NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 394

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ACETAMINOPHEN

(CAS NO. 103-90-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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NATIONAL TOXICOLOGY PROGRAM
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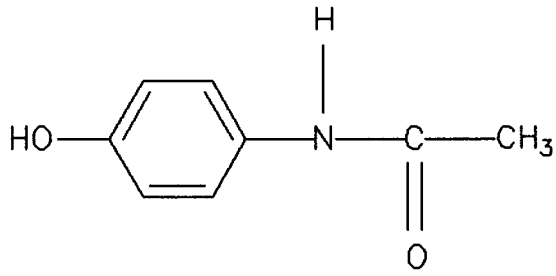
ABSTRACT



ACETAMINOPHEN

CAS No. 103-90-2

Chemical Formula: $C_8H_9NO_2$ Molecular Weight: 151.16

Synonyms: 4-Hydroxyacetanilide, N-Acetyl-*p*-aminophenol, Paracetamol

Acetaminophen is a widely consumed analgesic found in several nonprescription pharmaceuticals. Toxicology and carcinogenesis studies were conducted by administering acetaminophen (purity >99%) in feed to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary cells.

14-Day Studies

Rats were fed diets containing 0, 800, 1,600, 3,100, 6,200, or 12,500 ppm acetaminophen, and mice were fed diets containing 0, 250, 500, 1,000, 2,000, or 4,000 ppm acetaminophen. There were no deaths among any groups during the study; the final mean body weight of male rats that received 12,500 ppm was significantly lower than that of the controls. Final mean body weights of male and female mice and female rats that received acetaminophen were similar to those of the controls. Feed consumption by male and female rats that received 12,500 ppm acetaminophen was lower than that of the controls; feed consumption by all other exposed groups was higher than that of the controls.

13-Week Studies

Rats and mice were fed diets containing 0, 800, 1,600, 3,200, 6,200, 12,500, or 25,000 ppm acetaminophen. Two male and two female rats, and one male and one female mouse that received 25,000 ppm, and two male mice that received 12,500 ppm died from acetaminophen-related toxicity before the end of the studies. Final mean body weights of male and female rats and mice that received 12,500 or 25,000 ppm were lower than those of the controls. The patterns of feed consumption and reduced body weights that occurred among rats and mice that received diets containing 12,500 or 25,000 ppm were indicative of poor feed palatability.

Acetaminophen-related lesions were observed in the liver (necrosis, chronic active inflammation, hepatocytomegaly), kidney (tubule cast, tubule necrosis, tubule regeneration), reproductive organs (atrophy of testis, ovary, and uterus), thymus and lymph nodes (lymphoid depletion) of rats that received 25,000 ppm, and of the liver (chronic active inflammation, hepatocytomegaly) and testis (atrophy) of male rats receiving 12,500 ppm. Compound-related

lesions in mice were found in the liver (hepatocytomegaly, focal calcification, pigmentation, necrosis) of males that received 6,200, 12,500, or 25,000 ppm and females that received 12,000 or 25,000 ppm.

Dose selection for the 2-year studies was based on reduced body weights and the liver lesions observed in rats and mice at 12,500 and 25,000 ppm.

2-Year Studies

Diets containing 0, 600, 3,000, or 6,000 ppm acetaminophen were given continuously to groups of 60 rats and mice of each sex for up to 104 weeks. After 65 weeks of exposure, 10 animals from each group were evaluated for histopathology and for hematology, urinalysis, and clinical chemistry parameters.

Survival and mean body weights of rats that received acetaminophen were similar to those of the controls throughout the study. The average severity of nephropathy was increased in exposed male and female rats. In males this was associated with an increased incidence of parathyroid hyperplasia (renal hyperparathyroidism). The incidence of focal renal tubule hyperplasia was also increased in exposed male rats. The incidence of mononuclear cell leukemia was increased in exposed female rats and was significantly increased in the 6,000 ppm group (9/50; 17/50; 15/50; 24/50).

Survival of exposed and control mice was similar throughout the study. Mean body weights of mice that received acetaminophen were generally lower than those of the controls throughout the study. Although the incidence of thyroid follicular cell hyperplasia increased with dose among groups of exposed male and female mice, there was no increase in the incidence of follicular cell neoplasms. Renal tubule hyperplasia occurred in one low-dose and two high-dose males and a renal tubule adenoma was present in one low-dose and one high-dose male.

Genetic Toxicology

Acetaminophen was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 with or without S9. In cytogenetic tests with Chinese hamster ovary cells, acetaminophen induced sister chromatid exchanges and chromosomal aberrations in both the presence and absence of S9.

Conclusions

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of acetaminophen in male F344/N rats that received 600, 3,000, or 6,000 ppm. There was *equivocal evidence of carcinogenic activity* of acetaminophen in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *no evidence of carcinogenic activity* of acetaminophen in male and female B6C3F$_1$ mice that received 600, 3,000, or 6,000 ppm.

Nonneoplastic lesions associated with exposure to acetaminophen included increased severity of nephropathy and increased incidences of renal tubule hyperplasia and parathyroid hyperplasia in male rats, increased severity of nephropathy in female rats, and increased incidences of thyroid follicular cell hyperplasia in male and female mice.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on pages 10-11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Acetaminophen

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Feed concentration			
0, 600, 3,000, or 6,000 ppm acetaminophen	0, 600, 3,000, or 6,000 ppm acetaminophen	0, 600, 3,000, or 6,000 ppm acetaminophen	0, 600, 3,000, or 6,000 ppm acetaminophen
Body weights			
Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups lower than controls	Dosed groups lower than controls
2-Year survival rates			
27/50; 28/50; 23/50; 24/50	30/50; 34/50; 34/50; 28/50	32/50; 40/50; 31/50; 31/50	27/50; 32/50; 25/50; 38/50
Nonneoplastic effects			
Kidney: nephropathy severity grades (2.30, 2.56, 2.64, 2.78); renal tubule hyperplasia (1/50, 5/50, 3/50, 5/50) Parathyroid gland: hyperplasia (0/42, 4/45, 6/46, 8/45)	Kidney: nephropathy severity grades (1.44, 1.58, 1.64, 1.72)	Thyroid gland: follicular cell hyperplasia (0/49, 6/49, 12/50, 15/50)	Thyroid gland: follicular cell hyperplasia (2/48, 8/50, 11/50, 25/50)
Neoplastic effects			
None	None	None	None
Uncertain findings			
None	Mononuclear cell leukemia: 9/50; 17/50; 15/50; 24/50	None	None
Level of evidence of carcinogenic activity			
No evidence	Equivocal evidence	No evidence	No evidence
Genetic toxicology			
Salmonella typhimurium (gene mutation)	Negative in strains TA100, TA1535, TA1537, and TA98 with and without S9		
Sister chromatid exchanges (Chinese hamster ovary cells *in vitro*)	Positive with and without S9		
Chromosomal aberrations (Chinese hamster ovary cells *in vitro*)	Positive with and without S9		

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence** of carcinogenic activity describes 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 describes 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 describes studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No evidence** of carcinogenic activity describes studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity describes studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft technical report on Acetaminophen on November 19, 1990, 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:

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

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SUMMARY OF PEER REVIEW COMMENTS

On November 19, 1990, the draft Technical Report on the toxicology and carcinogenesis studies of acetaminophen received public review by the National Toxicology Program (NTP) 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, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of acetaminophen by discussing uses of the chemical, reporting on the experimental design for the studies, and reviewing the neoplasms and nonneoplastic lesions in male and female rats and mice. The proposed conclusions were *some evidence of carcinogenic activity* of acetaminophen in female F344/N rats based on increased incidences of mononuclear cell leukemia and *no evidence of carcinogenic activity* of acetaminophen in male F344/N rats or in male or female B6C3F$_1$ mice.

Dr. Garman, a principal reviewer, agreed with the proposed conclusions for male rats and male and female mice but had reservations about the conclusions for female rats. He asked for information on historical control frequency of multiple organ involvement for mononuclear cell leukemias in female rats. Dr. Irwin said there was no historical control database examining the degree of multiple organ involvement. Dr. S.L. Eustis, NIEHS, commented that in female rats, which have lower spontaneous incidence than males, a less extensive degree of organ involvement is typical, with the spleen and liver being the organs primarily affected.

Dr. Goodman, the second principal reviewer, agreed with the proposed conclusions. However, he suggested adding a dependent clause after the conclusion for female rats as follows, "a malignancy which exhibits a high spontaneous rate and variable incidence in controls." Dr. Goodman also said the possibility should be considered that the sister chromatid exchanges and chromosomal aberrations reported might be artifacts resulting from lysosome breakdown secondary to cytotoxicity, as opposed to a direct action of the chemical on DNA. Dr. E. Zeiger, NIEHS, commented that the way the studies are done would not provide information on such a mechanism.

Dr. Carlson, the third principal reviewer, agreed with the proposed conclusions. He noted the reference to the study by Sandler would suggest that epidemiology studies have been done in humans and wondered if there were other studies which might be relevant. (Editor's note: Per Dr. D. Sandler, most of such surveys involve combinations of analgesics rather than acetaminophen alone.)

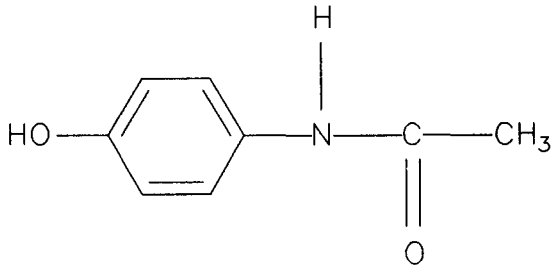
Dr. Gary M. Williams, representing McNeil Consumer Products, stated that acetaminophen played an important role in clinical medicine, and reports of neoplastic effects should be derived from sound data. He expressed the view that there was not an increased incidence of mononuclear cell leukemia in male rats in the NTP study, there was no dose-response or shortened neoplasm latency in females, there was extreme variability in leukemia across control groups, and studies by others had not reported increased incidence of leukemia. Dr. J.K. Haseman, NIEHS, disagreed, responding that indeed there was a significant dose-response in female rats, there was some indication of shortened neoplasm latency, and the historical variability in leukemia across laboratories was similar to that expected by chance alone.

Dr. Zeise expressed concern about the adequacy of the studies in mice, noting that survival, mean body weights, and clinical findings in subchronic and chronic studies suggested mice may have been able to tolerate a higher dose. She questioned administration of acetaminophen in feed rather than as bolus doses, which would be more similar to human exposure.

Dr. Garman moved that the Technical Report on acetaminophen be accepted with revisions discussed and the conclusions as written for male rats and male and female mice, *no evidence of carcinogenic activity*, but with the conclusion for female rats to be changed from *some evidence of carcinogenic activity* to *equivocal evidence of carcinogenic activity*. Dr. Ashby seconded the motion, supporting the change in the

conclusion for female rats because of cumulative uncertainty as to whether mononuclear cell leukemia in female rats was treatment related. Dr. Gold noted that in a 30-month study in Japan using F344 rats no increased incidence of mononuclear cell leukemia was observed. Dr. McKnight opined that with a variable neoplasm such as leukemia, the concurrent control should be given the most weight. Dr. Zeise offered an amendment that a statement be added to the conclusion that mice might have been able to tolerate higher doses. Dr. Carlson seconded the amendment which was defeated by nine no to two yes votes (Drs. Carlson and Zeise) with one abstention (Dr. McKnight). The main motion was then accepted by eight votes (Drs. Ashby, Davis, Garman, Gold, Hayden, Klaassen, Longnecker, and Zeise) to four (Drs. Carlson, Goodman, McKnight, and Silbergeld).

INTRODUCTION



ACETAMINOPHEN

CAS No. 103-90-2

Chemical Formula: $C_8H_9NO_2$ Molecular Weight: 151.16

Synonyms: 4-Hydroxyacetanilide, N-Acetyl-*p*-aminophenol, Paracetamol

PHYSICAL AND CHEMICAL PROPERTIES

Acetaminophen is an odorless white crystalline powder with a melting point of 169° to 170° C. It is slightly soluble in water and freely soluble in alcohol. In aqueous solutions the pK_a of the 4-hydroxyl group is 9.5. Acetaminophen possesses both analgesic and antipyretic properties (Gilman *et al.*, 1985). Although effective as an analgesic for certain kinds of pain, acetaminophen is considered to have only weak anti-inflammatory activity, attributed partly to the fact that acetaminophen is a poor inhibitor of the peripheral isozyme of prostaglandin H synthetase. The antipyretic effect appears to result from a central action on the hypothalamus to reduce the sensitivity of heat-regulating centers to endogenous pyrogens.

PRODUCTION, USE, AND HUMAN EXPOSURE

Acetaminophen is the active component of several nonprescription pharmaceuticals, including Tylenol®, one of the most widely used aspirin substitutes. Acetaminophen was first evaluated for pharmacologic activity in 1893 by von Mehring, who discovered its analgesic and antipyretic properties; however, it was not until the work of Brodie in the 1940's that serious consideration was given to its use in humans (Spooner and Harvey, 1976). Acetaminophen was first introduced as a prescription drug in the United States in 1955 and was approved by the Food and Drug Administration for sale as a nonprescription drug in 1960.

After oral administration, acetaminophen is rapidly absorbed from the gastrointestinal tract, reaches peak levels in plasma in 30 to 120 minutes, and decays with a half-time of 1 to 3 hours in humans and experimental animals (Clements *et al.*, 1978). Absorption occurs rapidly from the small intestine and slowly from the colon; there is no absorption from the stomach. In humans, the rate of absorption is controlled by the rate of gastric emptying and may, therefore, be influenced by the presence of food or by drugs that alter the rate of emptying. Food in the gastrointestinal tract does not affect the total amount of drug absorbed (Forrest *et al.*, 1982).

METABOLISM AND DISPOSITION

The metabolism of acetaminophen in humans and experimental animals can be accounted for by the pathways shown in Figure 1. The major metabolites in all experimental species are the 4-sulfate and 4-glucuronide conjugates, which are formed in the liver. A third pathway in the liver involves cytochrome P_{450}-catalyzed formation of N-acetyl-*p*-benzoquinoneimine (NAPQI), a reactive intermediate that may be reduced back to acetaminophen in an NADPH-dependent reaction or detoxified to form 3-(glutathione-S-yl) acetaminophen either by direct reaction with glutathione or in a glutathione transferase-catalyzed reaction (reviewed by Savides and Oehme, 1983; Hinson *et al.*, 1980a; Hinson, 1983).

Several metabolically important reactions occur in the kidney, a major site for conversion of the 3-glutathionyl conjugate to the 3-cysteinyl conjugate (Fischer, L.J., *et al.*, 1985). Following conversion, the latter is then *N*-acetylated in the liver to the 3-mercapturic acid conjugate, one of the major sulfur-containing urinary metabolites in most experimental species. The conversion of acetaminophen to *p*-aminophenol also occurs primarily in the kidney, and, as discussed below, *p*-aminophenol may be responsible for the nephrotoxicity associated with high doses of acetaminophen (Rush *et al.*, 1984).

Urinary excretion is the predominant pathway of elimination for all acetaminophen metabolites, although substantial quantities of both the 4-glucuronide and 3-glutathione conjugates are excreted initially in bile (Hinson *et al.*, 1982; Siegers *et al.*, 1983; Watari *et al.*, 1983; Hjelle and Klaassen, 1984; Siegers and Klaassen, 1984). In the intestine, the 4-glucuronide conjugate is hydrolyzed to the parent compound, which is reabsorbed. The 3-glutathione conjugate is converted to the 3-cysteinyl conjugate in the intestinal wall, which is relatively rich in γ-glutamyl-transpeptidase and aminopeptidase activity and serves as a major extrarenal site for this reaction.

Other minor pathways may also contribute under certain circumstances. Both 3-hydroxy- and 3-methoxy-acetaminophen have been identified in the urine of mice administered hepatotoxic doses of acetaminophen (Forte *et al.*, 1984) and in the urine of overdosed humans (Knox and Jurand, 1977). Mouse liver microsomes catalyze the formation of the 3-hydroxy derivatives in a reaction that is inducible by phenobarbital and inhibited by carbon monoxide, suggesting mixed-function oxidase involvement (Hinson *et al.*, 1980b; Forte *et al.*, 1984).

3-Thiomethyl-acetaminophen-4-sulfate and 3-thiomethyl-acetaminophen-4-glucuronide have been detected in the urine of rats and mice (Hart *et al.*, 1982), and the unconjugated metabolites have also been detected in the enzyme-hydrolyzed urine of dogs and humans administered acetaminophen (Klutch *et al.*, 1978; Gemborys and Mudge, 1981). Although the pathway by which these metabolites are formed has not been completely resolved, the metabolites do not appear to be derived from NAPQI. Direct insertion of a thiomethyl group at the 3-position of the ring and further metabolism of the 3-glutathione and/or 3-cysteinyl conjugates have been proposed as pathways.

Although the pathways involved in the metabolism of acetaminophen appear to be similar in humans and experimental animals, the overall pattern of metabolite excretion shows species differences, several of which are summarized in Table 1. Humans predominantly excrete the glucuronide conjugate, which usually accounts for 50% to 60% of total urinary metabolites: approximately 30% of the drug is excreted as the sulfate conjugate, 20% as the cysteine and mercapturic acid conjugates combined, and only small amounts are excreted as parent compound. Mice excrete glucuronide and sulfate conjugates in a pattern similar to that of humans. In contrast, rats excrete significantly more of the sulfate conjugate than the glucuronide conjugate in urine; the amount of parent compound excreted by rats is comparable to that of mice. The metabolite excretion pattern in hamsters appears to be more similar to that of mice and humans than to that of rats.

Where adequate data are available for various species or strains, the pattern of acetaminophen metabolite excretion has been observed to exhibit dose-dependent changes. At nontoxic doses approximating therapeutic levels, acetaminophen sulfate and acetaminophen glucuronide are the predominant metabolites in all experimental species. At higher doses, the percentage of administered dose converted to the sulfate conjugate decreases, signaling

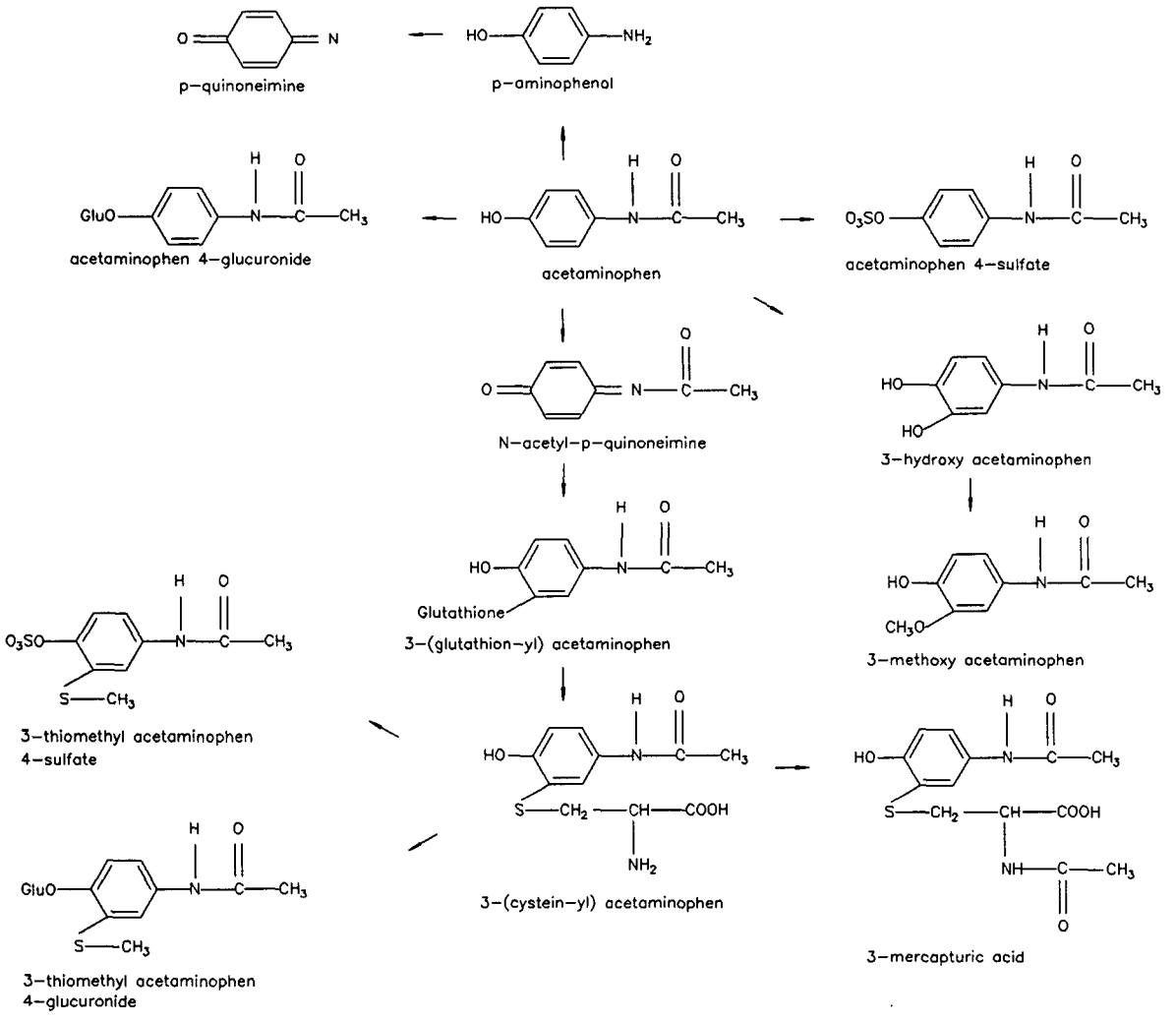


FIGURE 1
Major Pathways for Acetaminophen Metabolism

TABLE 1
Urinary Metabolites of Acetaminophen (APAP) Reported in Various Species[a]

Subject	APAP dose (mg/kg)	n	Route[b]	APAP-glucuronide	APAP-sulfate	APAP-cysteine	APAP-mercapturic acid	APAP	Other
Human[c]	1	3	p.o.	50	33		17[d]	0-2	
	2	3	p.o.	51	28		20[d]	0-2	
	3	3	p.o.	50	29		21[d]	0-2	
	4	3	p.o.	54	20		26[d]	0-2	
	O.D.<10	19	p.o.	62	14		21[d]		
	O.D.>10	11	p.o.	52	11		37[d]		
	50	1	p.o.	60	8		32[d]		
	0.650	5	p.o.	61	28	2	2	7	
	1.3	2	p.o.	63	5			2	31
Mouse	150	5	p.o.	48	14	19	2	12	5
	150	8	p.o.	47	17	25	3	7	
	350	32	p.o.	38	19	19	3	13	8
	50	4	p.o.	48	27		13	11	
	100	4	p.o.	48	25		12	13	
	200	4	p.o.	54	24		9	13	
	400	4	p.o.	61	20		6	14	
Rat	150	6	p.o.	21	65		8	6	
	50	4	i.p.	35	48		4	12	
	200	4	i.p.	35	47		3	15	
	400	4	i.p.	34	41		4	18	
	800	4	i.p.	42	24		4	30	
	1,200	4	i.p.	54	16		3	25	
Hamster	150	5	p.o.	46	27		11	7	8
	50	4	i.p.	40	38		14	9	
	100	6	i.p.	39	39		14	7	
Guinea pig	150	5	p.o.	88	10		2	1	

[a] Table from Savides and Oehme (1983); values expressed as percentage of dose recovered; APAP = N-acetyl-*p*-aminophenol
[b] p.o. = oral administration; i.p. = intraperitoneal administration
[c] Human doses administered in g/kg
[d] Values expressed as cysteine and mercapturic acid conjugates combined

saturation of the sulfation pathway, and the excretion of mercapturic acid and other sulfur-containing conjugates derived from the 3-glutathionyl and/or 3-cysteinyl conjugates increases, indicating an increase in the amount of parent compound converted to NAPQI. The data for humans and rats presented in Table 1 demonstrate this effect.

The dose dependency observed in acetaminophen metabolite profiles, especially the inverse dose relationship between sulfation and glucuronidation, is also apparent in the plasma elimination kinetics (Siegers *et al.*, 1978; Slattery and Levy, 1979; Galinski and Levy, 1981; Hjelle and Klaassen, 1984). As dose levels increase above therapeutic levels, elimination from plasma remains approximately exponential, and the half-time for elimination increases, reflecting saturation of the rapid, lower-capacity sulfation pathway and a shift to the slower, higher-capacity glucuronidation pathway. Although the majority of metabolites are ultimately excreted in the urine, the shift to the glucuronidation pathway is accompanied by a greater percentage of the administered dose appearing initially in the bile, so that biliary excretion predominates at high dose levels.

TOXICITY

Hepatotoxicity

In both humans and experimental animals, ingestion of acetaminophen in excess of therapeutic doses causes hepatotoxicity characterized by necrosis of centrilobular hepatocytes (Black, 1980, 1984; Prescott, 1983). The severity of hepatotoxicity increases with dose and at high doses leads to fulminating hepatic necrosis, which is often fatal. In humans, an acute dose of 15 g (approximately 210 mg/kg for a 70-kg adult) will cause severe hepatotoxicity; however, hepatotoxicity has also been reported in people who have ingested 7 to 10 g (100 to 143 mg/kg). In addition to being acutely toxic, ingestion of 3 to 5 g (50 to 70 mg/kg) of acetaminophen per day on a chronic basis (weeks to years) has been associated with chronic active hepatitis.

Numerous studies (Hinson, 1980, 1983; Gillette *et al.*, 1982; Guengerich and Liebler, 1985) that have examined the mechanism involved in acetaminophen-induced hepatotoxicity point to a reactive metabolite formed during cytochrome P_{450}-catalyzed reaction(s) as being responsible for the cytotoxicity ultimately leading to the death of hepatocytes. The most widely cited mechanism consistent with the experimental data identifies NAPQI as the reactive metabolite that is normally detoxified by reaction with glutathione. Upon depletion of glutathione, NAPQI begins to arylate cellular proteins, and perhaps other cellular components, eventually causing cell death. There is also mounting evidence to indicate that superoxide and hydrogen peroxide are formed during NAPQI formation, which, in the glutathione-depleted cell, initiates lipid peroxidation and contributes to cytotoxic events leading to hepatocellular death (Mitchell *et al.*, 1981; Farber and Gerson, 1984). This scheme is consistent with recent evidence indicating that oxidation of acetaminophen to NAPQI occurs via a free radical intermediate (Nelson *et al.*, 1981; Fischer and Mason, 1984; Fischer, V., *et al.*, 1985).

Kidney Toxicity

Although hepatotoxicity is the most frequent result of acute acetaminophen poisoning in humans, approximately 10% of severely overdosed patients also develop renal failure characterized by acute cortical necrosis (Prescott, 1983). Moreover, a recent study reported that long-term daily use of acetaminophen was associated with chronic renal disease (Sandler *et al.*, 1989). In experimental animals, acetaminophen causes cortical necrosis involving tubule cells of the proximal convoluted tubules (Rush *et al.*, 1984). The molecular events leading to death of proximal tubule cells may be somewhat similar to those occurring in the liver and involving cytochrome P_{450}-catalyzed formation of a reactive intermediate that depletes cellular glutathione and arylates cellular macromolecules. This is consistent with the cortical localization of cytochrome-P_{450} mixed-function oxidase activity and its presence in proximal tubule cells (Zenser and Davis, 1984).

There is also evidence to indicate that another pathway contributing to nephrotoxicity involves deacetylation of acetaminophen to *p*-aminophenol, which is subsequently activated in an NADPH-independent reaction to a reactive intermediate that depletes glutathione and arylates cellular macromolecules (Mudge *et al.*, 1978; Newton *et al.*, 1982a,b, 1983, 1985). The lack of dependence on NADPH implies that this reaction is not catalyzed by mixed-function oxidases. In F344/N rats, *p*-aminophenol is a nephrotoxin that arylates cellular protein and induces cortical necrosis indistinguishable from that produced by acetaminophen. Moreover, *p*-aminophenol is an excellent co-substrate in the pros-

taglandin H-synthetase (PHS)-catalyzed oxidation of arachidonic acid, and is oxidized during the reaction to *p*-benzoquinoneimine, a quinoneimine with properties essentially identical to those of NAPQI (Rush *et al.*, 1984; Zenser and Davis, 1984). Although the kidney is a major site of PHS activity, the activity is localized in the inner and outer medulla, and there is essentially no PHS activity detectable in the cortex. It is therefore unclear whether PHS activation is involved in the NADPH-independent contribution to the cortical nephrotoxicity of acetaminophen.

GENETIC TOXICOLOGY

No mutagenic activity was detected in bacterial test systems following treatment with acetaminophen (King *et al.*, 1979; Haworth *et al.*, 1983; Dybing *et al.*, 1984; Oldham *et al.*, 1986; Jasiewicz and Richardson, 1987). Tests for induction of sex-linked recessive lethal mutations in *Drosophila* (King *et al.*, 1979) and gene mutation induction in cultured V79 hamster cells (Sasaki *et al.*, 1983; Sawada *et al.*, 1985) were also negative.

Studies with acetaminophen indicate some evidence for clastogenicity, particularly in *in vitro* mammalian test systems. Induction of chromosomal aberrations (Sasaki *et al.*, 1980, 1983; Ishidate *et al.*, 1981; Sawada *et al.*, 1985; NTP, unpublished data) and sister chromatid exchanges (Sasaki, 1986; NTP, unpublished data) has been reported in cultured mammalian cells in the absence of exogenous metabolic activation. An equivocal increase in micronucleated *Tradescantia* pollen mother cells was reported after treatment of plants with an acetaminophen solution (Ma *et al.*, 1984), and a small, dose-related increase in frequency of micronuclei was observed in cultured rat kidney cells in the absence of exogenous metabolic activation (Dunn *et al.*, 1987).

A twofold increase in cells with micronuclei (0.19% versus 0.38%, $P<0.01$) was seen in buccal mucosa cells of human volunteers sampled 72 hours after consuming therapeutic doses (3 x 1,000 mg over an 8-hour period) of acetaminophen in tablet form (Topinka *et al.*, 1989). The incidence of chromosomal aberrations in peripheral lymphocytes was also investigated in these same subjects. An increase ($P<0.05$) in the frequency of aberrant cells, resulting solely from an increase in the number of chromatid breaks, was reported in blood samples taken 24 hours after initiation of the 8-hour exposure regimen (Kocisova *et al.*, 1988). The levels of aberrations declined to background levels at subsequent sampling times (72 hours and 168 hours after treatment initiation).

The induction of unscheduled DNA synthesis or DNA strand breakage by acetaminophen has been studied in cultured hepatocytes from a number of mammalian species. Two studies reported induction of unscheduled DNA synthesis in mouse hepatocytes treated *in vitro* (Dybing *et al.*, 1984; Holme and Soederlund, 1986). One of three studies in rat hepatocytes *in vitro* found a weak response for induction of unscheduled DNA synthesis (Milam and Byard, 1985; Holme and Soederlund, 1986; Sasaki, 1986), but no increase in DNA single strand breaks was observed in these cells (Dybing *et al.*, 1984). No unscheduled DNA synthesis was observed in guinea pig or hamster hepatocytes following *in vitro* exposure (Holme and Soederlund, 1986).

In several genetic toxicity assays of acetaminophen, there is a narrow range between the concentration of acetaminophen that is sufficient to produce a genotoxic effect and the concentration at which cytotoxicity occurs. Thus, cell death may sometimes occur concomitantly with genetic effects, thereby masking the latter.

The limited test data from structural analogues of acetaminophen, N-hydroxy-N-phenylacetamide and N-(2-hydroxyphenyl)acetamide, are consistent with results observed with the parent compound: tests for gene reversion (Hecht *et al.*, 1979) and inhibition of DNA synthesis (Lahitoava *et al.*, 1982) in bacteria were negative, as was a test for induction of sister chromatid exchanges by N-(2-hydroxyphenyl)-acetamide in human fibroblast cells (Wilmer *et al.*, 1981).

Mutagenicity information is available on three metabolites of acetaminophen: N-acetyl-*p*-benzoquinoneimine, N-hydroxyacetaminophen, and 4-aminophenol. N-acetyl-*p*-benzoquinoneimine, considered the major metabolite, and N-hydroxy-acetaminophen, were, like the parent compound, negative in bacterial gene mutation assays (Wirth *et al.*, 1980; Dybing *et al.*, 1984). N-Acetyl-*p*-benzoquinoneimine produced DNA single strand breaks in rat hepatoma cells but not in primary mouse hepatocytes (Dybing *et al.*, 1984). N-Hydroxy-acetaminophen was reported to inhibit DNA

acetaminophen was reported to inhibit DNA synthesis (Djordjevic *et al.*, 1986) and induce micronuclei (Dunn *et al.*, 1987) in rat NRK kidney fibroblasts. 4-Aminophenol has been extensively studied and, although the metabolite has no mutagenic activity in bacterial assays (McCann *et al.*, 1975; Probst *et al.*, 1981; DeFlora *et al.*, 1984; Zeiger *et al.*, 1988), it does have mutagenic activity in mammalian cell systems *in vitro*. Positive results were reported for gene mutation induction in mouse L5178Y lymphoma cells with S9 (Amacher and Turner, 1982; Oberly *et al.*, 1984) and for sister chromatid exchange induction in human lymphocytes without S9 (Takehisa and Kanaya, 1982). *In vivo* chromosomal aberrations (Mitra and Manna, 1971) and micronuclei (Wild *et al.*, 1980) were induced in bone marrow cells of mice administered 4-aminophenol by intraperitoneal injection, and sperm head abnormalities were observed in male mice treated intraperitoneally with 4-aminophenol (Topham, 1980).

In conclusion, the available test data on acetaminophen and its structural analogues and metabolites indicate that this chemical is not an effective mutagen in bacterial systems but does have potential for genotoxic activity in mammalian systems by virtue of its ability to induce gene mutations, chromosomal aberrations, and unscheduled DNA synthesis.

CARCINOGENICITY

The carcinogenic potential of acetaminophen in experimental animals has been examined in several types of studies. In the first published report involving long-term exposure to acetaminophen (Johansson, 1981), groups of 30 male Sprague-Dawley rats received diets containing 5,350 ppm phenacetin, 5,350 ppm phenazone, 1,020 ppm caffeine, a mixture of a pair of these drugs, or a mixture of all three drugs. An additional group of 30 male rats received 5,350 ppm acetaminophen in feed. All animals were maintained on these diets over their lifespans, which ranged from group means of 92 to 104 weeks (94 weeks for the controls). The group exposed to acetaminophen had a mean lifespan of 93 weeks. Although survival curves were not included in the report, the first exposed animal died during week 65 and the last during week 116. The first and last control rat deaths occurred during weeks 67 and 116. Group mean body weights at week 74 showed that the mean body weight of the exposed group was similar to that of the control group, but that the mean body weights of all other treated groups were significantly less than those of the control group.

Animals from all groups had some degree of renal papillary hyperplasia and bladder hyperplasia; however, the incidence and severity were increased in animals that received phenacetin either alone or in combination with the other agents. Neoplasms of the renal pelvis, bladder, and liver occurred in groups that received phenacetin, phenazone, and combinations of phenacetin, phenazone, and caffeine. The overall incidence of papillary hyperplasia was slightly increased among exposed rats (57%) compared to controls (43%); the severity of this lesion in exposed rats was also slightly greater than in the controls. Four animals from the group that received acetaminophen had bladder papillomas, as did two of the control animals. The authors concluded that acetaminophen demonstrated no toxic or carcinogenic effect.

Hiraga and Fuji (1985) evaluated the carcinogenic potential of acetaminophen in F344/DuCrj rats. Groups of 50 males received diets containing 4,500 or 9,000 ppm acetaminophen, and groups of 50 females received diets containing 6,500 or 13,000 ppm acetaminophen for 104 weeks. Survival and mean body weights of exposed animals were similar to controls; no increase in neoplasm incidence was observed among the animals that received the acetaminophen diets.

In a third dosed feed study (Flaks *et al.*, 1985), groups of 50 male and 50 female Leeds rats received 5,000 or 10,000 ppm acetaminophen, and groups of 40 males and 40 female rats received control diets for 18 months. Survival to 18 months among treated groups ranged from 45/50 to 49/50; all controls survived. No data on body weights were included. The incidence of neoplastic nodules of the liver was significantly increased, occurring in 20% of male and 20% of female rats that received the highest doses of acetaminophen; none were seen in controls. The incidences of transitional cell hyperplasia and bladder papillomas were increased in exposed rats, and several papillomas were accompanied by the presence of calculi. Bladder carcinomas were observed in high-dose males and in one-high dose and one low-dose female rat, but none of these lesions showed evidence of calculi.

In a study with mice (Flaks and Flaks, 1983), groups of 60 male and 60 female IF mice received diets containing 5,000 or 10,000 ppm acetaminophen for 18 months, and groups of 52 male and 52 female mice received control diets. Survival of males and females receiving 5,000 ppm diets (males, 54/60, females, 57/60) was similar to that of male (50/52) and female (48/52) controls. Survival of high-dose mice was reduced, and only 23/60 males and 47/60 females survived to study termination. Thirty-two of the high-dose males died of hepatocellular necrosis within 48 hours of starting the treated diets; the deaths of the high-dose females and five remaining high-dose males occurred throughout the study. Various nonneoplastic lesions were observed in the livers of mice from all treatment groups, although foci of cellular alteration were observed only in the high-dose males and females and low-dose males. Among high-dose mice surviving to the end of the study, 20/23 males had hepatocellular neoplasms, as did 9/47 females; hepatocellular neoplasms were also seen in one low-dose and one control male.

In another study with mice (Amo and Matsuyama, 1985), groups of 105 male and 105 female $B6C3F_1$ mice received 3,000 or 6,000 ppm acetaminophen in feed for 133 weeks, and groups of 50 male and 50 female mice received control diets. The survival and mean body weights of exposed and control animals were similar throughout the study. No neoplasms were associated with exposure to acetaminophen.

In a study designed to evaluate the promotional effect of chemically induced chronic renal and hepatic toxicity (Hagiwara and Ward, 1986), groups of 48 male and 48 female $B6C3F_1$ mice received diets containing 5,000 or 10,000 ppm acetaminophen for 40 weeks. After 2, 8, 24, and 40 weeks of exposure, groups of six mice were killed for evaluation of liver and kidney weights, histopathology, determination of thymidine kinase activity, and levels of DNA synthesis based on incorporation of trifluorothymidine or bromodeoxyuridine in the liver and kidney.

In the groups that received 10,000 ppm, mean body weights were 30% to 50% lower than those of the controls, and survival was decreased from 68% of the control value at week 24 to 45% of the control value at week 32. Relative liver weights were significantly increased at weeks 8 and 24, and relative kidney weights were significantly increased at weeks 2 and 24. Histologically, livers of high-dose mice showed hepatocytomegaly and focal to lobular massive hepatocellular necrosis and degeneration; however, no neoplasms or lesions judged to be preneoplastic were found. The hepatocyte labeling index was significantly elevated only at week 2 in the 10,000 ppm group; no increase in labeling index was observed in renal cortical tubule cells. The authors concluded that persistent or transient hepatic or renal hyperplasia resulting from exposure to 10,000 ppm acetaminophen was not associated with carcinogenic or neoplasm-promoting activity.

In a related study (Ward *et al.*, 1988), groups of male $B6C3F_1$ mice were treated as follows: one group of 120 mice received 10,000 ppm acetaminophen in feed; a second group of 60 mice received 5,000 ppm in feed; and a third group of 30 mice received control diets *ad libitum* for 72 weeks. A fourth group of 60 mice received a single intraperitoneal injection of diethylnitrosamine (DEN, 40 mg/kg) and 2 weeks later were started on diets containing 10,000 ppm acetaminophen, a fifth group of 60 mice received an injection of DEN and 2 weeks later were started on diets containing 5,000 ppm acetaminophen, and a control group of 30 mice received an injection of DEN followed by control diets. All groups of mice that received acetaminophen alone were killed after 72 weeks of exposure, and all DEN-exposed mice were killed after 24 weeks of exposure. The livers of all mice were examined histopathologically for neoplasms and nonneoplastic lesions associated with chemical exposure.

Mean body weights of mice that received 5,000 ppm acetaminophen in the diet (no DEN) were 14.8% lower than those of the controls after 24 weeks and 13.1% lower than those of the controls after 72 weeks of chemical exposure. Mean body weights of mice that received 10,000 ppm were 43.5% lower than those of the controls after 24 weeks and 49.5% lower after 72 weeks. Survival of high-dose mice was significantly reduced; after 24 weeks of exposure the survival rate of high-dose mice was 50% of that of the controls. Survival of low-dose mice was similar to that of the controls. Relative liver weights increased in the high-dose group at 24 and 72 weeks, but the increase was significant only at 72 weeks. The authors stated that mean body weights and survival of mice injected with DEN and then fed diets containing acetaminophen were similar to those

observed for mice that received acetaminophen alone, although no data were provided.

Nonneoplastic lesions characterized as centrilobular hepatocytomegaly, cirrhosis, pigment deposition, and necrosis of hepatocytes varying from focal to multifocal and from centrilobular to massive were present at high incidence (exact numbers not given) in mice that received diets containing 10,000 ppm and were responsible for the early deaths in this group. Mild hepatocytomegaly was present in most mice that received 5,000 ppm, with focal necrosis or cirrhosis present as incidental lesions in a few mice from this group. Focal hepatocellular proliferative lesions were not present in any mice after 24 weeks of acetaminophen exposure. After 70 weeks of exposure, approximately equal percentages were present in both dose groups and the control group; however, eosinophilic lesions were present only in the exposed animals. No hepatocellular carcinomas were observed in any of the groups after 72 weeks of exposure.

Mice that received the DEN injection and 10,000 ppm acetaminophen showed a significantly increased incidence of focal hepatocellular proliferative lesions (55%) compared to controls (7%). Seventy-five percent of the lesions observed in exposed mice were eosinophilic, while all lesions observed in the control group were basophilic. The incidence of these lesions in 5,000 ppm mice (13%) was slightly greater than the control incidence, but all the lesions were basophilic. On the basis of these results, the authors concluded that acetaminophen is a weak promotor of DEN-initiated hepatocytes, but is not carcinogenic when administered alone, even in the presence of severe hepatotoxicity.

Study Rationale

Because of its increasing use in over-the-counter products and the lack of knowledge about the risks associated with long-term exposure, acetaminophen was nominated by the FDA for carcinogenesis testing.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF ACETAMINOPHEN

Acetaminophen was obtained from S.B. Penick & Company in two lots. Lot number 7042-LAR-5 was used in both the 14-day and 13-week studies and most of the 2-year studies, and lot number 7032-LFR-57 was used in the final 2 to 6 months of the 2-year studies. The results of the purity, identity, and stability analyses conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), are presented in Appendix H.

Both lots of the study chemical were identified as acetaminophen by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopies. The purity of both lots was determined to be greater than 99% by elemental analyses, Karl Fischer water analysis, non-aqueous phenol group titration, thin-layer chromatography, and high-performance liquid chromatography (HPLC). Comparison of the two lots by HPLC showed no significant purity differences. As a supplement to these purity and identity analyses, the complete battery of United States Pharmacopeia tests was performed on lot 7042-LAR-5; all test results indicated that this lot met the requirements of USP for acetaminophen. Stability studies performed with HPLC found that acetaminophen was stable as a bulk chemical when stored protected from light for 2 weeks at temperatures up to 60° C. Throughout the studies, the bulk chemical was stored in sealed containers protected from light at 25° C. Stability of the bulk chemical was monitored by the study laboratory using infrared and ultraviolet spectroscopies. No change in the study material was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations were prepared weekly by mixing appropriate amounts of acetaminophen and feed (Table H1). Studies were conducted by the analytical chemistry laboratory to determine homogeneity and stability of acetaminophen in feed. Homogeneity was confirmed by spectroscopy while HPLC analysis was used to confirm stability at 20,000 ppm for at least 14 days when stored in the dark at temperatures up to 25° C. During the studies, dose formulations were stored at 0° ± 5° C for no longer than 2 weeks.

The study laboratory analyzed the dose formulations by ultraviolet spectroscopy once during the 14-day studies, twice during the 13-week studies, and at least once every 8 weeks during the 2-year studies (Tables H2, H3, and H4). Because 62 of 66 formulations were determined to be within 10% of the target concentration, it is estimated that 94% of the formulations prepared during the 2-year studies were within specifications (Table H4). Results of periodic referee analyses by the analytical chemistry laboratory agreed with the results of the study laboratory (Table H5).

14-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Kingston, NY) and held for 19 days before the studies began. Rats were 7 to 8 weeks old at the start of the studies, and mice were 8 to 9 weeks old. Groups of five rats of each sex received 0, 800, 1,600, 3,100, 6,200, or 12,500 ppm acetaminophen in feed for 14 consecutive days. Groups of five mice of each sex received 0, 250, 500, 1,000, 2,000, or 4,000 ppm acetaminophen in feed for 14 consecutive days. Rats and mice were observed for 1 day following the last dose. The rats and mice were housed five per cage, and water and feed were available *ad libitum*. Rats and mice were observed twice daily; clinical findings noted during the daily checks were recorded. The animals were weighed at study initiation and on days 7 and 14. Feed consumption was measured weekly. Necropsies were performed on all animals. No histopathology was performed. Further details are presented in Table 2.

13-WEEK STUDIES

Thirteen-week studies were conducted to evaluate cumulative toxic effects of continuous exposure to acetaminophen and to determine the chemical

concentrations to be used in the 2-year studies. Fischer 344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Kingston, NY), observed for 14 days, distributed to weight classes, and assigned to dose groups. Rats and mice were 7 weeks old when placed on study. Groups of 10 rats or mice of each sex received 0, 800, 1,600, 3,200, 6,200, 12,500, or 25,000 ppm acetaminophen in feed for 13 weeks. Rats and mice were housed five per cage, and water and feed were available *ad libitum*. Animals were observed twice daily; clinical findings noted during the daily checks were recorded. Each animal received an individual clinical examination once per week. Feed consumption was recorded 2 to 4 consecutive days per week. Animals were weighed at the start of the study and weekly thereafter. Further experimental details are presented in Table 2.

Survivors were killed at the end of the 13-week studies. Necropsies were performed on all animals except for one female mouse from each of the 0, 800, and 6,200 ppm groups which were killed due to pregnancy. The brain, heart, right kidney, liver, lung, right testis, and thymus of survivors were weighed at necropsy. Complete histopathologic examinations were performed on animals in the control and high-dose groups and on one male mouse in the 3,200 ppm group. Target organs were submitted for histopathology for the animals in the lower dose groups. Tissues examined for each group are listed in Table 2.

2-YEAR STUDIES

Study Design

Groups of 60 rats and mice of each sex were administered 0, 600, 3,000, or 6,000 ppm acetaminophen in feed *ad libitum* for up to 103 weeks. At 15 months, 10 rats and mice per sex per dose group were randomly selected for interim evaluations.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (rats: Kingston, NY; mice: Portage, MI) for use in the 2-year studies. The rats were 4 to 5 weeks old at receipt, and the mice were 5 to 6 weeks old. Rats were quarantined for 19 to 20 days, and mice were quarantined for 15 to 20 days. Five rats and mice per sex were randomly selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screens. Rats were 7 to 8 weeks old at study initiation, and mice were 8 to 9 weeks old. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

The rats and mice were housed five per cage. Feed (Appendix J) and water were available *ad libitum*. Cages were rotated every 2 weeks during the studies. Further details of animal maintenance are given in Table 2.

Clinical Observations and Pathology

Animals were observed twice daily; clinical findings noted during the daily checks were recorded. Rats were weighed at study initiation, weekly for 13 weeks, and monthly thereafter. Mice were weighed at study initiation, once a week for either 15 weeks (males) or 12 weeks (females) and monthly thereafter. Feed consumption was measured 1 week per month through week 12 and every 4 weeks thereafter (Appendix I).

At 15 months, 10 rats and mice per group were randomly selected for interim evaluations. One week prior to the interim evaluation urine was collected over a 24-hour period and the urine volume and total protein concentration (mice only) were determined. Blood was drawn from the jugular vein of rats or the tail of mice and the following hematology parameters measured: hematocrit, hemoglobin concentration, erythrocyte count, total leukocyte count, leukocyte differential count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and methemoglobin. Serum albumin and glucose concentrations in mice were determined on blood drawn from the jugular vein of mice. Further details are presented in Table 2.

Necropsies were performed on all animals found moribund, designated for the 15-month interim evaluations, or surviving to the end of the 2-year studies. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for

microscopic examination. The tissues and groups examined are listed in Table 2.

When the pathology evaluation was completed by the study laboratory pathologist and the pathology data entered into the Toxicology Data Management System (TDMS), the microscope slides, individual animal necropsy records, and pathology tables were forwarded to an independent pathology quality assessment laboratory. At this laboratory, individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated.

A quality assessment pathologist reviewed selected tissues for accuracy and consistency of lesion diagnosis. The following tissues were reviewed in all animals in all dose groups: male rats, kidney and Zymbal's gland; female rats, kidney and thyroid gland; male and female mice, thyroid gland. All diagnosed neoplasms in all tissues other than those already mentioned were reviewed in all animals, and all diagnoses (neoplasms and nonneoplastic lesions) were reviewed from a randomly selected 10% of the control and high-dose animals of each sex in each species. In addition, selected tissues from all animals in all dose groups of female rats and male mice were examined for the presence of proliferative lesions (hyperplasia and neoplasia). The tissues examined included: female rats, liver, spleen, and urinary bladder; male mice, adrenal gland, kidney, and nose. The kidneys from all male mice were also reviewed for the presence of renal tubule regeneration.

The quality assessment report and slides were submitted to the appropriate Pathology Working Group (PWG) Chair, who reviewed the slides of tissues with lesions possibly related to chemical administration, and of any other tissues for which there was disagreement in diagnoses between the laboratory and quality assessment pathologist. Representative histopathology slides of tissues and examples of disagreements in diagnosis between the laboratory and quality assessment pathologist were shown to the PWGs. Each PWG included the quality assessment pathologist and others experienced in rodent toxicologic pathology who examined the tissues without knowledge of dose group or previously rendered diagnoses. Whenever the consensus diagnosis of a PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). The final pathology data represent a consensus of contractor pathologists and the PWGs. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

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

Calculation of Incidence

The incidence of neoplasms or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which the site was examined. In most instances, the denominators include only those animals for which the site was examined histopathologically. However, when macroscopic examination was required to detect lesions (e.g., oral cavity) prior to tissue sampling for histopathology, or when lesions (e.g., lymphoma) could have occurred at multiple sites, the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

The majority of neoplasms 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, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The 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).

