NATIONAL TOXICOLOGY PROGRAM
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No. 330

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4-HEXYLRESORCINOL

(CAS NO. 136-77-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: 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.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4-HEXYLRESORCINOL

(CAS NO. 136-77-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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Public Health Service
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NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical 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 U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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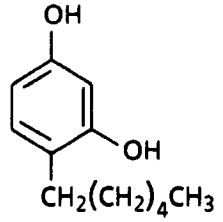

4-HEXYLRESORCINOL

CAS No. 136-77-6

$C_{12}H_{18}O_2$ Molecular weight 194.3

Synonyms: 4-hexyl-1,3-benzenediol; 4-hexyl-1,3-dihydroxybenzene

ABSTRACT

4-Hexylresorcinol, which is used as an anthelmintic and antiseptic, was nominated by the National Cancer Institute for study. Toxicology and carcinogenesis studies were conducted by administering 4-hexylresorcinol (greater than 99% pure) in corn oil by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex for 16 days, 13 weeks, or 2 years.

Sixteen-Day and Thirteen-Week Studies: In the 16-day studies, groups of five rats and five mice of each sex were administered 0, 31.3, 62.5, 125, 250, or 500 mg/kg 4-hexylresorcinol. Survival was not affected. Decreased body weights were seen for male rats that received 250 or 500 mg/kg 4-hexylresorcinol. No other effects were observed. In the 13-week studies, groups of 10 rats and 10 mice of each sex were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg of the chemical, 5 days per week. All rats and male mice and 9/10 female mice that received 1,000 mg/kg died before the end of the studies. Final mean body weights of male rats that received 250 or 500 mg/kg were 22% or 38% lower than that of the vehicle controls; final mean body weights of female rats that received 250 or 500 mg/kg were 16% or 9% lower. No compound-related gross or microscopic pathologic effects were observed in rats. No body weight effects were observed for mice. Mild to moderate nephropathy was dose related in male and female mice.

Based on these results, 2-year toxicology and carcinogenesis studies of 4-hexylresorcinol were conducted by administering 0, 62.5, or 125 mg/kg to groups of 50 F344/N rats and 50 $B6C3F_1$ mice of each sex, 5 days per week.

Body Weight and Survival in the Two-Year Studies: Mean body weights of high dose male rats were 7%-11% lower than those of the vehicle controls throughout the study. Mean body weights of low dose male and dosed female rats were similar to those of the vehicle controls. The body weights of dosed male and female mice were comparable to those of vehicle controls except during the last 16 weeks of the studies, when body weights were 6%-16% lower in the dosed groups. No significant differences in survival were observed between any groups of rats or mice of either sex (male rats: vehicle control, 30/50; low dose, 29/50; high dose, 33/50; female rats: 28/50; 32/50; 30/50; male mice: 36/50; 26/50; 30/50; female mice: 35/50; 32/50; 35/50).

Nonneoplastic and Neoplastic Lesions in the Two-Year Studies: Two astrocytomas and an oligodendroglioma were observed in high dose male rats, a glioma was observed in one low dose male rat, and

an oligodendroglioma was observed in one vehicle control male rat. These neoplasms were not considered to be related to 4-hexylresorcinol administration.

Focal medullary hyperplasia of the adrenal gland was observed at increased incidences in dosed male mice (5/50; 16/50; 10/49). Pheochromocytomas in male mice occurred with a marginal upward trend (1/50; 2/50; 5/49). Historically, these neoplasms are observed in about 1% of corn oil vehicle control $B6C3F_1$ male mice. The incidences of neoplasms of the harderian gland in male mice were slightly increased over those in the vehicle controls (adenomas or carcinomas, combined: 0/50; 4/50; 3/50).

Decreases were observed in the incidences of mononuclear cell leukemia in dosed male (12/49; 7/50; 1/50) and female (16/50; 3/50; 2/50) rats, hepatocellular adenomas or carcinomas (combined) in dosed male mice (21/50; 9/50; 9/50), and circulatory system tumors in male (10/50; 4/50; 2/50) and female (6/50; 2/49; 0/50) mice. These decreased incidences of tumors in rats and mice are considered to be possibly related to 4-hexylresorcinol administration.

The incidences and severity of nephropathy (male: 39/50; 43/50; 47/50; female: 7/50; 40/49; 47/50) and incidences of osteosclerosis (male: 5/50; 5/50; 15/50; female: 21/50; 25/49; 40/50) were increased in both dosed male and female mice and are considered to be related to chemical exposure.

Genetic Toxicology: 4-Hexylresorcinol was not mutagenic for *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without S9 metabolic activation. 4-Hexylresorcinol induced forward mutations at the TK locus in mouse L5178Y cells in the presence of S9; no response was observed in the absence of metabolic activation. In cytogenetic assays with cultured Chinese hamster ovary (CHO) cells, 4-hexylresorcinol caused an increase in the frequency of sister chromatid exchanges (SCEs) in the absence of metabolic activation; no induction of SCEs was observed in the presence of S9. Chromosomal aberrations were not induced in CHO cells with or without metabolic activation.

Data Audit: The data, documents, and pathology materials from the 2-year studies of 4-hexylresorcinol were audited at the NTP Archives. The audit findings show that the conduct of the studies is documented appropriately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of 4-hexylresorcinol for male or female F344/N rats given doses of 62.5 or 125 mg/kg. There was *equivocal evidence of carcinogenic activity* of 4-hexylresorcinol for male $B6C3F_1$ mice, as shown by marginally increased incidences of pheochromocytomas (and hyperplasia) of the adrenal medulla and of harderian gland neoplasms. There was *no evidence of carcinogenic activity* for female $B6C3F_1$ mice given doses of 62.5 or 125 mg/kg 4-hexylresorcinol. Decreased incidences of three tumor types were considered related to 4-hexylresorcinol administration: mononuclear cell leukemia in male and female rats, hepatocellular neoplasms in male mice, and circulatory system tumors in male and female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF 4-HEXYLRESORCINOL

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 62.5, or 125 mg/kg 4-hexylresorcinol in corn oil 5 d/wk	0, 62.5, or 125 mg/kg 4-hexylresorcinol in corn oil 5 d/wk	0, 62.5, or 125 mg/kg 4-hexylresorcinol in corn oil 5 d/wk	0, 62.5, or 125 mg/kg 4-hexylresorcinol in corn oil 5 d/wk
Survival rates in the 2-year study			
30/50; 29/50; 33/50	28/50; 32/50; 30/50	36/50; 26/50; 30/50	35/50; 32/50; 35/50
Nonneoplastic effects			
None	None	Focal medullary hyperplasia of adrenal gland; nephropathy; osteosclerosis	Nephropathy; osteosclerosis
Neoplastic effects			
None	None	Adrenal gland pheochromocytomas; harderian gland adenomas and carcinomas	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	Equivocal evidence	No evidence
Other considerations			
Decrease in mononuclear cell leukemia	Decrease in mononuclear cell leukemia	Decrease in circulatory system tumors; decrease in hepatocellular adenomas or carcinomas	Decrease in circulatory system tumors
Genetic toxicology			
Not mutagenic in Salmonella; induced forward mutations in mouse L5178Y cells with S9; did not induce chromosomal aberrations in CHO cells; induced SCEs in CHO cells without metabolic activation.			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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.

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.

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. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

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

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

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

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

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 4-Hexylresorcinol is based on the 13-week studies that began in March 1980 and ended in May 1980 and on the 2-year studies that began in March 1981 and ended in March 1983 at Physiological Research Laboratories (Minneapolis, Minnesota).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on 4-hexylresorcinol on March 4, 1987, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4-HEXYLRESORCINOL

On March 4, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of 4-hexylresorcinol received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. R.S. Chhabra, NTP, introduced the toxicology and carcinogenesis studies of 4-hexylresorcinol in rats and mice by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats, equivocal evidence of carcinogenic activity for male mice, no evidence of carcinogenic activity for female mice).

Dr. Perera, a principal reviewer, was unable to attend the meeting; her written comments were read by Dr. L. Hart, NIEHS. Dr. Perera agreed with the conclusions for female rats and male and female mice. She proposed that the conclusion for male rats be changed to equivocal evidence of carcinogenic activity, based on the occurrence of rare brain tumors: two astrocytomas and one oligodendroglioma in high dose animals. This incidence exceeded the historical vehicle control incidence as well as that seen in any corn oil vehicle control male F344/N rats. Dr. Chhabra noted that the occurrence of a brain tumor in the vehicle control group weakened the case for an association of the tumors with chemical administration. Dr. S. Eustis, NIEHS, stated that less import could be given to brain tumors of differing cell types than to tumors all of the same cell type. Dr. Hooper felt that the results still supported a conclusion of equivocal evidence of carcinogenic activity. Dr. Scala asked that there be more discussion of this point in the text of the report [see page 51].

