestine small																										12
Intestine small, duodenum																										10
Intestine small, ileum																										6
Intestine small, jejunum																										8
Polyp adenomatous																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																										1
Hepatocellular carcinoma multiple																X										1
Leukemia mononuclear						X																				2
Neoplastic nodule									X			X										X				3
Mesentery																										11
Fibrosarcoma, metastatic, spleen																										1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Pancreas							+								+											14
Fibrosarcoma, metastatic, spleen																										1
Salivary glands																										11
Stomach																										11
Stomach, forestomach																										11
Stomach, glandular																										11
Tooth																										10
CARDIOVASCULAR SYSTEM																										
Blood vessel																										12
Heart	+		+				+			+					+				+	+			+			23
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Pheochromocytoma malignant			X																							1
Pheochromocytoma benign					X						X						X	X								9
Bilateral, pheochromocytoma benign						X								X						X			X		X	5
Islets, pancreatic																										10
Parathyroid gland																										10
Pituitary gland																			+			+		+		19
Pars distalis, adenoma																			X					X		11
Pars distalis, carcinoma																										1
Thyroid gland																										10
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+				+					+	+	+		+						+	+	+		+	26
Mesothelioma malignant																										1
Penis																										1
Leukemia mononuclear																										1
Preputial gland		+		+											+											15
Adenoma		X		X																						4
Prostate																										13
Seminal vesicle																										5
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Bilateral, interstitial cell adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	33
Interstitial cell adenoma															X								X			11

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID DOSE (Continued)

WEEKS ON STUDY	049	052	068	068	072	075	077	079	082	082	083	098	101	102	102	103	103	104	105	105	105	105	105	105	105
CARCASS ID	201	111	132	203	205	154	153	131	193	155	164	165	173	133	195	112	171	135	113	115	122	125	134	141	144
HEMATOPOIETIC SYSTEM																									
Blood		+			+								+	+	+	+	+		+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Femoral, leukemia mononuclear					X																				
Lymph node	+	+	+	+	+	+	+	+	+	+	+							+							
Mediastinal, leukemia mononuclear					X																				
Lymph node, mandibular	+	+	A	+	+	+	+	+	+	+	+							+							
Leukemia mononuclear					X																				
Lymph node, mesenteric						+																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma													X												
Leukemia mononuclear					X																				
Osteosarcoma																									
Thymus	+	+	+	+	+	+	M	+	+	+	+							+							
Leukemia mononuclear					X																				
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	M	+	+	+	+	+	M								+			+		+	
Fibroadenoma																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+				+	+			+			+		+	
Keratoacanthoma															X										
Papilloma squamous																									
Sebaceous gland, adenoma																X									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma		X																							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+														
NERVOUS SYSTEM																									
Brain	+	+	A	+	+	+	+	+	+	+	+														
Cerebellum, meningioma malignant	X																								
Spinal cord	+	+																							
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+		+	+	+							+							
Leukemia mononuclear					X																				
Squamous cell carcinoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	M														
Trachea	+	+	+	+	+	+	+	+	+	+	+								+						
SPECIAL SENSES SYSTEM																									
Eye													+							+		+			
Harderian gland	+	+	+	+	+	+	+	+	+	M															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen													X												
Leukemia mononuclear					X																				
Ureter	+	+	+	+	+	+	+	+	+		+		+	+	+		+			+				+	
Urethra							+																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+									+					
Papilloma							X																		

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	18 5	20 2	11 4	12 1	16 3	17 4	14 2	14 3	15 1	15 2	17 5	18 2	19 4	12 3	12 4	14 5	16 1	16 2	17 2	18 1	18 3	18 4	19 1	19 2	20 4	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	39
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear						X																				1
Femoral, leukemia mononuclear																										1
Lymph node							+				+								+							15
Mediastinal, leukemia mononuclear																										1
Lymph node, mandibular																			+							12
Leukemia mononuclear																										1
Lymph node, mesenteric											+															2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma															X											2
Leukemia mononuclear						X																				2
Osteosarcoma							X																			1
Thymus							+								+											13
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland														+	+											13
Fibroadenoma														X	X											3
Skin					+									+	+											19
Keratoacanthoma																										1
Papilloma squamous					X																					1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma															X											1
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	49
Skeletal muscle																										11
NERVOUS SYSTEM																										
Brain																										10
Cerebellum, meningioma malignant																										1
Spinal cord																										2
RESPIRATORY SYSTEM																										
Lung																										11
Leukemia mononuclear																										1
Squamous cell carcinoma																										1
Nose																										10
Trachea							+																			13
SPECIAL SENSES SYSTEM																										
Eye		+	+	+	+	+					+			+	+	+		+								13
Harderian gland																										9
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, spleen																										1
Leukemia mononuclear																										1
Ureter	+	+		+	+			+	+			+		+	+					+		+				27
Urethra																										1
Urinary bladder																										12
Papilloma																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: HIGH DOSE

WEEKS ON STUDY	06 0	06 8	07 1	07 5	07 7	08 0	08 4	08 8	08 9	08 9	08 9	09 0	09 4	09 5	09 5	09 7	09 7	09 7	09 8	09 8	09 8	09 9	10 0	10 2	10 3	10 3
CARCASS ID	10 4	01 5	10 1	04 2	04 5	05 4	05 3	08 3	03 5	02 4	05 1	01 2	06 4	09 1	03 1	03 2	08 1	05 5	02 1	05 2	10 5	04 1	02 2	10 2	08 2
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine large, cecum	+	A	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	A	A	+	+	+	
Colon, rectum, osteosarcoma, metastatic, spleen			X																							
Intestine large, colon	+	A		+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine large, rectum	+	A		+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	
Intestine small	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine small, duodenum	+	A	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Fibrosarcoma, metastatic, spleen																				X				X		
Osteosarcoma, metastatic, spleen																										
Ileum, jejunum, osteosarcoma, metastatic, spleen			X																							
Intestine small, ileum	+	A		+	+	+	+	A	A	A	A	M	+	+	+	A	+	+	+	+	A	A	+	+	+	
Intestine small, jejunum	+	A		+	+	+	+	A	A	A	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	
Osteosarcoma, metastatic, spleen																										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Fibrosarcoma, metastatic, spleen						X													X	X				X		
Leukemia mononuclear								X										X								
Osteosarcoma, metastatic, spleen							X								X											
Mesentery	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrosarcoma, metastatic, spleen				X		X						X		X					X	X				X		
Leukemia mononuclear								X										X								
Mesothelioma malignant											X															
Osteosarcoma, metastatic, spleen			X				X						X		X							X				
Pancreas	+	A	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrosarcoma, metastatic, spleen				X								X							X	X				X		
Mesothelioma malignant																										
Osteosarcoma, metastatic, spleen			X										X		X							X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Stomach, forestomach	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Osteosarcoma, metastatic, spleen																										
Glandular, osteosarcoma, metastatic, spleen																										
Stomach, glandular	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Fibrosarcoma, metastatic, spleen																									X	
Osteosarcoma, metastatic, spleen			X																							
Tongue														+												
Papilloma squamous														X												
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	
Gingiva, squamous cell carcinoma																										
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pulmonary artery, fibrosarcoma, metastatic, spleen																									X	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Leukemia mononuclear								X																		
Capsule, fibrosarcoma, metastatic, spleen																									X	
Capsule, osteosarcoma, metastatic, spleen			X																							
Medulla, fibrosarcoma, metastatic, spleen												X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	A	+	+	+	
Leukemia mononuclear								X																		
Pheochromocytoma malignant									X																	
Pheochromocytoma benign										X				X		X	X				X				X	
Bilateral, pheochromocytoma benign																										
Islets, pancreatic	+	A	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																							X			
Carcinoma																										
Fibrosarcoma, metastatic, spleen												X								X				X		
Osteosarcoma, metastatic, spleen													X		X							X				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	
Adenoma																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	
Pars distalis, adenoma												X	X								X	X	X			
Pars distalis, adenoma, multiple																										
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	A	A	+	+	A	
C-cell, adenoma																				X			X			
C-cell, carcinoma																				X						
GENERAL BODY SYSTEM																										
Tissue, NOS							+																			
Osteosarcoma, metastatic, spleen							X																			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	0111	0333	0344	0993	0665	0773	0884	0992	0113	0223	0443	0444	0661	0711	1033	0255	0662	0663	0774	0885	0994	1014	0722	0775	0995	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Colon, rectum, osteosarcoma, metastatic, spleen																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrosarcoma, metastatic, spleen																										2
Osteosarcoma, metastatic, spleen		X										X								X						3
Ileum, jejunum, osteosarcoma, metastatic, spleen																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Osteosarcoma, metastatic, spleen						X																				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, spleen																										4
Leukemia mononuclear								X																		3
Osteosarcoma, metastatic, spleen	X	X							X			X							X		X					8
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, spleen			X	X																						9
Leukemia mononuclear																										2
Mesothelioma malignant																				X						2
Osteosarcoma, metastatic, spleen	X	X				X						X						X			X					11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma, metastatic, spleen				X																						6
Mesothelioma malignant																				X						1
Osteosarcoma, metastatic, spleen	X	X				X			X			X									X					10
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Osteosarcoma, metastatic, spleen												X														1
Glandular, osteosarcoma, metastatic, spleen		X																								1
Stomach, glandular	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibrosarcoma, metastatic, spleen																										1
Osteosarcoma, metastatic, spleen																										1
Tongue																										1
Papilloma squamous																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gingiva, squamous cell carcinoma	X																									1
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pulmonary artery, fibrosarcoma, metastatic, spleen																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Capsule, fibrosarcoma, metastatic, spleen																										1
Capsule, osteosarcoma, metastatic, spleen																										1
Medulla, fibrosarcoma, metastatic, spleen																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Pheochromocytoma malignant											X															1
Pheochromocytoma benign				X	X			X		X	X			X		X				X	X				X	13
Bilateral, pheochromocytoma benign			X										X		X				X				X	X	X	12
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Carcinoma																				X						1
Fibrosarcoma, metastatic, spleen				X																						4
Osteosarcoma, metastatic, spleen		X				X						X									X					7
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	45
Adenoma		X																								1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X				X						X		X							X				10
Pars distalis, adenoma, multiple											X															1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
C-cell, adenoma		X													X		X	X			X	X	X			9
C-cell, carcinoma																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Osteosarcoma, metastatic, spleen																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	06 60	06 68	07 71	07 75	07 77	08 80	08 84	08 88	08 89	08 89	09 90	09 94	09 95	09 95	09 97	09 97	09 98	09 98	09 98	09 99	10 00	10 02	10 03	10 03
CARCASS ID	10 04	01 55	10 01	04 42	04 45	05 54	05 53	08 83	03 35	02 24	05 11	01 12	06 64	09 91	03 31	03 32	08 81	05 55	02 21	05 52	10 05	04 41	02 22	10 02	08 82
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen														X									X		
Osteosarcoma, metastatic, spleen			X																			X			
Sarcoma																									X
Bilateral, mesothelioma malignant																									
Bilateral, osteosarcoma, metastatic, spleen							X																		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Adenocarcinoma					X																				
Adenoma																									
Prostate	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen				X																					
Osteosarcoma, metastatic, spleen			X																						
Seminal vesicle	+	+	+	+	+	+		M	+	+	+			+				+				+	+		+
Osteosarcoma, metastatic, spleen			X																			X			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant											X														
Osteosarcoma, metastatic, spleen							X																		
Bilateral, interstitial cell, adenoma							X	X	X	X		X	X	X		X	X	X	X	X	X	X		X	X
Interstitial cell, adenoma	X				X	X					X				X										
HEMATOPOIETIC SYSTEM																									
Blood					+	+		+					+	+					+	+			+	+	
Leukemia mononuclear								X											X						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, spleen							X																		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Mediastinal, fibrosarcoma, metastatic, spleen																				X	X				
Mediastinal, leukemia mononuclear								X											X						
Mediastinal, osteosarcoma, metastatic, spleen			X												X										
Mediastinal, pancreatic, fibrosarcoma, metastatic, spleen																								X	
Pancreatic, mesothelioma malignant																									
Renal, leukemia mononuclear								X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Leukemia mononuclear								X										X							
Lymph node, mesenteric						+		+				+			M			+							
Leukemia mononuclear								X										X							
Mediastinal, osteosarcoma, metastatic, spleen																									
Pancreatic, fibrosarcoma, metastatic, spleen												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																		X							
Fibrosarcoma				X		X			X		X	X		X			X		X	X			X		
Hemangiosarcoma									X	X													X		
Leukemia mononuclear								X										X							
Mesothelioma malignant																									
Osteosarcoma			X				X						X		X	X						X			
Thymus	M	A	M	M	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	A	+	+	+
Leukemia mononuclear								X																	
Osteosarcoma, metastatic, spleen							X																		
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	M	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	M	M	+	+	M
Fibroadenoma																		X							
Skin	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma																X	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, spleen															X							X			
Diaphragm, fibrosarcoma, metastatic, spleen												X								X				X	
Diaphragm, osteosarcoma, metastatic, spleen							X																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+																								
Spinal cord	+																								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen				X								X								X	X			X	
Hemangiosarcoma, metastatic, spleen										X															
Leukemia mononuclear								X										X							
Osteosarcoma, metastatic, spleen							X																		
Nose	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+
Nasolacrimal duct, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	0111	0133	0344	0993	0665	0733	0884	0992	0113	0123	0443	0444	0661	0711	1013	0225	0662	0663	0747	0885	0994	0114	0722	0755	0995	TISSUES TUMORS
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen																										2
Osteosarcoma, metastatic, spleen						X																				3
Sarcoma																										1
Bilateral, mesothelioma malignant																				X						1
Bilateral, osteosarcoma, metastatic, spleen																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Adenoma											X												X			2
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, spleen																										1
Osteosarcoma, metastatic, spleen						X															X					3
Seminal vesicle		M		+	+	+									+				+	+	+			+	+	23
Osteosarcoma, metastatic, spleen																										2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																				X						2
Osteosarcoma, metastatic, spleen		X										X														3
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma			X																							6
HEMATOPOIETIC SYSTEM																										
Blood		+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	31
Leukemia mononuclear								X																		3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinal, fibrosarcoma, metastatic, spleen																										2
Mediastinal, leukemia mononuclear								X																		3
Mediastinal, osteosarcoma, metastatic, spleen	X	X				X						X														6
Mediastinal, pancreatic, fibrosarcoma, metastatic, spleen																										1
Pancreatic, mesothelioma malignant																				X						1
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear								X																		3
Lymph node, mesenteric								+					+				+			+	+		+			10
Leukemia mononuclear								X																		3
Mediastinal, osteosarcoma, metastatic, spleen																					X					1
Pancreatic, fibrosarcoma, metastatic, spleen																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma														X												2
Fibrosarcoma			X	X						X	X		X							X			X			17
Hemangiosarcoma			X																							4
Leukemia mononuclear								X																		3
Mesothelioma malignant																				X						1
Osteosarcoma	X	X			X	X	X		X			X				X		X	X		X	X			X	19
Thymus	+	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	36
Leukemia mononuclear								X																		2
Osteosarcoma, metastatic, spleen																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	36
Fibroadenoma								X			X															3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma	X																									1
Subcutaneous tissue, fibroma											X														X	4
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										2
Diaphragm, fibrosarcoma, metastatic, spleen																										3
Diaphragm, osteosarcoma, metastatic, spleen																					X					2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen																										5
Hemangiosarcoma, metastatic, spleen																										1
Leukemia mononuclear								X																		3
Osteosarcoma, metastatic, spleen	X											X														3
Nose	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Nasolacrimal duct, squamous cell carcinoma																		X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	060	068	071	075	077	080	084	088	089	089	090	094	095	095	097	097	097	098	098	098	099	100	102	103	103
CARCASS ID	104	015	101	042	045	054	053	083	035	024	051	012	064	091	031	032	081	055	021	052	105	041	022	102	082
SPECIAL SENSES SYSTEM																									
Ear																									
Eye					+																		+		
Harderian gland	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	A	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen												X								X					
Leukemia mononuclear								X										X							
Osteosarcoma, metastatic, spleen			X												X										
Renal tubule, adenoma																									
Ureter	+		+	+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	A	+		+
Urethra							+						+		+								+	+	
Urinary bladder	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Fibrosarcoma, metastatic, spleen				X																				X	
Osteosarcoma, metastatic, spleen			X																						

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	011	033	034	093	065	073	084	092	013	023	043	044	061	071	103	025	062	063	074	085	094	014	072	075	095	TISSUES TUMORS
SPECIAL SENSES SYSTEM																										
Ear	+																									1
Eye	+				+	+	+		+	+						+	+		+			+		+	+	14
Harderian gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen				X																						3
Leukemia mononuclear								X																		3
Osteosarcoma, metastatic, spleen		X				X						X									X					6
Renal tubule, adenoma									X																	1
Ureter	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	44
Urethra			+				+			+		+	+										+			11
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrosarcoma, metastatic, spleen																										2
Osteosarcoma, metastatic, spleen																										1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
Adrenal Medulla: Pheochromocytoma				
Overall Rates (a)	13/49 (27%)	14/48 (29%)	14/48 (29%)	25/49 (51%)
Adjusted Rates (b)	53.8%	40.3%	40.7%	79.5%
Terminal Rates (c)	8/18 (44%)	11/31 (35%)	12/32 (38%)	15/21 (71%)
Day of First Observation	633	651	476	618
Life Table Tests (d)	P<0.001	P=0.158N	P=0.134N	P=0.061
Logistic Regression Tests (d)	P=0.003	P=0.358N	P=0.504N	P=0.028
Cochran-Armitage Trend Test (d)	P=0.003			
Fisher Exact Test (d)		P=0.475	P=0.475	P=0.011
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma				
Overall Rates (a)	13/49 (27%)	14/48 (29%)	15/48 (31%)	26/49 (53%)
Adjusted Rates (b)	53.8%	40.3%	43.6%	82.9%
Terminal Rates (c)	8/18 (44%)	11/31 (35%)	13/32 (41%)	16/21 (76%)
Day of First Observation	633	651	476	618
Life Table Tests (d)	P<0.001	P=0.158N	P=0.175N	P=0.041
Logistic Regression Tests (d)	P=0.001	P=0.358N	P=0.586N	P=0.017
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		P=0.475	P=0.386	P=0.006
Preputial Gland: Adenoma				
Overall Rates (a)	1/46 (2%)	(e) 7/12 (58%)	(e) 4/15 (27%)	2/48 (4%)
Adjusted Rates (b)	6.7%			10.0%
Terminal Rates (c)	1/15 (7%)			2/20 (10%)
Day of First Observation	729			729
Life Table Test (d)				P=0.602
Logistic Regression Test (d)				P=0.602
Fisher Exact Test (d)				P=0.516
Preputial Gland: Adenoma or Adenocarcinoma				
Overall Rates (a)	1/46 (2%)	(e) 7/12 (58%)	(e) 4/15 (27%)	3/48 (6%)
Adjusted Rates (b)	6.7%			12.0%
Terminal Rates (c)	1/15 (7%)			2/20 (10%)
Day of First Observation	729			535
Life Table Test (d)				P=0.393
Logistic Regression Test (d)				P=0.348
Fisher Exact Test (d)				P=0.325
Pancreatic Islets: Adenoma				
Overall Rates (a)	3/48 (6%)	(e) 0/4 (0%)	(e) 0/10 (0%)	1/46 (2%)
Adjusted Rates (b)	13.7%			3.6%
Terminal Rates (c)	2/18 (11%)			0/21 (0%)
Day of First Observation	633			712
Life Table Test (d)				P=0.243N
Logistic Regression Test (d)				P=0.274N
Fisher Exact Test (d)				P=0.325N
Pancreatic Islets: Adenoma or Carcinoma				
Overall Rates (a)	3/48 (6%)	(e) 0/4 (0%)	(e) 0/10 (0%)	2/46 (4%)
Adjusted Rates (b)	13.7%			8.2%
Terminal Rates (c)	2/18 (11%)			1/21 (5%)
Day of First Observation	633			712
Life Table Test (d)				P=0.418N
Logistic Regression Test (d)				P=0.451N
Fisher Exact Test (d)				P=0.520N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
Liver: Neoplastic Nodule				
Overall Rates (a)	0/49 (0%)	5/50 (10%)	3/49 (6%)	0/49 (0%)
Adjusted Rates (b)	0.0%	15.6%	9.4%	0.0%
Terminal Rates (c)	0/18 (0%)	5/32 (16%)	3/32 (9%)	0/21 (0%)
Day of First Observation		729	729	
Life Table Tests (d)	P=0.190N	P=0.103	P=0.238	(f)
Logistic Regression Tests (d)	P=0.190N	P=0.103	P=0.238	(f)
Cochran-Armitage Trend Test (d)	P=0.178N			
Fisher Exact Test (d)		P=0.030	P=0.121	(f)
Liver: Neoplastic Nodule or Hepatocellular Carcinoma				
Overall Rates (a)	1/49 (2%)	6/50 (12%)	5/49 (10%)	0/49 (0%)
Adjusted Rates (b)	5.6%	18.8%	15.0%	0.0%
Terminal Rates (c)	1/18 (6%)	6/32 (19%)	4/32 (13%)	0/21 (0%)
Day of First Observation	729	729	716	
Life Table Tests (d)	P=0.106N	P=0.196	P=0.279	P=0.469N
Logistic Regression Tests (d)	P=0.084N	P=0.196	P=0.241	P=0.469N
Cochran-Armitage Trend Test (d)	P=0.102N			
Fisher Exact Test (d)		P=0.059	P=0.102	P=0.500N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	1/49 (2%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.6%	6.3%	9.4%	12.3%
Terminal Rates (c)	0/18 (0%)	2/32 (6%)	3/32 (9%)	2/21 (10%)
Day of First Observation	626	729	729	680
Life Table Tests (d)	P=0.231	P=0.655	P=0.469	P=0.356
Logistic Regression Tests (d)	P=0.297	P=0.558	P=0.364	P=0.344
Cochran-Armitage Trend Test (d)	P=0.292			
Fisher Exact Test (d)		P=0.508	P=0.316	P=0.316
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	20/47 (43%)	(e) 13/18 (72%)	(e,g) 11/19 (58%)	11/46 (24%)
Adjusted Rates (b)	61.4%			38.7%
Terminal Rates (c)	7/18 (39%)			5/20 (25%)
Day of First Observation	455			654
Life Table Test (d)				P=0.023N
Logistic Regression Test (d)				P=0.027N
Fisher Exact Test (d)				P=0.045N
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	3/49 (6%)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	13.2%	5.2%	3.1%	14.7%
Terminal Rates (c)	1/18 (6%)	1/32 (3%)	1/32 (3%)	2/21 (10%)
Day of First Observation	680	626	729	676
Life Table Tests (d)	P=0.277	P=0.314N	P=0.150N	P=0.605
Logistic Regression Tests (d)	P=0.318	P=0.425N	P=0.222N	P=0.584
Cochran-Armitage Trend Test (d)	P=0.310			
Fisher Exact Test (d)		P=0.490N	P=0.301N	P=0.511
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	4/49 (8%)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	18.3%	9.8%	5.1%	14.7%
Terminal Rates (c)	2/18 (11%)	1/32 (3%)	1/32 (3%)	2/21 (10%)
Day of First Observation	680	626	361	676
Life Table Tests (d)	P=0.566	P=0.407N	P=0.164N	P=0.533N
Logistic Regression Tests (d)	P=0.586	P=0.568N	P=0.328N	P=0.552N
Cochran-Armitage Trend Test (d)	P=0.586			
Fisher Exact Test (d)		P=0.631N	P=0.329N	P=0.631N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
Spleen: Fibrosarcoma				
Overall Rates (a)	0/49 (0%)	1/50 (2%)	2/50 (4%)	17/50 (34%)
Adjusted Rates (b)	0.0%	2.7%	5.7%	47.1%
Terminal Rates (c)	0/18 (0%)	0/32 (0%)	1/32 (3%)	5/21 (24%)
Day of First Observation		687	702	522
Life Table Tests (d)	P<0.001	P=0.570	P=0.364	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.523	P=0.293	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.505	P=0.253	P<0.001
Spleen: Fibroma or Fibrosarcoma				
Overall Rates (a)	0/49 (0%)	1/50 (2%)	2/50 (4%)	19/50 (38%)
Adjusted Rates (b)	0.0%	2.7%	5.7%	51.9%
Terminal Rates (c)	0/18 (0%)	0/32 (0%)	1/32 (3%)	6/21 (29%)
Day of First Observation		687	702	522
Life Table Tests (d)	P<0.001	P=0.570	P=0.364	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.523	P=0.293	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.505	P=0.253	P<0.001
Spleen: Osteosarcoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	1/50 (2%)	19/50 (38%)
Adjusted Rates (b)	0.0%	0.0%	3.1%	62.8%
Terminal Rates (c)	0/18 (0%)	0/32 (0%)	1/32 (3%)	11/21 (52%)
Day of First Observation			729	494
Life Table Tests (d)	P<0.001	(f)	P=0.615	P<0.001
Logistic Regression Tests (d)	P<0.001	(f)	P=0.615	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		(f)	P=0.505	P<0.001
Spleen: Fibrosarcoma or Osteosarcoma				
Overall Rates (a)	0/49 (0%)	1/50 (2%)	3/50 (6%)	36/50 (72%)
Adjusted Rates (b)	0.0%	2.7%	8.7%	87.1%
Terminal Rates (c)	0/18 (0%)	0/32 (0%)	2/32 (6%)	16/21 (76%)
Week of First Observation		687	702	494
Life Table Tests (d)	P<0.001	P=0.570	P=0.236	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.485	P=0.140	P<0.001
Cochran-Armitage Trend Test (d)				
Fisher Exact Test (d)	P<0.001	P=0.505	P=0.125	P<0.001
Spleen: Fibrosarcoma, Osteosarcoma, or Hemangiosarcoma				
Overall Rates (a)	0/49 (0%)	1/50 (2%)	3/50 (6%)	38/50 (76%)
Adjusted Rates (b)	0.0%	2.7%	8.7%	87.9%
Terminal Rates (c)	0/18 (0%)	0/32 (0%)	2/32 (6%)	16/21 (76%)
Week of First Observation		687	702	494
Life Table Tests (d)	P<0.001	P=0.570	P=0.236	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.485	P=0.140	P<0.001
Cochran-Armitage Trend Test (d)				
Fisher Exact Test (d)	P<0.001	P=0.505	P=0.125	P<0.001
Testis: Interstitial Cell Adenoma				
Overall Rates (a)	36/49 (73%)	44/46 (96%)	44/50 (88%)	46/50 (92%)
Adjusted Rates (b)	94.4%	100%	100.0%	100.0%
Terminal Rates (c)	16/18 (89%)	30/30 (100%)	32/32 (100%)	21/21 (100%)
Day of First Observation	466	556	476	415
Life Table Tests (d)	P=0.064	P=0.096N	P=0.064N	P=0.376
Logistic Regression Tests (d)	P=0.082	P=0.059	P=0.084	P=0.048
Cochran-Armitage Trend Test (d)	P=0.073			
Fisher Exact Test (d)		P=0.003	P=0.056	P=0.014

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
Thyroid Gland: C-Cell Adenoma				
Overall Rates (a)	9/48 (19%)	(e) 2/8 (25%)	(e) 0/10 (0%)	9/45 (20%)
Adjusted Rates (b)	43.5%			36.1%
Terminal Rates (c)	7/18 (39%)			6/21 (29%)
Day of First Observation	554			686
Life Table Test (d)				P=0.440N
Logistic Regression Test (d)				P=0.507N
Fisher Exact Test (d)				P=0.543
Thyroid Gland: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	10/48 (21%)	(e) 3/8 (38%)	(e) 0/10 (0%)	9/45 (20%)
Adjusted Rates (b)	45.0%			36.1%
Terminal Rates (c)	7/18 (39%)			6/21 (29%)
Day of First Observation	554			686
Life Table Test (d)				P=0.341N
Logistic Regression Test (d)				P=0.422N
Fisher Exact Test (d)				P=0.563N
Circulatory System: Hemangiosarcoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	0.0%	12.0%
Terminal Rates (c)	0/18 (0%)	0/32 (0%)	0/32 (0%)	0/21 (0%)
Day of First Observation				618
Life Table Tests (d)	P=0.002	(f)	(f)	P=0.095
Logistic Regression Tests (d)	P=0.002	(f)	(f)	P=0.068
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		(f)	(f)	P=0.061
Hematopoietic System: Mononuclear Leukemia				
Overall Rates (a)	21/49 (43%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	59.7%	8.7%	5.2%	9.8%
Terminal Rates (c)	5/18 (28%)	2/32 (6%)	1/32 (3%)	1/21 (5%)
Day of First Observation	466	674	498	615
Life Table Tests (d)	P=0.001N	P<0.001N	P<0.001N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P<0.001N	P<0.001N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P<0.001N	P<0.001N	P<0.001N
All Sites: Malignant Mesothelioma				
Overall Rates (a)	1/49 (2%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	3.0%	8.0%	2.9%	7.1%
Terminal Rates (c)	0/18 (0%)	1/32 (3%)	0/32 (0%)	1/21 (5%)
Day of First Observation	639	651	716	624
Life Table Tests (d)	P=0.570	P=0.478	P=0.679N	P=0.543
Logistic Regression Tests (d)	P=0.587	P=0.333	P=0.749N	P=0.512
Cochran-Armitage Trend Test (d)	P=0.581			
Fisher Exact Test (d)		P=0.316	P=0.747N	P=0.508

(a) Number of tumor-bearing animals/number of animals examined at the site; doses calculated as *p*-chloroaniline.
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 that dosed group and the vehicle controls. 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 test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) No P value is reported because no tumors were observed in the dosed and vehicle control groups.
(g) A carcinoma was observed in a 12th animal.

TABLE A4a. HISTORICAL INCIDENCE OF SPLENIC CONNECTIVE TISSUE TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls (b)	
Iodinated glycerol	0/50
Malonaldehyde, sodium salt	0/50
Chlorpheniramine maleate	0/49
Tetrakis(hydroxymethyl)phosphonium chloride	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate	0/49
Methyl carbamate	(c) 1/50
TOTAL	1/298 (0.3%)
SD (d)	0.82%
Range (e)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(f) 8/1,906 (0.4%)
SD (d)	0.84%
Range (e)	
High	1/45
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Fibrosarcoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Sarcoma, NOS; no fibrosarcomas, osteosarcomas, or benign tumors have been observed.