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), a survival-adjusted procedure appropriate for rapidly lethal neoplasms, and the Fisher exact and Cochran-Armitage trend tests (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

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

Historical Control Data

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

Analysis of Continuous Variables

Absolute and relative organ weights from the 13-week studies and hematology, clinical chemistry, and urinalysis data from the 15-month interim evaluations were analyzed using the nonparametric comparison procedures of Dunn (1964) and Shirley (1977); Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons. Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

GENETIC TOXICITY

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

QUALITY ASSURANCE METHODS

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

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Acetaminophen

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (rats: Kingston, NY; mice: Portage, MI)
Time Held Before Study		
19 days	14 days	Rats: 19-20 days Mice: 15-20 days
Age When Placed on Study		
Rats: 7-8 weeks Mice: 8-9 weeks	7 weeks	Rats: 7-8 weeks Mice: 8-9 weeks
Date of First Dose		
23 February 1981	Rats: 7 July 1981 Mice: 14 July 1981	Rats: 29 November 1982 (males) or 14 December 1982 (females) Mice: 28 July 1982 (males) or 9 August 1982 (females)
Date of Last Dose		
8 March 1981	Rats: 9 October 1981 Mice: 16 October 1981	Rats: 19 November 1984 (males) or 4 December 1984 (females) Mice: 18 July 1984 (males) or 30 July 1984 (females)
Duration of Dosing		
14 consecutive days	13 weeks (7 days/week)	103 weeks (7 days/week)
Age When Killed		
Rats: 10-11 weeks Mice: 12-13 weeks	20 weeks	Rats: 112-114 weeks Mice: 112-114 weeks
Necropsy Dates		
Rats: 17 March 1981 Mice: 25 March 1981	Rats: 7-9 October 1981 Mice: 14-16 October 1981	Rats: 26 November-5 December 1984 (males) or 11-19 December 1984 (females) Mice: 25 July-2 August 1984 (males) or 7-10 August 1984 (females)
Size of Study Groups		
5 males and 5 females	10 males and 10 females	60 males and 60 females
Method of Sacrifice		
Carbon dioxide asphyxiation	Same as 14-day studies	Same as 14-day studies

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Acetaminophen (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Method of Animal Distribution		
Animals distributed to weight classes and then assigned to test and control groups so that all cage weights were equal for each sex and species.	Same as 14-day studies	Animals distributed to weight classes, assigned to cages and dose groups using random number tables, and randomized to initial rack position.
Animals per Cage		
5	5	5
Method of Animal Identification		
Ear punch	Ear punch	Ear punch
Diet		
NIH-07 Rat and Mouse Ration, powdered (Zeigler Bros., Inc., Gardners, PA); available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Water		
Tap water (City of Worcester Public Water Supply) via outside-the-cage automatic watering system (Edstrom Industries, Waterford, WI); available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Cages		
Polycarbonate, See-Through II System (Lab Products, Inc., Rochelle Park, NJ)	Same as 14-day studies	Same as 14-day studies
Bedding		
Aspen Bed heat-treated hardwood chips (American Excelsior Co., Baltimore, MD); changed twice weekly	Same as 14-day studies	Same as 14-day studies
Cage Filters		
Nonwoven fiber filters (Snow Filtration, Cincinnati, OH)	Nonwoven fiber filters (Snow Filtration, Cincinnati, OH or Lab Products, Inc., Rochelle Park, NJ)	Same as 14-day studies
Animal Room Environment		
Temperature: 21.6°-27.2° C Relative Humidity: 34%-73% Fluorescent light: 12 hours/day Room air changes: 12-15/hour	Temperature: 20.0°-25.6° C Relative Humidity: 32%-77% Fluorescent light: 12 hours/day Room air changes: >12/hour	Temperature: 18°-25° C Relative Humidity: 5%-71% Fluorescent light: 12 hours/day Room air changes: 11.2-11.6/hour
Doses		
Rats: 0, 800, 1,600, 3,100, 6,200, or 12,500 ppm acetaminophen in feed Mice: 0, 250, 500, 1,000, 2,000, or 4,000 ppm acetaminophen in feed	0, 800, 1,600, 3,200, 6,200, 12,500, or 25,000 ppm acetaminophen in feed	0, 600, 3,000, or 6,000 ppm acetaminophen in feed

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Acetaminophen (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice/day; body weight initially and once/week; feed consumption once/week by cage; clinical observations recorded as needed	Observed twice/day; body weight initially and once/week; feed consumption 2-4 consecutive days/week; clinical observations once/week	Observed twice/day Body weights: Rats - initially, weekly for 13 weeks, monthly thereafter; Mice - initially, weekly for 15 weeks (males), weekly for 12 weeks (females), monthly thereafter; Feed consumption measured 1 week/month through week 12 and every 4 weeks thereafter; Clinical observations: Rats - weekly for 13 weeks and monthly thereafter; Mice - initially, weekly for 15 weeks (males), weekly for 12 weeks (females), monthly thereafter
Necropsy, Histologic Examinations, and Supplemental Analyses		
Necropsy performed on all animals.	Necropsy performed on all animals. The following organ weights were measured: brain, heart, right kidney, liver, lungs, right testis, thymus. Complete histopathology on all control and high-dose animals and on one male mouse in the 3,200 ppm group. Tissue examined included: adrenal gland, blood smear, bone (sternebrae including marrow), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular, mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, seminal vesicles, skin, small intestine (duodenum, ileum, jejunum), spleen, stomach, testes, thymus, thyroid gland, trachea, urinary bladder, uterus, and gross lesions and tissue masses (with regional lymph nodes). The following target organs from 800 to 12,500 ppm male rats were examined: epididymis, liver, mesenteric lymph nodes, pituitary gland, prostate gland, salivary gland, seminal vesicles, and testes; from 800 to 12,500 ppm female rats: liver, mesenteric lymph nodes, ovary, salivary glands, and uterus; from 800 to 12,500 ppm male and female mice: liver.	Necropsy performed on all animals. Complete histopathology on all animals that died, were killed moribund or were killed at month 15 or study termination. Tissues examined were the same as in the 13-week studies. All cases of mononuclear cell leukemia in female rats were graded. Clinical pathology studies conducted at month 15. Hematology: hematocrit, hemoglobin, erythrocyte count, leukocyte count and differential, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration. Clinical chemistry (mice only): albumin, glucose, methemoglobin. Urinalysis: total protein (mice only), urine volume.

RESULTS

RATS

14-Day Studies

All rats survived to the end of the studies (Table 3). The final mean body weight of male rats receiving 12,500 ppm acetaminophen was 20% lower than the mean final body weight of controls. The average feed consumption by male and female rats receiving 12,500 ppm was lower than that of controls. No compound-related lesions were found at necropsy and no histopathology was performed.

TABLE 3
Survival, Mean Body Weights, and Feed Consumption of Rats in the 14-Day Feed Studies of Acetaminophen

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Control (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	115 ± 2.7	203 ± 5.0	88 ± 4.6		12	21
800	5/5	115 ± 3.5	191 ± 4.1	76 ± 5.8	94	12	19
1,600	5/5	115 ± 3.7	201 ± 5.4	86 ± 2.9	99	15	17
3,100	5/5	115 ± 3.7	206 ± 3.9	91 ± 2.4	101	15	20
6,200	5/5	115 ± 4.4	201 ± 7.7	86 ± 3.4	99	15	20
12,500	5/5	116 ± 3.8	163 ± 5.9**	47 ± 3.0**	80	10	14
Female							
0	5/5	98 ± 2.1	138 ± 1.9	40 ± 2.5		12	13
800	5/5	98 ± 1.9	146 ± 3.6	48 ± 1.9	106	14	13
1,600	5/5	99 ± 2.0	141 ± 1.4	41 ± 2.3	102	13	13
3,100	5/5	98 ± 2.3	146 ± 2.4	47 ± 3.4	106	13	14
6,200	5/5	99 ± 1.8	142 ± 2.6	43 ± 1.9	103	12	13
12,500	5/5	99 ± 2.5	133 ± 2.0	34 ± 2.7	96	10	10

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error
[c] Grams per animal per day, based on average consumption data

13-Week Studies

Two males and two females receiving 25,000 ppm acetaminophen died by week 7 of the studies (Table 4). Mean body weights of male and female rats receiving 25,000 ppm decreased for the first 2 weeks of the study and then, by week 3, began to increase, but at a slower rate than those of the controls (Figure 2). As a result, mean body weights of males and females that received 25,000 ppm were significantly lower than those of the controls throughout the studies. These results are consistent with poor feed palatability and wastage of the 25,000 ppm diet. Mean body weights of male and female rats that received 12,500 ppm were also lower than those of the controls throughout the study, but mean body weights of other exposed groups were similar to those of the controls.

TABLE 4
Survival and Mean Body Weights of Rats in the 13-Week Feed Studies of Acetaminophen

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Control (%)
		Initial	Final	Change	
Male					
0	10/10	111 ± 2.7	348 ± 5.3	237 ± 4.2	
800	10/10	111 ± 2.5	342 ± 10.5	230 ± 8.7	98
1,600	10/10	111 ± 2.5	347 ± 7.1	236 ± 5.7	100
3,200	10/10	111 ± 2.4	348 ± 5.7	237 ± 5.2	100
6,200	10/10	112 ± 2.1	332 ± 5.9	221 ± 4.6*	95
12,500	10/10	111 ± 2.0	298 ± 6.1**	187 ± 4.4**	86
25,000	8/10[c]	111 ± 2.4	159 ± 7.6**	48 ± 6.4**	46
Female					
0	10/10	100 ± 3.1	213 ± 3.8	113 ± 3.2	
800	10/10	100 ± 3.0	210 ± 3.0	111 ± 2.0	99
1,600	10/10	99 ± 2.6	209 ± 4.1	111 ± 3.7	98
3,200	10/10	99 ± 2.3	210 ± 2.9	111 ± 3.3	99
6,200	10/10	99 ± 2.4	208 ± 4.2	109 ± 3.3	98
12,500	10/10	98 ± 2.3	189 ± 3.5**	91 ± 2.7**	89
25,000	8/10[d]	97 ± 2.9	117 ± 7.9**	20 ± 6.7**	55

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Week of death: 6, 7
[d] Week of death: 5, 6

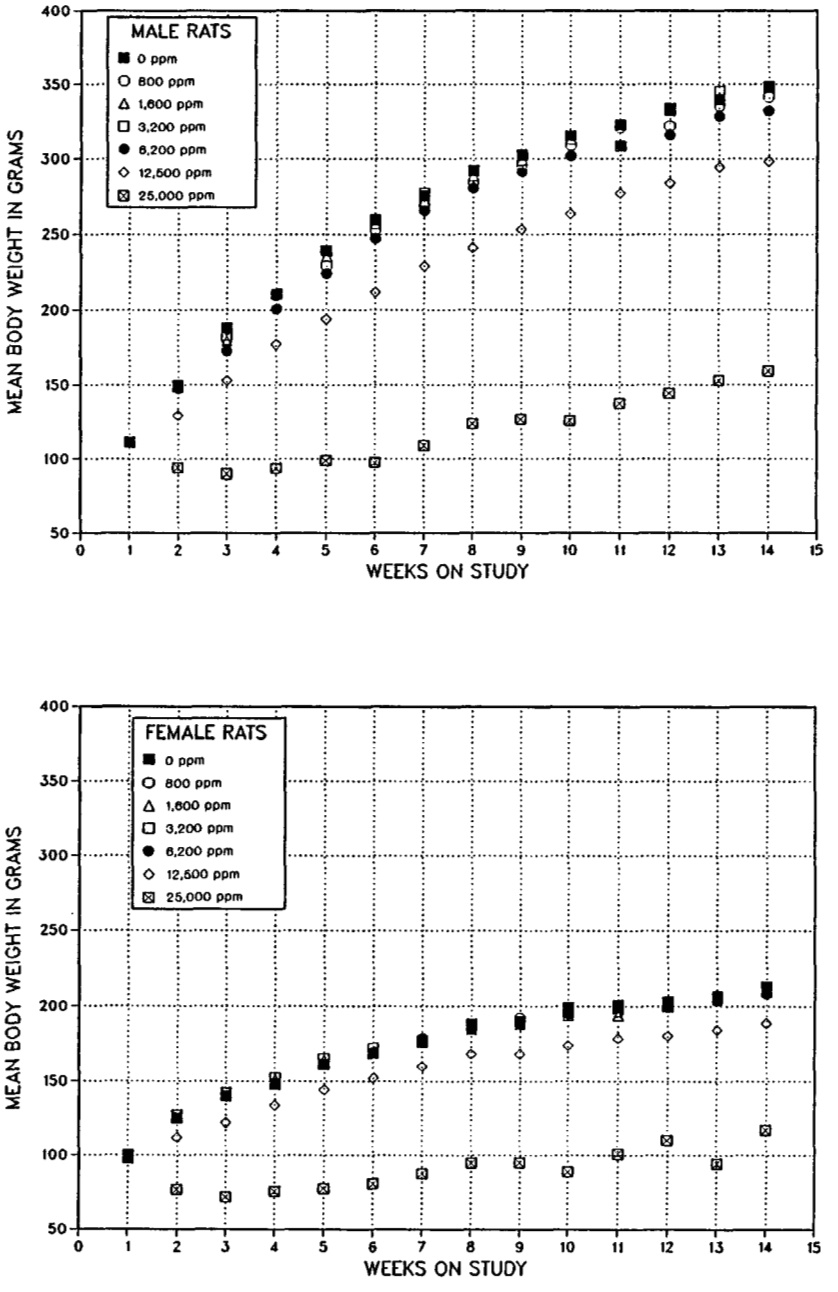


FIGURE 2
Growth Curves for Rats Given Feed Containing Acetaminophen for 13 Weeks

Feed consumption by rats receiving 25,000 ppm was lower than that of the controls through the sixth week of the study (males) and the fourth week of the study (females) and then rebounded to values greater than that of the controls for the remainder of the studies (Table 5). Feed consumption by rats receiving 800, 1,600, 3,200, 6,200, or 12,500 ppm acetaminophen was similar to that of the controls.

The absolute weight of several organs was decreased in the 12,500 and 25,000 ppm groups in accord with the lower body weights of the rats. Clinical findings noted during the study included smaller body size and dark yellow urine in the 12,500 and 25,000 ppm groups. Organ-weight-to-body-weight ratios were significantly increased for nearly all organs measured in the 25,000 ppm group and for several of the organs weighed in the 12,500 ppm group, most likely reflecting a greater effect of nutrient deficiency on the musculoskeletal system and body fat than on parenchymal organs. Significant compound-related increases in relative liver and kidney weights, which could not be attributed to lower mean body weights, were observed in the 800, 1,600, 3,200, and 6,200 ppm groups (Tables F1 and F2).

TABLE 5
Feed Consumption by Rats in the 13-Week Feed Studies of Acetaminophen[a]

Week on Study[b]	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
2	24.4	22.9	21.4	24.4	22.8	16.7	5.7
3	20.4	22.1	21.1	20.8	16.8	19.1	9.1
4	18.9	17.5	18.6	20.0	19.1	18.9	11.3
5	20.6	21.3	19.8	21.0	20.2	16.0	12.8
6	19.6	19.7	19.0	19.2	19.6	17.3	16.4
7	18.0	17.3	19.0	19.0	18.5	21.2	22.0
8	17.8	18.2	18.4	20.5	19.0	22.4	23.0
9	22.0	22.2	19.9	21.4	20.1	21.6	21.6
10	18.1	17.1	18.5	17.9	16.7	19.9	22.1
11	20.1	15.6	18.9	22.0	21.7	20.8	23.0
12	18.9	21.0	21.2	22.3	19.9	21.1	28.6
13	12.0	11.6	12.4	11.8	10.7	13.0	20.3
Female							
2	17.2	16.6	15.5	15.0	16.5	12.9	3.2
3	14.2	13.7	15.1	14.1	13.6	11.4	7.0
4	12.5	13.6	13.0	13.7	12.9	10.9	9.0
5	15.0	15.5	15.4	16.0	14.4	12.4	16.2
6	12.9	14.6	14.1	13.3	13.8	12.2	13.7
7	12.6	14.3	13.0	13.7	14.3	12.2	20.8
8	11.2	14.2	12.5	12.8	13.3	11.4	22.1
9	12.5	15.1	12.8	12.8	14.9	12.1	17.1
10	11.5	11.6	11.7	12.1	14.0	12.5	14.9
11	11.8	13.8	13.6	13.7	14.6	13.5	27.9
12	12.6	16.5	14.8	15.1	14.2	15.3	24.7
13	7.7	9.8	9.8	9.8	8.9	9.0	21.2

[a] Grams per animal per day
[b] Feed consumption inadvertently not recorded during first week of study

Lesions associated with administration of acetaminophen were observed in the liver, kidney, lymph nodes, reproductive organs, and thymus (Table 6).

Severe necrosis of hepatocytes involving all or most of the liver was observed in one 25,000 ppm male and two 25,000 ppm female rats; all three died before the end of the studies. Minimal to mild necrosis of individual or small clusters of hepatocytes adjacent to portal areas or vessels was observed in one high-dose male rat that died prior to study termination and in three high-dose females that survived to the end of the study. Chronic active inflammation of mild to moderate severity was seen in males and females that received 25,000 ppm and in males that received 12,500 ppm (Plate 1). These inflammatory lesions differed morphologically from the age-related lesions of minimal severity and were considered to be related to acetaminophen. In mildly affected livers, the inflammation occurred in scattered portal and perivascular areas while in more severely affected livers, larger numbers of portal areas were affected and the inflammation sometimes bridged adjacent portal areas. The inflammation was characterized by the accumulation of moderate numbers of mononuclear inflammatory cells and neutrophils that displaced adjacent hepatic cords. Inflammation was usually accompanied by proliferation of bile ducts, variable amounts of fibrosis, macrophages filled with fine golden pigment (presumably bile), and occasional scattered minute foci of mineralization. The inflammatory lesions and associated changes appeared to be secondary to hepatocellular necrosis. In addition to inflammation, minimal to moderate hepatocytomegaly (enlargement of hepatocytes) occurred in perivascular and periportal areas (Plate 2).

Hepatocytomegaly was characterized by hepatocytes with increased amounts of eosinophilic cytoplasm and sometimes enlarged or multiple nuclei. The lesion was present in scattered areas in minimally affected livers, and the number of areas involved increased with increasing severity of the lesion. With moderate hepatocytomegaly most portal areas and occasionally centrilobular hepatocytes were involved.

Acetaminophen-related effects were seen in the kidney of males and females fed 25,000 ppm diets. Minimal tubule regeneration was seen in several males from all dose groups and in a few females from most dose groups and the control group. This lesion consisted of scattered small tubules lined by small basophilic epithelial cells, typically accompanied by slight peritubular fibrosis and minimal mononuclear inflammatory cell infiltrate. The change was typical of that seen with the commonly occurring spontaneous age-related nephropathy of the F344/N rat and was not considered to be a compound-related effect. However, in approximately one half of the affected males and females from the 25,000 ppm groups, the severity of the lesion was noticeably greater. In these animals more tubules were involved, the amount of fibrosis and inflammation was greater than in the controls and low-dose animals, and neutrophils were present in the more severe lesions, suggestive of recent tissue damage. Moreover, one male and two females had tubule casts. These tubule casts consisted of proteinaceous or granular material within a few scattered tubules. One male rat had necrosis of the tubule epithelium.

Testicular atrophy was observed in all male rats that received 25,000 ppm and in one male from each of the 6,200 and 12,500 ppm groups. In the most severe cases, the lesion consisted of nearly complete loss of the germinal epithelium and was usually associated with complete absence of sperm in the epididymis. Atrophy of the uterus and ovary was observed in female rats that received 25,000 ppm. The atrophic ovaries were small and had fewer follicles and corpora lutea, while atrophic uteri appeared small on gross observation.

Minimal lymphocyte depletion of the thymus and lymph nodes was noted in several male and female rats from the 25,000 ppm groups. This change consisted of a slight loss of cortical lymphocytes. In some affected lymph nodes there was also a partial or total absence of observable lymphoid follicles. Lymphoid depletion was considered secondary to the severe weight depression in high-dose males and females.

Inflammation of the salivary gland (sialoadenitis) was seen in higher dose males and in high-dose females as well as in some controls. The lesion was compatible with infection by the sialodacryoadenitis virus and was not considered to be treatment related.

Dose Selection Rationale

The patterns of feed consumption and lower mean body weights in rats that received diets containing

TABLE 6
Incidences of Selected Lesions in Rats in the 13-Week Feed Studies of Acetaminophen[a]

Lesion	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
Liver							
Necrosis	0	0	0	0	0	0	2
Chronic active inflammation[b]	0	0	0	0	0	9**	10*
Hepatocytomegaly	0	0	0	0	0	6**	10*
Kidney							
Tubule regeneration	10 (1.0)	9 (1.0)	7 (1.0)	6 (1.0)	10 (1.0)	7 (1.0)	8 (1.6)
Tubule cast	0	0	0	0	0	0	1
Tubule necrosis	0	0	0	0	0	0	1
Testes							
Atrophy	0	0	0	0	1	1	10**
Thymus							
Lymphoid depletion	0[c]	0	0	0	0	0	7**
Lymph Node							
Lymphoid depletion	0	0	0	0	0	0	6**
Female							
Liver							
Necrosis	0	0	0	0	0	0	5*
Chronic active inflammation[b]	0	0	0	0	0	0	10**
Hepatocytomegaly	0	0	0	0	0	0	10**
Kidney							
Tubule regeneration	2 (1.0)	0	0	1 (1.0)	5 (1.0)	1 (1.0)	5 (2.4)
Tubule cast	0	0	0	0	0	0	2
Ovary							
Atrophy	0	0[c]	0	0	0	0	9**
Uterus							
Atrophy	0	0	0	0	0	0	7**[c]
Thymus							
Lymphoid depletion	0	0	0	0	0	0	1[d]
Lymph Node							
Lymphoid depletion	0	0	0	0	0	0	6**

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$
[a] Ten animals examined for each tissue unless otherwise indicated. Severity grades are given in parentheses; average severity grade of 1=minimal, 2=mild, 3=moderate.
[b] Diagnosed as postnecrotic cirrhosis by the study pathologist
[c] Nine animals examined
[d] Six animals examined

12,500 or 25,000 ppm acetaminophen were indicative of poor palatability. In addition, consumption of these diets induced compound-related toxic lesions in the liver. Therefore, both dietary concentrations had the potential to cause cumulative hepatotoxicity which could become life threatening in 2-year studies. Based on these results, dietary concentrations of 12,500 or 25,000 ppm acetaminophen were considered too high for the 2-year studies. At the next highest concentration used in the 13-week studies, 6,200 ppm, there was no evidence of poor feed palatability or frank liver toxicity; therefore, 6,000 ppm was selected as the high dose for the 2-year carcinogenicity studies. Because of the sharp dose response observed between 6,200 and 12,500 ppm, the cumulative nature of the hepatotoxicity observed in these studies, and the known hepatotoxicity of acetaminophen, doses intermediate between 6,200 and 12,500 ppm were not considered. The mid dose selected for rats was 3,000 ppm, one half the high dose, and a third dose of 600 ppm was selected to provide the possibility of extending dose response down to levels of potential human exposure.

2-Year Studies

Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of exposed rats were similar to those of the controls throughout the studies (Figure 3 and Tables 7 and 8). The average daily feed consumption of male and female rats in all dose groups was similar to that of the controls (Tables I1 and I2). The average amount of acetaminophen consumed per rat per day was approximately 30, 150, or 300 mg/kg for low-, mid-, or high-dose males, and 35, 160, or 320 mg/kg for low-, mid-, or high-dose females. There were no compound-related clinical findings.

Survival

Estimates of the probabilities of survival for male and female rats given feed containing acetaminophen and for controls are shown in Table 9 and in the Kaplan-Meier curves in Figure 4. Exposure to acetaminophen had no significant effect on survival.

Sentinel Animals

Positive serologic titers for rat coronavirus and sialodacryoadenitis virus (RCV/SDA) were found in sentinel animals at 6, 12, 18, and 24 months (Appendix K, Table K1). At 6 months, four of nine serum samples were positive for *Mycoplasma pulmonis*. Although the titers indicate exposure to these microbial agents, there was no clinical or histopathologic evidence of disease and no effect on body weight or survival.

15-Month Interim Evaluations

No neoplasms or evidence of chemical-related toxicity were observed in male or female rats after 15 months of exposure to acetaminophen. Increases in leukocytes, segmented neutrophils, and monocytes observed in high-dose females were considered incidental and not related to acetaminophen exposure (Table G1).

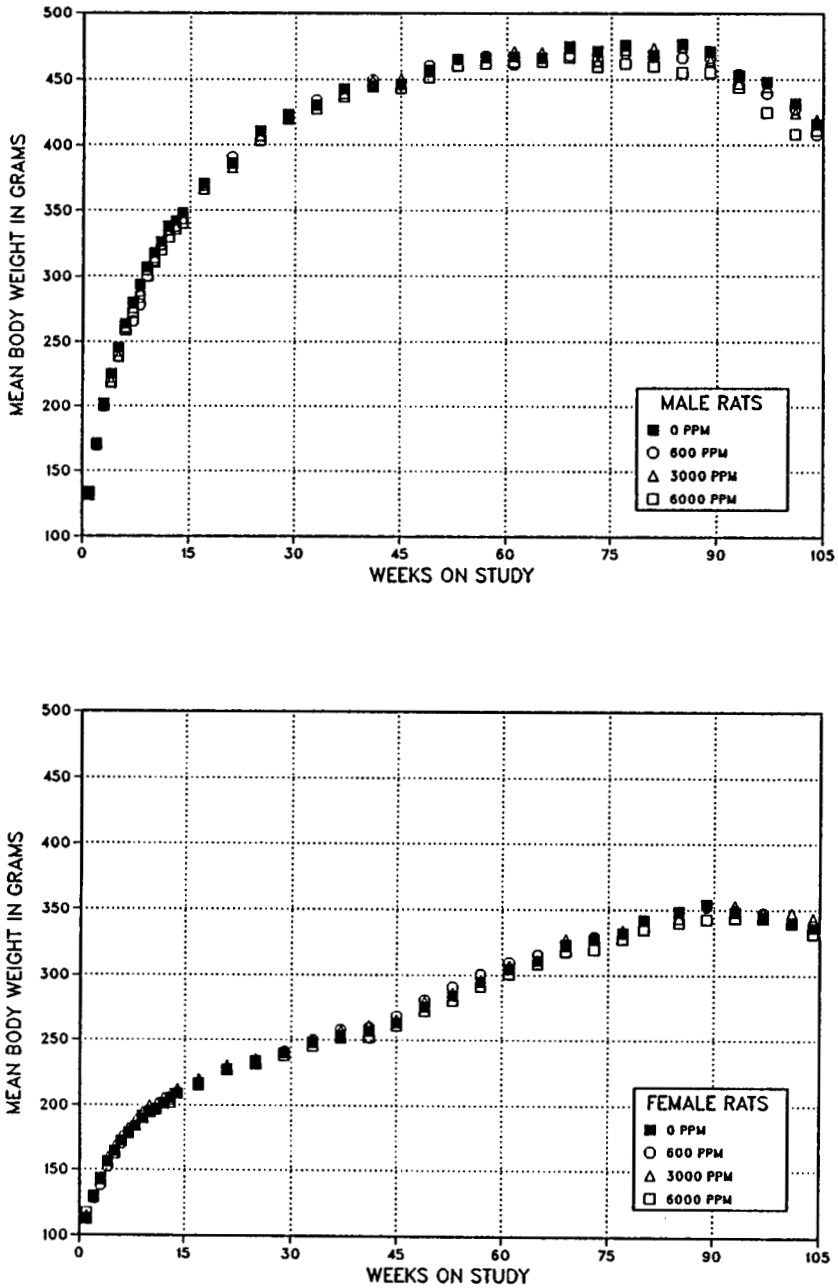


FIGURE 3
Growth Curves for Rats Given Feed Containing Acetaminophen for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Acetaminophen

Week on Study	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	134	60	133	100	60	132	99	60	134	100	60
2	171	60	169	99	60	170	99	60	171	100	60
3	202	60	200	99	60	201	100	60	200	99	60
4	225	60	222	99	60	219	97	60	218	97	60
5	246	60	243	99	60	239	97	60	238	97	60
6	264	60	261	99	60	261	99	60	259	98	60
7	280	60	266	95	60	276	98	60	272	97	60
8	294	60	279	95	60	289	98	60	284	97	60
9	307	60	300	98	60	305	99	60	300	98	60
10	318	60	312	98	60	314	99	60	310	98	60
11	326	60	323	99	60	324	99	60	319	98	60
12	339	60	335	99	60	335	99	60	330	97	60
13	342	60	338	99	60	338	99	60	336	98	60
14	348	60	344	99	60	344	99	60	340	98	60
17	371	60	369	100	60	366	99	60	366	99	60
21	386	60	391	101	60	383	99	60	386	100	60
25	411	60	407	99	60	407	99	60	404	98	60
29	423	60	422	100	60	420	99	60	420	99	60
33	430	60	434	101	60	431	100	60	427	99	60
37	442	60	442	100	60	439	99	60	436	99	60
41	444	60	449	101	60	449	101	60	445	100	60
45	447	60	446	100	60	451	101	60	443	99	59
49	457	60	460	101	60	456	100	60	452	99	59
53	465	60	465	100	60	466	100	60	460	99	59
57	466	60	468	100	60	468	100	60	462	99	59
61	467	60	461	99	60	471	101	60	463	99	59
65	466	60	466	100	60	471	101	59	463	99	58
69[a]	475	49	468	99	50	475	100	48	466	98	48
73	471	49	464	99	50	463	98	46	460	98	48
77	476	48	470	99	49	472	99	45	462	97	47
81	469	48	467	100	48	474	101	44	460	98	47
85	477	44	466	98	46	475	100	43	455	96	41
89	471	43	466	99	43	465	99	43	455	97	38
93	453	37	454	100	40	447	99	36	444	98	35
97	448	33	439	98	36	444	99	32	425	95	32
101	432	32	428	99	33	424	98	30	408	96	30
104	416	27	408	98	31	419	101	24	411	99	25
Mean for weeks											
1-13	265		260	98		262	99		259	98	
14-52	416		416	100		415	100		412	99	
53-104	461		456	99		460	100		450	98	

[a] Interim evaluation occurred

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Acetaminophen

Week on Study	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	112	60	113	100	60	115	102	60	117	104	60
2	129	60	128	99	60	130	101	60	130	101	60
3	143	60	138	96	60	145	101	60	142	99	60
4	156	60	152	98	60	160	102	60	156	100	60
5	164	60	162	99	60	168	103	60	162	99	60
6	172	60	170	99	60	176	102	60	172	98	60
7	178	60	177	100	60	182	103	60	179	101	60
8	184	60	184	100	60	189	103	60	184	100	60
9	190	60	190	100	60	195	103	60	191	101	60
10	195	60	195	100	60	200	103	60	194	99	60
11	197	60	196	100	60	202	102	60	197	100	60
12	202	60	202	100	60	206	102	60	201	100	60
13	206	60	204	99	60	209	102	60	202	98	60
14	209	60	210	100	60	213	102	60	209	100	60
17	217	60	217	100	60	220	101	60	215	99	60
21	227	60	228	100	60	230	102	60	227	100	60
25	234	60	233	100	60	236	101	60	232	99	60
29	240	60	241	100	60	242	101	60	238	99	60
33	248	60	250	101	60	250	101	60	245	99	60
37	253	60	258	102	60	258	102	60	252	99	59
41	257	60	260	101	60	262	102	60	252	98	59
45	263	60	269	102	60	266	101	60	261	99	58
49	276	60	281	102	60	280	102	60	272	99	58
53	285	60	291	102	60	287	101	60	281	99	57
57	295	59	300	102	60	296	100	59	291	99	57
61	305	58	310	102	60	308	101	59	301	99	57
65	311	58	316	101	60	312	100	59	309	99	57
69[a]	323	48	322	100	50	328	101	48	318	98	47
73	327	47	329	101	44	328	100	47	320	98	46
77	332	46	332	100	48	324	101	45	328	99	45
80	342	46	342	100	48	343	100	44	335	98	44
85	349	43	348	100	45	344	99	43	340	98	42
89	354	41	353	100	45	354	100	39	343	97	40
93	348	39	350	100	41	354	102	38	344	99	36
97	344	35	348	101	39	348	101	38	345	100	32
101	341	32	341	100	36	348	102	36	340	100	29
104	336	31	338	101	34	344	102	34	332	99	28
Mean for weeks											
1-13	171		170	99		175	102		171	100	
14-52	242		245	101		246	101		240	99	
53-104	328		330	101		330	101		323	99	

[a] Interim evaluation occurred

Table 9
Survival of Rats in the 2-Year Feed Studies of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Male				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10	10
Natural deaths	1	2	2	4
Moribund	22	20	25	22
Animals surviving until study termination	27	28	23	24
Percent survival at end of study	54	56	46	48
Survival analysis[b]	P=0.348	P=0.846N	P=0.548	P=0.631
Female				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10	10
Natural deaths	6	4	3	
Moribund kills	14	12	13	22
Animals surviving until study termination[c]	30	34	34	28
Percent survival at end of study	60	68	68	56
Survival analysis[b]	P=0.433	P=0.469N	P=0.590N	P=0.754

[a] Censored from survival analysis.
[b] The entry in the control column is the trend test result (Tarone, 1975). Subsequent entries are the results of pairwise tests (Cox, 1972). A lower mortality in a dose group is indicated by N.
[c] Includes animals that died the last week of study

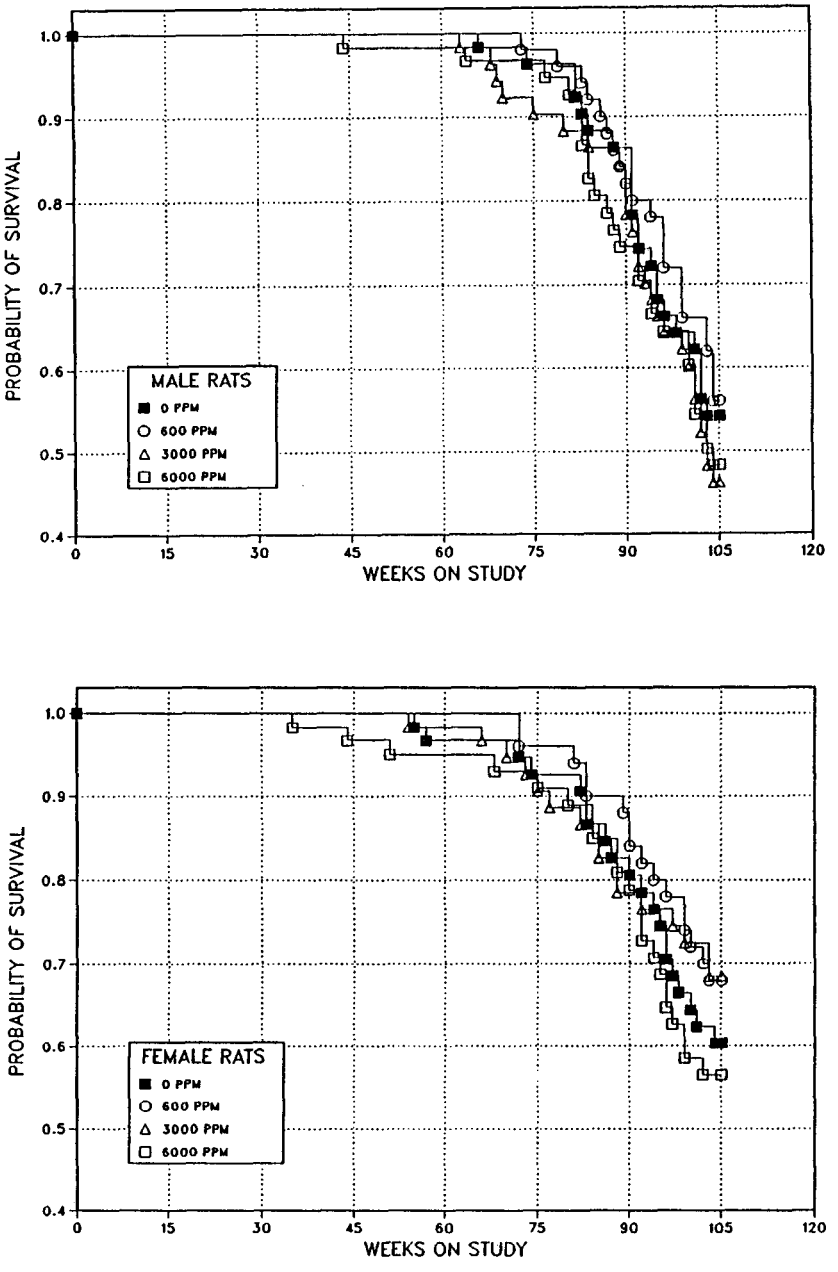


FIGURE 4
Kaplan-Meier Survival Curves for Rats Given Feed Containing Acetaminophen for 2 Years

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the hematopoietic system, liver, kidney, parathyroid gland, and Zymbal's gland in rats.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms occurring with an incidence of at least 5% in at least one animal group, and historical control incidences for selected neoplasms discussed in this section are presented in Appendixes A for male rats and B for female rats.

Hematopoietic System: The incidence of mononuclear cell leukemia occurred with a significant positive trend in female rats, and the incidence in the high-dose group was significantly greater than that of the controls (Table 10). The historical control incidence of mononuclear cell leukemia in untreated female rats for the study laboratory is 16.5% (range 6% to 28%); and for all NTP studies is 20.8% (range 6% to 40%; Table B4a). The incidences of mononuclear cell leukemia decreased slightly in exposed male rats (Table A1). Mononuclear cell leukemia is generally thought to originate in the spleen. As the disease progresses, neoplastic cells enter the vascular system and accumulate in other organs. The liver is usually the first extrasplenic site involved, and this is usually followed by involvement of the lung and lymph node. In advanced cases, practically any tissue can be involved. In some organs, particularly those that are highly vascular such as the lung, neoplastic involvement often consists primarily of the filling of blood vessel lumens with neoplastic cells. In solid organs, such as the pancreas or uterus, involvement usually consists of accumulation of neoplastic cells within the organ parenchyma with subsequent replacement of normal tissues. Table 11 shows the organ distribution of mononuclear cell leukemia in both control and acetaminophen-exposed females; for each dose group the degree of involvement of organs in addition to liver and spleen is indicated.

In the present study neoplastic cells were present in the liver and spleen of all control and exposed female rats diagnosed with mononuclear cell leukemia. In those animals with more advanced leukemia, neoplastic cells were present in a variety of other organs as well; lung and lymph node were commonly involved, but adrenal gland, heart, pancreas, thymus, stomach, uterus, and occasionally other organs were also sometimes affected. Leukemia in control females was predominantly confined to the liver and the spleen; the proportion of females with neoplastic cells in two or more organs, in addition to the liver and spleen, was increased in the exposed groups.

TABLE 10
Incidence of Mononuclear Cell Leukemia in Female Rats in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Overall rates[b]	9/50 (18%)	17/50 (34%)	15/50 (30%)	24/50 (48%)
Adjusted rates[c]	26.4%	42.8%	35.1%	56.3%
Terminal rates[d]	6/30 (20%)	12/34 (35%)	8/34 (24%)	10/28 (36%)
First incidence (days)	575	581	485	554
Life table tests[e]	P=0.003	P=0.116	P=0.188	P=0.003
Logistic regression test[e]	P=0.003	P=0.070	P=0.120	P=0.001

[a] 2-year historical incidence for untreated controls at study laboratory (mean): 66/399 (16.5%); 2-year historical incidence for untreated control groups in NTP studies (mean ± SD): 425/2,043 (20.8% ± 8.1%)
[b] Number of neoplasm-bearing animals/number of animals examined at site
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal.

TABLE 11
Organ Distribution of Mononuclear Cell Leukemia in Female F344/N Rats in the 2-Year Feed Study of Acetaminophen

Affected Organs and Tissue	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Liver and spleen only	4/9 (44%)	1/17 (6%)	3/15 (20%)	1/24 (4%)
One additional tissue	2/9 (22%)	0/17 (0%)	0/15 (0%)	2/24 (8%)
Two or more additional tissues	3/9 (33%)	16/17 (94%)	12/15 (80%)	21/24 (88%)

Liver: The incidence of basophilic foci of the liver was decreased in high-dose female rats (control, 38/50; low dose, 39/50; mid dose, 32/50; high dose, 20/50) (Table B5), and the incidence of granulomas was decreased in mid-dose and high-dose female rats (26/50; 15/50; 7/50; 8/50) (Table B1). Both lesions are commonly observed in aging F344/N rats and these decreases most likely were secondary to the increased incidence of mononuclear cell leukemia in exposed females. Leukemic infiltrate can fill liver sinusoids and cause degenerative changes in hepatocytes, which can obscure other lesions. Hepatocellular adenomas were observed in one low-dose and one mid-dose male rat (Table A1).

Kidney: The severity of nephropathy was significantly increased in exposed male rats. There was a nonsignificant increase in the severity of nephropathy in exposed female rats (Table 12). Nephropathy was typical of the spontaneously occurring lesion in aging F344/N rats. It consisted of a spectrum of lesions including varying degrees of tubule dilatation and distortion with occasional cyst formation; proteinaceous tubule casts; atrophy, regeneration, and hypertrophy of tubule epithelium; thickening of tubule and glomerular basement membranes; interstitial fibrosis; scattered foci of suppurative inflammation, primarily within degenerate tubules; and a scattering of varying numbers of mononuclear inflammatory cells within the interstitium. Regenerating tubule epithelial cells had basophilic nuclei and scant cytoplasm and formed a single cell layer. Severity was graded by the amount of renal parenchyma affected, as shown in Table 12.

Hyperplasia of the renal tubule epithelium occurred at slightly higher incidences in exposed male rats than in controls (Table 12). The incidence of renal tubule adenomas in exposed male rats was similar to that of the controls; a tubule adenoma occurred in one high-dose female rat (Table B1). Tubule cell hyperplasias in male rats were focal lesions characterized by increased numbers of tubule epithelial cells forming multiple layers which partially or totally filled the tubule lumen and sometimes caused slight dilation of the tubule. The hyperplastic cells generally resembled normal tubule epithelial cells. Compared with tubule hyperplasia, tubule adenomas were large, expansile nodules, generally greater than five tubule diameters in size, and consisted of large polygonal cells with abundant eosinophilic cytoplasm and large, pale-staining nuclei.

Parathyroid Gland: Hyperplasia of the parathyroid gland, characterized by bilateral diffuse enlargement of the gland, occurred with a dose-related increase in male rats (control, 0/42; low dose, 4/45; mid dose, 6/46; high dose, 8/45) (Table A5). Hyperplasias occurred in animals with marked nephropathy with the exception of one mid-dose and one high-dose animal, which had moderate nephropathy. The increased incidence of parathyroid gland hyperplasia was considered to be secondary to the increased severity of nephropathy in treated males.

Zymbal's Gland: Zymbal's gland carcinomas (Table 13) occurred in mid- and high-dose male rats and in one high-dose female rat. The historical control incidence of Zymbal's gland carcinomas for untreated rats in the study laboratory is 0.3% (range 0% to 2%) for males (Table A4b) and 0% for females (Table B4b). The historical control incidence for all NTP studies in males is 0.8% (range 0% to 8%), and in females 0.4% (range 0% to 4%).

TABLE 12
Kidney Lesions in Rats in the 2-Year Feed Studies of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Male				
Renal Tubule Epithelium: Hyperplasia				
Overall rates[a]	1/50 (2%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Nephropathy: Severity[b]				
Minimal (Grade 1)	6/50 (12%)	5/50 (10%)	7/50 (14%)	4/50 (8%)
Mild (Grade 2)	27/50 (54%)	19/50 (38%)	12/50 (24%)	12/50 (24%)
Moderate (Grade 3)	13/50 (26%)	19/50 (38%)	23/50 (46%)	21/50 (42%)
Marked (Grade 4)	4/50 (8%)	7/50 (14%)	8/50 (16%)	12/50 (24%)
Average severity grade	2.30	2.56*	2.64*	2.78*
Renal Tubule: Adenoma[c]				
Overall rates	3/50 (6%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rates[d]	11.1%	0.0%	13.0%	12.5%
Terminal rates[e]	3/27 (11%)	0/28 (0%)	3/23 (13%)	3/24 (13%)
First incidence (days)	729 (T)	–[f]	729 (T)	729 (T)
Logistic regression tests[g]	P=0.220	P=0.113N	P=0.589	P=0.610
Female				
Nephropathy: Severity				
Minimal (Grade 1)	30/50 (60%)	31/50 (62%)	23/50 (46%)	16/50 (32%)
Mild (Grade 2)	13/50 (26%)	10/50 (20%)	15/50 (30%)	15/50 (30%)
Moderate (Grade 3)	4/50 (8%)	4/50 (8%)	7/50 (14%)	8/50 (16%)
Marked (Grade 4)	1/50 (2%)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Average severity grade	1.44	1.58	1.64	1.72

* Significantly different (P≤0.05) from the control group by the Mann-Whitney U test
(T)Terminal sacrifice
[a] Number of animals with lesion or neoplasm/number of animals examined at site
[b] Number of animals with severity grade/number of animals examined. Severity grade was based on percent renal parenchyma involved: Minimal - usually less than 20% of cortex; mild - 20%-50% of cortex; moderate - 50%-75% of cortex; marked - greater than 75% of cortex
[c] 2-year historical incidence in untreated control groups at study laboratory (mean): 4/348 (1.1%); 2-year historical incidence for untreated control groups in NTP studies (mean ± SD): 12/1,990 (0.6% ± 1.3%)
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Not applicable; no neoplasms in animal group
[g] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. For all tests, a lower incidence in a dose group is indicated by N.

TABLE 13
Incidence of Zymbal's Gland Carcinoma in Male F344/N Rats in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Overall rates[b]	0/50 (0%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted rates[c]	0.0%	0.0%	10.4%	6.4%
Terminal rates[d]	0/27 (0%)	0/28 (0%)	1/23 (4%)	1/24 (4%)
First incidence (days)	–[f]	–	471	586
Logistic regression tests[e]	P=0.137	–	P=0.096	P=0.247

[a] 2-year historical incidence for untreated control groups at study laboratory (mean): 1/350 (0.3%); 2-year historical incidence for untreated control groups in NTP studies (mean ± SD): 16/1,996 (0.8% ± 1.3%)
[b] Number of neoplasm-bearing animals/number of animals examined at site
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.
[f] Not applicable; no neoplasms in animal group

MICE

14-Day Studies

All mice survived to the end of the studies (Table 14). Final mean body weights for exposed males and females were similar to those of the controls. Feed consumption in all exposed groups was greater than in the controls. No compound-related lesions were found at necropsy; no histopathology was performed.

TABLE 14
Survival, Mean Body Weights, and Feed Consumption of Mice in the 14-Day Feed Studies of Acetaminophen

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Control (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	23.7 ± 0.24	26.0 ± 0.45	2.3 ± 0.31		4.9	4.9
250	5/5	23.6 ± 0.32	25.3 ± 0.35	1.7 ± 0.17	97	5.5	5.9
500	5/5	24.4 ± 0.59	26.6 ± 0.36	2.2 ± 0.33	102	5.1	6.2
1,000	5/5	23.7 ± 0.21	26.6 ± 0.32	2.9 ± 0.33	102	5.1	5.8
2,000	5/5	23.6 ± 0.19	27.4 ± 0.49	3.8 ± 0.42	105	5.6	5.5
4,000	5/5	23.9 ± 0.35	25.8 ± 0.38	1.8 ± 0.59	99	5.1	5.7
Female							
0	5/5	19.5 ± 0.07	21.1 ± 0.30	1.6 ± 0.32		4.1	3.9
250	5/5	19.2 ± 0.20	21.0 ± 0.25	1.8 ± 0.21	100	5.4	6.4
500	5/5	19.0 ± 0.09	21.0 ± 0.24	2.0 ± 0.30	100	5.3	6.1
1,000	5/5	20.0 ± 0.52	21.4 ± 0.17	1.4 ± 0.55	101	5.7	5.9
2,000	5/5	19.4 ± 0.17	21.0 ± 0.30	1.6 ± 0.33	100	5.3	6.6
4,000	5/5	19.4 ± 0.14	21.3 ± 0.32	1.9 ± 0.28	101	7.5	9.1[d]

[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error. Differences from the control group are not significant by Dunn's or Shirley's test
[c] Grams per animal per day, based on average consumption data
[d] Food scratched out of hopper

13-Week Studies

One male and one female receiving 25,000 ppm and two males receiving 12,500 ppm acetaminophen died in the first week of the studies and one male receiving 3,200 ppm died during week 6 (Table 15). One female from each of the 0, 800, and 6,200 ppm groups was killed during week 2 of the study due to pregnancy.

Mean body weights of male and female mice that received 25,000 ppm and male mice that received 12,500 ppm decreased from their initial values during the first week of the study and then began to increase (Figure 5); however, mean body weights of male and female mice that received 12,500 and 25,000 ppm remained lower than those of the controls throughout the remainder of the study.

TABLE 15
Survival and Mean Body Weights of Mice in the 13-Week Feed Studies of Acetaminophen

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	23.6 ± 0.34	32.0 ± 0.48	8.4 ± 0.35	
800	10/10	24.0 ± 0.35	32.9 ± 0.66	9.0 ± 0.49	103
1,600	10/10	23.7 ± 0.34	31.5 ± 0.42	7.8 ± 0.28	98
3,200	9/10[c]	23.6 ± 0.36	32.9 ± 0.65	9.3 ± 0.62	103
6,200	10/10	23.6 ± 0.35	32.0 ± 0.70	8.5 ± 0.52	100
12,500	8/10[d]	23.9 ± 0.43	29.8 ± 0.79*	5.9 ± 0.63**	93
25,000	9/10[d]	23.8 ± 0.43	27.9 ± 0.25**	4.0 ± 0.45**	87
Female					
0	9/10[e]	19.2 ± 0.37	27.8 ± 0.79	8.6 ± 0.62	
800	9/10[e]	19.0 ± 0.39	27.5 ± 0.85	8.5 ± 0.68	99
1,600	10/10	19.1 ± 0.38	28.9 ± 1.16	9.7 ± 0.95	104
3,200	10/10	19.3 ± 0.34	28.1 ± 0.85	8.8 ± 0.67	101
6,200	9/10[e]	18.9 ± 0.32	27.7 ± 0.93	8.7 ± 0.74	100
12,500	10/10	19.4 ± 0.29	24.8 ± 0.70*	5.4 ± 0.50**	89
25,000	9/10[d]	19.4 ± 0.46	23.4 ± 0.54**	4.0 ± 0.36**	84

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 6
[d] Week of death: 1
[e] Killed week 2 due to pregnancy.

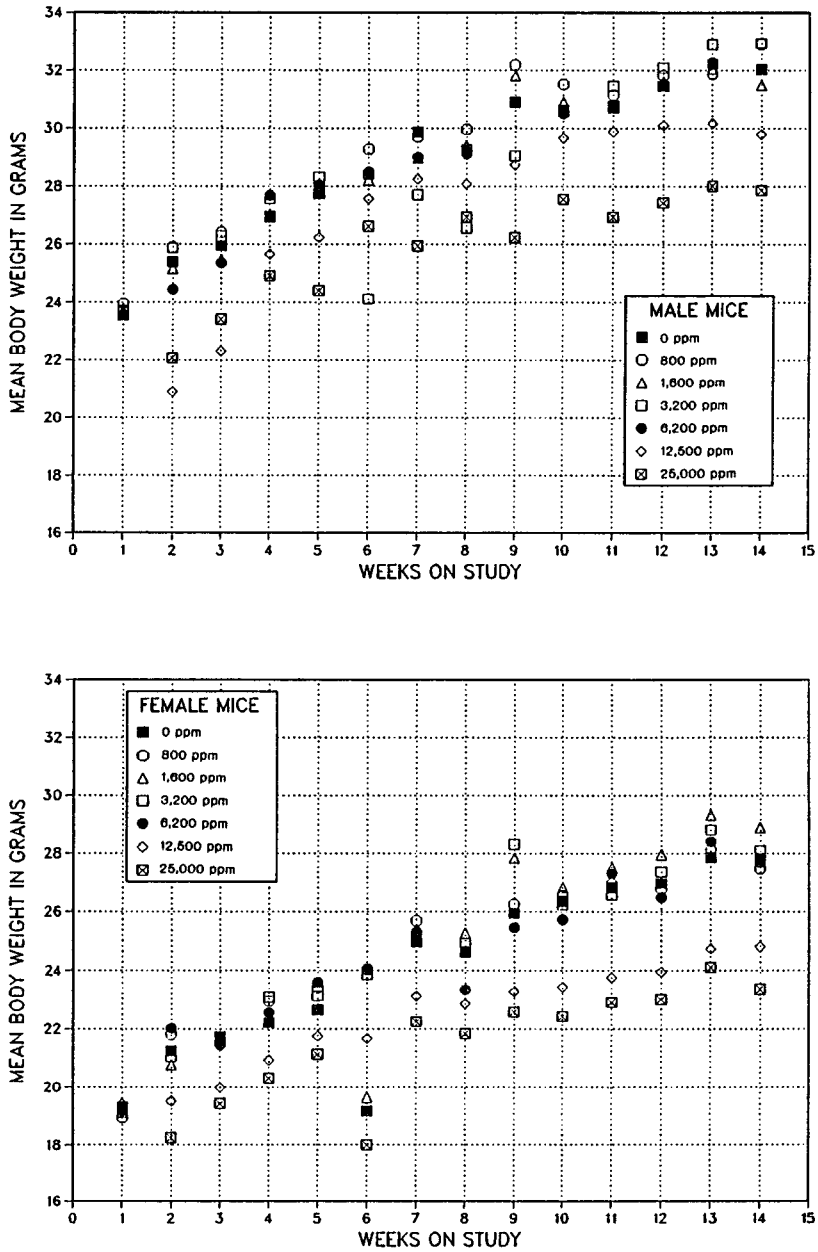


FIGURE 5
Growth Curves for Mice Given Feed Containing Acetaminophen for 13 Weeks

Feed consumption by male and female mice that received 6,200, 12,500, or 25,000 ppm acetaminophen was less than that of the controls during the first week of the study (Table 16). However, beginning at week 2, feed consumption by male and female mice receiving 12,500 or 25,000 ppm was greater than that of the controls and remained greater than that of the controls throughout the remainder of the study. These results are indicative of poor palatability and feed wastage at the 12,500 and 25,000 ppm dose levels. The only compound-related clinical finding was dark urine, which was observed among animals that received the 25,000 ppm diet.