As a second principal reviewer, Dr. Capen agreed with the conclusions as written. Commenting on the conclusion for male mice, he noted that although the mean historical incidence of pheochromocytomas in corn oil vehicle control male mice was only 1.3% (19/1,443), the range was 0% to 10% (5/49).

As a third principal reviewer, Dr. Sivak also agreed with the conclusions as written. His primary concern related to the rationale for selection of the gavage route, given that human exposure is via the skin. Dr. Chhabra responded that 4-hexylresorcinol is still used as an anthelmintic, given orally in tablets, and as an antiseptic in lozenges and mouthwash. He said that more emphasis would be given to the rationale of route selection. Dr. Sivak requested that more information on metabolism and distribution be included if available.

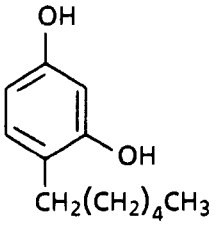
There was some discussion on the decreased incidences of several tumor types, whether this was related to the anti-infective properties of 4-hexylresorcinol and the implications for possible antineoplastic activity.

Dr. Capen moved that the Technical Report on 4-hexylresorcinol be accepted with revisions discussed and with the conclusions as written for male and female rats and female mice, no evidence of carcinogenic activity, and for male mice, equivocal evidence of carcinogenic activity. Dr. Popp seconded the motion, which was approved unanimously with seven votes.

I. INTRODUCTION

Use and Production
Toxicity of 4-Hexylresorcinol
Genetic Toxicology
Carcinogenicity of 4-Hexylresorcinol
Study Rationale

I. INTRODUCTION



4-HEXYLRESORCINOL

CAS No. 136-77-6

$C_{12}H_{18}O_2$ Molecular weight 194.3

Synonyms: 4-hexyl-1,3-benzenediol; 4-hexyl-1,3-dihydroxybenzene

4-Hexylresorcinol is a white, microcrystalline solid. It forms needle-shaped crystals with a melting point of 67.5°-69° C. Its boiling point is 333°-335° C. The chemical has a pungent odor and a sharp astringent taste. The chemical is soluble in ether, chloroform, acetone, alcohol, and vegetable oils; it is slightly soluble in petroleum ether and is soluble in water at 1 part to 2,000 (Merck Index, 1983).

Use and Production

4-Hexylresorcinol, a phenolic compound, has been used as an anthelmintic in human and veterinary medicine. It is used for treatment of whipworm, hookworm, Ascaris, Oxyuris, and dwarf tapeworm infestations (Lamson et al., 1935; Merck Index, 1983; *Remington's* Pharm. Sci., 1975). This drug is not as effective as some of the newer anthelmintics but has the advantage of low toxicity after oral administration. It has been useful in mixed parasitic infestation and also when more selective anthelmintics are either not available or contraindicated (Goodman and Gilman, 1970; Goodman et al., 1985).

The most widespread current use of 4-hexylresorcinol is as an antiseptic. It is an active component in antimicrobial soaps, health care personnel handwashes, preoperative skin preparations, skin antiseptic and wound cleansers, mouthwashes, and cold and cough preparations (Remington's Pharm. Sci., 1985; APA, 1982). 4-Hexylresorcinol is more effective than phenol as an antibacterial agent and is less toxic. The FDA Advisory Review Panel on Nonprescription Antimicrobial Drug Products has categorized this as one of the five over-the-counter drug ingredients that are safe and effective for use by consumers to clean superficial skin wounds (Hecht, 1978). As an aerosol, 4-hexylresorcinol can inactivate poliomyelitis III virus and adenovirus 3 in air or on wood or glass surfaces (Slobodenyuk and Karpukhin, 1970).

No production data for 4-hexylresorcinol were found. Although the 1977 TSCA Inventory reported that the American Hoechst Corporation had imported 4-hexylresorcinol before 1977, no 4-hexylresorcinol was imported during 1977 (USEPA, 1977).

Toxicity of 4-Hexylresorcinol

Information on the toxicity of 4-hexylresorcinol is very limited. The LD_{50} values for mice are reported to be 50 mg/kg by intraperitoneal injection and 750 mg/kg by subcutaneous injection (Dittmer, 1959). In rats and guinea pigs, oral LD_{50} values of 550 mg/kg and 400 mg/kg, respectively, have been reported (Lamson et al., 1935; Anderson et al., 1931). 4-Hexylresorcinol is less toxic than resorcinol or phenol. It is irritating to skin and the respiratory system and causes erosion of gastric and intestinal mucosa when administered at high concentrations (Gosselin et al., 1984; Fed. Regist., 1982). One incident of contact dermatitis related to 4-hexylresorcinol exposure of humans has been reported (Burrows and Irvine, 1982). In guinea pigs, 4-hexylresorcinol did not induce delayed contact

sensitivity when it was tested as one of a series of resorcinols to determine the relationship between structure and sensitizing capacity (Baer et al., 1966).

No information was available in the literature on studies of reproductive effects of 4-hexylresorcinol in laboratory animals. However, this chemical has been used as one of the constituents of spermicidal contraceptive preparations for humans (Boyland et al., 1966). 4-Hexylresorcinol was found to be a spermicide when tested by an in vitro human spermatozoa stripping technique (Brotherton, 1977).

One third of ingested 4-hexylresorcinol is absorbed and is excreted via the kidney as ethereal sulfate conjugates (Goodman and Gilman, 1970; Goodman et al., 1985). The unabsorbed chemical is excreted unchanged in the feces. (No experimental details of this study were given.) No other information on metabolism and disposition of this chemical was available in the literature.

Genetic Toxicology

Published reports on the mutagenic activity of 4-hexylresorcinol consist only of data from *Salmonella typhimurium* microsome assays. Cortinas de Nava et al. (1983) found no increase in the number of revertant colonies following incubation of strains TA98, TA100, TA1535, TA1537, or TA1538 in the standard plate incorporation technique of Ames et al. (1975) with or without metabolic activation from PCB-induced male Sprague Dawley rat liver S9, with up to 30 µg 4-hexylresorcinol. When tested in a preincubation protocol with doses up to 100 µg/plate, 4-hexylresorcinol was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of metabolic activation from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Mortelmans et al., 1986; Appendix E, Table E1).

4-Hexylresorcinol has demonstrated some mutagenic activity in cultured mammalian cells in NTP studies. It was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the presence of Aroclor 1254-induced F344 rat liver S9 at concentrations of 5-30 µg/ml; no response was observed in the absence of exogenous metabolic activation (Table E2). Exposure to 4-hexylresorcinol at doses up to 50 µg/ml did not produce chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells with or without Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table E4). However, in sister chromatid exchange (SCE) assays with CHO cells, the compound produced a positive response at doses of 18 and 20 µg/ml in the absence of S9; no increase in the frequency of SCEs was observed in the presence of S9 activation (Table E3).

A structural analog of 4-hexylresorcinol, olivetol (5-pentylresorcinol), induced mitotic chromosomal segregational errors seen as abnormal anaphase configurations in cultured human lymphocytes exposed at 5×10^{-5} M (Morishima et al., 1976a,b). In addition, [^{3}H]thymidine uptake was significantly decreased in these exposed lymphocyte cultures (Nahas et al., 1977). The authors suggest that olivetol may directly decrease DNA synthesis and indirectly induce abnormal anaphase configurations by inhibiting protein and RNA synthesis, thereby disrupting microtubule and spindle formation.

Carcinogenicity of 4-Hexylresorcinol

A single report was found in the literature on the evaluation of 4-hexylresorcinol for its potential carcinogenicity. Eight different constituents of proprietary spermicidal preparations including 4-hexylresorcinol (1% in gum tragacanth) were given by intravaginal injection to groups of 20 BALB/c mice (Boyland et al., 1966). 4-Hexylresorcinol was given twice a week for a total of 31 weeks. During the observation period of 20 months, one mouse developed squamous carcinomata of the cervix or vagina in the 4-hexylresorcinol-dosed group as compared with none in the vehicle control group. The authors concluded that results for carcinogenic potential of 4-hexylresorcinol were equivocal.