TABLE A4b. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE F344/N RATS (a)

Study	Incidence of Hemangiomas or Hemangiosarcomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls (b)	
Iodinated glycerol	0/50
Malonaldehyde, sodium salt	0/50
Chlorpheniramine maleate	(c) 2/50
Tetrakis(hydroxymethyl)phosphonium chloride	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate	0/50
Methyl carbamate	0/50
TOTAL	2/300 (0.7%)
SD (d)	1.63%
Range (e)	
High	2/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(f) 12/1,936 (0.6%)
SD (d)	1.23%
Range (e)	
High	2/50
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Hemangiomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes two hemangiomas

TABLE A4c. HISTORICAL INCIDENCE OF ADRENAL MEDULLARY TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence for All Water Gavage Vehicle Controls (b)			
Iodinated glycerol	23/50	5/50	28/50
Malonaldehyde, sodium salt	5/50	0/50	5/50
Chlorpheniramine maleate	21/49	0/49	21/49
Tetrakis(hydroxymethyl)phosphonium chloride	19/50	0/50	19/50
Tetrakis(hydroxymethyl)phosphonium sulfate	22/50	1/50	23/50
Methyl carbamate	23/50	4/50	25/50
TOTAL	113/299 (37.8%)	10/299 (3.3%)	121/299 (40.5%)
SD (c)	13.94%	4.50%	16.14%
Range (d)			
High	23/50	5/50	28/50
Low	5/50	0/50	5/50
Overall Historical Incidence for Untreated Controls			
TOTAL	459/1,915 (24.0%)	37/1,915 (1.9%)	489/1,915 (25.5%)
SD (c)	13.30%	2.70%	13.65%
Range (d)			
High	31/49	6/50	32/49
Low	2/50	0/50	3/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF TESTICULAR INTERSTITIAL CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls (b)	
Iodinated glycerol	46/50
Malonaldehyde, sodium salt	40/50
Chlorpheniramine maleate	44/49
Tetrakis(hydroxymethyl)phosphonium chloride	44/50
Tetrakis(hydroxymethyl)phosphonium sulfate	40/50
Methyl carbamate	43/50
TOTAL	257/299 (86.0%)
SD (c)	5.03%
Range (d)	
High	46/50
Low	40/50
Overall Historical Incidence for Untreated Controls	
TOTAL	1,677/1,910 (87.8%)
SD (c)	7.70%
Range (d)	
High	49/50
Low	32/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4e. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls (b)	
Iodinated glycerol	16/50
Malonaldehyde, sodium salt	7/50
Chlorpheniramine maleate	25/50
Tetrakis(hydroxymethyl)phosphonium chloride	19/50
Tetrakis(hydroxymethyl)phosphonium sulfate	30/50
Methyl carbamate	23/50
TOTAL	120/300 (40.0%)
SD (c)	16.00%
Range (d)	
High	30/50
Low	7/50
Overall Historical Incidence for Untreated Controls	
TOTAL	636/1,936 (32.9%)
SD (c)	14.62%
Range (d)	
High	36/50
Low	5/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4f. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence All Water Gavage Vehicle Controls (b)			
Iodinated glycerol	25/48	1/48	26/48
Malonaldehyde, sodium salt	20/47	0/47	20/47
Chlorpheniramine maleate	12/50	0/50	12/50
Tetrakis(hydroxymethyl)phosphonium chloride	17/50	1/50	18/50
Tetrakis(hydroxymethyl)phosphonium sulfate	21/50	0/50	21/50
Methyl carbamate	26/50	3/50	29/50
TOTAL	121/295 (41.0%)	5/295 (1.7%)	126/295 (42.7%)
SD (c)	10.82%	2.34%	12.33%
Range (d)			
High	25/48	3/50	29/50
Low	12/50	0/50	12/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(e) 417/1,830 (22.8%)	(f) 42/1,830 (2.3%)	(e,f) 459/1,830 (25.1%)
SD (c)	10.75%	2.85%	10.32%
Range (d)			
High	24/46	5/45	25/46
Low	2/39	0/50	2/39

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 32 chromophobe adenomas and 1 acidophil adenoma
(f) Includes seven chromophobe carcinomas and one adenocarcinoma, NOS

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	49	50	50	50
ALIMENTARY SYSTEM				
Esophagus	(49)	(5)	(13)	(50)
Foreign body	1 (2%)		2 (15%)	1 (2%)
Inflammation, necrotizing		1 (20%)	2 (15%)	1 (2%)
Intestine large, cecum	(46)	(5)	(6)	(44)
Dilatation				1 (2%)
Inflammation, chronic active				1 (2%)
Parasite metazoan				1 (2%)
Intestine large, colon	(46)	(5)	(9)	(45)
Parasite metazoan	1 (2%)			2 (4%)
Intestine large, rectum	(47)	(5)	(8)	(44)
Inflammation, chronic active	2 (4%)			
Parasite metazoan	2 (4%)		1 (13%)	4 (9%)
Intestine small, ileum	(46)	(5)	(6)	(39)
Dilatation				1 (3%)
Inflammation, chronic active				1 (3%)
Intestine small, jejunum	(46)	(6)	(8)	(41)
Dilatation				1 (2%)
Metaplasia, osseous		1 (17%)	1 (13%)	
Necrosis		1 (17%)		
Liver	(49)	(50)	(49)	(49)
Angiectasis		1 (2%)	2 (4%)	
Basophilic focus	14 (29%)	23 (46%)	31 (63%)	21 (43%)
Clear cell focus				2 (4%)
Degeneration, cystic	10 (20%)	16 (32%)	10 (20%)	12 (24%)
Eosinophilic focus	3 (6%)		1 (2%)	2 (4%)
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hepatodiaphragmatic nodule	3 (6%)	8 (16%)	2 (4%)	2 (4%)
Inflammation, chronic	8 (16%)	15 (30%)	19 (39%)	9 (18%)
Inflammation, necrotizing	4 (8%)	2 (4%)	5 (10%)	4 (8%)
Necrosis, coagulative	6 (12%)	4 (8%)	3 (6%)	9 (18%)
Pigmentation, hemosiderin	1 (2%)			26 (53%)
Vacuolization cytoplasmic	6 (12%)	4 (8%)	9 (18%)	1 (2%)
Bile duct, hyperplasia	41 (84%)	45 (90%)	43 (88%)	47 (96%)
Mesentery	(47)	(11)	(11)	(48)
Ectopic tissue				1 (2%)
Inflammation, chronic	6 (13%)	6 (55%)	2 (18%)	5 (10%)
Necrosis	3 (6%)	4 (36%)		
Pigmentation, hemosiderin			1 (9%)	1 (2%)
Pancreas	(48)	(8)	(14)	(47)
Inflammation, chronic				1 (2%)
Pigmentation, hemosiderin		1 (13%)	1 (7%)	
Acinus, atrophy	18 (38%)	3 (38%)	3 (21%)	13 (28%)
Acinus, hyperplasia			1 (7%)	1 (2%)
Duct, ectasia	1 (2%)	1 (13%)		
Salivary glands	(49)	(6)	(11)	(49)
Granuloma	1 (2%)			
Stomach, forestomach	(47)	(6)	(11)	(46)
Acanthosis	1 (2%)		1 (9%)	1 (2%)
Hyperkeratosis	1 (2%)		1 (9%)	1 (2%)
Inflammation, chronic active	2 (4%)		2 (18%)	
Inflammation, necrotizing		1 (17%)		
Stomach, glandular	(48)	(6)	(11)	(45)
Inflammation, chronic active	1 (2%)		1 (9%)	
Mineralization	1 (2%)			
Necrosis, coagulative	1 (2%)	2 (33%)		4 (9%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
ALIMENTARY SYSTEM (Continued)				
Tongue	(2)	(1)		(1)
Foreign body	2 (100%)			1 (100%)
Inflammation, chronic active	2 (100%)	1 (100%)		1 (100%)
Tooth	(49)	(5)	(10)	(49)
Peridontal tissue, foreign body				1 (2%)
Peridontal tissue, inflammation, chronic active	2 (4%)			2 (4%)
CARDIOVASCULAR SYSTEM				
Blood vessel	(49)	(8)	(12)	(50)
Mesenteric artery, inflammation, chronic active				1 (2%)
Mesenteric artery, necrosis, fibrinoid				1 (2%)
Mesenteric artery, intima, proliferation	1 (2%)			
Pulmonary artery, thrombus		1 (13%)		
Heart	(49)	(18)	(23)	(50)
Cardiomyopathy, chronic	44 (90%)	15 (83%)	22 (96%)	42 (84%)
Mineralization				1 (2%)
Atrium, thrombus	5 (10%)	1 (6%)		8 (16%)
Endocardium, proliferation	1 (2%)			
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(49)	(49)	(49)	(49)
Degeneration, fatty	10 (20%)	10 (20%)	10 (20%)	16 (33%)
Hematocyst				1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	17 (35%)	13 (27%)	19 (39%)	17 (35%)
Hypertrophy	1 (2%)	1 (2%)		
Necrosis, coagulative	2 (4%)	1 (2%)	1 (2%)	
Adrenal gland, medulla	(49)	(48)	(48)	(48)
Cyst			1 (2%)	
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	15 (31%)	21 (44%)	15 (31%)	17 (35%)
Mineralization	1 (2%)			
Islets, pancreatic	(48)	(4)	(10)	(46)
Degeneration	1 (2%)			
Parathyroid gland	(48)	(7)	(10)	(45)
Hyperplasia		1 (14%)		
Pituitary gland	(47)	(18)	(19)	(46)
Craniopharyngeal duct, cyst				1 (2%)
Pars distalis, angiectasis		1 (6%)	1 (5%)	
Pars distalis, cyst	3 (6%)			1 (2%)
Pars distalis, hemorrhage, acute			1 (5%)	
Pars distalis, hyperplasia	11 (23%)	2 (11%)	2 (11%)	13 (28%)
Pars distalis, pigmentation, hemosiderin		1 (6%)		
Pars intermedia, angiectasis		1 (6%)		
Thyroid gland	(48)	(8)	(10)	(45)
Inflammation, necrotizing				1 (2%)
Ultimobranchial cyst	1 (2%)			
C-cell, hyperplasia	19 (40%)	4 (50%)	4 (40%)	24 (53%)
Follicular cell, hyperplasia				2 (4%)
GENERAL BODY SYSTEM				
None				

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
GENITAL SYSTEM				
Epididymis	(49)	(20)	(26)	(50)
Atrophy, diffuse	1 (2%)			
Penis			(1)	
Concretion			1 (100%)	
Preputial gland	(46)	(12)	(15)	(48)
Hyperplasia	2 (4%)		1 (7%)	3 (6%)
Inflammation, chronic active	45 (98%)	6 (50%)	7 (47%)	43 (90%)
Prostate	(49)	(6)	(13)	(48)
Abscess				1 (2%)
Inflammation, chronic active	32 (65%)	4 (67%)	11 (85%)	29 (60%)
Seminal vesicle	(36)	(3)	(5)	(23)
Inflammation, chronic active	3 (8%)			
Testes	(49)	(46)	(50)	(50)
Interstitial cell, hyperplasia	26 (53%)	29 (63%)	23 (46%)	25 (50%)
Seminiferous tubule, atrophy	33 (67%)	44 (96%)	39 (78%)	46 (92%)
HEMATOPOIETIC SYSTEM				
Blood	(44)	(45)	(39)	(31)
Leukocytosis	1 (2%)			
Neutrophilia		2 (4%)	1 (3%)	6 (19%)
Bone marrow	(49)	(50)	(49)	(50)
Hyperplasia			1 (2%)	2 (4%)
Thrombus				1 (2%)
Femoral, hyperplasia	26 (53%)	36 (72%)	35 (71%)	46 (92%)
Femoral, hyperplasia, reticulum cell			3 (6%)	
Femoral, myelofibrosis	1 (2%)			
Lymph node	(49)	(16)	(15)	(49)
Mediastinal, cyst				2 (4%)
Mediastinal, edema				1 (2%)
Mediastinal, hemorrhage, acute				1 (2%)
Mediastinal, hyperplasia, plasma cell		1 (6%)		
Mediastinal, infiltration cellular, mast cell			1 (7%)	1 (2%)
Mediastinal, infiltration cellular, histiocytic				1 (2%)
Mediastinal, pigmentation, hemosiderin				2 (4%)
Pancreatic, ectopic tissue				1 (2%)
Pancreatic, infiltration cellular, histiocytic				2 (4%)
Pancreatic, pigmentation, hemosiderin				2 (4%)
Renal, cyst		1 (6%)		1 (2%)
Lymph node, mandibular	(48)	(7)	(12)	(48)
Cyst	4 (8%)			4 (8%)
Ectasia		1 (14%)	1 (8%)	
Lymph node, mesenteric	(10)	(5)	(2)	(10)
Cyst	2 (20%)	2 (40%)	1 (50%)	2 (20%)
Ectasia			1 (50%)	
Fibrosis		1 (20%)		
Infiltration cellular, histiocytic		1 (20%)		1 (10%)
Pigmentation, hemosiderin				1 (10%)
Spleen	(49)	(50)	(50)	(50)
Cyst				1 (2%)
Fibrosis	3 (6%)	11 (22%)	12 (24%)	41 (82%)
Granuloma				1 (2%)
Hematopoietic cell proliferation	31 (63%)	48 (96%)	42 (84%)	26 (52%)
Infarct, acute	1 (2%)			1 (2%)
Infiltration cellular, lipocyte				24 (48%)
Pigmentation, hemosiderin	37 (76%)	39 (78%)	48 (96%)	21 (42%)
Sinusoid, ectasia				1 (2%)
Thymus	(43)	(5)	(13)	(36)
Cyst	1 (2%)			1 (3%)
Inflammation, chronic active				1 (3%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
INTEGUMENTARY SYSTEM				
Mammary gland	(32)	(6)	(13)	(36)
Hyperplasia, cystic	25 (78%)	6 (100%)	10 (77%)	29 (81%)
Skin	(47)	(18)	(19)	(49)
Inflammation, chronic active	1 (2%)		1 (5%)	
Inflammation, necrotizing		1 (6%)		
Inflammation, suppurative		1 (6%)		
MUSCULOSKELETAL SYSTEM				
Bone	(48)	(50)	(49)	(50)
Femur, fibrous osteodystrophy		1 (2%)		
NERVOUS SYSTEM				
Brain	(49)	(5)	(10)	(50)
Compression	4 (8%)		2 (20%)	1 (2%)
Hemorrhage, acute	1 (2%)		1 (10%)	
Hydrocephalus	5 (10%)	1 (20%)	1 (10%)	2 (4%)
Infarct, chronic	1 (2%)			
Mineralization				1 (2%)
Spinal cord	(4)		(2)	(1)
Degeneration	1 (25%)			
RESPIRATORY SYSTEM				
Lung	(49)	(7)	(11)	(50)
Granuloma				1 (2%)
Hemorrhage, acute	3 (6%)			
Inflammation, chronic	2 (4%)	1 (14%)		4 (8%)
Inflammation, suppurative				2 (4%)
Pigmentation, hemosiderin	1 (2%)			
Alveolar epithelium, hyperplasia	3 (6%)			2 (4%)
Mediastinum, inflammation, chronic active		1 (14%)		1 (2%)
Nose	(48)	(5)	(10)	(46)
Inflammation, chronic active	6 (13%)			8 (17%)
Inflammation, suppurative		1 (20%)		1 (2%)
Nasolacrimal duct, inflammation, chronic active				1 (2%)
Nasolacrimal duct, inflammation, suppurative	4 (8%)		1 (10%)	3 (7%)
Septum, thrombus, multiple	1 (2%)			
Trachea	(49)	(5)	(13)	(49)
Inflammation, necrotizing			2 (15%)	1 (2%)
SPECIAL SENSES SYSTEM				
Eye	(7)	(11)	(13)	(14)
Hemorrhage, acute		1 (9%)		
Inflammation, chronic				1 (7%)
Cornea, inflammation, chronic active		1 (9%)		
Lens, cataract	4 (57%)	11 (100%)	12 (92%)	13 (93%)
Retina, atrophy	5 (71%)	11 (100%)	13 (100%)	13 (93%)
Harderian gland	(46)	(4)	(9)	(43)
Inflammation, chronic				3 (7%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
URINARY SYSTEM				
Kidney	(48)	(50)	(49)	(50)
Inflammation, hemorrhagic		1 (2%)		
Nephropathy, chronic	46 (96%)	50 (100%)	48 (98%)	46 (92%)
Renal tubule, degeneration		1 (2%)		
Renal tubule, pigmentation, hemosiderin	47 (98%)	49 (98%)	47 (96%)	50 (100%)
Urethra	(21)	(3)	(1)	(11)
Inflammation, hemorrhagic		1 (33%)		
Transitional epithelium, hyperplasia			1 (100%)	
Urinary bladder	(47)	(7)	(12)	(46)
Dilatation		1 (14%)		1 (2%)
Hemorrhage, acute	1 (2%)			
Inflammation, chronic active				2 (4%)
Inflammation, hemorrhagic		1 (14%)		
Transitional epithelium, hyperplasia				1 (2%)

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Intestine large, cecum	(40)	*(50)	*(50)	(46)
Leukemia mononuclear		1 (2%)		
Intestine large, colon	(47)	*(50)	*(50)	(46)
Leukemia mononuclear		1 (2%)		
Intestine small, duodenum	(49)	*(50)	*(50)	(48)
Adenocarcinoma, metastatic, uterus	1 (2%)			
Intestine small, ileum	(40)	*(50)	*(50)	(45)
Leukemia mononuclear		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Leukemia mononuclear	10 (20%)	2 (4%)	1 (2%)	1 (2%)
Neoplastic nodule	1 (2%)	1 (2%)		
Sarcoma, metastatic, skin				1 (2%)
Artery, adenocarcinoma, metastatic, uterus	1 (2%)			
Mesentery	*(50)	*(50)	*(50)	*(50)
Adenocarcinoma, metastatic, uterus	1 (2%)			1 (2%)
Leukemia mononuclear	5 (10%)	2 (4%)		
Lipoma			1 (2%)	
Pancreas	(50)	*(50)	*(50)	(49)
Adenocarcinoma, metastatic, uterus	1 (2%)			1 (2%)
Leukemia mononuclear	2 (4%)	1 (2%)		
Salivary glands	(50)	*(50)	*(50)	(49)
Carcinoma, metastatic, Zymbal gland		1 (2%)		
Leukemia mononuclear	1 (2%)			
Stomach, forestomach	(50)	*(50)	*(50)	(48)
Leukemia mononuclear	1 (2%)	1 (2%)		
Stomach, glandular	(50)	*(50)	*(50)	(48)
Adenocarcinoma, metastatic, uterus	1 (2%)			
Leukemia mononuclear	1 (2%)	1 (2%)		
Tongue	*(50)	*(50)	*(50)	*(50)
Papilloma squamous	2 (4%)		1 (2%)	
CARDIOVASCULAR SYSTEM				
Heart	(50)	*(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)		
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Leukemia mononuclear	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Capsule, adenocarcinoma, metastatic, uterus	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Leukemia mononuclear	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma benign	2 (4%)	3 (6%)	1 (2%)	6 (12%)
Islets, pancreatic	(50)	*(50)	*(50)	(48)
Adenoma	1 (2%)			1 (2%)
Leukemia mononuclear	1 (2%)			
Pituitary gland	(50)	*(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)			
Pars distalis, adenoma	20 (40%)	13 (26%)	17 (34%)	20 (40%)
Pars distalis, adenoma, multiple	1 (2%)			3 (6%)
Pars distalis, carcinoma				1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM (Continued)				
Thyroid gland	(49)	*(50)	*(50)	(48)
Leukemia mononuclear	1 (2%)			
Bilateral, C-cell, adenoma	1 (2%)			
C-cell, adenoma	4 (8%)		1 (2%)	5 (10%)
C-cell, carcinoma	1 (2%)		1 (2%)	1 (2%)
Follicular cell, adenoma				1 (2%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Clitoral gland	(45)	*(50)	*(50)	(48)
Adenoma	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Leukemia mononuclear	1 (2%)			
Ovary	(50)	*(50)	*(50)	(49)
Granulosa-theca tumor benign		2 (4%)		
Leukemia mononuclear	3 (6%)	1 (2%)		
Bilateral, adenocarcinoma, metastatic, uterus	1 (2%)			
Uterus	(50)	*(50)	*(50)	(50)
Adenocarcinoma	1 (2%)	1 (2%)		1 (2%)
Fibroma				1 (2%)
Leukemia mononuclear	2 (4%)			
Polyp stromal	4 (8%)	6 (12%)	7 (14%)	6 (12%)
Polyp stromal, multiple	1 (2%)			
Vagina	*(50)	*(50)	*(50)	*(50)
Polyp				1 (2%)
HEMATOPOIETIC SYSTEM				
Blood	*(50)	*(50)	*(50)	*(50)
Leukemia mononuclear	4 (8%)	2 (4%)		1 (2%)
Bone marrow	(50)	(48)	(50)	(47)
Femoral, leukemia mononuclear	2 (4%)	1 (2%)	1 (2%)	
Lymph node	(50)	*(50)	*(50)	(50)
Inguinal, leukemia mononuclear	1 (2%)			
Mediastinal, adenocarcinoma, metastatic, uterus	1 (2%)			1 (2%)
Mediastinal, leukemia mononuclear	7 (14%)	1 (2%)		
Mediastinal, sarcoma, metastatic skin				1 (2%)
Renal, leukemia mononuclear	1 (2%)			
Lymph node, mandibular	(49)	*(50)	*(50)	(49)
Leukemia mononuclear	5 (10%)	1 (2%)		
Lymph node, mesenteric	(7)	*(50)	*(50)	(9)
Leukemia mononuclear	2 (29%)	2 (4%)		
Spleen	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)			1 (2%)
Fibrosarcoma			1 (2%)	
Leukemia mononuclear	10 (20%)	2 (4%)	1 (2%)	1 (2%)
Osteosarcoma				1 (2%)
Thymus	(42)	*(50)	*(50)	(44)
Leukemia mononuclear	2 (5%)	2 (4%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
INTEGUMENTARY SYSTEM				
Mammary gland	(49)	*(50)	*(50)	(50)
Adenoma	1 (2%)	1 (2%)		3 (6%)
Fibroadenoma	6 (12%)	8 (16%)	12 (24%)	6 (12%)
Fibroadenoma, multiple	2 (4%)	2 (4%)	1 (2%)	
Leukemia mononuclear	1 (2%)			
Sarcoma, metastatic, skin				1 (2%)
Skin	(50)	*(50)	*(50)	(50)
Basosquamous tumor benign	1 (2%)			
Leukemia mononuclear	1 (2%)			
Subcutaneous tissue, fibroma	2 (4%)	2 (4%)		2 (4%)
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, neurofibroma		1 (2%)		
Subcutaneous tissue, sarcoma				1 (2%)
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	*(50)	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)			
Sarcoma, metastatic, skin				1 (2%)
NERVOUS SYSTEM				
Brain	(50)	*(50)	*(50)	(50)
Astrocytoma benign	1 (2%)			
RESPIRATORY SYSTEM				
Lung	(49)	*(50)	*(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)			1 (2%)
Leukemia mononuclear	9 (18%)	1 (2%)		1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Nose	(49)	*(50)	*(50)	(49)
Leukemia mononuclear	1 (2%)			
Osteosarcoma			1 (2%)	
SPECIAL SENSES SYSTEM				
Zymbal gland	*(50)	*(50)	*(50)	*(50)
Carcinoma		2 (4%)		
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)			1 (2%)
Leukemia mononuclear	6 (12%)	1 (2%)	1 (2%)	
Lipoma		1 (2%)		
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(50)	*(50)	*(50)
Leukemia mononuclear	10 (20%)	2 (4%)	1 (2%)	1 (2%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Terminal sacrifice	27	39	36	37
Dead	15	5	11	8
Moribund	8	6	3	5

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
TUMOR SUMMARY				
Total animals with primary neoplasms **	37	30	34	40
Total primary neoplasms	63	48	46	65
Total animals with benign neoplasms	32	27	31	36
Total benign neoplasms	51	42	42	59
Total animals with malignant neoplasms	10	6	4	6
Total malignant neoplasms	12	6	4	6
Total animals with secondary neoplasms ***	1	1		2
Total secondary neoplasms	11	1		11

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: VEHICLE CONTROL

WEEKS ON STUDY	012	027	029	030	053	058	069	075	076	077	078	080	087	088	089	090	091	094	095	101	102	104	104	105	105
CARCASS ID	833	744	783	832	781	821	754	741	805	762	804	742	792	801	745	802	771	825	794	784	775	885	763	764	772
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, cecum	+	+	+	A	A	A	A	+	+	A	A	+	+	A	+	+	+	A	+	+	+	M	A	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	M	A	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																				X					
Intestine small, ileum	+	+	+	A	+	A	A	A	+	A	+	+	+	A	+	+	+	A	A	+	+	A	M	+	+
Intestine small, jejunum	+	+	+	A	+	+	A	+	+	A	+	+	+	A	+	+	+	A	+	+	+	A	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X		X	X						X	X	X	X		X		
Neoplastic nodule																									
Artery, adenocarcinoma, metastatic, uterus																				X					
Mesentery	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																				X					
Leukemia mononuclear											X							X		X	X		X		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																				X					
Leukemia mononuclear																		X			X				
Pharynx	+																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																				X					
Leukemia mononuclear																		X							
Tongue	+														+					+					
Papilloma squamous															X					X					
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X							X			X		X		
Capsule, adenocarcinoma, metastatic, uterus																				X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X							X			X		X		
Pheochromocytoma benign												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Leukemia mononuclear																		X							
Parathyroid gland	+	+	M	M	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X		
Pars distalis, adenoma							X		X				X	X	X	X	X		X			X			
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Bilateral, c-cell, adenoma																								X	
C-cell, adenoma										X															
C-cell, carcinoma																					X				
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma																									
Leukemia mononuclear											X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X							X			X				
Bilateral, adenocarcinoma, metastatic, uterus																				X					
Oviduct	+	+		+		+		+	+		M	+	M	M		M		+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																				X					
Leukemia mononuclear											X							X							
Polyp stromal									X							X				X					
Polyp stromal, multiple																									

+: Tissue examined microscopically
: Not examined
–: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	793	803	815	752	761	773	791	811	823	834	751	755	765	782	795	835	743	753	774	812	813	814	822	824	831	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uterus																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X		X												10
Neoplastic nodule																								X		1
Artery, adenocarcinoma, metastatic, uterus																										1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear																										5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear																										2
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear																										1
Tongue																										3
Papilloma squamous																										2
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Capsule, adenocarcinoma, metastatic, uterus																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Pheochromocytoma benign														X												2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pars distalis, adenoma	X		X		X		X							X	X	X				X	X			X	X	20
Pars distalis, adenoma, multiple				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Bilateral, c-cell, adenoma																										1
C cell, adenoma											X							X			X					4
C cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	45
Adenoma					X																					1
Leukemia mononuclear																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Bilateral, adenocarcinoma, metastatic, uterus																										1
Oviduct	+	+	+	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Leukemia mononuclear																										2
Polyp stromal										X																4
Polyp stromal, multiple															X											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	012	027	029	030	053	058	069	075	076	077	078	080	087	088	089	090	091	094	095	101	102	104	104	105	105
CARCASS ID	833	744	783	832	781	821	754	741	805	762	804	742	792	801	745	802	771	825	794	784	775	785	763	764	772
HEMATOPOIETIC SYSTEM																									
Blood		+	+						+						+						+			+	+
Leukemia mononuclear									X												X				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear									X		X														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, leukemia mononuclear																					X				
Mediastinal, adenocarcinoma, metastatic, uterus																				X					
Mediastinal, leukemia mononuclear									X		X							X	X	X	X		X		
Renal, leukemia mononuclear																							X		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X							X	X		X		X		
Lymph node, mesenteric			+	+												+					+	+	+		
Leukemia mononuclear																					X		X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																				X					
Leukemia mononuclear									X		X	X						X	X	X	X		X		
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Leukemia mononuclear											X										X				
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma													X												
Fibroadenoma						X																X			
Fibroadenoma, multiple																									
Leukemia mononuclear											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign												X													
Leukemia mononuclear											X														
Subcutaneous tissue, fibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																									
Peripheral nerve			+	+		+																			
Spinal cord		+	+	+	+	+																			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																				X					
Leukemia mononuclear									X		X	X						X	X	X	X		X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Leukemia mononuclear																		X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye									+								+							+	
Harderian gland	+	+	+	+	M	+	M	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																				X					
Leukemia mononuclear									X		X							X		X	X		X		
Ureter		+						+		+					+		+		+	+	+		+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	793	803	815	752	761	773	791	811	823	834	751	755	765	782	795	835	743	753	774	812	813	814	822	824	831	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Leukemia mononuclear												X		X												4
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, leukemia mononuclear																										1
Mediastinal, adenocarcinoma, metastatic, uterus																										1
Mediastinal, leukemia mononuclear																										7
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										5
Lymph node, mesenteric																								+		7
Leukemia mononuclear																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear												X		X												10
Thymus	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	42
Leukemia mononuclear																										2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Fibroadenoma	X					X									X									X		6
Fibroadenoma, multiple																X				X						2
Leukemia mononuclear																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign																										1
Leukemia mononuclear																										1
Subcutaneous tissue, fibroma							X										X								2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Leukemia mononuclear																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma benign							X																			1
Peripheral nerve																										3
Spinal cord																										5
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear														X												9
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye	+			+			+		+		+	+	+		+								+			12
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear																										6
Ureter		+		+					+			+	+			+		+		+						17
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: LOW DOSE

WEEKS ON STUDY	020	062	087	087	089	095	099	099	103	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	6683	7334	6444	7111	7114	6654	6744	7223	6884	6533	7333	6441	6425	6555	6661	8757	6822	7022	7112	7113	7212	7331	7335	6551	6552
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+			+	+		+														
Intestine large	+	+	+	+	+						+														
Intestine large, cecum	M	A	+	+	+																				
Leukemia mononuclear					X																				
Intestine large, colon	+	+	+	+	+						+														
Leukemia mononuclear					X																				
Intestine large, rectum	M	A	+	+	+																				
Intestine small	+	+	+	+	+																				
Intestine small, duodenum	M	A	+	+	+																				
Intestine small, ileum	M	A	+	+	+																				
Leukemia mononuclear					X																				
Intestine small, jejunum	+	+	+	+	+																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X														
Neoplastic nodule								X																	
Mesentery	+		+	+	+						+						+								
Leukemia mononuclear					X						X														
Pancreas	+	+	+	+	+						+														
Leukemia mononuclear					X																				
Salivary glands	+	+	+	+	+	+			+	+															
Carcinoma, metastatic, Zymbal gland										X															
Stomach	+	+	+	+	+																				
Stomach, forestomach	+	+	+	+	+																				
Leukemia mononuclear					X																				
Stomach, glandular	+	A	+	+	+																				
Leukemia mononuclear					X																				
Tooth		+	+	+	+																				
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+				+		+														
Heart	+	+	+	+	+				+													+			
Leukemia mononuclear					X																				
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear											X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+																				
Parathyroid gland	+	M	+	+	+																				
Pituitary gland	+	+	+	+	+		+	+	+		+	+	+	+	+		+	+			+				+
Pars distalis, adenoma			X	X				X	X			X	X								X				
Thyroid gland	+	+	+	+	+			+																	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	+	M	+	M						+														
Adenoma																									
Ovary	+	+	+	+	+														+			+			
Granulosa-theca tumor benign																									
Leukemia mononuclear					X																				
Oviduct	+																		+			+			
Uterus	+	+	+	+	+			+			+		+		+				+						
Adenocarcinoma																									
Polyp stromal								X			X				X				X						

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	662	671	685	691	692	695	703	715	724	725	732	743	764	765	773	781	793	794	704	845	863	872	701	705	722	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										8
Intestine large							+																			7
Intestine large, cecum							+																			4
Leukemia mononuclear																										1
Intestine large, colon																										6
Leukemia mononuclear																										1
Intestine large, rectum																										3
Intestine small																										5
Intestine small, duodenum																										3
Intestine small, ileum																										3
Leukemia mononuclear																										1
Intestine small, jejunum																										5
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Neoplastic nodule																										1
Mesentery				+																						7
Leukemia mononuclear																										2
Pancreas																										6
Leukemia mononuclear																										1
Salivary glands																										8
Carcinoma, metastatic, Zymbal gland																										1
Stomach																										5
Stomach, forestomach																										5
Leukemia mononuclear																										1
Stomach, glandular																										4
Leukemia mononuclear																										1
Tooth																										4
CARDIOVASCULAR SYSTEM																										
Blood vessel					+																					8
Heart																										7
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Leukemia mononuclear																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pheochromocytoma benign	X								X													X				3
Islets, pancreatic																										5
Parathyroid gland																										4
Pituitary gland	+	+	+			+	+	+	+	+		+			+	+	+	+			+	+		+		33
Pars distalis, adenoma	X						X		X		X					X						X				13
Thyroid gland																										6
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland									+							+										5
Adenoma									X																	1
Ovary		+			+					+				+				+		+	+		+			15
Granulosa-theca tumor benign																				X			X			2
Leukemia mononuclear																										1
Oviduct		+			+					+				+				+			+		+			10
Uterus				+				+									+						M	+		14
Adenocarcinoma								X																		1
Polyp stromal				X													X									6