Reductions in absolute liver and heart weights in males and females in the 25,000 ppm group and of liver weights of females in the 12,500 ppm group were most likely a result of the lower final mean body weights of these groups (Table F3). Final mean body weights of mice receiving 12,500 or 25,000 ppm were significantly lower than those of the controls. Relative brain and testis weights were increased in male mice that received 25,000 ppm and relative brain, heart, and kidney weights were increased in females that received 12,500 or 25,000 ppm. Because of the poor feed palatability of the diets at the 12,500 and 25,000 ppm dose levels, these increases were

TABLE 16
Feed Consumption by Mice in the 13-Week Feed Studies of Acetaminophen[a]

Week on Study	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
1	5.4	5.4	5.1	5.2	4.5	2.6	2.6
2	5.4	5.3	5.2	5.0	5.1	7.9	12.8
3	5.5	5.6	5.7	5.4	5.6	12.4	11.5
4	5.9	5.6	7.2	6.3	5.5	11.9	12.3
5	5.6	5.7	6.0	5.7	5.8	9.1	14.8
6	6.1	6.1	6.0	8.2	5.8	11.4	13.0
7	5.2	6.1	5.6	6.1	5.8	10.0	11.7
8	5.8	6.9	7.8	9.6	6.3	12.7	14.0
9	4.1	4.8	5.3	7.9	5.1	8.6	9.1
10	5.2	5.4	6.6	7.0	5.8	10.6	11.5
11	5.6	6.3	5.8	6.5	6.1	10.1	11.1
12	4.4	4.3	4.3	4.7	4.0	7.1	7.5
13	5.5	5.9	6.0	6.4	5.6	12.1	11.3
Female							
1	5.3	5.3	3.6	4.8	3.9	2.4	2.6
2	6.5	5.4	5.5	5.3	4.7	8.7	12.2
3	6.3	5.4	5.5	6.0	5.4	8.0	10.7
4	6.5	6.5	5.6	6.0	6.0	8.6	11.6
5	5.4	6.5	4.3	5.8	6.8	8.3	9.5
6	11.1	6.7	11.1	5.9	7.7	11.6	16.1
7	6.4	6.2	6.2	5.9	6.6	9.8	9.2
8	6.2	6.3	5.7	6.4	7.2	11.8	11.8
9	5.3	5.5	4.8	4.6	5.6	7.9	7.8
10	5.6	6.1	5.4	5.8	7.8	7.8	10.9
11	6.0	6.8	6.1	6.8	6.7	10.1	10.0
12	4.5	4.5	4.5	4.5	5.3	7.0	7.4
13	6.9	6.6	5.9	6.3	6.6	13.0	10.7

[a] Grams per animal per day

attributed to a relatively greater effect of reduced nutrient intake on the musculoskeletal system and body fat than on parenchymal organs. Relative kidney weights were also increased in 6,200 ppm females; since body weights and feed consumption of this group were similar to those of the controls, the increase in relative kidney weights is considered a chemical-related effect (Table F4).

Histopathologic lesions of the liver occurred in male mice that received diets containing 6,200, 12,500, or 25,000 ppm acetaminophen and in female mice that received 12,500 or 25,000 ppm (Table 17). The animals that died within the first week of the study had severe coagulation necrosis of hepatocytes which occasionally was confined to centrilobular areas but usually involved entire lobules or clusters of adjacent lobules. The other liver lesions observed in animals surviving to the end of the study included minimal to moderate cytomegaly (cellular enlargement) of centrilobular hepatocytes (Plate 3) with occasional karyomegaly (nuclear enlargement). The enlarged hepatocytes often extended between centrilobular areas, and affected hepatocytes had abundant finely granular eosinophilic cytoplasm. A number of the animals also had large cells filled with pale, yellow-brown pigment (Plate 4) or minute bits of mineral (focal calcification) adjacent to portal areas or beneath the liver capsule.

TABLE 17
Incidences of Selected Liver Lesions in Mice in the 13-Week Feed Studies of Acetaminophen

	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
Number examined	10	10	10	10	10	10	10
Hepatocytomegaly	0	0	0	0	3	8**	9**
Focal calcification	0	0	0	0	0	4*	4*
Pigmentation	0	0	0	0	1	3	6**
Necrosis	0	0	0	0	0	3	1
Female							
Number examined	9	9	10	10	9	10	10
Hepatocytomegaly	0	0	0	0	0	0	4*
Focal calcification	0	0	0	0	0	1	1
Pigmentation	0	0	0	0	0	3	4*
Necrosis	0	0	0	0	0	0	1

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$

Dose Selection Rationale

The patterns of feed consumption and body weight changes observed among 12,500 and 25,000 ppm mice during the 13-week studies were indicative of poor feed palatability. Treatment-related histopathologic lesions were present in the livers of male mice that received 6,200, 12,500, or 25,000 ppm and female mice that received 12,500 or 25,000 ppm and were considered responsible for the death of one male and one female that received 25,000 ppm and one male that received 12,500 ppm. Based on these results, dietary concentrations of 12,500 or 25,000 ppm were considered life threatening for 2-year studies. Minimal hepatocytomegaly was present in the livers of three male mice that received 6,200 ppm; however, the potential for this lesion to become life threatening in a 2-year study was considered small. In addition, no liver lesions were observed in females that received 6,200 ppm. Therefore, 6,000 ppm was selected as the high dose and 3,000 ppm as the mid dose for the 2-year studies in mice. A low dose of 600 ppm was included to extend the range of possible dose response to concentrations which approximate those of potential human exposure.

2-Year Studies

Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of exposed mice were generally lower than those of the controls throughout the studies (Tables 18 and 19 and Figure 6). The average daily feed consumption of male and female mice in all dose groups was similar to that of the controls (Tables I3 and I4). The average amount of acetaminophen consumed per mouse per day was approximately 90, 450, or 1,000 mg/kg for low-, mid-, or high-dose males and 110, 600, or 1,200 mg/kg for low-, mid-, or high-dose females. No chemical-related clinical findings were observed.

Survival

Survival of male and female mice receiving acetaminophen was similar to that of the controls. Estimates of the probabilities of survival are shown in Table 20 and in the Kaplan-Meier curves in Figure 7.

Sentinel Animals

Positive serologic titers for mouse hepatitis virus were detected in 5 of 10 serum samples at 24 months; however, there was no clinical evidence of disease associated with infection. In other NTP studies, subclinical infection with this virus was shown to have no effect on body weight, survival, or neoplasm incidence (Rao *et al.*, 1989).

15-Month Interim Evaluations

No neoplasms or evidence of compound-related toxicity were observed in mice after 15 months of acetaminophen exposure. Changes in hematologic parameters did not show any obvious relation to chemical exposure and were considered incidental (Table G2).

TABLE 18
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Acetaminophen

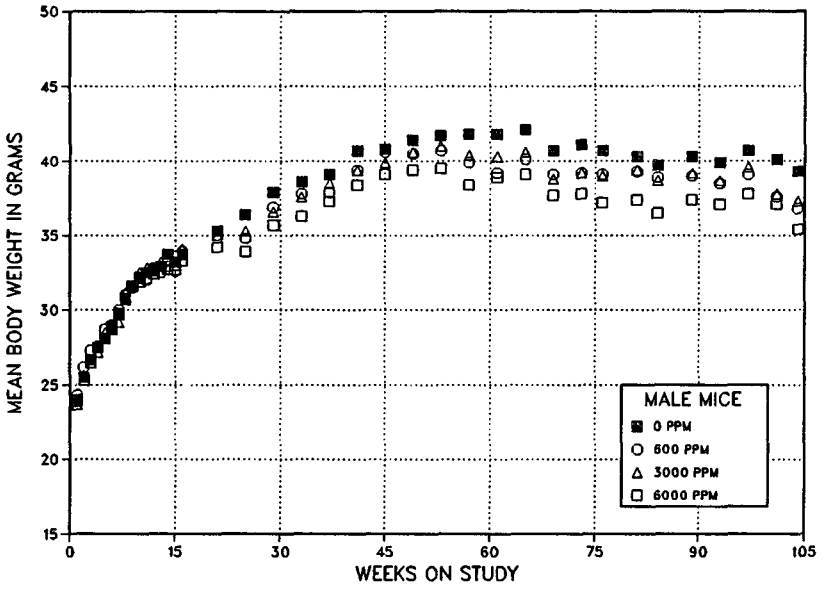
Week on Study	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.0	60	24.3	101	60	23.7	99	60	23.9	100	60
2	25.5	60	26.2	103	60	25.7	101	60	25.3	99	59
3	26.7	60	27.3	102	60	26.5	99	60	26.5	99	59
4	27.5	60	27.6	100	60	27.2	99	60	27.5	100	59
5	28.1	60	28.7	102	60	28.5	101	60	28.1	100	59
6	28.9	60	29.0	100	60	28.8	100	60	28.7	99	59
7	29.8	60	30.0	101	60	29.2	98	60	29.7	100	59
8	30.8	60	31.0	101	60	31.2	101	60	30.7	100	59
9	31.6	60	31.5	100	60	31.7	100	60	31.6	100	59
10	32.2	60	32.1	100	60	32.5	101	60	31.9	99	59
11	32.5	60	32.0	99	60	32.8	101	60	32.1	99	59
12	32.7	60	32.8	100	59	32.6	100	60	31.8	97	59
13	32.9	60	32.5	99	59	33.2	101	60	32.4	99	58
14	33.7	60	32.9	98	58	32.7	97	60	32.7	97	58
15	33.2	60	32.6	98	58	33.0	99	60	32.7	99	58
16	33.7	60	33.9	101	57	34.1	101	60	33.3	99	58
21	35.3	60	35.0	99	56	35.0	99	60	34.2	97	58
25	36.4	60	34.7	95	56	35.3	97	60	33.9	93	57
29	37.9	59	36.8	97	56	36.6	97	60	35.7	94	57
33	38.6	59	37.8	98	56	37.6	97	60	36.3	94	57
37	39.1	59	37.9	97	56	38.5	99	60	37.3	95	57
41	40.7	58	39.4	97	56	39.4	97	60	38.4	94	57
45	40.8	57	40.6	100	56	39.9	98	60	39.1	96	56
49	41.4	57	40.5	98	56	40.6	98	60	39.4	95	56
53	41.7	57	40.7	98	56	41.0	98	60	39.5	95	56
57	41.8	57	39.9	96	56	40.4	97	60	38.4	92	56
61	41.8	56	39.2	94	56	40.3	96	60	38.9	93	54
65	42.1	56	40.1	95	54	40.6	96	60	39.1	93	54
69[a]	40.7	45	39.1	96	44	38.8	95	49	37.7	93	44
73	41.1	44	39.2	95	43	39.2	95	49	37.8	92	44
76	40.7	44	39.1	96	43	39.0	96	47	37.2	91	42
81	40.3	43	39.3	98	43	39.4	98	47	37.4	93	42
84	39.7	40	38.9	98	43	38.7	98	46	36.5	92	40
89	40.3	40	39.0	97	43	39.2	97	45	37.4	93	39
93	39.9	39	38.5	97	43	38.7	97	44	37.1	93	37
97	40.7	35	39.1	96	40	39.6	97	36	37.8	93	35
101	40.1	34	37.6	94	40	37.8	94	33	37.1	93	35
104	39.3	32	36.8	94	40	37.3	95	31	35.4	90	31
Mean for weeks											
1-13	29.5		29.6	101		29.5	100		30.0	99	
14-52	37.4		36.1	98		36.6	98		35.6	97	
53-104	40.7		39.0	96		39.3	97		37.7	93	

[a] Interim evaluation occurred.

TABLE 19
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Acetaminophen

Week on Study	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.2	60	19.1	100	60	18.7	97	60	18.9	98	60
2	19.8	60	19.3	98	60	19.3	98	60	19.4	98	60
3	21.0	60	20.9	100	60	21.2	101	56	20.9	100	60
4	20.7	60	20.5	99	60	20.7	100	56	20.7	100	60
5	22.5	60	22.7	101	60	22.9	102	56	22.3	99	60
6	22.6	60	22.7	100	60	23.1	102	56	22.5	100	60
7	23.3	60	22.5	97	60	23.4	100	56	23.3	100	60
8	23.7	60	23.9	101	60	23.8	100	56	23.6	100	60
9	24.4	60	24.8	102	60	25.5	105	56	23.2	95	60
10	23.9	60	24.3	102	60	24.4	102	56	24.0	100	60
11	24.6	60	25.1	102	60	24.7	100	56	24.5	100	60
12	25.5	60	25.6	100	60	25.1	98	56	24.9	98	60
13	26.2	60	26.0	99	60	25.1	96	56	25.0	95	60
17	27.7	60	27.9	101	60	27.0	98	56	26.9	97	60
21	29.6	60	29.8	101	60	28.6	97	56	29.2	99	60
25	31.5	60	30.7	98	60	30.4	97	56	30.3	96	60
29	33.0	60	32.3	98	60	32.1	97	56	31.5	96	60
33	35.2	60	34.4	98	60	34.8	99	56	33.7	96	60
37	37.0	60	36.4	98	60	35.6	96	56	36.4	98	59
41	39.2	60	37.2	95	60	37.3	95	56	37.5	96	59
45	40.8	60	38.7	95	60	38.5	94	56	39.8	98	59
49	42.0	60	40.0	95	60	40.4	96	56	39.9	95	59
53	43.5	60	40.7	94	60	39.9	92	56	40.8	94	59
57	43.1	60	40.1	93	60	40.7	94	56	41.0	95	59
61	44.9	59	41.3	92	60	41.3	92	55	41.7	93	59
65	44.1	59	41.8	95	59	42.7	97	55	43.0	98	59
69[a]	44.7	49	42.6	95	48	42.1	94	45	42.3	95	49
73	45.3	48	43.4	96	48	42.5	94	43	42.6	94	49
77	46.1	47	43.7	95	47	42.8	93	42	43.4	94	48
81	46.7	43	45.0	96	44	43.3	93	37	43.2	93	47
85	46.8	42	44.6	95	44	43.2	92	37	43.5	93	46
89	46.1	41	44.0	95	42	40.4	88	35	42.4	92	44
93	46.5	37	45.2	97	38	41.4	89	33	44.1	95	39
97	46.5	34	44.9	97	35	41.6	90	31	45.2	97	38
101	46.0	33	44.4	97	32	41.0	89	29	45.2	98	38
104	46.0	28	43.5	95	32	40.4	88	26	43.9	95	38
Mean for weeks											
1-13	22.9		22.9	100		22.9	100		22.6	99	
14-52	35.1		34.2	98		33.9	97		33.9	97	
53-104	45.5		43.2	95		39.1	92		43.0	95	

[a] Interim evaluation occurred.



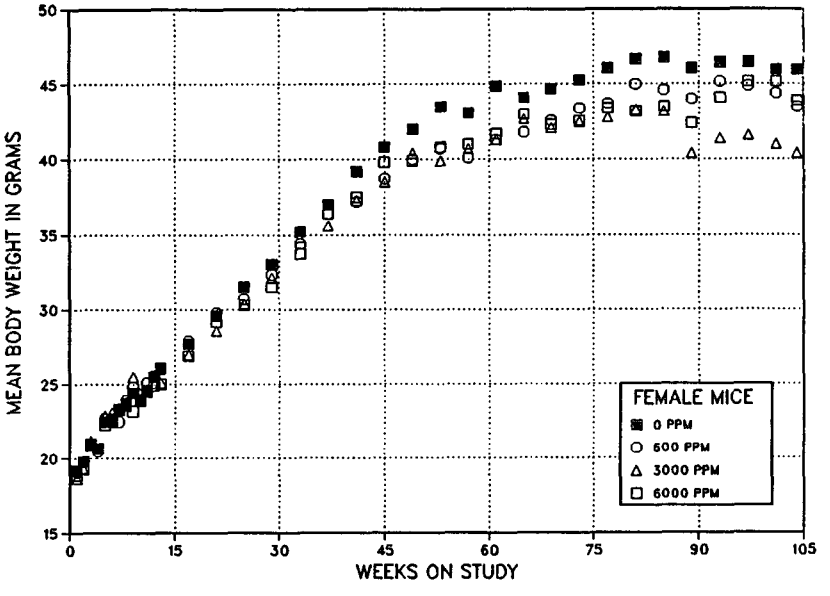


FIGURE 6
Growth Curves for Mice Given Feed Containing Acetaminophen for 2 Years

TABLE 20
Survival of Mice in the 2-Year Feed Studies of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Male				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10	10
Natural deaths	5	7	3	9
Moribund kills	13	3	16	10
Animals surviving until study termination	32	40	31	31
Percent survival at end of study	64	80	62	62
Survival analyses[b]	P=0.292	P=0.152N	P=1.000N	P=0.942
Female				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10	10
Natural deaths	2	9		4
Moribund kills	21	9	21	8
Accidental deaths[a]			4	
Animals surviving until study termination	27	32	25	38
Percent survival at end of study	54	64	50	76
Survival analyses[b]	P=0.105N	P=0.477N	P=0.935	P=0.053N

[a] Censored from survival analyses
[b] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. For all tests, a negative trend or a lower mortality in a dose group is indicated by N.

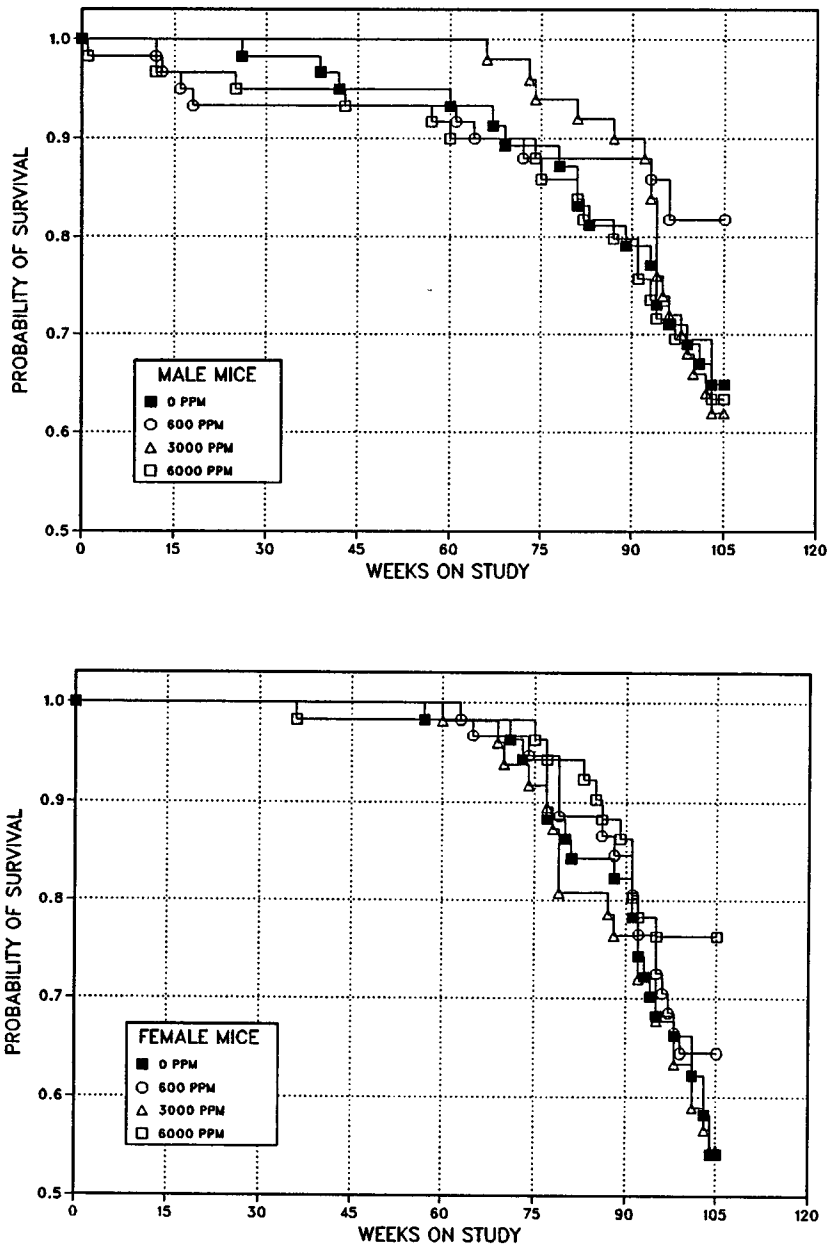


FIGURE 7
Kaplan-Meier Survival Curves for Mice Given Feed Containing Acetaminophen for 2 Years

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the thyroid gland and kidney in mice.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms occurring with an incidence of at least 5% in at least one animal group, and historical control incidences for selected neoplasms discussed in this section are presented in Appendix C for male mice and D for female mice.

Thyroid Gland: The incidence of hyperplasia of thyroid follicular cells was increased in exposed male and female mice (Table 21). The incidence of follicular cell neoplasms was not increased in male mice. In female mice, follicular cell adenomas occurred in several treated mice, but not in controls. The historical control incidence of thyroid neoplasms in female mice from the study laboratory is 1.3% (range 0% to 10%; Table C4) and, for all NTP studies, 2.8% (range 0% to 15%; Table D4).

Follicular cell hyperplasia and neoplasia represent a morphologic continuum. Hyperplasia involved multiple scattered follicles and was characterized by slightly enlarged follicles that were lined by large cuboidal to low-columnar epithelium that sometimes projected, to varying degrees, into the follicular lumen (Plate 5). Areas of hyperplasia were poorly demarcated and blended with the surrounding parenchyma. Adenomas were discrete, well-demarcated nodular masses that compressed the adjacent parenchyma (Plate 6). Cells within adenomas generally appeared relatively well differentiated, sometimes occurred in multiple layers, and often formed complex papillary or follicular structures. Carcinomas had less discrete borders, sometimes showing localized invasion, and were composed of follicular cells that exhibited cellular atypia and pleomorphism and a tendency to grow in solid clusters or sheets.

Kidney: A renal tubule cell adenoma occurred in one low-dose and one high-dose male mouse (Table C1). Renal tubule hyperplasia occurred in one low-dose and in two high-dose males (Table C5). No neoplasms or hyperplasias of the renal tubules were observed in female mice (Tables D1 and D5).

GENETIC TOXICOLOGY

The results of the NTP short-term genotoxicity tests with acetaminophen indicate that this chemical is not a gene mutagen in bacteria, but induces chromosomal effects in mammalian cell cultures. Acetaminophen was not mutagenic when tested in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 at concentrations of 100 to 10,000 μg/plate with a preincubation protocol in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983; Table E1). In cytogenicity tests with Chinese hamster ovary cells, acetaminophen induced sister chromatid exchanges (Table E2) and chromosomal aberrations (Table E3) in both the presence and absence of Aroclor 1254-induced Sprague-Dawley rat liver S9. In the sister chromatid exchange test, positive responses were observed over a concentration range of 5 to 150 μg/mL in the absence of S9; with S9, only the highest dose tested, 5,000 μg/mL, produced a significant increase in sister chromatid exchanges. In the chromosomal aberration test without S9, acetaminophen concentrations of 1,257 to 5,000 μg/mL produced highly significant increases in the percentage of aberrant cells, with some dose levels showing over 40% aberrant cells; a delayed harvest protocol was used to offset acetaminophen-induced cell cycle delay and allow accumulation of sufficient metaphases for analysis. With S9, only the 5,000 μg/mL dose level produced a significant increase in aberrations.

TABLE 21
Incidences of Thyroid Gland Nonneoplastic Lesions and Neoplasms in Mice in the 2-Year Feed Studies of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Male				
Follicular Cell Hyperplasia				
Overall rates[a]	0/49 (0%)	6/49 (12%)	12/50 (24%)	15/50 (30%)
Adjusted rates[b]	0.0%	15.0%	37.4%	45.4%
Terminal rates[c]	0/32 (0%)	6/40 (15%)	11/31 (35%)	13/31 (42%)
First incidence (days)	–[e]	729 (T)	695	715
Logistic regression tests[d]	P<0.001	P=0.032	P<0.001	P<0.001
Follicular Cell Adenoma				
Overall rates	2/49 (4%)	1/49 (2%)	2/50 (4%)	1/50 (2%)
Follicular Cell Carcinoma				
Overall rates	1/49 (2%)	0/49 (0%)	1/50 (2%)	0/50 (0%)
Follicular Cell Adenoma or Carcinoma[f]				
Overall rates	3/49 (6%)	1/49 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates	9.4%	2.5%	9.0%	3.2%
Terminal rates	3/32 (9%)	1/40 (3%)	2/31 (6%)	1/31 (3%)
First incidence (days)	729 (T)	729 (T)	666	729 (T)
Logistic regression tests	P=0.401N	P=0.229N	P=0.641N	P=0.316N
Female				
Follicular Cell Hyperplasia				
Overall rates	2/48 (4%)	8/50 (16%)	11/50 (22%)	25/50 (50%)
Adjusted rates	6.0%	23.6%	44.0%	67.6%
Terminal rates	0/0	0/0	0/0	0/1 (0%)
First incidence (days)	611	549	730 (T)	730 (T)
Logistic regression tests	P<0.001	P=0.085	P=0.004	P<0.001
Follicular Cell Adenoma				
Overall rates	0/48 (0%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Follicular Cell Carcinoma				
Overall rates	0/48 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Follicular Cell Adenoma or Carcinoma[g]				
Overall rates	0/48 (0%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rates	0.0%	3.1%	8.0%	5.4%
Terminal rates	0/27 (0%)	1/32 (3%)	2/25 (8%)	2/37 (5%)
First incidence (days)	–[e]	730 (T)	730 (T)	730 (T)
Logistic regression tests	P=0.229	P=0.534	P=0.221	P=0.310

(T)Terminal sacrifice

[a] Number of animals with lesion or neoplasm/number of animals examined at site

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

[c] Observed incidence at terminal kill

[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Not applicable; no lesions in animal group

[f] 2-year historical incidence for untreated control groups at study laboratory (mean): 10/473 (2.1%); 2-year historical incidence for untreated control groups in NTP studies (mean ± SD): 43/2,149 (2.0% ± 2.2%) (includes one papillary adenoma)

[g] 2-year historical incidence for female untreated control groups at study laboratory (mean): 6/469 (1.3%); 2-year historical incidence for female untreated control groups in NTP studies (mean ± SD): 59/2,134 (2.8% ± 3.4%)

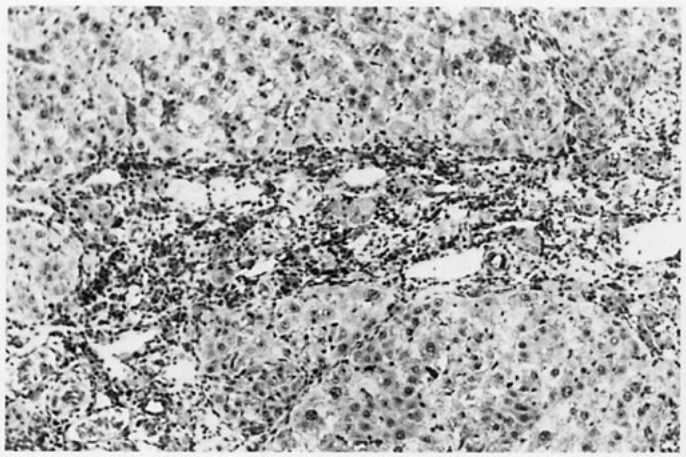


PLATE 1
Chronic active inflammation in the liver of an F344/N rat receiving 25,000 ppm acetaminophen in the 13-week feed study. Infiltrate of inflammatory cells extends between portal areas and displaces hepatocytes. H&E, 100×

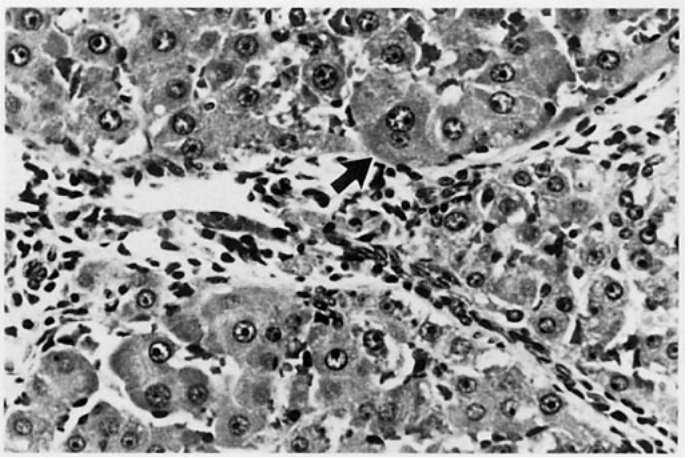


PLATE 2
Hepatocytomegaly (enlargement) of periportal hepatocytes (arrow) in the liver of an F344/N rat receiving 25,000 ppm acetaminophen in the 13-week feed study. H&E, 300×

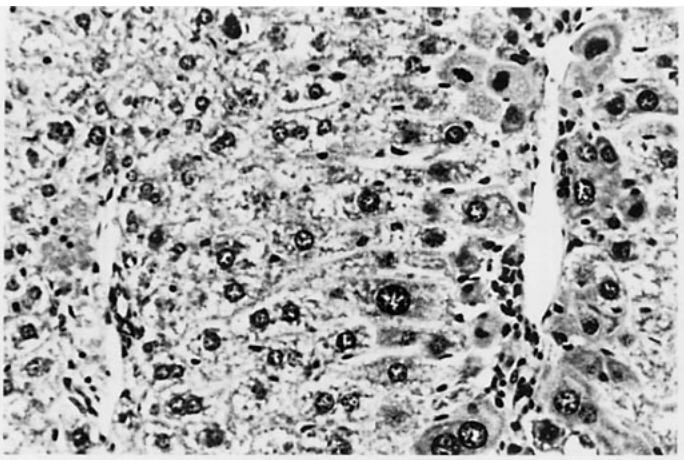


PLATE 3
Hepatocytomegaly of centrilobular hepatocytes in the liver of a B6C3F$_1$ mouse receiving 25,000 ppm acetaminophen in the 13-week feed study. Hepatocytes surrounding the central vein (right side of field) are considerably enlarged compared with those adjacent to the portal area (left side of field). H&E, 240×

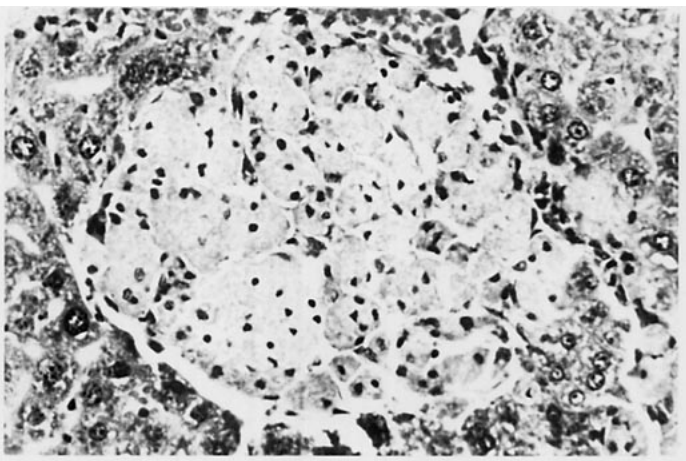


PLATE 4
Cluster of pigment containing macrophages in the liver of a B6C3F$_1$ mouse receiving 12,500 ppm acetaminophen in the 13-week feed study. H&E, 300×

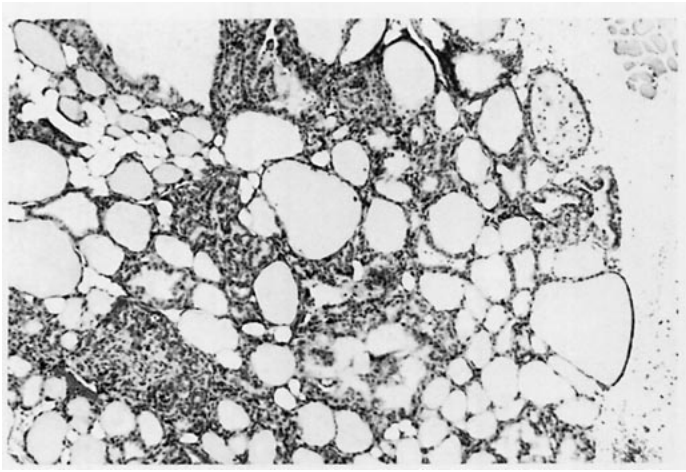


PLATE 5
Follicular cell hyperplasia in the thyroid gland of a $B6C3F_1$ mouse receiving 6,000 ppm acetaminophen in the 2-year feed study. H&E, 75×

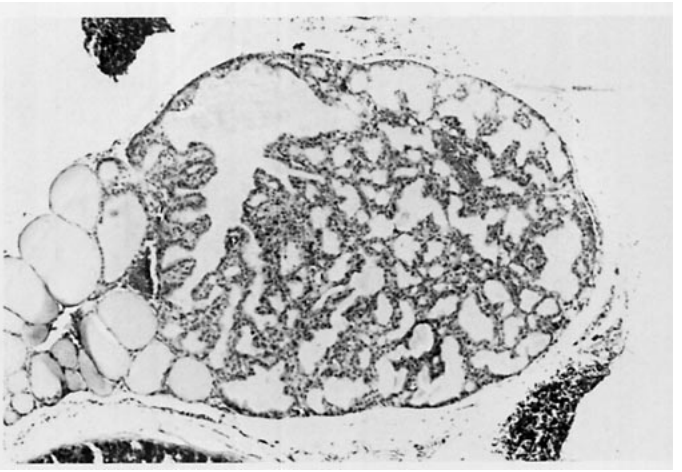


PLATE 6
Follicular cell adenoma in the thyroid gland of a $B6C3F_1$ mouse receiving 3,000 ppm acetaminophen in the 2-year feed study. H&E, 60×

DISCUSSION AND CONCLUSIONS

Acetaminophen is the active component of several over-the-counter nonsteroidal analgesic/antipyretic preparations. Since being approved for nonprescription pharmaceutical preparations in 1960, acetaminophen has come into widespread use as an aspirin substitute. Because of this significant and continuing human consumption and the desire for more information concerning the risks associated with long-term exposure, acetaminophen was evaluated for carcinogenic potential in F344/N rats and B6C3F$_1$ mice.

In 13-week studies, consumption of diets containing 25,000 ppm acetaminophen was associated with reduced survival, reduced mean body weights, and increased incidences of toxic lesions in both rats and mice. The deaths that occurred prior to the end of the study in animals that received 25,000 ppm were attributed to complications associated with acetaminophen-related hepatotoxicity. Reduced mean body weights and increased incidences in hepatotoxic lesions also occurred in groups that received 12,500 ppm acetaminophen. Although intraperitoneal administration of acetaminophen at relatively high doses (250 to 900 mg/kg) to F344/N rats results in loss of renal function and induces severe renal tubule necrosis within 24 hours (Newton *et al.*, 1983), there was little indication of nephrotoxicity in rats and no indication of nephrotoxicity in mice in the present 13-week studies.

Testicular atrophy was present in male rats and atrophy of the uterus and ovaries was observed in female rats that received 25,000 ppm acetaminophen. Testicular atrophy and impaired spermatogenesis in acetaminophen-exposed male rats has been reported previously (Jacqueson *et al.*, 1984). However, it is unclear from the present 13-week studies whether the uterine and ovarian atrophy observed at the 25,000 ppm level is the result of a direct toxic effect of acetaminophen on these organs or whether the atrophy is a consequence of reduced body weight.

Feed consumption and body weight data indicated poor palatability of the 25,000 ppm diet for both rats and mice and of the 12,500 ppm diet for mice. This was particularly evident during the first 2 weeks of the 13-week studies, during which time groups receiving 12,500 or 25,000 ppm consumed less feed than controls and actually lost weight. It was unclear from the 13-week studies whether the mean body weights of animals receiving the 25,000 or 12,500 ppm diets would eventually achieve control weights.

Reduced feed consumption and lower mean body weights have been reported in other studies involving dietary exposure to acetaminophen. Groups of 20 male Sprague-Dawley rats were given diets containing 0, 5,000, 10,000, or 15,000 ppm acetaminophen for 12 weeks. Mean body weights of groups that received 10,000 or 15,000 ppm acetaminophen were depressed 27% or 50% after 6 weeks of exposure, and 21% or 51% after 12 weeks. Moreover, feed consumption by groups that received 10,000 or 15,000 ppm diets was less than that of controls: the consumption by 15,000 ppm rats was 37% lower than that by controls after 6 weeks and 21% lower after 12 weeks (Johansson *et al.*, 1989).

In another study, administration of diets containing 5,000 or 10,000 ppm acetaminophen to male B6C3F$_1$ mice was associated with reduced weight gain; the groups that received 10,000 ppm acetaminophen had marked reductions in weight gain compared to controls (Hagiwara and Ward, 1986). Survival was also reduced in both groups during the first 16 weeks of the study, and by week 24, approximately 50% of the animals that received 10,000 ppm diets had died.

In the present 13-week studies of rats and mice, the dose response for reduced mean body weights and incidence of hepatotoxicity increased sharply above 6,200 ppm. There were indications of poor feed palatability with both 12,500 and 25,000 ppm diets, and dietary concentrations above 6,000 ppm were considered potentially toxic and perhaps life threatening in 2-year rat and mouse studies. Therefore 6,000 ppm was selected as the high dose and 3,000 ppm as the mid dose for the present 2-year studies. The low dose selected was 600 ppm; based on average feed consumption data for F344/N rats available at the start of the 2-year study, this dose provided the opportunity to extend the dose response for any observed lesions to levels approximating those

to which humans may be exposed. Chronic active hepatitis in humans has been associated with daily ingestion of 3 to 5 grams (50 to 70 mg/kg) of acetaminophen (Prescott, 1983) and long-term daily use has been associated with chronic renal disease (Sandler *et al.*, 1989).

In the current 2-year rat studies, mean body weights, feed consumption, and survival of males and females that received diets containing acetaminophen were similar to those of controls.

The incidence of mononuclear cell leukemia in female rats followed a significant dose-related increase among groups receiving acetaminophen. In the 6,000 ppm group, the incidence was significantly higher (48%) than control incidence and exceeds the historical control range for female rats (6%-40%). Moreover, the incidence in the concurrent controls (18%) was similar to the historical control rate for the study laboratory (16.5%) and the overall historical rate (20.8%), and the significance of the increase could not be attributed to a low control rate. The proportion of early death female rats diagnosed with leukemia also increased with dose: control, 15% (3/20); low dose, 31% (5/16); mid dose, 44% (7/16); high dose, 64% (14/22). Among all female rats with leukemia, the proportion dying prior to week 100 increased with dose: control, 22% (2/9); low dose, 24% (4/17); mid dose, 33% (5/15); high dose, 58% (14/24). On average, leukemias were detected one month earlier in the high-dose group than in the controls, suggesting a shortening of neoplasm latency. In addition there was an increase in the extent of multiple organ involvement in the organ distribution of mononuclear cell leukemia in groups of exposed female rats compared to controls (Table 11).

Although these results support an association between exposure to acetaminophen and increased incidences of mononuclear cell leukemia, there are also a number of factors which argue against this association. The incidence of mononuclear cell leukemia in male rats decreased with dose and therefore did not support the increase observed in females. Mononuclear cell leukemia is a fatal neoplasm, and the increased incidence and earlier appearance in the exposed groups might be expected to be accompanied by reduced survival; however, the total number of female rats dying or killed moribund was similar among exposed and control groups, indicating that the increased incidence of leukemia was not associated with increased mortality. And finally, the relatively high spontaneous rate of mononuclear cell leukemia and its variable incidence in controls increases the likelihood that such differences in neoplasm incidence among groups could occur by chance.

The NTP staff originally proposed that the mononuclear cell leukemia in female rats be interpreted as "*some evidence of carcinogenic activity.*" In reviewing the study, the Board of Scientific Counselors Peer Review Panel also noted the generally high and variable background rate of this neoplasm in Fischer rats, and the lack of concordance of this study result with a lifetime study of acetaminophen in Fischer rats in Japan (see commentary on pages 10-11). Thus the Panel voted to adopt a conclusion of "*equivocal evidence of carcinogenic activity*" of acetaminophen in female rats.

The severity of nephropathy increased with dose among groups of exposed male rats and was significantly greater in all groups of exposed male rats than in controls. The severity of nephropathy in female rats also increased with dose but the increase was not as great as that observed in males; it could be argued that females might have tolerated higher dietary concentrations of acetaminophen. However, the steep dose response above 6,200 ppm, which includes poor feed palatability, reduced body weights, and evidence of hepatotoxicity associated with consumption of the 12,500 ppm diet, is an indication that doses higher than 6,000 ppm would have resulted in more severe nephropathy in the 2-year studies. This suggests that female rats would probably not have tolerated a doubling of the 6,000 ppm dietary concentration. Therefore, 6,000 ppm was considered an adequate high dose for rats in the 2-year studies.

Nephropathy is an age-related degenerative disease commonly observed in rats, and the chemical-related exacerbation observed in the present studies is consistent with the demonstrated nephrotoxicity of acetaminophen. The dose-dependent increase in parathyroid hyperplasia observed in male rats is an indication that nephropathy was severe enough to significantly compromise renal function. Hyperparathyroidism frequently accompanies severe nephropathy in rats because the progressive loss of renal function disrupts calcium and phosphorus homeostasis, leading to prolonged stimulation of the parathyroid gland with resulting hyperplasia and

elevated secretion of parathyroid hormone. Severe exacerbation of nephropathy induced by chemical exposure is life threatening and has been the cause of reduced survival among exposed rats in several NTP 2-year studies.

The increased severity of nephropathy in male rats was accompanied by an increased incidence of focal hyperplasia of the renal tubule epithelium; however, no increase in tubule cell neoplasms was observed. In addition, there were no renal transitional cell neoplasms or preneoplastic lesions in male or female rats.

In studies conducted with F344/N and Sprague-Dawley rats, administration of acetaminophen at doses up to 15,000 ppm in feed was not associated with increased incidences of kidney or bladder neoplasms (Johansson, 1981; Hiraga and Fuji, 1985). Moreover, in a recent study reported by Johansson *et al.* (1989) administration of diets containing 10,000 or 15,000 ppm phenacetin or antipyrine to Sprague-Dawley rats caused a marked increase in proliferation of the urothelium as determined by ^{3}H-thymidine pulse labeling index. Acetaminophen at the same dietary concentrations also increased urothelial cell proliferation but the increase was less than half that observed for phenacetin or antipyrine. Rats that received 15,000 ppm diets of antipyrine or acetaminophen exhibited renal papillary necrosis. Flaks *et al.* (1985) fed Leeds rats diets containing 5,000 or 10,000 ppm acetaminophen. The incidence of neoplastic liver nodules increased in both male and female rats that received 10,000 ppm diets and the incidence of bladder neoplasms increased in both sexes that received 5,000 or 10,000 ppm diets; however, no increase in the incidence of renal lesions was reported.

Dysplasia of the urothelium and transitional cell neoplasms of the kidney and bladder have been associated with nephropathy in humans resulting from chronic exposure to phenacetin or phenacetin-containing analgesic mixtures (IARC, 1987). Phenacetin also induces neoplasms of the bladder and renal pelvis in Sprague-Dawley rats. Although Sandler *et al.* (1989) have found an association between daily use of acetaminophen and an increased risk of chronic renal disease in humans, no association between acetaminophen use and increased risk of renal cancer has been observed.

Zymbal's gland carcinomas occurred in four male rats that received 3,000 ppm, two male rats that received 6,000 ppm, and one female rat that received 6,000 ppm; none were observed in the control or low-dose groups. However, the incidence did not follow a clear dose response and there was no indication of any chemically induced toxicity to the Zymbal's gland or of an increased incidence of preneoplastic lesions. Moreover, the incidences in males were within the range (0% to 8%) observed in groups of untreated controls.

Increased incidences of Zymbal's gland neoplasms have occurred in nine previous NTP 2-year dosed feed studies: 3-amino-9-ethylcarbazole hydrochloride (NCI, 1978a), C.I. Basic Red 9 monohydrochloride (NTP, 1986), cupferron (NCI, 1978b), 2,4-diaminoanisole sulfate (NCI, 1978c), 3,3′-dimethoxybenzidine dihydrochloride (NTP, 1990), hydrazobenzene (NCI, 1978d), 5-nitroacenaphthene (NCI, 1978e), 5-nitro-*o*-anisidine (NCI, 1978f), and 4,4′-thiodianiline (NCI, 1978g). In these studies the incidences of Zymbal's gland neoplasms were increased in both male and female rats. In addition, these compounds are aromatic amino or nitro compounds that are bacterial mutagens, exhibit carcinogenic activity at sites other than the Zymbal's gland in rats, and are carcinogenic in mice.

Although acetaminophen is an aromatic amino compound, it was not mutagenic in bacteria, the incidence of Zymbal's gland neoplasms in male rats was not dose related, and the sexes responded unequally. Therefore both the genotoxic and carcinogenic activity of acetaminophen in the present study differ from the results with other aromatic amino/nitro compounds; the increased incidences of Zymbal's gland neoplasms in male and female rats were not considered related to acetaminophen exposure.

In the study reported by Hiraga and Fuji (1985) male F344 rats received diets containing 0, 4,500, or 9,000 ppm acetaminophen, and female rats received diets containing 0, 6,500, or 13,000 ppm acetaminophen for 2 years. No compound-related effects were noted in the Zymbal's gland, in the kidney, or in the incidence of mononuclear cell leukemia. One papilloma, one adenocarcinoma, and three squamous cell carcinomas of the Zymbal's gland occurred in control males, but no Zymbal's gland neoplasms were observed in exposed rats of

either sex. The incidence of mononuclear cell leukemia in females was 14%, 24%, and 20% in the control, low-dose, and high-dose groups, and in males, 24%, 18%, and 16%; there was no dose-related increase in the incidence of mononuclear cell leukemia. A renal tubule adenoma occurred in one high-dose male, a transitional cell carcinoma of the bladder occurred in another high-dose male, and a transitional cell carcinoma of the renal pelvis occurred in one high-dose female. Although the authors observed tubule cell hyperplasias in two high-dose male rats and one high-dose female, there was no discussion of any other nonneoplastic lesions which may have occurred, making it difficult to make a direct comparison to the present study.

Dietary exposure to these acetaminophen concentrations did not reduce survival or body weight gain of male rats (Hiraga and Fuji, 1985). However, significantly lower feed consumption was noted for low- and high-dose males during the first 3 weeks of the study. Mean body weights of 13,000 ppm female rats were slightly lower than those of controls throughout the entire study. The authors state that female rats receiving the 13,000 ppm diets consumed significantly less feed than controls for the first 23 weeks, indicating a potential palatability problem. Since no actual feed consumption data were included in the report, it is difficult to compare directly to the present study. However, if feed consumption by female rats receiving the 13,000 ppm diet was sufficiently low, it is possible that the actual amount of acetaminophen ingested by this group was similar to or only slightly greater than the amounts ingested by the 6,500 ppm group. This could account for the absence of hepatotoxicity in female rats after 2 years of exposure to a 13,000 ppm diet when 12,500 ppm in the present study induced obvious hepatotoxicity after 13 weeks. Moreover, since the dietary concentrations given to males (4,500 or 9,000 ppm) were lower than those given to females, even moderately lower feed consumption by males would mean that the actual exposures were comparable to those in the present study.

In the current 2-year mouse studies survival of males and females that received diets containing acetaminophen was similar to survival of controls. Mean body weights of exposed male mice were lower than mean body weights of controls throughout most of the study; mean body weights of males in the 6,000 ppm group were approximately 10% lower than the controls from week 70 to the end of the study. Mean body weights of female mice were also somewhat lower than those of the controls throughout most of the study, with the greatest difference observed in the group receiving the 3,000 ppm diet. Since feed consumption by all groups of mice was similar, the lower body weights of exposed groups were not related to palatability.

Renal tubule adenomas were present in one low-dose and one high-dose male mouse. These are uncommon neoplasms in male mice; none were diagnosed out of 1,650 untreated controls in the Carcinogenesis Bioassay Data System database, although a total of eight renal tubule carcinomas were found. In 519 control male mice from the eight most recently completed dosed feed studies, one tubule adenoma was observed. In the present studies, the incidence of neoplasms was not dose related since it was unchanged over a tenfold increase in dose, and the minimal renal tubule hyperplasia that occurred was not indicative of a chemically induced response. There was also no indication of nephrotoxicity. Therefore, because of the low incidence of proliferative lesions and absence of further indication of chemically related response in the kidney, these adenomas were not considered to be related to acetaminophen exposure.

The incidence of thyroid follicular cell hyperplasia increased markedly with dose in both male and female mice fed diets containing acetaminophen, and in groups that received 6,000 ppm the incidence was significantly greater than that of the controls. Although follicular cell neoplasms were present at low incidence in both control and exposed male and female mice, the incidence of these neoplasms appeared unrelated to the increased incidence in thyroid follicular cell hyperplasia. The incidence of hyperplasia increased from 12% to 30% in males and 16% to 50% in females over the dose range of 600 to 6,000 ppm (22 to 222 mg/kg body weight per day); the incidence of neoplasms in males was unaffected by exposure, and in females the incidence of neoplasms increased slightly from 1/50 in the low-dose group to 2/50 in the mid-dose and high-dose groups. Moreover, both neoplasms in high-dose female mice were adenomas; the only carcinoma occurred in a female from the 3,000 ppm group. The historical control incidence of combined thyroid neoplasms in female mice in dosed feed studies is 2.8%, with the range of control incidence being 0% to 15%. There-

fore the variability in the incidence of thyroid neoplasms observed among groups in the present study (0% to 4%) is well within the range of normal variation.

The thyroid hyperplasia observed in exposed mice is indicative of thyroid stimulation in response to a reduction in the level of circulating thyroid hormones. If thyroid stimulation is sustained for a sufficient period of time, it may cause the thyroid to enlarge, and eventually some hyperplasias may progress to neoplasms. However, the absence of thyroid enlargement, the focal nature of the hyperplasias, and the lack of convincing evidence supporting a progression from hyperplasia to neoplasia suggest that the thyroid hyperplasias developed late in the study or the hyperplasias resulted from low-level thyroid stimulation.

The possibility that chronic but low-level thyroid stimulation might be involved is supported by the report of Nakamura *et al.* (1989), who demonstrated that acetaminophen is an excellent substrate for thyroid peroxidase purified from hog thyroid microsomes. Thyroid peroxidase plays an important role in the synthesis of thyroid hormones by catalyzing the iodination of the tyrosine side chains in thyroglobulin and the subsequent coupling of iodotyrosine side chains to form iodothyronine residues, which include precursors to T_3 and T_4. Acetaminophen could possibly compete with the tyrosine side chains of thyroglobulin for peroxidase, causing an apparent reduction in iodination and/or coupling. Ultimately this could lead to reduced rates of thyroid hormone synthesis and hence lower circulating hormone levels.

The present study is the fourth long-term study of acetaminophen conducted in B6C3F$_1$ mice; previous studies have been reported by Amo and Matsuyama (1985), Hagiwara and Ward (1986), and Ward *et al.* (1988). The study reported by Amo and Matsuyama was a dietary study conducted at the same dose levels (3,000 and 6,000 ppm) as those used in the present NTP study, but involved chemical exposure for 133 weeks prior to termination. These dietary concentrations of acetaminophen were not associated with increased incidences of any neoplasms. In the studies conducted by Hagiwara and Ward (1986) and Ward *et al.* (1988), male mice were given dietary concentrations of 5,000 or 10,000 ppm acetaminophen. In both studies, dietary concentrations of 10,000 ppm were associated with markedly reduced body weights and reduced survival compared to controls during the first year of the study. In the study by Hagiwara and Ward, overall survival of the 10,000 ppm group was only 16% after 72 weeks. Severe liver toxicity was present in all mice that died early and was the most probable cause of death. Dietary concentrations of 5,000 ppm were associated with body weights 13% to 14% less than controls, but not with a significant reduction in survival. Exposure to acetaminophen was not associated with increased incidences of neoplasms in either of these studies at 5,000 or 10,000 ppm; however, these studies were terminated after 72 weeks.