There has been no epidemiologic study to show the specific relationship between 4-hexylresorcinol exposure and carcinogenicity in humans. Mouthwash use and its correlation to oral cavity cancer were assessed by means of retrospective studies in women (Wynder et al., 1983). These results did not demonstrate an association between daily mouthwash use and oral cancer.

Study Rationale

4-Hexylresorcinol is one of six phenolic antiseptics studied by the NCI/NTP in the past or under evaluation at present. The other five are phenol (NCI, 1980), hexachlorophene (NCI, 1978), *o*-phenylphenol (NTP, 1986), resorcinol, and cresol. 4-Hexylresorcinol was nominated by the NCI for study because of widespread human exposure and a lack of long-term toxicity and carcinogenicity information.

Short-term (16-day and 13-week) and long-term (2-year) toxicology and carcinogenesis studies of 4-hexylresorcinol were conducted by gavage in corn oil. The chemical was administered orally, since human exposure is predominantly oral. The gavage route was selected because the chemical was found to be unstable in feed.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 4-HEXYLRESORCINOL

USP-grade, unformulated 4-hexylresorcinol was obtained in one lot (lot no. 20818/02) from American Hoechst Corporation (Summerfield, New Jersey). Purity, identity, and stability analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). (MRI reports on analyses performed in support of the 4-hexylresorcinol studies are on file at NIEHS.) Lot no. 20818/02 was obtained as a white, microcrystalline solid with a melting point of 66.5°-68.0° C. Infrared (Figure 1), ultraviolet/visible, and nuclear magnetic resonance (Figure 2) spectra were consistent with the literature spectra (Sadtler Standard Spectra) of 4-hexylresorcinol.

Cumulative data on lot no. 20818/02 indicated a purity of greater than 99%. Results of elemental analyses for carbon, hydrogen, and oxygen agreed with theoretical values. Water content by Karl Fischer titration was 0.11%. Results of nonaqueous titration of one phenolic group with tetrabutylammonium hydroxide indicated a purity of 100.1%. Thin-layer chromatography on silica gel plates with a toluene:acetic acid (80:20) solvent system indicated a major spot and two trace impurities. Chromatography with an acetone:hexanes (50:50) solvent system indicated a single spot. Visualization was by ultraviolet light (254 nm) and a spray of 0.4% 2,6-dibromoquinonechloroimide in methanol; plates were placed in a chamber containing 25% ammonium hydroxide after being sprayed. Three impurity peaks with a combined area totaling 0.32% of the major peak area were detected by high-performance liquid chromatography on a μBondapak C_{18} column with a mobile phase of 1% aqueous acetic acid:1% acetic acid in methanol (45:55) at a flow rate of 2 ml/minute and ultraviolet detection at 280 nm. Five impurity peaks with a combined area that was 0.52% of the major peak area were detected with a solvent ratio of 25:75 and a flow rate of 1 ml/minute. Results from the two high-performance liquid chromatographic systems indicated a total of six impurities with a combined area that was 0.6% of the major peak area.

Stability studies performed by the high-performance liquid chromatographic system described above with a solvent ratio of 20:80 and a flow rate of 2 ml/minute indicated that 4-hexylresorcinol was stable as a bulk chemical for 2 weeks at temperatures from −20° to 60° C. The study laboratory stored several portions at −20° C as reference samples, and the remainder was stored at room temperature. Periodic reanalysis of the bulk chemical and reference samples was conducted at the study laboratory by ultraviolet and infrared spectroscopy or high-performance liquid chromatography. For analysis by ultraviolet spectroscopy, 4-hexylresorcinol was dissolved in methanol and the absorbance read at 281 or 282 nm. High-performance liquid chromatography was performed with the system described above with a 20:80 solvent ratio and a flow rate of 1-2 ml/minute. No notable deterioration of the study chemical was observed over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

4-Hexylresorcinol and corn oil were mixed to yield the desired concentrations (Table 1). 4-Hexylresorcinol (100 mg/ml) in corn oil was found to be stable when stored for 14 days in the dark at room temperature. Analyses were performed by gas chromatography with a 3% SP2100 column and flame ionization detection after extraction with acetonitrile and derivatization with *N,O*-bis-(trimethylsilyl)-trifluoroacetamide containing 1% trimethylchlorosilane. In the 2-year studies, 4-hexylresorcinol/corn oil mixtures were stored at room temperature for no longer than 2 weeks.

To confirm that correct concentrations were prepared, dose mixtures were analyzed approximately every 8 weeks at the study laboratory by measuring the absorption of acetonitrile extracts at 257 nm. Dose mixtures were analyzed once during the 13-week studies. The results ranged from 96.0% to 103.4% of the target concentrations (Table 2). During the 2-year studies,

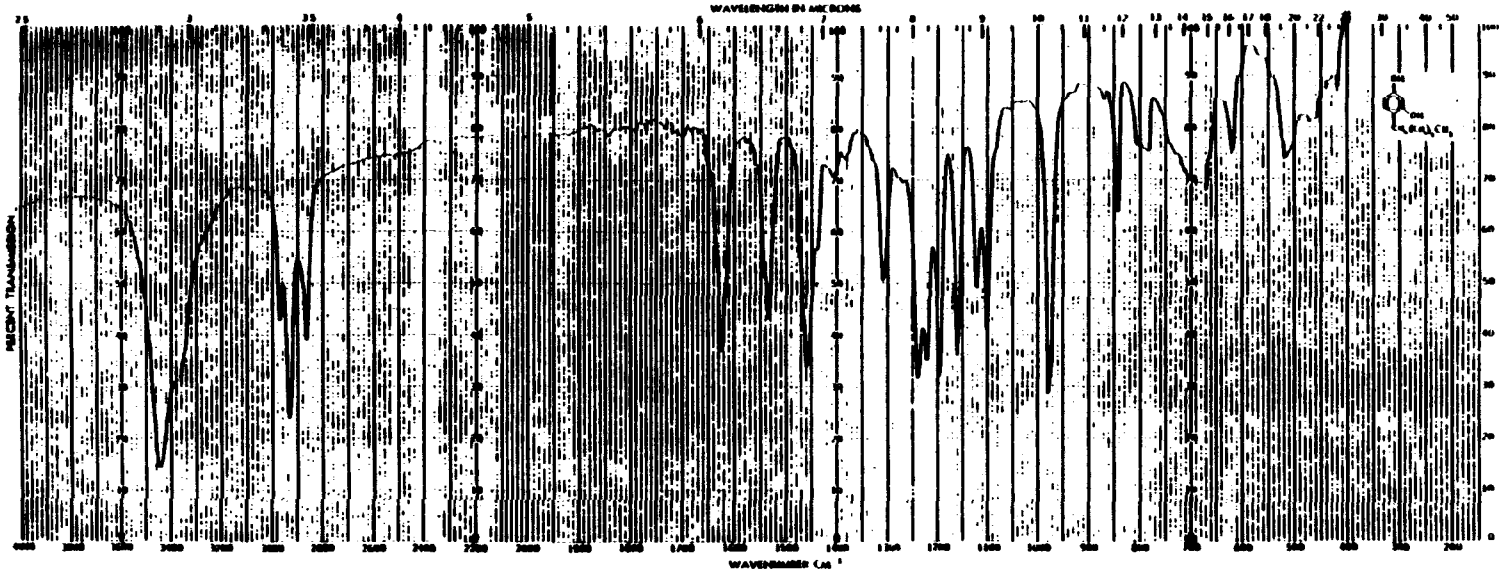


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF 4-HEXYLRESORCINOL (LOT NO. 20818/02)