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE
(Continued)

WEEKS ON STUDY	020	062	087	087	089	095	099	099	103	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	683	734	644	711	714	654	674	723	684	653	733	641	642	655	661	675	682	702	712	713	721	731	735	651	652
HEMATOPOIETIC SYSTEM																									
Blood			+	+	+		+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X														
Bone marrow	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear					X																				
Lymph node	+	+	+	+	+	+			+	+	+														
Mediastinal, leukemia mononuclear											X														
Lymph node, mandibular	+	+	+	+	+	+			+																
Leukemia mononuclear					X																				
Lymph node, mesenteric					+				M		+														
Leukemia mononuclear					X						X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X														
Thymus	+	+	+	+	+				+		+														
Leukemia mononuclear					X						X														
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+						+				+						+		+		
Adenoma																									
Fibroadenoma																					X		X		
Fibroadenoma, multiple															X										
Skin	+	+	+	+	+		+	+		+					+						+		+		
Subcutaneous tissue, fibroma			X																						
Subcutaneous tissue, fibrosarcoma							X																		
Subcutaneous tissue, neurofibroma								X																	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+																				
Peripheral nerve		+																							
Spinal cord		+																							
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+																				
Leukemia mononuclear					X																				
Nose	M	+	+	+	+																				
Trachea	M	+	+	+	+			+	+		+														
SPECIAL SENSES SYSTEM																									
Eye					+		+	+		+		+	+	+	+		+	+	+		+	+		+	+
Harderian gland		+	+	+	+																				
Zymbal gland										+											+				
Carcinoma										X											X				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Lipoma																									
Ureter		+		+	+			+	+				+		+		+							
Urinary bladder	+	+	+	+	+																				

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	662	671	685	691	692	695	703	715	724	725	732	643	664	665	673	681	693	694	704	645	663	672	701	705	722	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	48
Femoral, leukemia mononuclear																										1
Lymph node					+		+			+																12
Mediastinal, leukemia mononuclear																										1
Lymph node, mandibular																										7
Leukemia mononuclear																										1
Lymph node, mesenteric							+			+																4
Leukemia mononuclear																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Thymus					+																					8
Leukemia mononuclear																										2
INTEGUMENTARY SYSTEM																										
Mammary gland					+	+	+		+	+						+			+				+		+	17
Adenoma																X										1
Fibroadenoma					X	X	X		X														X		X	8
Fibroadenoma, multiple																			X							2
Skin					+	+	+		+			+				+			+				+		+	20
Subcutaneous tissue, fibroma												X														2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, neurofibroma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle																										5
NERVOUS SYSTEM																										
Brain																										5
Peripheral nerve																										1
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung																										5
Leukemia mononuclear																										1
Nose																										4
Trachea					+																					8
SPECIAL SENSES SYSTEM																										
Eye				+	+	+	+	+	+	+	+	+		+				+	+	+	+			+	+	+	32
Harderian gland						+		+																		6
Zymbal gland																										2
Carcinoma																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lipoma						X																				1
Ureter									+		+					+							+			12
Urinary bladder																										5

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: MID DOSE

WEEKS ON STUDY	048	075	077	079	082	083	085	087	090	090	094	101	102	103	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	631	583	601	575	564	541	615	555	604	553	543	592	542	581	545	584	585	593	602	603	612	613	622	625	632
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+															
Intestine large	+	+	+	+	+	+	+	+	+	+											+				
Intestine large, cecum	A	A	A	A	A	A	A	+	+	A											+				
Intestine large, colon	+	A	A	A	+	+	+	+	+	+															
Intestine large, rectum	M	+	A	A	+	+	+	+	M	+															
Intestine small	+	+	+	+	+	+	+	+	+	+															
Intestine small, duodenum	+	+	+	A	+	A	+	+	+	+															
Intestine small, ileum	A	A	M	A	A	A	A	+	+	A															
Intestine small, jejunum	A	A	A	A	+	A	A	+	M	A															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Mesentery	+	+	+	+	+	+		+	+	+											+				
Lipoma																					X				
Pancreas	+	+	+	+	+	+	+	+	+	+													+		
Salivary glands	+	+	+	+	+	+	+	+	+	+				+											
Stomach	+	+	+	+	+	+	+	+	+	+															
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+															
Stomach, glandular	+	+	A	+	+	+	+	+	+	+															
Tongue																									
Papilloma squamous																									
Tooth	+	+	+	+	+	+	+	+	+	+															
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+															
Heart	+	+	+	+	+	+	+	+	+	+															
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Pheochromocytoma benign																									
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+															
Parathyroid gland	+	M	+	+	+	+	+	+	+	+															
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+		+				+	+			+	+	+	+
Pars distalis, adenoma		X	X	X		X			X			X		X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+										+					
C-cell, adenoma				X																					
C-cell, carcinoma																				X					
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+															
Adenoma								X																	
Ovary	+	+	+	+	+	+	+	+	+	+					+										
Oviduct		+		+	+		+								+										
Uterus	+	+	+	+	+	+	+	+	+	+			+						+		+	+		+	
Polyp stromal	X				X	X		X													X				
HEMATOPOIETIC SYSTEM																									
Blood								I	+					+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear													X												
Lymph node	+	+	+	+	+	+	+	+	+	+	+			+					+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+			+					+						
Lymph node, mesenteric																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									X
Leukemia mononuclear													X												
Thymus	+	+	+	+	+	+	+	+	+	+															
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+				+			+	+							
Fibroadenoma			X				X		X					X			X	X							
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+				+			+	+							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+															
Spinal cord	+																								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+															
Nose	+	+	+	+	+	+	+	+	+	+				+											
Osteosarcoma														X											
Trachea	+	+	+	+	+	+	+	+	+	+															
SPECIAL SENSES SYSTEM																									
Eye															+	+		+	+	+	+	+	+	+	+
Harderian gland	+	+		+	+	+	+	+	+	+															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Ureter	+		+	+				+	+							+								+	
Urinary bladder	+	M	A	+	+	+	+	+	+	+															

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: MID DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	634	551	561	565	571	573	595	621	623	544	552	554	562	563	574	591	605	611	624	633	572	582	594	614	635	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus													+									+				12
Intestine large																+										12
Intestine large, cecum																										3
Intestine large, colon																+										8
Intestine large, rectum																										6
Intestine small																										10
Intestine small, duodenum																										8
Intestine small, ileum																										2
Intestine small, jejunum																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesentery																							+			11
Lipoma																										1
Pancreas											+															12
Salivary glands													+													12
Stomach																										10
Stomach, forestomach																										9
Stomach, glandular																										9
Tongue																	+									1
Papilloma squamous																	X									1
Tooth																										10
CARDIOVASCULAR SYSTEM																										
Blood vessel													+									+				12
Heart																										10
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pheochromocytoma benign									X																	1
Islets, pancreatic																										9
Parathyroid gland																										9
Pituitary gland	+	+	+	+		+	+		+	+		+	+		+			+		+	+			+	+	35
Pars distalis, adenoma	X	X				X			X	X			X		X			X			X				X	17
Thyroid gland																										11
C-cell, adenoma																										1
C-cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																				+						11
Adenoma																										1
Ovary													+						+				+	+		15
Oviduct													+										+	+		8
Uterus		+					+					+				+							+			20
Polyp stromal												X				X										7
HEMATOPOIETIC SYSTEM																										
Blood		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										1
Lymph node											+		+			+						+				17
Lymph node, mandibular													+													14
Lymph node, mesenteric																+										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Leukemia mononuclear																										1
Thymus																						+				11
INTEGUMENTARY SYSTEM																										
Mammary gland		+			+					+	+		+		+				+	+					+	22
Fibroadenoma		X			X						X		X		X										X	12
Fibroadenoma, multiple																			X							1
Skin		+			+					+	+		+		+				+						+	21
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										10
NERVOUS SYSTEM																										
Brain																										10
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung																						+				11
Nose																										11
Osteosarcoma																										1
Trachea													+							+		+				13
SPECIAL SENSES SYSTEM																										
Eye	+	+				+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	31
Harderian gland																		+		+						11
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Ureter			+													+								+	+	11
Urinary bladder																										8

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: HIGH DOSE

WEEKS ON STUDY	073	076	076	079	083	085	088	089	092	095	099	101	102	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	505	494	535	522	443	474	532	462	455	524	523	475	485	453	481	491	502	511	515	441	445	451	454	463	472
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	A	+	+	A	A	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Sarcoma, metastatic, skin										X															
Mesentery	+	+	+	+			+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus													X												
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma benign																		X		X					
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Parathyroid gland	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X			X					X	X	X											X	X	
Pars distalis, adenoma, multiple																									X
Pars distalis, carcinoma									X																
Thyroid gland	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						+		+	
C-cell, carcinoma																						X		X	
Follicular cell, adenoma			X																						
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma							X										X								
Ovary	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct		+	M	+	+	+	M			+	+	+		+	+	+	+	+	+		+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X												
Fibroma																									
Polyp stromal																		X							
Vagina						+																			
Polyp						X																			

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	49 5	50 1	50 3	53 1	44 2	46 5	47 3	48 2	48 4	51 3	51 4	52 1	52 5	53 4	44 4	45 2	46 1	46 4	47 1	48 3	49 2	49 3	50 4	51 2	53 3	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X					1
Sarcoma, metastatic, skin																										1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X					1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X					1
Pheochromocytoma benign										X			X						X					X		6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X				X			X				X		X	X	X		X		X	X	20
Pars distalis, adenoma, multiple			X										X													3
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C cell, adenoma														X									X		X	5
C cell, carcinoma												X														1
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Adenoma								X					X													4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Oviduct	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Fibroma																									X	1
Polyp stromal						X		X			X			X					X							6
Vagina																										1
Polyp																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	073	076	076	079	083	085	088	089	092	095	099	101	102	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	505	494	535	522	443	474	532	462	455	524	523	475	485	453	481	491	502	511	515	441	445	451	454	463	472
HEMATOPOIETIC SYSTEM																									
Blood		+	+			+		+		+	+			+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, adenocarcinoma, metastatic, uterus													X												
Mediastinal, sarcoma, metastatic, skin										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric			+					+					+		+										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus													X												
Leukemia mononuclear																									
Osteosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Fibroadenoma											X											X	X		
Sarcoma, metastatic, skin										X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma			X																						
Subcutaneous tissue, sarcoma										X															
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin										X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus													X												
Leukemia mononuclear																									
Sarcoma, metastatic, skin										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye								+		+	+				+	+	+	+	+		+		+	+	+
Harderian gland	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus													X												
Ureter										+		+			+									+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: *HIGH DOSE* (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	495	501	503	531	442	465	473	482	484	513	514	521	525	534	444	452	461	464	471	483	492	493	504	512	533	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leukemia mononuclear																					X					1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, adenocarcinoma, metastatic, uterus																										1
Mediastinal, sarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric			+					+										+		+		+				9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear																					X					1
Osteosarcoma															X											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	44
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																		X						3
Fibroadenoma																		X						X	X	6
Sarcoma, metastatic, skin																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma				X																						2
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Leukemia mononuclear																					X					1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+		+	+	+	+	+			+	+	+	+		+	+	+			+	+	+	31
Harderian gland	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Ureter						+		+							+		+					+				9
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
Adrenal Medulla: Pheochromocytoma				
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	6.2%	7.7%	2.8%	16.2%
Terminal Rates (c)	1/27 (4%)	3/39 (8%)	1/36 (3%)	6/37 (16%)
Day of First Observation	557	729	729	729
Life Table Tests (d)	P=0.091	P=0.650	P=0.415N	P=0.248
Logistic Regression Tests (d)	P=0.077	P=0.553	P=0.488N	P=0.192
Cochran-Armitage Trend Test (d)	P=0.062			
Fisher Exact Test (d)		P=0.500	P=0.500N	P=0.134
Clitoral Gland: Adenoma				
Overall Rates (a)	1/45 (2%)	(e) 1/5 (20%)	(e) 1/11 (9%)	4/48 (8%)
Adjusted Rates (b)	4.3%			10.6%
Terminal Rates (c)	1/23 (4%)			3/35 (9%)
Day of First Observation	729			616
Life Table Test (d)				P=0.309
Logistic Regression Test (d)				P=0.265
Fisher Exact Test (d)				P=0.201
Mammary Gland: Adenoma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.6%	2.6%	0.0%	8.1%
Terminal Rates (c)	0/27 (0%)	1/39 (3%)	0/36 (0%)	3/37 (8%)
Day of First Observation	605	729		729
Life Table Tests (d)	P=0.155	P=0.692N	P=0.475N	P=0.407
Logistic Regression Tests (d)	P=0.140	P=0.769N	P=0.543N	P=0.351
Cochran-Armitage Trend Test (d)	P=0.128			
Fisher Exact Test (d)		P=0.753N	P=0.500N	P=0.309
Mammary Gland: Fibroadenoma				
Overall Rates (a)	8/50 (16%)	10/50 (20%)	13/50 (26%)	6/50 (12%)
Adjusted Rates (b)	26.6%	25.6%	31.8%	15.7%
Terminal Rates (c)	6/27 (22%)	10/39 (26%)	9/36 (25%)	5/37 (14%)
Day of First Observation	400	729	539	688
Life Table Tests (d)	P=0.138N	P=0.487N	P=0.375	P=0.192N
Logistic Regression Tests (d)	P=0.174N	P=0.582	P=0.233	P=0.275N
Cochran-Armitage Trend Test (d)	P=0.229N			
Fisher Exact Test (d)		P=0.398	P=0.163	P=0.387N
Mammary Gland: Adenoma or Fibroadenoma				
Overall Rates (a)	9/50 (18%)	11/50 (22%)	13/50 (26%)	9/50 (18%)
Adjusted Rates (b)	28.5%	28.2%	31.8%	23.6%
Terminal Rates (c)	6/27 (22%)	11/39 (28%)	9/36 (25%)	8/37 (22%)
Day of First Observation	400	729	539	688
Life Table Tests (d)	P=0.307N	P=0.457N	P=0.475	P=0.342N
Logistic Regression Tests (d)	P=0.371N	P=0.572	P=0.311	P=0.469N
Cochran-Armitage Trend Test (d)	P=0.451N			
Fisher Exact Test (d)		P=0.402	P=0.235	P=0.602N
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	21/50 (42%)	(e) 13/33 (39%)	(e) 17/35 (49%)	23/50 (46%)
Adjusted Rates (b)	56.9%			53.0%
Terminal Rates (c)	12/27 (44%)			17/37 (46%)
Day of First Observation	482			511
Life Table Test (d)				P=0.294N
Logistic Regression Test (d)				P=0.573N
Fisher Exact Test (d)				P=0.420

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma				
Overall Rates (a)	21/50 (42%)	(e) 13/33 (39%)	(e) 17/35 (49%)	24/50 (48%)
Adjusted Rates (b)	56.9%			54.1%
Terminal Rates (c)	12/27 (44%)			17/37 (46%)
Day of First Observation	482			511
Life Table Test (d)				P=0.353N
Logistic Regression Test (d)				P=0.507
Fisher Exact Test (d)				P=0.344
Subcutaneous Tissue: Fibroma or Neurofibroma				
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	7.4%	6.8%	0.0%	4.7%
Terminal Rates (c)	2/27 (7%)	1/39 (3%)	0/36 (0%)	1/37 (3%)
Day of First Observation	729	605		529
Life Table Tests (d)	P=0.507N	P=0.647	P=0.177N	P=0.594N
Logistic Regression Tests (d)	P=0.559N	P=0.559	P=0.178N	P=0.679N
Cochran-Armitage Trend Test (d)	P=0.555N			
Fisher Exact Test (d)		P=0.500	P=0.247N	P=0.691
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	7.4%	6.8%	0.0%	4.7%
Terminal Rates (c)	2/27 (7%)	1/39 (3%)	0/36 (0%)	1/37 (3%)
Day of First Observation	729	605		529
Life Table Tests (d)	P=0.506N	P=0.649	P=0.177N	P=0.594N
Logistic Regression Tests (d)	P=0.560N	P=0.557	P=0.178N	P=0.679N
Cochran-Armitage Trend Test (d)	P=0.555N			
Fisher Exact Test (d)		P=0.500	P=0.247N	P=0.691N
Subcutaneous Tissue: Fibroma, Neurofibroma, Sarcoma, or Fibrosarcoma				
Overall Rates (a)	2/50 (4%)	4/50 (8%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	7.4%	8.9%	0.0%	7.1%
Terminal Rates (c)	2/27 (7%)	1/39 (3%)	0/36 (0%)	1/37 (3%)
Day of First Observation	729	605		529
Life Table Tests (d)	P=0.600	P=0.500	P=0.177N	P=0.621
Logistic Regression Tests (d)	P=0.544	P=0.390	P=0.178N	P=0.521
Cochran-Armitage Trend Test (d)	P=0.549			
Fisher Exact Test (d)		P=0.339	P=0.247N	P=0.500
Thyroid Gland: C-Cell Adenoma				
Overall Rates (a)	5/49 (10%)	(e) 0/6 (0%)	(e) 1/11 (9%)	5/48 (10%)
Adjusted Rates (b)	16.9%			13.5%
Terminal Rates (c)	4/27 (15%)			5/37 (14%)
Day of First Observation	537			729
Life Table Test (d)				P=0.436N
Logistic Regression Test (d)				P=0.541N
Fisher Exact Test (d)				P=0.617
Thyroid Gland: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	6/49 (12%)	(e) 0/6 (0%)	(e) 2/11 (18%)	6/48 (13%)
Adjusted Rates (b)	19.7%			16.2%
Terminal Rates (c)	4/27 (15%)			6/37 (16%)
Day of First Observation	537			729
Life Table Test (d)				P=0.410N
Logistic Regression Test (d)				P=0.515N
Fisher Exact Test (d)				P=0.606

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	2 mg/kg	6 mg/kg	18 mg/kg
Uterus: Stromal Polyp				
Overall Rates (a)	5/50 (10%)	(e) 6/14 (43%)	(e) 7/20 (35%)	6/50 (12%)
Adjusted Rates (b)	15.0%			16.2%
Terminal Rates (c)	2/27 (7%)			6/37 (16%)
Day of First Observation	529			729
Life Table Test (d)				P=0.560N
Logistic Regression Test (d)				P=0.596
Fisher Exact Test (d)				P=0.500
Hematopoietic System: Mononuclear Leukemia				
Overall Rates (a)	10/50 (20%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	27.2%	4.6%	2.6%	2.7%
Terminal Rates (c)	2/27 (7%)	0/39 (0%)	0/36 (0%)	1/37 (3%)
Day of First Observation	529	617	711	729
Life Table Tests (d)	P=0.010N	P=0.005N	P=0.003N	P=0.002N
Logistic Regression Tests (d)	P=0.013N	P=0.015N	P=0.004N	P=0.004N
Cochran-Armitage Trend Test (d)	P=0.012N			
Fisher Exact Test (d)		P=0.014N	P=0.004N	P=0.004N

(a) Number of tumor-bearing animals/number of animals examined at the site; doses calculated as *p*-chloroaniline.
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 that dosed group and the vehicle controls. 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 test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues

TABLE B4a. HISTORICAL INCIDENCE OF SPLENIC SARCOMAS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls (b)	
Iodinated glycerol	0/48
Malonaldehyde, sodium salt	0/50
Chlorpheniramine maleate	0/50
Tetrakis(hydroxymethyl)phosphonium chloride	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate	0/49
Methyl carbamate	0/50
TOTAL	0/297 (0.0%)
SD (c)	0.00%
Range (d)	
High	0/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(e) 1/1,961 (0.05%)
SD (c)	0.40%
Range (d)	
High	1/40
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Sarcoma, NOS; no fibrosarcomas or osteosarcomas have been observed.

TABLE B4b. HISTORICAL INCIDENCE OF ADRENAL MEDULLARY TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls	
	Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence for All Water Gavage Vehicle Controls (b)		
Iodinated glycerol	1/49	2/49
Malonaldehyde, sodium salt	4/50	5/50
Chlorpheniramine maleate	3/50	3/50
Tetrakis(hydroxymethyl)phosphonium chloride	2/50	2/50
Tetrakis(hydroxymethyl)phosphonium sulfate	4/47	4/47
Methyl carbamate	4/49	4/49
TOTAL	18/295 (6.1%)	20/295 (6.8%)
SD (c)	2.63%	2.49%
Range (d)		
High	4/47	5/50
Low	1/49	2/50
Overall Historical Incidence for Untreated Controls		
TOTAL	92/1,968 (4.7%)	99/1,968 (5.0%)
SD (c)	3.75%	3.70%
Range (d)		
High	8/50	8/50
Low	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4c. HISTORICAL INCIDENCE OF LEUKEMIA IN FEMALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls (b)	
Iodinated glycerol	15/50
Malonaldehyde, sodium salt	5/50
Chlorpheniramine maleate	11/50
Tetrakis(hydroxymethyl)phosphonium chloride	4/50
Tetrakis(hydroxymethyl)phosphonium sulfate	23/49
Methyl carbamate	17/50
TOTAL	75/299 (25.1%)
SD (c)	14.90%
Range (d)	
High	23/49
Low	4/50
Overall Historical Incidence for Untreated Controls	
TOTAL	383/1,983 (19.3%)
SD (c)	6.66%
Range (d)	
High	15/50
Low	3/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) The methyl carbamate study was conducted at Microbiological Associates, and the iodinated glycerol study was conducted at EG&G Mason Research Institute; all other studies were performed by Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Esophagus	(50)	(8)	(12)	(50)
Foreign body	6 (12%)	1 (13%)	3 (25%)	
Inflammation, chronic active	1 (2%)			
Intestine large, cecum	(40)	(4)	(3)	(46)
Inflammation, chronic active		1 (25%)		
Parasite metazoan	1 (3%)	1 (25%)		1 (2%)
Intestine large, colon	(47)	(6)	(8)	(46)
Inflammation, chronic active				1 (2%)
Inflammation, necrotizing			1 (13%)	
Parasite metazoan	4 (9%)		1 (13%)	3 (7%)
Intestine large, rectum	(45)	(3)	(6)	(47)
Parasite metazoan	3 (7%)		1 (17%)	2 (4%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus	38 (76%)	45 (90%)	46 (92%)	44 (88%)
Clear cell focus		1 (2%)		3 (6%)
Degeneration, cystic		1 (2%)		
Degeneration, fatty	1 (2%)			
Fibrosis	1 (2%)			
Hepatodiaphragmatic nodule	5 (10%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic	32 (64%)	30 (60%)	32 (64%)	36 (72%)
Inflammation, necrotizing	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Necrosis, coagulative			2 (4%)	1 (2%)
Pigmentation, hemosiderin				1 (2%)
Vacuolization cytoplasmic	3 (6%)	3 (6%)		1 (2%)
Bile duct, hyperplasia	8 (16%)	3 (6%)	1 (2%)	9 (18%)
Portal vein, intima, proliferation			1 (2%)	
Mesentery	(49)	(7)	(11)	(47)
Inflammation, chronic		2 (29%)	2 (18%)	8 (17%)
Necrosis		2 (29%)		1 (2%)
Pancreas	(50)	(6)	(12)	(49)
Ectopic tissue				1 (2%)
Inflammation, chronic			2 (17%)	2 (4%)
Acinus, atrophy	13 (26%)	1 (17%)	3 (25%)	15 (31%)
Pharynx	(1)			
Inflammation, chronic active	1 (100%)			
Salivary glands	(50)	(8)	(12)	(49)
Inflammation, chronic active				1 (2%)
Stomach, forestomach	(50)	(5)	(9)	(48)
Acanthosis	1 (2%)			
Hyperkeratosis	1 (2%)			
Inflammation, chronic active	1 (2%)	1 (20%)		2 (4%)
Stomach, glandular	(50)	(4)	(9)	(48)
Inflammation, chronic active	1 (2%)			1 (2%)
Necrosis, coagulative	1 (2%)	1 (25%)		
Tooth	(50)	(4)	(10)	(50)
Inflammation, chronic active	1 (2%)			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
CARDIOVASCULAR SYSTEM				
Blood vessel	(49)	(8)	(12)	(49)
Mesenteric artery, inflammation, chronic active				2 (4%)
Heart	(50)	(7)	(10)	(50)
Cardiomyopathy, chronic	32 (64%)	2 (29%)	7 (70%)	44 (88%)
Inflammation, chronic active				1 (2%)
Coronary artery, inflammation, chronic active	1 (2%)	1 (14%)		
Endocardium, proliferation		1 (14%)		
Valve, inflammation, chronic active	1 (2%)			
ENDOCRINE SYSTEM				
Adrenal gland	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule			1 (2%)	
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)		1 (2%)	
Cyst		1 (2%)		
Degeneration, fatty	4 (8%)	10 (20%)	9 (18%)	11 (22%)
Hyperplasia	13 (26%)	23 (46%)	18 (36%)	20 (40%)
Hypertrophy	1 (2%)	2 (4%)		
Necrosis	3 (6%)			
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Hyperplasia	4 (8%)	4 (8%)	7 (14%)	24 (48%)
Pituitary gland	(50)	(33)	(35)	(50)
Pars distalis, angiectasis	2 (4%)	1 (3%)		
Pars distalis, atypical cells			1 (3%)	
Pars distalis, cyst	2 (4%)	3 (9%)	7 (20%)	12 (24%)
Pars distalis, degeneration, cystic				1 (2%)
Pars distalis, hyperplasia	17 (34%)	18 (55%)	9 (26%)	16 (32%)
Pars distalis, inflammation, chronic				1 (2%)
Pars nervosa, hyperplasia, glandular				2 (4%)
Thyroid gland	(49)	(6)	(11)	(48)
Cyst	1 (2%)			
Inflammation, chronic active				1 (2%)
C-cell, hyperplasia	25 (51%)	3 (50%)	2 (18%)	39 (81%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Clitoral gland	(45)	(5)	(11)	(48)
Hyperplasia	2 (4%)	1 (20%)	1 (9%)	5 (10%)
Inflammation, chronic active	8 (18%)	1 (20%)	1 (9%)	7 (15%)
Duct, dilatation			1 (9%)	
Ovary	(50)	(15)	(15)	(49)
Cyst	4 (8%)		4 (27%)	4 (8%)
Uterus	(50)	(14)	(20)	(50)
Dilatation	2 (4%)	2 (14%)	5 (25%)	6 (12%)
Hemorrhage, chronic				1 (2%)
Inflammation, chronic active		1 (7%)	1 (5%)	1 (2%)
Endometrium, hyperplasia, cystic, glandular	9 (18%)	1 (7%)	3 (15%)	8 (16%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM				
Blood	(32)	(45)	(37)	(43)
Lymphopenia	1 (3%)			
Neutropenia	1 (3%)			
Neutrophilia	1 (3%)	2 (4%)		3 (7%)
Bone marrow	(50)	(48)	(50)	(47)
Femoral, atrophy	1 (2%)	1 (2%)		
Femoral, hemorrhage, acute		1 (2%)		
Femoral, hyperplasia	11 (22%)	12 (25%)	21 (42%)	37 (79%)
Femoral, hyperplasia, re cell				4 (9%)
Femoral, hyperplasia, reticulum cell	1 (2%)	2 (4%)	7 (14%)	7 (15%)
Lymph node	(50)	(12)	(17)	(50)
Bronchial, pigmentation, hemosiderin				1 (2%)
Mediastinal, cyst				2 (4%)
Mediastinal, infiltration cellular, histiocytic				2 (4%)
Mediastinal, inflammation, suppurative			1 (6%)	
Mediastinal, necrosis	1 (2%)			
Pancreatic, pigmentation, hemosiderin				1 (2%)
Renal, cyst			1 (6%)	
Renal, inflammation, chronic active			1 (6%)	
Lymph node, mandibular	(49)	(7)	(14)	(49)
Cyst				2 (4%)
Hemorrhage	1 (2%)			
Hyperplasia, plasma cell	1 (2%)			1 (2%)
Infiltration cellular, histiocytic	1 (2%)			
Necrosis	1 (2%)			
Lymph node, mesenteric	(7)	(4)	(1)	(9)
Cyst		1 (25%)	1 (100%)	
Ectasia		1 (25%)		
Edema	2 (29%)		1 (100%)	
Hemorrhage	1 (14%)		1 (100%)	
Hyperplasia, lymphoid				1 (11%)
Infiltration cellular, histiocytic	1 (14%)			
Necrosis	1 (14%)			
Spleen	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Depletion lymphoid	1 (2%)			
Fibrosis	1 (2%)	2 (4%)	3 (6%)	42 (84%)
Hematopoietic cell proliferation	41 (82%)	48 (96%)	48 (96%)	32 (64%)
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, lipocyte				11 (22%)
Inflammation, chronic active				1 (2%)
Necrosis	1 (2%)			
Pigmentation, hemosiderin	39 (78%)	49 (98%)	49 (98%)	48 (96%)
Capsule, cyst				3 (6%)
Thymus	(42)	(8)	(11)	(44)
Depletion lymphoid	1 (2%)			
Necrosis	1 (2%)			
INTEGUMENTARY SYSTEM				
Mammary gland	(49)	(17)	(22)	(50)
Hyperplasia, cystic	34 (69%)	11 (65%)	17 (77%)	48 (96%)
Skin	(50)	(20)	(21)	(50)
Inflammation, chronic active	1 (2%)			
Inflammation, necrotizing			1 (5%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	(49)	(5)	(10)	(50)
Inflammation, chronic active	1 (2%)			1 (2%)
NERVOUS SYSTEM				
Brain	(50)	(5)	(10)	(50)
Compression	4 (8%)	1 (20%)	4 (40%)	5 (10%)
Hydrocephalus	3 (6%)	1 (20%)		4 (8%)
Thrombus	1 (2%)			
RESPIRATORY SYSTEM				
Lung	(49)	(5)	(11)	(50)
Granuloma				1 (2%)
Hemorrhage, acute	1 (2%)			
Inflammation, chronic active	5 (10%)			1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)			2 (4%)
Mediastinum, inflammation, chronic active	1 (2%)		1 (9%)	1 (2%)
Nose	(49)	(4)	(11)	(49)
Foreign body	1 (2%)			
Inflammation, chronic active	3 (6%)			11 (22%)
Nasolacrimal duct, inflammation, chronic active				2 (4%)
Nasolacrimal duct, inflammation, suppurative	2 (4%)			4 (8%)
SPECIAL SENSES SYSTEM				
Eye	(12)	(32)	(31)	(31)
Inflammation, chronic	1 (8%)		1 (3%)	1 (3%)
Anterior chamber, inflammation, suppurative				1 (3%)
Cornea, inflammation, chronic		1 (3%)		
Lens, cataract	10 (83%)	30 (94%)	30 (97%)	30 (97%)
Retina, atrophy	11 (92%)	32 (100%)	31 (100%)	31 (100%)
Harderian gland	(42)	(6)	(11)	(44)
Atrophy				1 (2%)
Inflammation, chronic	1 (2%)			6 (14%)
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Inflammation, chronic active				1 (2%)
Nephropathy, chronic	39 (78%)	39 (78%)	45 (90%)	41 (82%)
Renal tubule, pigmentation, hemosiderin	44 (88%)	48 (96%)	50 (100%)	50 (100%)
Urinary bladder	(50)	(5)	(8)	(49)
Inflammation, chronic active				1 (2%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	50	49	50	50
ALIMENTARY SYSTEM				
Gallbladder	(45)	*(49)	*(50)	(47)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic			1 (2%)	
Intestine large, colon	(48)	*(49)	*(50)	(48)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, duodenum	(48)	*(49)	*(50)	(45)
Lymphoma malignant lymphocytic			1 (2%)	
Intestine small, jejunum	(47)	*(49)	*(50)	(47)
Adenocarcinoma	1 (2%)			
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)	
Peyer's patch, lymphoma malignant lymphocytic		1 (2%)	2 (4%)	
Peyer's patch, lymphoma malignant mixed	2 (4%)			1 (2%)
Liver	(50)	(49)	(50)	(50)
Cholangiocarcinoma		1 (2%)		
Hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hemangiosarcoma, multiple		1 (2%)		3 (6%)
Hepatocellular carcinoma	2 (4%)	7 (14%)	8 (16%)	13 (26%)
Hepatocellular carcinoma, multiple	1 (2%)		3 (6%)	4 (8%)
Hepatocellular adenoma	7 (14%)	11 (22%)	8 (16%)	3 (6%)
Hepatocellular adenoma, multiple	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Hepatocholangiocarcinoma			1 (2%)	
Lymphoma malignant histiocytic	3 (6%)	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic			3 (6%)	
Lymphoma malignant mixed	1 (2%)			1 (2%)
Mesentery	*(50)	*(49)	*(50)	*(50)
Lymphoma malignant histiocytic	1 (2%)			
Pancreas	(49)	*(49)	*(50)	(49)
Hemangiosarcoma				1 (2%)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed	1 (2%)			1 (2%)
Salivary glands	(50)	*(49)	*(50)	(49)
Lymphoma malignant mixed				1 (2%)
Stomach, forestomach	(49)	*(49)	*(50)	(48)
Papilloma squamous	2 (4%)			
Stomach, glandular	(50)	*(49)	*(50)	(48)
Adenocarcinoma				1 (2%)
Lymphoma malignant lymphocytic			1 (2%)	
Serosa, fibrosarcoma, metastatic, skin				1 (2%)
CARDIOVASCULAR SYSTEM				
Heart	(50)	*(49)	*(50)	(50)
Fibrosarcoma, metastatic, multiple, skin				1 (2%)
Lymphoma malignant lymphocytic			1 (2%)	
Epicardium, sarcoma			1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM				
Adrenal gland	(49)	*(49)	*(50)	(50)
Capsule, adenoma				2 (4%)
Adrenal gland, cortex	(49)	*(49)	*(50)	(50)
Fibrosarcoma, metastatic, skin				1 (2%)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic			2 (4%)	
Lymphoma malignant mixed	1 (2%)			
Adrenal gland, medulla	(49)	*(49)	*(50)	(50)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic			1 (2%)	
Pituitary gland	(40)	*(49)	*(50)	(41)
Lymphoma malignant lymphocytic			1 (2%)	
Thyroid gland	(50)	*(49)	*(50)	(48)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic			1 (2%)	
C-cell, adenoma		1 (2%)		
Follicular cell, adenoma	4 (8%)			3 (6%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(49)	*(49)	*(50)	(49)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed				1 (2%)
Prostate	(48)	*(49)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)	
Testes	(49)	*(49)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)	
Interstitial cell, adenoma	1 (2%)			
HEMATOPOIETIC SYSTEM				
Blood	*(50)	*(49)	*(50)	*(50)
Lymphoma malignant lymphocytic			1 (2%)	
Bone marrow	(50)	*(49)	*(50)	(50)
Lymphoma malignant histiocytic	2 (4%)			
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed	1 (2%)			1 (2%)
Femoral, hemangiosarcoma	1 (2%)			2 (4%)
Lymph node	(49)	*(49)	*(50)	(49)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant mixed				1 (2%)
Lumbar, lymphoma malignant mixed				1 (2%)
Mediastinal, lymphoma malignant histiocytic	2 (4%)			
Mediastinal, lymphoma malignant lymphocytic			2 (4%)	
Mediastinal, lymphoma malignant mixed	3 (6%)			1 (2%)
Pancreatic, lymphoma malignant mixed	1 (2%)			1 (2%)
Renal, lymphoma malignant lymphocytic			1 (2%)	
Renal, lymphoma malignant mixed	1 (2%)			1 (2%)
Lymph node, mandibular	(48)	*(49)	*(50)	(49)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic	1 (2%)		3 (6%)	
Lymphoma malignant mixed	3 (6%)			2 (4%)
Mast cell tumor benign				1 (2%)
Melanoma malignant, metastatic, skin		1 (2%)		
Mediastinal, fibrosarcoma, metastatic, skin				1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)				
Lymph node, mesenteric	(22)	*(49)	*(50)	(17)
Hemangiosarcoma	1 (5%)			
Lymphoma malignant histiocytic	2 (9%)			
Lymphoma malignant lymphocytic	1 (5%)	2 (4%)	5 (10%)	
Lymphoma malignant mixed	3 (14%)			1 (6%)
Spleen	(50)	(47)	(49)	(49)
Hemangiosarcoma	3 (6%)	2 (4%)		5 (10%)
Lymphoma malignant histiocytic	3 (6%)		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		5 (10%)	
Lymphoma malignant mixed	3 (6%)			2 (4%)
Thymus	(36)	*(49)	*(50)	(27)
Lymphoma malignant histiocytic	1 (3%)			
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed				1 (4%)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
INTEGUMENTARY SYSTEM				
Skin	(49)	*(49)	*(50)	(49)
Basosquamous tumor benign				1 (2%)
Papilloma squamous			1 (2%)	
Subcutaneous tissue, fibroma	3 (6%)	4 (8%)	5 (10%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	6 (12%)	3 (6%)	8 (16%)	4 (8%)
Subcutaneous tissue, fibrosarcoma, multiple			1 (2%)	
Subcutaneous tissue, lymphoma malignant lymphocytic			1 (2%)	
Subcutaneous tissue, melanoma malignant		1 (2%)		
Subcutaneous tissue, sarcoma			1 (2%)	
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	*(50)	*(49)	*(50)	*(50)
Intercostal, fibrosarcoma, metastatic, skin				1 (2%)
NERVOUS SYSTEM				
Brain	(50)	*(49)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)	
RESPIRATORY SYSTEM				
Lung	(50)	*(49)	*(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	4 (8%)	5 (10%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	3 (6%)	1 (2%)	3 (6%)	3 (6%)
Fibrosarcoma, metastatic, multiple, skin				1 (2%)
Hemangiosarcoma, metastatic, liver				1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)	2 (4%)	9 (18%)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Lymphoma malignant histiocytic	2 (4%)			
Lymphoma malignant lymphocytic			2 (4%)	
Lymphoma malignant mixed	1 (2%)			1 (2%)
Melanoma malignant, metastatic, skin		1 (2%)		
Mediastinum, sarcoma			1 (2%)	
Nose	(50)	*(49)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
SPECIAL SENSES SYSTEM				
Harderian gland	*(50)	*(49)	*(50)	*(50)
Adenoma	5 (10%)	2 (4%)	1 (2%)	4 (8%)
Adenoma, multiple				1 (2%)
Lymphoma malignant histiocytic	2 (4%)			
Lymphoma malignant lymphocytic			1 (2%)	
URINARY SYSTEM				
Kidney	(50)	*(49)	*(50)	(49)
Lymphoma malignant histiocytic	2 (4%)			
Lymphoma malignant lymphocytic			2 (4%)	
Lymphoma malignant mixed	1 (2%)			2 (4%)
Urinary bladder	(49)	*(49)	*(50)	(50)
Lymphoma malignant lymphocytic			2 (4%)	
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(49)	*(50)	*(50)
Lymphoma malignant mixed	5 (10%)			3 (6%)
Lymphoma malignant histiocytic	3 (6%)	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic	2 (4%)	2 (4%)	8 (16%)	
Hemangiosarcoma	4 (8%)	4 (8%)	1 (2%)	10 (20%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Terminal sacrifice	43	36	29	35
Moribund	3	6	12	9
Dead	4	7	9	6
Missing		1		
TUMOR SUMMARY				
Total animals with primary neoplasms **	40	30	35	36
Total primary neoplasms	56	46	59	59
Total animals with benign neoplasms	23	20	17	18
Total benign neoplasms	29	26	22	21
Total animals with malignant neoplasms	25	16	28	27
Total malignant neoplasms	27	20	37	38
Total animals with secondary neoplasms ***	1	2	3	10
Total secondary neoplasms	1	4	4	16
Total animals with malignant neoplasms			1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: VEHICLE CONTROL