The study by Hagiwara and Ward (1986) included an initiation-promotion experiment in which groups of mice received initiating doses of diethylnitrosamine (DEN), followed by diets containing 0, 5,000, or 10,000 ppm acetaminophen for an additional 70 weeks (total study duration was 72 weeks). The incidence and density of focal hepatocellular proliferative lesions were increased in the DEN-initiated group that received diets containing 10,000 ppm acetaminophen, but there was no increase in the incidence of these lesions in the DEN control group or the DEN-initiated group that received 5,000 ppm acetaminophen. Moreover, exposure to acetaminophen did not increase the incidence of hepatocellular adenomas or carcinomas in any group.

The results of all four long-term studies indicate that dietary concentrations of 5,000 to 6,000 ppm provide an adequate high dose for evaluation of the carcinogenic activity of acetaminophen in B6C3F$_1$ mice. In each study the consumption of diets containing 5,000 ppm or 6,000 ppm was associated with reduced weight gain. The studies of Hagiwara and Ward (1986) and Ward *et al.* (1988) also demonstrate the steepness of the toxic dose response over the range of dietary concentrations from 5,000 to 10,000 ppm acetaminophen; the marked body weight reduction, significant early mortality, and severe hepatotoxicity associated with consumption of diets containing 10,000 ppm acetaminophen indicate clearly that this concentration is inappropriate for a 2-year study in B6C3F$_1$ mice. This is similar to the conclusion reached by Maruyama and Williams (1988) based on a retrospective examination of histopathology data obtained from previous dosed feed studies of acetaminophen conducted in NIH mice (Weisburger *et al.*, 1973) or B6C3F$_1$ mice (Amo and Matsuyama, 1985).

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of acetaminophen in male F344/N rats that received 600, 3,000 or 6,000 ppm. There was *equivocal evidence of carcinogenic activity* of acetaminophen in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *no evidence of carcinogenic activity* of acetaminophen in male and female $B6C3F_1$ mice that received 600, 3,000, or 6,000 ppm.

Nonneoplastic lesions associated with exposure to acetaminophen included increased severity of nephropathy and increased incidences of renal tubule hyperplasia and parathyroid hyperplasia in male rats, increased severity of nephropathy in female rats, and increased incidences of thyroid follicular cell hyperplasia in male and female mice.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on pages 10-11.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Moribund	22	20	25	22
Natural deaths	1	2	2	4
Survivors				
Terminal sacrifice	27	28	23	24
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(48)	(49)	(49)	(48)
Intestine large, colon	(48)	(49)	(50)	(50)
Intestine large, rectum	(50)	(47)	(47)	(49)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Intestine small, ileum	(49)	(48)	(48)	(46)
Intestine small, jejunum	(50)	(48)	(49)	(49)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma		1 (2%)	1 (2%)	
Histiocytic sarcoma				1 (2%)
Mesentery	(3)	(9)	(3)	(2)
Liposarcoma			1 (33%)	
Pancreas	(49)	(49)	(47)	(47)
Acinus, adenoma				1 (2%)
Acinus, carcinoma				1 (2%)
Pharynx			(1)	
Palate, papilloma squamous			1 (100%)	
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(46)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Tongue		(1)		
Papilloma squamous		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma			1 (2%)	
Adrenal gland, medulla	(44)	(49)	(49)	(46)
Ganglioneuroma			1 (2%)	
Pheochromocytoma malignant	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Pheochromocytoma benign	11 (25%)	17 (35%)	13 (27%)	16 (35%)
Bilateral, pheochromocytoma benign	5 (11%)	3 (6%)	4 (8%)	3 (7%)
Islets, pancreatic	(49)	(49)	(46)	(48)
Adenoma	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Carcinoma		1 (2%)	1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Endocrine System (continued)				
Pituitary gland	(48)	(49)	(49)	(48)
Pars distalis, adenoma	16 (33%)	27 (55%)	19 (39%)	19 (40%)
Pars distalis, carcinoma	1 (2%)			1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, carcinoma				1 (2%)
C-cell, adenoma	4 (8%)	8 (16%)	1 (2%)	6 (12%)
C-cell, carcinoma	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma	1 (2%)			1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(48)	(50)	(49)	(47)
Adenoma	2 (4%)	6 (12%)	2 (4%)	5 (11%)
Carcinoma	3 (6%)	6 (12%)	3 (6%)	5 (11%)
Prostate	(47)	(49)	(50)	(49)
Seminal vesicle	(48)	(49)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Liposarcoma, metastatic			1 (2%)	
Bilateral, interstitial cell, adenoma	29 (58%)	36 (72%)	35 (70%)	33 (66%)
Bilateral, interstitial cell, carcinoma	1 (2%)			
Interstitial cell, adenoma	13 (26%)	9 (18%)	13 (26%)	10 (20%)
Hematopoietic System				
Blood	(25)	(8)	(10)	(23)
Bone marrow	(50)	(50)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Lymph node	(50)	(50)	(50)	(49)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Mediastinal, histiocytic sarcoma				1 (2%)
Lymph node, mandibular	(47)	(45)	(49)	(45)
Histiocytic sarcoma				1 (2%)
Lymph node, mesenteric	(49)	(50)	(50)	(48)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)	1 (2%)		
Histiocytic sarcoma				1 (2%)
Sarcoma		1 (2%)		
Thymus	(40)	(37)	(40)	(42)
Histiocytic sarcoma				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Integumentary System				
Mammary gland	(36)	(34)	(35)	(36)
Fibroadenoma	4 (11%)	5 (15%)	1 (3%)	1 (3%)
Skin	(50)	(50)	(48)	(49)
Basal cell adenoma	1 (2%)			1 (2%)
Basal cell carcinoma				1 (2%)
Keratoacanthoma	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Papilloma squamous	2 (4%)			1 (2%)
Squamous cell carcinoma	1 (2%)			1 (2%)
Subcutaneous tissue, fibroma	6 (12%)	4 (8%)	2 (4%)	
Subcutaneous tissue, fibrosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)		
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Osteoma				1 (2%)
Skeletal muscle		(1)		(1)
Hemangiosarcoma				1 (100%)
Nervous System				
Brain	(49)	(50)	(50)	(49)
Astrocytoma malignant			1 (2%)	
Carcinoma, metastatic, pituitary gland	1 (2%)			1 (2%)
Glioma malignant				1 (2%)
Granular cell tumor NOS				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma		1 (2%)		1 (2%)
Carcinoma, metastatic, adrenal gland			1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)	1 (2%)		
Carcinoma, metastatic, Zymbal's gland			1 (2%)	
Hemangiosarcoma, metastatic, spleen	1 (2%)			
Histiocytic sarcoma				1 (2%)
Pheochromocytoma malignant, metastatic		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal gland				1 (2%)
Nose	(49)	(50)	(50)	(49)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Special Senses System				
Ear	(3)	(2)		(3)
Papilloma squamous				1 (33%)
Eye	(3)	(5)	(11)	(8)
Carcinoma, metastatic, harderian gland		1 (20%)		
Harderian gland	(4)	(5)	(9)	(6)
Carcinoma		1 (20%)		
Zymbal's gland			(4)	(2)
Carcinoma			4 (100%)	2 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hamartoma				1 (2%)
Lipoma				1 (2%)
Renal tubule, adenoma	3 (6%)		3 (6%)	3 (6%)
Urinary bladder	(49)	(48)	(47)	(46)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	27 (54%)	26 (52%)	24 (48%)	20 (40%)
Mesothelioma benign		1 (2%)		
Mesothelioma malignant	2 (4%)	5 (10%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	50	50	50
Total primary neoplasms	148	178	142	152
Total animals with benign neoplasms	47	50	50	49
Total benign neoplasms	103	129	102	109
Total animals with malignant neoplasms	34	34	34	35
Total malignant neoplasms	45	50	40	42
Total animals with metastatic neoplasms	3	3	3	2
Total metastatic neoplasms	3	4	3	2
Total animals with neoplasms uncertain-benign or malignant				1
Total uncertain neoplasms				1

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 0 ppm

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

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

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 4 3	0 5 3	0 6 1	0 6 2	0 6 3	0 8 1	0 8 2	1 1 2	1 1 3	0 9 2	0 1 1	0 3 1	0 3 4	0 4 1	0 4 2	0 5 1	0 5 2	0 7 1	0 7 2	0 7 3	0 9 1	1 0 1	1 0 2	1 0 4	1 0 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+			+																	3
Pancreas	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	44
Pheochromocytoma malignant																									X	1
Pheochromocytoma benign			X						X		X			X						X				X		11
Bilateral, pheochromocytoma benign												X	X									X				5
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X				X									2
Parathyroid gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma				X							X					X	X	X	X	X	X			X		16
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X													X		4
C-cell, carcinoma															X					X						3
Follicular cell, carcinoma																										1
General Body System																										
None																										

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

Number of Days on Study	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
	6	1	6	6	7	8	1	3	3	3	3	4	4	5	6	6	7	8	0	0	1	1	1	3	3
	0	4	8	8	9	2	2	1	2	2	5	0	1	2	1	1	0	2	3	8	2	4	8	6	6
Carcass ID Number	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	0	0	0
	2	6	1	9	1	4	8	6	8	8	3	7	9	2	1	2	4	2	1	5	5	2	9	2	2
	5	5	5	5	4	5	5	4	3	4	5	4	4	4	3	3	4	3	5	5	4	2	3	1	2
Genital System																									
Coagulating gland											+														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X						X	
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X				X	X		X					X	X	X	X				X	X	X	X	X
Bilateral, interstitial cell, carcinoma													X												
Interstitial cell, adenoma				X				X			X							X	X						
Hematopoietic System																									
Blood																								+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X												X						
Thymus	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	M	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																			X						
Keratoacanthoma								X			X	X													
Squamous cell carcinoma																X									
Squamous cell papilloma																X									X
Subcutaneous tissue, fibroma		X				X			X					X						X			X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Carcinoma, metastatic, pituitary gland			X																						
Spinal cord									+																

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 4 3	0 5 3	0 6 1	0 6 2	0 6 3	0 8 1	0 8 2	1 1 2	1 1 3	0 9 2	0 1 1	0 3 1	0 3 4	0 4 1	0 4 2	0 5 1	0 5 2	0 7 1	0 7 2	0 7 3	0 9 1	1 0 1	1 0 2	1 0 4	1 0 5	Total Tissues/ Tumors
Genital System																											
Coagulating gland																											1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																											2
Carcinoma				X										X												X	3
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	47
Seminal vesicle	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X	X	X			X	X	X	X	X	X	X	X	X		X				X		X	X		29
Bilateral, interstitial cell, carcinoma																											1
Interstitial cell, adenoma	X	X				X	X										X		X		X		X				13
Hematopoietic System																											
Blood	I	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											2
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	M	+	+	M	+	+		40
Integumentary System																											
Mammary gland	M	+	+	+	+	M	+	+	M	+	+	+	M	M	M	+	+	M	+	+	+	M	+	M	M		36
Fibroadenoma		X									X	X											X				4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																											1
Keratoacanthoma																											3
Squamous cell carcinoma																											1
Squamous cell papilloma																											2
Subcutaneous tissue, fibroma																											6
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland																											1
Spinal cord																											1

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

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

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 4 3	0 5 3	0 6 1	0 6 2	0 6 3	0 8 1	0 8 2	1 1 2	1 1 3	0 9 2	0 1 1	0 3 1	0 3 4	0 4 1	0 4 2	0 5 1	0 5 2	0 7 1	0 7 2	0 7 3	0 9 1	1 0 1	1 0 2	1 0 4	1 0 5	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																	X		2
Carcinoma, metastatic, thyroid gland																										1
Hemangiosarcoma, metastatic, spleen																										1
Nose	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear										+												+				3
Eye																						+				3
Harderian gland									+												+					4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma					X															X					X	3
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X	X	X	X	X		X						X	X					X				27
Mesothelioma malignant												X			X											2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 2 2	2 2 3	2 4 1	2 4 2	2 4 3	2 4 4	2 4 5	1 4 2	1 4 1	1 5 1	1 5 2	1 6 1	2 1 1	2 1 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 1	1 9 1	1 9 2	2 0 1	2 0 2	2 1 4	2 3 4	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																									1
Mesentery				+	+		+				+														9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue															+										1
Squamous cell papilloma															X										1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant	X																								1
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																		1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant			X			X																			2
Pheochromocytoma benign	X									X				X	X		X							X	X	17
Bilateral, pheochromocytoma benign				X																			X			3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X			X											X									4
Carcinoma																										1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X			X	X				X			X	X				X				X		X	X	X	27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X			X				X									X					X	8
C-cell, carcinoma		X			X																	X				3
Follicular cell, adenoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	5 0 6	5 4 9	5 7 9	5 8 5	6 0 0	6 0 3	6 1 3	6 1 9	6 2 4	6 3 5	6 5 2	6 6 9	6 7 0	6 7 1	6 8 7	6 8 7	6 9 2	7 1 5	7 1 8	7 2 3	7 2 3	7 3 5	7 3 2	7 3 2
Carcass ID Number	1 9 5	2 2 5	2 0 5	1 6 5	2 2 4	1 5 5	1 5 4	1 5 3	2 3 5	1 7 5	1 6 4	1 9 4	2 1 3	1 8 4	1 4 3	1 9 3	1 8 3	2 0 4	2 0 3	1 6 2	2 3 3	1 3 5	1 3 2	1 3 3	2 2 1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Carcinoma		X									X						X		X						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X			X	X	X			X		X				X		X	X			X	X		X	X	X
Interstitial cell, adenoma		X								X		X	X	X		X			X				X			
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X								
Sarcoma																									
Thymus	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	M	+	+
Fibroadenoma													X								X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma							X				X														
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 2 2	2 2 3	2 4 1	2 4 2	2 4 3	2 4 4	2 4 5	1 4 2	1 4 1	1 5 1	1 5 2	1 6 1	2 1 1	2 1 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 1	1 9 1	1 9 2	2 0 1	2 0 2	2 3 1	2 3 4	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X				X		X							X		X										6
Carcinoma															X				X							6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X		36
Interstitial cell, adenoma																X										9
Hematopoietic System																										
Blood			+				+	+						+				+	+			+	+			8
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland					X																					1
Lymph node, mandibular	+	M	M	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Sarcoma																	X									1
Thymus	M	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	M	M	M	+	+	M	+	+	37
Integumentary System																										
Mammary gland	+	M	M	+	M	M	M	+	+	+	+	+	+	+	M	+	M	M	+	M	M	+	+	+	M	34
Fibroadenoma	X													X										X		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma	X																X									2
Subcutaneous tissue, fibroma	X											X														4
Subcutaneous tissue, hemangiosarcoma						X																				1
Subcutaneous tissue, sarcoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
	0	4	7	8	0	0	1	1	2	3	5	6	7	7	8	8	9	1	1	2	2	3	3
	6	9	9	5	0	3	3	9	4	5	2	9	0	1	7	7	2	5	8	3	3	5	2	2	2
Carcass ID Number	1	2	2	1	2	1	1	1	2	1	1	1	2	1	1	1	1	2	2	1	2	1	1	1	2
	9	2	0	6	2	5	5	5	3	7	6	9	1	8	4	9	8	0	0	6	3	3	3	3	2
	5	5	5	5	4	5	4	3	5	5	4	4	3	4	3	3	3	4	3	2	3	5	2	3	1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																	+								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma																								X	
Carcinoma, metastatic, thyroid gland																									
Pheochromocytoma malignant, metastatic																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																	+				+				
Carcinoma, metastatic, harderian gland																									
Harderian gland																	+				+				
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X			X			X	X	X	X		X		X					
Mesothelioma benign																X									
Mesothelioma malignant	X												X			X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 2 2	2 2 3	2 4 1	2 4 2	2 4 3	2 4 4	2 4 5	1 4 2	1 4 1	1 5 1	1 5 2	1 6 1	2 1 1	2 1 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 1	1 9 1	1 9 2	2 0 1	2 0 2	2 3 1	2 3 4	Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																										2
Alveolar/bronchiolar carcinoma																											1
Carcinoma, metastatic, thyroid gland					X																						1
Pheochromocytoma malignant, metastatic						X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear															+											+	2
Eye																				+	+					+	5
Carcinoma, metastatic, harderian gland																					X						1
Harderian gland																				+	+					+	5
Carcinoma																					X						1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X			X	X	X	X		X			X			X	X	X			X	X		X		26
Mesothelioma benign																											1
Mesothelioma malignant				X							X																5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 1 9	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 2 4	2 6 3	2 5 2	2 6 1	2 6 2	2 7 1	2 7 3	2 8 1	2 8 2	3 0 1	3 1 2	3 1 3	3 1 4	3 3 1	3 3 3	3 5 1	3 5 2	3 5 3	3 5 4	3 6 1	3 6 2	3 6 3	3 2 1	3 2 2	3 2 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery																										3
Liposarcoma																										1
Pancreas		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pharynx																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																							X			1
Adrenal gland, medulla	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ganglioneuroma																										1
Pheochromocytoma malignant																X			X							2
Pheochromocytoma benign							X		X					X			X			X	X	X				13
Bilateral, pheochromocytoma benign	X			X							X													X		4
Islets, pancreatic	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																	X									2
Carcinoma							X																			1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X	X		X						X		X				X		X		X	X	X	19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																				X						1
C-cell, carcinoma																			X							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	4 4 4 4 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 4 7 7 8 2 6 8 2 2 2 2 3 3 4 4 5 6 7 9 9 0 0 1 1 1 1 1 8 4 1 0 2 0 4 7 7 5 8 2 8 5 1 0 2 8 3 3 0 4 5
Carcass ID Number	2 3 3 2 2 3 3 2 3 3 3 3 2 2 3 3 2 3 2 3 2 3 2 2 2 8 5 0 7 5 6 4 9 1 2 4 6 9 8 3 0 6 4 7 4 6 0 5 9 5 5 5 5 4 5 5 5 4 5 5 4 4 2 4 5 3 5 2 2 1 4 2 4 1 3
General Body System	
None	
Genital System	
Coagulating gland	+
Epididymis	+ +
Penis	+
Preputial gland	M +
Adenoma	X
Carcinoma	X X
Prostate	+ +
Seminal vesicle	+ +
Testes	+ +
Liposarcoma, metastatic	X
Bilateral, interstitial cell, adenoma	X X X X X X X X X
Interstitial cell, adenoma	X X X X X X X X
Hematopoietic System	
Blood	
Bone marrow	+ +
Lymph node	+ +
Lymph node, mandibular	+ + + + + + + + + + + + M + + + + + + + + + + + +
Lymph node, mesenteric	+ +
Spleen	+ +
Thymus	M + + + + + + + + + + + + + + M M + M + + + M + + M
Integumentary System	
Mammary gland	M + + + + M + M + M + + + M + + + + + M + + + + +
Fibroadenoma	X
Skin	+ + + + + + + + + M + + + M + + + + + + + + + + +
Keratoacanthoma	X
Subcutaneous tissue, fibroma	X X
Subcutaneous tissue, fibrosarcoma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Astrocytoma malignant	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 1 9	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3		
Carcass ID Number	3 2 4	2 6 3	2 5 2	2 6 1	2 6 2	2 7 1	2 7 3	2 8 1	2 8 2	3 0 1	3 1 2	3 1 3	3 1 4	3 3 1	3 3 3	3 3 1	3 5 2	3 5 3	3 5 4	3 6 1	3 6 2	3 6 3	3 2 1	3 2 2	3 2 3	Total Tissues/ Tumors	
General Body System																											
None																											
Genital System																											
Coagulating gland																										1	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Penis																										1	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma						X																				2	
Carcinoma												X														3	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Liposarcoma, metastatic																										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	35	
Interstitial cell, adenoma															X					X			X		13	
Hematopoietic System																											
Blood	+					+	+	+	+	+				+	+		+								+	10	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	40	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	M	M	+	+	M	M	+	+	+	+	M	+	M	M	+	+	+	M	M	35	
Fibroadenoma																										1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Keratoacanthoma																X										2	
Subcutaneous tissue, fibroma																										2	
Subcutaneous tissue, fibrosarcoma	X																									1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Astrocytoma malignant																										1	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	4 4 4 4 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 4 7 7 8 2 6 8 2 2 2 2 3 3 4 4 5 6 7 9 9 0 0 1 1 1 1 1 8 4 1 0 2 0 4 7 7 5 8 2 8 5 1 0 2 8 3 3 0 4 5
Carcass ID Number	2 3 3 2 2 3 3 2 3 3 3 3 2 2 3 3 2 3 2 3 2 3 2 2 2 8 5 0 7 5 6 4 9 1 2 4 6 9 8 3 0 6 4 7 4 6 0 5 9 5 5 5 5 4 5 5 5 4 5 5 4 4 2 4 5 3 5 2 2 1 4 2 4 1 3
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Carcinoma, metastatic, adrenal gland	
Carcinoma, metastatic, Zymbal's gland	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+ + + + + + +
Harderian gland	+ + + + + + +
Zymbal's gland	+ + +
Carcinoma	X X X
Urinary System	
Kidney	+ +
Renal tubule, adenoma	
Urinary bladder	A + + + + M + + + + + + + M + + + + + + + + + + + +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X X X X X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 1 9	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 2 4	2 6 3	2 5 2	2 6 1	2 6 2	2 7 1	2 7 3	2 8 1	2 8 2	3 0 1	3 1 2	3 1 3	3 1 4	3 3 1	3 3 3	3 5 1	3 5 2	3 5 3	3 5 4	3 6 1	3 6 2	3 6 3	3 2 1	3 2 2	3 2 3	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X				2
Carcinoma, metastatic, adrenal gland																							X				1
Carcinoma, metastatic, Zymbal's gland																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye				+									+						+	+		+					11
Harderian gland				+									+							I		+					9
Zymbal's gland																									+		4
Carcinoma																									X		4
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma				X										X		X											3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X	X	X	X	X				X	X	X	X									X	24

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 3 4	3 7 2	3 7 3	3 8 2	3 9 1	3 9 2	3 9 3	4 0 1	4 0 2	4 1 2	4 3 2	4 5 1	4 5 2	4 6 1	4 6 3	4 6 4	4 6 5	4 7 3	4 7 5	4 8 1	4 8 2	4 2 1	4 2 2	4 3 1	4 4 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Mesentery			+																						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Acinus, adenoma										X															1
Acinus, carcinoma									X																1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth					+																				1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Pheochromocytoma malignant					X																				2
Pheochromocytoma benign				X		X		X	X	X			X			X		X	X			X		X		16
Bilateral, pheochromocytoma benign																									X	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma								X																		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X			X	X	X				X	X	X		X			X									19
Pars distalis, carcinoma		X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, carcinoma																										1
C-cell, adenoma		X		X																						6
C-cell, carcinoma																										2
Follicular cell, carcinoma															X											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	3	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	0	4	3	6	7	7	7	8	8	9	0	1	1	4	4	5	5	6	9	9	0	0	1	1
	5	2	3	4	7	7	9	5	6	1	6	3	9	3	4	4	7	9	5	5	1	4	4	8	9
Carcass ID Number	4	4	4	4	4	4	4	3	4	3	4	4	4	4	4	4	3	4	3	4	4	3	4	4	3
	4	5	5	4	1	4	2	8	5	8	8	4	8	1	3	3	8	2	9	0	0	7	2	0	9
	5	5	4	4	5	3	5	5	3	4	5	2	3	4	5	3	3	4	5	5	4	4	3	3	4
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis		+																							
Preputial gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma						X																			
Carcinoma			X	X																					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X		X	X	X	X	X	X		X					X			X		X
Interstitial cell, adenoma		X	X	X			X				X					X	X					X			
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma													X												
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Histiocytic sarcoma													X												
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Histiocytic sarcoma													X												
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	M	+	+	+	+	+	M
Fibroadenoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									
Keratoacanthoma																				X					
Squamous cell carcinoma																			X						
Squamous cell papilloma																									
Subcutaneous tissue, fibrosarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																				X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 3 4	3 7 2	3 7 3	3 8 2	3 9 1	3 9 2	3 9 3	4 0 1	4 0 2	4 1 2	4 3 2	4 5 1	4 5 2	4 6 1	4 6 3	4 6 4	4 6 5	4 7 3	4 7 5	4 8 1	4 8 2	4 2 1	4 2 2	4 3 1	4 4 1	Total Tissues/ Tumors
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																									1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X			X							X					X									5
Carcinoma			X											X										X	5
Prostate	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	33
Interstitial cell, adenoma							X																X		10
Hematopoietic System																									
Blood	+	+	+	+	+	+	+	+		+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	23
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinal, histiocytic sarcoma																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	45
Histiocytic sarcoma																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Thymus	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	M	+	+	+	+	42
Histiocytic sarcoma																									1
Integumentary System																									
Mammary gland	+	+	M	M	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	36
Fibroadenoma																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma			X																						1
Basal cell carcinoma																		X							1
Keratoacanthoma																									1
Squamous cell carcinoma																									1
Squamous cell papilloma																							X		1
Subcutaneous tissue, fibrosarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	3	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	0	4	3	6	7	7	7	8	8	9	0	1	1	4	4	5	5	6	9	9	0	0	1	1
	5	2	3	4	7	7	9	5	6	1	6	3	9	3	4	4	7	9	5	5	1	4	8	9
Carcass ID Number	4	4	4	4	4	4	4	3	4	3	4	4	4	4	4	4	3	4	3	4	4	3	4	4	3
	4	5	5	4	1	4	2	8	5	8	8	4	8	1	3	3	8	2	9	0	0	7	2	0	9
	5	5	4	4	5	3	5	5	3	4	5	2	3	4	5	3	3	4	5	5	4	4	3	3	4
Musculoskeletal System (continued)																									
Skeletal muscle																									
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Carcinoma, metastatic, pituitary gland																									
Glioma malignant	X																								
Granular cell tumor NOS																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma								X			X														
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma													X												
Pheochromocytoma malignant, metastatic, adrenal gland																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																									
Ear					+																				
Squamous cell papilloma																									
Eye			+		+	+														+					
Harderian gland						+												+		+					
Zymbal's gland									+																
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hamartoma																				X					
Lipoma																									
Renal tubule, adenoma																									
Urinary bladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma													X												
Leukemia mononuclear		X				X	X			X		X					X		X	X	X		X	X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 3 4	3 7 2	3 7 3	3 8 2	3 9 1	3 9 2	3 9 3	4 0 1	4 0 2	4 1 2	4 3 2	4 5 1	4 5 2	4 6 1	4 6 3	4 6 4	4 6 5	4 7 3	4 7 5	4 8 1	4 8 2	4 2 1	4 2 2	4 3 1	4 4 1	Total Tissues/ Tumors
Musculoskeletal System (continued)																									
Skeletal muscle																+									1
Hemangiosarcoma																X									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland		X																							1
Glioma malignant																									1
Granular cell tumor NOS																	X								1
Spinal cord	+																								1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X									3
Alveolar/bronchiolar carcinoma						X																			1
Histiocytic sarcoma																									1
Pheochromocytoma malignant, metastatic, adrenal gland																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Ear										+					+										3
Squamous cell papilloma															X										1
Eye													+					+		+			+		8
Harderian gland													+					+					+		6
Zymbal's gland										+															2
Carcinoma										X															2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hamartoma																									1
Lipoma			X																						1
Renal tubule, adenoma							X	X															X		3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Leukemia mononuclear		X					X						X	X	X	X			X		X	X			20

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	16/44 (36%)	20/49 (41%)	17/49 (35%)	19/46 (41%)
Adjusted rates[b]	51.4%	54.6%	57.0%	63.0%
Terminal rates[c]	10/24 (42%)	12/28 (43%)	10/22 (45%)	12/22 (55%)
First incidence (days)	635	549	642	586
Life table tests[d]	P=0.230	P=0.444	P=0.401	P=0.250
Logistic regression tests[d]	P=0.277	P=0.490	P=0.588N	P=0.296
Cochran-Armitage test[d]	P=0.443			
Fisher exact test[d]		P=0.411	P=0.519N	P=0.396
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates	17/44 (39%)	22/49 (45%)	19/49 (39%)	21/46 (46%)
Adjusted rates	54.9%	60.3%	64.2%	67.7%
Terminal rates	11/24 (46%)	14/28 (50%)	12/22 (55%)	13/22 (59%)
First incidence (days)	635	549	642	586
Life table tests	P=0.175	P=0.387	P=0.317	P=0.190
Logistic regression tests	P=0.208	P=0.429	P=0.513	P=0.220
Cochran-Armitage test	P=0.386			
Fisher exact test		P=0.345	P=0.579	P=0.323
Kidney: Adenoma (NOS: Cortex, Pelvis, or Transitional Epithelium)				
Overall rates	3/50 (6%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rates	11.1%	0.0%	13.0%	12.5%
Terminal rates	3/27 (11%)	0/28 (0%)	3/23 (13%)	3/24 (13%)
First incidence (days)	729 (T)	–[e]	729 (T)	729 (T)
Life table tests	P=0.220	P=0.113N	P=0.589	P=0.610
Logistic regression tests	P=0.220	P=0.113N	P=0.589	P=0.610
Cochran-Armitage test	P=0.287			
Fisher exact test		P=0.121N	P=0.661N	P=0.661N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	2/50 (4%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rates	7.4%	5.9%	7.5%	8.7%
Terminal rates	2/27 (7%)	1/28 (4%)	1/23 (4%)	1/24 (4%)
First incidence (days)	729 (T)	635	703	585
Life table tests	P=0.324	P=0.682N	P=0.644	P=0.457
Logistic regression tests	P=0.373	P=0.683N	P=0.673	P=0.503
Cochran-Armitage test	P=0.381			
Fisher exact test		P=0.691N	P=0.691N	P=0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	2/50 (4%)	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted rates	7.4%	9.4%	7.5%	12.7%
Terminal rates	2/27 (7%)	2/28 (7%)	1/23 (4%)	2/24 (8%)
First incidence (days)	729 (T)	635	703	585
Life table tests	P=0.245	P=0.516	P=0.644	P=0.295
Logistic regression tests	P=0.285	P=0.520	P=0.673	P=0.331
Cochran-Armitage test	P=0.304			
Fisher exact test		P=0.500	P=0.691N	P=0.339

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Mammary Gland: Fibroadenoma				
Overall rates	4/50 (8%)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rates	14.8%	15.9%	3.8%	3.1%
Terminal rates	4/27 (15%)	3/28 (11%)	0/23 (0%)	0/24 (0%)
First incidence (days)	729 (T)	670	715	695
Life table tests	P=0.067N	P=0.535	P=0.225N	P=0.209N
Logistic regression tests	P=0.056N	P=0.545	P=0.201N	P=0.197N
Cochran-Armitage test	P=0.045N			
Fisher exact test		P=0.500	P=0.181N	P=0.181N
Pancreatic Islets: Adenoma				
Overall rates	2/49 (4%)	4/49 (8%)	2/46 (4%)	1/48 (2%)
Adjusted rates	7.7%	13.1%	7.4%	4.2%
Terminal rates	2/26 (8%)	3/27 (11%)	1/22 (5%)	1/24 (4%)
First incidence (days)	729 (T)	613	661	729 (T)
Life table tests	P=0.249N	P=0.353	P=0.643	P=0.528N
Logistic regression tests	P=0.237N	P=0.357	P=0.652	P=0.528N
Cochran-Armitage test	P=0.216N			
Fisher exact test		P=0.339	P=0.667	P=0.508N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	2/49 (4%)	5/49 (10%)	3/46 (7%)	1/48 (2%)
Adjusted rates	7.7%	15.7%	11.8%	4.2%
Terminal rates	2/26 (8%)	3/27 (11%)	2/22 (9%)	1/24 (4%)
First incidence (days)	729 (T)	613	661	729 (T)
Life table tests	P=0.226N	P=0.234	P=0.434	P=0.528N
Logistic regression tests	P=0.215N	P=0.232	P=0.443	P=0.528N
Cochran-Armitage test	P=0.194N			
Fisher exact test		P=0.218	P=0.470	P=0.508N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	16/48 (33%)	27/49 (55%)	19/49 (39%)	19/48 (40%)
Adjusted rates	45.0%	62.0%	56.7%	51.7%
Terminal rates	9/27 (33%)	12/28 (43%)	10/23 (43%)	8/24 (33%)
First incidence (days)	568	549	582	564
Life table tests	P=0.479	P=0.068	P=0.227	P=0.262
Logistic regression tests	P=0.414N	P=0.025	P=0.337	P=0.314
Cochran-Armitage test	P=0.374N			
Fisher exact test		P=0.025	P=0.365	P=0.336
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	17/48 (35%)	27/49 (55%)	19/49 (39%)	20/48 (42%)
Adjusted rates	46.2%	62.0%	56.7%	54.7%
Terminal rates	9/27 (33%)	12/28 (43%)	10/23 (43%)	9/24 (38%)
First incidence (days)	568	549	582	564
Life table tests	P=0.450	P=0.096	P=0.288	P=0.262
Logistic regression tests	P=0.438N	P=0.039	P=0.429	P=0.323
Cochran-Armitage test	P=0.403N			
Fisher exact test		P=0.040	P=0.448	P=0.338

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Preputial Gland: Adenoma				
Overall rates	2/48 (4%)	6/50 (12%)	2/49 (4%)	5/47 (11%)
Adjusted rates	6.9%	19.6%	6.4%	17.8%
Terminal rates	1/25 (4%)	5/28 (18%)	1/23 (4%)	3/24 (13%)
First incidence (days)	682	600	521	577
Life table tests	P=0.346	P=0.170	P=0.671	P=0.205
Logistic regression tests	P=0.376	P=0.163	P=0.682N	P=0.207
Cochran-Armitage test	P=0.382			
Fisher exact test		P=0.148	P=0.684N	P=0.209
Preputial Gland: Carcinoma				
Overall rates	3/48 (6%)	6/50 (12%)	3/49 (6%)	5/47 (11%)
Adjusted rates	12.0%	16.6%	10.0%	16.1%
Terminal rates	3/25 (12%)	2/28 (7%)	1/23 (4%)	3/24 (13%)
First incidence (days)	729 (T)	549	642	533
Life table tests	P=0.429	P=0.296	P=0.631	P=0.338
Logistic regression tests	P=0.463	P=0.271	P=0.661N	P=0.344
Cochran-Armitage test	P=0.462			
Fisher exact test		P=0.264	P=0.651N	P=0.345
Preputial Gland: Adenoma or Carcinoma				
Overall rates	5/48 (10%)	12/50 (24%)	5/49 (10%)	10/47 (21%)
Adjusted rates	18.5%	34.1%	16.0%	32.5%
Terminal rates	4/25 (16%)	7/28 (25%)	2/23 (9%)	6/24 (25%)
First incidence (days)	682	549	521	533
Life table tests	P=0.298	P=0.090	P=0.588	P=0.119
Logistic regression tests	P=0.337	P=0.074	P=0.623N	P=0.121
Cochran-Armitage test	P=0.340			
Fisher exact test		P=0.065	P=0.617N	P=0.121
Skin: Keratoacanthoma				
Overall rates	3/50 (6%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rates	7.2%	7.1%	6.6%	3.1%
Terminal rates	0/27 (0%)	2/28 (7%)	1/23 (4%)	0/24 (0%)
First incidence (days)	631	729 (T)	620	695
Life table tests	P=0.291N	P=0.493N	P=0.530N	P=0.333N
Logistic regression tests	P=0.238N	P=0.517N	P=0.468N	P=0.275N
Cochran-Armitage test	P=0.246N			
Fisher exact test		P=0.500N	P=0.500N	P=0.309N
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	6/50 (12%)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted rates	15.1%	11.5%	5.8%	0.0%
Terminal rates	0/27 (0%)	2/28 (7%)	0/23 (0%)	0/24 (0%)
First incidence (days)	514	613	655	–
Life table tests	P=0.015N	P=0.348N	P=0.165N	P=0.025N
Logistic regression tests	P=0.005N	P=0.421N	P=0.102N	P=0.010N
Cochran-Armitage test	P=0.009N			
Fisher exact test		P=0.370N	P=0.134N	P=0.013N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	6/50 (12%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rates	15.1%	11.5%	9.6%	2.2%
Terminal rates	0/27 (0%)	2/28 (7%)	0/23 (0%)	0/24 (0%)
First incidence (days)	514	613	655	577
Life table tests	P=0.064N	P=0.348N	P=0.283N	P=0.076N
Logistic regression tests	P=0.028N	P=0.421N	P=0.205N	P=0.033N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=0.370N	P=0.243N	P=0.056N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rates	6/50 (12%)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rates	15.1%	14.9%	9.6%	2.2%
Terminal rates	0/27 (0%)	3/28 (11%)	0/23 (0%)	0/24 (0%)
First incidence (days)	514	613	655	577
Life table tests	P=0.049N	P=0.470N	P=0.283N	P=0.076N
Logistic regression tests	P=0.021N	P=0.548N	P=0.205N	P=0.033N
Cochran-Armitage test	P=0.030N			
Fisher exact test		P=0.500N	P=0.243N	P=0.056N
Testes: Adenoma				
Overall rates	42/50 (84%)	45/50 (90%)	48/50 (96%)	42/50 (84%)
Adjusted rates	97.6%	95.7%	100.0%	97.5%
Terminal rates	26/27 (96%)	26/28 (93%)	23/23 (100%)	23/24 (96%)
First incidence (days)	514	506	441	442
Life table tests	P=0.200	P=0.509	P=0.063	P=0.314
Logistic regression tests	P=0.469	P=0.351	P=0.023	P=0.493
Cochran-Armitage test	P=0.489N			
Fisher exact test		P=0.277	P=0.046	P=0.607N
Thyroid Gland (C-cell): Adenoma				
Overall rates	4/50 (8%)	8/50 (16%)	1/50 (2%)	6/50 (12%)
Adjusted rates	13.3%	25.6%	4.3%	18.4%
Terminal rates	2/27 (7%)	6/28 (21%)	1/23 (4%)	2/24 (8%)
First incidence (days)	682	619	729 (T)	533
Life table tests	P=0.538	P=0.210	P=0.219N	P=0.332
Logistic regression tests	P=0.527N	P=0.200	P=0.194N	P=0.361
Cochran-Armitage test	P=0.488N			
Fisher exact test		P=0.178	P=0.181N	P=0.370
Thyroid Gland (C-cell): Carcinoma				
Overall rates	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rates	11.1%	10.7%	4.3%	5.5%
Terminal rates	3/27 (11%)	3/28 (11%)	1/23 (4%)	0/24 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	606
Life table tests	P=0.377N	P=0.649N	P=0.362N	P=0.540N
Logistic regression tests	P=0.352N	P=0.649N	P=0.362N	P=0.517N
Cochran-Armitage test	P=0.317N			
Fisher exact test		P=0.661N	P=0.309N	P=0.500N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	7/50 (14%)	11/50 (22%)	2/50 (4%)	8/50 (16%)
Adjusted rates	23.7%	35.7%	8.7%	23.0%
Terminal rates	5/27 (19%)	9/28 (32%)	2/23 (9%)	2/24 (8%)
First incidence (days)	682	619	729 (T)	533
Life table tests	P=0.445N	P=0.252	P=0.117N	P=0.438
Logistic regression tests	P=0.383N	P=0.256	P=0.092N	P=0.482
Cochran-Armitage test	P=0.330N			
Fisher exact test		P=0.218	P=0.080N	P=0.500
Zymbal's Gland: Carcinoma				
Overall rates	0/50 (0%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted rates	0.0%	0.0%	10.4%	6.4%
Terminal rates	0/27 (0%)	0/28 (0%)	1/23 (4%)	1/24 (4%)
First incidence (days)	–	–	471	586
Life table tests	P=0.066	–	P=0.060	P=0.222
Logistic regression tests	P=0.137	–	P=0.096	P=0.247
Cochran-Armitage test	P=0.078			
Fisher exact test		–	P=0.059	P=0.247
All Organs: Mononuclear Leukemia				
Overall rates	27/50 (54%)	26/50 (52%)	24/50 (48%)	20/50 (40%)
Adjusted rates	63.4%	64.9%	62.4%	54.5%
Terminal rates	12/27 (44%)	15/28 (54%)	10/23 (43%)	9/24 (38%)
First incidence (days)	568	549	484	442
Life table tests	P=0.270N	P=0.419N	P=0.531N	P=0.262N
Logistic regression tests	P=0.084N	P=0.498N	P=0.354N	P=0.122N
Cochran-Armitage test	P=0.078N			
Fisher exact test		P=0.500N	P=0.345N	P=0.115N
All Organs: Mesothelioma (Benign or Malignant)				
Overall rates	2/50 (4%)	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted rates	7.4%	13.9%	0.0%	0.0%
Terminal rates	2/27 (7%)	2/28 (7%)	0/23 (0%)	0/24 (0%)
First incidence (days)	729 (T)	506	–	–
Life table tests	P=0.031N	P=0.244	P=0.274N	P=0.264N
Logistic regression tests	P=0.022N	P=0.210	P=0.274N	P=0.264N
Cochran-Armitage test	P=0.023N			
Fisher exact test		P=0.218	P=0.247N	P=0.247N
All Organs: Benign Neoplasms				
Overall rates	47/50 (94%)	50/50 (100%)	50/50 (100%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	27/27 (100%)	28/28 (100%)	23/23 (100%)	24/24 (100%)
First incidence (days)	514	506	441	442
Life table tests	P=0.133	P=0.517	P=0.147	P=0.214
Logistic regression tests	P=0.053	P=0.171	P=0.045	P=0.086
Cochran-Armitage test	P=0.327			
Fisher exact test		P=0.121	P=0.121	P=0.309

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
All Organs: Malignant Neoplasms				
Overall rates	34/50 (68%)	34/50 (68%)	34/50 (68%)	35/50 (70%)
Adjusted rates	78.5%	80.0%	77.6%	80.0%
Terminal rates	18/27 (67%)	20/28 (71%)	14/23 (61%)	16/24 (67%)
First incidence (days)	568	506	471	305
Life table tests	P=0.217	P=0.463N	P=0.362	P=0.330
Logistic regression tests	P=0.491	P=0.575N	P=0.580N	P=0.523
Cochran-Armitage test	P=0.446			
Fisher exact test		P=0.585N	P=0.585N	P=0.500
All Organs: Benign or Malignant Neoplasms				
Overall rates	49/50 (98%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	27/27 (100%)	28/28 (100%)	23/23 (100%)	24/24 (100%)
First incidence (days)	514	506	441	305
Life table tests	P=0.148	P=0.482N	P=0.227	P=0.265
Logistic regression tests	P=0.095	P=0.638	P=0.247	P=0.276
Cochran-Armitage test	P=0.351			
Fisher exact test		P=0.500	P=0.500	P=0.500

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined at site.
[b] Kaplan-Meier estimated lifetime neoplasm incidence after adjustment for intercurrent mortality.
[c] Observed incidence at terminal kill.
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. Logistic regression is an alternative method for analyzing the incidence of non-fatal neoplasms. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute[a]			
4,4′-Methylenedianiline 2HCl	0/50	0/50	0/50
C.I. Basic Red 9	0/49	0/49	0/49
Monuron	0/50	0/50	0/50
8-Hydroxyquinoline	1/50	0/50	1/50
2-Biphenylamine HCl	0/49	0/49	0/49
Pentaerythritol tetranitrate	0/50	0/50	0/50
Acetaminophen	3/50	0/50	3/50
Total	4/348 (1.1%)		4/348 (1.1%)
Overall Historical Incidence[a]			
Total	12/1,990 (0.6%)	7/1,990 (0.4%)	19/1,990 (1.0%)
Standard Deviation	1.3%	0.9%	1.7%
Range	0%–6%	0%–4%	0%–6%

[a] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990)

TABLE A4b
Historical Incidence of Zymbal's Gland Carcinoma in Untreated Male F344/N Rats

Study	Incidence in Controls
Historical Incidence at EG&G Mason Research Institute[a]	
4,4′-Methylenedianiline 2HCl	0/50
C.I. Basic Red 9	1/50
Monuron	0/50
8-Hydroxyquinoline	0/50
2-Biphenylamine HCl	0/50
Pentaerythritol tetranitrate	0/50
Acetaminophen	0/50
Total	1/350 (0.3%)
Overall Historical Incidence[b]	
Total	16/1,996 (0.8%)
Standard Deviation	1.3%
Range	0%–8%

[a] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 1 March 1989 for carcinoma, NOS)
[b] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990 for carcinoma, NOS)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Moribund	22	20	25	22
Natural deaths	1	2	2	4
Survivors				
Terminal sacrifice	27	28	23	24
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(48)	(49)	(49)	(48)
Parasite metazoan	6 (13%)	5 (10%)	7 (14%)	4 (8%)
Ulcer	1 (2%)	1 (2%)		
Intestine large, colon	(48)	(49)	(50)	(50)
Parasite metazoan	9 (19%)	8 (16%)	5 (10%)	5 (10%)
Intestine large, rectum	(50)	(47)	(47)	(49)
Parasite metazoan	12 (24%)	10 (21%)	7 (15%)	8 (16%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Artery, inflammation, chronic	1 (2%)			
Muscularis, hypertrophy		1 (2%)	1 (2%)	
Intestine small, jejunum	(50)	(48)	(49)	(49)
Ulcer				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)	1 (2%)	
Basophilic focus	6 (12%)	2 (4%)	1 (2%)	2 (4%)
Clear cell focus	1 (2%)			2 (4%)
Congestion		1 (2%)	2 (4%)	1 (2%)
Cytoplasmic alteration, focal	1 (2%)			
Eosinophilic focus				1 (2%)
Fatty change	9 (18%)	7 (14%)	9 (18%)	3 (6%)
Granuloma	2 (4%)	1 (2%)		
Hemorrhage, focal	1 (2%)			
Hepatodiaphragmatic nodule	3 (6%)	5 (10%)	5 (10%)	4 (8%)
Hyperplasia, focal	3 (6%)	1 (2%)	1 (2%)	4 (8%)
Hyperplasia, multifocal	1 (2%)			
Necrosis, focal	3 (6%)	5 (10%)	6 (12%)	1 (2%)
Bile duct, hyperplasia	42 (84%)	44 (88%)	43 (86%)	43 (86%)
Centrilobular, necrosis				1 (2%)
Subserosa, thrombus	1 (2%)			
Mesentery	(3)	(9)	(3)	(2)
Accessory spleen	1 (33%)			
Edema				1(50%)
Fibrosis		1 (11%)		
Inflammation, acute		1 (11%)		
Fat, necrosis	1 (33%)	3 (33%)	2 (67%)	1 (50%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Alimentary System (continued)				
Pancreas	(49)	(49)	(47)	(47)
Congestion			1 (2%)	
Ectopic tissue				1 (2%)
Edema		1 (2%)	1 (2%)	
Hemorrhage, focal			1 (2%)	
Pigmentation, hemosiderin, focal		1 (2%)		
Acinus, atrophy, focal	26 (53%)	17 (35%)	16 (34%)	20 (43%)
Artery, hypertrophy			1 (2%)	
Artery, inflammation, chronic	2 (4%)			
Salivary glands	(50)	(50)	(50)	(50)
Karyomegaly	45 (90%)	44 (88%)	46 (92%)	48 (96%)
Stomach, forestomach	(49)	(50)	(46)	(50)
Acanthosis	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Bulla				1 (2%)
Hyperkeratosis		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, basal cell	3 (6%)		4 (9%)	1 (2%)
Inflammation, acute			1 (2%)	
Inflammation, chronic	1 (2%)			1 (2%)
Perforation		1 (2%)	1 (2%)	
Ulcer	4 (8%)	2 (4%)	3 (7%)	1 (2%)
Serosa, inflammation, chronic	1 (2%)			
Stomach, glandular	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Inflammation, chronic	1 (2%)			1 (2%)
Mineralization		1 (2%)	1 (2%)	2 (4%)
Ulcer			1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	40 (80%)	40 (80%)	42 (84%)	35 (70%)
Dilatation			1 (2%)	
Atrium, inflammation, chronic	1 (2%)	1 (2%)		
Atrium, thrombus	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Congestion			1 (2%)	
Cytoplasmic alteration, focal	4 (8%)	6 (12%)	9 (18%)	3 (6%)
Hemorrhage, focal				1 (2%)
Hyperplasia, focal		1 (2%)		
Necrosis, focal	2 (4%)			
Vacuolization cytoplasmic	1 (2%)		1 (2%)	1 (2%)
Adrenal gland, medulla	(44)	(49)	(49)	(46)
Hyperplasia				2 (4%)
Hyperplasia, focal	8 (18%)	9 (18%)	8 (16%)	5 (11%)
Necrosis, focal		1 (2%)		
Islets, pancreatic	(49)	(49)	(46)	(48)
Hyperplasia	1 (2%)	1 (2%)		2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Endocrine System (continued)				
Parathyroid gland	(42)	(45)	(46)	(45)
Hyperplasia		4 (9%)	6 (13%)	8 (18%)
Pituitary gland	(48)	(49)	(49)	(48)
Pars distalis, angiectasis	1 (2%)		2 (4%)	
Pars distalis, cyst	2 (4%)	4 (8%)	1 (2%)	2 (4%)
Pars distalis, hyperplasia, focal	18 (38%)	15 (31%)	15 (31%)	10 (21%)
Pars distalis, pigmentation, hemosiderin	2 (4%)		1 (2%)	
Pars intermedia, pigmentation, hemosiderin			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	15 (30%)	12 (24%)	17 (34%)	13 (26%)
Follicle, cyst	1 (2%)			1 (2%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Degeneration, focal				1 (2%)
Penis			(1)	(1)
Concretion			1 (100%)	1 (100%)
Preputial gland	(48)	(50)	(49)	(47)
Abscess	3 (6%)	1 (2%)	5 (10%)	3 (6%)
Cyst	2 (4%)	1 (2%)		
Ectasia	1 (2%)			
Hyperplasia			2 (4%)	
Inflammation, acute	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	17 (35%)	15 (30%)	13 (27%)	15 (32%)
Inflammation, subacute			1 (2%)	
Prostate	(47)	(49)	(50)	(49)
Abscess				1 (2%)
Atrophy	13 (28%)	16 (33%)	17 (34%)	13 (27%)
Hyperplasia, focal	1 (2%)			3 (6%)
Inflammation, acute	6 (13%)	6 (12%)	5 (10%)	5 (10%)
Inflammation, chronic	7 (15%)	6 (12%)	5 (10%)	7 (14%)
Inflammation, subacute			1 (2%)	
Metaplasia, squamous	1 (2%)			
Seminal vesicle	(48)	(49)	(50)	(50)
Atrophy	30 (63%)	35 (71%)	32 (64%)	29 (58%)
Dilatation			1 (2%)	2 (4%)
Inflammation, acute		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Hemorrhage			1 (2%)	
Hypospermia				1 (2%)
Artery, inflammation		1 (2%)		
Interstitial cell, hyperplasia	1 (2%)	2 (4%)	5 (10%)	3 (6%)
Seminiferous tubule, atrophy	37 (74%)	36 (72%)	33 (66%)	25 (50%)
Seminiferous tubule, hypospermia	1 (2%)	3 (6%)	2 (4%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Hyperplasia	19 (38%)	20 (40%)	20 (40%)	20 (41%)
Myelofibrosis		3 (6%)	2 (4%)	3 (6%)
Lymph node	(50)	(50)	(50)	(49)
Inguinal, infiltration cellular, plasma cell				1 (2%)
Lumbar, infiltration cellular, plasma cell				1 (2%)
Mediastinal, congestion	1 (2%)	1 (2%)	1 (2%)	
Mediastinal, infiltration cellular, plasma cell	1 (2%)	1 (2%)		1 (2%)
Mediastinal, lymphatic, angiectasis	1 (2%)			1 (2%)
Pancreatic, congestion	1 (2%)		1 (2%)	
Pancreatic, infiltration cellular, plasma cell		1 (2%)		
Pancreatic, lymphatic, angiectasis	1 (2%)			
Renal, congestion		1 (2%)		
Renal, infiltration cellular, plasma cell				2 (4%)
Renal, lymphatic, angiectasis				1 (2%)
Lymph node, mandibular	(47)	(45)	(49)	(45)
Angiectasis			1 (2%)	
Congestion		1 (2%)	4 (8%)	
Granuloma				1 (2%)
Hyperplasia, lymphoid				1 (2%)
Infiltration cellular, plasma cell	34 (72%)	38 (84%)	38 (78%)	27 (60%)
Lymphatic, angiectasis	3 (6%)	5 (11%)		5 (11%)
Lymph node, mesenteric	(49)	(50)	(50)	(48)
Congestion	3 (6%)	1 (2%)	4 (8%)	3 (6%)
Granuloma	23 (47%)	30 (60%)	25 (50%)	22 (46%)
Infiltration cellular, plasma cell				1 (2%)
Lymphatic, angiectasis	7 (14%)	2 (4%)	5 (10%)	4 (8%)
Spleen	(50)	(50)	(50)	(50)
Congestion	2 (4%)		1 (2%)	1 (2%)
Fibrosis, focal	2 (4%)	3 (6%)		6 (12%)
Granuloma	1 (2%)			
Hematopoietic cell proliferation	11 (22%)	13 (26%)	15 (30%)	20 (40%)
Necrosis, focal				1 (2%)
Pigmentation, hemosiderin	4 (8%)	9 (18%)	8 (16%)	5 (10%)
Thrombus			1 (2%)	
Capsule, fibrosis, focal			1 (2%)	
Thymus	(40)	(37)	(40)	(42)
Atrophy	1 (3%)			
Congestion				1 (2%)
Integumentary System				
Mammary gland	(36)	(34)	(35)	(36)
Abscess		1 (3%)		
Ectasia	5 (14%)	5 (15%)	3 (9%)	5 (14%)
Galactocele	3 (8%)	1 (3%)		
Hypertrophy				1 (3%)
Skin	(50)	(50)	(48)	(49)
Acanthosis	1 (2%)			
Hyperkeratosis	1 (2%)			2 (4%)
Hyperplasia, basal cell	1 (2%)	1 (2%)		
Dermis, fibrosis		1 (2%)		
Subcutaneous tissue, lymphatic, dilatation			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Musculoskeletal System				
None				
Nervous System				
Brain	(49)	(50)	(50)	(49)
Hydrocephalus	6 (12%)	4 (8%)	4 (8%)	4 (8%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Fungus		1 (2%)		
Granuloma		2 (4%)		
Hemorrhage, focal			1 (2%)	
Inflammation, subacute, focal		1 (2%)		
Alveolar epithelium, metaplasia	1 (2%)	3 (6%)	4 (8%)	3 (6%)
Alveolus, inflammation, acute, focal				1 (2%)
Interstitium, inflammation, chronic				1 (2%)
Peribronchial, inflammation, chronic	25 (50%)	20 (40%)	15 (30%)	18 (36%)
Pleura, fibrosis	1 (2%)			
Pleura, inflammation, chronic, focal				1 (2%)
Nose	(49)	(50)	(50)	(49)
Cyst		1 (2%)		
Fibrosis			1 (2%)	
Fungus	6 (12%)	4 (8%)	3 (6%)	3 (6%)
Hemorrhage	2 (4%)			1 (2%)
Inflammation, acute	4 (8%)	5 (10%)	6 (12%)	4 (8%)
Inflammation, chronic	20 (41%)	22 (44%)	17 (34%)	10 (20%)
Metaplasia, squamous	35 (71%)	30 (60%)	30 (60%)	22 (45%)
Parasite metazoan				2 (4%)
Special Senses System				
Eye	(3)	(5)	(11)	(8)
Anterior chamber, fibrosis			1 (9%)	
Anterior chamber, inflammation, acute				1 (13%)
Lens, degeneration	1 (33%)			2 (25%)
Retina, degeneration				2 (25%)
Retrobulbar, hemorrhage				1 (13%)
Harderian gland	(4)	(5)	(9)	(6)
Inflammation, chronic			2 (22%)	
Pigmentation	4 (100%)	4 (80%)	9 (100%)	6 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Atrophy, focal	1 (2%)			
Congestion				1 (2%)
Cyst			1 (2%)	
Fibrosis, focal			1 (2%)	1 (2%)
Mineralization, focal		1 (2%)		1 (2%)
Nephropathy	50 (100%)	50 (100%)	50 (100%)	49 (98%)
Cortex, necrosis, focal			1 (2%)	1 (2%)
Interstitial tissue, hyperplasia				1 (2%)
Pelvis, transitional epithelium, hyperplasia			1 (2%)	
Renal tubule, cyst	2 (4%)	2 (4%)	1 (2%)	4 (8%)
Renal tubule, hyperplasia	1 (2%)	5 (10%)	3 (6%)	5 (10%)
Renal tubule, necrosis, focal		1 (2%)		
Renal tubule, pigmentation	3 (6%)	5 (10%)	2 (4%)	1 (2%)
Transitional epithelium, hyperplasia	1 (2%)			1 (2%)
Transitional epithelium, hyperplasia, focal	2 (4%)			1 (2%)
Urinary bladder	(49)	(48)	(47)	(46)
Concretion		2 (4%)	1 (2%)	
Inflammation, chronic		2 (4%)	1 (2%)	
Artery, inflammation, chronic	1 (2%)			