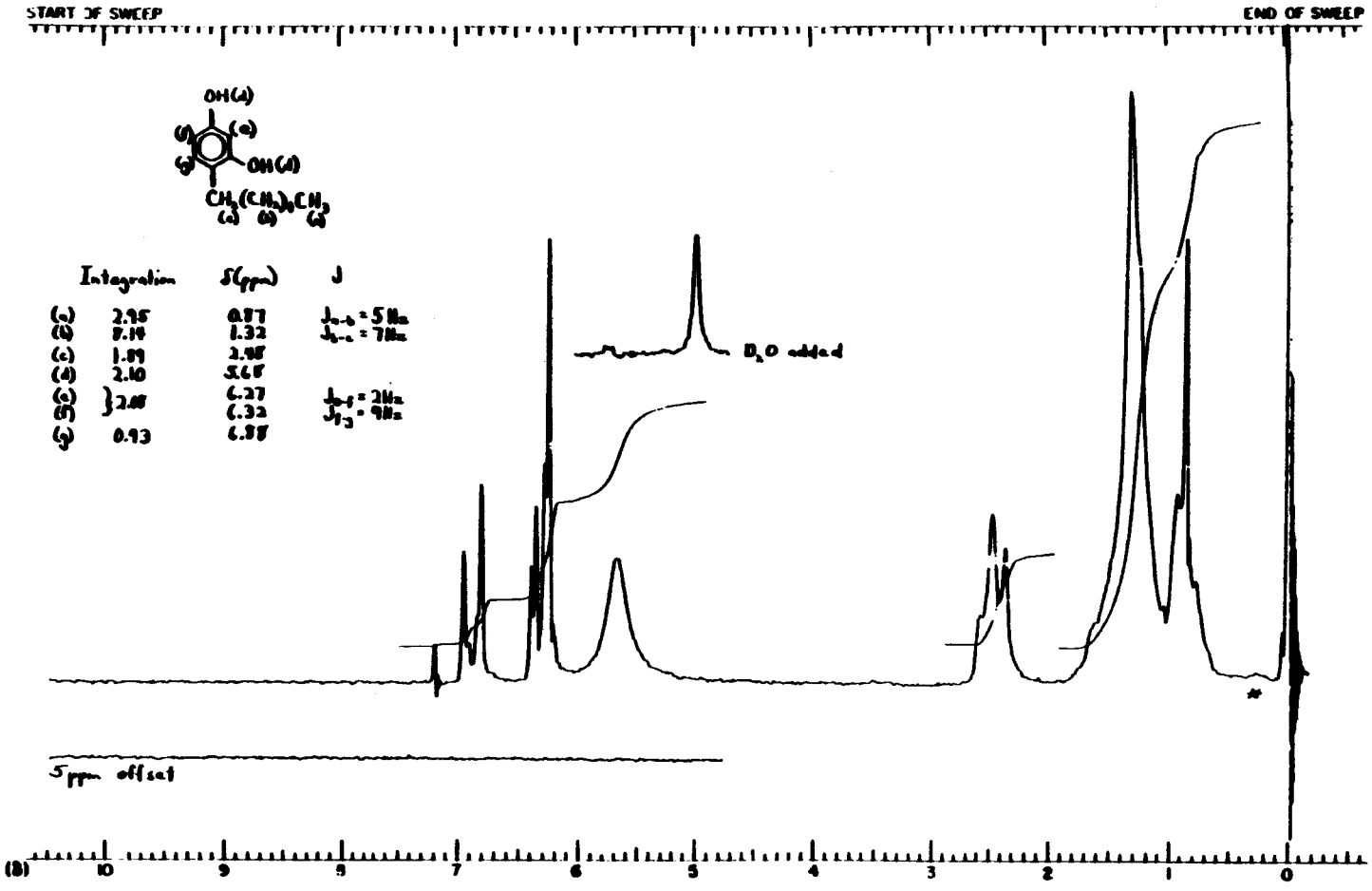


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4-HEXYLRESORCINOL (LOT NO. 20818/02)

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Not available	4-Hexylresorcinol added to appropriate volume of corn oil and homogenized for 30 sec with a Brinkman Polytron® homogenizer. Formulated mixture transferred to light-protected containers equipped with magnetic stir bar and sealed	4-Hexylresorcinol weighed and transferred to mixing vessel containing required weight of corn oil. Mixture blended by homogenization with Brinkman Polytron® homogenizer, Model PT 10-35, for 60 sec at dial setting no. 5, followed by 2 minutes at dial setting no. 8
Maximum Storage Time		
Not available	1 wk	2 wk
Storage Conditions		
Room temperature in the dark	5° C in the dark	Stored at room temperature in amber bottles with magnetic stir bars

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-HEXYLRESORCINOL (a)

Target Concentration (mg/ml)	Determined Concentration (mg/ml) (b)	Determined as a Percent of Target
6.21	6.42	103.4
12.35	12.20	98.8
24.22	23.48	96.9
46.75	46.27	99.0
87.42	83.96	96.0
154.75	151.92	98.2

(a) Date mixed: 2/26/80
(b) Results of duplicate analysis

the concentration of 4-hexylresorcinol in dose mixtures varied from 97.1% to 107.2% of the target concentrations (Table 3). Because all dose mixtures analyzed were within 10% of the target concentrations, it is estimated that dose mixtures were prepared within specifications throughout the studies. Referee analyses were periodically performed by the analytical chemistry laboratory. Good agreement was generally found between the results of the study and analytical chemistry laboratories (Table 4).

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Date Mixed	Concentration of 4-Hexylresorcinol in Corn Oil for Target Concentration (mg/ml) (a)		
	6.25	12.5	25.0
03/03/81	6.40	13.0	26.4
04/21/81	6.39	13.4	25.9
05/25/81	6.07	12.6	26.2
06/23/81	6.26	12.8	25.8
09/22/81	6.12	13.1	25.9
12/01/81	6.16	12.7	26.4
01/19/82	6.28	12.4	26.3
03/02/82	6.22	12.7	25.3
04/06/82	6.17	12.7	25.2
06/21/82	6.14	12.7	25.1
08/31/82	6.56	12.7	24.5
11/02/82	6.65	12.8	26.5
12/01/82	6.64	12.6	26.3
01/20/83	6.58	13.0	26.1
Mean (mg/ml)	6.33	12.8	25.9
Standard deviation	0.205	0.25	0.60
Coefficient of variation (percent)	3.2	2.0	2.3
Range (mg/ml)	6.07-6.65	12.4-13.4	24.5-26.5
Number of samples	14	14	14

(a) Results of duplicate analysis

TABLE 4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
03/03/81	6.25	6.40	6.18
09/22/81	25.0	25.9	25.0
04/06/82	12.5	12.7	12.5
12/01/82	6.25	6.64	6.60
01/20/83	25.0	26.1	25.8

(a) Results of duplicate analysis
(b) Results of triplicate analysis

SIXTEEN-DAY STUDIES

Five-week-old male and female F344/N rats and 4- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Laboratories and held for 18 days before the studies began. Groups of five rats and five mice of each sex were administered 0, 31.3, 62.5, 125, 250, or 500 mg/kg 4-hexylresorcinol in corn oil by gavage for 12 days (not including weekends) with at least 2 consecutive days of dosing before the animals were killed. The total period of the study was 16 days. Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 5. The rats and mice were observed twice per day and were weighed on days 1, 8, and 15. A necropsy was performed on all animals. Tissues from 10% of the animals in the 250 and 500 mg/kg groups were examined histologically.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 4-hexylresorcinol and to determine the doses to be used in the 2-year studies. Four-week-old male and female F344/N rats and 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and quarantined for 20 days before the studies began. The animals were housed five per cage in polycarbonate cages. Feed and water were available ad libitum.

Groups of 10 rats and 10 mice of each sex were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg 4-hexylresorcinol in corn oil by gavage, 5 days per week for 13 weeks. Animals were checked twice per day; moribund animals were killed. Animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were administered 0, 62.5, or 125 mg/kg 4-hexylresorcinol in corn oil by gavage, 5 days per week for 103 weeks (rats) or 102 weeks (mice).