WEEKS ON STUDY	071	072	078	085	094	096	096	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	322	344	312	345	371	351	321	341	352	355	361	362	363	382	402	332	405	315	323	324	331	334	343	354	374
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X																		
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Lymphoma malignant histiocytic							X																		
Lymphoma malignant lymphocytic													X												
Peyer's patch, lymphoma malignant mixed										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Hepatocellular carcinoma																				X					
Hepatocellular carcinoma, multiple									X																
Hepatocellular adenoma									X								X						X	X	
Hepatocellular adenoma, multiple												X													
Lymphoma malignant histiocytic	X						X								X										
Lymphoma malignant mixed					X																				
Mesentery							+																		
Lymphoma malignant histiocytic							X																		
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X																		
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous								X													X				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic	X																								
Lymphoma malignant mixed					X																				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic	X																								
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic	X																								
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Seminal vesicle		+	+		+				+		+				+		+			+	+	+	+		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma									X																

+: Tissue examined microscopically
: Not examined
–: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	381	392	394	313	314	325	342	353	364	373	385	391	393	401	403	404	311	333	335	365	372	375	383	384	395	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Lymphoma malignant histiocytic																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma														X												1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Peyer's patch, lymphoma malignant mixed				X																						2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																					X					2
Hepatocellular carcinoma																					X					2
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X									X						X								7
Hepatocellular adenoma, multiple										X																2
Lymphoma malignant histiocytic																										3
Lymphoma malignant mixed																										1
Mesentery																										1
Lymphoma malignant histiocytic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																						X				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	M	+	+	+	M	M	M	+	+	M	M	+	I	+	+	+	+	M	+	+	M	+	+	+	36
Pituitary gland	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Follicular cell, adenoma		X				X	X												X							4
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+													+												2
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle				+				+			+						+	+			+	+	+			19
Testes	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																										1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	071	072	078	085	094	096	096	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	322	344	312	345	371	351	321	341	352	355	361	362	363	382	402	332	405	315	323	324	331	334	343	354	374
HEMATOPOIETIC SYSTEM																									
Blood				+							+														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic	X														X										
Lymphoma malignant mixed					X																				
Femoral, hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, lymphoma malignant histiocytic	X						X																		
Mediastinal, lymphoma malignant mixed					X																				X
Pancreatic, lymphoma malignant mixed											X														
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X																		
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed					X																				
Lymph node, mesenteric	+	M	M	+	M	M	M	+	M	M	M	M	+	M	+	M	M	M	+	M	M	+	M	M	+
Hemangiosarcoma								X																	
Lymphoma malignant histiocytic	X														X										
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Lymphoma malignant histiocytic	X						X								X										
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed					X																				X
Thymus	+	M	+	M	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+
Lymphoma malignant histiocytic							X																		
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma		X		X		X																			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																	X								
Hepatocellular carcinoma, metastatic, liver									X																
Lymphoma malignant histiocytic	X														X										
Lymphoma malignant mixed					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																				+				+	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X							X						X	
Lymphoma malignant histiocytic	X						X																		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic	X						X																		
Lymphoma malignant mixed					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	381	392	394	313	314	325	342	353	364	373	385	391	393	401	403	404	411	333	335	365	372	375	383	384	395	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed																										1
Femoral, hemangiosarcoma																					X					1
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinal, lymphoma malignant histiocytic																										2
Mediastinal, lymphoma malig. mixed																						X				3
Pancreatic, lymphoma malignant mixed																										1
Renal, lymphoma malignant mixed																						X				1
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																		X								1
Lymphoma malignant mixed				X																		X				3
Lymph node, mesenteric	+	+	+	+	M	M	+	M	+	M	M	+	+	+	M	M	+	+	+	M	M	M	+	+	M	22
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																		X								1
Lymphoma malignant mixed				X																		X				3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																X					X					3
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic																		X								1
Lymphoma malignant mixed																						X				3
Thymus	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	M	+	M	I	+	+	+	+	+	+	36
Lymphoma malignant histiocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma			X				X																X			3
Subcutaneous tissue, fibrosarcoma													X					X					X			6
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X						X											X	4
Alveolar/bronchiolar adenoma, multiple																				X						1
Alveolar/bronchiolar carcinoma									X													X				3
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X				X						5
Lymphoma malignant histiocytic																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed																										1
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: LOW DOSE

WEEKS ON STUDY	019	036	054	062	069	091	096	096	097	097	101	101	102	102	102	104	104	104	104	104	104	105	105	105	105	105
CARCASS ID	221	252	285	273	213	304	241	294	232	253	271	274	234	255	222	245	261	282	291	301	311	231	251	254	265	
ALIMENTARY SYSTEM																										
Esophagus		+	+	+	+	+																				
Gallbladder		A	A	A	A	A																				
Intestine large		+	+	+	+	+							+													
Intestine large, cecum		A	+	M	A	A																				
Intestine large, colon		+	+	+	+	+							+													
Cholangiocarcinoma, metastatic, liver													X													
Intestine large, rectum		A	+	A	A	A																				
Intestine small		+	+	+	A	A																				
Intestine small, duodenum		+	+	I	A	A																				
Intestine small, ileum		+	+	M	A	A																				
Intestine small, jejunum		+	+	+	A	A																				
Peyer's patch, lymphoma malignant lymphocytic																										
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma													X													
Hemangiosarcoma																		X								
Hemangiosarcoma, multiple					X																					
Hepatocellular carcinoma						X	X		X	X			X													X
Hepatocellular adenoma				X			X				X			X		X				X						
Hepatocellular adenoma, multiple								X																		
Lymphoma malignant histiocytic														X												
Pancreas		+	+	+	A	A																				
Salivary glands		+	+	+	+	+																				
Stomach		+	+	+	+	+																				
Stomach, forestomach		+	+	+	+	+																				
Stomach, glandular		+	+	+	+	+																				
Tooth		+	+	+	+	+																				
CARDIOVASCULAR SYSTEM																										
Heart		+	+	+	+	+																				
ENDOCRINE SYSTEM																										
Adrenal gland		+	+	+	+	+																				
Adrenal gland, cortex		+	+	+	+	+																				
Adrenal gland, medulla		+	+	I	+	+																				
Islets, pancreatic		M	+	+	A	A																				
Parathyroid gland		M	+	+	+	+																				
Pituitary gland		+	+	+	+	M																				
Thyroid gland		+	+	+	+	+																				
C-cell, adenoma					X																					
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis		+	+	+	+	+																				
Penis				+																						
Preputial gland		+								+																
Prostate		+	+	+	+	M																				
Seminal vesicle				+																						
Testes		+	+	+	+	+																				
HEMATOPOIETIC SYSTEM																										
Bone marrow		+	+	+	A	A																				
Lymph node		+	+	+	+	+		+	+	+	+	+	+					+			+	+	+			
Lymph node, mandibular		+	+	+	+	+						+									+					
Melanoma malignant, metastatic, skin						X																				
Lymph node, mesenteric		M	M	M	+	M		+	+	+	+	+	+					+				+	+			
Lymphoma malignant lymphocytic										X																
Spleen		+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma							X												X							
Thymus		M	A	M	I	M																				
INTEGUMENTARY SYSTEM																										
Mammary gland		M	M	M	M	M																				
Skin		+	+	+	+	+	+	+		+	+	+		+	+	+			+		+		+		+	
Subcutaneous tissue, fibroma								X								X										
Subcutaneous tissue, fibrosarcoma																								X		
Subcutaneous tissue, melanoma malignant						X																				
MUSCULOSKELETAL SYSTEM																										
Bone		+	+	+	+	+	+	+		+				+		+			+		+		+		+	
NERVOUS SYSTEM																										
Brain		+	+	+	+	+																				
RESPIRATORY SYSTEM																										
Lung		+	+	+	+	+												+	+	+						
Alveolar/bronchiolar adenoma																		X	X	X						
Alveolar/bronchiolar carcinoma																										
Hepatocellular carcinoma, metastatic, liver						X																				
Melanoma malignant, metastatic, skin						X																				
Nose		+	+	+	+	+																				
Trachea		+	+	+	+	+																				
SPECIAL SENSES SYSTEM																										
Harderian gland		M	+	+	+	M																				
Adenoma																										
URINARY SYSTEM																										
Kidney		+	+	+	+	+																				
Urinary bladder		+	A	+	A	A						+										+		+		

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	272	283	293	303	215	224	233	255	263	264	302	305	212	243	262	281	284	292	214	223	235	242	244	275	295	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										5
Gallbladder																										
Intestine large																										6
Intestine large, cecum																										1
Intestine large, colon																										6
Cholangiocarcinoma, metastatic, liver																										1
Intestine large, rectum																										1
Intestine small															+											4
Intestine small, duodenum																										2
Intestine small, ileum																										2
Intestine small, jejunum															+											4
Peyer's patch, lymphoma malignant lymphocytic															X											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangiocarcinoma																										1
Hemangiosarcoma																										1
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma													X													7
Hepatocellular adenoma		X										X		X						X	X					11
Hepatocellular adenoma, multiple											X							X	X							4
Lymphoma malignant histiocytic																										1
Pancreas																										3
Salivary glands																										5
Stomach																										5
Stomach, forestomach																										5
Stomach, glandular																										5
Tooth																										5
CARDIOVASCULAR SYSTEM																										
Heart																										5
ENDOCRINE SYSTEM																										
Adrenal gland																										5
Adrenal gland, cortex																										5
Adrenal gland, medulla																										4
Islets, pancreatic																										2
Parathyroid gland																										4
Pituitary gland																										4
Thyroid gland																										5
C-cell, adenoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis																										5
Penis																										1
Preputial gland		+																								3
Prostate																										4
Seminal vesicle																										1
Testes																										5
HEMATOPOIETIC SYSTEM																										
Bone marrow																										3
Lymph node		+	+		+	+							+	+	+		+		+				+			25
Lymph node, mandibular					+																					8
Melanoma malignant, metastatic, skin																										1
Lymph node, mesenteric		+	+			+							+	+	+		+		+				+			19
Lymphoma malignant lymphocytic															X											2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										2
Thymus																										
INTEGUMENTARY SYSTEM																										
Mammary gland																										
Skin	+				+		+		+	+		+				+		+	+	+				M		27
Subcutaneous tissue, fibroma																X				X						4
Subcutaneous tissue, fibrosarcoma							X											X								3
Subcutaneous tissue, melanoma malignant																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+		+		+	+	+	+	+	+		+					+	+	+			+			+	28
NERVOUS SYSTEM																										
Brain																										5
RESPIRATORY SYSTEM																										
Lung												+											+			10
Alveolar/bronchiolar adenoma												X														4
Alveolar/bronchiolar carcinoma																							X			1
Hepatocellular carcinoma, metastatic, liver																										1
Melanoma malignant, metastatic, skin																										1
Nose																										5
Trachea																										5
SPECIAL SENSES SYSTEM																										
Harderian gland								+						+												5
Adenoma								X						X												2
URINARY SYSTEM																										
Kidney	+																									6
Urinary bladder					+				+							+										8

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: MID DOSE

WEEKS ON STUDY	056	061	064	073	074	076	084	094	096	096	096	096	096	096	097	097	099	099	101	101	104	104	104	104	104
CARCASS ID	11 12	11 91	12 02	11 71	11 51	12 05	14 44	11 14	12 04	20 05	13 02	16 04	17 04	20 04	18 04	19 03	13 03	20 02	17 02	17 05	18 01	11 05	12 01	13 01	16 05
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	M	+	+																		
Gallbladder	A	A	A	+	A	+	+																		
Lymphoma malignant lymphocytic				X																					
Intestine large	+	+	+	+	+	+	+																		
Intestine large, cecum	+	A	A	+	A	+	+																		
Intestine large, colon	+	+	+	+	+	+	+																		
Intestine large, rectum	+	A	A	+	+	+	+																		
Intestine small	+	+	+	+	+	+	+				+			+											
Intestine small, duodenum	+	+	A	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
Intestine small, ileum	+	A	A	M	M	+	+																		
Intestine small, jejunum	+	A	+	+	+	+	+				+			+											
Lymphoma malignant lymphocytic				X																					
Peyer's patch, lymphoma malignant lymphocytic											X			X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma					X	X				X				X	X	X					X				
Hepatocellular carcinoma, multiple								X				X					X								
Hepatocellular adenoma			X		X								X												X
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma							X																		
Lymphoma malignant histiocytic																			X						
Lymphoma malignant lymphocytic		X		X																					X
Pancreas	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic		X																							
Salivary glands	+	+	+	+	+	+	+																		
Stomach	+	+	+	+	+	+	+																		
Stomach, forestomach	+	+	+	+	+	+	+																		
Stomach, glandular	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
Tooth	+	+	+	+	+	+	+																		
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+												+						
Lymphoma malignant lymphocytic				X																					
Epicardium, sarcoma							X																		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+																		
Adrenal gland, cortex	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic		X		X																					
Adrenal gland, medulla	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic		X																							
Islets, pancreatic	+	+	+	M	+	+	+																		
Parathyroid gland	M	M	M	M	+	M	M																		
Pituitary gland	I	+	M	+	+	+	M																		
Lymphoma malignant lymphocytic				X																					
Thyroid gland	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
Penis																			+	+					
Preputial gland									+													+			
Prostate	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
Seminal vesicle																		+			+				
Testes	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
HEMATOPOIETIC SYSTEM																									
Blood	+			+																					
Lymphoma malignant lymphocytic				X																					
Bone marrow	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
Lymph node	+	+	+	+	+	+	+		+	+	+	+		+	+				+	+			+	+	
Lymphoma malignant histiocytic																			X						
Mediastinal, lymphoma malignant lymphocytic		X		X																					
Renal, lymphoma malignant lymphocytic				X																					
Lymph node, mandibular	+	+	+	+	+	+	+																		+
Lymphoma malignant lymphocytic		X		X																					X
Lymph node, mesenteric	M	M	M	+	M	M	M		+	+	+	+		+	+					+			+		
Lymphoma malignant lymphocytic				X										X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																			X						
Lymphoma malignant lymphocytic		X		X																					X
Thymus	M	M	M	+	+	M	+																		
Lymphoma malignant lymphocytic				X																					
Sarcoma, metastatic, uncertain primary site							X																		

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	111	123	141	161	163	192	194	195	201	203	113	135	143	155	182	185	134	152	154	162	173	142	145	153	183	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										6
Gallbladder																		+								4
Lymphoma malignant lymphocytic																										1
Intestine large																										7
Intestine large, cecum																										4
Intestine large, colon																										7
Intestine large, rectum																										5
Intestine small																										9
Intestine small, duodenum																										6
Lymphoma malignant lymphocytic																										1
Intestine small, ileum																										3
Intestine small, jejunum																										8
Lymphoma malignant lymphocytic																										1
Peyer's patch, lymphoma malignant lymphocytic																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X																			1
Hepatocellular carcinoma																		X								8
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma								X			X												X	X		8
Hepatocellular adenoma, multiple												X	X													2
Hepatocholangiocarcinoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										3
Pancreas																										7
Lymphoma malignant lymphocytic																										1
Salivary glands																										7
Stomach																										7
Stomach, forestomach																										7
Stomach, glandular																										7
Lymphoma malignant lymphocytic																										1
Tooth																										7
CARDIOVASCULAR SYSTEM																										
Heart																										8
Lymphoma malignant lymphocytic																										1
Epicardium, sarcoma																										1
ENDOCRINE SYSTEM																										
Adrenal gland																										7
Adrenal gland, cortex																										7
Lymphoma malignant lymphocytic																										2
Adrenal gland, medulla																										7
Lymphoma malignant lymphocytic																										1
Islets, pancreatic																										6
Parathyroid gland																										1
Pituitary gland																										4
Lymphoma malignant lymphocytic																										1
Thyroid gland																										7
Lymphoma malignant lymphocytic																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis																										7
Lymphoma malignant lymphocytic																										1
Penis																										2
Preputial gland														+					+		+					5
Prostate																										7
Lymphoma malignant lymphocytic																										1
Seminal vesicle																										2
Testes																										7
Lymphoma malignant lymphocytic																										1
HEMATOPOIETIC SYSTEM																										
Blood																										2
Lymphoma malignant lymphocytic																										1
Bone marrow																										7
Lymphoma malignant lymphocytic																										1
Lymph node		+	+		+			+		+			+	+	+			+			+			+		28
Lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										2
Renal, lymphoma malig. lymphocytic																										1
Lymph node, mandibular			+																							9
Lymphoma malignant lymphocytic																										3
Lymph node, mesenteric		+	+		+			+		+			+	+	+			+			+			+		20
Lymphoma malignant lymphocytic		X			X																X					5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic		X			X																					5
Thymus																										3
Lymphoma malignant lymphocytic																										1
Sarcoma, metastatic, uncertain primary site																										1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	056	061	064	073	074	076	084	094	096	096	096	096	096	096	097	097	099	099	101	101	104	104	104	104	104
CARCASS ID	112	191	222	171	151	125	144	114	124	205	132	164	174	204	184	193	133	202	172	175	181	115	121	131	165
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M																		
Skin	+	+	+	+	+	+	+		+	+	+	+	+	+		+				+		+	+	M	
Papilloma squamous																									
Subcutaneous tissue, fibroma																X						X			
Subcutaneous tissue, fibrosarcoma	X		X						X		X	X	X												
Subcutaneous tissue, fibrosarcoma, multiple																				X					
Subcutaneous tissue, lymphoma malignant lymphocytic				X																					
Subcutaneous tissue, sarcoma										X															
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+		+				+					+		+		+	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+											+	+				
Alveolar/bronchiolar adenoma			X						X											X					
Alveolar/bronchiolar carcinoma									X												X				
Hepatocellular carcinoma, metastatic, liver						X		X																	
Hepatocholangiocarcinoma, metastatic, liver							X																		
Lymphoma malignant lymphocytic		X		X																					
Mediastinum, sarcoma							X																		
Nose	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic				X																					
Trachea	+	+	+	+	+	+	+																		
SPECIAL SENSES SYSTEM																									
Eye						+																			
Harderian gland	M	+	+	+	+	+	M									+									
Adenoma																									
Lymphoma malignant lymphocytic				X																					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+			+	+														
Lymphoma malignant lymphocytic		X		X																					
Urinary bladder	+	+	+	+	+	+	+											+			+				
Lymphoma malignant lymphocytic				X																					

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	111	123	141	161	163	192	194	195	201	203	213	235	243	255	282	285	334	352	354	362	373	442	445	453	483		TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Mammary gland																											
Skin	+	+				+		+	+	+	+		+				+				+			+			28
Papilloma squamous						X																					1
Subcutaneous tissue, fibroma								X									X				X						5
Subcutaneous tissue, fibrosarcoma								X																X			8
Subcutaneous tissue, fibrosarcoma, multiple																											1
Subcutaneous tissue, lymphoma malignant lymphocytic																											1
Subcutaneous tissue, sarcoma																											1
MUSCULOSKELETAL SYSTEM																											
Bone		+			+		+	+	+	+	+		+						+				+	+	+		26
NERVOUS SYSTEM																											
Brain																											7
Lymphoma malignant lymphocytic																											1
RESPIRATORY SYSTEM																											
Lung							+														+			+			14
Alveolar/bronchiolar adenoma																					X			X			5
Alveolar/bronchiolar carcinoma							X																				3
Hepatocellular carcinoma, metastatic, liver																											2
Hepatocholangiocarcinoma, metastatic, liver																											1
Lymphoma malignant lymphocytic																											2
Mediastinum, sarcoma																											1
Nose																											7
Lymphoma malignant lymphocytic																											1
Trachea																											7
SPECIAL SENSES SYSTEM																											
Eye																											1
Harderian gland																							+				7
Adenoma																							X				1
Lymphoma malignant lymphocytic																											1
URINARY SYSTEM																											
Kidney						+																					10
Lymphoma malignant lymphocytic																											2
Urinary bladder		+						+																			11
Lymphoma malignant lymphocytic		X																									2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: HIGH DOSE