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

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	6	4	3	
Moribund	14	12	13	22
Survivors				
Terminal sacrifice	28	34	34	27
Died last week of study	2			1
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(47)	(48)	(50)	(50)
Intestine large, colon	(48)	(49)	(49)	(49)
Intestine small, duodenum	(48)	(50)	(50)	(50)
Intestine small, ileum	(43)	(46)	(48)	(50)
Liver	(50)	(50)	(50)	(50)
Mesentery	(6)	(3)	(6)	(8)
Sarcoma	1 (17%)			
Pancreas	(47)	(49)	(49)	(48)
Pharynx				(1)
Palate, papilloma squamous				1 (100%)
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(49)
Stomach, glandular	(48)	(50)	(50)	(50)
Tooth	(1)	(1)		(1)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(49)
Adenoma	1 (2%)			
Adrenal gland, medulla	(39)	(47)	(44)	(47)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign	3 (8%)	6 (13%)	6 (14%)	4 (9%)
Islets, pancreatic	(46)	(49)	(48)	(47)
Adenoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Pituitary gland	(47)	(50)	(50)	(49)
Pars distalis, adenoma	23 (49%)	31 (62%)	27 (54%)	24 (49%)
Pars distalis, carcinoma	1 (2%)		2 (4%)	1 (2%)
Thyroid gland	(49)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	9 (18%)	4 (8%)	6 (12%)	7 (14%)
C-cell, carcinoma	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma				2 (4%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
General Body System				
Tissue NOS	(2)	(1)		
Sarcoma	1 (50%)	1 (100%)		
Squamous cell carcinoma	1 (50%)			
Genital System				
Clitoral gland	(43)	(47)	(43)	(40)
Adenoma	3 (7%)	1 (2%)	6 (14%)	5 (13%)
Carcinoma	4 (9%)	5 (11%)	3 (7%)	2 (5%)
Papilloma squamous	1 (2%)			
Bilateral, adenoma	2 (5%)			
Ovary	(49)	(50)	(50)	(49)
Granulosa cell neoplasm benign	1 (2%)			
Luteoma	1 (2%)			
Uterus	(49)	(50)	(50)	(50)
Leiomyoma		1 (2%)		
Leiomyosarcoma	1 (2%)	1 (2%)		
Polyp stromal	15 (31%)	12 (24%)	14 (28%)	10 (20%)
Hematopoietic System				
Blood	(31)	(6)	(4)	(29)
Bone marrow	(49)	(49)	(49)	(50)
Lymph node	(50)	(49)	(50)	(50)
Lymph node, mandibular	(43)	(46)	(45)	(44)
Lymph node, mesenteric	(48)	(48)	(49)	(50)
Spleen	(50)	(50)	(50)	(50)
Sarcoma				1 (2%)
Thymus	(39)	(42)	(36)	(42)
Thymoma benign	1 (3%)			
Integumentary System				
Mammary gland	(46)	(47)	(48)	(43)
Adenocarcinoma		1 (2%)	1 (2%)	2 (5%)
Fibroadenoma	19 (41%)	23 (49%)	20 (42%)	18 (42%)
Fibroadenoma, multiple		1 (2%)		
Skin	(50)	(46)	(48)	(48)
Basal cell adenoma		1 (2%)		
Basal cell carcinoma	1 (2%)			
Papilloma squamous		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibroma	2 (4%)	2 (4%)		
Subcutaneous tissue, fibrosarcoma	2 (4%)			2 (4%)
Subcutaneous tissue, schwannoma, malignant	1 (2%)			
Musculoskeletal System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Nervous System				
Brain	(49)	(50)	(50)	(50)
Astrocytoma malignant				1 (2%)
Carcinoma, metastatic, pituitary gland	1 (2%)		1 (2%)	1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)		
Alveolar/bronchiolar carcinoma				1 (2%)
Carcinoma, metastatic, thyroid gland				1 (2%)
Carcinoma adenosquamous	1 (2%)			
Nose	(47)	(50)	(50)	(50)
Adenoma				1 (2%)
Special Senses System				
Zymbal's gland	(1)			(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Sarcoma			1 (2%)	
Renal tubule, adenoma				1 (2%)
Urinary bladder	(44)	(45)	(49)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	9 (18%)	17 (34%)	15 (30%)	24 (48%)
Lymphoma malignant lymphocytic	1 (2%)			
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	46	49	46
Total primary neoplasms	108	117	107	112
Total animals with benign neoplasms	41	44	45	40
Benign neoplasms	83	88	81	73
Total animals with malignant neoplasms	21	23	21	33
Total malignant neoplasms	25	29	26	39
Total animals with metastatic neoplasms	1		1	2
Total metastatic neoplasms	1		1	2

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 0 ppm

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 9 4	4 9 5	5 0 2	5 1 1	5 1 2	5 1 4	5 2 2	5 4 1	5 4 2	5 4 3	5 4 4	5 6 1	5 7 1	5 7 2	5 8 1	5 8 2	5 8 3	5 9 1	5 9 2	5 9 3	5 9 4	5 9 5	6 0 1	6 0 2	6 0 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery												+	+					+					+			6
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Heart	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Adrenal gland, medulla	+	+	+	I	+	+	+	+	M	+	+	I	+	+	+	M	I	+	+	+	+	+	+	+	+	39
Pheochromocytoma benign		X																		X			X			3
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma						X																				1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	M	I	+	+	+	+	M	+	M	+	+	+	42
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Pars distalis, adenoma	X		X		X			X				X		X		X	X			X		X	X		X	23
Pars distalis, carcinoma		X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma								X								X							X			9
C-cell, carcinoma		X																								1
General Body System																										
Tissue NOS																										2
Sarcoma																										1
Squamous cell carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 0 ppm (continued)

Number of Days on Study	3 3 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 8 9 0 1 7 7 7 9 0 2 4 5 6 6 6 7 8 9 0 2 2 3 3 3 3 0 6 1 7 4 5 8 6 7 5 4 2 4 8 8 9 3 7 4 4 9 0 6 6 6
Carcass ID Number	5 5 5 5 6 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 5 5 3 2 0 6 6 3 6 5 6 0 3 3 8 1 5 8 7 5 4 0 9 9 9 5 4 4 5 4 5 4 3 3 3 2 5 2 1 5 5 2 4 5 1 5 4 1 2 3
Genital System	
Clitoral gland	M M + + + + M + + + M M + + + + + + + M + + + + +
Adenoma	
Carcinoma	X X
Squamous cell papilloma	
Bilateral, adenoma	
Ovary	+ +
Granulosa cell tumor benign	
Luteoma	X
Uterus	+ +
Leiomyosarcoma	X
Polyp stromal	X X X X X X X X X
Hematopoietic System	
Blood	+ + + + + +
Bone marrow	+ + + + + A + + + + + + + + + + + + + + + + + + +
Lymph node	+ +
Lymph node, mandibular	M + + + + A + + + M + + + + + + + + M + + + + + +
Lymph node, mesenteric	+ + + + M M + + + + + + + + + + + + + + + + + + +
Spleen	+ +
Thymus	+ + + + + + + + + + + M + + M + M M M M M + + + +
Thymoma benign	X
Integumentary System	
Mammary gland	+ M + +
Fibroadenoma	X X X X X X X X
Skin	+ +
Basal cell carcinoma	X
Subcutaneous tissue, fibroma	
Subcutaneous tissue, fibrosarcoma	X
Subcutaneous tissue, schwannoma malignant	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Nervous System	
Brain	+ +
Carcinoma, metastatic, pituitary gland	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 9 4	4 9 5	5 0 2	5 1 1	5 1 2	5 1 4	5 2 2	5 4 1	5 4 2	5 4 3	5 4 4	5 6 1	5 7 1	5 7 2	5 8 1	5 8 2	5 8 3	5 9 1	5 9 2	5 9 3	5 9 4	5 9 5	6 0 1	6 0 2	6 0 3	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		43
Adenoma									X							X		X								3
Carcinoma								X													X					4
Squamous cell papilloma							X																			1
Bilateral, adenoma	X																X									2
Ovary	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor benign																					X					1
Luteoma																										1
Uterus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Polyp stromal		X						X				X	X						X		X	X				15
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	39
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	46
Fibroadenoma		X	X	X					X	X		X				X		X			X		X			19
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Subcutaneous tissue, fibroma													X							X						2
Subcutaneous tissue, fibrosarcoma		X																								2
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland		X																								1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 0 ppm (continued)

Number of Days on Study	3 3 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 8 9 0 1 7 7 7 9 0 2 4 5 6 6 6 7 8 9 0 2 2 3 3 3 3 0 6 1 7 4 5 8 6 7 5 4 2 4 8 8 9 3 7 4 4 9 0 6 6 6
Carcass ID Number	5 5 5 5 6 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 5 5 3 2 0 6 6 3 6 5 6 0 3 3 8 1 5 8 7 5 4 0 9 9 9 5 4 4 5 4 5 4 3 3 3 2 5 2 1 5 5 2 4 5 1 5 4 1 2 3
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Carcinoma adenosquamous	X
Nose	+ + + + + A + + + + + + + A + + + + + + + + + + +
Trachea	+ +
Special Senses System	
Ear	+ + +
Eye	+ + + + + + + + + + +
Harderian gland	+ + + + + + + + + + +
Zymbal's gland	
Urinary System	
Kidney	+ +
Urinary bladder	+ + + A A A + + + + + + + A + + + + + + + + + A + + +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X
Lymphoma malignant lymphocytic	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 9 4	4 9 5	5 0 2	5 1 1	5 1 2	5 1 4	5 2 2	5 4 1	5 4 2	5 4 3	5 4 4	5 6 1	5 7 1	5 7 2	5 8 1	5 8 2	5 8 3	5 9 1	5 9 2	5 9 3	5 9 4	5 9 5	6 0 1	6 0 2	6 0 3	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																											1
Carcinoma adenosquamous																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear																											3
Eye				+	+																						9
Harderian gland					+																						8
Zymbal's gland				+																							1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X							X									X							9
Lymphoma malignant lymphocytic																	X										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	6 3 3	6 4 3	6 4 4	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 3	6 6 4	6 7 1	6 7 2	6 7 3	6 7 4	6 8 1	6 8 3	6 8 4	6 9 1	6 9 2	7 0 2	7 1 1	7 1 2	7 1 3	7 1 4	7 2 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+										+												3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																									+	1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	47
Pheochromocytoma malignant																										1
Pheochromocytoma benign								X				X			X									X		6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X																		2
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X					X	X	X	X		X	X	X	X	X	X	X				X		31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma																		X				X				4
C-cell, carcinoma	X							X																		3
Follicular cell, adenoma																								X		1
General Body System																										
Tissue NOS																										1
Sarcoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	4 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7
	9 0 6 7 8 1 2 2 4 5 7 8 8 9 1 1 3 3 3 3 3 3 3 3 3
	9 1 2 6 1 8 6 7 4 5 0 9 9 4 0 6 5 5 5 5 5 5 6 6 6
Carcass ID Number	6 7 6 7 6 7 7 7 7 6 6 6 6 6 6 6 6 6 6 6 6 7 6 6 6
	7 0 1 1 9 2 2 0 2 2 5 6 9 3 4 8 1 1 1 2 3 2 2 3 3
	5 3 3 5 5 5 4 1 3 3 5 5 4 5 5 5 1 2 4 2 4 1 1 1 2
Genital System	
Clitoral gland	+ + + M + + + M + + + + + + + + + + + + + + + + +
Adenoma	X
Carcinoma	X X
Ovary	+ +
Uterus	+ +
Leiomyoma	
Leiomyosarcoma	X
Polyp stromal	X X X X
Vagina	
Hematopoietic System	
Blood	+ +
Bone marrow	+ I
Lymph node	+ +
Lymph node, mandibular	+ M + + + + + M + + + + + + + + + M + + + + + + + +
Lymph node, mesenteric	+ + + + + + + + + + A + + + + + + + + + + + + + +
Spleen	+ +
Thymus	+ + + + + + + + + + A + + + + + + + + + + + + + M
Integumentary System	
Mammary gland	M +
Adenocarcinoma	
Fibroadenoma	X X X X X X X X X X
Fibroadenoma, multiple	X
Skin	+ + + + + + + + + + + + + + + + + + + M + + + + +
Basal cell adenoma	
Squamous cell papilloma	X
Subcutaneous tissue, fibroma	X X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	
Nose	+ +
Trachea	+ +

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	6 3 3	6 4 3	6 4 4	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 3	6 6 4	6 7 1	6 7 2	6 7 3	6 7 4	6 8 1	6 8 3	6 8 4	6 9 1	6 9 2	7 0 2	7 1 1	7 1 2	7 1 3	7 1 4	7 2 2	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Carcinoma			X		X																	X				5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma		X																								1
Leiomyosarcoma																										1
Polyp stromal	X					X		X			X	X						X				X				12
Vagina						+																				1
Hematopoietic System																										
Blood										+					+							+			+	6
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	42
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																	X									1
Fibroadenoma			X		X		X	X	X	X	X			X	X		X	X	X	X		X			X	23
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	46
Basal cell adenoma														X												1
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	6 3 3	6 4 3	6 4 4	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 3	6 6 4	6 7 1	6 7 2	6 7 3	6 7 4	6 8 1	6 8 3	6 8 4	6 9 1	6 9 2	7 0 2	7 1 1	7 1 2	7 1 3	7 1 4	7 2 2		Total Tissues/ Tumors
Special Senses System																											
Ear					+																						1
Eye					+	+														+			+				11
Harderian gland						+																	+				8
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X		X					X				X	X	X	X		X			X				X	17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm

Number of Days on Study	3 7 2	4 5 6	4 8 5	5 0 6	5 1 9	5 3 4	5 7 0	5 9 0	5 9 1	6 1 1	6 1 3	6 4 4	6 7 6	6 8 9	7 1 5	7 1 8	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5
Carcass ID Number	8 3 5	7 8 5	8 4 5	7 6 4	8 4 4	7 7 5	8 0 4	8 2 5	7 9 5	7 8 4	7 9 4	8 1 4	7 8 3	8 3 4	7 5 5	8 2 4	7 5 1	7 5 2	7 5 4	8 1 2	8 1 3	7 3 1	7 3 2	7 3 3	7 3 4
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+																	+					+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X				X						X	X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X				
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X			X			X						X	X	X	X		X	X	X	X	
Pars distalis, carcinoma																							X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								
C-cell, carcinoma																X	X							
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M
Adenoma										X												X		
Carcinoma																							X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 3 5	7 4 1	7 4 2	7 4 3	7 6 1	7 6 3	7 7 1	7 7 2	7 7 3	7 8 1	7 8 2	7 9 1	7 9 2	7 9 3	8 0 1	8 0 2	8 0 3	8 1 1	8 2 1	8 2 2	8 2 3	8 3 1	8 3 2	8 3 3	8 4 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+																		+		+				6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	I	+	M	+	+	+	+	44
Pheochromocytoma benign						X																			X	6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	48
Adenoma																										1
Parathyroid gland	M	+	M	+	M	+	+	+	+	+	I	+	+	+	M	+	M	M	+	+	+	M	M	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X			X	X		X		X	X				X	X		X			X	27
Pars distalis, carcinoma													X													2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X																	X			X	X		X	X	6
C-cell, carcinoma					X																					3
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenoma					X					X				X						X						6
Carcinoma				X	X																					3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm
(continued)

Number of Days on Study	3 7 2	4 5 6	4 8 5	5 0 6	5 1 9	5 3 4	5 7 0	5 9 0	5 9 1	6 1 1	6 1 3	6 4 4	6 7 6	6 8 9	7 1 5	7 1 8	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	8 3 5	7 8 5	8 4 5	7 6 4	8 4 4	7 7 5	8 0 4	8 2 5	7 9 5	7 8 4	7 9 4	8 1 4	7 8 3	8 3 4	7 5 5	8 2 4	7 5 1	7 5 2	7 5 4	8 1 2	8 1 3	7 3 1	7 3 2	7 3 3	7 3 4
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal	X							X	X	X						X			X		X		X		
Hematopoietic System																									
Blood																							+		+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	M	+	M	M	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma				X				X		X				X						X					X
Skin	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear			+																						
Eye			+	+									+		+										
Harderian gland													+		+										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 3 5	7 4 1	7 4 2	7 4 3	7 6 1	7 6 3	7 7 1	7 7 2	7 7 3	7 8 1	7 8 2	7 9 1	7 9 2	7 9 3	8 0 1	8 0 2	8 0 3	8 1 1	8 2 1	8 2 2	8 2 3	8 3 1	8 3 2	8 3 3	8 4 2	Total Tissues/ Tumors
Genital System (continued)																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X		X					X			X	X							X			14
Hematopoietic System																										
Blood					+			+																		4
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	I	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	M	+	+	M	M	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	36
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma	X																									1
Fibroadenoma	X		X	X	X						X		X	X		X		X	X	X		X	X	X		20
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	M	+	+	48
Squamous cell papilloma																X										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland													X													1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye					+													+			+					7
Harderian gland					+													+			+					5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 3,000 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 3 5	7 4 1	7 4 2	7 4 3	7 6 1	7 6 3	7 7 1	7 7 2	7 7 3	7 8 1	7 8 2	7 9 1	7 9 2	7 9 3	8 0 1	8 0 2	8 0 3	8 1 1	8 2 1	8 2 2	8 2 3	8 3 1	8 3 2	8 3 3	8 4 2	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X			X				X									X					15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm

Number of Days on Study	2 4 5	3 0 8	3 5 4	4 7 1	5 1 9	5 5 4	5 8 5	5 8 5	6 1 1	6 1 4	6 2 8	6 3 9	6 4 0	6 4 0	6 5 2	6 6 2	6 6 8	6 7 2	6 7 8	6 9 0	6 9 3	7 0 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	8 6 5	9 6 5	9 6 4	9 1 5	8 8 5	9 6 3	8 8 4	9 6 2	9 1 4	8 5 5	9 0 4	9 1 3	8 7 5	8 8 3	8 9 5	8 5 4	9 5 5	9 4 4	9 7 2	8 9 1	8 7 4	8 7 3	8 5 1	8 5 2	8 5 3
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery															+		+				+	+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Pharynx																									
Palate, squamous cell papilloma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+														
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma									X																
Parathyroid gland	M	M	M	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X		X		X		X				X				X				X		X
Pars distalis, carcinoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X									
C-cell, carcinoma																	X								
Follicular cell, carcinoma												X													
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	8 6 2	8 6 4	9 5 4	8 8 2	9 3 1	9 3 2	9 3 4	9 3 5	9 4 1	9 4 2	9 4 3	9 5 1	9 5 2	8 7 1	8 8 1	8 8 4	9 1 2	9 2 2	8 9 3	9 9 1	9 0 1	9 0 3	9 1 1	9 2 2	9 2 4	9 2 5	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+	+	+				+																		8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pharynx																			+								1
Palate, squamous cell papilloma																			X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																											1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign		X				X				X										X							4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Adenoma																											1
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X		X	X				X					X	X	X		X	X	X	X	X	X	X			24
Pars distalis, carcinoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X	X								X		X								X	X				7
C-cell, carcinoma																											1
Follicular cell, carcinoma																								X			2
General Body System																											
None																											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm
(continued)

Number of Days on Study	2 4 5	3 0 8	3 5 4	4 7 1	5 1 9	5 5 4	5 8 5	5 8 5	6 1 1	6 1 4	6 2 8	6 3 9	6 4 0	6 4 0	6 5 2	6 6 2	6 6 8	6 7 2	6 7 8	6 9 0	6 9 3	7 0 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	8 6 5	9 6 5	9 6 4	9 1 5	8 8 5	9 6 3	8 8 4	9 6 2	9 1 4	8 5 5	9 0 4	9 1 3	8 7 5	8 8 3	8 9 5	8 5 4	9 5 5	9 4 4	9 7 2	8 6 1	8 7 4	8 7 3	8 5 1	8 5 2	8 5 3
Genital System																									
Clitoral gland	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+
Adenoma													X								X				X
Carcinoma		X																							
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X		X				X		X	X										X
Vagina											+														
Hematopoietic System																									
Blood																						+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+
Integumentary System																									
Mammary gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma									X											X					
Fibroadenoma				X	X								X	X				X					X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibrosarcoma																				X		X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Carcinoma, metastatic, pituitary gland																								X	
Peripheral nerve				+																					
Spinal cord	+			+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, thyroid gland																	X								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	8 6 2	8 6 4	9 5 4	8 8 2	9 3 1	9 3 2	9 3 4	9 3 5	9 4 1	9 4 2	9 4 3	9 5 1	9 5 2	8 7 1	8 8 1	8 9 4	9 1 2	8 9 2	8 9 3	9 0 1	9 0 3	9 1 1	9 2 2	9 2 4	9 2 5	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	40
Adenoma																				X			X			5
Carcinoma												X														2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal															X					X			X		X	10
Vagina																					+					2
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	29
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																					X					1
Thymus	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	43
Adenocarcinoma																										2
Fibroadenoma		X	X			X			X					X			X	X	X	X	X	X			18
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																					X					1
Subcutaneous tissue, fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Carcinoma, metastatic, pituitary gland																										1
Peripheral nerve																										1
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																				X						1
Carcinoma, metastatic, thyroid gland																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm
(continued)

Number of Days on Study	2 4 5	3 0 8	3 5 4	4 7 1	5 1 9	5 5 4	5 8 5	5 8 5	5 8 5	6 1 1	6 1 4	6 2 8	6 3 9	6 4 0	6 4 0	6 5 2	6 6 2	6 6 8	6 7 2	6 7 8	6 9 0	6 9 3	7 0 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	8 6 5	9 6 5	9 6 4	9 1 5	8 8 5	9 6 3	8 8 4	9 6 2	9 1 4	8 5 5	9 0 4	9 1 3	8 7 5	8 8 3	8 9 5	8 5 4	8 5 5	9 5 4	9 4 4	8 7 2	9 6 1	8 7 4	8 7 3	8 5 1	8 5 2	8 5 3
Respiratory System (continued)																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear										+																
Eye	+			+			+			+										+		+				
Harderian gland							+													+		+				
Zymbal's gland			+																							
Carcinoma			X																							
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																		X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X	X		X	X	X	X	X		X	X	X	X	X	X	X				X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Acetaminophen: 6,000 ppm
(continued)

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	730	731	731	731	731	732	732	732	732	732	732	732	732	
Carcass ID Number	86 2	86 4	95 4	88 2	90 1	93 2	93 4	93 5	93 1	94 1	94 2	94 3	95 1	95 2	97 1	88 1	89 4	91 2	99 2	90 3	90 1	90 3	91 1	92 2	92 4	92 5	Total Tissues/ Tumors
Respiratory System (continued)																											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear																							+				2
Eye					+										+										+		9
Harderian gland															+										+		5
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X						X						X		X	X				X	X		X	24

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	3/39 (8%)	6/47 (13%)	6/44 (14%)	4/47 (9%)
Adjusted rates[b]	12.5%	17.8%	18.4%	16.0%
Terminal rates[c]	3/24 (13%)	5/32 (16%)	4/29 (14%)	4/25 (16%)
First incidence (days)	729 (T)	689	644	729 (T)
Life table tests[d]	P=0.502	P=0.389	P=0.325	P=0.523
Logistic regression tests[d]	P=0.541	P=0.399	P=0.315	P=0.523
Cochran-Armitage test[d]	P=0.485N			
Fisher exact test[d]		P=0.344	P=0.306	P=0.605
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates	3/39 (8%)	7/47 (15%)	6/44 (14%)	4/47 (9%)
Adjusted rates	12.5%	19.8%	18.4%	16.0%
Terminal rates	3/24 (13%)	5/32 (16%)	4/29 (14%)	4/25 (16%)
First incidence (days)	729 (T)	644	644	729 (T)
Life table tests	P=0.553N	P=0.277	P=0.325	P=0.523
Logistic regression tests	P=0.497N	P=0.287	P=0.315	P=0.523
Cochran-Armitage test	P=0.410N			
Fisher exact test		P=0.245	P=0.306	P=0.605
Clitoral Gland: Adenoma				
Overall rates	5/43 (12%)	1/47 (2%)	6/43 (14%)	5/40 (13%)
Adjusted rates	17.2%	3.0%	19.9%	18.8%
Terminal rates	5/29 (17%)	1/33 (3%)	5/28 (18%)	3/22 (14%)
First incidence (days)	729 (T)	729 (T)	611	640
Life table tests	P=0.114	P=0.074N	P=0.477	P=0.475
Logistic regression tests	P=0.125	P=0.074N	P=0.463	P=0.493
Cochran-Armitage test	P=0.187			
Fisher exact test		P=0.082N	P=0.500	P=0.583
Clitoral Gland: Carcinoma				
Overall rates	4/43 (9%)	5/47 (11%)	3/43 (7%)	2/40 (5%)
Adjusted rates	12.3%	13.9%	10.7%	6.5%
Terminal rates	2/29 (7%)	3/33 (9%)	3/28 (11%)	1/22 (5%)
First incidence (days)	679	670	729 (T)	308
Life table tests	P=0.275N	P=0.574	P=0.503N	P=0.426N
Logistic regression tests	P=0.214N	P=0.570	P=0.528N	P=0.297N
Cochran-Armitage test	P=0.212N			
Fisher exact test		P=0.557	P=0.500N	P=0.373N
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	9/43 (21%)	6/47 (13%)	8/43 (19%	7/40 (18%)
Adjusted rates	28.5%	16.8%	26.8%	24.6%
Terminal rates	7/29 (24%)	4/33 (12%)	7/28 (25%)	4/22 (18%)
First incidence (days)	679	670	611	308
Life table tests	P=0.386	P=0.209N	P=0.519N	P=0.579N
Logistic regression tests	P=0.455	P=0.199N	P=0.549N	P=0.482N
Cochran-Armitage test	P=0.527			
Fisher exact test		P=0.225N	P=0.500N	P=0.454N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Mammary Gland: Fibroadenoma				
Overall rates	19/50 (38%)	24/50 (48%)	20/50 (40%)	18/50 (36%)
Adjusted rates	47.8%	61.0%	52.0%	52.9%
Terminal rates	10/30 (33%)	19/34 (56%)	16/34 (47%)	13/28 (46%)
First incidence (days)	517	576	506	471
Life table tests	P=0.426N	P=0.384	P=0.514N	P=0.555
Logistic regression tests	P=0.338N	P=0.261	P=0.507	P=0.540N
Cochran-Armitage test	P=0.261N			
Fisher exact test		P=0.210	P=0.500	P=0.500N
Mammary Gland: Fibroadenoma or Adenocarcinoma				
Overall rates	19/50 (38%)	24/50 (48%)	20/50 (40%)	20/50 (40%)
Adjusted rates	47.8%	61.0%	52.0%	55.5%
Terminal rates	10/30 (33%)	19/34 (56%)	16/34 (47%)	13/28 (46%)
First incidence (days)	517	576	506	471
Life table tests	P=0.473	P=0.384	P=0.514N	P=0.407
Logistic regression tests	P=0.509N	P=0.261	P=0.507	P=0.463
Cochran-Armitage test	P=0.421N			
Fisher exact test		P=0.210	P=0.500	P=0.500
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	23/47 (49%)	31/50 (62%)	27/50 (54%)	24/49 (49%)
Adjusted rates	60.5%	71.3%	66.9%	68.9%
Terminal rates	14/28 (50%)	22/34 (65%)	21/34 (62%)	17/27 (63%)
First incidence (days)	517	501	456	471
Life table tests	P=0.531	P=0.309	P=0.540	P=0.435
Logistic regression tests	P=0.374N	P=0.152	P=0.387	P=0.522
Cochran-Armitage test	P=0.296N			
Fisher exact test		P=0.138	P=0.384	P=0.579
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	24/47 (51%)	31/50 (62%)	29/50 (58%)	25/49 (51%)
Adjusted rates	63.4%	71.3%	72.0%	72.0%
Terminal rates	15/28 (54%)	22/34 (65%)	23/34 (68%)	18/27 (67%)
First incidence (days)	517	501	456	471
Life table tests	P=0.469	P=0.379	P=0.489	P=0.432
Logistic regression tests	P=0.442N	P=0.210	P=0.316	P=0.519
Cochran-Armitage test	P=0.346N			
Fisher exact test		P=0.189	P=0.315	P=0.579N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	4/50 (8%)	2/50 (4%)	0/50 (0%)	2/50 (4%)
Adjusted rates	11.8%	5.0%	0.0%	6.6%
Terminal rates	3/30 (10%)	1/34 (3%)	0/34 (0%)	0/28 (0%)
First incidence (days)	396	562	–[e]	690
Life table tests	P=0.278N	P=0.297N	P=0.053N	P=0.369N
Logistic regression tests	P=0.220N	P=0.406N	P=0.062N	P=0.329N
Cochran-Armitage test	P=0.246N			
Fisher exact test		P=0.339N	P=0.059N	P=0.339N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rates	9/49 (18%)	5/50 (10%)	6/50 (12%)	7/50 (14%)
Adjusted rates	24.7%	12.7%	17.6%	23.7%
Terminal rates	5/30 (17%)	2/34 (6%)	6/34 (18%)	6/28 (21%)
First incidence (days)	578	618	729 (T)	662
Life table tests	P=0.527	P=0.155N	P=0.231N	P=0.450N
Logistic regression tests	P=0.531N	P=0.187N	P=0.268N	P=0.407N
Cochran-Armitage test	P=0.478N			
Fisher exact test		P=0.183N	P=0.274N	P=0.376N
Thyroid Gland (C-cell): Carcinoma				
Overall rates	1/49 (2%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rates	3.3%	8.0%	8.6%	2.9%
Terminal rates	1/30 (3%)	2/34 (6%)	2/34 (6%)	0/28 (0%)
First incidence (days)	729 (T)	626	718	668
Life table tests	P=0.490N	P=0.349	P=0.352	P=0.743
Logistic regression tests	P=0.470N	P=0.326	P=0.336	P=0.759
Cochran-Armitage test	P=0.439N			
Fisher exact test		P=0.316	P=0.316	P=0.747N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	10/49 (20%)	8/50 (16%)	9/50 (18%)	8/50 (16%)
Adjusted rates	27.7%	20.0%	25.7%	25.9%
Terminal rates	6/30 (20%)	4/34 (12%)	8/34 (24%)	6/28 (21%)
First incidence (days)	578	618	718	662
Life table tests	P=0.518N	P=0.317N	P=0.409N	P=0.461N
Logistic regression tests	P=0.464N	P=0.378N	P=0.471N	P=0.413N
Cochran-Armitage test	P=0.403N			
Fisher exact test		P=0.379N	P=0.480N	P=0.379N
Uterus: Stromal Polyp				
Overall rates	15/50 (30%)	12/50 (24%)	14/50 (28%)	10/50 (20%)
Adjusted rates	41.9%	31.9%	34.9%	27.6%
Terminal rates	10/30 (33%)	9/34 (26%)	9/34 (26%)	5/28 (18%)
First incidence (days)	574	627	372	554
Life table tests	P=0.313N	P=0.224N	P=0.394N	P=0.241N
Logistic regression tests	P=0.239N	P=0.263N	P=0.497N	P=0.197N
Cochran-Armitage test	P=0.211N			
Fisher exact test		P=0.326N	P=0.500N	P=0.178N
All Organs: Mononuclear Cell Leukemia				
Overall rates	9/50 (18%)	17/50 (34%)	15/50 (30%)	24/50 (48%)
Adjusted rates	26.4%	42.8%	35.1%	56.3%
Terminal rates	6/30 (20%)	12/34 (35%)	8/34 (24%)	10/28 (36%)
First incidence (days)	575	581	485	554
Life table tests	P=0.003	P=0.116	P=0.188	P=0.003
Logistic regression tests	P=0.003	P=0.070	P=0.120	P=0.001
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.055	P=0.121	P=0.001

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
All Organs: Benign Neoplasms				
Overall rates	41/50 (82%)	44/50 (88%)	45/50 (90%)	40/50 (80%)
Adjusted rates	91.1%	91.6%	97.8%	90.7%
Terminal rates	26/30 (87%)	30/34 (88%)	33/34 (97%)	24/28 (86%)
First incidence (days)	517	501	372	471
Life table tests	P=0.359	P=0.456N	P=0.569	P=0.463
Logistic regression tests	P=0.522N	P=0.420	P=0.174	P=0.591
Cochran-Armitage test	P=0.334N			
Fisher exact test		P=0.288	P=0.194	P=0.500N
All Organs: Malignant Neoplasms				
Overall rates	21/50 (42%)	23/50 (46%)	21/50 (42%)	33/50 (66%)
Adjusted rates	51.1%	53.1%	49.1%	69.9%
Terminal rates	11/30 (37%)	14/34 (41%)	13/34 (38%)	14/28 (50%)
First incidence (days)	380	581	485	245
Life table tests	P=0.011	P=0.543N	P=0.455N	P=0.028
Logistic regression tests	P=0.016	P=0.401	P=0.578	P=0.017
Cochran-Armitage test	P=0.011			
Fisher exact test		P=0.420	P=0.580N	P=0.013
All Organs: Benign or Malignant Neoplasms				
Overall rates	47/50 (94%)	46/50 (92%)	49/50 (98%)	46/50 (92%)
Adjusted rates	95.9%	93.9%	100.0%	92.0%
Terminal rates	28/30 (93%)	31/34 (91%)	34/34 (100%)	24/28 (86%)
First incidence (days)	380	501	372	245
Life table tests	P=0.247	P=0.210N	P=0.425N	P=0.453
Logistic regression tests	P=0.545N	P=0.454N	P=0.305	P=0.482N
Cochran-Armitage test	P=0.545N			
Fisher exact test		P=0.500N	P=0.309	P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined at site.
[b] Kaplan-Meier estimated lifetime neoplasm incidence after adjustment for intercurrent mortality.
[c] Observed incidence at terminal kill.
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. Logistic regression is an alternative method for analyzing the incidence of non-fatal neoplasms. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Leukemias in Untreated Female F344/N Rats

Study	Incidence in Controls
Historical Incidence at EG&G Mason Research Institute[a]	
4,4′-Methylenedianiline 2HCl	3/50
C.I. Basic Red 9	11/50
Monuron	11/50
8-Hydroxyquinoline	6/50
Butyl benzyl phthalate	7/49
2-Biphenylamine HCl	5/50
Pentaerythritol tetranitrate	14/50
4-Hydroxyacetanilide	9/50
Total	66/399 (16.5%)
Standard Deviation	7.9%
Range	6%–28%
Overall Historical Incidences[b]	
Total	425/2,043 (20.8%)
Standard Deviation	8.1%
Range	6%–40%

[a] Toxicology Data Management System compilation (data as of 22 December 1989 for lymphocytic, monocytic, mononuclear, or undifferentiated leukemia) and Carcinogenesis Bioassay Data System compilation (data as of 1 March 1989 for lymphocytic, mononuclear, or myelomonocytic leukemia or leukemia NOS)
[b] Toxicology Data Management System compilation (data as of 22 December 1989 for lymphocytic, monocytic, mononuclear, or undifferentiated leukemia) and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990)

TABLE B4b
Historical Incidence of Zymbal's Gland Carcinoma in Untreated Female F344/N Rats

Study	Incidence in Controls
Historical Incidence at EG&G Mason Research Institute[a]	
4,4′-Methylenedianiline 2HCl	0/50
C.I. Basic Red 9	0/50
Monuron	0/50
8-Hydroxyquinoline	0/50
Butyl benzyl phthalate	0/49
2-Biphenylamine HCl	0/50
Pentaerythritol tetranitrate	0/50
4-Hydroxyacetanilide	0/50
Overall Historical Incidence[b]	
Total	8/2,043 (0.4%)
Standard Deviation	0.8%
Range	0%–4%

[a] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 1 March 1989 for carcinoma, NOS)
[b] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990 for carcinoma, NOS)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	6	4	3	
Moribund	14	12	13	22
Survivors				
Terminal sacrifice	28	34	3427	
Died last week of study	2			1
Animals examined microscopically	50	50	5050	
Alimentary System				
Intestine large, cecum	(47)	(48)	(50)	(50)
Parasite metazoan	2 (4%)	7 (15%)	4 (8%)	5 (10%)
Intestine large, colon	(48)	(49)	(49)	(49)
Parasite metazoan	10 (21%)	7 (14%)	3 (6%)	7 (14%)
Intestine large, rectum	(49)	(49)	(50)	(50)
Parasite metazoan	2 (4%)	9 (18%)	9 (18%)	10 (20%)
Artery, inflammation, chronic			1 (2%),	
Intestine small, duodenum	(48)	(50)	(50)	(50)
Artery, inflammation, chronic			1 (2%)	
Intestine small, jejunum	(48)	(48)	(50)	(50)
Parasite metazoan	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Basophilic focus	38 (76%)	39 (78%)	32 (64%)	20 (40%)
Clear cell focus	1 (2%)			2 (4%)
Cyst			1 (2%)	
Fatty change	15 (30%)	5 (10%)	11 (22%)	17 (34%)
Granuloma	26 (52%)	15 (30%)	7 (14%)	8 (16%)
Hepatodiaphragmatic nodule	10 (20%)	8 (16%)	8 (16%)	6 (12%)
Hyperplasia, focal	4 (8%)	2 (4%)	2 (4%)	8 (16%)
Hyperplasia, multifocal			1 (2%)	
Inflammation, chronic, focal	1 (2%)			
Necrosis, focal	2 (4%)	5 (10%)	5 (10%)	2 (4%)
Bile duct, cyst			1 (2%)	1 (2%)
Bile duct, hyperplasia	15 (30%)	15 (30%)	13 (26%)	19 (38%)
Hepatocyte, hyperplasia		1 (2%)		
Perivascular, inflammation, chronic			1 (2%)	
Mesentery	(6)	(3)	(6)	(8)
Fat, necrosis	5 (83%)	2 (67%)	6 (100%)	8 (100%)
Pancreas	(47)	(49)	(49)	(48)
Angiectasis			1 (2%)	1 (2%)
Edema			1 (2%)	
Acinus, atrophy, focal	15 (32%)	12 (24%)	9 (18%)	9 (19%)
Artery, inflammation, chronic			1 (2%)	
Duct ectasia				1 (2%)
Stomach	(50)	(50)	(50)	(50)
Hyperkeratosis	1 (2%)			
Hyperplasia, basal cell	1 (2%)			
Inflammation, chronic	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(49)
Acanthosis	1 (2%)		2 (4%)	1 (2%)
Diverticulum	1 (2%)			
Hyperkeratosis	1 (2%)		1 (2%)	4 (8%)
Hyperplasia, basal cell	3 (6%)	5 (10%)		
Ulcer	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Epithelium, inflammation, acute	1 (2%)			
Perivascular, inflammation, chronic		1 (2%)		
Submucosa, edema		1 (2%)		
Stomach, glandular	(48)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		2 (4%)	4 (8%)
Mineralization	1 (2%)			1 (2%)
Ulcer	1 (2%)			
Artery, inflammation, chronic			1 (2%)	
Cardiovascular System				
Blood vessel		(1)		
Inflammation, subacute		1 (100%)		
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	27 (55%)	29 (58%)	28 (56%)	30 (60%)
Artery, inflammation, chronic			1 (2%)	1 (2%)
Coronary artery, inflammation, chronic		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(49)
Atrophy	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Congestion	2 (4%)	1 (2%)		1 (2%)
Cytoplasmic alteration, focal	12 (24%)	7 (14%)	6 (12%)	13 (27%)
Hyperplasia	2 (4%)			
Hypertrophy		2 (4%)		
Necrosis, focal	1 (2%)		1 (2%)	
Vacuolization cytoplasmic			1 (2%)	
Adrenal gland, medulla	(39)	(47)	(44)	(47)
Hyperplasia	1 (3%)			
Hyperplasia, focal	4 (10%)		5 (11%)	5 (11%)
Parathyroid gland	(42)	(46)	(37)	(42)
Hyperplasia		2 (4%)		
Pituitary gland	(47)	(50)	(50)	(49)
Pars distalis, angiectasis	5 (11%)	1 (2%)	4 (8%)	4 (8%)
Pars distalis, cyst	22 (47%)	20 (40%)	17 (34%)	22 (45%)
Pars distalis, hemorrhage	2 (4%)	2 (4%)	1 (2%)	
Pars distalis, hyperplasia, focal	7 (15%)	6 (12%)	10 (20%)	9 (18%)
Pars intermedia, cyst		1 (2%)	1 (2%)	
Pars intermedia, hyperplasia			1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, hyperplasia	25 (51%)	26 (52%)	21 (42%)	15 (30%)
Follicle, cyst			1 (2%)	
Follicular cell, hyperplasia				3 (6%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
General Body System				
None				
Genital System				
Clitoral gland	(43)	(47)	(43)	(40)
Abscess	5 (12%)	3 (6%)	2 (5%)	3 (8%)
Cyst	1 (2%)	5 (11%)	4 (9%)	1 (3%)
Ectasia	1 (2%)		1 (2%)	
Fibrosis			1 (2%)	
Inflammation, acute	2 (5%)	2 (4%)		
Inflammation, chronic	3 (7%)	1 (2%)	2 (5%)	
Ovary	(49)	(50)	(50)	(49)
Angiectasis			1 (2%)	
Atrophy		2 (4%)	1 (2%)	
Congestion				2 (4%)
Cyst	4 (8%)	3 (6%)	6 (12%)	3 (6%)
Uterus	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Atrophy	1 (2%)	2 (4%)	2 (4%)	
Dilatation		2 (4%)		1 (2%)
Inflammation, chronic active	1 (2%)			
Mineralization, focal	1 (2%)			
Prolapse	1 (2%)	1 (2%)		
Thrombus	2 (4%)	2 (4%)	1 (2%)	
Endometrium, cyst		2 (4%)	3 (6%)	
Endometrium, hyperplasia, cystic	2 (4%)	2 (4%)		
Serosa, inflammation, acute		1 (2%)		
Vagina		(1)		(2)
Cyst		1 (100%)		
Metestrus				2 (100%)
Hematopoietic System				
Blood	(31)	(6)	(4)	(29)
Lymphocytosis				1 (3%)
Bone marrow	(49)	(49)	(49)	(50)
Hyperplasia	6 (12%)	12 (24%)	7 (14%)	17 (34%)
Myelofibrosis	5 (10%)	2 (4%)	5 (10%)	2 (4%)
Lymph node	(50)	(49)	(50)	(50)
Inguinal, lymphatic, angiectasis				1 (2%)
Mediastinal, congestion	2 (4%)	3 (6%)	1 (2%)	
Mediastinal, granuloma		1 (2%)		
Mediastinal, infiltration cellular, plasma cell				1 (2%)
Mediastinal, lymphatic, angiectasis			1 (2%)	
Pancreatic, congestion	2 (4%)			
Renal, angiectasis		1 (2%)		
Renal, congestion			1 (2%)	
Renal, granuloma		1 (2%)		
Renal, pigmentation			1 (2%)	
Lymph node, mandibular	(43)	(46)	(45)	(44)
Congestion	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Granuloma	2 (5%)			
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, plasma cell	32 (74%)	38 (83%)	35 (78%)	28 (64%)
Lymphatic, angiectasis		1 (2%)		1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(48)	(49)	(50)
Congestion	1 (2%)	2 (4%)	3 (6%)	4 (8%)
Granuloma	36 (75%)	38 (79%)	34 (69%)	27 (54%)
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, plasma cell				1 (2%)
Artery, inflammation, acute			1 (2%)	
Artery, thrombus			1 (2%)	
Lymphatic, angiectasis		2 (4%)		
Spleen	(50)	(50)	(50)	(50)
Congestion		1 (2%)		
Granuloma	3 (6%)		1 (2%)	3 (6%)
Hematopoietic cell proliferation	33 (66%)	29 (58%)	23 (46%)	19 (38%)
Hemorrhage			1 (2%)	
Infarct			1 (2%)	1 (2%)
Pigmentation, hemosiderin	23 (46%)	22 (44%)	28 (56%)	19 (38%)
Capsule, hemorrhage			1 (2%)	
Thymus	(39)	(42)	(36)	(42)
Congestion	1 (3%)		1 (3%)	
Cyst		2 (5%)	1 (3%)	1 (2%)
Integumentary System				
Mammary gland	(46)	(47)	(48)	(43)
Abscess		1 (2%)		
Ectasia	8 (17%)	2 (4%)	4 (8%)	3 (7%)
Galactocele	13 (28%)	8 (17%)	10 (21%)	8 (19%)
Hypertrophy				1 (2%)
Inflammation, acute				1 (2%)
Skin	(50)	(46)	(48)	(48)
Abscess	1 (2%)	1 (2%)		
Cyst epithelial inclusion				1 (2%)
Hemorrhage, focal				1 (2%)
Hyperkeratosis	1 (2%)			
Ulcer		1 (2%)		
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Hyperostosis	7 (14%)	3 (6%)	6 (12%)	10 (20%)
Skeletal muscle	(1)			
Myopathy degenerative	1 (100%)			
Nervous System				
Brain	(49)	(50)	(50)	(50)
Hemorrhage	3 (6%)		2 (4%)	1 (2%)
Hydrocephalus	7 (14%)	5 (10%)	5 (10%)	6 (12%)
Choroid plexus, perivascular, inflammation, chronic		1 (2%)		
Peripheral nerve				(1)
Degeneration				1 (100%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	3 (6%)	5 (10%)	2 (4%)	1 (2%)
Fungus			1 (2%)	
Hemorrhage, focal	3 (6%)		1 (2%)	
Infiltration cellular, histiocytic	2 (4%)			
Alveolar epithelium, metaplasia	1 (2%)			1 (2%)
Peribronchial, inflammation, chronic	20 (40%)	18 (36%)	22 (44%)	22 (44%)
Nose	(47)	(50)	(50)	(50)
Abscess		1 (2%)		
Fungus	3 (6%)	2 (4%)		2 (4%)
Hemorrhage	2 (4%)			
Inflammation, acute	4 (9%)	7 (14%)		4 (8%)
Inflammation, chronic	17 (36%)	21 (42%)	16 (32%)	14 (28%)
Metaplasia, squamous	10 (21%)	14 (28%)	18 (36%)	14 (28%)
Respiratory epithelium, degeneration, hyaline	6 (13%)	1 (2%)	1 (2%)	4 (8%)
Special Senses System				
Ear	(3)	(1)	(1)	(2)
Inflammation, chronic		1 (100%)		
Ulcer, multifocal			1 (100%)	
Eye	(9)	(11)	(7)	(9)
Cornea, inflammation, acute, focal		1 (9%)		
Lens, degeneration				2 (22%)
Retina, degeneration		2 (18%)	1 (14%)	3 (33%)
Harderian gland	(8)	(8)	(5)	(5)
Inflammation, chronic	2 (25%)	1 (13%)	1 (20%)	
Pigmentation	7 (88%)	7 (88%)	4 (80%)	5 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Abscess, multiple	1 (2%)			
Calculus gross observation				1 (2%)
Cyst	1 (2%)			1 (2%)
Inflammation, chronic				1 (2%)
Nephropathy	48 (96%)	49 (98%)	47 (94%)	43 (86%)
Artery, inflammation, chronic			1 (2%)	
Artery, inflammation, subacute		1 (2%)		
Pelvis, transitional epithelium, hyperplasia				2 (4%)
Renal tubule, cyst		1 (2%)		
Renal tubule, degeneration			1 (2%)	
Renal tubule, hyperplasia				1 (2%)
Renal tubule, pigmentation	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Urinary bladder	(44)	(45)	(49)	(50)
Calculus gross observation				1 (2%)
Inflammation, chronic		6 (13%)	2 (4%)	1 (2%)
Artery, inflammation, chronic			1 (2%)	
Transitional epithelium, hyperplasia, diffuse				1 (2%)
Transitional epithelium, hyperplasia, focal			3 (6%)	