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female $\times$ C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks of age. The animals were quarantined at the study laboratory for 2 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 6-7 weeks of age and mice at 7-8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

TABLE II-5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
0, 31.3, 62.5, 125, 250, or 500 mg/kg 4-hexylresorcinol in corn oil by gavage; dose vol: rats--5 ml/kg; mice--10 ml/kg	0, 62.5, 125, 250, 500, or 1,000 mg/kg 4-hexylresorcinol in corn oil by gavage; dose vol: rats--5 ml/kg; mice--10 ml/kg	0, 62.5, or 125 mg/kg 4-hexylresorcinol in corn oil by gavage; dose vol: rats--5 ml/kg; mice--10 ml/kg
Date of First Dose		
9/4/79	3/3/80	Rats--3/10/81; mice--3/24/81
Date of Last Dose		
9/19/79	5/29/80	Rats--2/28/83; mice--3/4/83
Duration of Dosing		
5 × wk for 12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk (rats) or 102 wk (mice)
Type and Frequency of Observation		
Observed 2 × d; weighed on d 1, 8, and 15	Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed and clinical exams 1 × wk for 13 wk and 1 × 4 wk thereafter
Necropsy and Histologic Examination		
Necropsy performed on all animals; tissues from 10% of the animals in the 250 and 500 mg/kg groups examined histologically	Necropsy performed on all animals; the following tissues from all vehicle controls, animals that died before the end of the studies, and all animals in the two highest dose groups examined histologically: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions and tissue masses, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae or femur or vertebrae including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder; kidneys of all animals examined	Necropsy performed on all animals; histologic exams performed on all vehicle control and high dose rats and mice; tissues examined same as 13-wk studies; tissues examined in low dose groups: male rats--adrenal glands, kidneys, liver, lungs, pancreas, spleen, and thyroid gland; female rats--kidneys, liver, lungs, and spleen; male mice--adrenal glands, bone, kidneys, liver, and lungs; female mice--bone, kidneys, liver, lungs, pituitary gland, and thyroid gland
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory		
Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification		
Rats--tail mark; mice--ear punch	Toe clip	Toe clip and ear clip

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 4-HEXYLRESORCINOL (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Time Held Before Study		
18 d	20 d	14 d
Age When Placed on Study		
Rats--8 wk; mice--7-9 wk	Rats--7 wk; mice--8-9 wk	Rats--6-7 wk; mice--7-8 wk
Age When Killed		
Rats--10 wk; mice--9-11 wk	Rats--20 wk; mice--21-23 wk	Rats--110-111 wk; mice--111-112 wk
Necropsy Dates		
Rats--9/19/79-9/20/79; mice--9/19/79	Rats--6/2/80-6/3/80; mice--6/3/80-6/4/80	Rats--3/7/83-3/10/83; mice--3/21/83-3/24/83
Method of Animal Distribution		
Animals assigned to groups according to a table of random numbers	Same as 16-d studies	By tables of random numbers
Feed		
Rodent Laboratory Chow 5001 Meal® (Ralston Purina Co., St. Louis, MO)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding		
Aspen wood chips (Minnesota Sawdust and Shavings Co., Anoka, MN)	Same as 16-d studies	Heat-treated aspen wood shavings (Minnesota Sawdust and Shavings Co., Anoka, MN)
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies; softened with sodium zeolite to < 1 grain/gal hardness and then filtered
Cages		
Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 16-d studies	Same as 16-d studies
Cage Filters		
Reemay polyester filters (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--18.9°-22.2° C; hum--52%-64%; light 12 h/d;	Temp--22.2°-24.4° C; hum--40%-60%; light 12 h/d;	Temp--23.3° ± 1.1° C; hum--50% ± 10%; fluorescent light 12 h/d; 15 room air changes/h

The C57BL/6N mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Cages were not rotated during the studies. Further experimental details are given in Table 5.

Clinical Examinations and Pathology

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

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and vehicle control animals and on low dose animals dying through month 21 of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

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

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

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathology results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

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

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values for tumor analyses are one-sided.

Life Table Analysis--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the studies were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the studies, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analysis--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the studies were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this

approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SIXTEEN-DAY STUDIES

Administration of 4-hexylresorcinol did not cause deaths in any of the dose groups (Table 6). Final mean body weights of male rats that received 250 or 500 mg/kg 4-hexylresorcinol were 8% or 16% lower than that of the vehicle controls. Final mean body weights of dosed and vehicle control female rats were comparable. Rats that received 500 mg/kg were hyperexcitable.

Since toxicity end points in female rats were not altered by administration of 4-hexylresorcinol, doses of 0, 62.5, 125, 250, 500, and 1,000 mg/kg were selected for the 13-week studies.

THIRTEEN-WEEK STUDIES

The survival and mean body weights of rats in the 13-week gavage studies of 4-hexylresorcinol are given in Table 7. All rats that received 1,000 mg/kg of 4-hexylresorcinol died during week 1 of the studies. Final mean body weights of rats that received 250 or 500 mg/kg were 22% or 38% lower than that of the vehicle controls for males and 16% or 9% lower for females.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	152 ± 6	193 ± 6	+41 ± 5	--
31.3	5/5	155 ± 8	200 ± 8	+45 ± 2	104
62.5	5/5	144 ± 10	195 ± 7	+51 ± 3	101
125	5/5	158 ± 9	201 ± 6	+43 ± 6	104
250	5/5	143 ± 3	177 ± 5	+34 ± 4	92
500	5/5	145 ± 5	162 ± 4	+17 ± 3	84
FEMALE					
0	5/5	116 ± 2	135 ± 4	+19 ± 2	--
31.3	5/5	111 ± 2	129 ± 2	+18 ± 1	96
62.5	5/5	117 ± 3	138 ± 4	+21 ± 2	102
125	5/5	115 ± 2	130 ± 2	+15 ± 1	96
250	5/5	115 ± 2	125 ± 2	+10 ± 2	93
500	5/5	115 ± 3	127 ± 3	+12 ± 2	94

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 9/10	142 ± 1	329 ± 6	+187 ± 6	--
62.5	(d) 8/10	140 ± 2	330 ± 5	+190 ± 5	100
125	(d) 9/10	152 ± 1	312 ± 4	+160 ± 4	86
250	(e) 5/10	126 ± 4	256 ± 10	+133 ± 12	78
500	(f) 1/10	148 ± 3	205	+63	62
1,000	(g) 0/10	148 ± 1	(h)	(h)	(h)
FEMALE					
0	10/10	109 ± 1	186 ± 3	+77 ± 3	--
62.5	10/10	113 ± 1	191 ± 2	+78 ± 1	103
125	(d) 7/10	107 ± 0	182 ± 1	+75 ± 1	98
250	(i) 8/10	104 ± 1	156 ± 4	+53 ± 4	84
500	(j) 2/10	114 ± 1	170 ± 18	+56 ± 17	91
1,000	(g) 0/10	109 ± 1	(h)	(h)	(h)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) All deaths gavage related
(e) Week of death: 1,1,2,9 (one death gavage related)
(f) Week of death: all 1 (three deaths gavage related)
(g) Week of death: all 1
(h) No data are reported due to the 100% mortality in this group.
(i) Week of death: 1,5
(j) Week of death: 1,1,1,1,1,1,7,9

Clinical signs of toxicity included nasal discharge, ocular irritation, alopecia, diarrhea, and cachexia. At necropsy, reduction in the size of the seminal vesicles was seen in 4/10 males at 1,000 mg/kg, 6/10 males at 500 mg/kg, and 1/10 males at 250 mg/kg. Hypospermatogenesis was seen microscopically in 4/10 males in the 1,000 mg/kg group, and hypoplasia of the seminal vesicles was seen in 5/10 males at 1,000 mg/kg and in 3/10 males at 500 mg/kg.

Dose Selection Rationale: The large number of deaths occurring in the three highest dose groups of each sex early in the studies (mostly during the first 3 weeks) may be related to the acute toxicity of the chemical. Doses of 0, 62.5, and 125 mg/kg 4-hexylresorcinol in corn oil by gavage were selected for rats in the 2-year studies because in the 13-week studies:

1. Deaths occurred at 500 mg/kg and higher in each sex. Deaths in lower dose groups were gavage-related accidents.
2. Body weight gains were reduced at 250 mg/kg in both males and females. The weight gain of males, but not females, at 125 mg/kg was less than that of the vehicle controls.
3. No histopathologic lesions or affected organs were identified in rats given 125 mg/kg or less of the chemical.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 7%-11% lower than those of the vehicle controls after week 8 (Table 8 and Figure 3). Mean body weights of low dose male and dosed female rats were similar to those of the vehicle controls throughout the studies. No compound-related clinical signs were observed.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Weeks on Study	Vehicle Control		62.5 mg/kg			125 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	111	50	110	99	50	111	100	50
1	168	50	167	99	50	165	98	50
2	204	50	201	99	50	198	97	50
3	229	50	226	99	50	220	96	50
4	252	50	247	98	50	240	95	50
5	271	50	265	98	50	257	95	49
6	287	50	279	97	50	270	94	49
7	299	50	293	98	49	282	94	49
8	294	50	286	97	49	274	93	48
9	309	50	300	97	48	285	92	48
10	326	49	318	98	48	303	93	48
11	338	49	328	97	48	313	93	48
12	351	49	340	97	48	325	93	47
13	355	49	344	97	47	328	92	47
17	381	49	373	98	47	346	91	47
22	415	49	404	97	47	371	89	47
26	438	49	429	98	47	392	89	47
29	452	49	443	98	47	407	90	47
34	470	49	463	99	47	426	91	47
38	478	49	470	98	47	431	90	47
43	491	49	486	99	47	450	92	46
47	502	47	497	99	46	459	91	46
51	510	47	508	100	46	468	92	46
55	518	46	516	100	46	474	92	45
60	525	46	523	100	46	480	91	45
64	535	46	529	99	46	489	91	45
69	526	46	527	100	44	480	91	45
73	523	45	523	100	43	477	91	43
77	523	42	515	98	41	479	92	42
82	521	41	527	101	39	479	92	41
86	519	38	523	101	38	479	92	40
90	515	37	514	100	37	472	92	40
95	503	36	501	100	36	467	93	38
99	503	31	506	101	33	465	92	34
103	488	30	489	100	29	445	91	34
104	--	30	--	--	29	--	--	33
FEMALE								
0	93	50	93	100	50	94	101	50
1	124	50	125	101	50	122	98	50
2	139	50	140	101	50	137	99	49
3	150	50	151	101	50	147	98	48
4	161	50	159	99	50	156	97	48
5	171	50	169	99	50	166	97	48
6	176	50	173	98	50	171	97	48
7	182	50	177	97	48	177	97	47
8	182	50	181	99	48	178	98	47
9	187	50	182	97	48	178	95	47
10	195	49	192	98	48	186	95	47
11	196	49	192	98	48	190	97	47
12	200	49	193	97	48	192	96	47
13	201	49	195	97	48	193	96	44
17	211	49	204	97	47	200	95	41
22	219	49	213	97	47	203	93	41
26	223	49	221	99	46	212	95	39
29	227	48	226	100	46	220	97	39
34	234	48	233	100	46	228	97	39
38	236	48	232	98	46	231	98	37
43	247	48	244	99	46	241	98	36
47	252	48	251	100	46	248	98	36
51	257	48	258	100	42	253	98	36
55	267	47	269	101	42	263	99	36
60	276	47	277	100	41	273	99	36
64	285	47	285	100	41	282	99	36
69	292	46	294	101	41	286	98	36
73	297	46	301	101	41	291	98	35
77	306	45	311	102	41	301	98	34
82	316	43	319	101	40	310	98	34
86	319	41	323	101	37	314	98	34
90	323	37	328	102	36	317	98	34
95	324	35	337	104	35	323	100	32
99	337	32	342	101	33	331	98	31
103	333	28	338	102	32	328	98	30
104	--	28	--	--	32	--	--	30

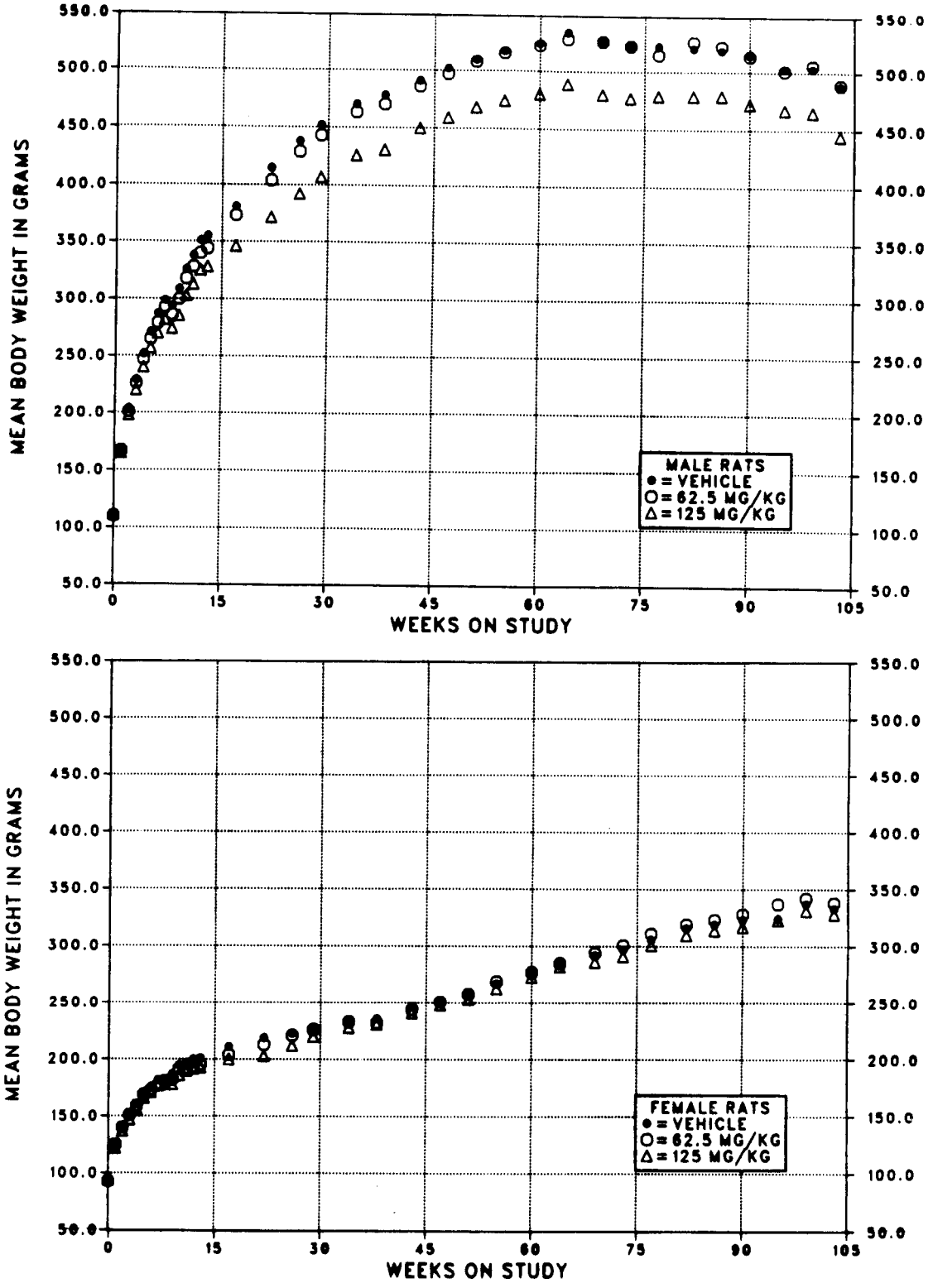


FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED 4-HEXYLRESORCINOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered 4-hexylresorcinol at the doses used in these studies and for vehicle controls are shown in Table 9 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex, although a number of females (3 vehicle control, 8 low dose, and 14 high dose) died during the first year of the study before they were at risk for developing most tumors. Unadjusted survival curves in which all deaths (including gavage-related deaths) are regarded as natural are given in Figure 5. These unadjusted survival curves better illustrate the reduced number of high dose female rats at risk for tumor development during the second year of the study.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the anterior pituitary gland, brain, hematopoietic system, and thyroid gland.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in corn oil vehicle control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in corn oil vehicle control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	14	14
Accidentally killed (c)	2	7	3
Killed at termination	30	28	33
Died during termination period	0	1	0
Survival P values (d)	0.452	0.602	0.527
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	16	11
Accidentally killed (c)	1	2	9
Killed at termination	28	32	30
Survival P values (d)	0.211	0.586	0.237

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) All accidental deaths were gavage related.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