WEEKS ON STUDY	057	070	072	075	086	090	096	097	098	098	098	099	099	104	104	104	104	104	104	104	104	104	104	105	105
CARCASS ID	013	012	081	074	053	065	063	031	085	095	103	094	083	092	064	034	035	043	045	052	061	073	105	021	024
ALIMENTARY SYSTEM																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	M	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, lymphoma malignant mixed										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X										X														
Hemangiosarcoma, multiple														X		X									
Hepatocellular carcinoma					X	X					X	X		X	X	X			X						
Hepatocellular carcinoma, multiple		X	X							X															
Hepatocellular adenoma																								X	
Hepatocellular adenoma, multiple																									
Lymphoma malignant mixed																									
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Stomach	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																			X						
Serosa, fibrosarcoma, metastatic, skin													X												
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, multiple, skin													X												
ENDOCRINE																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin													X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	I	+	I	+	+	+	+
Thyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymphoma malignant mixed																									
Preputial gland							+															+		+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle		+																							+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Femoral, hemangiosarcoma														X											
Lymph node	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lumbar, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant mixed																									
Pancreatic, lymphoma malignant mixed																									
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Mast cell tumor benign																								X	
Mediastinal, fibrosarcoma, metastatic, skin													X												
Lymph node, mesenteric	+		M	M	M	M	M	M	+	M	+	+	M	+	M	M	M	M	+	+	M	M	M	M	M
Lymphoma malignant mixed																									
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X				X				X											
Lymphoma malignant mixed																									
Thymus	M	+	+	+	+	+	M	M	M	M	M	M	M	M	M	M	+	M	I	M	M	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	025	041	042	075	082	102	015	072	091	104	111	022	032	033	054	084	114	023	044	051	055	062	071	093	101	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Peyer's patch, lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																					X					3
Hemangiosarcoma, multiple																									X	3
Hepatocellular carcinoma					X			X						X			X					X				13
Hepatocellular carcinoma, multiple																X										4
Hepatocellular adenoma		X					X																			3
Hepatocellular adenoma, multiple																									X	1
Lymphoma malignant mixed																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymphoma malignant mixed						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed						X																				1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Serosa, fibrosarcoma, metastatic, skin																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, multiple, skin																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																				X					X	2
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	38
Pituitary gland	+	+	+	+	+	+	M	+	+	+	M	I	+	+	+	M	M	+	+	+	+	+	+	+	41
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma					X			X																		3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed						X																				1
Preputial gland			+														+									5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+																									3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malig nant mixed																					X					1
Femoral, hemangiosarcoma																									X	2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																					X					1
Lumbar, lymphoma malignant mixed																					X					1
Mediastinal, lymphoma malig. mixed																					X					1
Pancreatic, lymphoma malignant mixed																					X					1
Renal, lymphoma malignant mixed																					X					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed						X															X					2
Mast cell tumor benign																										1
Mediastinal, fibrosarcoma, metastatic, skin																										1
Lymph node, mesenteric	M	M	M	+	+	M	M	+	M	M	+	M	M	M	M	+	M	M	+	+	+	+	M	M	+	17
Lymphoma malignant mixed																					X					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma														X											X	5
Lymphoma malignant mixed						X															X					2
Thymus	+	+	M	+	I	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	M	M	+	I	27
Lymphoma malignant mixed																					X					1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	057	070	072	075	086	090	096	097	098	098	098	099	099	104	104	104	104	104	104	104	104	104	104	105	105
CARCASS ID	013	012	081	074	053	065	063	031	085	095	103	094	083	092	064	034	035	043	045	052	061	073	105	021	024
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Subcutaneous tissue, fibroma																	X								
Subcutaneous tissue, fibrosarcoma									X				X		X					X					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+					+				+								
Intercostal, fibrosarcoma, metastatic, skin													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X					X										
Alveolar/bronchiolar carcinoma															X										
Fibrosarcoma, metastatic, multiple, skin													X												
Hemangiosarcoma, metastatic, liver																X									
Hepatocellular carcinoma, metastatic, liver			X			X				X	X			X		X			X						
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	M	+	+	+	M	+
Adenoma																		X			X				
Adenoma, multiple													X												
URINARY SYSTEM																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	025	041	042	075	082	102	015	072	091	104	011	022	032	033	054	084	014	023	044	051	055	062	071	093	101	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor benign														X												1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										4
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										3
Intercostal, fibrosarcoma, metastatic, skin																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X	X																								4
Alveolar/bronchiolar carcinoma													X						X							3
Fibrosarcoma, metastatic, multiple, skin																										1
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver								X								X										9
Lymphoma malignant mixed																					X					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye								+			+								+							3
Harderian gland	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	M	+	40
Adenoma																		X	X							4
Adenoma, multiple																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed						X															X					2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Harderian Gland: Adenoma				
Overall Rates (a)	5/50 (10%)	2/49 (4%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	11.6%	5.6%	3.4%	13.8%
Terminal Rates (c)	5/43 (12%)	2/36 (6%)	1/29 (3%)	4/35 (11%)
Day of First Observation	728	728	728	690
Life Table Tests (d)	P=0.279	P=0.293N	P=0.214N	P=0.502
Logistic Regression Tests (d)	P=0.310	P=0.293N	P=0.214N	P=0.576
Cochran-Armitage Trend Test (d)	P=0.350			
Fisher Exact Test (d)		P=0.226N	P=0.102N	P=0.630
Liver: Hepatocellular Adenoma				
Overall Rates (a)	9/50 (18%)	15/49 (31%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	20.9%	36.0%	29.1%	11.4%
Terminal Rates (c)	9/43 (21%)	10/36 (28%)	7/29 (24%)	4/35 (11%)
Day of First Observation	728	432	443	728
Life Table Tests (d)	P=0.044N	P=0.060	P=0.205	P=0.209N
Logistic Regression Tests (d)	P=0.020N	P=0.097	P=0.478	P=0.209N
Cochran-Armitage Trend Test (d)	P=0.019N			
Fisher Exact Test (d)		P=0.109	P=0.500	P=0.117N
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	3/50 (6%)	7/49 (14%)	11/50 (22%)	17/50 (34%)
Adjusted Rates (b)	7.0%	16.3%	25.9%	37.9%
Terminal Rates (c)	3/43 (7%)	2/36 (6%)	1/29 (3%)	8/35 (23%)
Day of First Observation	728	637	514	490
Life Table Tests (d)	P<0.001	P=0.127	P=0.011	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.149	P=0.034	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.151	P=0.020	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	11/50 (22%)	21/49 (43%)	20/50 (40%)	21/50 (42%)
Adjusted Rates (b)	25.6%	46.4%	47.0%	47.1%
Terminal Rates (c)	11/43 (26%)	12/36 (33%)	8/29 (28%)	12/35 (34%)
Day of First Observation	728	432	443	490
Life Table Tests (d)	P=0.081	P=0.012	P=0.007	P=0.010
Logistic Regression Tests (d)	P=0.117	P=0.019	P=0.045	P=0.027
Cochran-Armitage Trend Test (d)	P=0.115			
Fisher Exact Test (d)		P=0.022	P=0.041	P=0.026
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	5/50 (10%)	(e) 4/10 (40%)	(e) 5/14 (36%)	4/50 (8%)
Adjusted Rates (b)	11.6%			10.5%
Terminal Rates (c)	5/43 (12%)			2/35 (6%)
Day of First Observation	728			682
Life Table Test (d)				P=0.611N
Logistic Regression Test (d)				P=0.546N
Fisher Exact Test (d)				P=0.500N
Lung: Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	3/50 (6%)	(e) 1/10 (10%)	(e) 3/14 (21%)	3/50 (6%)
Adjusted Rates (b)	7.0%			8.3%
Terminal Rates (c)	3/43 (7%)			2/35 (6%)
Day of First Observation	728			725
Life Table Test (d)				P=0.566
Logistic Regression Test (d)				P=0.594
Fisher Exact Test (d)				P=0.661N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	8/50 (16%)	(e) 5/10 (50%)	(e) 7/14 (50%)	6/50 (12%)
Adjusted Rates (b)	18.6%			15.9%
Terminal Rates (c)	8/43 (19%)			4/35 (11%)
Day of First Observation	728			682
Life Table Test (d)				P=0.538N
Logistic Regression Test (d)				P=0.456N
Fisher Exact Test (d)				P=0.387N
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	3/50 (6%)	4/49 (8%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	7.0%	10.4%	16.2%	2.9%
Terminal Rates (c)	3/43 (7%)	3/36 (8%)	4/29 (14%)	1/35 (3%)
Day of First Observation	728	667	674	728
Life Table Tests (d)	P=0.228N	P=0.416	P=0.180	P=0.381N
Logistic Regression Tests (d)	P=0.191N	P=0.465	P=0.255	P=0.381N
Cochran-Armitage Trend Test (d)	P=0.174N			
Fisher Exact Test (d)		P=0.489	P=0.357	P=0.309N
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (a)	6/50 (12%)	3/49 (6%)	9/50 (18%)	4/50 (8%)
Adjusted Rates (b)	12.8%	8.3%	21.8%	10.2%
Terminal Rates (c)	3/43 (7%)	3/36 (8%)	2/29 (7%)	1/35 (3%)
Day of First Observation	502	728	389	682
Life Table Tests (d)	P=0.496N	P=0.317N	P=0.180	P=0.450N
Logistic Regression Tests (d)	P=0.428N	P=0.221N	P=0.496	P=0.321N
Cochran-Armitage Trend Test (d)	P=0.436N			
Fisher Exact Test (d)		P=0.254N	P=0.288	P=0.370N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	8/50 (16%)	7/49 (14%)	13/50 (26%)	5/50 (10%)
Adjusted Rates (b)	17.2%	18.6%	32.5%	12.9%
Terminal Rates (c)	5/43 (12%)	6/36 (17%)	5/29 (17%)	2/35 (6%)
Day of First Observation	502	667	389	682
Life Table Tests (d)	P=0.317N	P=0.601	P=0.068	P=0.379N
Logistic Regression Tests (d)	P=0.226N	P=0.507N	P=0.273	P=0.249N
Cochran-Armitage Trend Test (d)	P=0.232N			
Fisher Exact Test (d)		P=0.517N	P=0.163	P=0.277N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma				
Overall Rates (a)	6/50 (12%)	3/49 (6%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	12.8%	8.3%	23.8%	10.2%
Terminal Rates (c)	3/43 (7%)	3/36 (8%)	2/29 (7%)	1/35 (3%)
Day of First Observation	502	728	389	682
Life Table Tests (d)	P=0.491N	P=0.317N	P=0.125	P=0.450N
Logistic Regression Tests (d)	P=0.423N	P=0.221N	P=0.388	P=0.321N
Cochran-Armitage Trend Test (d)	P=0.431N			
Fisher Exact Test (d)		P=0.254N	P=0.207	P=0.370N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma				
Overall Rates (a)	8/50 (16%)	7/49 (14%)	14/50 (28%)	5/50 (10%)
Adjusted Rates (b)	17.2%	18.6%	34.1%	12.9%
Terminal Rates (c)	5/43 (12%)	6/36 (17%)	5/29 (17%)	2/35 (6%)
Day of First Observation	502	667	389	682
Life Table Tests (d)	P=0.316N	P=0.601	P=0.046	P=0.379N
Logistic Regression Tests (d)	P=0.225N	P=0.507N	P=0.204	P=0.249N
Cochran-Armitage Trend Test (d)	P=0.231N			
Fisher Exact Test (d)		P=0.517N	P=0.114	P=0.277N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Thyroid Gland: Follicular Cell Adenoma				
Overall Rates (a)	4/50 (8%)	(e) 0/5 (0%)	(e) 0/7 (0%)	3/48 (6%)
Adjusted Rates (b)	9.3%			8.6%
Terminal Rates (c)	4/43 (9%)			3/35 (9%)
Day of First Observation	728			728
Life Table Test (d)				P=0.612N
Logistic Regression Test (d)				P=0.612N
Fisher Exact Test (d)				P=0.523N
Circulatory System: Hemangiosarcoma				
Overall Rates (a)	4/50 (8%)	4/49 (8%)	1/50 (2%)	10/50 (20%)
Adjusted Rates (b)	9.3%	9.7%	3.4%	23.9%
Terminal Rates (c)	4/43 (9%)	2/36 (6%)	1/29 (3%)	5/35 (14%)
Day of First Observation	728	479	728	399
Life Table Tests (d)	P=0.011	P=0.560	P=0.315N	P=0.047
Logistic Regression Tests (d)	P=0.014	P=0.639N	P=0.315N	P=0.083
Cochran-Armitage Trend Test (d)	P=0.014			
Fisher Exact Test (d)		P=0.631	P=0.181N	P=0.074
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	10/50 (20%)	3/49 (6%)	9/50 (18%)	3/50 (6%)
Adjusted Rates (b)	21.6%	7.7%	23.9%	8.0%
Terminal Rates (c)	7/43 (16%)	1/36 (3%)	4/29 (14%)	2/35 (6%)
Day of First Observation	496	674	423	682
Life Table Tests (d)	P=0.149N	P=0.072N	P=0.443	P=0.074N
Logistic Regression Tests (d)	P=0.095N	P=0.037N	P=0.397N	P=0.034N
Cochran-Armitage Trend Test (d)	P=0.098N			
Fisher Exact Test (d)		P=0.039N	P=0.500N	P=0.036N

(a) Number of tumor-bearing animals/number of animals examined at the site; doses calculated as *p*-chloroaniline.
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 that dosed group and the vehicle controls. 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 test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues

TABLE C4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	8/50	2/50	10/50
Chlorpheniramine maleate (c)	10/50	6/50	16/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	8/49	10/49	17/49
Malonaldehyde, sodium salt (c)	4/50	14/50	17/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	9/48	10/48	18/48
Methyl carbamate (d)	9/50	5/50	14/50
Chlorinated trisodium phosphate (b)	6/50	9/50	14/50
TOTAL	54/347 (15.6%)	56/347 (16.1%)	106/347 (30.5%)
SD (e)	4.21%	8.03%	5.83%
Range (f)			
High	10/50	14/50	18/48
Low	4/50	2/50	10/50
Overall Historical Incidence for Untreated Controls			
TOTAL	259/2,032 (12.7%)	379/2,032 (18.7%)	609/2,032 (30.0%)
SD (e)	7.21%	6.50%	7.59%
Range (f)			
High	(g) 22/50	15/50	(h) 29/50
Low	0/49	4/50	8/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Second highest: 12/50
(h) Second highest: 20/50

TABLE C4b. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	0/50	0/50
Chlorpheniramine maleate (c)	1/50	0/50	1/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50	0/50	0/50
Malonaldehyde, sodium salt (c)	1/50	0/50	1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50	4/50	4/50
Methyl carbamate (d)	1/50	1/50	2/50
Chlorinated trisodium phosphate (b)	1/50	2/50	3/50
TOTAL	4/350 (1.1%)	7/350 (2.0%)	11/350 (3.1%)
SD (e)	1.07%	3.06%	3.02%
Range (f)	1/50	4/50	4/50
Low	0/50	0/50	0/50
High			
Overall Historical Incidence for Untreated Controls			
TOTAL	26/2,040 (1.3%)	73/2,040 (3.6%)	98/2,040 (4.8%)
SD (e)	2.68%	2.46%	3.99%
Range (f)			
High	7/50	5/49	10/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE C4c. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence for All Water Gavage Vehicle Controls		
Iodinated glycerol (b)	10/50	10/50
Chlorpheniramine maleate (c)	9/50	9/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	9/50	9/50
Malonaldehyde, sodium salt (c)	4/50	4/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	2/50	2/50
Methyl carbamate (d)	4/50	4/50
Chlorinated trisodium phosphate (b)	4/50	4/50
TOTAL	42/350 (12.0%)	42/350 (12.0%)
SD (e)	6.43%	6.43%
Range (f)		
High	10/50	10/50
Low	2/50	2/50
Overall Historical Incidence for Untreated Controls		
TOTAL	248/2,040 (12.2%)	252/2,040 (12.4%)
SD (e)	6.83%	6.94%
Range (f)		
High	16/50	16/50
Low	1/50	1/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	50	49	50	50
ALIMENTARY SYSTEM				
Gallbladder	(45)		(4)	(47)
Necrosis, acute, multifocal			1 (25%)	
Lumen, crystals, diffuse				1 (2%)
Submucosa, fibrosis, diffuse			1 (25%)	
Intestine large, colon	(48)	(6)	(7)	(48)
Inflammation, necrotizing, acute, multifocal		1 (17%)		
Parasite metazoan		1 (17%)		3 (6%)
Intestine large, rectum	(46)	(1)	(5)	(50)
Parasite metazoan				2 (4%)
Liver	(50)	(49)	(50)	(50)
Amyloid deposition, multifocal			1 (2%)	
Angiectasis, focal	1 (2%)			2 (4%)
Angiectasis, multifocal				3 (6%)
Clear cell focus, focal	1 (2%)			
Cyst		1 (2%)	1 (2%)	
Hematopoietic cell proliferation, diffuse	1 (2%)			2 (4%)
Hematopoietic cell proliferation, focal			1 (2%)	
Hematopoietic cell proliferation, multifocal	6 (12%)	4 (8%)	6 (12%)	3 (6%)
Inflammation		1 (2%)		
Inflammation, acute, multifocal				1 (2%)
Inflammation, chronic, multifocal			2 (4%)	
Inflammation, chronic active, multifocal				1 (2%)
Necrosis, acute, multifocal				1 (2%)
Necrosis, chronic active, focal	1 (2%)			
Necrosis, chronic active, multifocal		1 (2%)	1 (2%)	6 (12%)
Necrosis, coagulative, focal			1 (2%)	
Thrombus, chronic				2 (4%)
Vacuolization cytoplasmic, focal		1 (2%)		
Bile duct, hyperplasia, multifocal			2 (4%)	
Centrilobular, necrosis, acute, multifocal	1 (2%)			
Centrilobular, vacuolization cytoplasmic, diffuse	4 (8%)			4 (8%)
Hepatocyte, cytomegaly, diffuse			1 (2%)	
Hepatocyte, hyperplasia, focal			1 (2%)	
Kupffer cell, pigmentation, hemosiderin				50 (100%)
Pancreas	(49)	(3)	(7)	(49)
Inflammation, chronic, multifocal				1 (2%)
Acinus, atrophy, focal				1 (2%)
Acinus, atrophy, multifocal	6 (12%)			4 (8%)
Tooth	(50)	(5)	(7)	(50)
Incisor, dysplasia, multifocal				1 (2%)
Molar, dysplasia	1 (2%)			1 (2%)
Peridontal tissue, foreign body, focal	2 (4%)			
Peridontal tissue, foreign body, multifocal	1 (2%)			
Peridontal tissue, inflammation, chronic active, focal	3 (6%)			4 (8%)
Peridontal tissue, inflammation, chronic active, multifocal	6 (12%)			3 (6%)
CARDIOVASCULAR SYSTEM				
Heart	(50)	(5)	(8)	(50)
Coronary artery, inflammation, chronic active, focal				1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM				
Adrenal gland	(49)	(5)	(7)	(50)
Capsule, ectopic tissue	2 (4%)			
Capsule, hyperplasia, focal	2 (4%)	1 (20%)		1 (2%)
Capsule, hyperplasia, multifocal	44 (90%)	1 (20%)	4 (57%)	44 (88%)
Adrenal gland, cortex	(49)	(5)	(7)	(50)
Cyst				2 (4%)
Hyperplasia, focal	11 (22%)			5 (10%)
Hyperplasia, multifocal				1 (2%)
Hypertrophy, focal	9 (18%)			10 (20%)
Hypertrophy, multifocal	5 (10%)			
Necrosis, acute, focal				1 (2%)
Vacuolization cytoplasmic, focal				1 (2%)
Adrenal gland, medulla	(49)	(4)	(7)	(50)
Hyperplasia, focal	1 (2%)			
Parathyroid gland	(36)	(4)	(1)	(38)
Cyst				1 (3%)
Pituitary gland	(40)	(4)	(4)	(41)
Pars distalis, cyst	1 (3%)			2 (5%)
Pars distalis, cyst, multiple				1 (2%)
Pars distalis, hyperplasia, focal				1 (2%)
Thyroid gland	(50)	(5)	(7)	(48)
Inflammation, chronic active, multifocal	1 (2%)			
Follicle, cyst, multiple	1 (2%)			
Follicular cell, hyperplasia, focal	1 (2%)			
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(49)	(5)	(7)	(49)
Infiltration cellular, lymphocytic, multifocal				2 (4%)
Inflammation, chronic, multifocal				1 (2%)
Inflammation, chronic active, multifocal				4 (8%)
Penis		(1)	(2)	
Concretion, chronic active, multifocal		1 (100%)		
Inflammation, chronic active, multifocal		1 (100%)		
Preputial gland	(2)	(3)	(5)	(5)
Atrophy, diffuse	2 (100%)			
Atrophy, multifocal			1 (20%)	1 (20%)
Inflammation, chronic active, diffuse	1 (50%)			
Inflammation, chronic active, multifocal		2 (67%)	1 (20%)	1 (20%)
Inflammation, suppurative, multifocal			2 (40%)	
Duct, dilatation, focal		1 (33%)	1 (20%)	
Duct, dilatation, multifocal	1 (50%)		2 (40%)	
Prostate	(48)	(4)	(7)	(50)
Inflammation, acute, diffuse				1 (2%)
Inflammation, chronic active, multifocal		1 (25%)		1 (2%)
Epithelium, hyperplasia, focal				1 (2%)
Testes	(49)	(5)	(7)	(50)
Germinal epithelium, degeneration, chronic, multifocal				1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM				
Blood	(2)		(2)	
Neutrophilia	2 (100%)		1 (50%)	
Bone marrow	(50)	(3)	(7)	(50)
Hyperplasia, neutrophil, diffuse	3 (6%)		1 (14%)	5 (10%)
Hyperplasia, neutrophil, multifocal	1 (2%)			
Thrombus, chronic active	1 (2%)			
Femoral, angiectasis, focal				2 (4%)
Lymph node	(49)	(25)	(28)	(49)
Mediastinal, hematopoietic cell proliferation, diffuse	1 (2%)			
Mediastinal, hematopoietic cell proliferation, multifocal	2 (4%)			1 (2%)
Pancreatic, hematopoietic cell proliferation, multifocal	1 (2%)			
Renal, hyperplasia, plasma cell, multifocal	1 (2%)			
Lymph node, mandibular	(48)	(8)	(9)	(49)
Depletion lymphoid, diffuse		1 (13%)		
Hematopoietic cell proliferation, multifocal	1 (2%)			
Hyperplasia, lymphoid, multifocal	2 (4%)	3 (38%)	1 (11%)	
Hyperplasia, plasma cell, multifocal	2 (4%)		1 (11%)	3 (6%)
Lymphocyte, necrosis, multifocal				1 (2%)
Lymph node, mesenteric	(22)	(19)	(20)	(17)
Angiectasis, multifocal			1 (5%)	
Hematocyst, chronic active				1 (6%)
Hematopoietic cell proliferation, multifocal	10 (45%)	18 (95%)	18 (90%)	14 (82%)
Hemorrhage, multifocal	4 (18%)			
Hyperplasia, lymphoid, diffuse	1 (5%)			
Hyperplasia, lymphoid, multifocal				1 (6%)
Inflammation, chronic, multifocal				1 (6%)
Inflammation, granulomatous, focal			1 (5%)	
Inflammation, suppurative, multifocal		1 (5%)		
Spleen	(50)	(47)	(49)	(49)
Amyloid deposition, multifocal			1 (2%)	
Angiectasis, focal			1 (2%)	2 (4%)
Angiectasis, multifocal			1 (2%)	
Lymphoid follicle, depletion lymphoid, multifocal		1 (2%)		
Lymphoid follicle, necrosis, acute, multifocal		1 (2%)		
Red pulp, angiectasis, focal				1 (2%)
Red pulp, fibrosis	1 (2%)			
Red pulp, fibrosis, multifocal		1 (2%)		1 (2%)
Red pulp, hematopoietic cell proliferation, diffuse	50 (100%)	47 (100%)	49 (100%)	48 (98%)
Red pulp, pigmentation, hemosiderin, multifocal	37 (74%)	47 (100%)	45 (92%)	48 (98%)
Thymus	(36)		(3)	(27)
Cyst, multiple				1 (4%)
Depletion lymphoid, multifocal				1 (4%)
Necrosis, acute, multifocal	1 (3%)			2 (7%)
INTEGUMENTARY SYSTEM				
Skin	(49)	(27)	(28)	(49)
Acanthosis, diffuse	1 (2%)	3 (11%)	5 (18%)	4 (8%)
Acanthosis, focal		2 (7%)		1 (2%)
Acanthosis, multifocal	9 (18%)	4 (15%)	2 (7%)	7 (14%)
Alopecia				1 (2%)
Hyperkeratosis, multifocal	1 (2%)			1 (2%)
Inflammation, chronic active, multifocal		1 (4%)		
Parasite external	7 (14%)			12 (24%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
INTEGUMENTARY SYSTEM				
Skin (Continued)	(49)	(27)	(28)	(49)
Ulcer	6 (12%)	9 (33%)	8 (29%)	5 (10%)
Ulcer, multiple				4 (8%)
Sebaceous gland, hyperplasia, focal		1 (4%)		
Subcutaneous tissue, fibrosis, diffuse	1 (2%)	1 (4%)	4 (14%)	3 (6%)
Subcutaneous tissue, fibrosis, focal	1 (2%)	2 (7%)	1 (4%)	1 (2%)
Subcutaneous tissue, fibrosis, multifocal	5 (10%)	4 (15%)	1 (4%)	2 (4%)
Subcutaneous tissue, inflammation, acute, multifocal		1 (4%)		
Subcutaneous tissue, inflammation, chronic active, diffuse		1 (4%)	2 (7%)	
Subcutaneous tissue, inflammation, chronic active, focal		2 (7%)		1 (2%)
Subcutaneous tissue, inflammation, chronic active, multifocal	2 (4%)	5 (19%)	1 (4%)	7 (14%)
Subcutaneous tissue, inflammation, multifocal			1 (4%)	
Subcutaneous tissue, mineralization, multifocal			1 (4%)	
MUSCULOSKELETAL SYSTEM				
Bone	(49)	(28)	(26)	(50)
Bilateral, joint, radius, hyperostosis	1 (2%)			
Bilateral, joint, tarsal, hyperostosis	10 (20%)	21 (75%)	16 (62%)	11 (22%)
Bilateral, joint, tarsal, metaplasia, osseous, multifocal	10 (20%)	21 (75%)	16 (62%)	11 (22%)
Joint, tarsal, hyperostosis	11 (22%)	2 (7%)	4 (15%)	9 (18%)
Joint, tarsal, metaplasia, osseous, multifocal	11 (22%)	2 (7%)	4 (15%)	9 (18%)
NERVOUS SYSTEM				
None				
RESPIRATORY SYSTEM				
Lung	(50)	(10)	(14)	(50)
Alveolar epithelium, hyperplasia, focal	1 (2%)		1 (7%)	4 (8%)
Interstitium, inflammation, acute, diffuse				1 (2%)
Interstitium, inflammation, acute, multifocal				1 (2%)
Interstitium, inflammation, chronic active, focal	1 (2%)			
Interstitium, inflammation, chronic active, multifocal	1 (2%)	1 (10%)		
Nose	(50)	(5)	(7)	(50)
Respiratory epithelium, inflammation, acute, multifocal			1 (14%)	1 (2%)
SPECIAL SENSES SYSTEM				
Eye	(2)		(1)	(3)
Cataract	1 (50%)			1 (33%)
Inflammation, chronic, multifocal				1 (33%)
Lens, cataract, multifocal			1 (100%)	
Retina, atrophy, multifocal			1 (100%)	
Harderian gland	(50)	(5)	(7)	(40)
Inflammation, chronic active, multifocal			1 (14%)	
Acinus, dilatation, diffuse	1 (2%)			
Acinus, hyperplasia, multifocal				1 (3%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
URINARY SYSTEM				
Kidney	(50)	(6)	(10)	(49)
Amyloid deposition, multifocal			1 (10%)	
Cyst				1 (2%)
Infarct, chronic, focal		1 (17%)	1 (10%)	
Inflammation, suppurative, acute, multifocal		3 (50%)		
Mineralization, focal		1 (17%)		
Nephropathy, chronic, focal	3 (6%)			1 (2%)
Nephropathy, chronic, multifocal	2 (4%)		3 (30%)	7 (14%)
Bilateral, hydronephrosis, acute, multifocal	1 (2%)			
Cortex, inflammation, chronic, multifocal				1 (2%)
Perivascular, infiltration cellular, lymphocytic, multifocal				1 (2%)
Renal tubule, atypical cells, multifocal				1 (2%)
Renal tubule, degeneration, multifocal				1 (2%)
Renal tubule, pigmentation, hemosiderin, multifocal				4 (8%)
Renal tubule, regeneration, focal	1 (2%)			
Renal tubule, regeneration, multifocal	33 (66%)			30 (61%)
Urinary bladder	(49)	(8)	(11)	(50)
Dilatation	1 (2%)		4 (36%)	
Dilatation, diffuse		7 (88%)		
Submucosa, congestion, multifocal	1 (2%)			
Submucosa, necrosis, acute, multifocal				1 (2%)

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Gallbladder	(47)	*(50)	*(50)	(46)
Lymphoma malignant lymphocytic	1 (2%)			
Intestine small, jejunum	(46)	*(50)	*(50)	(48)
Lymphoma malignant histiocytic				1 (2%)
Peyer's patch, lymphoma malignant lymphocytic	1 (2%)			
Peyer's patch, lymphoma malignant mixed	1 (2%)			1 (2%)
Peyer's patch, lymphoma malignant undifferentiated cell type	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic			1 (2%)	
Hemangiosarcoma	1 (2%)			1 (2%)
Hepatocellular carcinoma	1 (2%)	2 (4%)		3 (6%)
Hepatocellular carcinoma, multiple				2 (4%)
Hepatocellular adenoma	5 (10%)	6 (12%)	6 (12%)	8 (16%)
Hepatocellular adenoma, multiple		1 (2%)	2 (4%)	
Lymphoma malignant histiocytic	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	6 (12%)	4 (8%)	3 (6%)	
Lymphoma malignant mixed	3 (6%)	1 (2%)		2 (4%)
Lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)	
Mesentery	*(50)	*(50)	*(50)	*(50)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant mixed	2 (4%)			
Pancreas	(48)	*(50)	*(50)	(49)
Lymphoma malignant histiocytic	2 (4%)	1 (2%)		
Lymphoma malignant lymphocytic	3 (6%)		1 (2%)	1 (2%)
Lymphoma malignant mixed	1 (2%)			1 (2%)
Salivary glands	(47)	*(50)	*(50)	(48)
Lymphoma malignant histiocytic	1 (2%)			1 (2%)
Lymphoma malignant lymphocytic	6 (13%)		1 (2%)	2 (4%)
Lymphoma malignant mixed	2 (4%)			1 (2%)
Stomach, forestomach	(48)	*(50)	*(50)	(46)
Lymphoma malignant lymphocytic			1 (2%)	
Papilloma squamous	1 (2%)	1 (2%)		
CARDIOVASCULAR SYSTEM				
Heart	(50)	*(50)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)	
Lymphoma malignant undifferentiated cell type			1 (2%)	
ENDOCRINE SYSTEM				
Adrenal gland	(50)	*(50)	*(50)	(49)
Capsule, adenoma	2 (4%)			
Adrenal gland, cortex	(50)	*(50)	*(50)	(49)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)	
Adrenal gland, medulla	(50)	*(50)	*(50)	(49)
Lymphoma malignant lymphocytic			1 (2%)	
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign	2 (4%)			
Islets, pancreatic	(48)	*(50)	*(50)	(49)
Carcinoma			1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM (Continued)				
Pituitary gland	(46)	*(50)	*(50)	(42)
Lymphoma malignant lymphocytic	1 (2%)			
Pars distalis, adenoma	3 (7%)	1 (2%)	2 (4%)	3 (7%)
Thyroid gland	(49)	*(50)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)			
Follicular cell, adenoma	3 (6%)			2 (4%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Ovary	(50)	*(50)	*(50)	(47)
Cystadenoma	1 (2%)			1 (2%)
Fibrosarcoma, metastatic, skin				1 (2%)
Granulosa cell tumor benign	1 (2%)			
Lymphoma malignant histiocytic	2 (4%)	1 (2%)		
Lymphoma malignant lymphocytic	3 (6%)		1 (2%)	
Lymphoma malignant mixed	1 (2%)			
Follicle, adenoma	1 (2%)			
Periovarian tissue, lymphoma malignant lymphocytic	2 (4%)			
Periovarian tissue, lymphoma malignant mixed				1 (2%)
Uterus	(50)	*(50)	*(50)	(48)
Hemangioma	1 (2%)			
Lymphoma malignant histiocytic	1 (2%)	2 (4%)		
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)	
Lymphoma malignant mixed	1 (2%)			
Polyp			1 (2%)	
Polyp stromal	1 (2%)	1 (2%)		1 (2%)
Cervix, lymphoma malignant histiocytic		1 (2%)		
HEMATOPOIETIC SYSTEM				
Blood	(50)	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)	
Lymphoma malignant undifferentiated cell type			1 (2%)	
Bone marrow	(48)	*(50)	*(50)	(49)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic			1 (2%)	
Femoral, lymphoma malignant lymphocytic	1 (2%)			
Lymph node	(48)	*(50)	*(50)	(47)
Bronchial, lymphoma malignant lymphocytic				1 (2%)
Bronchial, lymphoma malignant mixed				1 (2%)
Lumbar, lymphoma malignant histiocytic	2 (4%)			
Lumbar, lymphoma malignant lymphocytic	2 (4%)		1 (2%)	
Lumbar, lymphoma malignant mixed				1 (2%)
Mediastinal, fibrosarcoma, metastatic, skin				1 (2%)
Mediastinal, lymphoma malignant histiocytic	2 (4%)		1 (2%)	1 (2%)
Mediastinal, lymphoma malignant lymphocytic	5 (10%)		1 (2%)	1 (2%)
Mediastinal, lymphoma malignant mixed	3 (6%)			1 (2%)
Mediastinal, lymphoma malignant undifferentiated cell type			1 (2%)	
Pancreatic, lymphoma malignant lymphocytic			1 (2%)	1 (2%)
Renal, fibrosarcoma, metastatic, skin	1 (2%)			
Renal, lymphoma malignant histiocytic	1 (2%)			
Renal, lymphoma malignant lymphocytic	1 (2%)		1 (2%)	
Renal, lymphoma malignant mixed	1 (2%)			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)				
Lymph node, mandibular	(46)	*(50)	*(50)	(47)
Lymphoma malignant histiocytic	2 (4%)		1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	9 (20%)		2 (4%)	4 (9%)
Lymphoma malignant mixed	5 (11%)			2 (4%)
Lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)	
Lymph node, mesenteric	(8)	*(50)	*(50)	(3)
Lymphoma malignant histiocytic	2 (25%)			
Lymphoma malignant lymphocytic	2 (25%)		2 (4%)	
Lymphoma malignant mixed	3 (38%)			2 (67%)
Lymphoma malignant undifferentiated cell type	1 (13%)			
Spleen	(50)	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Lymphoma malignant histiocytic	3 (6%)	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	9 (18%)	8 (16%)	3 (6%)	5 (10%)
Lymphoma malignant mixed	6 (12%)	1 (2%)		3 (6%)
Lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)	
Thymus	(41)	*(50)	*(50)	(35)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic	4 (10%)			
Lymphoma malignant mixed	4 (10%)			2 (6%)
Lymphoma malignant undifferentiated cell type			1 (2%)	
INTEGUMENTARY SYSTEM				
Mammary gland	(38)	*(50)	*(50)	(44)
Adenocarcinoma		1 (2%)		
Adenoma		1 (2%)		
Skin	(50)	*(50)	*(50)	(49)
Subcutaneous tissue, fibrosarcoma	1 (2%)		3 (6%)	3 (6%)
Subcutaneous tissue, lymphoma malignant histiocytic		1 (2%)		
Subcutaneous tissue, lymphoma malignant lymphocytic			1 (2%)	
MUSCULOSKELETAL SYSTEM				
Bone	(49)	*(50)	*(50)	(50)
Cranium, osteoma		1 (2%)		
Sacrum, osteosarcoma				1 (2%)
Skeletal muscle	*(50)	*(50)	*(50)	*(50)
Abdominal, lymphoma malignant lymphocytic	1 (2%)			
NERVOUS SYSTEM				
Brain	(48)	*(50)	*(50)	(49)
Choroid plexus, lymphoma malignant lymphocytic	1 (2%)			
RESPIRATORY SYSTEM				
Lung	(50)	*(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	2 (4%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)		2 (4%)
Carcinoma, metastatic, islets, pancreatic			1 (2%)	
Fibrosarcoma, metastatic, skin	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)		2 (4%)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
RESPIRATORY SYSTEM				
Lung (Continued)	(50)	*(50)	*(50)	(50)
Lymphoma malignant lymphocytic	5 (10%)		1 (2%)	3 (6%)
Lymphoma malignant mixed	3 (6%)			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal gland			1 (2%)	
Mediastinum, fibrosarcoma, metastatic, skin				1 (2%)
Nose	(50)	*(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)	
SPECIAL SENSES SYSTEM				
Harderian gland	(50)	*(50)	*(50)	*(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)	4 (8%)
Lymphoma malignant lymphocytic			1 (2%)	
URINARY SYSTEM				
Kidney	(50)	*(50)	*(50)	(49)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic	7 (14%)	2 (4%)	1 (2%)	3 (6%)
Lymphoma malignant mixed	3 (6%)			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)	
Renal tubule, adenoma				1 (2%)
Urinary bladder	(48)	*(50)	*(50)	(44)
Fibrosarcoma, metastatic, skin	1 (2%)			
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic	4 (8%)			
Lymphoma malignant mixed	1 (2%)			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)			
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(50)	*(50)	*(50)
Lymphoma malignant histiocytic	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Lymphoma malignant mixed	6 (12%)	1 (2%)		3 (6%)
Lymphoma malignant lymphocytic	10 (20%)	8 (16%)	3 (6%)	5 (10%)
Hemangioma	1 (2%)			
Hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)	
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Terminal sacrifice	39	42	44	41
Moribund	5	4	3	4
Dead	5	1	3	5
Dosing accident	1	3		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
TUMOR SUMMARY				
Total animals with primary neoplasms **	36	26	21	31
Total primary neoplasms	54	32	24	44
Total animals with benign neoplasms	20	15	12	17
Total benign neoplasms	29	15	13	22
Total animals with malignant neoplasms	24	16	10	21
Total malignant neoplasms	25	17	11	22
Total animals with secondary neoplasms ***	1	1	2	4
Total secondary neoplasms	3	1	3	5