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

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Moribund	13	3	16	10
Natural deaths	5	7	3	9
Survivors				
Terminal sacrifice	32	40	31	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(41)	(43)	(47)	(40)
Intestine small, duodenum	(48)	(42)	(49)	(45)
Adenocarcinoma	1 (2%)			
Intestine small, ileum	(48)	(45)	(48)	(44)
Intestine small, jejunum	(47)	(43)	(47)	(45)
Adenocarcinoma		1 (2%)	2 (4%)	
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma	1 (2%)			
Hemangiosarcoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Hepatocellular carcinoma	7 (14%)	1 (2%)	6 (12%)	3 (6%)
Hepatocellular adenoma	11 (22%)	8 (16%)	5 (10%)	4 (8%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Pancreas	(47)	(49)	(50)	(48)
Salivary glands	(50)	(49)	(50)	(49)
Stomach, forestomach	(49)	(49)	(50)	(49)
Papilloma squamous	1 (2%)		3 (6%)	2 (4%)
Stomach, glandular	(50)	(47)	(49)	(48)
Adenocarcinoma				1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Endocrine System				
Adrenal gland	(50)	(48)	(49)	(49)
Capsule, adenoma		1 (2%)		
Subcapsular, adenoma			1 (2%)	
Adrenal gland, cortex	(50)	(48)	(49)	(49)
Adrenal gland, medulla	(47)	(48)	(48)	(48)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign		4 (8%)	1 (2%)	1 (2%)
Pituitary gland	(48)	(39)	(39)	(46)
Thyroid gland	(49)	(49)	(50)	(50)
Follicular cell, adenoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Follicular cell, adenoma, multiple			1 (2%)	
Follicular cell, carcinoma	1 (2%)		1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Prostate	(48)	(42)	(47)	(48)
Seminal vesicle	(49)	(49)	(49)	(50)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(49)
Lymph node	(49)	(47)	(47)	(47)
Axillary, fibrosarcoma, metastatic	1 (2%)			
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Renal, histiocytic sarcoma			1 (2%)	
Lymph node, mandibular	(43)	(20)	(17)	(40)
Lymph node, mesenteric	(43)	(45)	(47)	(42)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma			1 (2%)	
Spleen	(50)	(50)	(49)	(48)
Hemangioma		1 (2%)		
Hemangiosarcoma	2 (4%)			
Histiocytic sarcoma			1 (2%)	
Thymus	(11)	(18)	(28)	(22)
Integumentary System				
Skin	(48)	(49)	(50)	(50)
Basal cell carcinoma		1 (2%)		
Hemangioma			1 (2%)	
Hemangiosarcoma		1 (2%)		
Papilloma squamous	1 (2%)		2 (4%)	
Trichoepithelioma	1 (2%)			
Subcutaneous tissue, fibroma	1 (2%)		1 (2%)	
Subcutaneous tissue, fibrosarcoma	5 (10%)	5 (10%)	3 (6%)	6 (12%)
Subcutaneous tissue, lipoma			1 (2%)	
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Peripheral nerve			(1)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (16%)	5 (10%)	5 (10%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		2 (4%)
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Fibrosarcoma, metastatic, skin	1 (2%)		1 (2%)	
Hemangiosarcoma, metastatic, liver				1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)		2 (4%)	2 (4%)
Nose	(47)	(40)	(46)	(44)
Papilloma squamous		1 (3%)	1 (2%)	
Special Senses System				
Ear			(1)	
Neurofibroma			1 (100%)	
Harderian gland	(4)	(3)	(4)	(3)
Adenoma	4 (100%)	2 (67%)	3 (75%)	3 (100%)
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Renal tubule, adenoma		1 (2%)		1 (2%)
Urinary bladder	(47)	(46)	(46)	(45)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Lymphoma malignant, lymphocytic	1 (2%)	1 (2%)		
Lymphoma malignant mixed	6 (12%)	3 (6%)	2 (4%)	2 (4%)
Lymphoma malignant undifferentiated cell			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	35	29	31	28
Total primary neoplasms	56	41	46	37
Total animals with benign neoplasms	23	22	21	20
Total benign neoplasms	29	25	28	22
Total animals with malignant neoplasms	25	14	17	13
Total malignant neoplasms	27	16	18	15
Total animals with metastatic neoplasms	4		3	6
Total metastatic neoplasms	5		3	6

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm

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

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 3 2	0 3 3	0 4 1	0 5 1	0 5 2	0 2 3	0 2 4	0 4 2	0 6 1	0 6 2	0 6 3	0 6 4	0 7 1	0 7 2	0 7 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	1 0 2	1 1 1	1 2 1	1 2 2	1 2 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma		X																								1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hemangiosarcoma									X																	2
Hepatocellular carcinoma																	X	X								7
Hepatocellular adenoma									X				X						X				X	X		11
Histiocytic sarcoma																										1
Mesentery						+														+					+	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous							X																			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																			+					+		2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	M	M	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	M	M	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma			X																			X				2
Follicular cell, carcinoma																				X						1
General Body System																										
Tissue NOS																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	1 7 6	2 6 7	2 9 3	4 1 9	4 6 3	4 7 9	5 4 1	5 6 1	5 6 3	5 7 8	6 1 8	6 5 1	6 5 4	6 5 4	6 7 1	6 8 9	7 0 3	7 1 8	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 1 5	0 5 5	0 8 4	1 1 4	0 3 4	0 5 4	1 1 3	0 8 2	0 7 4	0 5 3	0 6 5	0 8 1	0 4 4	0 4 5	0 4 3	0 1 5	0 2 5	1 1 2	0 1 1	0 1 2	0 1 3	0 1 4	0 2 1	0 2 2	0 3 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis			+											+											
Preputial gland		+	+		M		+			+	+	+	+	+							+				
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood																		+							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, fibrosarcoma, metastatic																	X								
Lymph node, mandibular	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+
Lymph node, mesenteric	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	M	M	M	+	+	+	+	+	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M
Integumentary System																									
Mammary gland	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Trichoepithelioma										X															
Subcutaneous tissue, fibroma																						X			
Subcutaneous tissue, fibrosarcoma					X	X											X				X	X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 3 2	0 3 3	0 4 1	0 5 1	0 5 2	0 2 3	0 2 4	0 4 2	0 6 1	0 6 2	0 6 3	0 6 4	0 7 1	0 7 2	0 7 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	1 0 2	1 1 1	1 2 1	1 2 2	1 2 3	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										2
Preputial gland			+				+	+	+			+	+			+		+								17
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Axillary, fibrosarcoma, metastatic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																X		2
Thymus	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M	11
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	+	2
Skin	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Papilloma squamous									X																	1
Trichoepithelioma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 3 2	0 3 3	0 4 1	0 5 1	0 5 2	0 2 3	0 2 4	0 4 2	0 6 1	0 6 2	0 6 3	0 6 4	0 7 1	0 7 2	0 7 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	1 0 2	1 1 1	1 2 1	1 2 2	1 2 3	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X							X		X		X	X	X							8
Cholangiocarcinoma, metastatic, liver																										1
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland							+																+			4
Adenoma							X																X			4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed		X			X	X		X				X														6

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 8 4	1 8 1	1 8 2	1 9 1	1 9 2	1 9 3	1 9 4	2 0 1	2 0 2	2 0 3	2 0 4	2 0 5	2 1 1	2 1 2	2 1 3	2 1 4	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 4 1	2 4 2	2 4 3	2 4 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma																					X					1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									X	1
Hepatocellular carcinoma																										1
Hepatocellular adenoma	X				X	X						X							X					X		8
Mesentery									+			+														2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth																				+						1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Capsule, adenoma																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																		X								1
Pheochromocytoma benign		X															X					X			4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	37
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	39
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																				X						1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	0 7 8	0 8 7	1 1 1	1 2 2	4 2 4	4 4 2	5 0 2	6 5 1	6 7 1	6 7 1	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 8 5	1 6 5	1 6 4	2 1 5	2 4 5	1 9 5	1 5 2	2 3 4	1 3 4	1 3 4	1 3 1	1 3 2	1 3 3	1 4 1	1 4 2	1 4 3	1 4 4	1 5 1	1 6 1	1 6 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 3
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	+				+																			
Preputial gland					+					+	+		+	+			+	+		+	+	+	+	
Prostate	M	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	M	+	M	M	+	M	+	+	M	M	+	+	M	M	M	M	+	+	M	M	M	M	+
Lymph node, mesenteric	M	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Thymus	M	M	+	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	+	+	+	M	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																								
Hemangiosarcoma																								
Subcutaneous tissue, fibrosarcoma										X											X			
Musculoskeletal System																								
Bone	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 8 4	1 8 1	1 8 2	1 9 1	1 9 2	1 9 3	1 9 4	2 0 1	2 0 2	2 0 3	2 0 4	2 0 5	2 1 1	2 1 2	2 1 3	2 1 4	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 4 1	2 4 2	2 4 3	2 4 4	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										2
Preputial gland	+		+	+			+		+							+	+			+		+		+	+	22
Prostate	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	42
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mandibular	+	+	M	+	M	+	+	M	M	+	+	+	M	M	M	+	M	M	M	+	M	M	M	M	+	20
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma								X																		1
Thymus	+	M	M	M	+	+	M	+	+	M	M	M	M	+	M	M	M	+	+	M	+	M	M	M	M	18
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	3
Skin	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell carcinoma																		X								1
Hemangiosarcoma								X																		1
Subcutaneous tissue, fibrosarcoma										X		X										X				5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	0 7 8	0 8 7	1 1 1	1 2 2	4 2 4	4 4 2	5 0 2	6 5 1	6 7 1	6 7 1	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 8 5	1 6 5	1 6 4	2 1 5	2 4 5	1 9 5	1 5 2	2 3 4	1 3 4	1 4 5	1 3 1	1 3 2	1 3 3	1 4 1	1 4 2	1 4 3	1 4 4	1 5 1	1 6 1	1 6 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 3
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X						X					X	
Alveolar/bronchiolar adenoma, multiple												X													
Alveolar/bronchiolar carcinoma									X																
Nose	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	M	+
Papilloma squamous															X										
Trachea	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	A	+	A	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic								X																	
Lymphoma malignant mixed																								X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	18404	18801	18802	18901	19002	19003	19004	20001	20002	20003	20004	20005	21001	21102	21103	21104	21201	21202	21203	21301	21402	21501	21502	21503	21504	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X											X													5
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										1
Nose	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	40
Papilloma squamous																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye							+			+	+															3
Harderian gland							+			+	+															3
Adenoma							X				X															2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																								X		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed							X														X					3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 7 1	2 7 2	2 8 1	2 8 2	2 8 3	2 9 1	2 9 2	2 9 3	3 0 2	3 0 3	3 1 1	3 1 2	3 1 3	3 2 1	3 3 1	3 3 2	3 4 1	3 4 2	3 4 3	3 5 1	3 5 2	3 5 3	3 5 4	3 5 5	3 6 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																									2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									2
Hepatocellular carcinoma								X																	6
Hepatocellular adenoma											X	X													5
Histiocytic sarcoma																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous													X										X		3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth		+																							1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcapsular, adenoma																X									1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Pheochromocytoma benign																									1
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	M	M	M	M	+	+	M	+	M	M	+	+	+	+	M	+	+	+	M	M	+	M	28
Pituitary gland	+	M	+	+	M	I	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	39
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																							X		1
Follicular cell, adenoma, multiple										X															1
Follicular cell, carcinoma																									1
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	4 6 1	5 1 0	5 1 2	5 6 3	6 0 8	6 4 4	6 4 7	6 5 0	6 5 4	6 5 5	6 5 7	6 5 7	6 6 1	6 6 6	6 6 0	6 8 7	6 8 5	6 9 9	7 0 5	7 1 9	7 3 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 6 4	3 4 5	2 7 3	2 9 5	2 6 4	3 3 5	3 6 3	3 2 3	3 0 1	3 2 2	2 6 3	3 0 4	3 3 4	3 4 4	3 3 3	3 1 4	2 9 -4	2 8 4	3 6 2	2 5 1	2 5 2	2 5 3	2 5 4	2 6 1	2 6 2
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis										+															
Preputial gland							+	+					+				+	+				+		+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Renal, histiocytic sarcoma																X									
Lymph node, mandibular	+	+	M	+	M	M	M	M	M	M	M	M	M	+	M	M	M	M	+	+	M	M	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Thymus	M	M	+	+	I	+	M	M	+	M	M	M	M	+	M	M	M	M	M	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																X									
Papilloma squamous																									
Subcutaneous tissue, fibroma											X														
Subcutaneous tissue, fibrosarcoma									X		X													X	
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 7 1	2 7 2	2 8 1	2 8 2	2 8 3	2 9 1	2 9 2	2 9 3	3 0 2	3 0 3	3 1 1	3 1 2	3 1 3	3 2 3	3 3 1	3 3 1	3 3 2	3 4 1	3 4 2	3 4 3	3 5 1	3 5 2	3 5 3	3 5 4	3 5 5	3 6 1	**Total Tissues/ Tumors**
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																											1
Preputial gland	+		+							+														+		+	12
Prostate	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Seminal vesicle	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																			X								1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Renal, histiocytic sarcoma																											1
Lymph node, mandibular	M	+	M	M	+	+	M	M	M	+	+	M	+	+	M	M	M	M	+	M	M	M	+	M	M		17
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Histiocytic sarcoma																											1
Thymus	+	+	M	+	+	+	M	M	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+		28
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	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																											1
Papilloma squamous				X													X										2
Subcutaneous tissue, fibroma																											1
Subcutaneous tissue, fibrosarcoma																											3
Subcutaneous tissue, lipoma			X																								1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
Number of Days on Study	6	1	1	6	0	4	4	5	5	5	5	5	6	6	8	8	9	0	1	3	3	3	3	3	3
	1	0	2	3	8	4	7	0	4	5	7	7	1	6	0	7	5	9	5	1	1	1	1	1	1
	3	3	2	2	2	3	3	3	3	3	2	3	3	3	3	3	2	2	3	2	2	2	2	2	2
Carcass ID Number	6	4	7	9	6	3	6	2	0	2	6	0	3	4	3	1	9	8	6	5	5	5	5	6	6
	4	5	3	5	4	5	3	3	1	2	3	4	4	4	3	4	4	4	2	1	2	3	4	1	2
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																			+						
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X			X						X
Fibrosarcoma, metastatic, skin									X																
Hepatocellular carcinoma, metastatic, liver							X						X												
Nose	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear						+																			
Neurofibroma						X																			
Eye																									
Harderian gland																	+	+	+						
Adenoma																		X	X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymphoma malignant mixed																							X		
Lymphoma malignant undifferentiated cell type																			X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 7 1	2 7 2	2 8 1	2 8 2	2 8 3	2 9 1	2 9 2	2 9 3	3 0 2	3 0 3	3 1 1	3 1 2	3 1 3	3 2 1	3 3 1	3 3 2	3 4 1	3 4 2	3 4 3	3 5 1	3 5 2	3 5 3	3 5 4	3 5 5	3 6 1	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																			+							1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X					X				5
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	46
Papilloma squamous												X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Neurofibroma																										1
Eye													+													1
Harderian gland													+													4
Adenoma													X													3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant mixed																			X							2
Lymphoma malignant undifferentiated cell type																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	385	381	401	402	411	413	414	421	422	423	424	432	433	441	442	451	462	463	464	471	472	473	474	481	482	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma																						X				3
Hepatocellular adenoma														X						X						4
Mesentery														M												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous					X							X														2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma			X																							1
Tooth					+																					2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign										X																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	M	+	M	+	M	+	+	+	+	M	M	+	+	+	+	M	M	M	+	M	+	M	+	28
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																			X							1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	0	0	1	3	3	4	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	0	8	6	0	9	1	1	2	6	7	0	3	3	5	5	7	1	1	1	2	2	2	3	3
	7	4	9	1	8	4	2	3	3	0	5	2	7	0	4	6	5	5	7	9	9	9	0	0
Carcass ID Number	4	4	4	4	4	3	4	4	4	4	4	4	4	4	3	4	3	4	4	3	3	3	3	3
	8	6	0	1	0	9	3	8	8	5	7	5	5	3	8	0	7	4	6	7	7	9	7	8
	5	1	5	2	4	5	4	4	3	4	5	3	2	1	4	3	4	3	5	2	3	1	1	2
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis									+															
Preputial gland		+		+		M			+						+	+	+		+		+			+
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	M	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																X								
Lymph node, mandibular	M	M	+	+	M	M	M	+	M	+	M	M	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	M	+	+	M	+	+	+	+	+	A	+	+	+	M	M	M	+	+	+	+
Hepatocellular carcinoma, metastatic, liver													X											
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	M	+	M	+	M	+	+	M	+	M	M	M	M	+	+	M	+	M	+	M	M	M
Integumentary System																								
Mammary gland	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X			X				X			X	X					
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 8 5	3 8 1	4 0 1	4 0 2	4 1 1	4 1 3	4 1 4	4 2 1	4 2 2	4 2 3	4 2 4	4 3 2	4 3 3	4 4 1	4 4 2	4 5 1	4 6 2	4 6 3	4 6 4	4 7 1	4 7 2	4 7 3	4 7 4	4 8 1	4 8 2	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland					+					+																11
Prostate	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Hepatocellular carcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	M	+	M	+	M	M	+	M	M	+	+	M	M	M	+	M	M	M	+	M	+	M	+	+	+	22
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	+	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																							X			6
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 8 5	3 8 1	4 0 1	4 0 2	4 1 1	4 1 3	4 1 4	4 2 1	4 2 2	4 2 3	4 2 4	4 3 2	4 3 3	4 4 1	4 4 2	4 5 1	4 6 2	4 6 3	4 6 4	4 7 1	4 7 2	4 7 3	4 7 4	4 8 1	4 8 2	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X	X	X						X				X	X										9
Alveolar/bronchiolar adenoma, multiple																						X				1
Alveolar/bronchiolar carcinoma																										2
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																						X				2
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	M	+	44
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland													+						+							3
Adenoma													X						X							3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																							X			1
Urethra																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed									X														X			2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	0/47 (0%)	4/48 (8%)	1/48 (2%)	1/48 (2%)
Adjusted rates[b]	0.0%	9.9%	2.5%	3.4%
Terminal rates[c]	0/31 (0%)	3/39 (8%)	0/30 (0%)	1/29 (3%)
First incidence (days)	–[e]	671	657	729 (T)
Life table tests[d]	P=0.455N	P=0.095	P=0.521	P=0.487
Logistic Regression tests[d]	P=0.404N	P=0.073	P=0.492	P=0.487
Cochran-Armitage test[d]	P=0.391N			
Fisher exact test[d]		P=0.061	P=0.505	P=0.505
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates	0/47 (0%)	5/48 (10%)	1/48 (2%)	1/48 (2%)
Adjusted rates	0.0%	12.4%	2.5%	3.4%
Terminal rates	0/31 (0%)	4/39 (10%)	0/30 (0%)	1/29 (3%)
First incidence (days)	–	671	657	729 (T)
Life table tests	P=0.354N	P=0.056	P=0.521	P=0.487
Logistic Regression tests	P=0.303N	P=0.041	P=0.492	P=0.487
Cochran-Armitage test	P=0.290N			
Fisher exact test		P=0.030	P=0.505	P=0.505
Harderian Gland: Adenoma				
Overall rates	4/50 (8%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rates	12.0%	5.0%	9.1%	8.6%
Terminal rates	3/32 (9%)	2/40 (5%)	1/31 (3%)	2/31 (6%)
First incidence (days)	703	729 (T)	709	523
Life table tests	P=0.539	P=0.246N	P=0.514N	P=0.514N
Logistic Regression tests	P=0.564N	P=0.275N	P=0.477N	P=0.511N
Cochran-Armitage test	P=0.545N			
Fisher exact test		P=0.339N	P=0.500N	P=0.500N
Liver: Hepatocellular Adenoma				
Overall rates	11/50 (22%)	8/50 (16%)	5/50 (10%)	4/50 (8%)
Adjusted rates	29.4%	19.4%	14.7%	11.7%
Terminal rates	7/32 (22%)	7/40 (18%)	4/31 (13%)	3/31 (10%)
First incidence (days)	479	502	512	512
Life table tests	P=0.052N	P=0.180N	P=0.092N	P=0.059N
Logistic Regression tests	P=0.030N	P=0.297N	P=0.079N	P=0.049N
Cochran-Armitage test	P=0.029N			
Fisher exact test		P=0.306N	P=0.086N	P=0.045N
Liver: Hepatocellular Carcinoma				
Overall rates	7/50 (14%)	1/50 (2%)	6/50 (12%)	3/50 (6%)
Adjusted rates	17.6%	2.5%	15.6%	8.7%
Terminal rates	2/32 (6%)	1/40 (3%)	2/31 (6%)	1/31 (3%)
First incidence (days)	563	729 (T)	647	637
Life table tests	P=0.452N	P=0.024N	P=0.465N	P=0.182N
Logistic Regression tests	P=0.389N	P=0.033N	P=0.531N	P=0.161N
Cochran-Armitage test	P=0.386N			
Fisher exact test		P=0.030N	P=0.500N	P=0.159N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	16/50 (32%)	9/50 (18%)	10/50 (20%)	7/50 (14%)
Adjusted rates	39.8%	21.8%	25.9%	19.7%
Terminal rates	9/32 (28%)	8/40 (20%)	5/31 (16%)	4/31 (13%)
First incidence (days)	479	502	512	512
Life table tests	P=0.108N	P=0.038N	P=0.136N	P=0.046N
Logistic Regression tests	P=0.056N	P=0.080N	P=0.126N	P=0.031N
Cochran-Armitage test	P=0.054N			
Fisher exact test		P=0.083N	P=0.127N	P=0.028N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	8/50 (16%)	6/50 (12%)	5/50 (10%)	10/50 (20%)
Adjusted rates	24.2%	15.0%	15.0%	29.8%
Terminal rates	7/32 (22%)	6/40 (15%)	3/31 (10%)	8/31 (26%)
First incidence (days)	718	729 (T)	687	563
Life table tests	P=0.166	P=0.228N	P=0.299N	P=0.368
Logistic Regression tests	P=0.208	P=0.248N	P=0.256N	P=0.378
Cochran-Armitage test	P=0.262			
Fisher exact test		P=0.387N	P=0.277N	P=0.398
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	8/50 (16%)	7/50 (14%)	5/50 (10%)	12/50 (24%)
Adjusted rates	24.2%	17.0%	15.0%	33.6%
Terminal rates	7/32 (22%)	6/40 (15%)	3/31 (10%)	8/31 (26%)
First incidence (days)	718	671	687	563
Life table tests	P=0.085	P=0.325N	P=0.299N	P=0.210
Logistic Regression tests	P=0.115	P=0.391N	P=0.256N	P=0.206
Cochran-Armitage test	P=0.146			
Fisher exact test		P=0.500N	P=0.277N	P=0.227
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rates	5/50 (10%)	5/50 (10%)	3/50 (6%)	6/50 (12%)
Adjusted rates	13.0%	12.1%	7.9%	15.8%
Terminal rates	2/32 (6%)	4/40 (10%)	1/31 (3%)	1/31 (3%)
First incidence (days)	463	671	654	523
Life table tests	P=0.396	P=0.527N	P=0.346N	P=0.485
Logistic Regression tests	P=0.462	P=0.631N	P=0.417N	P=0.506
Cochran-Armitage test	P=0.463			
Fisher exact test		P=0.630N	P=0.357N	P=0.500
Stomach (Forestomach): Squamous Papilloma				
Overall rates	1/50 (2%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rates	3.1%	0.0%	8.7%	6.5%
Terminal rates	1/32 (3%)	0/40 (0%)	2/31 (6%)	2/31 (6%)
First incidence (days)	729 (T)	–	654	729 (T)
Life table tests	P=0.148	P=0.455N	P=0.307	P=0.489
Logistic Regression tests	P=0.168	P=0.455N	P=0.327	P=0.489
Cochran-Armitage test	P=0.185			
Fisher exact test		P=0.500N	P=0.309	P=0.500

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	3/49 (6%)	1/49 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates	9.4%	2.5%	9.0%	3.2%
Terminal rates	3/32 (9%)	1/40 (3%)	2/31 (6%)	1/31 (3%)
First incidence (days)	729 (T)	729 (T)	666	729 (T)
Life table tests	P=0.436N	P=0.229N	P=0.653	P=0.316N
Logistic Regression tests	P=0.401N	P=0.229N	P=0.641N	P=0.316N
Cochran-Armitage test	P=0.364N			
Fisher exact test		P=0.309N	P=0.651N	P=0.301N
All Organs: Hemangiosarcoma				
Overall rates	4/50 (8%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rates	11.4%	5.0%	5.0%	2.4%
Terminal rates	3/32 (9%)	2/40 (5%)	0/31 (0%)	0/31 (0%)
First incidence (days)	541	729 (T)	650	570
Life table tests	P=0.192N	P=0.258N	P=0.333N	P=0.192N
Logistic Regression tests	P=0.161N	P=0.327N	P=0.335N	P=0.181N
Cochran-Armitage test	P=0.160N			
Fisher exact test		P=0.339N	P=0.339N	P=0.181N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	4/50 (8%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rates	11.4%	5.0%	7.8%	2.4%
Terminal rates	3/32 (9%)	2/40 (5%)	0/31 (0%)	0/31 (0%)
First incidence (days)	541	729 (T)	650	570
Life table tests	P=0.232N	P=0.258N	P=0.493N	P=0.192N
Logistic Regression tests	P=0.195N	P=0.327N	P=0.498N	P=0.181N
Cochran-Armitage test	P=0.193N			
Fisher exact test		P=0.339N	P=0.500N	P=0.181N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	7/50 (14%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rates	19.9%	9.7%	9.4%	6.5%
Terminal rates	5/32 (16%)	3/40 (8%)	2/31 (6%)	2/31 (6%)
First incidence (days)	267	651	715	729 (T)
Life table tests	P=0.101N	P=0.173N	P=0.175N	P=0.092N
Logistic Regression tests	P=0.070N	P=0.259N	P=0.152N	P=0.084N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.262N	P=0.159N	P=0.080N
All Organs: Benign Neoplasms				
Overall rates	23/50 (46%)	22/50 (44%)	21/50 (42%)	20/50 (40%)
Adjusted rates	60.1%	52.3%	54.4%	56.3%
Terminal rates	17/32 (53%)	20/40 (50%)	14/31 (45%)	16/31 (52%)
First incidence (days)	479	502	512	512
Life table tests	P=0.532	P=0.188N	P=0.441N	P=0.396N
Logistic Regression tests	P=0.339N	P=0.430N	P=0.302N	P=0.374N
Cochran-Armitage test	P=0.299N			
Fisher exact test		P=0.500N	P=0.420N	P=0.343N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
All Organs: Malignant Neoplasms				
Overall rates	25/50 (50%)	14/50 (28%)	17/50 (34%)	13/50 (26%)
Adjusted rates	56.3%	32.6%	40.6%	31.8%
Terminal rates	13/32 (41%)	11/40 (28%)	7/31 (23%)	4/31 (13%)
First incidence (days)	267	651	647	523
Life table tests	P=0.136N	P=0.009N	P=0.112N	P=0.035N
Logistic Regression tests	P=0.049N	P=0.020N	P=0.085N	P=0.012N
Cochran-Armitage test	P=0.046N			
Fisher exact test		P=0.020N	P=0.078N	P=0.011N
All Organs: Benign or Malignant Neoplasms				
Overall rates	35/50 (70%)	29/50 (58%)	31/50 (62%)	28/50 (56%)
Adjusted rates	77.6%	65.9%	70.1%	66.3%
Terminal rates	22/32 (69%)	25/40 (63%)	18/31 (58%)	17/31 (55%)
First incidence (days)	267	502	512	512
Life table tests	P=0.466N	P=0.030N	P=0.314N	P=0.207N
Logistic Regression tests	P=0.192N	P=0.136N	P=0.195N	P=0.125N
Cochran-Armitage test	P=0.173N			
Fisher exact test		P=0.149N	P=0.263N	P=0.107N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined at site.
[b] Kaplan-Meier estimated lifetime neoplasm incidence after adjustment for intercurrent mortality.
[c] Observed incidence at terminal kill.
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. Logistic regression is an alternative method for analyzing the incidence of non-fatal neoplasms. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Male B6C3F$_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute[a]			
4,4′-Methylenedianiline 2HCl	0/47	0/47	0/47
Monuron	2/46	0/46	2/46
8-Hydroxyquinoline	0/50	0/50	0/50
Butyl Benzyl Phthalate	1/47	1/47	2/47
C.I. Basic Red 9	1/50	0/50	1/50
Boric Acid	0/44	0/44	0/44
Pentachloronitrobenzene	0/44	0/44	0/44
2-Biphenylamine HCl	0/46	0/46	0/46
Acetaminophen	2/50	1/50	3/50
Pentaerythritol Tetranitrate	1/49	1/49	2/49
Total	7/473 (1.5%)	3/473 (0.6%)	10/473 (2.1%)
Standard deviation	1.7%	1.0%	2.4%
Range	0%–4%	0%–2%	0%–6%
Overall Historical Incidence[b]			
Total	37/2,149 (1.7%)	5/2,149 (0.2%)	43/2,149 (2.0%)[c]
Standard deviation	2.0%	0.7%	2.2%
Range	0%–6%	0%–2%	0%–7%

[a] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 1 March 1989)
[b] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990)
[c] Includes one papillary adenoma

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Moribund	13	3	16	10
Natural deaths	5	7	3	9
Survivors				
Terminal sacrifice	32	40	31	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(47)	(48)	(48)	(49)
Acanthosis				1 (2%)
Cyst				1 (2%)
Hyperkeratosis				1 (2%)
Gallbladder	(41)	(43)	(47)	(40)
Inflammation, chronic, focal	1 (2%)			
Intestine large, cecum	(49)	(50)	(48)	(47)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, chronic		1 (2%)		
Intestine large, colon	(48)	(46)	(49)	(47)
Hyperplasia, lymphoid	1 (2%)			
Intestine large, rectum	(49)	(47)	(47)	(47)
Artery, inflammation, chronic	1 (2%)			
Intestine small	(49)	(47)	(49)	(48)
Hyperplasia, lymphoid	1 (2%)			
Intestine small, ileum	(48)	(45)	(48)	(44)
Amyloid deposition		1 (2%)		1 (2%)
Intestine small, jejunum	(47)	(43)	(47)	(45)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Liver	(50)	(50)	(50)	(50)
Abscess	1 (2%)			1 (2%)
Abscess, multiple	1 (2%)			
Basophilic focus		1 (2%)	2 (4%)	
Cytoplasmic alteration, focal		4 (8%)		
Fatty change	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule	2 (4%)			
Infarct				1 (2%)
Mineralization, focal	1 (2%)			
Necrosis, focal	3 (6%)	3 (6%)	6 (12%)	3 (6%)
Thrombus			1 (2%)	
Hepatocyte, hyperplasia, focal	1 (2%)	1 (2%)	2 (4%)	
Perivascular, inflammation, chronic	2 (4%)	1 (2%)		5 (10%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Alimentary System (continued)				
Mesentery	(4)	(2)		(1)
Hemorrhage		1 (50%)		
Fat, necrosis	4 (100%)	1 (50%)		
Pancreas	(47)	(49)	(50)	(48)
Congestion			2 (4%)	
Edema				1 (2%)
Inflammation, chronic, focal	4 (9%)	10 (20%)	5 (10%)	9 (19%)
Acinus, atrophy	3 (6%)		1 (2%)	
Acinus, hyperplasia	1 (2%)			
Acinus, vacuolization cytoplasmic			1 (2%)	
Duct, ectasia			1 (2%)	
Periductular, inflammation, acute	1 (2%)			
Salivary glands	(50)	(49)	(50)	(49)
Congestion			1 (2%)	
Hyperplasia, lymphoid	2 (4%)		1 (2%)	
Inflammation, chronic, focal	38 (76%)	36 (73%)	35 (70%)	31 (63%)
Karyomegaly		1 (2%)		
Stomach, forestomach	(49)	(49)	(50)	(49)
Acanthosis		1 (2%)	2 (4%)	
Cyst	1 (2%)			
Cyst epithelial inclusion		1 (2%)		
Hyperkeratosis	1 (2%)		1 (2%)	
Hyperplasia, squamous	1 (2%)			
Inflammation, chronic	1 (2%)			
Stomach, glandular	(50)	(47)	(49)	(48)
Inflammation, acute	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic	7 (14%)	2 (4%)	5 (10%)	4 (8%)
Mineralization		1 (2%)	1 (2%)	1 (2%)
Mineralization, focal		1 (2%)		
Tooth	(2)	(1)	(1)	(2)
Abscess	2 (100%)	1 (100%)	1 (100%)	1 (50%)
Inflammation, acute				1 (50%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy		1 (2%)		2 (4%)
Inflammation, chronic, focal				1 (2%)
Karyomegaly				1 (2%)
Atrium, thrombus				1 (2%)
Coronary artery, inflammation, acute				1 (2%)
Coronary artery, inflammation, chronic	1 (2%)			2 (4%)
Myocardium, inflammation, acute, focal				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Endocrine System				
Adrenal gland	(50)	(48)	(49)	(49)
Capsule, hyperplasia	1 (2%)			
Adrenal gland, cortex	(50)	(48)	(49)	(49)
Accessory adrenal cortical nodule				1 (2%)
Cytoplasmic alteration, focal	5 (10%)	10 (21%)	5 (10%)	6 (12%)
Hypertrophy				1 (2%)
Inflammation, chronic		1 (2%)		
Adrenal gland, medulla	(47)	(48)	(48)	(48)
Congestion				1 (2%)
Hyperplasia	8 (17%)	7 (15%)	5 (10%)	5 (10%)
Inflammation, acute				1 (2%)
Islets, pancreatic	(47)	(48)	(48)	(48)
Hyperplasia	11 (23%)	4 (8%)	9 (19%)	7 (15%)
Pituitary gland	(48)	(39)	(39)	(46)
Pars distalis, congestion			2 (5%)	1 (2%)
Pars distalis, cyst	3 (6%)	1 (3%)	3 (8%)	1 (2%)
Pars distalis, hyperplasia, focal		1 (3%)		
Thyroid gland	(49)	(49)	(50)	(50)
Congestion			1 (2%)	
Inflammation, chronic, focal	5 (10%)		2 (4%)	3 (6%)
C-cell, hyperplasia	1 (2%)			
Follicle, cyst			1 (2%)	
Follicle, inflammation, acute, focal				1 (2%)
Follicular cell, hyperplasia, focal		6 (12%)	12 (24%)	15 (30%)
General Body System				
Tissue NOS	(1)			
Abscess	1 (100%)			
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Ectopic tissue				1 (2%)
Inflammation, chronic		3 (6%)		1 (2%)
Spermatocele		1 (2%)		
Duct, dilatation		1 (2%)		
Penis	(2)	(2)	(1)	(1)
Abscess		1 (50%)	1 (100%)	
Inflammation, acute	1 (50%)			1 (100%)
Inflammation, subacute		1 (50%)		
Necrosis	1 (50%)			1 (100%)
Preputial gland	(17)	(22)	(12)	(11)
Abscess	4 (24%)	8 (36%)	6 (50%)	3 (27%)
Ectasia	4 (24%)	3 (14%)	3 (25%)	1 (9%)
Inflammation, chronic	11 (65%)	13 (59%)	4 (33%)	6 (55%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Genital System (continued)				
Prostate	(48)	(42)	(47)	(48)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, acute	2 (4%)			
Inflammation, chronic	9 (19%)	10 (24%)	5 (11%)	7 (15%)
Inflammation, subacute		1 (2%)		
Seminal vesicle	(49)	(49)	(49)	(50)
Abscess				1 (2%)
Atrophy	3 (6%)		1 (2%)	1 (2%)
Dilatation	4 (8%)		1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, acute			1 (2%)	
Inflammation, chronic		1 (2%)		1 (2%)
Testes	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Hemorrhage			1 (2%)	
Hypospermia, focal	1 (2%)		1 (2%)	
Mineralization		4 (8%)		2 (4%)
Capsule, fibrosis			1 (2%)	
Capsule, inflammation, chronic		1 (2%)		
Seminiferous tubule, atrophy	5 (10%)	6 (12%)	2 (4%)	2 (4%)
Hematopoietic System				
Blood	(1)			
Hypochromasia	1 (100%)			
Bone marrow	(50)	(49)	(50)	(49)
Hyperplasia, neutrophil	4 (8%)	7 (14%)	6 (12%)	4 (8%)
Lymph node	(49)	(47)	(47)	(47)
Axillary, hyperplasia, lymphoid				1 (2%)
Axillary, infiltration cellular, plasma cell				2 (4%)
Inguinal, congestion		1 (2%)		
Inguinal, hyperplasia, lymphoid	1 (2%)			
Inguinal, infiltration cellular, plasma cell	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Lumbar, hyperplasia, lymphoid	2 (4%)	1 (2%)		
Lumbar, infiltration cellular, plasma cell	1 (2%)	1 (2%)	2 (4%)	
Lumbar, inflammation, acute				1 (2%)
Mediastinal, hyperplasia, lymphoid		1 (2%)	1 (2%)	
Mediastinal, infiltration cellular, plasma cell			1 (2%)	1 (2%)
Pancreatic, congestion				1 (2%)
Renal, congestion		1 (2%)	1 (2%)	
Renal, hyperplasia, lymphoid	2 (4%)			
Renal, infiltration cellular, plasma cell	1 (2%)	1 (2%)	1 (2%)	1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(43)	(20)	(17)	(40)
Hyperplasia, lymphoid	1 (2%)		1 (6%)	
Infiltration cellular, plasma cell	19 (44%)	15 (75%)	11 (65%)	31 (78%)
Lymph node, mesenteric	(43)	(45)	(47)	(42)
Congestion	14 (33%)	18 (40%)	13 (28%)	17 (40%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, plasma cell		1 (2%)		
Infiltration cellular, histiocytic	1 (2%)			
Inflammation, acute	1 (2%)			
Lymphatic, angiectasis				1 (2%)
Spleen	(50)	(50)	(49)	(48)
Atrophy	1 (2%)			
Congestion			2 (4%)	
Depletion lymphoid				1 (2%)
Hematopoietic cell proliferation	19 (38%)	18 (36%)	16 (33%)	17 (35%)
Hyperplasia, lymphoid	6 (12%)	2 (4%)	5 (10%)	1 (2%)
Infiltration cellular, plasma cell			1 (2%)	
Inflammation, acute	1 (2%)		1 (2%)	
Thymus	(11)	(18)	(28)	(22)
Hyperplasia, lymphoid		1 (6%)	1 (4%)	
Infiltration cellular, plasma cell				1 (5%)
Integumentary System				
Skin	(48)	(49)	(50)	(50)
Alopecia				1 (2%)
Fibrosis	1 (2%)			1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic, focal		1 (2%)		
Ulcer	6 (13%)	3 (6%)		3 (6%)
Dermis, inflammation, chronic	2 (4%)			1 (2%)
Epidermis, inflammation, acute	1 (2%)			
Perivascular, inflammation				1 (2%)
Scrotal, subcutaneous tissue, thrombus			1 (2%)	
Scrotal, subcutaneous tissue, lymphatic, dilatation				1 (2%)
Subcutaneous tissue, abscess				1 (2%)
Subcutaneous tissue, hyperplasia, lymphoid	1 (2%)			1 (2%)
Subcutaneous tissue, infiltration cellular, plasma cell				1 (2%)
Subcutaneous tissue, inflammation, acute				1 (2%)
Subcutaneous tissue, mineralization, focal			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Hyperostosis	1 (2%)			
Cranium, fibrous osteodystrophy	1 (2%)			
Tarsal, fibrosis			1 (2%)	
Tarsal, hyperostosis	44 (88%)	35 (71%)	41 (82%)	39 (78%)
Tarsal, inflammation, acute			1 (2%)	1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage, focal		1 (2%)		
Mineralization, focal	19 (38%)	23 (46%)	19 (38%)	18 (36%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	3 (6%)		2 (4%)
Granuloma		1 (2%)		
Hemorrhage, focal			1 (2%)	
Hyperplasia, lymphoid			1 (2%)	
Infiltration cellular, histiocytic	1 (2%)	6 (12%)	1 (2%)	1 (2%)
Inflammation, chronic, focal				1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)			
Alveolar epithelium, metaplasia			1 (2%)	2 (4%)
Bronchiole, epithelium, hyperplasia		1 (2%)	1 (2%)	
Bronchus, foreign body		1 (2%)		
Perivascular, inflammation, chronic	22 (44%)	24 (48%)	9 (18%)	21 (42%)
Pleura, inflammation, chronic	1 (2%)			1 (2%)
Nose	(47)	(40)	(46)	(44)
Inflammation, chronic	1 (2%)	7 (18%)	5 (11%)	2 (5%)
Metaplasia, squamous	17 (36%)	20 (50%)	19 (41%)	13 (30%)
Respiratory epithelium, degeneration, hyaline	21 (45%)	25 (63%)	30 (65%)	19 (43%)
Special Senses System				
Eye		(3)	(1)	
Cornea, degeneration		1 (33%)		
Cornea, inflammation, acute		1 (33%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Abscess		1 (2%)		
Congestion	2 (4%)	3 (6%)	4 (8%)	4 (8%)
Cyst			1 (2%)	2 (4%)
Fibrosis, focal		2 (4%)		
Glomerulosclerosis	7 (14%)	1 (2%)	3 (6%)	6 (12%)
Hydronephrosis	1 (2%)			
Hyperplasia, lymphoid	2 (4%)		1 (2%)	
Inflammation, acute, focal	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic, focal	26 (52%)	18 (37%)	22 (44%)	28 (56%)
Inflammation, subacute		1 (2%)		
Mineralization	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Necrosis, focal			1 (2%)	4 (8%)
Nephropathy, focal				1 (2%)
Capsule, fibrosis	1 (2%)			
Papilla, necrosis		2 (4%)		1 2%)
Pelvis, inflammation, acute	1 (2%)			
Renal tubule, atrophy, focal			1 (2%)	
Renal tubule, casts		1 (2%)		1 (2%)
Renal tubule, degeneration			1 (2%)	1 (2%)
Renal tubule, dilatation			1 (2%)	
Renal tubule, hyperplasia, focal		1 (2%)		2 (4%)
Renal tubule, necrosis			1 (2%)	
Renal tubule, regeneration	25 (50%)	15 (31%)	16 (32%)	25 (50%)
Urethra				(2)
Hemorrhage				1 (50%)
Inflammation, acute				2 (100%)
Urinary bladder	(47)	(46)	(46)	(45)
Calculus gross observation	1 (2%)	1 (2%)		
Calculus micro observation only		1 (2%)		
Concretion	1 (2%)	1 (2%)		2 (4%)
Ectasia			1 (2%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, chronic, focal	23 (49%)	25 (54%)	18 (39%)	19 (42%)
Inflammation, chronic active	2 (4%)			
Inflammation, subacute		1 (2%)		
Artery, inflammation, chronic	1 (2%)			
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Moribund	21	9	21	8
Natural deaths	2	9		4
Accidental deaths			4	
Survivors				
Terminal sacrifice	27	32	25	38
Animals examined microscopically	50	50	50	51
Alimentary System				
Gallbladder	(42)	(45)	(44)	(46)
Intestine large, cecum	(49)	(45)	(49)	(48)
Sarcoma			1 (2%)	
Intestine small, duodenum	(48)	(44)	(47)	(50)
Hemangiosarcoma		1 (2%)		
Intestine small, ileum	(48)	(43)	(48)	(47)
Intestine small, jejunum	(47)	(42)	(46)	(48)
Adenocarcinoma	1 (2%)			
Liver	(49)	(50)	(50)	(49)
Hemangiosarcoma			1 (2%)	
Hemangiosarcoma, metastatic, intestine small		1 (2%)		
Hepatocellular carcinoma				1 (2%)
Hepatocellular adenoma	3 (6%)	4 (8%)	7 (14%)	2 (4%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Mesentery	(4)	(4)	(3)	(1)
Pancreas	(49)	(48)	(47)	(49)
Salivary glands	(46)	(49)	(50)	(50)
Stomach, forestomach	(48)	(49)	(49)	(48)
Stomach, glandular	(47)	(46)	(50)	(48)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal gland, cortex	(49)	(49)	(46)	(49)
Adrenal gland, medulla	(46)	(46)	(45)	(47)
Pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(48)	(47)	(43)	(49)
Adenoma		1 (2%)		
Carcinoma	1 (2%)			
Pituitary gland	(46)	(43)	(42)	(45)
Pars distalis, adenoma	14 (30%)	16 (37%)	7 (17%)	14 (31%)
Pars distalis, carcinoma	1 (2%)	1 (2%)	1 (2%)	
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(48)	(50)	(50)	(50)
Follicular cell, adenoma		1 (2%)	1 (2%)	2 (4%)
Follicular cell, carcinoma			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Genital System				
Ovary	(47)	(49)	(49)	(50)
Cystadenoma		2 (4%)	1 (2%)	
Hemangioma		1 (2%)		
Uterus	(49)	(50)	(50)	(49)
Hemangioma				1 (2%)
Hemangiosarcoma	1 (2%)	1 (2%)		
Histiocytic sarcoma			1 (2%)	
Polyp stromal	1 (2%)		1 (2%)	1 (2%)
Endometrium, adenocarcinoma	1 (2%)			
Hematopoietic System				
Bone marrow	(49)	(49)	(49)	(49)
Lymph node	(49)	(47)	(49)	(49)
Lymph node, mandibular	(41)	(26)	(29)	(44)
Histiocytic sarcoma	1 (2%)			
Lymph node, mesenteric	(44)	(45)	(45)	(43)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Spleen	(49)	(50)	(50)	(49)
Hemangioma		1 (2%)		
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Thymus	(23)	(30)	(30)	(34)
Integumentary System				
Mammary gland	(25)	(20)	(28)	(17)
Adenoacanthoma		1 (5%)		
Adenocarcinoma	1 (4%)			1 (6%)
Skin	(47)	(48)	(49)	(48)
Hemangiosarcoma	1 (2%)			
Melanoma malignant				1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma, multiple			1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)		1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	4 (8%)	4 (8%)	4 (8%)
Carcinoma, metastatic			1 (2%)	
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma				1 (2%)
Nose	(47)	(44)	(45)	(38)
Special Senses System				
Eye	(1)	(1)	(1)	
Carcinoma, metastatic			1 (100%)	
Harderian gland	(5)	(2)	(2)	(2)
Adenoma	4 (80%)	2 (100%)	1 (50%)	2 (100%)
Carcinoma	1 (20%)		1 (50%)	
Urinary System				
Kidney	(49)	(49)	(50)	(49)
Histiocytic sarcoma		1 (2%)		
Urinary bladder	(49)	(46)	(44)	(46)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(51)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Leukemia	1 (2%)			1 (2%)
Lymphoma malignant (NOS)		1 (2%)		
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	2 (4%)	3 (6%)		3 (6%)
Lymphoma malignant mixed	8 (16%)	6 (12%)	7 (14%)	13 (25%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	35	28	24	35
Total primary neoplasms	45	48	37	49
Total animals with benign neoplasms	22	22	17	22
Total benign neoplasms	24	32	22	26
Total animals with malignant neoplasms	20	15	14	19
Total malignant neoplasms	21	16	15	23
Total animals with metastatic neoplasms	1	1	2	1
Total metastatic neoplasms	1	1	3	1

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary neoplasms: all neoplasms except metastatic neoplasms.