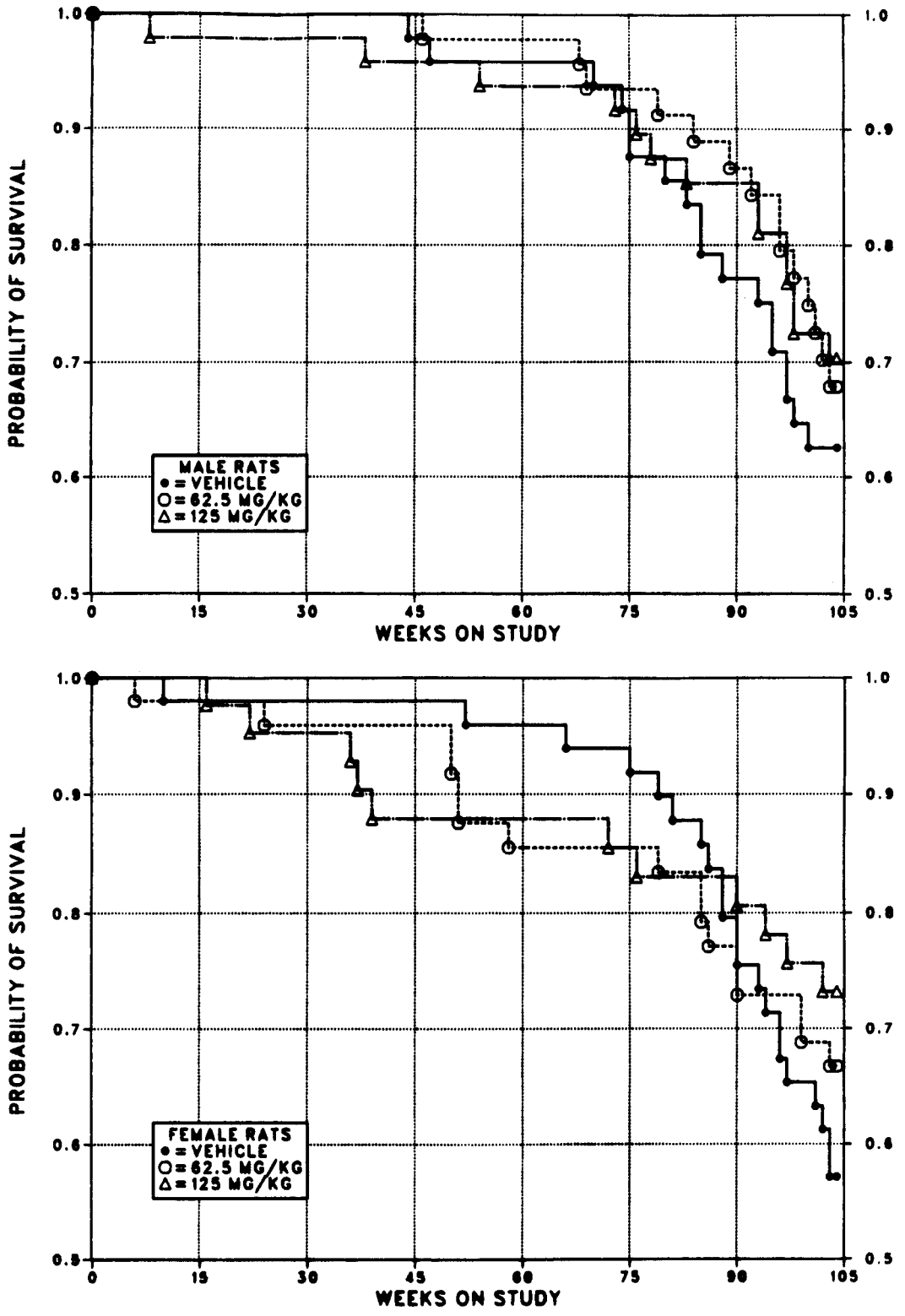


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 4-HEXYLRESORCINOL IN CORN OIL FOR TWO YEARS

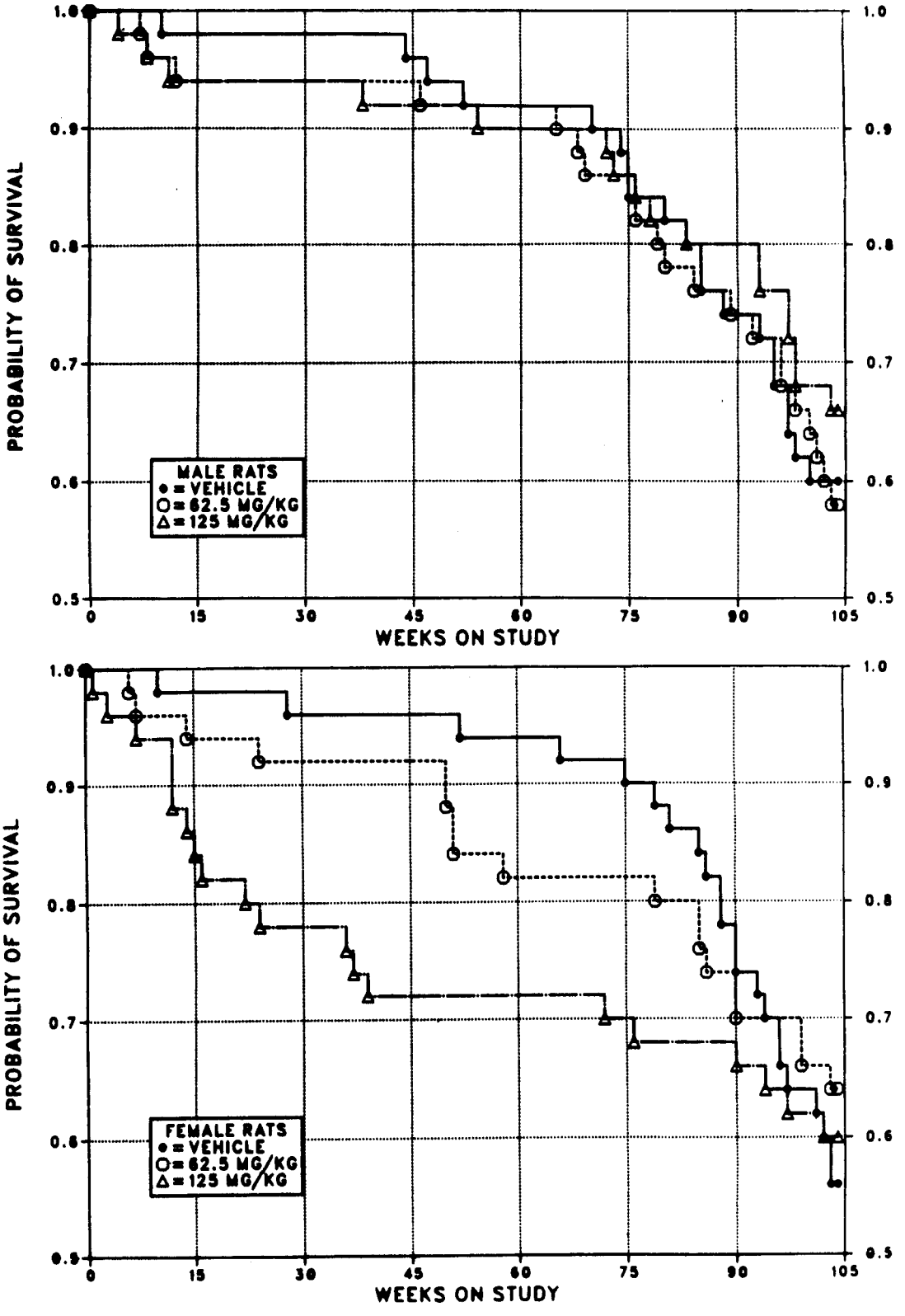


FIGURE 5. UNADJUSTED SURVIVAL CURVES FOR RATS ADMINISTERED 4-HEXYLRESORCINOL IN CORN OIL FOR TWO YEARS

Anterior Pituitary Gland: Although the overall incidences of adenomas and adenomas or carcinomas (combined) were similar in dosed and vehicle control female rats, the incidental tumor test indicated a significant positive trend and high dose effect for these neoplasms (Table 10). This effect reflects in part the early deaths observed in the high dose group; the incidences of pituitary gland neoplasms in animals surviving until the appearance of the first tumor (week 76) were as follows: vehicle control, 21/45; low dose, 22/41; high dose, 24/35. These tumors tended to occur earlier in vehicle controls than in dosed animals. This marginal effect was not considered to be biologically significant.

Brain: Two astrocytomas and an oligodendroglioma were observed in three high dose male rats, a glioma was observed in one low dose male rat, and an oligodendroglioma was observed in one vehicle control male rat. The historical incidence of gliomas, oligodendrogliomas, or astrocytomas (combined) is 16/1,446 (1.1%). No more than two glial cell tumors have been observed in any corn oil vehicle control male F344/N rat group; however, it is not clear whether these tumors are related to 4-hexylresorcinol administration.

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with negative trends; the incidences in high dose male rats and dosed female rats were significantly lower than those in the vehicle controls (Table 11).

Thyroid Gland: The incidence of C-cell adenomas or carcinomas (combined) in male rats occurred with a negative trend; the incidences of C-cell adenomas and adenomas or carcinomas (combined) in low dose male rats were significantly lower than those in the vehicle controls (Table 12). In female rats, the incidences of C-cell adenomas or carcinomas (combined) were as follows: 6/50 in the vehicle control, 2/16 in the low dose, and 2/50 in the high dose group.