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: VEHICLE CONTROL

WEEKS ON STUDY	001	021	069	076	096	096	100	100	102	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
CARCASS ID	7655	7955	7952	7114	7511	7744	7822	7883	7622	7533	7111	7122	7133	7244	7331	7322	7334	7422	7433	7555	7811	7844	7922	7944	8003
ALIMENTARY SYSTEM																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Intestine large	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, lymphoma malignant lymphocytic																									
Peyer's patch, lymphoma malignant mixed						X																			
Peyer's patch, lymphoma malignant undifferentiated cell type																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma			X																						
Hepatocellular adenoma						X																			X
Lymphoma malignant histiocytic							X		X		X														
Lymphoma malignant lymphocytic					X										X					X					X
Lymphoma malignant mixed						X				X														X	
Lymphoma malignant undifferentiated cell type																									
Mesentery						+				+															
Lymphoma malignant mixed						X				X															
Pancreas	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X		X														
Lymphoma malignant lymphocytic					X										X										
Lymphoma malignant mixed										X															
Salivary glands	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X										X					X					
Lymphoma malignant mixed						X				X															
Stomach	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous													X												
Stomach, glandular	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	M	M	+	M	+	+	M	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Pars distalis, adenoma																									
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Follicular cell, adenoma																			X						
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma													X												
Granulosa cell tumor benign																									
Lymphoma malignant histiocytic									X		X														
Lymphoma malignant lymphocytic					X					X					X										
Lymphoma malignant mixed						X																			
Follicle, adenoma																									
Periovarian tissue, lymphoma malignant lymphocytic																				X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																X									
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed										X															
Polyp stromal																									

+: Tissue examined microscopically
: Not examined
–: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	8055	7155	7233	7441	7455	7722	8001	7222	7225	7444	7661	7733	7755	8585	7991	8044	7221	7355	7711	7993	7333	7554	7663	7644	8002	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Peyer's patch, lymphoma malignant lymphocytic											X															1
Peyer's patch, lymphoma malignant mixed																										1
Peyer's patch, lymphoma malignant undifferentiated cell type						X																				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
Hepatocellular carcinoma																										1
Hepatocellular adenoma						X												X				X				5
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic	X															X										6
Lymphoma malignant mixed																										3
Lymphoma malignant undifferentiated cell type						X																				1
Mesentery																										2
Lymphoma malignant mixed																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																							X			3
Lymphoma malignant mixed																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic											X					X							X			6
Lymphoma malignant mixed																										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma									X								X									2
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X														X						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Lymphoma malignant lymphocytic																										1
Pars distalis, adenoma			X								X													X		3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Follicular cell, adenoma												X								X						3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Granulosa cell tumor benign																						X				1
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed																										1
Follicle, adenoma					X																					1
Periovarian tissue, lymphoma malignant lymphocytic																X										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Polyp stromal					X																					1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	001	021	069	076	096	096	100	100	102	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
CARCASS ID	765	795	752	814	751	774	822	833	762	753	711	712	713	724	731	732	734	742	743	755	781	784	792	794	803
HEMATOPOIETIC SYSTEM																									
Blood					+																				
Lymphoma malignant lymphocytic					X																				
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X														
Femoral, lymphoma malignant lymphocytic					X																				
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant histiocytic									X		X														
Lumbar, lymphoma malignant lymphocytic					X										X										
Mediastinal, lymphoma malignant histiocytic									X		X														
Mediastinal, lymphoma malignant lymphocytic					X										X										
Mediastinal, lymphoma malignant mixed						X		X																	
Renal, fibrosarcoma, metastatic, skin				X																					
Renal, lymphoma malignant histiocytic							X																		
Renal, lymphoma malignant lymphocytic					X																				
Renal, lymphoma malignant mixed						X																			
Lymph node, mandibular	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X		X														
Lymphoma malignant lymphocytic					X										X					X	X				X
Lymphoma malignant mixed						X		X		X														X	
Lymphoma malignant undifferentiated cell type																									
Lymph node, mesenteric	M	M	M	M	+	+	+	+	M	+	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M
Lymphoma malignant histiocytic							X				X														
Lymphoma malignant lymphocytic					X										X										
Lymphoma malignant mixed						X		X		X															
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Lymphoma malignant histiocytic							X		X		X														
Lymphoma malignant lymphocytic					X										X					X	X				X
Lymphoma malignant mixed						X		X		X														X	
Lymphoma malignant undifferentiated cell type																									
Thymus	+	M	+	M	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X															X					
Lymphoma malignant mixed						X		X		X														X	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	M	+	+	+	+	+	M	M	+	M	+	+	+	+	+	M	M	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Abdominal, lymphoma malignant lymphocytic					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Choroid plexus, lymphoma malignant lymphocytic															X										
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X									X		X									
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin				X																					
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X										X										X
Lymphoma malignant mixed						X				X														X	
Lymphoma malignant undifferentiated cell type																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																							+		
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X						X		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X										X					X	X				X
Lymphoma malignant mixed						X				X														X	
Lymphoma malignant undifferentiated cell type																									
Urinary bladder	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin				X																					
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X										X										
Lymphoma malignant mixed										X															
Lymphoma malignant undifferentiated cell type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	805	715	723	741	745	772	801	722	725	744	761	773	775	785	791	804	721	735	771	793	733	754	763	764	802	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Lymphoma malignant lymphocytic																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Femoral, lymphoma malignant lymphocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lumbar, lymphoma malig. histiocytic																										2
Lumbar, lymphoma malig. lymphocytic																										2
Mediastinal, lymphoma malignant histiocytic																										2
Mediastinal, lymphoma malignant lymphocytic											X					X							X			5
Mediastinal, lymphoma malig mixed								X																		3
Renal, fibrosarcoma, metastatic, skin																										1
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malig lymphocytic																										1
Renal, lymphoma malignant mixed																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic	X										X					X							X			9
Lymphoma malignant mixed									X																	5
Lymphoma malignant undifferentiated cell type						X																				1
Lymph node, mesenteric	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	8
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																										3
Lymphoma malignant undifferentiated cell type						X																				1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic	X										X					X							X			9
Lymphoma malignant mixed								X										X								6
Lymphoma malignant undifferentiated cell type						X																				1
Thymus	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic	X																						X			4
Lymphoma malignant mixed																										4
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	38
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	49
Skeletal muscle																										1
Abdominal, lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Choroid plexus, lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X											X				5
Alveolar/bronchiolar carcinoma								X																		1
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic	X																						X			5
Lymphoma malignant mixed																										3
Lymphoma malignant undifferentiated cell type						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Adenoma						X																				3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic	X										X															7
Lymphoma malignant mixed																										3
Lymphoma malignant undifferentiated cell type						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic											X												X			4
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type						X																				1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: LOW DOSE

WEEKS ON STUDY	0 0 1	0 0 1	0 0 1	0 6 3	0 7 6	0 9 8	1 0 2	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	6 1 4	6 2 1	6 3 2	6 9 5	6 1 3	6 3 4	6 4 4	6 1 2	6 2 3	6 5 2	6 5 4	6 6 1	6 7 2	6 7 3	7 0 3	7 0 4	6 1 1	6 3 5	6 4 5	6 5 5	6 6 5	6 8 3	6 8 5	6 9 1	6 9 3
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+																					
Gallbladder	+	+	A	A	+																					
Intestine large	+	+	+	+	+																					
Intestine large, cecum	+	+	M	+	+																					
Intestine large, colon	+	+	+	+	+																					
Intestine large, rectum	+	+	M	+	+																					
Intestine small	+	+	A	+	+																					
Intestine small, duodenum	+	+	A	+	+																					
Intestine small, ileum	+	+	A	+	+																					
Intestine small, jejunum	+	+	A	+	+																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																										
Hepatocellular adenoma																		X	X							
Hepatocellular adenoma, multiple																										
Lymphoma malignant histiocytic					X																					
Lymphoma malignant lymphocytic																		X	X							
Lymphoma malignant mixed																										
Mesentery						+		+																		
Pancreas	+	+	+	+	+	+																				
Lymphoma malignant histiocytic					X																					
Salivary glands	+	+	+	+	+																					
Stomach	+	+	+	+	+																					
Stomach, forestomach	+	+	+	+	+																					
Papilloma squamous				X																						
Stomach, glandular	+	+	+	+	+																					
Tooth	+	+	+	+	+																					
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+																					
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+																					
Adrenal gland, cortex	+	+	+	+	+																					
Adrenal gland, medulla	+	+	+	+	+																					
Islets, pancreatic	+	+	+	+	+																					
Parathyroid gland	M	M	M	+	+																					
Pituitary gland	+	+	M	+	+								+													
Pars distalis, adenoma													X													
Thyroid gland	+	M	+	+	+																					
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+		+	+		+					+		+									
Lymphoma malignant histiocytic					X																					
Uterus	+	+	+	+	+	+	+		+	+		+		+		+	+	+	+	+		+	+	+		
Lymphoma malignant histiocytic					X																	X				
Polyp stromal																										
Cervix, lymphoma malignant histiocytic																										
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+																					
Lymph node	+	+	+	+	+																					
Lymph node, mandibular	+	+	+	+	+																					
Lymph node, mesenteric	M	M	M	M	M																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X															
Lymphoma malignant histiocytic																										
Lymphoma malignant lymphocytic																		X	X		X					
Lymphoma malignant mixed																										
Thymus	+	+	+	+	M																					
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	+	+															+						
Adenocarcinoma																				X						
Adenoma																										
Skin	+	+	+	+	+															+						
Subcutaneous tissue lymphoma malignant histiocytic					X																					
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+										+											
Cranium, osteoma															X											
NERVOUS SYSTEM																										
Brain	+	+	+	+	+																					
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+						+															
Alveolar/bronchiolar adenoma											X															
Alveolar/bronchiolar carcinoma																										
Hepatocellular carcinoma, metastatic liver																										
Nose	+	+	+	+	+																					
Trachea	+	+	+	+	+																					
SPECIAL SENSES SYSTEM																										
Eye									+																	
Harderian gland	+	M	M	+	+				+																	
Adenoma									X																	
URINARY SYSTEM																										
Kidney	+	+	+	+	+														+							
Lymphoma malignant lymphocytic																			X							
Urinary bladder	+	+	+	+	+																					

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	694	641	651	662	705	615	622	624	631	633	642	664	674	675	701	625	643	653	663	671	681	682	684	692	702		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											5
Gallbladder																											3
Intestine large																											5
Intestine large, cecum																											4
Intestine large, colon																											5
Intestine large, rectum																											4
Intestine small																											4
Intestine small, duodenum																											4
Intestine small, ileum																											4
Intestine small, jejunum																											4
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma						X																X					2
Hepatocellular adenoma	X																	X						X	X		6
Hepatocellular adenoma, multiple																	X										1
Lymphoma malignant histiocytic																			X								2
Lymphoma malignant lymphocytic	X										X																4
Lymphoma malignant mixed							X																				1
Mesentery																											2
Pancreas																						+					7
Lymphoma malignant histiocytic																											1
Salivary glands																											5
Stomach																											5
Stomach, forestomach																											5
Papilloma squamous																											1
Stomach, glandular																											5
Tooth																											5
CARDIOVASCULAR SYSTEM																											
Heart																											5
ENDOCRINE SYSTEM																											
Adrenal gland																											5
Adrenal gland, cortex																											5
Adrenal gland, medulla																											5
Islets, pancreatic																											5
Parathyroid gland																											2
Pituitary gland												M															5
Pars distalis, adenoma																											1
Thyroid gland																											4
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Ovary																+				+		+				+	14
Lymphoma malignant histiocytic																											1
Uterus	+	+	+	+	+		+		+	+	+		+	+	+		+		+	+	+		+	+	+		38
Lymphoma malignant histiocytic																											2
Polyp stromal															X												1
Cervix, lymphoma malignant histiocytic																			X								1
HEMATOPOIETIC SYSTEM																											
Bone marrow																											5
Lymph node																											5
Lymph node, mandibular																											5
Lymph node, mesenteric																											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																											1
Lymphoma malignant histiocytic																			X								1
Lymphoma malignant lymphocytic	X				X						X									X				X			8
Lymphoma malignant mixed							X																				1
Thymus																											4
INTEGUMENTARY SYSTEM																											
Mammary gland									+																		5
Adenocarcinoma																											1
Adenoma									X																		1
Skin									+																		7
Subcutaneous tissue, lymphoma malignant histiocytic																											1
MUSCULOSKELETAL SYSTEM																											
Bone																											6
Cranium, osteoma																											1
NERVOUS SYSTEM																											
Brain																											5
RESPIRATORY SYSTEM																											
Lung																+						+					8
Alveolar/bronchiolar adenoma																						X					2
Alveolar/bronchiolar carcinoma																						X					1
Hepatocellular carcinoma, metastatic, liver																						X					1
Nose																											5
Trachea																											5
SPECIAL SENSES SYSTEM																											
Eye																											1
Harderian gland																											4
Adenoma																											1
URINARY SYSTEM																											
Kidney																				+							7
Lymphoma malignant lymphocytic																				X							2
Urinary bladder																											5

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: MID DOSE

WEEKS ON STUDY	075	076	090	096	096	097	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	574	563	523	594	551	583	511	524	532	571	582	591	513	515	522	525	543	555	561	572	575	584	512	521	531
ALIMENTARY SYSTEM																									
Esophagus	+	+	+																						
Gallbladder	M	+	A																						
Intestine large	+	+	+																						
Intestine large, cecum	+	+	A																						
Intestine large, colon	+	+	+																						
Intestine large, rectum	+	+	A																						
Intestine small	+	+	+																						
Intestine small, duodenum	+	+	+																						
Intestine small, ileum	M	+	+																						
Intestine small, jejunum	A	+	+																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																									
Hepatocellular adenoma								X										X							
Hepatocellular adenoma, multiple							X																		
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant undifferentiated cell type	X																								
Mesentery			+		+	+																			
Lymphoma malignant histiocytic			X																						
Pancreas	+	+	+			+																			
Lymphoma malignant lymphocytic		X																							
Salivary glands	+	+	+																						
Lymphoma malignant lymphocytic		X																							
Stomach	+	+	+																						
Stomach, forestomach	+	+	+																						
Lymphoma malignant lymphocytic		X																							
Stomach, glandular	+	+	+																						
Tooth	+	+	+																						
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+																						
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant undifferentiated cell type	X																								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+																						
Adrenal gland, cortex	+	+	+																						
Lymphoma malignant lymphocytic		X																							
Adrenal gland, medulla	+	+	+																						
Lymphoma malignant lymphocytic		X																							
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+																						
Carcinoma																									
Parathyroid gland	+	+	+																						
Pituitary gland	+	+	+							+			+										+		
Pars distalis, adenoma													X										X		
Thyroid gland	+	+	+																						
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+		+		+	+	+	+						+			+	+			+		+
Lymphoma malignant lymphocytic		X																							
Uterus	+	+	+	+			+	+		+	+	+	+	+		+	+	+	+			+	+	+	+
Lymphoma malignant lymphocytic																									
Polyp											X														

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	533	534	535	542	544	553	565	585	601	545	552	554	562	581	595	602	514	541	564	573	592	593	603	604	605	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										3
Gallbladder																				+						2
Intestine large																										3
Intestine large, cecum																										2
Intestine large, colon																										3
Intestine large, rectum																										2
Intestine small																										3
Intestine small, duodenum																										3
Intestine small, ileum																										2
Intestine small, jejunum																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																				X						1
Hepatocellular adenoma								X			X							X				X			6
Hepatocellular adenoma, multiple																	X									2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic	X									X																3
Lymphoma malignant undifferentiated cell type																										1
Mesentery																										3
Lymphoma malignant histiocytic																										1
Pancreas																				+						5
Lymphoma malignant lymphocytic																										1
Salivary glands																										3
Lymphoma malignant lymphocytic																										1
Stomach				+																						4
Stomach, forestomach																										3
Lymphoma malignant lymphocytic																										1
Stomach, glandular																										3
Tooth																										3
CARDIOVASCULAR SYSTEM																										
Heart																										3
Lymphoma malignant lymphocytic																										1
Lymphoma malignant undifferentiated cell type																										1
ENDOCRINE SYSTEM																										
Adrenal gland																+										4
Adrenal gland, cortex																+										4
Lymphoma malignant lymphocytic																										1
Adrenal gland, medulla																+										4
Lymphoma malignant lymphocytic																										1
Pheochromocytoma malignant																X										1
Islets, pancreatic																				+						4
Carcinoma																				X						1
Parathyroid gland																										3
Pituitary gland																										6
Pars distalis, adenoma																										2
Thyroid gland																										3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary						+							+							+					+	17
Lymphoma malignant lymphocytic																										1
Uterus	+	+	+		+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	42
Lymphoma malignant lymphocytic										X																1
Polyp																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	075	076	090	096	096	097	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	574	563	523	594	551	583	511	524	532	571	582	591	513	515	522	525	543	555	561	572	575	584	512	521	531
HEMATOPOIETIC SYSTEM																											
Blood	+	+																									
Lymphoma malignant lymphocytic		X																									
Lymphoma malignant undifferentiated cell type	X																										
Bone marrow	+	+	+																								
Lymphoma malignant lymphocytic		X																									
Lymph node	+	+	+	+																				+			
Lumbar, lymphoma malignant lymphocytic																											
Mediastinal, lymphoma malignant histiocytic			X																								
Mediastinal, lymphoma malignant lymphocytic		X																									
Mediastinal, lymphoma malignant undifferentiated cell type	X																										
Pancreatic, lymphoma malignant lymphocytic		X																									
Renal, lymphoma malignant lymphocytic																											
Lymph node, mandibular	+	+	+	M																				+			
Lymphoma malignant histiocytic			X																								
Lymphoma malignant lymphocytic		X																									
Lymphoma malignant undifferentiated cell type	X																										
Lymph node, mesenteric	M	+	M	+																				+			
Lymphoma malignant lymphocytic		X																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																											
Lymphoma malignant lymphocytic		X																									
Lymphoma malignant undifferentiated cell type	X																										
Thymus	+	M	M																								
Lymphoma malignant undifferentiated cell type	X																										
INTEGUMENTARY SYSTEM																											
Mammary gland	+	+	+																								
Skin	+	+	+	+					+																		
Subcutaneous tissue, fibrosarcoma				X																							
Subcutaneous tissue, lymphoma malignant lymphocytic		X																									
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+																								
NERVOUS SYSTEM																											
Brain	+	+	+																								
RESPIRATORY SYSTEM																											
Lung	+	+	+		+																						
Alveolar/bronchiolar adenoma																											
Carcinoma, metastatic, islets, pancreatic																											
Lymphoma malignant histiocytic			X																								
Lymphoma malignant lymphocytic		X																									
Lymphoma malignant undifferentiated cell type	X																										
Pheochromocytoma malignant, metastatic, adrenal gland																											
Nose	+	+	+																								
Lymphoma malignant lymphocytic		X																									
Trachea	+	+	+																								
SPECIAL SENSES SYSTEM																											
Harderian gland	M	+	+											+													
Adenoma														X													
Lymphoma malignant lymphocytic		X																									
URINARY SYSTEM																											
Kidney	+	+	+																								
Lymphoma malignant lymphocytic		X																									
Lymphoma malignant undifferentiated cell type	X																										
Urinary bladder	+	+	+																								

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	53 3	53 4	53 5	54 2	54 4	55 3	56 5	58 5	60 1	54 5	55 2	55 5	56 2	58 1	59 5	60 2	51 4	54 1	56 4	57 3	59 2	59 3	60 3	60 4	60 5	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant undifferentiated cell type																										1
Bone marrow																										3
Lymphoma malignant lymphocytic																										1
Lymph node	+																	+		M						7
Lumbar, lymphoma malig. lymphocytic	X																									1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malignant undifferentiated cell type																										1
Pancreatic, lymphoma malignant lymphocytic																										1
Renal, lymphoma malig lymphocytic	X																									1
Lymph node, mandibular	+																									5
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic	X																									2
Lymphoma malignant undifferentiated cell type																										1
Lymph node, mesenteric	+																			M						4
Lymphoma malignant lymphocytic	X																									2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									1
Lymphoma malignant lymphocytic	X									X																3
Lymphoma malignant undifferentiated cell type																										1
Thymus																										1
Lymphoma malignant undifferentiated cell type																										1
INTEGUMENTARY SYSTEM																										
Mammary gland																										3
Skin				+													+									7
Subcutaneous tissue, fibrosarcoma				X													X									3
Subcutaneous tissue, lymphoma malignant lymphocytic																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										3
NERVOUS SYSTEM																										
Brain																										3
RESPIRATORY SYSTEM																										
Lung																+				+		+				7
Alveolar/bronchiolar adenoma																						X				1
Carcinoma, metastatic, islets, pancreatic																				X						1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant undifferentiated cell type																										1
Pheochromocytoma malignant, metastatic, adrenal gland																X										1
Nose																										3
Lymphoma malignant lymphocytic																										1
Trachea																										3
SPECIAL SENSES SYSTEM																										
Harderian gland																										3
Adenoma																										1
Lymphoma malignant lymphocytic																										1
URINARY SYSTEM																										
Kidney																		+								4
Lymphoma malignant lymphocytic																										1
Lymphoma malignant undifferentiated cell type																										1
Urinary bladder																										3

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE: HIGH DOSE

WEEKS ON STUDY	066	079	087	088	091	096	101	101	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105
CARCASS ID	46 3	44 3	44 5	46 4	48 5	42 5	47 1	43 2	46 2	41 3	41 4	43 4	44 1	45 3	45 4	49 3	41 2	43 1	43 3	45 1	46 5	48 3	50 5	42 4	47 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic								X																	
Peyer's patch, lymphoma malignant mixed													X												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Hepatocellular carcinoma				X												X									
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma									X									X							X
Lymphoma malignant histiocytic			X																						
Lymphoma malignant mixed																									
Mesentery	+	+																							
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic																							X		
Lymphoma malignant mixed																									
Stomach	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Stomach, glandular	+	+	A	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X																						
Adrenal gland, medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Pars distalis, adenoma													X												
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma													X												
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									X
Fibrosarcoma, metastatic, skin						X																			
Periovarian tissue, lymphoma malignant mixed																									
Uterus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
HEMATOPOIETIC SYSTEM																									
Blood								+			+														+
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Bronchial, lymphoma malignant lymphocytic																									
Bronchial, lymphoma malignant mixed																									
Lumbar, lymphoma malignant mixed																									
Mediastinal, fibrosarcoma, metastatic, skin																									
Mediastinal, lymphoma malignant histiocytic			X																						
Mediastinal, lymphoma malignant lymphocytic																							X		
Mediastinal, lymphoma malignant mixed																									
Pancreatic, lymphoma malignant lymphocytic																							X		
Lymph node, mandibular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic																							X		
Lymphoma malignant mixed																									
Lymph node, mesenteric	M	M	M	M	A	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Lymphoma malignant mixed													X												
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic																					X		X		
Lymphoma malignant mixed													X												
Thymus	M	+	M	M	M	M	+	M	+	M	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	474	482	492	501	411	415	442	455	461	472	475	481	494	495	503	421	422	423	435	444	452	484	491	502	504	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Peyer's patch, lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma		X																								3
Hepatocellular carcinoma, multiple							X								X											2
Hepatocellular adenoma							X	X					X		X							X				8
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed												X												X		2
Mesentery												+														3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic										X																1
Lymphoma malignant mixed																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic														X												2
Lymphoma malignant mixed												X														1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	I	+	M	+	+	+	42
Pars distalis, adenoma							X		X																	3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																X										2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Cystadenoma																										1
Fibrosarcoma, metastatic, skin																										1
Perіovarian tissue, lymphoma malignant mixed												X														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Polyp stromal														X												1
HEMATOPOIETIC SYSTEM																										
Blood																										3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bronchial, lymphoma malignant lymphocytic														X												1
Bronchial, lymphoma malignant mixed												X														1
Lumbar, lymphoma malignant mixed												X														1
Mediastinal, fibrosarcoma, metastatic, skin																		X								1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malig mixed																								X		1
Pancreatic, lymphoma malignant lymphocytic																										1
Lymph node, *mandibular*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic				X						X				X												4
Lymphoma malignant mixed												X												X		2
Lymph node, mesenteric	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M	M	3
Lymphoma malignant mixed												X														2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic				X						X				X												5
Lymphoma malignant mixed												X												X		3
Thymus	+	M	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	35
Lymphoma malignant mixed												X												X		2

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	066	079	087	088	091	096	101	101	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105
CARCASS ID	463	443	445	464	485	425	471	432	462	413	414	434	441	453	454	493	412	431	433	451	465	483	505	424	473
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+
Skin	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma						X																			X
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sacrum, osteosarcoma											X														
Skeletal muscle							+																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma												X													
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic																							X		
Lymphoma malignant mixed																									
Mediastinum, fibrosarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye		+											I												
Harderian gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Adenoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																					X				
Lymphoma malignant mixed																									
Renal tubule, adenoma																									
Urinary bladder	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE
(Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	474	482	492	501	511	515	442	455	461	472	475	481	494	495	503	521	522	423	435	444	452	484	491	502	504	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma																		X								3
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sacrum, osteosarcoma																										1
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X							X							2
Alveolar/bronchiolar carcinoma											X															2
Hepatocellular carcinoma, metastatic, liver		X					X																			2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic										X				X												3
Lymphoma malignant mixed												X														1
Mediastinum, fibrosarcoma, metastatic, skin																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma			X												X					X						4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic				X										X												3
Lymphoma malignant mixed												X														1
Renal tubule, adenoma													X													1
Urinary bladder	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+	44
Lymphoma malignant mixed												X														1

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Harderian Gland: Adenoma				
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	7.7%	2.4%	2.3%	9.8%
Terminal Rates (c)	3/39 (8%)	1/42 (2%)	1/44 (2%)	4/41 (10%)
Day of First Observation	728	728	728	728
Life Table Tests (d)	P=0.225	P=0.279N	P=0.263N	P=0.527
Logistic Regression Tests (d)	P=0.225	P=0.279N	P=0.263N	P=0.527
Cochran-Armitage Trend Test (d)	P=0.222			
Fisher Exact Test (d)		P=0.309N	P=0.309N	P=0.500
Liver: Hepatocellular Adenoma				
Overall Rates (a)	5/50 (10%)	7/50 (14%)	8/50 (16%)	8/50 (16%)
Adjusted Rates (b)	12.3%	16.7%	18.2%	19.0%
Terminal Rates (c)	4/39 (10%)	7/42 (17%)	8/44 (18%)	7/41 (17%)
Day of First Observation	672	728	728	722
Life Table Tests (d)	P=0.310	P=0.428	P=0.354	P=0.308
Logistic Regression Tests (d)	P=0.305	P=0.374	P=0.302	P=0.287
Cochran-Armitage Trend Test (d)	P=0.301			
Fisher Exact Test (d)		P=0.380	P=0.277	P=0.277
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	1/50 (2%)	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	2.1%	4.8%	0.0%	11.7%
Terminal Rates (c)	0/39 (0%)	2/42 (5%)	0/44 (0%)	4/41 (10%)
Day of First Observation	480	728		616
Life Table Tests (d)	P=0.034	P=0.512	P=0.492N	P=0.117
Logistic Regression Tests (d)	P=0.028	P=0.509	P=0.500N	P=0.082
Cochran-Armitage Trend Test (d)	P=0.032N			
Fisher Exact Test (d)		P=0.500	P=0.500N	P=0.102
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	6/50 (12%)	9/50 (18%)	8/50 (16%)	11/50 (22%)
Adjusted Rates (b)	14.1%	21.4%	18.2%	25.4%
Terminal Rates (c)	4/39 (10%)	9/42 (21%)	8/44 (18%)	9/41 (22%)
Day of First Observation	480	728	728	616
Life Table Tests (d)	P=0.171	P=0.335	P=0.472	P=0.174
Logistic Regression Tests (d)	P=0.180	P=0.278	P=0.395	P=0.146
Cochran-Armitage Trend Test (d)	P=0.161			
Fisher Exact Test (d)		P=0.288	P=0.387	P=0.143
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	5/50 (10%)	(e) 2/8 (25%)	(e) 1/7 (14%)	2/50 (4%)
Adjusted Rates (b)	12.2%			4.9%
Terminal Rates (c)	4/39 (10%)			2/41 (5%)
Day of First Observation	666			728
Life Table Test (d)				P=0.203N
Logistic Regression Test (d)				P=0.206N
Fisher Exact Test (d)				P=0.218N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	6/50 (12%)	(e) 2/8 (25%)	(e) 1/7 (14%)	4/50 (8%)
Adjusted Rates (b)	14.7%			9.8%
Terminal Rates (c)	5/39 (13%)			4/41 (10%)
Day of First Observation	666			728
Life Table Test (d)				P=0.344N
Logistic Regression Test (d)				P=0.356N
Fisher Exact Test (d)				P=0.370N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	3/46 (7%)	(e) 1/5 (20%)	(e) 2/6 (33%)	3/42 (7%)
Adjusted Rates (b)	8.1%			8.8%
Terminal Rates (c)	3/37 (8%)			3/34 (9%)
Day of First Observation	728			728
Life Table Test (d)				P=0.624
Logistic Regression Test (d)				P=0.624
Fisher Exact Test (d)				P=0.617
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.1%	0.0%	0.0%	7.0%
Terminal Rates (c)	0/39 (0%)	0/42 (0%)	2/44 (5%)	2/41 (5%)
Day of First Observation	527		667	667
Life Table Tests (d)	P=0.131	P=0.504N	P=0.337	P=0.321
Logistic Regression Tests (d)	P=0.117	P=0.473N	P=0.260	P=0.268
Cochran-Armitage Trend Test (d)	P=0.126			
Fisher Exact Test (d)		P=0.500N	P=0.309	P=0.309
Thyroid Gland: Follicular Cell Adenoma				
Overall Rates (a)	3/49 (6%)	(e) 0/4 (0%)	(e) 0/3 (0%)	2/49 (4%)
Adjusted Rates (b)	7.7%			4.9%
Terminal Rates (c)	3/39 (8%)			2/41 (5%)
Day of First Observation	728			728
Life Table Test (d)				P=0.477N
Logistic Regression Test (d)				P=0.477N
Fisher Exact Test (d)				P=0.500N
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	19/50 (38%)	12/50 (24%)	5/50 (10%)	10/50 (20%)
Adjusted Rates (b)	41.3%	27.8%	10.3%	23.0%
Terminal Rates (c)	12/39 (31%)	11/42 (26%)	2/44 (5%)	8/41 (20%)
Day of First Observation	666	528	521	609
Life Table Tests (d)	P=0.082N	P=0.083N	P=0.001N	P=0.041N
Logistic Regression Tests (d)	P=0.071N	P=0.104N	P=0.001N	P=0.032N
Cochran-Armitage Trend Test (d)	P=0.078N			
Fisher Exact Test (d)		P=0.097N	P<0.001N	P=0.038N