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 1 2	5 1 3	5 1 4	5 2 1	5 2 2	5 0 1	5 1 5	5 1 3	5 3 2	5 4 1	5 5 1	5 5 2	5 5 3	5 5 4	5 6 1	5 7 1	5 7 2	5 8 1	5 8 2	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	6 0 3	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma						X																			1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X				X							X											3
Mesentery							+								+										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	46
Pheochromocytoma malignant																							X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma								X																	1
Parathyroid gland	M	M	+	+	+	M	+	I	+	+	M	+	+	+	+	+	M	+	+	M	+	M	M	+	M	26
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Pars distalis, adenoma				X			X		X		X							X		X				X		14
Pars distalis, carcinoma																	X								1
Pars intermedia, adenoma		X																							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	3 4 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 9 9 0 3 3 3 5 6 1 3 3 4 4 4 5 6 8 0 0 1 1 2 2 3 3 7 1 6 4 4 6 5 4 1 4 5 2 2 7 3 0 4 1 2 5 9 2 6 2 2
Carcass ID Number	5 4 5 5 6 4 5 5 5 4 5 5 5 5 5 5 5 4 5 5 6 5 4 5 4 9 2 4 0 9 4 5 3 9 7 0 0 8 6 0 6 8 9 9 2 0 8 9 1 5 5 4 3 5 4 2 5 3 3 3 3 4 5 3 2 2 4 2 4 3 4 3 1 1
Genital System	
Ovary	+ A + + +
Uterus	+ A + + +
Hemangiosarcoma	X
Polyp stromal	
Endometrium, adenocarcinoma	
Hematopoietic System	
Blood	+
Bone marrow	+ A + + +
Lymph node	+ A + + +
Lymph node, mandibular	+ M + + + + + + + + M M + + + + + + M + + A + + M
Histiocytic sarcoma	
Lymph node, mesenteric	+ + + + + + + + + + + + + M + + + + + + M M + + +
Histiocytic sarcoma	
Spleen	+ A + + +
Thymus	M M + + + + + M M + + + + M M M M M M M + M M M M
Integumentary System	
Mammary gland	M + M + + + + + + + M + + + + M M + + M + M M M M
Adenocarcinoma	X
Skin	+ M +
Hemangiosarcoma	X
Musculoskeletal System	
Bone	+ +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 1 2	5 1 3	5 1 4	5 2 1	5 2 2	5 0 1	5 1 5	5 3 1	5 3 2	5 4 1	5 5 1	5 5 2	5 5 3	5 5 4	5 6 1	5 7 1	5 7 2	5 8 1	5 8 2	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	6 0 3	Total Tissues/ Tumors
Genital System																										
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	47
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Polyp stromal													X													1
Endometrium, adenocarcinoma					X																					1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	41
Histiocytic sarcoma																X										1
Lymph node, mesenteric	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	44
Histiocytic sarcoma																X										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	+	M	M	+	M	+	M	+	M	+	M	M	+	+	+	+	+	M	+	+	M	M	+	M	23
Integumentary System																										
Mammary gland	M	+	+	M	M	M	M	M	M	M	+	+	M	+	M	M	M	+	+	+	M	M	M	+	+	M	25
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	3 9 7	4 9 1	5 0 6	5 3 4	5 3 4	5 3 6	5 5 5	5 6 4	6 1 1	6 3 4	6 3 5	6 4 2	6 4 2	6 4 7	6 5 3	6 6 0	6 8 4	7 0 1	7 0 2	7 1 5	7 1 9	7 2 2	7 2 6	7 3 2	7 3 2
Carcass ID Number	5 4 5	4 9 5	5 2 4	5 4 3	6 0 5	4 9 4	5 4 2	5 5 5	5 3 3	4 9 3	5 7 3	5 0 3	5 0 4	5 8 5	5 6 3	5 0 2	5 6 2	5 8 4	5 9 2	5 9 4	5 2 3	6 0 4	5 8 3	4 9 1	5 1 1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Nose	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear	+																								
Eye											+														
Harderian gland									+		+							+					+		
Adenoma											X							X					X		
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia																						X			
Lymphoma malignant lymphocytic																			X						
Lymphoma malignant mixed			X		X			X					X			X								X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 0 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 1 2	5 1 3	5 1 4	5 2 1	5 2 2	5 0 1	5 1 5	5 1 1	5 3 2	5 4 1	5 5 1	5 5 2	5 5 3	5 5 4	5 6 1	5 7 1	5 7 2	5 8 1	5 8 2	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	6 0 3	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																	X									1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear																										1
Eye																										1
Harderian gland																							+			5
Adenoma																							X			4
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																X										1
Leukemia																										1
Lymphoma malignant lymphocytic					X																					2
Lymphoma malignant mixed														X			X									8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	6 3 4	6 3 5	6 4 1	6 4 2	6 4 3	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	7 1 1	7 1 2	7 1 3	7 2 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	M	M	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	M	M	+	+	+	+	+	39
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Hemangiosarcoma			X																							1
Intestine small, ileum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, intestine small			X																							1
Hepatocellular adenoma																						X	X			4
Histiocytic sarcoma																			X							1
Mesentery													+	+												4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	46
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Parathyroid gland	+	+	+	M	M	M	+	+	+	M	+	+	M	+	+	M	M	+	M	+	M	+	+	+	+	32
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	43
Pars distalis, adenoma			X	X		X		X					X		X	X										16
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma					X																					1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	4 3 6	4 4 9	5 1 6	5 4 7	5 4 9	5 5 1	5 9 9	6 1 4	6 3 3	6 3 4	6 3 8	6 3 8	6 6 1	6 6 1	6 6 7	6 7 8	6 8 0	6 9 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2
Carcass ID Number	6 7 5	6 2 5	6 5 5	6 1 4	7 2 3	6 2 3	6 9 5	6 8 5	7 0 5	6 6 4	6 2 2	7 0 4	6 7 3	7 2 2	7 0 3	7 0 2	6 9 4	7 0 1	6 1 1	6 1 2	6 1 3	6 2 1	6 3 1	6 3 2	6 3 3
Genital System																									
Ovary	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																						X	X		
Hemangioma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	A	+	M	M	+	+	M	+	M	M	M	M	M	M	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Hemangiosarcoma																		X							
Histiocytic sarcoma																									
Thymus	M	M	+	M	+	+	+	+	+	+	A	M	+	M	+	M	M	+	+	+	+	+	+	M	M
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	M	M	M	M	M	+	M	M	M
Adenoacanthoma																									
Skin	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	6 3 4	6 3 5	6 4 1	6 4 2	6 4 3	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	7 1 1	7 1 2	7 1 3	7 2 1	Total Tissues/ Tumors
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																										2
Hemangioma						X																				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mandibular	+	M	+	+	+	+	M	M	M	+	+	M	+	M	M	M	M	M	M	+	+	+	M	M	+	26
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma																			X							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										1
Histiocytic sarcoma																			X							1
Thymus	+	+	M	+	+	+	+	M	I	+	M	+	+	M	M	M	+	+	+	+	M	+	M	M	+	30
Integumentary System																										
Mammary gland	M	M	+	M	M	M	M	M	+	M	M	M	M	+	+	M	M	M	M	M	M	M	+	M	+	20
Adenoacanthoma																									X	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	4 3 6	4 4 9	5 1 6	5 4 7	5 4 9	5 5 1	5 9 9	6 1 4	6 3 3	6 3 4	6 3 8	6 3 8	6 6 1	6 6 1	6 6 7	6 7 8	6 8 0	6 9 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2
Carcass ID Number	6 7 5	6 2 5	6 5 5	6 1 4	7 2 3	6 2 3	6 9 5	6 8 5	7 0 5	6 6 4	6 2 2	7 0 4	6 7 3	7 2 2	7 0 3	7 0 2	6 9 4	7 0 1	6 1 1	6 1 2	6 1 3	6 2 1	6 3 1	6 3 2	6 3 3
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X	X										X			
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	+	A	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant								X																	
Lymphoma malignant lymphocytic			X		X																				
Lymphoma malignant mixed										X					X				X						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 600 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	6 3 4	6 3 5	6 4 1	6 4 2	6 4 3	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	7 1 1	7 1 2	7 1 3	7 2 1	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										4
Nose	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	44
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear							+																			1
Eye																						+				1
Harderian gland																			+			+				2
Adenoma																			X			X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																			X							1
Lymphoma malignant																										1
Lymphoma malignant lymphocytic						X																				3
Lymphoma malignant mixed	X										X					X										6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	
Carcass ID Number	7 3 1	7 3 2	7 3 3	7 3 4	7 4 1	7 4 3	7 5 1	7 5 2	7 8 1	7 8 2	7 8 3	7 9 1	8 0 1	8 0 2	8 0 3	8 1 1	8 1 2	8 1 3	8 2 1	8 2 2	8 3 1	8 3 2	8 3 3	8 3 4	7 4 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular adenoma	X								X													X				7
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth						+																				1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Adrenal gland, cortex	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Adrenal gland, medulla	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	M		43
Parathyroid gland	M	+	M	M	M	+	M	M	M	M	+	M	+	M	M	+	M	M	+	+	+	+	+	M	M	26
Pituitary gland	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	M	+	M	+	+	M	+	+	+	+	42
Pars distalis, adenoma	X							X	X											X						7
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma														X												1
Follicular cell, carcinoma									X																	1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	0 0 0 0 4 4 4 5 5 5 5 5 5 6 6 6 6 6 6 6 7 7 7 7 0 0 0 0 1 8 8 1 3 4 4 5 5 0 1 3 4 5 5 8 8 0 0 1 2 8 8 8 9 4 0 8 6 4 0 9 1 1 7 0 9 2 9 9 4 4 1 5 6 6
Carcass ID Number	8 8 8 8 8 8 7 7 7 7 7 7 8 7 7 7 7 7 8 7 8 8 7 7 7 4 4 4 4 0 1 5 7 7 9 7 8 4 9 3 6 4 9 0 6 2 2 8 5 6 3 4 5 2 5 4 4 3 2 4 1 5 1 3 5 3 5 2 4 2 4 3 4 3 1
Genital System	
Ovary	+ +
Cystadenoma	X
Uterus	+ +
Histiocytic sarcoma	
Polyp stromal	X
Hematopoietic System	
Bone marrow	+ + + + + + + + + + M + + + + + + + + + + + + +
Lymph node	+ + M +
Lymph node, mandibular	+ M M + M + + + + M M + M + + + M + M M + + + M +
Lymph node, mesenteric	M + M A + + + + + + + + + + M + + + + + + + + +
Spleen	+ +
Thymus	+ M M M M + M + + + + + + M M M + + + M M M + M +
Integumentary System	
Mammary gland	M + + + M M + + + + + + + + + + + M + M + M M M M
Skin	+ + + + M +
Subcutaneous tissue, fibrosarcoma	X
Subcutaneous tissue, fibrosarcoma, multiple	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Carcinoma, metastatic, pituitary gland	X
Spinal cord	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Carcinoma, metastatic	X
Nose	+ + + + + + + + + + + + + + M + M + + + + + + M +
Trachea	+ +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	
Carcass ID Number	7 3 1	7 3 2	7 3 3	7 3 4	7 4 1	7 4 3	7 5 1	7 5 2	7 8 1	7 8 2	7 8 3	7 9 1	8 0 1	8 0 2	8 0 3	8 1 1	8 1 2	8 1 3	8 2 1	8 2 2	8 3 1	8 3 2	8 3 3	8 3 4	7 4 2	Total Tissues/ Tumors
Genital System																										
Ovary	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma	X																									1
Polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	M	+	M	+	+	+	M	M	+	+	M	M	M	M	M	+	+	+	+	M	+	+	M	+	29
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	M	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+	+	+	M	M	+	30
Integumentary System																										
Mammary gland	+	M	M	M	+	M	+	M	M	+	+	M	M	M	+	M	+	+	M	+	+	M	+	M	+	28
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, fibrosarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X	X		X							4
Carcinoma, metastatic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	0	0	0	0	4	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7
	0	0	0	0	1	8	8	1	3	4	4	5	5	0	1	3	4	5	5	8	8	0	1	2
	8	8	8	9	4	0	8	6	4	0	9	1	1	7	0	9	2	9	9	4	4	1	6	6
Carcass ID Number	8	8	8	8	8	8	7	7	7	7	7	7	8	7	7	7	7	7	8	7	8	8	7	7	7
	4	4	4	4	0	1	5	7	7	9	7	8	4	9	3	6	4	9	0	6	2	2	8	5	6
	3	4	5	2	5	4	4	3	2	4	1	5	1	3	5	3	5	2	4	2	4	3	4	3	1
Special Senses System																									
Ear					+				+										+			+			
Eye																				+					
Carcinoma, metastatic																				X					
Harderian gland																				+					
Adenoma																									
Carcinoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	A	A	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed																						X		X	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 3,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	
Carcass ID Number	7 3 1	7 3 2	7 3 3	7 3 4	7 4 1	7 4 3	7 5 1	7 5 2	7 8 1	7 8 2	7 8 3	7 9 1	8 0 1	8 0 2	8 0 3	8 1 1	8 1 2	8 1 3	8 2 1	8 2 2	8 3 1	8 3 2	8 3 3	8 3 4	7 4 2	Total Tissues/ Tumors
Special Senses System																										
Ear									+			+														6
Eye																										1
Carcinoma, metastatic																										1
Harderian gland					+																					2
Adenoma					X																					1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma	X																									1
Lymphoma malignant mixed			X														X					X		X	7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	
Carcass ID Number	8 9 2	9 0 1	9 0 2	9 0 3	9 0 4	9 0 5	9 0 1	9 1 2	9 1 3	9 1 4	9 2 1	9 2 2	9 3 1	9 3 2	9 3 3	9 3 4	9 4 3	9 4 4	8 8 3	9 4 1	9 4 2	9 5 2	9 6 1	9 6 2	9 5 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	45
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																										1
Hepatocellular adenoma															X											2
Histiocytic sarcoma																										1
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	+	+	M	I	M	+	+	M	M	+	+	M	M	+	+	+	+	M	+	+	M	M	M	+	31
Pituitary gland	+	+	+	+	+	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars distalis, adenoma		X					X		X	X		X	X					X				X	X	X		14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma	X							X																		2
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	2 5 1	5 2 2	5 3 6	5 7 9	5 9 3	5 9 6	6 2 0	6 3 1	6 3 2	6 3 5	6 4 2	6 6 1	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	8 7 5	8 7 4	9 3 5	9 4 5	9 5 3	9 2 3	8 7 3	8 8 4	8 8 5	8 9 5	8 9 4	8 9 3	8 5 1	8 5 2	8 5 3	8 6 1	8 6 2	8 6 3	8 6 4	8 6 5	8 7 1	8 7 2	8 8 1	8 8 2	8 9 1
Genital System																									
Clitoral gland			+																						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Polyp stromal																									
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mandibular	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	+	+	M	M	+	+
Lymph node, mesenteric	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	M	M	M	+	M	+	M	+	M	M	M	M	+	M
Adenocarcinoma					X																				
Skin	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma malignant										X															
Subcutaneous tissue, fibrosarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Hepatocellular carcinoma, metastatic, liver						X																			
Histiocytic sarcoma			X																						
Nose	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	
Carcass ID Number	8 9 2	9 0 1	9 0 2	9 0 3	9 0 4	9 0 5	9 1 1	9 1 2	9 1 3	9 1 4	9 2 1	9 2 2	9 3 1	9 3 2	9 3 3	9 3 4	9 4 3	9 4 4	8 8 3	9 4 1	9 4 2	9 5 2	9 6 1	9 6 2	9 5 1	Total Tissues/ Tumors
Genital System																										
Clitoral gland																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Hemangioma									X																	1
Polyp stromal						X																				1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	M	M	+	M	M	M	M	+	+	+	M	+	M	+	+	M	+	+	+	M	+	+	M	+	34
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	17
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Melanoma malignant																										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X	X					X																			4
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	M	+	+	M	+	+	M	M	M	+	+	+	M	+	+	M	+	+	+	+	+	M	+	38
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	2	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	5	2	3	7	9	9	2	3	3	3	4	6	3	3	3	3	3	3	3	3	3	3	3	3	3
	1	2	6	9	3	6	0	1	2	5	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	8	8	9	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	7	7	3	4	5	2	7	8	8	9	9	9	5	5	5	6	6	6	6	6	7	7	8	8	9
	5	4	5	5	3	3	3	4	5	5	4	3	1	2	3	1	2	3	4	5	1	2	1	2	1
Special Senses System																									
Harderian gland																+					+				
Adenoma																X					X				
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Leukemia	X																								
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic																						X			
Lymphoma malignant mixed					X	X	X		X			X													X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Acetaminophen: 6,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	
Carcass ID Number	8 9 2	9 0 1	9 0 2	9 0 3	9 0 4	9 0 5	9 1 1	9 1 2	9 1 3	9 1 4	9 2 1	9 2 2	9 3 1	9 3 2	9 3 3	9 3 4	9 4 3	9 4 4	9 8 3	9 4 1	9 4 2	9 5 2	9 6 1	9 6 2	9 5 1	Total Tissues/ Tumors
Special Senses System																										
Harderian gland																										2
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic						X														X						3
Lymphoma malignant mixed				X					X							X							X	X	X	12

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Acetaminophen

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Harderian Gland: Adenoma				
Overall rates[a]	4/50 (8%)	2/50 (4%)	1/50 (2%)	2/51 (4%)
Adjusted rates[b]	12.2%	6.3%	4.0%	5.3%
Terminal rates[c]	1/27 (4%)	2/32 (6%)	1/25 (4%)	2/38 (5%)
First incidence (days)	635	730 (T)	730 (T)	730 (T)
Life table tests[d]	P=0.218N	P=0.295N	P=0.215N	P=0.235N
Logistic regression tests[d]	P=0.260N	P=0.325N	P=0.212N	P=0.301N
Cochran-Armitage test[d]	P=0.279N			
Fisher exact test[d]		P=0.339N	P=0.181N	P=0.329N
Harderian Gland: Adenoma or Carcinoma				
Overall rates	5/50 (10%)	2/50 (4%)	2/50 (4%)	2/51 (4%)
Adjusted rates	14.3%	6.3%	7.1%	5.3%
Terminal rates	1/27 (4%)	2/32 (6%)	1/25 (4%)	2/38 (5%)
First incidence (days)	611	730 (T)	684	730 (T)
Life table tests	P=0.173N	P=0.188N	P=0.270N	P=0.144N
Logistic regression tests	P=0.214N	P=0.211N	P=0.252N	P=0.200N
Cochran-Armitage test	P=0.220N			
Fisher exact test		P=0.218N	P=0.218N	P=0.210N
Liver: Hepatocellular Adenoma				
Overall rates	3/49 (6%)	4/50 (8%)	7/50 (14%)	2/49 (4%)
Adjusted rates	11.1%	11.9%	22.3%	5.3%
Terminal rates	3/27 (11%)	3/32 (9%)	3/25 (12%)	2/38 (5%)
First incidence (days)	730 (T)	667	549	730 (T)
Life table tests	P=0.318N	P=0.584	P=0.132	P=0.346N
Logistic regression tests	P=0.396N	P=0.535	P=0.127	P=0.346N
Cochran-Armitage test	P=0.438N			
Fisher exact test		P=0.511	P=0.167	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	3/49 (6%)	4/50 (8%)	7/50 (14%)	3/49 (6%)
Adjusted rates	11.1%	11.9%	22.3%	7.4%
Terminal rates	3/27 (11%)	3/32 (9%)	3/25 (12%)	2/38 (5%)
First incidence (days)	730 (T)	667	549	596
Life table tests	P=0.461N	P=0.584	P=0.132	P=0.520N
Logistic regression tests	P=0.558N	P=0.535	P=0.127	P=0.620N
Cochran-Armitage test	P=0.534			
Fisher exact test		P=0.511	P=0.167	P=0.661N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	1/50 (2%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rates	3.7%	10.9%	14.7%	10.5%
Terminal rates	1/27 (4%)	2/32 (6%)	3/25 (12%)	4/38 (11%)
First incidence (days)	730 (T)	638	659	730 (T)
Life table tests	P=0.353	P=0.217	P=0.158	P=0.294
Logistic regression tests	P=0.277	P=0.182	P=0.145	P=0.294
Cochran-Armitage test	P=0.244			
Fisher exact test		P=0.181	P=0.181	P=0.181

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	14/46 (30%)	16/43 (37%)	7/42 (17%)	14/45 (31%)
Adjusted rates	42.7%	48.8%	27.7%	39.3%
Terminal rates	8/25 (32%)	12/28 (43%)	4/19 (21%)	12/33 (36%)
First incidence (days)	536	634	534	596
Life table tests	P=0.183N	P=0.531	P=0.181N	P=0.317N
Logistic regression tests	P=0.301N	P=0.342	P=0.179N	P=0.553N
Cochran-Armitage test	P=0.335N			
Fisher exact test		P=0.326	P=0.103N	P=0.562
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	15/46 (33%)	17/43 (40%)	8/42 (19%)	14/45 (31%)
Adjusted rates	46.1%	49.9%	30.0%	39.3%
Terminal rates	9/25 (36%)	12/28 (43%)	4/19 (21%)	12/33 (36%)
First incidence (days)	536	549	534	596
Life table tests	P=0.131N	P=0.537	P=0.202N	P=0.236N
Logistic regression tests	P=0.226N	P=0.337	P=0.202N	P=0.458N
Cochran-Armitage test	P=0.253N			
Fisher exact test		P=0.323	P=0.114N	P=0.529N
All Organs: Hemangiosarcoma				
Overall rates	2/50 (4%)	3/50 (6%)	1/50 (2%)	0/51 (0%)
Adjusted rates	4.9%	9.1%	3.8%	0.0%
Terminal rates	0/27 (0%)	2/32 (6%)	0/25 (0%)	0/38 (0%)
First incidence (days)	536	691	726	-[a]
Life table tests	P=0.067N	P=0.537	P=0.532N	P=0.227N
Logistic regression tests	P=0.077N	P=0.494	P=0.489N	P=0.219N
Cochran-Armitage test	P=0.076N			
Fisher exact test		P=0.500	P=0.500N	P=0.243N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	2/50 (4%)	4/50 (8%)	1/50 (2%)	1/51 (2%)
Adjusted rates	4.9%	12.1%	3.8%	2.6%
Terminal rates	0/27 (0%)	3/32 (9%)	0/25 (0%)	1/38 (3%)
First incidence (days)	536	691	726	730 (T)
Life table tests	P=0.134N	P=0.385	P=0.532N	P=0.447N
Logistic regression tests	P=0.164N	P=0.335	P=0.489N	P=0.497N
Cochran-Armitage test	P=0.163N			
Fisher exact test		P=0.339	P=0.500N	P=0.492N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or NOS)				
Overall rates	10/50 (20%)	10/50 (20%)	7/50 (14%)	16/51 (31%)
Adjusted rates	26.9%	25.1%	24.9%	35.8%
Terminal rates	4/27 (15%)	5/32 (16%)	4/25 (16%)	10/38 (26%)
First incidence (days)	506	516	701	457 (I)
Life table tests	P=0.296	P=0.510N	P=0.386N	P=0.397
Logistic regression tests	P=0.102	P=0.579	P=0.358N	P=0.128
Cochran-Armitage test	P=0.102			
Fisher exact test		P=0.598N	P=0.298N	P=0.140

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Acetaminophen
(continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
All Organs: Benign Neoplasms				
Overall rates	22/50 (44%)	22/50 (44%)	17/50 (34%)	22/51 (43%)
Adjusted rates	61.6%	57.5%	51.7%	54.8%
Terminal rates	14/27 (52%)	16/32 (50%)	10/25 (40%)	20/38 (53%)
First incidence (days)	536	634	534	596
Life table tests	P=0.167N	P=0.370N	P=0.335N	P=0.151N
Logistic regression tests	P=0.375N	P=0.543N	P=0.336N	P=0.437N
Cochran-Armitage test	P=0.428N			
Fisher exact test		P=0.580N	P=0.206N	P=0.545N
All Organs: Malignant Neoplasms				
Overall rates	20/50 (40%)	15/50 (30%)	14/50 (28%)	19/51 (37%)
Adjusted rates	50.0%	38.1%	42.0%	39.9%
Terminal rates	9/27 (33%)	9/32 (28%)	6/25 (24%)	10/38 (26%)
First incidence (days)	506	516	642	251
Life table tests	P=0.289N	P=0.146N	P=0.269N	P=0.193N
Logistic regression tests	P=0.522	P=0.207N	P=0.214N	P=0.537N
Cochran-Armitage test	P=0.523			
Fisher exact test		P=0.201N	P=0.146N	P=0.469N
All Organs: Benign or Malignant Neoplasms				
Overall rates	35/50 (70%)	28/50 (56%)	24/50 (48%)	35/51 (69%)
Adjusted rates	81.0%	67.7%	66.2%	72.8%
Terminal rates	19/27 (70%)	19/32 (59%)	13/25 (52%)	25/38 (66%)
First incidence (days)	506	516	534	251
Life table tests	P=0.210N	P=0.061N	P=0.123N	P=0.085N
Logistic regression tests	P=0.440	P=0.093N	P=0.060N	P=0.520N
Cochran-Armitage test	P=0.444			
Fisher exact test		P=0.107N	P=0.021N	P=0.526N

(T)Terminal sacrifice
(I)Interim sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined at site.
[b] Kaplan-Meier estimated lifetime neoplasm incidence after adjustment for intercurrent mortality.
[c] Observed incidence at terminal kill.
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. Logistic regression is an alternative method for analyzing the incidence of non-fatal neoplasms. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. For all tests, a negative trend or lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group.

TABLE D4
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Female B6C3F$_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute[a]			
4,4′-Methylenedianiline 2HCl	0/50	0/50	0/50
C.I. Basic Red 9	0/45	0/45	0/45
Monuron	0/42	0/42	0/42
8-Hydroxyquinoline	4/48	1/48	5/48
Butyl Benzyl Phthalate	0/45	0/45	0/45
Boric Acid	0/45	0/45	0/45
Pentachloronitrobenzene	0/48	0/48	0/48
2-Biphenylamine HCl	0/46	0/46	0/46
Acetaminophen	0/50	0/50	0/50
Pentaerythritol Tetranitrate	1/50	0/50	1/50
Total	5/469 (1.1%)	1/469 (0.2%)	6/469 (1.3%)
Standard deviation	2.6%	0.6%	3.3%
Range	0%–8%	0%–2%	0%–10%
Overall Historical Incidence[b]			
Total	49/2,134 (2.3%)	10/2,134 (0.5%)	59/2,134 (2.8%)
Standard deviation	2.8%	1.3%	3.4%
Range	0%–8%	0%–6%	0%–15%

[a] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 1 March 1989)
[b] Toxicology Data Management System compilation (data as of 22 December 1989) and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Acetaminophen[a]

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Moribund	21	9	21	8
Natural deaths	2	9		4
Accidental deaths			4	
Survivors				
Terminal sacrifice	27	32	25	38
Animals examined microscopically	50	50	50	51
Alimentary System				
Gallbladder	(42)	(45)	(44)	(46)
Degeneration, hyaline				1 (2%)
Inflammation, chronic, focal				1 (2%)
Serosa, inflammation, chronic				1 (2%)
Intestine, large, cecum	(49)	(45)	(49)	(48)
Hyperplasia, lymphoid				1 (2%)
Intestine large, colon	(47)	(44)	(47)	(48)
Parasite		1 (2%)		
Intestine large, rectum	(47)	(46)	(49)	(48)
Artery, inflammation		1 (2%)		
Intestine small, ileum	(48)	(43)	(48)	(47)
Amyloid deposition		1 (2%)	1 (2%)	
Intestine small, jejunum	(47)	(42)	(46)	(48)
Amyloid deposition				1 (2%)
Liver	(49)	(50)	(50)	(49)
Angiectasis, focal	2 (4%)			
Clear cell focus	1 (2%)			
Congestion	1 (2%)			
Cytoplasmic alteration, focal	1 (2%)		1 (2%)	
Eosinophilic focus				1 (2%)
Fatty change	9 (18%)	4 (8%)	4 (8%)	3 (6%)
Hematopoietic cell proliferation	6 (12%)	3 (6%)	5 (10%)	5 (10%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Inflammation, acute	1 (2%)			1 (2%)
Inflammation, granulomatous, focal				1 (2%)
Mixed cell focus		1 (2%)		1 (2%)
Necrosis, focal	14 (29%)	3 (6%)	6 (12%)	9 (18%)
Artery, mineralization		1 (2%)		
Centrilobular, necrosis			1 (2%)	
Hepatocyte, hyperplasia, focal				1 (2%)
Periductular, fibrosis			1 (2%)	
Perivascular, inflammation, chronic	9 (18%)	9 (18%)	13 (26%)	12 (24%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Alimentary System (continued)				
Mesentery	(4)	(4)	(3)	(1)
Hemorrhage		1 (25%)		
Inflammation, acute	1 (25%)	1 (25%)	2 (67%)	
Fat, necrosis	3 (75%)	2 (50%)	1 (33%)	1 (100%)
Pancreas	(49)	(48)	(47)	(49)
Hyperplasia, lymphoid				1 (2%)
Inflammation, chronic, focal	21 (43%)	17 (35%)	14 (30%)	19 (39%)
Acinus, atrophy	4 (8%)	1 (2%)		
Acinus, hyperplasia	1 (2%)			
Artery, inflammation, chronic				1 (2%)
Duct, ectasia	2 (4%)	1 (2%)		
Salivary glands	(46)	(49)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		2 (4%)
Hypoplasia			1 (2%)	
Inflammation, chronic, focal	33 (72%)	32 (65%)	29 (58%)	31 (62%)
Stomach	(48)	(49)	(50)	(48)
Inflammation, chronic		1 (2%)		
Stomach, forestomach	(48)	(49)	(49)	(48)
Acanthosis	3 (6%)			
Cyst epithelial inclusion			1 (2%)	
Hyperkeratosis	4 (8%)	2 (4%)		
Hyperplasia, squamous		1 (2%)	1 (2%)	
Inflammation, acute	1 (2%)			
Stomach, glandular	(47)	(46)	(50)	(48)
Inflammation, acute			1 (2%)	
Inflammation, chronic	9 (19%)	8 (17%)	6 (12%)	5 (10%)
Inflammation, chronic, active	2 (4%)			
Mineralization, focal			2 (4%)	
Artery, inflammation			1 (2%)	
Tooth		(1)	(1)	(1)
Abscess			1 (100%)	
Inflammation, acute		1 (100%)		1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)	1 (2%)		
Inflammation, acute		1 (2%)		
Inflammation, chronic, focal	3 (6%)			
Mineralization, focal				1 (2%)
Atrium, thrombus		1 (2%)		
Coronary artery, inflammation, acute	1 (2%)			
Coronary artery, inflammation, chronic				1 (2%)
Pericardium, inflammation, acute	2 (4%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Endocrine System				
Adrenal gland	(49)	(49)	(46)	(49)
Capsule, hyperplasia	2 (4%)	2 (4%)		1 (2%)
Subcapsular, hyperplasia				1 (2%)
Adrenal gland, cortex	(49)	(49)	(46)	(49)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Angiectasis				1 (2%)
Atrophy		2 (4%)		
Congestion		1 (2%)	2 (4%)	1 (2%)
Cyst		1 (2%)		
Cytoplasmic alteration, focal	1 (2%)	1 (2%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Vacuolization cytoplasmic	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Adrenal gland, medulla	(46)	(46)	(45)	(47)
Congestion	1 (2%)		3 (7%)	1 (2%)
Hyperplasia		1 (2%)		
Islets, pancreatic	(48)	(47)	(43)	(49)
Hyperplasia	7 (15%)	2 (4%)	2 (5%)	6 (12%)
Pituitary gland	(46)	(43)	(42)	(45)
Congestion				1 (2%)
Pars distalis, angiectasis	1 (2%)			1 (2%)
Pars distalis, cyst			1 (2%)	
Pars distalis, hyperplasia	2 (4%)		2 (5%)	
Pars distalis, hyperplasia, focal	13 (28%)	6 (14%)	13 (31%)	13 (29%)
Thyroid gland	(48)	(50)	(50)	(50)
Inflammation, acute, focal		1 (2%)		
Inflammation, chronic		2 (4%)		
Inflammation, chronic, focal	4 (8%)	5 (10%)	2 (4%)	11 (22%)
Follicular cell, cyst				1 (2%)
Follicular cell, hyperplasia, focal	2 (4%)	8 (16%)	11 (22%)	25 (50%)
General Body System				
None				
Genital System				
Clitoral gland				(1)
Dilatation				1 (100%)
Ovary	(47)	(49)	(49)	(50)
Abscess	5 (11%)	8 (16%)	8 (16%)	3 (6%)
Congestion		2 (4%)		1 (2%)
Cyst	17 (36%)	20 (41%)	12 (24%)	10 (20%)
Hemorrhage	1 (2%)			1 (2%)
Hyperplasia, lymphoid	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Genital System (continued)				
Ovary (continued)				
Inflammation, acute			1 (2%)	
Inflammation, chronic			1 (2%)	
Inflammation, granulomatous				1 (2%)
Thrombus			2 (4%)	
Corpus luteum, hypertrophy	1 (2%)			
Follicle, hemorrhage		2 (4%)		
Uterus	(49)	(50)	(50)	(49)
Abscess	3 (6%)		2 (4%)	
Angiectasis				1 (2%)
Atrophy		1 (2%)		
Dilatation	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Inflammation, acute	2 (4%)	5 (10%)	3 (6%)	1 (2%)
Thrombus			1 (2%)	1 (2%)
Endometrium, angiectasis	2 (4%)			
Endometrium, cyst			1 (2%)	
Endometrium, hyperplasia, cystic	33 (67%)	33 (66%)	35 (70%)	31 (63%)
Hematopoietic System				
Bone marrow	(49)	(49)	(49)	(49)
Angiectasis			1 (2%)	
Hyperplasia, lymphoid				1 (2%)
Hyperplasia, neutrophil	8 (16%)	10 (20%)	13 (27%)	2 (4%)
Myelofibrosis	30 (61%)	27 (55%)	21 (43%)	35 (71%)
Lymph node	(49)	(47)	(49)	(49)
Axillary, hyperplasia, lymphoid			1 (2%)	
Lumbar, congestion	1 (2%)	2 (4%)		
Lumbar, infiltration, cellular, plasma	4 (8%)	2 (4%)	1 (2%)	
Lumbar, inflammation, acute	1 (2%)	1 (2%)		
Lymphatic, angiectasis			1 (2%)	
Mediastinal, abscess	1 (2%)		1 (2%)	1 (2%)
Mediastinal, congestion		1 (2%)		
Mediastinal, hyperplasia, lymphoid	1 (2%)			
Mediastinal, infiltration, cellular, plasma cell	1 (2%)	5 (11%)	2 (4%)	
Pancreatic, infiltration, cellular, plasma cell		1 (2%)		
Renal, angiectasis	1 (2%)			
Renal, congestion		2 (4%)		
Renal, infiltration, cellular, plasma	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Renal, necrosis		1 (2%)		
Renal, lymphatic, angiectasis		1 (2%)	1 (2%)	
Lymph node, mandibular	(41)	(26)	(29)	(44)
Congestion		1 (4%)		1 (2%)
Hematopoietic cell proliferation		1 (4%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Hematopoietic System (continued)				
Lymph node, mandibular (continued)				
Hyperplasia, lymphoid	2 (5%)			1 (2%)
Infiltration cellular, plasma cell	6 (15%)	6 (23%)	7 (24%)	9 (20%)
Inflammation, acute		1 (4%)		
Lymph node, mesenteric	(44)	(45)	(45)	(43)
Amyloid deposition				1 (2%)
Congestion	4 (9%)	2 (4%)	3 (7%)	2 (5%)
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid	2 (5%)		3 (7%)	1 (2%)
Infiltration cellular, plasma cell	1 (2%)	2 (4%)	1 (2%)	
Infiltration cellular, histiocytic	1 (2%)	1 (2%)		
Inflammation, acute	2 (5%)			
Spleen	(49)	(50)	(50)	(49)
Congestion				1 (2%)
Hematopoietic cell proliferation	31 (63%)	37 (74%)	32 (64%)	36 (73%)
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid	11 (22%)	8 (16%)	5 (10%)	8 (16%)
Inflammation, acute			1 (2%)	
Pigmentation, hemosiderin		1 (2%)	4 (8%)	
Thymus	(23)	(30)	(30)	(34)
Congestion				1 (3%)
Hyperplasia, lymphoid	2 (9%)			
Infiltration cellular, plasma cell	1 (4%)	1 (3%)		
Integumentary System				
Skin	(47)	(48)	(49)	(48)
Ulcer			1 (2%)	
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Sternum, necrosis		1 (2%)		
Tarsal, hyperostosis		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Congestion			2 (4%)	
Hemorrhage, focal		1 (2%)		
Hydrocephalus	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Mineralization, focal	24 (48%)	31 (62%)	28 (56%)	31 (62%)
Artery, inflammation, chronic	1 (2%)			
Choroid plexus, inflammation, Chronic, focal	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Acetaminophen (continued)

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)	5 (10%)	1 (2%)
Giant cell		1 (2%)		
Granuloma		2 (4%)		
Hemorrhage, focal	1 (2%)		1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, histiocytic	1 (2%)	1 (2%)	2 (4%)	
Inflammation, acute, focal		1 (2%)		
Alveolar epithelium, metaplasia			1 (2%)	1 (2%)
Perivascular, inflammation, chronic	33 (66%)	27 (54%)	22 (44%)	32 (64%)
Pleura, inflammation, acute	2 (4%)			1 (2%)
Pleura, inflammation, chronic	1 (2%)			
Nose	(47)	(44)	(45)	(38)
Inflammation, chronic	4 (9%)	1 (2%)	5 (11%)	
Metaplasia, squamous	18 (38%)	15 (34%)	10 (22%)	6 (16%)
Respiratory epithelium, Degeneration hyaline	28 (60%)	30 (68%)	27 (60%)	22 (58%)
Special Senses System				
Ear	(1)	(1)	(6)	
Inflammation, chronic			1 (17%)	
Eye	(1)	(1)	(1)	
Degeneration		1 (100%)		
Retina, degeneration	1 (100%)			
Urinary System				
Kidney	(49)	(49)	(50)	(49)
Atrophy, focal		1 (2%)	1 (2%)	
Congestion	3 (6%)			1 (2%)
Glomerulosclerosis	13 (27%)	5 (10%)	8 (16%)	8 (16%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, plasma cell		1 (2%)		
Inflammation, chronic, focal	25 (51%)	22 (45%)	26 (52%)	26 (53%)
Mineralization			1 (2%)	
Artery, inflammation, chronic	1 (2%)			
Cortex, degeneration				1 (2%)
Cortex, necrosis, focal	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Interstitial tissue, inflammation		1 (2%)		
Papilla, necrosis		1 (2%)		
Renal tubule, pigmentation			1 (2%)	
Renal tubule, regeneration	6 (12%)		1 (2%)	2 (4%)
Urinary bladder	(49)	(46)	(44)	(46)
Inflammation, chronic, focal	37 (76%)	30 (65%)	35 (80%)	36 (78%)
Artery, inflammation, chronic				1 (2%)
Transitional epithelium, hyperplasia, focal		2 (4%)		

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

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM PROTOCOL

Testing was performed as reported by Ames *et al.* (1975) with modifications as listed below and described in greater detail in Haworth *et al.* (1983) and Zeiger *et al.* (1988). Acetaminophen was sent to the laboratories as a coded aliquot from the Radian Corporation (Austin, TX), and was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and 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 prior to 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.

In this assay, each test consists of triplicate plates of concurrent positive and negative controls and of at least five doses of acetaminophen. Tests were repeated for all negative assays and all positive assays were retested under the conditions which elicited the positive response.

A positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which is not dose related, not reproducible, or is 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.

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1987) and is briefly described as follows. Acetaminophen was sent to the laboratories as a coded aliquot from Radian Corporation (Austin, TX). Acetaminophen was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of acetaminophen; the high dose was limited by toxicity and did not exceed 5,000 μg/mL.

In the SCE test without S9, CHO cells were incubated for 26 hours with acetaminophen in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing acetaminophen was removed and replaced with fresh medium containing BrdU and Colcemid, and incubation was continued for 1.5 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 study chemical, serum-free medium, and S9 for 1.5 hours. The medium was then removed and replaced with medium containing BrdU and no acetaminophen, and 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 Abs test without S9, cells were incubated in McCoy's 5A medium with acetaminophen for 18 hours. Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with acetaminophen and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 25 or 50 second-division metaphase cells were scored for frequency of SCEs per cell from each dose; 58 to 200 first-division metaphase cells were scored at each dose for the chromosomal aberrations test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing ten 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. For aberration data, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<.003$) effect on the slope of the curve or on a dose point ($P<0.05$) was sufficient for a test conclusion of positive.

RESULTS

Acetaminophen was not mutagenic when tested in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 at concentrations of 100 to 10,000 μg/plate with a preincubation protocol in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983, Table E1). In cytogenetic tests with Chinese hamster ovary (CHO) cells, acetaminophen induced SCEs (Table E2) and Abs (Table E3) in both the presence and absence of Aroclor-1254 induced Sprague-Dawley rat liver S9. In the SCE test, positive responses were observed over a concentration range of 5 to 150 μg/mL in the absence of S9; with S9, only the highest dose tested, 5,000 μg/mL, produced a significant increase in SCE. In the chromosomal aberration test without S9, acetaminophen concentrations of 1,257 to 5,000 μg/mL produced highly significant increases in the percentage of aberrant cells, with some dose levels showing more than 40% aberrant cells; a delayed harvest protocol was used to offset acetaminophen-induced cell cycle delay and allow accumulation of sufficient metaphases for analysis. With S9, only the 5,000 μg/mL dose level produced a significant increase in aberrations.

TABLE E1
Mutagenicity of Acetaminophen in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	141 ± 12.2	110 ± 5.8	117 ± 6.1	91 ± 5.7	145 ± 13.5	97 ± 8.0
	100	138 ± 4.3	104 ± 11.3	109 ± 11.4	95 ± 2.0	143 ± 6.7	101 ± 3.7
	333	131 ± 6.0	115 ± 6.5	107 ± 5.5	91 ± 1.9	132 ± 5.8	120 ± 9.2
	1,000	145 ± 6.3	94 ± 2.6	114 ± 6.2	85 ± 4.0	141 ± 8.3	104 ± 6.5
	3,333	140 ± 12.1	106 ± 10.3	112 ± 5.3	100 ± 8.9	141 ± 3.8	108 ± 6.7
	10,000	119 ± 13.0	93 ± 6.2	96 ± 0.7	87 ± 8.1	137 ± 4.7	87 ± 6.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		2,102 ± 41.3	1,190 ± 57.0	1,983 ± 73.9	1,262 ± 13.9	1,731 ± 125.8	1,055 ± 40.6
TA1535	0	17 ± 3.2	17 ± 2.1	12 ± 2.0	8 ± 1.2	10 ± 1.7	11 ± 0.7
	100	25 ± 2.2	17 ± 2.9	6 ± 1.8	8 ± 0.3	12 ± 0.3	8 ± 0.7
	333	23 ± 1.8	15 ± 1.5	8 ± 0.3	10 ± 3.8	9 ± 1.5	12 ± 1.9
	1,000	18 ± 1.2	13 ± 1.2	9 ± 2.3	10 ± 1.2	9 ± 1.2	10 ± 3.2
	3,333	16 ± 2.2	15 ± 3.2	6 ± 1.3	12 ± 2.0	9 ± 1.0	10 ± 0.9
	10,000	18 ± 2.1	13 ± 1.2	7 ± 1.5	13 ± 1.2	8 ± 1.5	8 ± 0.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		1,524 ± 39.8	990 ± 28.4	119 ± 15.5	74 ± 2.9	68 ± 8.7	60 ± 4.9
TA1537	0	5 ± 0.6	7 ± 2.0	9 ± 2.6	8 ± 2.1	14 ± 0.3	9 ± 2.8
	100	9 ± 2.6	7 ± 2.6	8 ± 0.9	9 ± 0.9	8 ± 2.1	7 ± 2.4
	333	7 ± 1.9	8 ± 0.7	10 ± 2.6	6 ± 0.9	13 ± 0.9	11 ± 1.9
	1,000	4 ± 0.6	5 ± 1.5	10 ± 1.5	7 ± 1.5	11 ± 3.2	6 ± 1.2
	3,333	6 ± 0.3	7 ± 1.3	9 ± 1.5	7 ± 0.3	8 ± 0.9	8 ± 1.9
	10,000	4 ± 0.6	5 ± 0.6	9 ± 2.6	6 ± 0.3	9 ± 1.8	9 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		199 ± 24.5	383 ± 20.1	159 ± 14.6	124 ± 6.3	133 ± 1.7	67 ± 0.9
TA98	0	18 ± 3.2	14 ± 1.2	27 ± 4.1	22[c]	26 ± 5.3	25 ± 3.6
	100	19 ± 2.2	14 ± 1.5	31 ± 3.3	21 ± 2.7	27 ± 2.2	24 ± 3.0
	333	18 ± 2.3	20 ± 2.7	26 ± 4.5	25 ± 2.9	34 ± 2.1	30 ± 2.0
	1,000	16 ± 1.2	14 ± 1.7	29 ± 3.2	24 ± 4.5	28 ± 3.2	24 ± 4.5
	3,333	17 ± 3.1	16 ± 0.9	26 ± 1.5	25 ± 3.1	25 ± 4.0	24 ± 4.5
	10,000	16 ± 2.3	14 ± 0.3	19 ± 1.8	22 ± 1.3	26 ± 3.0	20 ± 2.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		1,779 ± 27.1	1,440 ± 77.0	1,945 ± 17.2	1,668 ± 49.6	1,657 ± 37.9	1,022 ± 28.3

[a] Study performed at EG&G Mason Research Institute. The detailed protocol and these data are presented in Haworth *et al.* (1983). Cells and study compound or solvent (dimethylsulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by toxicity or solubility, but did not exceed 10 mg/plate; 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± the standard error from 3 plates.

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

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Acetaminophen[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosomes	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
-S9[c]								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,032	392	0.37	7.8	25.5	
Mitomycin-C	0.0010	50	1,035	594	0.57	11.9	25.5	51.09
	0.0100	5	105	215	2.04	43.0	25.5	439.07
4-Hydroxyacetanilide (Acetaminophen)								
	5.0	50	1,041	476	0.45	9.5	25.5	20.38*
	16.7	50	1,035	589	0.56	11.8	25.5	49.82*
	50.0	50	1,024	544	0.53	10.9	25.5	39.86*
	166.7	0					31.6[d]	
								P≤0.001
Trial 2								
Summary: Weak positive								
Dimethylsulfoxide		25	512	224	0.43	9.0	25.5	
Mitomycin-C	0.0010	25	512	292	0.57	11.7	25.5	30.36
	0.0100	5	104	200	1.92	40.0	25.5	339.56
4-Hydroxyacetanilide (Acetaminophen)								
	49.8	25	515	255	0.49	10.2	25.5	13.17
	100.5	25	514	262	0.50	10.5	25.5	16.51
	150.0	25	517	442	0.85	17.7	30.8[d]	95.41*
	200.0	0					30.8[d]	
								P≤0.001
+S9[e]								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,038	381	0.36	7.6	25.5	
Cyclophosphamide	0.4	50	1,025	638	0.62	12.8	25.5	69.58
	2.0	5	104	158	1.51	31.6	25.5	313.90
4-Hydroxyacetanilide (Acetaminophen)								
	500.0	50	1,036	452	0.43	9.0	25.5	18.86
	1,666.7	50	1,034	426	0.41	8.5	25.5	12.24
	5,000.0	50	1,041	644	0.61	12.9	25.5	68.54*
								P≤0.001

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Acetaminophen (continued)

* Statistically significant effect on slope of dose-response curve ($P<0.003$) or on a dose point ($P<0.05$).
[a] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987).
[b] Percent increase in SCEs/chromosome of culture exposed to acetaminophen relative to those of culture exposed to solvent. Values at least 20% above control levels are considered significant.
[c] In the absence of S9, cells were incubated with acetaminophen 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 to 3 hours.
[d] Acetaminophen induced a delay in the cell division cycle and the harvest time extended to maximize the portion of second division cells available for analysis.
[e] In the presence of S9, cells were incubated with acetaminophen or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 to 3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Acetaminophen[a]

-S9[b]					+S9[d]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1					**Trial 1**				
Harvest time: 20.0 h[c]					Harvest time: 12.0 h				
Summary: Positive					Summary: Weak positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	6	0.03	3.0		200	5	0.03	2.5
Mitomycin-C					Cyclophosphamide				
0.05	200	38	0.19	16.0	7.5	200	15	0.08	7.5
0.08	25	20	0.80	56.0	37.5	25	10	0.40	24.0
4-Hydroxyacetanilide (Acetaminophen)					4-Hydroxyacetanilide (Acetaminophen)				
1,257	60	60	1.00	43.3*	2,513	200	6	0.03	3.0
2,513	58	27	0.47	27.6*	3,750	200	13	0.07	4.5
3,750	75	50	0.67	42.7*	5,000	200	31	0.16	11.0*
5,000	200	30	0.15	8.5*					
				P=0.011					P=0.001
					Trial 2				
					Harvest time: 12.0 h				
					Summary: Weak positive				
					Dimethylsulfoxide				
						100	2	0.02	2.0
					Cyclophosphamide:				
					7.5	100	17	0.17	17.0
					37.5	25	20	0.80	56.0
					4-Hydroxyacetanilide (Acetaminophen)				
					3,800	100	10	0.10	5.0
					4,400	100	10	0.10	8.0
					5,000	100	15	0.15	12.0*
									P=0.002

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Acetaminophen (continued)

* Statistically significant effect on slope of dose-response curve ($P<0.003$) or on a dose point ($P<0.05$).
[a] Study performed at Litton Bionetics, Inc.; Abs =aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1987).
[b] In the absence of S9, cells were incubated with acetaminophen or solvent 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] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphase at harvest.
[d] In the presence of S9, cells were incubated with acetaminophen or solvent 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 livers of Aroclor 1254-induced male Sprague-Dawley rats.