(a) Number of tumor-bearing animals/number of animals examined at the site; doses calculated as *p*-chloroaniline.
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 that dosed group and the vehicle controls. 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 test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues

TABLE D4. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence for All Water Gavage Vehicle Controls		
Iodinated glycerol (b)	26/50	26/50
Chlorpheniramine maleate (c)	17/50	18/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	21/50	21/50
Malonaldehyde, sodium salt (c)	13/50	13/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	16/50	18/50
Methyl carbamate (d)	14/50	14/50
Chlorinated trisodium phosphate (b)	12/50	12/50
TOTAL	119/350 (34.0%)	122/350 (34.9%)
SD (e)	9.93%	9.92%
Range (f)		
High	26/50	26/50
Low	12/50	12/50
Overall Historical Incidence for Untreated Controls		
TOTAL	617/2,040 (30.2%)	636/2,040 (31.2%)
SD (e)	13.32%	12.83%
Range (f)		
High	(g) 37/50	(g) 38/50
Low	5/50	6/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Second highest: 31/50

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	50	50	50	50
Animals removed	50	50	50	50
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Gallbladder	(47)	(3)	(2)	(46)
Infiltration cellular, lymphocytic, multifocal				1 (2%)
Lumen, pigmentation, diffuse				1 (2%)
Mucosa, cyst				1 (2%)
Intestine large, colon	(47)	(5)	(3)	(48)
Parasite metazoan	3 (6%)			
Intestine small, duodenum	(46)	(4)	(3)	(48)
Inflammation, chronic, focal	1 (2%)			
Ulcer, chronic, focal	1 (2%)			
Intestine small, jejunum	(46)	(4)	(2)	(48)
Necrosis, acute, diffuse				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis, focal	1 (2%)			
Basophilic focus	1 (2%)			1 (2%)
Clear cell focus	1 (2%)	2 (4%)		
Cytomegaly, focal			1 (2%)	1 (2%)
Hematopoietic cell proliferation, multifocal	15 (30%)	29 (58%)	24 (48%)	31 (62%)
Necrosis, acute, multifocal	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Thrombus, chronic				1 (2%)
Vacuolization cytoplasmic, focal			1 (2%)	1 (2%)
Bile duct, cyst		1 (2%)		
Centrilobular, necrosis, acute, multifocal				1 (2%)
Hepatocyte, karyomegaly, focal	1 (2%)	1 (2%)		
Kupffer cell, pigmentation, hemosiderin			1 (2%)	46 (92%)
Periportal, inflammation, multifocal	1 (2%)			
Serosa, inflammation, suppurative, chronic, multifocal				1 (2%)
Sinusoid, infiltration cellular, polymorphonuclear, diffuse	1 (2%)			
Mesentery	(2)	(2)	(3)	(3)
Inflammation, chronic active, multifocal		2 (100%)	2 (67%)	1 (33%)
Inflammation, suppurative, chronic, multifocal				2 (67%)
Pancreas	(48)	(7)	(5)	(49)
Inflammation, chronic active, multifocal		1 (14%)	1 (20%)	
Inflammation, suppurative, chronic, multifocal				1 (2%)
Acinus, atrophy, diffuse	1 (2%)			
Acinus, atrophy, focal	1 (2%)			2 (4%)
Acinus, atrophy, multifocal	1 (2%)	1 (14%)	2 (40%)	5 (10%)
Duct, cyst		1 (14%)		1 (2%)
Duct, cyst, multiple	1 (2%)			
Duct, ectasia, focal				1 (2%)
Duct, ectasia, multifocal			1 (20%)	
Duct, inflammation, chronic, multifocal	1 (2%)			
Salivary glands	(47)	(5)	(3)	(48)
Infiltration cellular, lymphocytic, multifocal				3 (6%)
Acinus, atrophy, focal				1 (2%)
Stomach, forestomach	(48)	(5)	(3)	(46)
Acanthosis, focal				1 (2%)
Hyperkeratosis, focal				1 (2%)
Ulcer, acute, focal				1 (2%)
Stomach, glandular	(48)	(5)	(3)	(47)
Cyst				1 (2%)
Necrosis, acute, focal	1 (2%)			

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
CARDIOVASCULAR SYSTEM				
Heart	(50)	(5)	(3)	(50)
Atrium, inflammation, chronic, focal			1 (33%)	
Coronary artery, inflammation, chronic active multifocal				1 (2%)
Epicardium, inflammation, acute, multifocal		1 (20%)		
ENDOCRINE SYSTEM				
Adrenal gland	(50)	(5)	(4)	(49)
Accessory adrenal cortical nodule	1 (2%)			
Capsule, cyst	1 (2%)			
Capsule, hyperplasia, cystic, glandular, multifocal	1 (2%)			
Capsule, hyperplasia, focal				1 (2%)
Capsule, hyperplasia, multifocal	48 (96%)	2 (40%)	3 (75%)	48 (98%)
Corticomedullary junction, degeneration, fatty, multifocal				1 (2%)
Adrenal gland, cortex	(50)	(5)	(4)	(49)
Degeneration, fatty, focal				1 (2%)
Hematopoietic cell proliferation, multifocal				1 (2%)
Hyperplasia, focal	1 (2%)			1 (2%)
Hyperplasia, multifocal	1 (2%)			
Hypertrophy, focal	2 (4%)			2 (4%)
Hypertrophy, multifocal	1 (2%)			1 (2%)
Adrenal gland, medulla	(50)	(5)	(4)	(49)
Hyperplasia, focal	1 (2%)			
Infiltration cellular, plasma cell, focal				1 (2%)
Pituitary gland	(46)	(5)	(6)	(42)
Pars distalis, cyst	3 (7%)			1 (2%)
Pars distalis, cyst, multiple	1 (2%)			
Pars distalis, hyperplasia, focal	5 (11%)		1 (17%)	6 (14%)
Pars distalis, hyperplasia, multifocal	2 (4%)			
Thyroid gland	(49)	(4)	(3)	(49)
Necrosis, acute, focal	1 (2%)			
Follicular cell, hyperplasia				1 (2%)
Follicular cell, hyperplasia, focal	1 (2%)			1 (2%)
Follicular cell, hyperplasia, multifocal				1 (2%)
Interstitium, inflammation, chronic, focal				1 (2%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Ovary	(50)	(14)	(17)	(47)
Angiectasis, focal				1 (2%)
Angiectasis, multifocal	1 (2%)		1 (6%)	
Inflammation, suppurative, chronic, multifocal				2 (4%)
Thrombus, chronic active	1 (2%)	1 (7%)		
Corpus luteum, angiectasis, multifocal				1 (2%)
Follicle, cyst	10 (20%)	7 (50%)	11 (65%)	14 (30%)
Follicle, cyst, multiple	3 (6%)			1 (2%)
Periovarian tissue, cyst	3 (6%)	1 (7%)	5 (29%)	1 (2%)
Periovarian tissue, infiltration cellular, lymphocytic, multifocal				1 (2%)
Periovarian tissue, inflammation, chronic active, multifocal		1 (7%)		
Rete ovarii, cyst				1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
GENITAL SYSTEM (Continued)				
Uterus	(50)	(38)	(42)	(48)
Inflammation, suppurative, chronic, multifocal		1 (3%)		2 (4%)
Endometrium, angiectasis, multifocal	1 (2%)			
Endometrium, hyperplasia, cystic, glandular, multifocal	45 (90%)	35 (92%)	41 (98%)	43 (90%)
Mucosa, metaplasia, squamous, multifocal				1 (2%)
Myometrium, angiectasis, multifocal	1 (2%)			
HEMATOPOIETIC SYSTEM				
Blood	(1)		(2)	(3)
Neutrophilia				3 (100%)
Bone marrow	(48)	(5)	(3)	(49)
Femoral, angiectasis, focal	1 (2%)			
Femoral, hyperplasia, neutrophil, diffuse				2 (4%)
Femoral, myelofibrosis, multifocal	3 (6%)			4 (8%)
Lymph node	(48)	(5)	(7)	(47)
Mediastinal, hyperplasia, lymphoid, diffuse				2 (4%)
Pancreatic, inflammation, chronic active, multifocal			1 (14%)	
Renal, hyperplasia, lymphoid, diffuse				1 (2%)
Lymph node, mandibular	(46)	(5)	(5)	(47)
Hyperplasia, lymphoid, diffuse				1 (2%)
Hyperplasia, plasma cell, multifocal				1 (2%)
Lymphatic, angiectasis, diffuse			1 (20%)	
Lymph node, mesenteric	(8)		(4)	(3)
Cyst			1 (25%)	
Hematopoietic cell proliferation, multifocal			1 (25%)	
Lymphatic, ectasia, focal	1 (13%)			
Spleen	(50)	(50)	(50)	(49)
Capsule, hyperplasia, multifocal				1 (2%)
Capsule, inflammation, chronic active, multifocal			1 (2%)	
Lymphoid follicle, necrosis, acute, multifocal	1 (2%)	2 (4%)		
Red pulp, hematopoietic cell proliferation, diffuse	48 (96%)	50 (100%)	49 (98%)	48 (98%)
Red pulp, pigmentation, hemosiderin, multifocal	45 (90%)	47 (94%)	49 (98%)	49 (100%)
Thymus	(41)	(4)	(1)	(35)
Depletion lymphoid, multifocal				1 (3%)
Necrosis, acute, multifocal	1 (2%)	3 (75%)		
Medulla, thymocyte, hyperplasia, diffuse	1 (2%)			
INTEGUMENTARY SYSTEM				
Mammary gland	(38)	(5)	(3)	(44)
Hyperplasia, cystic, multifocal			2 (67%)	
Skin	(50)	(7)	(7)	(49)
Parasite external	3 (6%)			
Ulcer			2 (29%)	
Subcutaneous tissue, fibrosis, multifocal			1 (14%)	
Subcutaneous tissue, inflammation, chronic active, multifocal			2 (29%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
MUSCULOSKELETAL SYSTEM				
Bone	(49)	(6)	(3)	(50)
Bilateral, joint, tarsal, hyperostosis	1 (2%)			
Bilateral, joint, tarsal, metaplasia, osseous, multifocal	1 (2%)			
Cranium, fibrous osteodystrophy				1 (2%)
Cranium, hyperostosis, focal				1 (2%)
NERVOUS SYSTEM				
Brain	(48)	(5)	(3)	(49)
Hemorrhage, multifocal	1 (2%)			
Necrosis, acute, multifocal			1 (33%)	
Hypothalamus, compression, focal				1 (2%)
Meninges, infiltration cellular, lymphocytic, multifocal	1 (2%)			2 (4%)
Meninges, inflammation, chronic active, multifocal				1 (2%)
RESPIRATORY SYSTEM				
Lung	(50)	(8)	(7)	(50)
Alveolar epithelium, hyperplasia, focal		1 (13%)		3 (6%)
Alveolus, hemorrhage, multifocal			1 (14%)	1 (2%)
Interstitium, inflammation, chronic, multifocal	2 (4%)			
Interstitium, inflammation, chronic active, focal				1 (2%)
Interstitium, inflammation, chronic active, multifocal	1 (2%)			
Mediastinum, foreign body, multifocal	1 (2%)	3 (38%)		
Perivascular, hyperplasia, lymphoid, multifocal	1 (2%)			
Perivascular, inflammation, chronic, multifocal				1 (2%)
Pleura, inflammation, acute, diffuse		1 (13%)		
SPECIAL SENSES SYSTEM				
Eye	(1)	(1)		(1)
Degeneration, diffuse				1 (100%)
Cornea, inflammation, necrotizing, chronic active, diffuse		1 (100%)		
Harderian gland	(48)	(4)	(3)	(47)
Inflammation, chronic active, diffuse	1 (2%)			
Acinus, hyperplasia, multifocal				1 (2%)
URINARY SYSTEM				
Kidney	(50)	(7)	(4)	(49)
Inflammation, chronic active, multifocal			1 (25%)	
Mineralization, multifocal				1 (2%)
Nephropathy, chronic, diffuse	1 (2%)			
Nephropathy, chronic, focal	3 (6%)			1 (2%)
Nephropathy, chronic, multifocal	1 (2%)			1 (2%)
Capsule, fibrosis, chronic, focal			1 (25%)	
Glomerulus, amyloid deposition, multifocal	1 (2%)			
Glomerulus, inflammation, chronic, multifocal				3 (6%)
Perivascular, infiltration cellular, plasma cell, multifocal				1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *p*-CHLOROANILINE HYDROCHLORIDE (Continued)

	Vehicle Control	Low Dose	Mid Dose	High Dose
URINARY SYSTEM				
Kidney (Continued)	(50)	(7)	(4)	(49)
Renal tubule, cytoplasmic alteration, diffuse		1 (14%)		
Renal tubule, dilatation, diffuse				1 (2%)
Renal tubule, pigmentation, hemosiderin, multifocal				38 (78%)
Renal tubule, regeneration, focal	3 (6%)			
Renal tubule, regeneration, multifocal	4 (8%)			3 (6%)

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. 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 viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both 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.

Fifteen B6C3F$_1$ mice and 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 and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (18, 24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (6 mo)	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (18, 24 mo)	RCV (rat coronavirus) (6 mo) Sendai (6 mo)	RCV/SDA (sialodacryoadenitis virus) (18, 24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
18	--	None positive
24	--	None positive
MICE		
6	--	None positive
18	1/10	MHV
24	1/10 2/10	PVM MHV

(a) Blood samples were taken from sentinel animals at 6 and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX F

ANALYSIS OF ORGAN WEIGHTS FOR RATS AND MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE

TABLE F1. ANALYSIS OF ORGAN WEIGHTS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg
MALE						
No. weighed	10	10	10	10	10	10
Body weight (b)	328 ± 12.1	336 ± 5.5	345 ± 3.8	350 ± 12.0	332 ± 8.6	(c) 285 ± 8.5
Brain	1,927 ± 15	1,919 ± 10	1,957 ± 16	1,935 ± 16	1,884 ± 22	(c) 1,850 ± 24
Heart	935 ± 20	988 ± 28	993 ± 15	980 ± 16	1,003 ± 26	1,007 ± 43
Kidney	1,202 ± 30	1,174 ± 29	1,219 ± 17	1,173 ± 21	1,146 ± 27	1,132 ± 37
Liver (grams)	13.0 ± 0.42	12.4 ± 0.26	13.0 ± 0.31	13.0 ± 0.37	13.3 ± 0.49	12.3 ± 0.45
Lung	1,638 ± 50	1,652 ± 61	1,697 ± 72	1,616 ± 54	1,681 ± 70	(d) 1,444 ± 49
Right testis	1,396 ± 33	1,404 ± 14	1,467 ± 18	1,487 ± 27	1,454 ± 22	1,403 ± 26
Spleen	(e)	804 ± 16	1,057 ± 19	(f) 1,638 ± 25	(f) 3,368 ± 54	(f) 4,748 ± 161
Thymus	286 ± 10	261 ± 11	265 ± 8	290 ± 15	(d) 329 ± 16	(c) 225 ± 10
FEMALE						
No. weighed	9	10	10	10	10	9
Body weight (b)	200 ± 2.4	198 ± 2.5	199 ± 2.6	189 ± 9.2	195 ± 2.3	194 ± 2.6
Brain	1,784 ± 17	1,765 ± 21	1,799 ± 15	1,778 ± 14	1,779 ± 12	1,761 ± 15
Heart	628 ± 16	639 ± 17	686 ± 17	643 ± 10	665 ± 26	(c) 744 ± 33
Kidney	698 ± 13	691 ± 14	722 ± 20	724 ± 19	739 ± 12	(c) 792 ± 19
Liver	7,079 ± 201	6,392 ± 162	7,073 ± 134	6,909 ± 143	7,228 ± 156	7,481 ± 223
Lung	1,100 ± 48	1,143 ± 28	(d) 1,272 ± 35	1,230 ± 58	1,098 ± 43	1,113 ± 27
Spleen	447 ± 13	(c) 607 ± 9	(c) 806 ± 15	(c) 1,422 ± 30	(c) 2,413 ± 71	(c) 3,527 ± 57
Thymus	229 ± 7	230 ± 9	222 ± 15	244 ± 11	229 ± 9	202 ± 6

(a) Mean in milligrams ± standard error, except as noted. P values are vs. the vehicle controls: Dunnett's test was used when a nonsignificant result was obtained by the Jonckheere trend test; otherwise Williams' test was used (Dunnett, 1980; Jonckheere, 1954; Williams, 1971, 1972); doses calculated as *p*-chloroaniline.
(b) Absolute necropsy body weight (in grams) ± standard error
(c) $P<0.01$ vs. vehicle controls
(d) $P<0.05$ vs. vehicle controls
(e) Spleen weights not recorded for vehicle controls; reported P values vs. the 5 mg/kg group.
(f) $P<0.01$ vs. the 5 mg/kg group

TABLE F2. ANALYSIS OF ORGAN WEIGHTS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *p*-CHLOROANILINE HYDROCHLORIDE (a)

	Vehicle Control	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
MALE						
No. weighed	10	10	10	10	10	8
Body weight (b)	32.1 ± 1.14	32.3 ± 0.97	31.6 ± 1.07	33.5 ± 0.45	32.8 ± 0.65	31.9 ± 1.13
Brain	447 ± 5.8	459 ± 5.4	449 ± 7.5	449 ± 6.1	455 ± 5.4	440 ± 8.7
Heart	157 ± 10.2	163 ± 6.2	170 ± 7.0	(c) 192 ± 10.0	(c) 188 ± 9.8	(c) 190 ± 9.2
Kidney	270 ± 8.2	278 ± 9.4	281 ± 10.6	282 ± 5.7	273 ± 7.6	273 ± 13.4
Liver	1,664 ± 49	1,543 ± 67	1,576 ± 71	1,800 ± 46	1,817 ± 44	1,813 ± 66
Lung	228 ± 12	253 ± 12	268 ± 18	264 ± 14	(c) 279 ± 15	(d) 287 ± 13
Spleen	69 ± 4	(c) 107 ± 5	(d) 132 ± 21	(d) 196 ± 12	(d) 266 ± 10	(d) 398 ± 14
Right testis	113 ± 3.9	119 ± 2.9	(c) 127 ± 4.0	118 ± 4.1	114 ± 3.3	111 ± 3.2
Thymus	34 ± 2.6	42 ± 4.0	43 ± 3.3	32 ± 2.9	33 ± 2.6	33 ± 2.7
FEMALE						
No. weighed	9	10	10	9	7	8
Body weight (b)	27.2 ± 0.66	25.8 ± 0.47	25.1 ± 0.77	26.0 ± 0.58	27.4 ± 0.65	26.9 ± 0.48
Brain	486 ± 7.4	461 ± 8.6	461 ± 6.7	460 ± 9.2	472 ± 8.1	471 ± 5.6
Heart	134 ± 3.9	144 ± 4.8	134 ± 6.1	142 ± 8.6	158 ± 11.0	145 ± 5.0
Kidney	202 ± 8.7	187 ± 2.7	182 ± 5.1	189 ± 9.3	187 ± 10.5	200 ± 5.9
Liver	1,475 ± 39	1,300 ± 32	1,245 ± 61	1,388 ± 63	1,459 ± 54	1,603 ± 38
Lung	225 ± 6	225 ± 13	212 ± 11	262 ± 15	242 ± 10	244 ± 17
Spleen	93 ± 5	97 ± 5	125 ± 6	(d) 206 ± 14	(d) 293 ± 17	(d) 532 ± 24
Thymus	46 ± 2.9	48 ± 2.5	43 ± 2.4	46 ± 3.0	39 ± 2.2	43 ± 3.9

(a) Mean in milligrams ± standard error, except as noted. P values are vs. the vehicle controls: Dunnett's test was used when a nonsignificant result was obtained by the Jonckheere trend test; otherwise Williams' test was used (Dunnett, 1980; Jonckheere, 1954; Williams, 1971, 1972); doses calculated as *p*-chloroaniline.
(b) Absolute necropsy body weight (in grams) ± standard error
(c) $P<0.05$
(d) $P<0.01$

APPENDIX G

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

Pelleted Diet: November 1981 to December 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE G1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

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

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.59 ± 0.94	22.2-26.3	26
Crude fat (percent by weight)	4.96 ± 0.52	3.3-5.7	26
Crude fiber (percent by weight)	3.39 ± 0.52	2.9-5.6	26
Ash (percent by weight)	6.51 ± 0.49	5.7-7.3	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,084 ± 4,821	3,600-24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	16.9 ± 2.42	12.0-21.0	26
Riboflavin (ppm)	7.6 ± 0.85	7.58-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.30 ± 0.13	1.11-1.63	26
Phosphorus (percent)	0.97 ± 0.05	0.88-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.52 ± 0.13	0.29-0.77	26
Cadmium (ppm) (a)	<0.10		26
Lead (ppm)	0.76 ± 0.62	0.33-3.37	26
Mercury (ppm) (a)	<0.05		26
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	26
Aflatoxins (ppb) (a)	<5.0		26
Nitrate nitrogen (ppm) (b)	8.66 ± 4.47	0.10-22.0	26
Nitrite nitrogen (ppm) (b)	2.16 ± 1.97	0.10-7.20	26
BHA (ppm) (c)	4.63 ± 4.74	2.0-17.0	26
BHT (ppm) (c)	2.67 ± 2.58	0.9-12.0	26
Aerobic plate count (CFU/g) (d)	41,212 ± 34,610	4,900-130,000	26
Coliform (MPN/g) (e)	48.42 ± 123	3.0-460	26
E. coli (MPN/g) (a)	<3.0		26
Total nitrosamines (ppb) (f)	5.25 ± 5.80	1.7-30.9	26
N-Nitrosodimethylamine (ppb) (f)	4.12 ± 5.83	0.8-30.0	26
N-Nitrosopyrrolidine (ppb) (f)	1.13 ± 0.46	0.81-2.9	26
Pesticides (ppm)			
α-BHC (a,g)	<0.01		26
β-BHC (a)	<0.02		26
γ-BHC-Lindane (a)	<0.01		26
δ-BHC (a)	<0.01		26
Heptachlor (a)	<0.01		26
Aldrin (a)	<0.01		26
Heptachlor epoxide (a)	<0.01		26
DDE (a)	<0.01		26
DDD (a)	<0.01		26
DDT (a)	<0.01		26
HCB (a)	<0.01		26
Mirex (a)	<0.01		26
Methoxychlor (a)	<0.05		26
Dieldrin (a)	<0.01		26
Endrin (a)	<0.01		26
Telodrin (a)	<0.01		26
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		26
Estimated PCBs (a)	<0.2		26
Ronnel (a)	<0.01		26
Ethion (a)	<0.02		26
Trithion (a)	<0.05		26
Diazinon (a)	<0.1		26
Methyl parathion (a)	<0.02		26
Ethyl parathion (a)	<0.02		26
Malathion (h)	0.10 ± 0.09	0.05-0.45	26
Endosulfan I (a)	<0.01		26
Endosulfan II (a)	<0.01		25
Endosulfan sulfate (a)	<0.03		26

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) All values were corrected for percent recovery.
(g) BHC = hexachlorocyclohexane or benzene hexachloride
(h) Thirteen batches contained more than 0.05 ppm.

APPENDIX H

DISTRIBUTION AND DISPOSITION OF *p*-CHLOROANILINE AND *p*-CHLOROANILINE HYDROCHLORIDE IN F344 RATS

APPENDIX H. DISTRIBUTION AND DISPOSITION

A study of the distribution and disposition of *p*-chloroaniline and *p*-chloroaniline hydrochloride in F344 rats was conducted at the University of Arizona under the sponsorship of the National Toxicology Program (NIEHS contract no. NO1-ES-8-2130). The laboratory report is on file at the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

OVERVIEW OF *p*-CHLOROANILINE PHARMACOKINETICS IN F344 RATS

In F344 rats, *p*-chloroaniline was rapidly eliminated after a single oral dose. The primary route of excretion was the urine, where approximately 75% of the administered carbon-14 appeared within 24 hours, and approximately 10% was found in the feces. Elimination was found to be independent of dose within a hundredfold dose range (0.3-30 mg/kg). Seven days after administration, the only tissue containing significant amounts of radioactivity was the erythrocyte fraction of whole blood.

The excretory profile after a single 0.3 mg/kg intravenous dose of [^{14}C]*p*-chloroaniline was essentially identical to that following oral administration. Urinary excretion of carbon-14 was rapid, with approximately 60% of the dose appearing in urine within 4 hours. By 24 hours, only 4% of the urinary carbon-14 was present as *p*-chloroaniline, and less than 1% of the dose appeared in the feces. No *p*-chloroacetanilide, a major circulating metabolite of *p*-chloroaniline, was detected in either urine or feces over a 3-day period.

There were no apparent tissue depots of *p*-chloroaniline or metabolites after a single intravenous dose of 3 mg/kg except for erythrocytes. Tissue levels of carbon-14 peaked 30 minutes to 1 hour after intravenous administration, with the highest percentage of dose being found in liver, muscle, fat, and skin. Elimination from all tissues followed bi-exponential kinetics.

The pharmacokinetics of *p*-chloroacetanilide followed mono-exponential decay kinetics with an appearance phase. The appearance half-life ($t_{\alpha\frac{1}{2}}$) of *p*-chloroacetanilide was about 10 minutes, and the elimination ($t_{\beta\frac{1}{2}}$) was on the order of 1.5-2 hours.

These results demonstrate that after intravenous administration to F344 rats, *p*-chloroaniline is rapidly *N*-acetylated to *p*-chloroacetanilide as the first step in metabolism and excretion of *p*-chloroaniline. The absence of any *p*-chloroacetanilide in the urine indicates further metabolism of *p*-chloroacetanilide prior to excretion via that route.

MATERIALS AND METHODS

Chemicals and Animals

Uniformly ring-labeled [^{14}C]*p*-chloroaniline (specific activity 5.0 mCi/mmol) was purchased from KOR Inc. (Cambridge, Massachusetts). Unlabeled *p*-chloroaniline was purchased from Aldrich Chemical Co. (Milwaukee, Wisconsin) and was recrystallized twice from ethanol:water (1:1) before use. Spectrophotometric-grade *p*-nitrophenol was obtained from Sigma Chemical Co. (Milwaukee, Wisconsin). *p*-Chloroacetanilide was prepared by refluxing *p*-chloroaniline with acetic anhydride. Recrystallization from 50% acetic acid produced colorless needles with a melting point of 176°-178° C (compared with 177°-178° C, Merck, 1983). Mass spectra of the synthesized *p*-chloroacetanilide confirmed its structure. *p*-Chloroglycoanilide was prepared by the method of Shapiro et al. (1959). The identity of this material was confirmed by proton magnetic resonance spectroscopy and mass spectrometry. Heptane sulfonic acid sodium salt was obtained from Eastman Kodak Co. (Rochester, New York), and high-performance liquid chromatography-grade acetonitrile was purchased from Burdick and Jackson Laboratories (Muskegon, Michigan). Inactin® (methylpropyl-*N'*-ethylthiobarbiturate) was obtained from Andrew Lockwood Association (Madison, Wisconsin). All other chemicals were of reagent or scintillation quality as required.

Male F344 rats weighing 150-200 g, purchased from M.A. Bioproducts (Walkersville, Maryland), were housed individually in stainless steel metabolism cages designed to separate urine from feces and were provided with feed and water ad libitum.

Distribution/Disposition Studies

The effect of dose on the disposition of *p*-chloroaniline after oral administration of 0.3, 3, or 30 mg/kg *p*-chloroaniline in 0.01 N hydrochloric acid was determined in rats (three animals per dose). Rats at the two higher doses received 40 µCi/kg, and those at the lowest dose received 9 µCi/kg. Urine and feces were collected daily and analyzed for total carbon-14, and the percentage of excreted dose was calculated. Urine samples (0.5 ml) were added directly to Betaphase scintillation fluid (Westchem Products, San Diego, California) and analyzed directly by liquid scintillation counting (LS-100C Beckman Instruments, Fullerton, California). Feces were digested in 15 ml of 0.5 N sodium hydroxide, and 0.5 g aliquots were oxidized to carbon[^{14}C] dioxide in a Packard Tri-Carb sample oxidizer (Packard Instruments, Downers Grove, Illinois), as previously described (Miller et al., 1982).

Tissue distribution and pharmacokinetic studies were conducted in rats after a single intravenous injection via the tail vein with 3 mg/kg *p*-chloroaniline (30 µCi/kg) dissolved in a mixture of ethanol:propylene glycol:water (1:1:8). Three animals were killed at times ranging from 15 minutes to 3 days. Tissues saved for analysis included brain, lung, liver, kidney, spleen, small intestine, testis, renal fat, muscle, and skin. Urinary bladder and intestinal contents were combined with that day's urine and feces, respectively. Blood was obtained by cardiac puncture, and a 1-ml aliquot was immediately mixed with two volumes of acetonitrile for later analysis for *p*-chloroaniline. The remainder of the sample was stored at 4° C in heparinized glass tubes. Tissue samples were kept frozen at −10° C prior to analysis.

Tissue aliquots (0.1-0.5 g) were analyzed in duplicate for total carbon-14 as previously described. The percentage of the total dose found in tissues was based on the wet tissue weight, with estimates of 9%, 50%, 7%, and 16% of the total body weight being used for blood, muscle, fat, and skin, respectively (Matthews and Anderson, 1975).

Biliary Excretion

Bile was collected from the common bile duct of anesthetized (100 mg/kg Inactin®) rats after cannulation with PE10 polyethylene tubing (Clay Adams, New York). After 30 minutes of bile collection, 3 mg/kg *p*-chloroaniline (30 µCi/kg) was administered via the tail vein. Bile samples were collected at 30-minute intervals for 6.0 hours. Duplicate 25-µl samples were assayed directly by liquid scintillation counting for quantification of total carbon-14. Pooled 6-hour samples were also analyzed for *p*-chloroaniline as described below for urine.