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS IN THE 13-WEEK FEED STUDIES

TABLE F1
Organ Weights for Rats in the 13-Week Feed Studies of Acetaminophen[a]

Organ	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
n	9	10	10	10	10	10	8
Necropsy Body weight	345 ± 6	346 ± 10	348 ± 7	345 ± 6	327 ± 6	294 ± 6**	156 ± 9**
Liver	12.17 ± 0.22	14.39 ± 0.70	13.80 ± 0.54	14.44 ± 0.72[b]	13.31 ± 0.56	13.53 ± 0.50	7.84 ± 0.38*
Brain	1.97 ± 0.02	1.97 ± 0.02	2.04 ± 0.08	1.96 ± 0.02	1.94 ± 0.02	1.90 ± 0.02*	1.74 ± 0.03**
Heart	0.99 ± 0.04	0.97 ± 0.04	0.97 ± 0.03	0.92 ± 0.03	0.96 ± 0.03	0.86 ± 0.01**	0.51 ± 0.03**
Lungs	1.52 ± 0.10	1.71 ± 0.09	1.64 ± 0.08[b]	1.67 ± 0.04	1.71 ± 0.08	1.48 ± 0.06	0.93 ± 0.05**
Right kidney	1.16 ± 0.03[b]	1.36 ± 0.03	1.28 ± 0.04	1.29 ± 0.04	1.30 ± 0.03	1.21 ± 0.02	0.85 ± 0.03
Right testis	1.54 ± 0.02[c]	1.44 ± 0.05	1.56 ± 0.03	1.51 ± 0.04	1.45 ± 0.04	1.20 ± 0.07**	0.40 ± 0.03**
Thymus	0.31 ± 0.04	0.27 ± 0.03	0.27 ± 0.03	0.26 ± 0.01	0.29 ± 0.02	0.26 ± 0.01	0.13 ± 0.01**
Female							
n	10	10	10	10	10	10	8
Necropsy Body weight	212 ± 4	211 ± 3	208 ± 4	208 ± 3	205 ± 4	188 ± 3**	118 ± 8**
Liver	7.20 ± 0.26	8.21 ± 0.22	7.73 ± 0.23	8.31 ± 0.14	7.49 ± 0.15	7.55 ± 0.27	6.42 ± 0.36
Brain	1.90 ± 0.02	1.90 ± 0.02	1.80 ± 0.04	1.83 ± 0.01	1.84 ± 0.02	1.83 ± 0.02	1.60 ± 0.02**
Heart	0.70 ± 0.08	0.68 ± 0.02	0.63 ± 0.01	0.62 ± 0.01	0.62 ± 0.02	0.58 ± 0.01*	0.42 ± 0.02**
Lungs	1.10 ± 0.06	1.25 ± 0.05	1.36 ± 0.08	1.24 ± 0.07	1.18 ± 0.06	1.21 ± 0.07	0.79 ± 0.06
Right kidney	0.73 ± 0.05	0.82 ± 0.02	0.77 ± 0.01	0.79 ± 0.01	0.79 ± 0.01	0.76 ± 0.02	0.66 ± 0.03
Thymus	0.28 ± 0.01	0.29 ± 0.02	0.26 ± 0.01	0.24 ± 0.01*	0.22 ± 0.01**	0.23 ± 0.01**	0.11 ± 0.02**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Organ weights and body weights are expressed in grams (mean ± standard error).
[b] n=9
[c] n=8

TABLE F2
Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Studies of Acetaminophen[a]

Organ	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
n	9	10	10	10	10	10	8
Necropsy Body weight	345 ± 6	346 ± 10	348 ± 7	345 ± 6	327 ± 6	294 ± 6**	156 ± 9**
Liver	35.3 ± 0.5	41.4 ± 1.2**	39.6 ± 0.9**	41.9 ± 1.7**[b]	40.5 ± 1.1**	46.0 ± 1.1**	50.4 ± 1.5**
Brain	5.70 ± 0.09	5.72 ± 0.15	5.91 ± 0.35	5.68 ± 0.08	5.93 ± 0.10	6.51 ± 0.12**	11.34 ± 0.54**
Heart	2.86 ± 0.07	2.81 ± 0.07	2.78 ± 0.06	2.67 ± 0.04	2.94 ± 0.06	2.93 ± 0.05	3.28 ± 0.11**
Lungs	4.43 ± 0.35	4.95 ± 0.20	4.66 ± 0.20[b]	4.85 ± 0.15	5.24 ± 0.26	5.04 ± 0.21	5.99 ± 0.22**
Right kidney	3.36 ± 0.10[b]	3.94 ± 0.12**	3.67 ± 0.09*	3.73 ± 0.08*	3.96 ± 0.05**	4.12 ± 0.05**	5.47 ± 0.17**
Right testis	4.48 ± 0.08[c]	4.17 ± 0.16	4.49 ± 0.10	4.37 ± 0.12	4.45 ± 0.09	4.08 ± 0.24	2.57 ± 0.17**
Thymus	0.92 ± 0.12	0.78 ± 0.09	0.78 ± 0.08	0.76 ± 0.04	0.89 ± 0.04	0.88 ± 0.02	0.83 ± 0.03
Female							
n	10	10	10	10	10	10	8
Necropsy Body weight	212 ± 4	211 ± 3	208 ± 4	208 ± 3	205 ± 4	188 ± 3**	118 ± 8
Liver	33.9 ± 0.9	38.8 ± 0.7**	37.1 ± 0.9**	40.1 ± 0.8**	36.6 ± 0.8**	40.1 ± 1.2**	55.5 ± 3.2**
Brain	8.80 ± 0.12	8.82 ± 0.09	8.60 ± 0.25	8.83 ± 0.11	8.96 ± 0.14	9.74 ± 0.07**	14.02 ± 0.91**
Heart	3.33 ± 0.38	3.20 ± 0.06	3.03 ± 0.04	2.97 ± 0.07	3.04 ± 0.08	3.09 ± 0.04	3.56 ± 0.11*
Lungs	5.18 ± 0.25	5.94 ± 0.26	6.56 ± 0.42**	5.97 ± 0.30*	5.74 ± 0.28*	6.44 ± 0.33**	6.71 ± 0.23**
Right kidney	3.43 ± 0.22	3.88 ± 0.07**	3.72 ± 0.04*	3.82 ± 0.06**	3.84 ± 0.04**	4.01 ± 0.05**	5.75 ± 0.39**
Thymus	1.32 ± 0.05	1.37 ± 0.07	1.24 ± 0.06	1.15 ± 0.06	1.07 ± 0.07**	1.24 ± 0.08	0.89 ± 0.10**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Organ weights and body weights are expressed in grams; organ-weight-to-body-weight ratios are expressed as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] n=8

TABLE F3
Organ Weights for Mice in the 13-Week Feed Studies of Acetaminophen[a]

Organ	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
n	10	10	10	9	10	8	9
Necropsy Body weight	31.3 ± 0.6	32.8 ± 0.6	31.8 ± 0.6	32.6 ± 0.6	31.2 ± 0.6	29.6 ± 0.7	27.9 ± 0.2**
Liver	1.544 ± 0.056	1.595 ± 0.048	1.695 ± 0.063	1.590 ± 0.050	1.619 ± 0.035	1.553 ± 0.066	1.307 ± 0.028**
Brain	0.465 ± 0.006	0.453 ± 0.007	0.471 ± 0.007	0.472 ± 0.005	0.483 ± 0.005	0.473 ± 0.003	0.482 ± 0.005
Heart	0.158 ± 0.005	0.160 ± 0.004	0.168 ± 0.006	0.158 ± 0.003	0.160 ± 0.004	0.158 ± 0.005	0.136 ± 0.004**
Lungs	0.232 ± 0.016	0.207 ± 0.006	0.226 ± 0.006	0.205 ± 0.007	0.277 ± 0.019	0.244 ± 0.009	0.210 ± 0.004
Right kidney	0.285 ± 0.010	0.325 ± 0.007	0.317 ± 0.007	0.304 ± 0.008	0.297 ± 0.008	0.297 ± 0.012	0.265 ± 0.006
Right testis	0.118 ± 0.002	0.113 ± 0.005[b]	0.119 ± 0.002	0.115 ± 0.002	0.122 ± 0.004	0.112 ± 0.007[c]	0.114 ± 0.002
Thymus	0.044 ± 0.004	0.034 ± 0.003	0.034 ± 0.006	0.038 ± 0.003	0.040 ± 0.003	0.043 ± 0.004	0.046 ± 0.003
Female							
n	9	9	10	10	9	10	9
Necropsy Body weight	28.7 ± 1.0	28.0 ± 1.0	28.5 ± 1.1	27.7 ± 0.7	27.6 ± 0.9	24.7 ± 0.7**	23.8 ± 0.5**
Liver	1.506 ± 0.103	1.363 ± 0.043	1.365 ± 0.057	1.405 ± 0.030	1.465 ± 0.054[d]	1.233 ± 0.048*	1.243 ± 0.038*
Brain	0.495 ± 0.007	0.500 ± 0.005	0.489 ± 0.005	0.488 ± 0.007	0.506 ± 0.008	0.505 ± 0.007	0.482 ± 0.006
Heart	0.132 ± 0.003	0.130 ± 0.003	0.130 ± 0.004	0.127 ± 0.002	0.141 ± 0.008[d]	0.127 ± 0.003	0.122 ± 0.003*
Lungs	0.249 ± 0.026	0.227 ± 0.009	0.261 ± 0.029	0.254 ± 0.020	0.252 ± 0.022	0.223 ± 0.017	0.243 ± 0.023
Right kidney	0.199 ± 0.006	0.212 ± 0.009	0.211 ± 0.008	0.210 ± 0.005	0.226 ± 0.007*	0.204 ± 0.005	0.183 ± 0.007
Thymus	0.057 ± 0.005	0.059 ± 0.005	0.050 ± 0.002	0.053 ± 0.004	0.050 ± 0.004	0.055 ± 0.005	0.052 ± 0.004

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights and body weights are expressed in grams (mean ± standard error).
[b] n=9
[c] n=7
[d] n=8

TABLE F4
Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Studies of Acetaminophen[a]

Organ	0 ppm	800 ppm	1,600 ppm	3,200 ppm	6,200 ppm	12,500 ppm	25,000 ppm
Male							
n	10	10	10	9	10	8	9
Necropsy Body weight	31.3 ± 0.6	32.8 ± 0.6	31.8 ± 0.6	32.6 ± 0.6	31.2 ± 0.6	29.6 ± 0.7	27.9 ± 0.2**
Liver	49.2 ± 1.4	48.6 ± 1.1	53.3 ± 1.4	49.0 ± 1.8	51.9 ± 0.7	52.5 ± 1.6	46.9 ± 1.0
Brain	14.9 ± 0.3	13.8 ± 0.3	14.9 ± 0.3	14.5 ± 0.3	15.5 ± 0.3	16.1 ± 0.4	17.3 ± 0.1**
Heart	5.1 ± 0.2	4.9 ± 0.1	5.3 ± 0.2	4.9 ± 0.1	5.1 ± 0.1	5.4 ± 0.2	4.9 ± 0.1
Lungs	7.4 ± 0.5	6.3 ± 0.2	7.2 ± 0.3	6.3 ± 0.3	8.9 ± 0.6	8.3 ± 0.4	7.5 ± 0.2
Right kidney	9.1 ± 0.3	9.9 ± 0.2	10.0 ± 0.2	9.4 ± 0.3	9.5 ± 0.2	10.0 ± 0.2	9.5 ± 0.2
Right testis	3.8 ± 0.1	3.4 ± 0.2[b]	3.7 ± 0.1	3.5 ± 0.1	3.9 ± 0.1	3.9 ± 0.3[c]	4.1 ± 0.0*
Thymus	1.4 ± 0.1	1.0 ± 0.1	1.1 ± 0.2	1.2 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.6 ± 0.1
Female							
n	9	9	10	10	9	10	9
Necropsy Body weight	28.7 ± 1.0	28.0 ± 1.0	28.5 ± 1.1	27.7 ± 0.7	27.6 ± 0.9	24.7 ± 0.7**	23.8 ± 0.5
Liver	52.4 ± 3.1	48.8 ± 0.6	48.0 ± 1.3	50.8 ± 1.0	53.7 ± 0.9[d]	49.8 ± 1.2	52.2 ± 1.3
Brain	17.4 ± 0.6	18.0 ± 0.5	17.4 ± 0.6	17.7 ± 0.5	18.5 ± 0.7	20.5 ± 0.4**	20.3 ± 0.5**
Heart	4.6 ± 0.2	4.7 ± 0.1	4.6 ± 0.1	4.6 ± 0.1	5.1 ± 0.3[d]	5.2 ± 0.1**	5.1 ± 0.1*
Lungs	8.7 ± 0.9	8.1 ± 0.2	9.1 ± 0.9	9.2 ± 0.6	9.3 ± 1.0	9.1 ± 0.7	10.2 ± 1.0
Right kidney	7.0 ± 0.2	7.6 ± 0.3	7.5 ± 0.2	7.6 ± 0.1	8.2 ± 0.2**	8.3 ± 0.1**	7.7 ± 0.2**
Thymus	2.0 ± 0.1	2.1 ± 0.1	1.8 ± 0.1	1.9 ± 0.2	1.8 ± 0.1	2.2 ± 0.2	2.2 ± 0.2

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights and body weights are expressed in grams; organ-weight-to-body-weight ratios are expressed as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] n=7
[d] n=8

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1
Hematology and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Studies of Acetaminophen[a]

Analysis	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Male				
n	9	10	10	10
Hematocrit (%)	45.3 ± 0.5	45.8 ± 1.1	45.6 ± 0.7	46.2 ± 1.3
Hemoglobin (g/dL)	17.0 ± 0.2	17.0 ± 0.3	17.2 ± 0.1	17.5 ± 0.5
Methemoglobin (%)	0.416 ± 0.065	0.510 ± 0.134	0.422 ± 0.069	0.527 ± 0.077
Erythrocytes (10^6/mm^3)	9.95 ± 0.11	10.01 ± 0.11	10.09 ± 0.14	10.08 ± 0.26
Nucleated erythrocytes (10^3/mm^3)	0.043 ± 0.012	0.029 ± 0.013	0.027 ± 0.009	0.040 ± 0.019
Leukocytes (10^3/μL)	4.11 ± 0.026	3.99 ± 0.25	4.22 ± 0.21	5.01 ± 0.50
Segmented neutrophils (10^3/μL)	1.48 ± 0.15	1.42 ± 0.17	1.52 ± 0.14	2.00 ± 0.42
Lymphocytes (10^3/μL)	2.55 ± 0.14	2.45 ± 0.16	2.55 ± 0.16	2.88 ± 0.17
Monocytes (10^3/μL)	0.05 ± 0.01	0.09 ± 0.02	0.09 ± 0.02	0.10 ± 0.03
Eosinophils (10^3/μL)	0.04 ± 0.02	0.02 ± 0.01	0.06 ± 0.01	0.03 ± 0.01
Mean cell hemoglobin (pg)	17.1 ± 0.1	17.0 ± 0.2	17.1 ± 0.2	17.4 ± 0.1
Mean cell hemoglobin concentration (%)	37.7 ± 0.3	37.1 ± 0.5	37.9 ± 0.4	37.8 ± 0.2
Mean cell volume (μ^3)	45.6 ± 0.3	45.8 ± 0.7	45.1 ± 0.3	45.8 ± 0.3
Urine volume (mL/16 hr)	4.71 ± 0.64	5.64 ± 0.47	5.96 ± 0.55	6.28 ± 0.34
Female				
n	10	10	10	10
Hematocrit (%)	42.6 ± 1.8	41.6 ± 1.2	42.5 ± 1.7	42.1 ± 1.6
Hemoglobin (g/dL)	16.0 ± 0.2	16.3 ± 0.3	15.7 ± 0.1	15.4 ± 0.5
Methemoglobin (%)	0.318 ± 0.035	0.462 ± 0.095	0.585 ± 0.149	0.491 ± 0.086
Erythrocytes (10^6/mm^3)	7.93 ± 0.27	7.38 ± 0.38	7.82 ± 0.41	7.90 ± 0.34
Nucleated erythrocytes (10^3/mm^3)	0.046 ± 0.010	0.046 ± 0.007	0.057 ± 0.008	0.118 ± 0.071
Leukocytes (10^3/μL)	1.88 ± 0.09	1.95 ± 0.06	2.01 ± 0.09	2.73 ± 0.47**
Segmented neutrophils (10^3/μL)	0.50 ± 0.27	0.53 ± 0.17	0.57 ± 0.04	1.08 ± 0.31**
Lymphocytes (10^3/μL)	1.33 ± 0.06	1.38 ± 0.06	1.39 ± 0.08	1.59 ± 0.16
Monocytes (10^3/μL)	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.01*
Eosinophils (10^3/μL)	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Mean cell hemoglobin (pg)	20.4 ± 0.7	22.7 ± 1.4	20.6 ± 1.2	19.7 ± 0.6
Mean cell hemoglobin concentration (%)	38.0 ± 1.3	39.4 ± 1.5	37.3 ± 1.4	36.8 ± 0.9
Mean cell volume (μ^3)	53.7 ± 1.2	57.3 ± 2.0	54.9 ± 1.6	53.5 ± 1.0
Urine volume (mL/16 hr)	5.81 ± 0.50[b]	5.84 ± 0.73[b]	4.56 ± 0.42[b]	4.93 ± 0.71

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error for groups of 10 animals, unless otherwise specified.
[b] n=9

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Studies of Acetaminophen[a]

Analysis	0 ppm	600 ppm	3,000 ppm[b]	6,000 ppm
Male				
Hematocrit (%)	38.3 ± 1.1	39.3 ± 0.8	34.8 ± 1.5	37.8 ± 0.7
Hemoglobin (g/dL)	13.3 ± 0.3	13.5 ± 0.3	12.4 ± 0.6	13.3 ± 0.3
Methemoglobin (%)	0.381 ± 0.045	0.558 ± 0.099	0.517 ± 0.038	0.484 ± 0.088
Erythrocytes (10^6/mm^3)	8.60 ± 0.31	8.71 ± 0.20	7.77 ± 0.43	8.50 ± 0.24
Nucleated erythrocytes (10^3/mm^3)	0.016 ± 0.009	0.032 ± 0.011	0.029 ± 0.013	0.027 ± 0.012
Leukocytes (10^3/μL)	3.26 ± 0.19	3.02 ± 0.22	2.88 ± 0.43	2.97 ± 0.50
Segmented neutrophils (10^3/μL)	1.33 ± 0.14	1.89 ± 0.25	1.65 ± 0.36	1.67 ± 0.31
Lymphocytes (10^3/μL)	1.82 ± 0.17	1.09 ± 0.18*	1.12 ± 0.18*	1.17 ± 0.27*
Monocytes (10^3/μL)	0.08 ± 0.02	0.02 ± 0.01*	0.09 ± 0.02	0.08 ± 0.02
Eosinophils (10^3/μL)	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
Mean cell hemoglobin (pg)	15.5 ± 0.3	15.5 ± 0.1	16.0 ± 0.3	15.6 ± 0.1
Mean cell hemoglobin concentration (%)	34.7 ± 0.4	34.4 ± 0.5	35.6 ± 0.5	35.1 ± 0.6
Mean cell volume (μ^3)	44.7 ± 0.6	45.2 ± 0.6	44.8 ± 1.1	44.5 ± 0.7
Urine volume (mL/16 hr)	0.690 ± 0.081	0.990 ± 0.158	0.900 ± 0.163[c]	1.200 ± 0.111**[c]
Female				
Hematocrit (%)	40.8 ± 1.0	39.6 ± 0.6	38.9 ± 1.3	42.4 ± 1.6
Hemoglobin (g/dL)	14.6 ± 0.2	14.7 ± 0.1	14.2 ± 0.3	14.6 ± 0.2
Methemoglobin (%)	0.309 ± 0.044	0.360 ± 0.034	0.285 ± 0.040	0.327 ± 0.041
Erythrocytes (10^6/mm^3)	9.18 ± 0.14	9.28 ± 0.08	9.09 ± 0.26	9.15 ± 0.14
Nucleated erythrocytes (10^3/mm^3)	0.038 ± 0.010	0.060 ± 0.024	0.036 ± 0.008	0.061 ± 0.027
Leukocytes (10^3/μL)	1.36 ± 0.10	2.09 ± 0.36	1.47 ± 0.14	1.86 ± 0.37
Segmented neutrophils (10^3/μL)	0.47 ± 0.03	0.57 ± 0.04*	0.63 ± 0.04**	0.72 ± 0.15*
Lymphocytes (10^3/μL)	0.829 ± 0.113	1.419 ± 0.333	0.771 ± 0.127	1.025 ± 0.247
Monocytes (10^3/μL)	0.05 ± 0.01	0.08 ± 0.02	0.07 ± 0.01	0.09 ± 0.02*
Eosinophils (10^3/μL)	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Mean cell hemoglobin (pg)	15.9 ± 0.2	15.8 ± 0.1	15.7 ± 0.3	16.0 ± 0.1
Mean cell hemoglobin concentration (%)	35.8 ± 0.8	37.2 ± 0.4	36.7 ± 0.7	34.9 ± 1.2
Mean cell volume (μ^3)	44.5 ± 0.8	42.5 ± 0.34	42.9 ± 0.7	46.3 ± 1.6
Albumin (g/dL)	3.92 ± 0.29[c]	3.76 ± 0.06	3.76 ± 0.10	3.79 ± 0.07[c]
Serum glucose (mg/dL)	121 ± 11[c]	117 ± 6	111 ± 7	121 ± 10[c]
Urine volume (mL/16 hr)	0.750 ± 1.141	0.467 ± 0.088[c]	0.770 ± 0.094	0.710 ± 0.121

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error for groups of 10 animals, unless otherwise specified.
[b] Six male animals were examined for hematology data
[c] Nine animals were examined

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF ACETAMINOPHEN

Acetaminophen was obtained in two lots from S.B. Penick & Company. Lot 7042-LAR-5 was obtained on 16 October 1980, and Lot 7032-LFR-57 was obtained on 30 May 1984. Purity and identity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the acetaminophen studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the study chemical, a white microcrystalline solid, were identified as acetaminophen by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of acetaminophen, as shown in Figures H1 and H2 (*Sadtler Standard Spectra*).

The purity of both lots was determined by elemental analyses, Karl Fischer water analysis, non-aqueous acid titration, and chromatographic analyses. Titration of the phenol group was performed in *t*-butanol:acetone (15:10) with 0.1 N tetrabutylammonium hydroxide in methanol:isopropanol (1:9). Thin-layer chromatography was performed on silica gel plates with two solvent systems: 1) toluene:methanol (70:30), and 2) ethyl acetate 100%. Visualization was accomplished with short (254 nm) and long (366 nm) wavelength ultraviolet light and with 0.5% 4-dimethylaminobenzaldehyde in isopropanol (w/v) followed by a spray of 2 N hydrochloric acid and heating at 100° C for 20 minutes. Acetanilide was used as the reference standard. High-performance liquid chromatography (HPLC) was performed with a μBondapak C_{18} column in two solvent systems: 1) water:acetonitrile (88:12 for Lot 7042-LAR-5; 90:10 for Lot 7032-LFR-57) at a flow rate of 1 mL/min, and 2) water (100%) at a flow rate of 2 mL/min (used only for Lot 7042-LAR-5). Ultraviolet detection was at 254 nm. Major peak comparison of the two lots was performed by HPLC with the same system using a solvent ratio of 95:5 water:acetonitrile and 0.16 mg/mL uracil as an internal standard.

For Lot 7042-LAR-5, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with theoretical values. Karl Fischer analysis of this lot indicated the presence of 0.23% water. Titration of the phenol group indicated a purity of 99.7%. This lot passed the United States Pharmacopeia (USP) test for sulfate with less than 0.02% sulfate present. Thin-layer chromatography indicated a major product spot in both solvent systems. HPLC of this lot by one solvent system indicated two impurities with a combined peak area of 0.72% relative to that of the major peak. The second solvent system indicated one impurity with a relative peak area of 0.03%. As a supplement to the identity and purity analyses, the complete battery of USP tests was performed on Lot 7042-LAR-5. All tests indicated that this lot met the requirements of USP for acetaminophen.

For Lot 7032-LFR-57, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with theoretical values. Karl Fischer analysis indicated the presence of less than 0.05% water. Titration of the phenol group indicated a purity of 100.8%. Thin-layer chromatography indicated a major product spot in both solvent systems. HPLC of this lot indicated no impurities greater than or equal to 0.1% relative to the major peak area. Major peak comparison indicated that this lot was identical to Lot 7042-LAR-5.

Stability studies performed by HPLC with the system described above using a solvent ratio of 60:40 water:acetonitrile and with 0.02% acetophenone added as an internal standard indicated that acetaminophen, when protected from light, was stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C. During the 2-year studies, the stability of the bulk chemical was monitored by the study laboratory using ultraviolet and infrared spectroscopy; no degradation of the study material was seen throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate quantities of acetaminophen with feed in a blender (Patterson-Kelley Twin Shell with intensifier bar) (Table H1). Dose formulations were prepared once for the 14-day studies and weekly during the 13-week and 2-year studies.

Studies were conducted by the analytical chemistry laboratory to determine homogeneity and stability of the dosed feed preparations. For homogeneity analyses, the formulations were extracted with methanol and the concentrations determined by an ultraviolet method at 247 nm. For the stability studies, the formulations were extracted using a methanol/acetic acid (95/5) solution and then injected into a HPLC system equipped with a μBondapak C_{18} column and a 254 nm detector. The mobile phase was methanol:water (24:76) with a flow rate of 1 mL/minute.

Acetaminophen at the 20,000 ppm dose level mixed in rodent feed (NIH-07 Rat and Mouse Ration) produced a homogeneous blend and was found to be stable when stored protected from light in sealed containers at temperatures up to 25° C. There was a 4% loss of chemical in feed stored 2 weeks at 45° C.

Periodic analyses of the dose formulations of acetaminophen were conducted at the study laboratory and at the analytical chemistry laboratory using ultraviolet spectroscopy. For the 14-day studies, dose formulations were analyzed prior to study initiation (Table H2). For the 13-week studies, dose formulations were analyzed prior to study initiation and at the midpoint of the study (Table H3). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks using a slightly modified ultraviolet spectroscopic procedure. Dose formulations were extracted with methanol (except the 600 ppm dose formulation, which was extracted with acetonitrile), centrifuged, and diluted with the extracting solvent; the acetaminophen concentration was then determined by ultraviolet spectroscopy at 249 nm. Because 62 of 66 formulations were within 10% of the target concentrations, it was estimated that 94% of the formulations were within 10% of the target concentrations. The sample from the first 600 ppm formulation exceeded the target level by 15%. Follow-up studies indicated a homogeneity problem caused by irregularity of particle size of the bulk chemical. Dose formulations used from 3 September 1982 through the end of the study were made with bulk chemical preground to pass through an 80-size mesh. HPLC and nonaqueous titration of the bulk chemical before and after pregrinding indicated no decomposition as a result of the particle size reduction. Results of the dose formulation analyses for the chronic studies are presented in Table H4. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table H5).

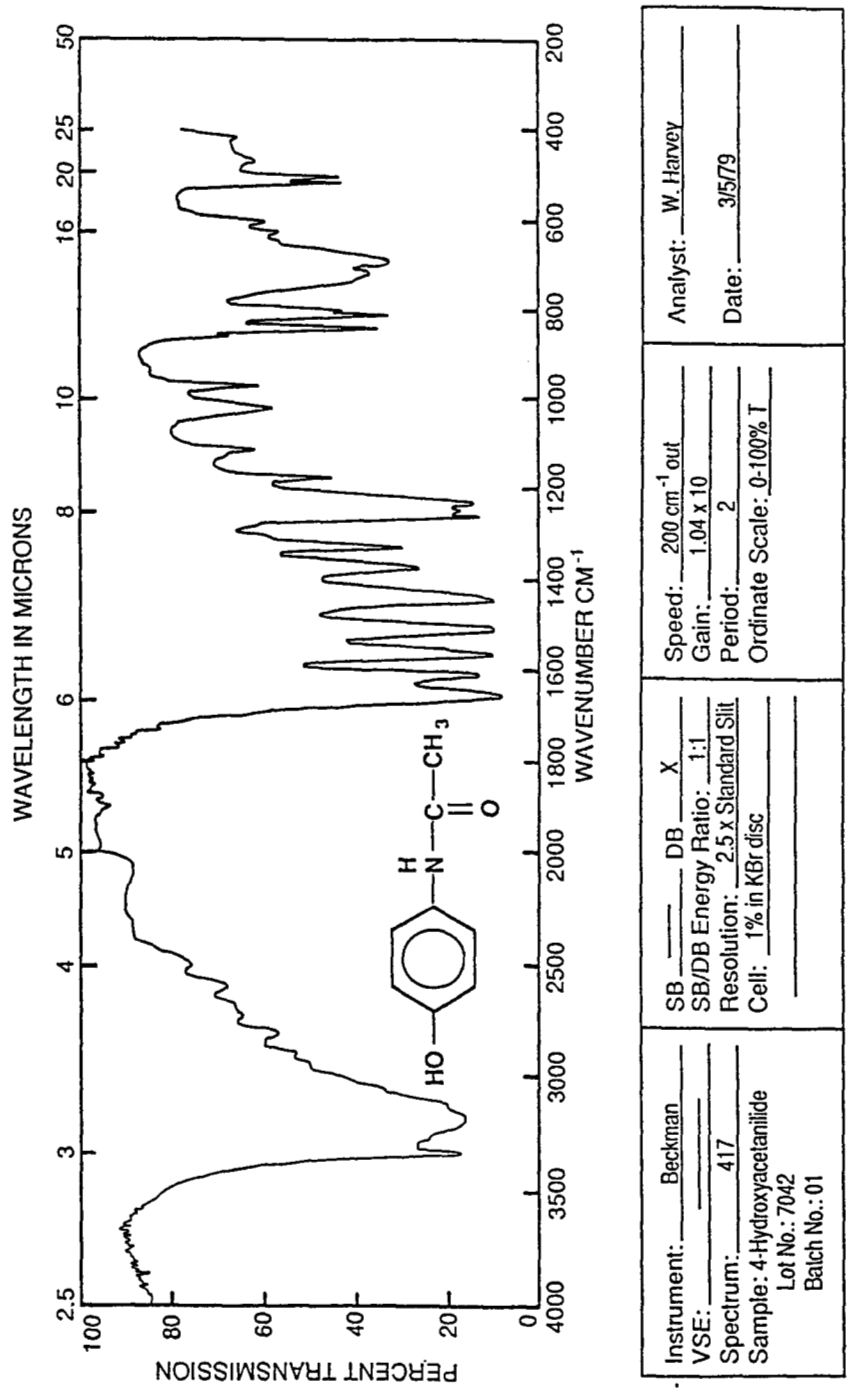

FIGURE H1
Infrared Absorption Spectrum of Acetaminophen

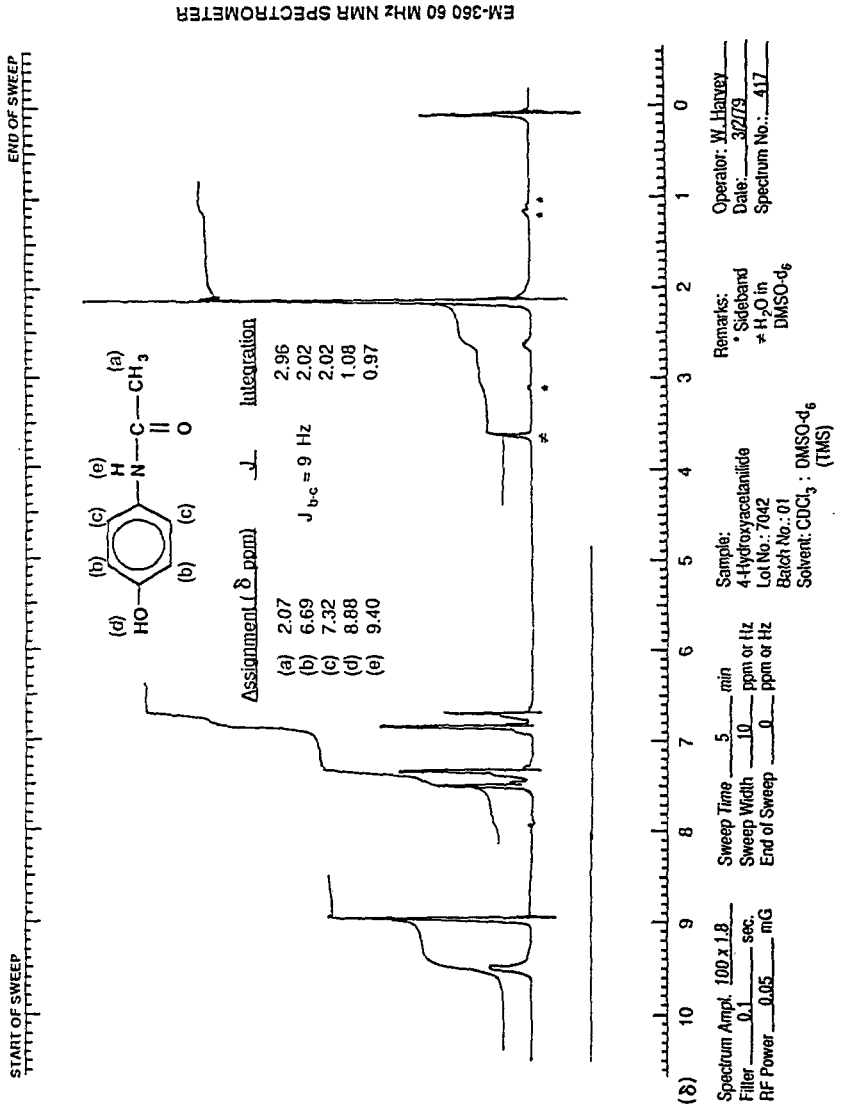

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Acetaminophen

TABLE H1
Preparation and Storage of Dose Formulations in the Feed Studies of Acetaminophen

14-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Dose formulations mixed once (w:w). Chemical-feed premix using mortar and pestle; premix and remainder of feed layered into blender with intensifier bar and mixed for 15 min.	Dose formulations mixed weekly (w:w). Chemical-feed premix using mortar and pestle; premix and remainder of feed layered into blender with intensifier bar and mixed for 15 min.	Same as 13-week studies
Lot		
7042-LAR-5	7042-LAR-5	7042-LAR-5 7032-LFR-57
Maximum Storage Time		
Two weeks from date of preparation.	Same as 14-day studies	Same as 14-day studies
Storage Conditions		
Cold room at approximately 4° C Protected from light	Same as 14-day studies	Same as 14-day studies

TABLE H2
Results of Analysis of Dose Formulations in the 14-Day Feed Studies of Acetaminophen

Date Prepared	Date Analyzed	Target Concentration (ppm)	Average Concentration (ppm)	% Difference from Target
18 February 1981	19 February 1981	250	300[a]	+20[d]
		250	250[b]	0
		250	270[c]	+10
		500	520	+5
		800	1,030	+29[d]
		1,000	1,330	+32[d]
18 February 1981	20 February 1981	1,600	1,700	+6
		2,000	2,000	0
		3,100	3,080	−1
		4,000	4,030	+1
		6,200	6,300	+1
		12,500	12,300[a]	−2
		12,500	13,000[b]	+4
		12,500	12,300[c]	−2

[a] Sample selection from top left zone of PK Blender
[b] Sample selection from top right zone of PK Blender
[c] Sample selection from bottom of PK Blender
[d] Remixed and analyzed; found to be within 10% of target concentration

TABLE H3
Results of Analysis of Dose Formulations in the 13-Week Feed Studies of Acetaminophen

Date Prepared	Date Analyzed	Target Concentration (ppm)	Average Concentration (ppm)	% Difference from Target
30 June 1981	1 July 1981	800	875[a]	+9
		800	780[b]	−3
		800	755[c]	−6
		1,600	1,780	+11
		3,200	3,350	+3
30 June 1981	2 July 1981	6,200	6,400	+3
		12,500	12,800	+2
		25,000	25,000[a]	0
		25,000	25,100[b]	0
		25,000	25,400[c]	+2
27 August 1981	28 August 1981	800	730	−9
		1,600	1,550	−3
		3,200	3,050	−5
		6,200	6,300	+2
		12,500	13,300	+6
		25,000	25,500	+2

[a] Sample selection from top left zone of PK Blender
[b] Sample selection from top right zone of PK Blender
[c] Sample selection from bottom of PK Blender

TABLE H4
Results of Analysis of Dose Formulations in the 2-Year Feed Studies of Acetaminophen

Date Prepared	Date Analyzed	Target Concentration (ppm)	Average Concentration (ppm)[a]	% Difference from Target
20 July 1982	21 July 1982	600	690	+15[b]
		3,000	3,005	0
		6,000	5,705	−5
27 July 1982	27 July 1982	600	690	+15[c]
		600	760	+27[c]
		600	610	+1
29 July 1982	30 July 1982[d]	600	590	−1
29 July 1982	3 August 1982	600	550	−9
		600	620	+3
		600	580	−4
		600	580	−2
3 September 1982[e]	7 September 1982	600	570	−5
		600	600	0
		600	610	0
3 September 1982[e]	8 September 1982	6,000	5,770	−4
		6,000	6,310	+5
		6,000	5,820	−3
5 November 1982	9 November 1982	600	575	−4
		3,000	2,900	−3
		6,000	5,750	−4
23 December 1982	28 December 1982	600	580	−3
		3,000	2,900	−3
		6,000	5,750	−4
21 January 1983	24 January 1983	600	590	−2
		3,000	2,950	−2
		6,000	5,900	−2
1 April 1983	5 April 1983	600	560	−6
		3,000	2,850	−5
		6,000	5,850	−3
31 May 1983	1 June 1983	600	570	−5
		3,000	2,925	−3
		6,000	5,600	−7
22 July 1983	26 July 1983	600	570	−6
22 July 1983	27 July 1983	3,000	2,900	−3
		6,000	5,800	−4
26 August 1983	29 August 1983	600	560	−7
		3,000	2,900	−3
		6,000	5,700	−5

TABLE H4
Results of Analysis of Dose Formulations in the 2-Year Feed Studies of Acetaminophen (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Average Concentration (ppm)	% Difference from Target
14 October 1983	18 August 1983	600	590	−2
		3,000	2,900	−3
		6,000	5,800	−3
9 December 1983	13 December 1983	600	580	−3
		3,000	3,050	+2
		6,000	5,950	−1
20 January 1984	24 January 1984	600	565	−6
		3,000	2,900	−3
		6,000	5,550	−8
9 March 1984	13 March 1984	600	520	−13[f]
		3,000	2,800	−7
		6,000	5,500	−8
14 March 1984	14 March 1984	600	575	−4
27 April 1984	1 May 1984	600	580	−3
		3,000	2,850	−5
		6,000	5,800	−3
8 June 1984	12 June 1984	600	610	+1
		3,000	2,900	−2
		6,000	5,900	−2
27 July 1984	31 July 1984	600	580	−3
		3,000	2,800	−7
		6,000	5,500	−8
7 September 1984	9 September 1984	600	580	−3
		3,000	3,050	+2
		6,000	5,750	−4
9 November 1984	13 November 1984	600	590	−2
		3,000	3,000	0
		6,000	5,800	−3

[a] Results were of triplicate samples prior to September 1982 and of duplicate samples after September 1982
[b] Exceeds 10% tolerance limit; blended and analyzed on 27 July 1982
[c] Exceeds 10% tolerance limit after reblending
[d] Dose formulation within ±10% tolerance limit; sample pregrinding to reduce particle size of the chemical produced homogeneous formulation
[e] Sample taken from random zones of dose formulation; top left, top right, and bottom of the PK Blender, respectively to recheck homogeneity after milling of bulk chemical to reduce particle size
[f] Exceeds 10% tolerance limit; replacement dose formulation prepared on 14 March 1984

TABLE H5
Results of Referee Analysis of Dose Formulations in the 2-Year Feed Studies of Acetaminophen

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
21 July 1982	600	690	687
21 January 1983	3,000	2,950	2,950
22 July 1983	6,000	5,750	5,530
20 January 1984	600	565	611
8 June 1984	3,000	2,950	2,920

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

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

TABLE I1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Acetaminophen

	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]
1	15.4	134	15.6	133	70	15.9	132	361	16.4	134	737
2	16.4	171	16.0	169	57	16.3	170	287	16.6	171	581
5	18.1	246	18.0	243	45	19.0	239	239	19.1	238	482
6	17.8	264	16.7	261	38	18.2	261	209	17.2	259	398
8	15.4	294	17.2	279	37	16.0	289	167	15.2	284	320
9	23.0	307	22.7	300	46	22.2	305	218	21.0	300	419
11	18.8	326	17.9	323	33	17.6	324	162	17.3	319	326
12	18.2	339	18.0	335	32	17.8	335	160	17.6	330	320
13	20.5	342	18.9	338	34	21.0	338	187	18.5	336	330
17	19.7	371	20.5	369	33	19.6	366	160	18.9	366	309
21	16.3	386	21.1	391	32	18.2	383	142	18.7	386	292
25	19.8	411	17.6	407	26	19.1	407	141	17.5	404	260
29	17.9	423	18.2	422	26	19.3	420	138	17.0	420	244
33	19.7	430	20.9	434	29	20.8	431	145	20.9	427	293
37	18.2	442	18.9	442	26	18.7	439	128	17.8	436	245
41	20.8	444	22.1	449	29	21.5	449	144	20.4	445	275
45	18.0	447	16.7	446	22	19.4	451	129	16.1	443	217
49	21.4	457	21.6	460	28	20.4	456	135	20.8	452	276
53	21.4	465	20.9	465	27	23.4	466	151	21.3	460	277
57	20.6	466	20.1	468	26	20.9	468	134	21.0	462	273
61	20.0	467	20.5	461	27	20.6	471	131	19.4	463	251
65	19.0	466	19.5	466	25	19.2	471	123	19.6	463	253
69	19.4	475	19.7	468	25	19.7	475	124	19.0	466	244
73	15.2	471	15.3	464	20	14.8	463	96	16.3	460	213
77	15.1	476	15.1	470	19	15.4	472	98	14.6	462	190
81	13.1	469	15.0	467	19	14.3	474	91	14.7	460	192
85	16.1	477	17.2	466	22	16.9	475	107	16.6	455	219
89	14.8	471	14.9	466	19	13.4	465	86	14.9	455	196
93	11.6	453	12.8	454	17	11.7	447	79	13.9	444	188
97	13.3	448	13.5	439	18	14.2	444	96	14.0	425	197
101	12.4	432	14.5	428	20	14.3	424	101	13.9	408	204
104	13.5	416	13.5	408	20	14.9	419	106	14.4	411	211
Mean for weeks											
1-13	18.2	269	17.9	264	43	18.2	266	221	17.6	264	435
14-52	19.1	423	19.7	424	28	19.7	422	140	18.7	420	268
52-104	16.1	461	16.6	456	22	16.7	460	109	16.7	450	222

[a] Grams of feed consumed per animal per day
[b] Milligrams of acetaminophen consumed per day per kilogram of body weight

TABLE I2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Acetaminophen

	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]
1	11.6	112	11.3	113	60	12.3	115	320	12.2	117	626
2	11.1	129	11.2	128	53	11.7	130	268	10.8	130	500
4	13.8	156	17.7	152	70	14.2	160	267	13.2	156	509
5	12.3	164	12.7	162	47	13.3	168	237	11.9	162	439
8	13.2	184	14.4	184	47	13.8	189	219	13.6	184	444
9	12.7	190	13.4	190	42	13.4	195	206	12.2	191	383
13	12.9	206	13.0	204	38	12.8	209	184	12.6	202	374
17	13.1	217	13.4	217	37	13.4	220	183	12.6	215	351
21	13.8	227	13.2	228	35	14.1	230	184	12.4	227	329
25	13.1	234	12.5	233	32	13.0	236	165	12.2	232	316
29	12.0	240	12.4	241	31	12.4	242	154	11.8	238	298
33	13.3	248	14.4	250	34	13.9	250	167	13.1	245	320
37	12.5	253	14.0	258	33	13.0	258	151	12.1	252	289
41	13.6	257	12.9	260	30	14.6	262	167	12.7	252	302
45	12.9	263	15.5	269	35	15.1	266	170	13.6	261	312
49	14.2	276	13.9	281	30	14.0	280	150	13.6	272	300
53	14.3	285	15.5	291	32	14.9	287	156	14.3	281	307
57	13.5	295	13.7	300	27	13.9	296	141	13.5	291	277
61	13.9	305	15.3	310	30	15.1	308	147	14.6	301	292
65	15.7	311	15.8	316	30	16.0	312	154	15.8	309	307
69	16.6	323	15.6	322	29	15.6	328	142	15.1	318	285
73	9.9	327	9.9	329	18	9.1	328	83	10.1	320	189
77	10.4	332	10.3	332	19	9.9	334	89	10.8	328	199
80	13.1	342	12.9	342	23	12.5	343	110	12.6	335	226
89	12.1	354	12.0	353	20	12.8	354	108	12.8	343	225
93	11.7	348	11.5	350	20	11.8	354	100	11.5	344	201
97	11.1	344	11.5	348	20	11.3	348	97	11.4	345	198
101	10.3	341	11.7	341	21	11.7	348	101	11.5	340	203
104	11.0	336	11.4	338	20	11.7	344	102	11.6	332	209
Mean for weeks											
1-13	12.5	163	13.4	162	51	13.1	167	243	12.4	163	468
14-52	13.1	246	13.6	248	33	13.7	249	166	12.7	244	313
52-104	12.6	326	12.9	329	24	12.8	330	118	12.7	322	240

[a] Grams of feed consumed per animal per day
[b] Milligrams of acetaminophen consumed per day per kilogram of body weight

TABLE I3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Acetaminophen

	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]
2	4.8	25.5	5.1	26.6	117	5.2	25.7	603	5.4	25.3	1,286
5	6.3	28.1	5.3	28.7	110	6.1	28.5	642	6.4	28.1	1,376
9	5.4	31.6	6.2	31.5	118	6.7	31.7	630	6.9	31.6	1,302
13	5.6	32.9	5.7	32.5	106	5.8	33.2	520	6.2	32.4	1,139
16	5.8	33.7	5.4	33.9	95	5.5	34.1	483	5.7	33.3	1,024
17			9.8	31.6	186				11.6	33.6	2,077
21	6.1	35.3	5.8	35.0	100	5.8	35.0	499	6.3	34.2	1,110
25	5.1	36.4	4.9	34.8	84	5.2	35.3	444	4.9	33.9	876
29	6.0	37.9	5.7	36.9	92	5.7	36.6	464	6.1	35.7	1,020
33	5.5	38.6	5.6	37.8	89	5.5	37.6	438	6.0	36.3	995
37	5.9	39.1	5.8	37.9	92	5.4	38.5	424	5.9	37.3	948
41	6.1	40.7	5.5	39.4	84	5.5	39.4	416	6.3	38.4	989
45	5.6	40.8	5.2	40.6	77	4.8	39.9	365	5.6	39.1	853
49	5.2	41.4	5.2	40.5	77	5.2	40.6	382	5.6	39.4	845
57	5.3	41.8	5.3	39.9	79	5.0	40.4	371	5.5	38.4	858
61	5.8	41.8	5.0	39.2	77	5.1	40.3	376	5.4	38.9	833
65	5.4	42.1	5.7	40.1	86	5.4	40.6	402	5.5	39.1	843
69	5.5	40.7	5.1	39.1	78	5.1	38.8	396	5.9	37.7	947
73	5.6	41.1	5.3	39.2	82	5.3	39.2	409	5.3	37.8	839
76	5.6	40.7	5.0	39.1	77	5.3	39.0	411	5.4	37.2	873
81	5.2	40.3	4.7	39.3	71	4.9	39.4	376	5.0	37.4	800
84	6.1	39.7	5.4	38.9	84	5.7	38.7	442	5.9	36.5	964
89	5.6	40.3	4.7	39.0	72	4.9	39.2	375	5.0	37.4	800
93	5.3	39.9	4.7	38.5	73	4.8	38.7	376	5.1	37.1	824
97	5.4	40.7	4.5	39.1	69	5.3	39.6	402	5.1	37.8	804
101	5.4	40.1	5.3	37.6	84	6.0	37.8	477	5.5	37.1	895
104	6.1	39.3	5.7	36.8	94	6.6	37.3	527	6.8	35.4	1,158
Mean for weeks											
1-13	5.5	29.5	5.6	29.7	113	5.9	29.8	599	6.2	29.4	1,276
14-52	5.7	38.2	5.9	36.8	98	5.4	37.4	435	6.4	36.1	1,074
52-104	5.6	40.7	5.1	38.9	79	5.4	39.2	411	5.5	37.5	880

[a] Grams of feed consumed per animal per day
[b] Milligrams of acetaminophen day per kilogram of body weight

TABLE I4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Acetaminophen

	0 ppm		600 ppm			3,000 ppm			6,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b]
2	5.3	19.8	5.3	19.3	165	5.2	19.3	807	5.0	19.4	1,558
4	6.1	20.7	5.9	20.5	174	6.0	20.7	873	6.1	20.7	1,768
5	7.5	22.5	7.0	22.7	184	7.2	22.9	944	7.4	22.3	2,003
9	6.1	24.4	6.5	24.8	158	6.5	25.5	769	6.6	23.2	1,707
13	7.0	26.2	6.5	26.0	150	7.2	25.1	857	7.9	25.0	1,898
17	5.7	27.7	5.8	27.9	124	5.4	27.0	604	6.1	26.9	1,350
21	5.7	29.6	6.4	29.8	129	6.7	28.6	708	6.7	29.2	1,377
25	6.3	31.5	6.0	30.7	117	6.3	30.4	618	6.2	30.3	1,221
29	5.5	33.0	5.9	32.3	110	6.4	32.1	599	6.2	31.5	1,187
33	5.5	35.2	5.7	34.4	99	5.6	34.8	483	5.9	33.7	1,059
37	6.1	37.0	7.3	36.4	120	7.4	35.6	622	7.6	36.4	1,254
41	6.6	39.2	6.5	37.2	104	6.5	37.3	527	6.5	37.5	1,033
45	6.3	40.8	6.5	38.7	101	6.5	38.5	507	6.7	39.8	1,012
49	6.3	42.0	6.3	40.0	95	6.4	40.4	474	6.6	39.9	989
53	6.4	43.5	5.9	40.7	87	6.1	39.9	456	6.1	40.8	891
57	6.5	43.1	6.4	40.1	96	6.9	40.7	505	6.6	41.0	966
61	6.5	44.9	6.0	41.3	87	6.7	41.3	488	6.1	41.7	878
65	5.0	44.1	5.6	41.8	81	6.2	42.7	437	5.7	43.0	798
69	7.1	44.7	7.7	42.6	109	8.0	42.1	570	7.7	42.3	1,087
73	7.5	45.3	7.4	43.4	103	7.9	42.5	554	7.4	42.6	1,045
77	7.6	46.1	7.2	43.7	99	8.1	42.8	567	7.5	43.4	1,034
81	7.4	46.7	7.0	45.0	93	6.9	43.3	481	6.6	43.2	923
85	7.0	46.8	6.5	44.6	87	6.6	43.2	459	6.2	43.5	856
89	7.7	46.1	6.8	44.0	93	7.0	40.4	517	6.8	42.4	962
93	8.2	46.5	7.7	45.2	102	7.2	41.4	525	7.8	44.1	1,061
97	10.2	46.5	8.0	44.9	106	8.0	41.6	575	8.4	45.2	1,121
101	9.9	46.0	8.7	44.4	117	8.9	41.0	652	8.7	45.2	1,152
104	9.7	46.0	8.1	43.5	111	9.4	40.4	695	7.6	43.9	1,042
Mean for weeks											
1-13	6.4	22.7	6.2	22.7	166	6.4	22.7	850	6.6	22.1	1,787
14-52	6.0	35.1	6.3	34.2	111	6.4	33.9	571	6.5	33.9	1,165
52-104	7.6	45.5	7.1	43.2	98	7.4	41.7	534	7.1	43.0	987

[a] Grams of feed consumed per animal per day
[b] Milligrams of acetaminophen consumed per day per kilogram of body weight

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

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

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

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

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

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
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 J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.77 ± 1.09	21.2–25.9	30
Crude fat (% by weight)	5.25 ± 0.59	4.2–6.3	30
Crude fiber (% by weight)	3.53 ± 0.34	2.8–4.5	30
Ash (% by weight)	6.68 ± 0.24	6.3–7.3	30
Amino Acids (% of total diet)			
Arginine	1.320 ± 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	0.655–1.050	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 (% of total diet)			
Linoleic	2.290 ± 0.313	1.830–2.520	5
Linolenic	0.258 ± 0.040	0.210–0.308	5
Vitamins			
Vitamin A (IU/kg)	11,453 ± 4,299	4,200–22,000	30
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)	18.80 ± 3.73	12.0–31.0	30
Riboflavin (ppm)	7.60 ± 0.85	6.10–8.20	5
Niacin (ppm)	97.80 ± 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	5.60–8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80–3.70	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 (%)	1.23 ± 0.12	0.97–1.43	29
Phosphorus (%)	0.95 ± 0.05	0.86–1.10	30
Potassium (%)	0.900 ± 0.098	0.772–0.971	3
Chloride (%)	0.513 ± 0.114	0.380–0.635	5
Sodium (%)	0.323 ± 0.043	0.258–0.371	5
Magnesium (%)	0.167 ± 0.012	0.151–0.181	5
Sulfur (%)	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	81.70–99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10–58.20	5
Copper (ppm)	10.72 ± 2.76	8.090–15.39	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 J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.53 ± 0.16	0.18–0.77	30
Cadmium (ppm)[b]	0.11 ± 0.03	0.10–0.20	30
Lead (ppm)	0.63 ± 0.49	0.24–2.93	30
Mercury (ppm)	<0.05		30
Selenium (ppm)	0.31 ± 0.06	0.21–0.45	30
Aflatoxins (ppb)	<5.0		30
Nitrate nitrogen (ppm)	9.93 ± 4.81	2.50–22.0	30
Nitrite nitrogen (ppm)	1.18 ± 1.47	0.10–6.10	30
BHA (ppm)[c]	3.77 ± 4.67	2.00–20.05	30
BHT (ppm)[c]	3.03 ± 2.41	1.00–13.00	30
Aerobic plate count (CFU/g)[d]	145,057 ± 140,491	6,200–420,000	30
Coliform (MPN/g)[e]	635 ± 877	3.00–2400.00	30
E. coli (MPN/g)[f]	13.47 ± 37.19	3.00–150.00	30
E. coli (MPN/g)[g]	3.71 ± 2.49	3.00–15.00	28
Total nitrosamines (ppb)[h]	5.78 ± 5.56	0.80–30.30	30
N-Nitrosodimethylamine (ppb)[h]	4.95 ± 5.58	0.50–30.00	30
N-Nitrosopyrrolidine (ppb)[h]	0.83 ± 0.72	0.30–2.70	30
Pesticides (ppm)			
α-BHC[i]	<0.01		30
β-BHC	<0.02		30
γ-BHC	<0.01		30
δ-BHC	<0.01		30
Heptachlor	<0.01		30
Aldrin	<0.01		30
Heptachlor epoxide	<0.01		30
DDE	<0.01		30
DDD	<0.01		30
DDT	<0.01		30
HCB	<0.01		30
Mirex	<0.01		30
Methoxychlor	<0.05		30
Dieldrin	<0.01		30
Endrin	<0.01		30
Telodrin	<0.01		30
Chlordane	<0.05		30
Toxaphene	<0.1		30
Estimated PCBs	<0.2		30
Ronnel	<0.01		30
Ethion	<0.02		30
Trithion	<0.05		30
Diazinon	<0.1		30
Methyl parathion	<0.02		30
Ethyl parathion	<0.02		30
Malathion[j]	0.14 ± 0.16	0.05–0.81	30
Endosulfan I	<0.01		30
Endosulfan II	<0.01		30
Endosulfan sulfate	<0.03		30

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

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Three lots contained more than 0.10 ppm; lots milled on 22 February 1982, 14 March 1984, and 9 May 1984 were measured at 0.20 ppm.
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony-forming unit
[e] MPN = most probable number
[f] The mean, SD, and range include the large value of 150 MPN obtained in batches milled on 26 August 1982 and 17 October 1984.
[g] The mean, SD, and range exclude the large value of 150 MPN obtained in batches milled on 26 August 1982 and 17 October 1984.
[h] All values were corrected for percent recovery.
[i] BHC = hexachlorocyclohexane or benzene hexachloride
[j] Fourteen lots contained >0.05 ppm.

APPENDIX K
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Rats

Fifteen F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from 10 control animals, five per sex. Blood from each collection was appropriately processed, shipped to Microbiological Associates (Bethesda, MD), and screened for the following:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	6, 12, and 18 months
Sendai	6, 12, and 18 months
KRV (Kilham rat virus)	6, 12, 18, and 24 months
H-1 (Toolan's H-1 virus)	6, 12, 18, and 24 months
ELISA	
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	6, 12, 18, and 24 months
Mycoplasma pulmonis	6 and 24 months
Mycoplasma arthritidis	24 months
PVM	24 months
Sendai	24 months

Mice

Fifteen B6C3F$_1$ mice of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from 10 control animals, five per sex. Blood from each collection was appropriately processed, shipped to Microbiological Associates (Bethesda, MD), and screened for the following:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6, 12, 18, and 24 months
Reovirus	6, 12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	6, 12, 18, and 24 months

Method of Analysis (continued)	Time of Analysis
Polyoma virus	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Ectromelia virus (mouse pox)	6, 12, 18, and 24 months
Complement Fixation	
Mouse adenoma virus	6, 12, 18, and 24 months
LCM (lymphocytic choriomeningitis virus)	6, 12, 18, and 24 months
ELISA	
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
Immunofluorescent Antibody	
MHV	24 months

Test results for rats and mice are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Feed Studies of Acetaminophen

Interval (months)	Number of Animals	Positive Serologic Reaction for
Rats		
6	9/9	Sendai
	9/9	RCV/SDA
	4/9	*M. pulmonis*[a]
12	2/10	Sendai
	10/10	RCV/SDA
18	5/10	Sendai
	4/10	RCV/SDA
24	10/10	Sendai
	4/10	RCV/SDA
Mice		
6	0/10	None positive
12	0/10	None positive
18	0/10	None positive
24	5/10	MHV

[a] Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positives.

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4′-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF JANUARY 1993 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene

TR No.	CHEMICAL
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
415	Polysorbate 80
419	HC Hellow 4

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