Separation of *p*-Chloroaniline from Metabolites

p-Chloroaniline was separated from its metabolites in those tissues that contained greater than 1% of the administered dose and was assayed by high-performance liquid chromatography. Blood samples for high-performance liquid chromatography analysis were added to two volumes of acetonitrile at the time of collection, and the protein precipitate was separated by centrifugation. The supernatant was then extracted with two additional volumes of acetonitrile. The extracts were pooled and washed with 1 ml of hexane to remove lipids. The hexane layer was discarded, since it contained less than 100 disintegrations per minute (dpm) of carbon-14. The pooled acetonitrile extracts were evaporated to near dryness under a stream of dry nitrogen before the addition of 200 µl of a mixture of acetonitrile: water:acetic acid (25:24:1) which contained 40 µg/ml unlabeled *p*-chloroaniline and *p*-nitrophenol. The protein pellets remaining after the acetonitrile extractions were oxidized to carbon[^{14}C]

dioxide to determine nonextractable radioactivity. Urine samples were diluted with an equal volume of acetonitrile containing 40 µg/ml *p*-chloroaniline and *p*-nitrophenol prior to high-performance liquid chromatographic analysis. All other tissues were solubilized in 0.5 N sodium hydroxide at 40° C for 24 hours and extracted twice with a diethyl ether:acetonitrile:hexane (8:1:1) mixture. The pooled extracts were concentrated under a stream of dry nitrogen. The residue was dissolved in 1 ml of acetonitrile and extracted with 1 ml of hexane. The hexane washes contained notable quantities of metabolites which were taken into account in the calculations. The washed acetonitrile extracts from tissue homogenates were then treated as those for blood. These extraction procedures recovered more than 90% of the [^{14}C]*p*-chloroaniline added to control blood, liver homogenates, and urine samples; stability studies showed that *p*-chloroaniline and *p*-chloroacetanilide levels were unaffected by these procedures. However, recovery of total carbon-14 from tissues was between 30% and 80% regardless of the time point, and that from blood ranged from 80% at 15 minutes to less than 1% by 24 hours, suggesting that substantial binding may have occurred. This nonextractable radioactivity was assumed to be unidentified metabolites of *p*-chloroaniline.

For high-performance liquid chromatographic analysis, a 250 × 4.6 mm Spherisorb 5 µ C-6 reverse phase column (Chromanetics Inc., Baltimore, Maryland) was used. The mobile phase was acetonitrile:water:acetic acid (37:62:1), containing 5 mM heptane sulfonic acid as an ion-pairing agent at a 1.5 ml/minute flow rate. A Spectra Physics Model 3500 B high-performance liquid chromatography system was used with a Spectra Physics model 8200 ultraviolet detector set at 254 nm. With this system, *p*-chloroglycoanilide, *p*-nitrophenol, *p*-chloroacetanilide, and *p*-chloroaniline elute at 4, 5, 6, and 7 minutes, respectively. Quantification of tissue extracts was accomplished by collecting the column effluent at 1-minute intervals (*p*-chloroaniline and *p*-chloroacetanilide were collected as discrete peaks) and analyzing for carbon-14 by liquid scintillation counting. With this method, the limit of detection was determined to be 100 dpm above background.

Pharmacokinetic Analysis

Pharmacokinetic analyses were performed on the distribution data for total carbon-14, *p*-chloroacetanilide, and *p*-chloroaniline in blood, tissues, and excreta by the nonlinear regression program NONLIN (Metzler, 1969). The equations used to derive the kinetic curves representing the best statistical fit ($P < 0.05$) to the data were described by Gibaldi and Perrier (1975).

The concentration (C) of *p*-chloroaniline and of total carbon-14 was best described by the bi-exponential equation I:

$$\text{I. } C = Ae^{-\alpha_1 t} + Be^{-\alpha_2 t}$$

For total carbon-14 in urine and feces, the data were best described by equation II:

$$\text{II. } C = A(1 - e^{\alpha t})$$

The presence of total carbon-14 showed an appearance phase in the intestinal contents which fit equation III:

$$\text{III. } C = A(e^{-\alpha_1 t} - e^{-\alpha_2 t})$$

The previous equation (III) was also used to fit the *p*-chloroacetanilide data for all tissues except liver and blood. Data for liver and blood were described by equation IV:

$$\text{IV. } C = Ae^{-\alpha t}$$

In the above equations, A and B are constants and α_1 and α_2 are first and second phase rate constants, respectively. Time (t) is in hours.

RESULTS

After oral administration of 0.3, 3, or 30 mg/kg *p*-chloroaniline, [^{14}C]*p*-chloroaniline equivalents were rapidly excreted. At 24 hours, 77% of the dose appeared in the urine and 10% in the feces. After 7 days, 83.7% ± 7.9% of the dose had been excreted in the urine and 10.8% ± 1.9% in the feces (Figure H1). At this time, the only tissue containing greater than 1% of the administered dose was the cellular component of blood, which contained 1%-2% of the dose. Since excretion was found to be independent of dose, the mid dose of 3 mg/kg was used for subsequent intravenous studies.

Total Carbon-14 Kinetics

After an intravenous injection of [^{14}C]*p*-chloroaniline, total radioactivity was rapidly distributed, with maximal levels being reached in most tissues within 15 minutes. At this time, muscle (34%), fat (14%), skin (12%), liver (8%), and blood (7%) contained the majority of radioactivity, and the small intestine and kidney each contained approximately 3% of the dose. The elimination of total carbon-14 from all tissues was best described by first order biphasic elimination kinetics (Figures H2 and H3). The initial elimination half-lives were similar for all tissues and ranged between 1.5 and 4 hours. By 8 hours, approximately 90% of the administered dose was eliminated from the blood and tissues into the urine and feces. Because of this rapid elimination, accurate terminal decay rate constants were difficult to determine but were calculated to be approximately 48 hours. The terminal elimination phase of carbon-14 equivalents represented only 6% of the dose, and 4% of the dose was found in whole blood (Figure H4).

p-Chloroaniline Kinetics

Accurate determination of the rate of *p*-chloroaniline elimination from tissues was difficult because of its rapid disappearance. Tissues analyzed displayed bi-exponential decay kinetics with initial half-lives of approximately 8 minutes and terminal half-lives of 3-4 hours, except for adipose tissue and small intestine which had terminal half-lives of 29 and 23 hours, respectively (Table H1). With blood, muscle, fat, and skin, the best fit for the kinetic curve was determined after deleting data at 1 hour. These tissues had concentrations of *p*-chloroaniline at 1 hour which were considerably higher than at the other time points. The results at 1 hour were confirmed in a repeated experiment; therefore, the data were not considered to be in error.

p-Chloroacetanilide Pharmacokinetics

The kinetics of *p*-chloroacetanilide in those tissues examined followed monophasic elimination kinetics preceded by a short appearance phase in all tissues except liver and whole blood (Table H2). The distribution of *p*-chloroacetanilide was similar to that of total carbon-14, with the highest levels being found in muscle, skin, fat, liver, and blood. The half-life of appearance of *p*-chloroacetanilide was approximately 10 minutes, and the elimination half-life was 3 hours.

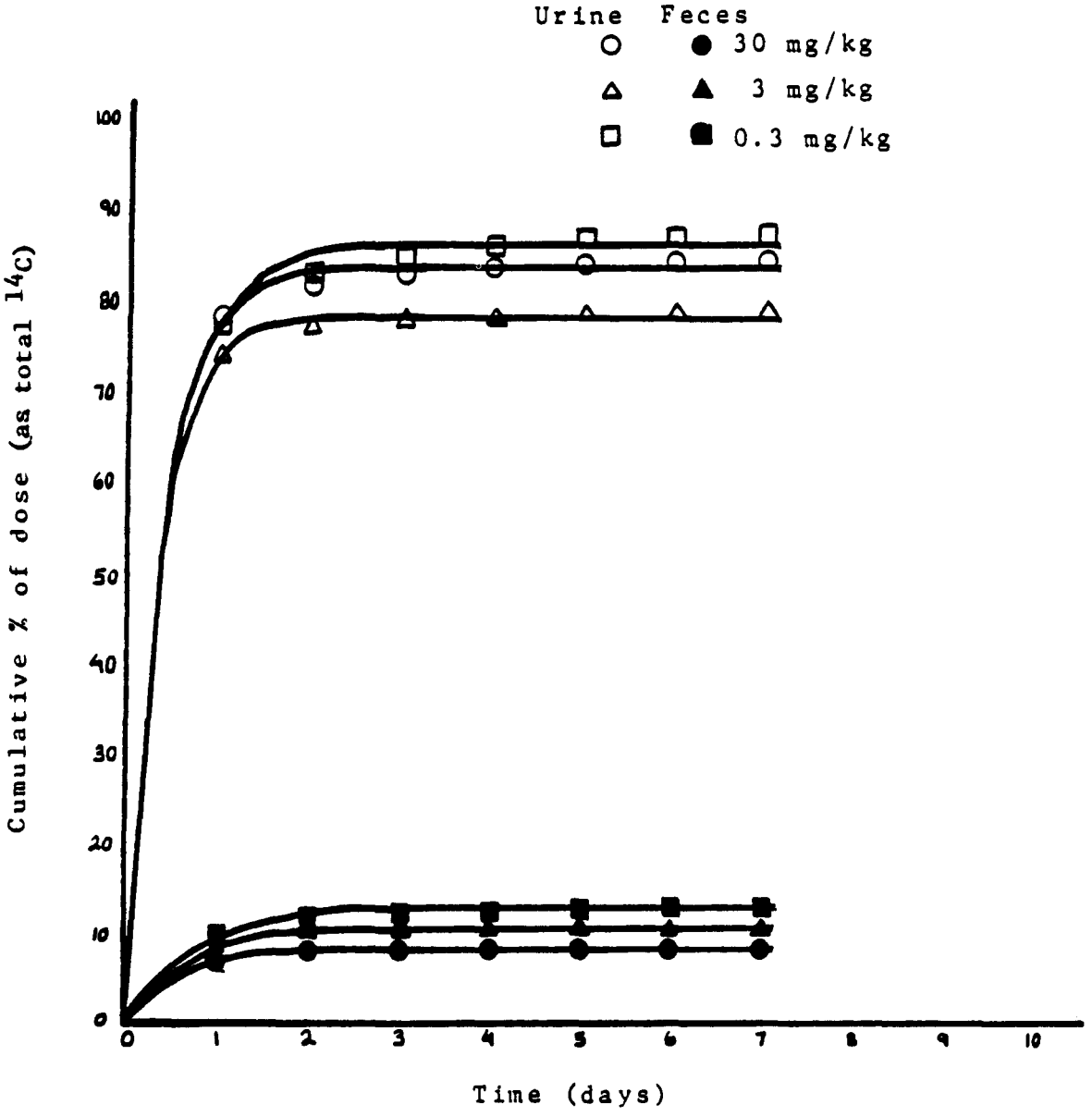

FIGURE H1. EXCRETION OF CARBON-14 IN F344 RATS AFTER GAVAGE ADMINISTRATION OF [^{14}C]*p*-CHLOROANILINE IN AQUEOUS HYDROCHLORIC ACID

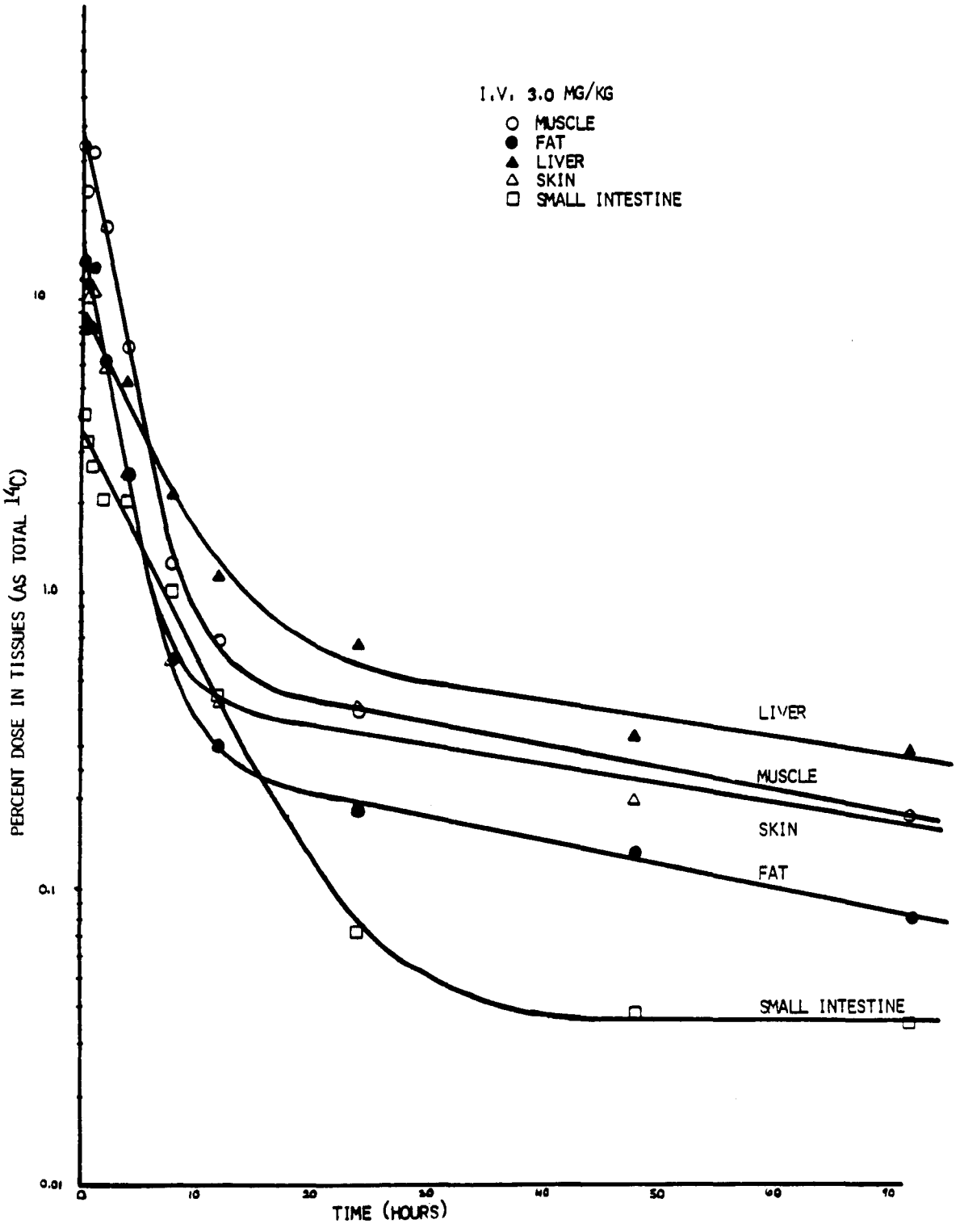

FIGURE H2. ELIMINATION OF CARBON-14 FROM THE MUSCLE, FAT, LIVER, SKIN, AND SMALL INTESTINE OF F344 RATS AFTER INTRAVENOUS ADMINISTRATION OF [^{14}C]*p*-CHLOROANILINE

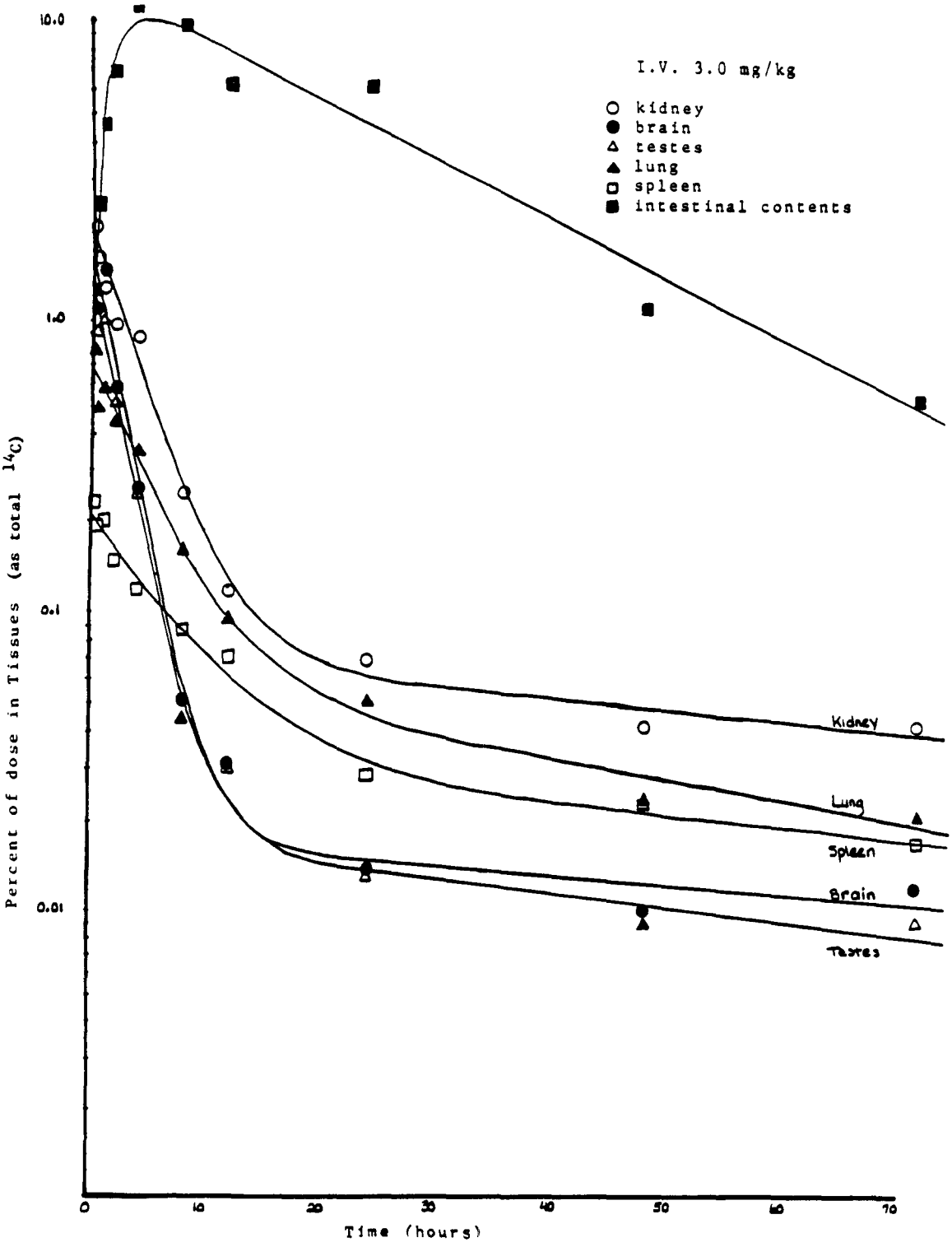

FIGURE H3. ELIMINATION OF CARBON-14 IN THE KIDNEY, BRAIN, TESTIS, LUNG, SPLEEN, AND INTESTINAL CONTENTS OF F344 RATS AFTER INTRAVENOUS ADMINISTRATION OF [^{14}C]*p*-CHLOROANILINE

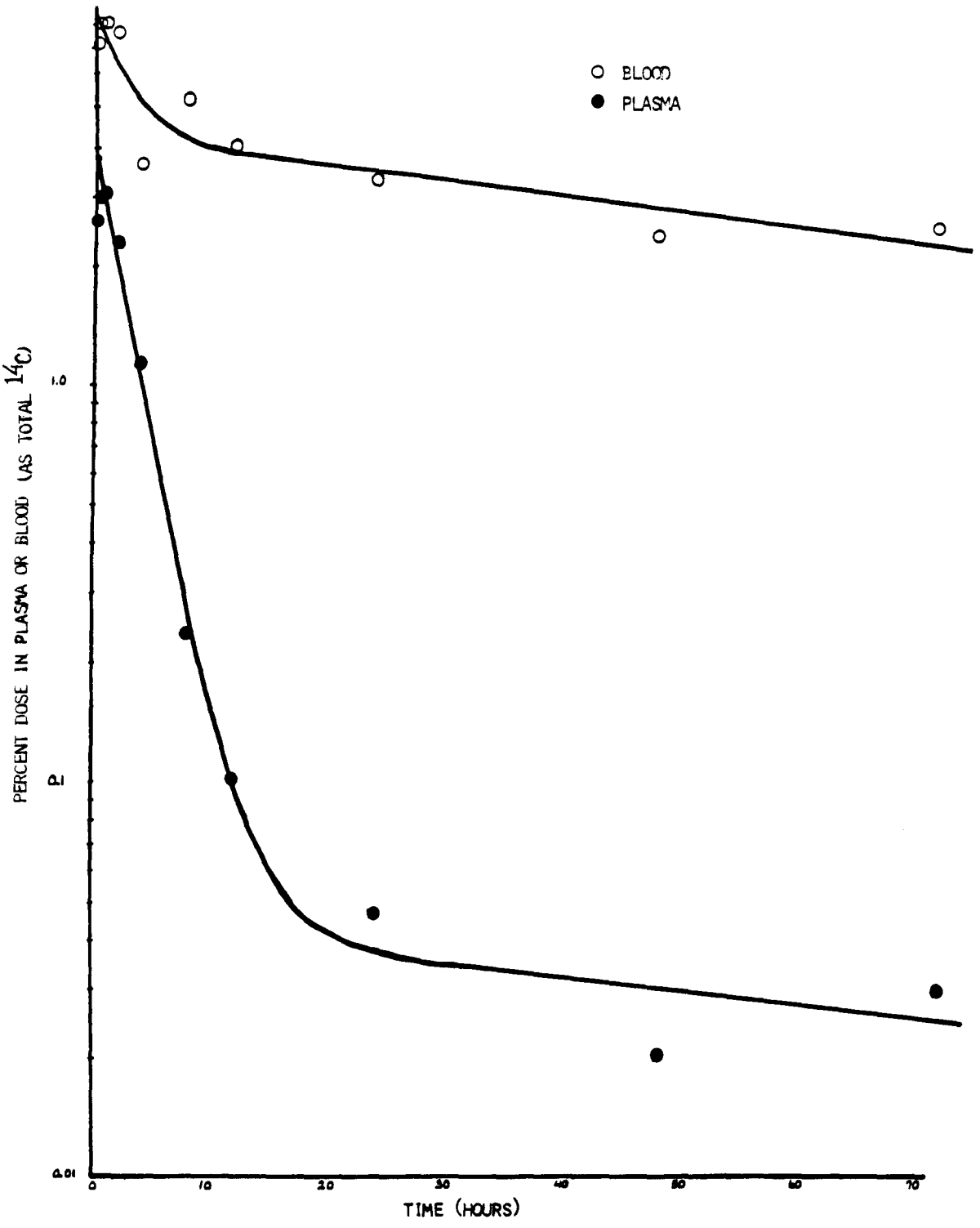

FIGURE H4. BLOOD AND PLASMA LEVELS OF CARBON-14 IN F344 RATS AFTER INTRAVENOUS ADMINISTRATION OF [^{14}C]*p*-CHLOROANILINE (3 mg/kg)

TABLE H1. ELIMINATION OF *p*-CHLOROANILINE FROM TISSUES OF F344 RATS ADMINISTERED *p*-CHLOROANILINE BY INTRAVENOUS INJECTION (a)

Tissue	A (percent)	α	t_α (hours)	B (percent)	β	t_β (hours)
Kidney	1.31	7.9	0.087	0.36	0.17	3.87
Small intestine	1.12	3.7	0.187	0.59	0.03	23
Adipose tissue	3.59	3.8	0.182	0.28	0.02	29
Muscle	22.6	5.6	0.124	1.3	0.12	5.4
Skin	8.60	5.10	0.124	0.58	0.17	4.0
Whole blood	0.82	7.90	0.087	0.01	0.15	4.56

(a) Dose = 3 mg/kg; data fitted to equation I described in the Materials and Methods section of Appendix H.

TABLE H2. THE CONCENTRATION OF *p*-CHLOROACETANILIDE IN TISSUES OF F344 RATS ADMINISTERED *p*-CHLOROANILINE BY INTRAVENOUS INJECTION

Tissue	A (percent)	α	t_α (hours)	β	t_β (hours)
Liver	3.00	--	--	0.23	(a) 3.04
Whole blood	7.43	--	--	0.25	(a) 2.74
Kidney	1.0	4.4	0.15	0.48	1.44
Small intestine	1.71	10.5	0.07	0.30	2.30
Muscle	39.4	4.4	0.16	0.48	1.44
Adipose tissue	7.9	4.8	0.15	0.36	1.90
Skin	7.8	10.0	0.069	0.39	1.76

(a) Dose = 3 mg/kg. Liver and blood data were fitted to equation IV described in the Materials and Methods section of Appendix H; all other data were fitted to equation I.

Biliary Excretion of [^{14}C]*p*-Chloroaniline

The biliary excretion of total carbon-14 occurred rapidly after intravenous administration of [^{14}C]*p*-chloroaniline (Figure H5). Cumulative recovery accounted for 25% ± 2.7% of the dose after 6.0 hours of collection. High-performance liquid chromatographic analysis of pooled bile extracts revealed only small amounts of *p*-chloroaniline (10%) and *p*-chloroacetanilide (7%), with the remainder being unidentified polar metabolites.

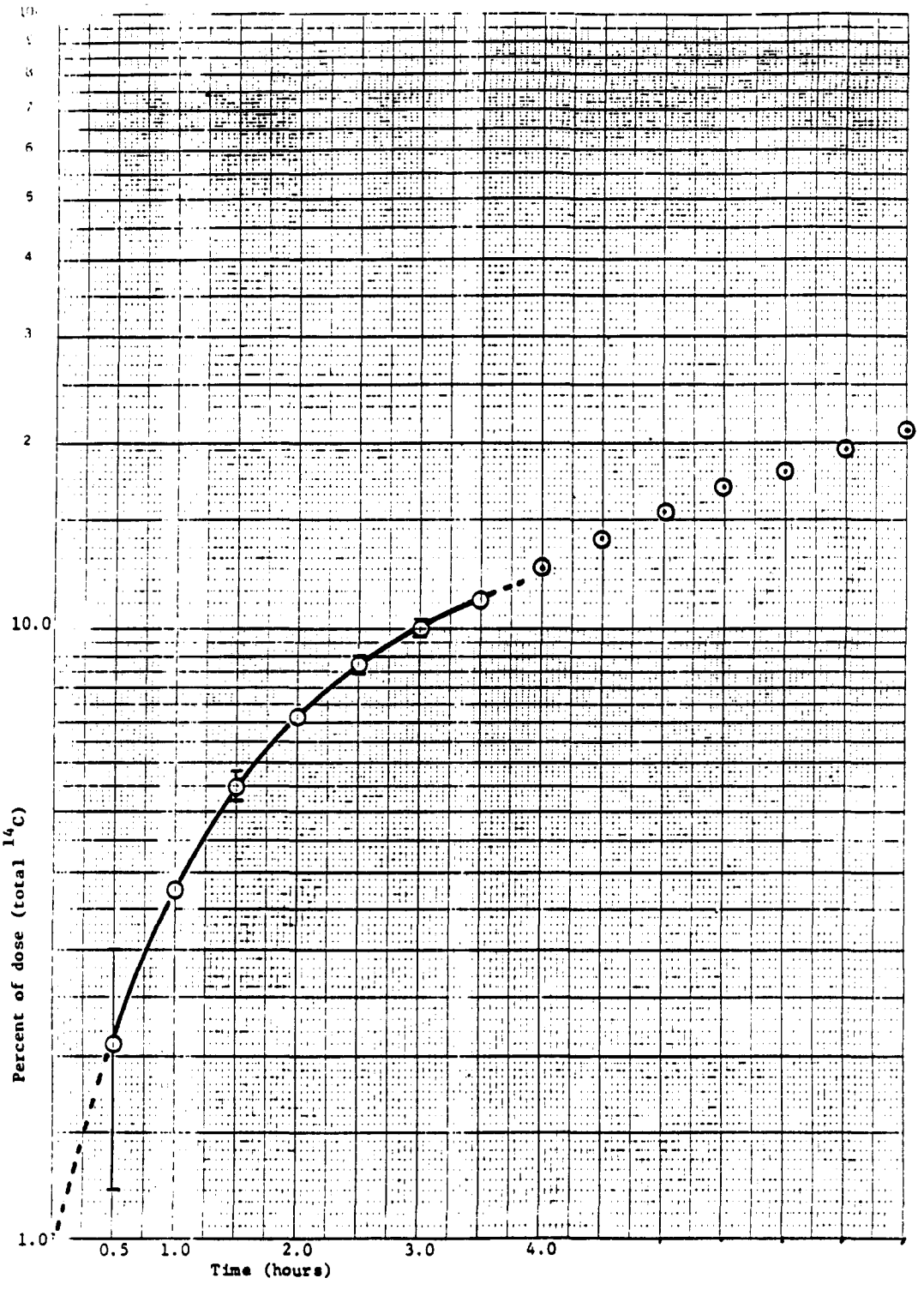

FIGURE H5. BILIARY EXCRETION OF CARBON-14 IN F344 RATS AFTER INTRAVENOUS ADMINISTRATION OF [^{14}C]*p*-CHLOROANILINE (3 mg/kg)

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft NTP Technical Report No. 351 for the 2-year studies of *p*-chloroaniline hydrochloride in rats and mice were audited for accuracy, consistency, completeness, and compliance with the Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (fully implemented by the National Toxicology Program [NTP] beginning October 1, 1981). The studies were conducted by Battelle Columbus Laboratories (Columbus, Ohio). Dosing of animals by gavage began on January 25, 1982, for rats and on February 8, 1982, for mice. The retrospective audit was conducted for the National Institute of Environmental Health Sciences (NIEHS) at the NTP Archives during September, October, and November 1987 by Argus Research Laboratories, Inc. The complete audit report is on file at the NIEHS. The audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight data and clinical observation data for a random 10% sample of animals in each study group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning disposition codes, condition codes, tissue accountability, correlation of masses or clinical signs recorded at the last inlife observation with gross observations and microscopic diagnoses, and correlations between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of rats in all study groups, plus other relevant cases to verify animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group to examine for proper match and inventory.
(8) All red-lined diagnoses on the intermediate pathology table to verify incorporation of changes in the final tables.
(9) Correlation between the data, results, and procedures for the 2-year studies presented in the preliminary Technical Report and the records available at the NTP Archives.

The archival records documented adequately all inlife procedures and events except for the disposition of surplus animals. The records documented the preparation, analysis, and administration of doses. A random sample of group mean body weights was recalculated and found to be accurate. Of the external masses observed inlife, 139/149 in rats and 211/212 in mice were correlated with necropsy observations. The date of death recorded at necropsy for one mid dose male mouse did not agree with the date entered into the computer at the time of animal removal; survival for that group appeared to be 28 rather than 29 mice. Clinical signs were recorded in a generally consistent manner. Hematologic and clinical chemical data were not audited.

Review of the pathology specimens showed that individual animal identifiers (clipped toes and ears) were present and correct in the tissue bags for 99/100 rats and 87/95 mice examined. Followup on animals with less than complete and correct identifiers indicated that individual animal identity had been maintained. The audit found seven untrimmed potential lesions in rats (none in target organs) and none in mice. All gross observations made at necropsy were correlated with microscopic observations, except for one in one rat. Tissue slides and blocks were inspected, and sections matched each other properly. All diagnoses on intermediate tables had been incorporated into the final pathology tables.

Details of these and other audit findings are presented in the audit reports. In conclusion, the data and results presented in the Technical Report for the 2-year gavage studies of *p*-chloroaniline hydrochloride are supported by the records at the NTP Archives.

☆ U.S.G.P.O.: 1989-245-988