TABLE 10. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (a)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Focal Hyperplasia			
Overall Rates	3/50 (6%)	12/50 (24%)	4/50 (8%)
Adenoma			
Overall Rates	21/50 (42%)	22/50 (44%)	22/50 (44%)
Adjusted Rates	52.9%	60.8%	66.5%
Terminal Rates	10/28 (36%)	18/32 (56%)	19/30 (63%)
Week of First Observation	79	85	76
Life Table Tests	P=0.487	P=0.518N	P=0.515
Incidental Tumor Tests	P=0.062	P=0.273	P=0.057
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adenoma or Carcinoma (b)			
Overall Rates	21/50 (42%)	22/50 (44%)	24/50 (48%)
Adjusted Rates	52.9%	60.8%	72.6%
Terminal Rates	10/28 (36%)	18/32 (56%)	21/30 (70%)
Week of First Observation	79	85	76
Life Table Tests	P=0.339	P=0.518N	P=0.373
Incidental Tumor Tests	P=0.023	P=0.273	P=0.021

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix B, Table B3 (footnotes).
(b) Historical incidence in NTP studies (mean ± SD): 561/1,407 (40% ± 8%)

TABLE 11. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
MALE (a)			
Overall Rates	12/49 (24%)	7/50 (14%)	1/50 (2%)
Adjusted Rates	32.9%	19.3%	3.0%
Terminal Rates	7/30 (23%)	2/29 (7%)	1/33 (3%)
Week of First Observation	70	80	104
Life Table Tests	P=0.001N	P=0.178N	P=0.001N
Incidental Tumor Tests	P=0.001N	P=0.149N	P=0.002N
FEMALE (b)			
Overall Rates	16/50 (32%)	3/50 (6%)	2/50 (4%)
Adjusted Rates	42.1%	8.3%	6.1%
Terminal Rates	8/28 (29%)	2/32 (6%)	0/30 (0%)
Week of First Observation	79	50	94
Life Table Tests	P<0.001N	P=0.001N	P=0.001N
Incidental Tumor Tests	P<0.001N	P=0.002N	P=0.016N

(a) Historical incidence of leukemia in NTP studies (mean ± SD): 202/1,450 (14% ± 8%)
(b) Historical incidence of leukemia in NTP studies (mean ± SD): 271/1,450 (19% ± 9%)

TABLE 12. ANALYSIS OF THYROID GLAND C-CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Hyperplasia			
Overall Rates	14/49 (29%)	20/49 (41%)	17/48 (35%)
Adenoma			
Overall Rates	12/49 (24%)	3/49 (6%)	7/48 (15%)
Adjusted Rates	37.1%	10.3%	21.2%
Terminal Rates	10/30 (33%)	3/29 (10%)	7/33 (21%)
Week of First Observation	85	104	104
Life Table Tests	P=0.069N	P=0.013N	P=0.102N
Incidental Tumor Tests	P=0.087N	P=0.014N	P=0.145N
Carcinoma			
Overall Rates	1/49 (2%)	1/49 (2%)	0/48 (0%)
Adenoma or Carcinoma (a)			
Overall Rates	13/49 (27%)	4/49 (8%)	7/48 (15%)
Adjusted Rates	40.2%	13.8%	21.2%
Terminal Rates	11/30 (37%)	4/29 (14%)	7/33 (21%)
Week of First Observation	85	104	104
Life Table Tests	P=0.041N	P=0.017N	P=0.064N
Incidental Tumor Tests	P=0.053N	P=0.018N	P=0.094N

(a) Historical incidence in NTP studies (mean ± SD): 181/1,417 (13% ± 6%)

SIXTEEN-DAY STUDIES

Administration of 4-hexylresorcinol did not affect the survival of animals (Table 13). Final mean body weights of dosed and vehicle control mice were comparable. No compound-related clinical signs were observed.

Since toxicity end points in this experiment were not altered by administration of 4-hexylresorcinol in either male or female mice, doses of 0, 62.5, 125, 250, 500, and 1,000 mg/kg were selected for the 13-week studies.

THIRTEEN-WEEK STUDIES

All male mice and 9/10 female mice that received 1,000 mg/kg 4-hexylresorcinol died during the first week of the studies (Table 14). No clinical signs related to administration of the chemical were reported. Final mean body weights of male mice that received 250 or 500 mg/kg were 6% or 5% lower than that of the vehicle controls. Final mean body weights of dosed and vehicle control female mice were comparable. Mild to moderate nephropathy was observed in 1/10 males at 62.5 mg/kg, 4/10 males and 1/10 females at 125 mg/kg, 8/10 males and 7/10 females at 250 mg/kg, and 7/10 males and 10/10 females at 500 mg/kg.

Dose Selection Rationale: Doses of 62.5 and 125 mg/kg 4-hexylresorcinol in corn oil by gavage were selected for mice in the 2-year studies because in the 13-week studies:

1. Deaths occurred in males at 500 mg/kg and higher and in females at 1,000 mg/kg.
2. Only 1/10 males and 1/10 females given 62.5 mg/kg and 125 mg/kg 4-hexylresorcinol, respectively, had minimal nephropathy.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	26.6 ± 0.9	27.3 ± 0.9	+0.7 ± 0.1	--
31.3	5/5	27.1 ± 0.9	28.2 ± 0.7	+1.1 ± 0.2	103.3
62.5	5/5	27.7 ± 1.1	29.1 ± 1.0	+1.4 ± 0.4	106.6
125	5/5	26.6 ± 0.9	27.6 ± 1.1	+1.0 ± 0.4	101.1
250	5/5	26.3 ± 1.0	27.4 ± 0.9	+1.1 ± 0.5	100.4
500	5/5	25.1 ± 0.3	26.8 ± 0.6	+1.7 ± 0.4	98.2
FEMALE					
0	5/5	21.4 ± 0.4	22.0 ± 0.4	+0.6 ± 0.3	--
31.3	5/5	23.7 ± 1.0	23.8 ± 0.7	+0.1 ± 0.3	108.2
62.5	5/5	21.7 ± 1.0	22.4 ± 1.3	+0.7 ± 0.5	101.8
125	5/5	21.4 ± 0.9	21.6 ± 0.5	+0.2 ± 0.6	98.2
250	(d) 4/5	19.8 ± 1.1	21.6 ± 1.6	+1.5 ± 0.2	98.2
500	5/5	23.2 ± 0.7	24.0 ± 0.7	+0.8 ± 0.3	109.1

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death due to gavage error

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	25.6 ± 1.3	36.5 ± 0.8	+10.9 ± 0.7	--
62.5	10/10	27.4 ± 0.3	38.5 ± 0.5	+11.1 ± 0.5	105.5
125	10/10	26.7 ± 0.2	38.0 ± 0.3	+11.3 ± 0.4	104.1
250	10/10	24.5 ± 0.4	34.3 ± 1.0	+9.8 ± 0.6	94.0
500	(d) 6/10	28.7 ± 0.3	34.6 ± 0.9	+5.9 ± 1.0	94.8
1,000	(e) 0/10	27.2 ± 0.3	(f)	(f)	(f)
FEMALE					
0	10/10	20.8 ± 0.1	25.8 ± 0.3	+5.0 ± 0.3	--
62.5	10/10	20.3 ± 0.2	25.2 ± 0.4	+4.9 ± 0.4	97.7
125	(g) 9/10	20.7 ± 0.2	26.5 ± 0.7	+5.8 ± 0.6	102.7
250	10/10	19.4 ± 0.3	26.0 ± 0.4	+6.6 ± 0.3	100.8
500	10/10	22.2 ± 0.3	27.4 ± 0.4	+5.2 ± 0.4	106.2
1,000	(e) 1/10	21.4 ± 0.2	25.6	+4.9	99.2

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 9,12,12; the fourth death was due to gavage error.
(e) Week of death: all 1
(f) No data are reported due to 100% mortality in this group.
(g) Death due to gavage error

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were 9%-11% lower than those of the vehicle controls after week 80 (Table 15 and Figure 6). Mean body weights of low dose male mice were 6%-8% lower than those of the vehicle controls after week 80. Mean body weights of high dose female mice were 4%-10% lower after week 88. Mean body weights of low dose female mice were lower than those of the vehicle controls after week 6 and were 6%-16% lower after week 67. No compound-related clinical signs were observed.

TABLE 15. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

Weeks on Study	Vehicle Control		62.5 mg/kg			125 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	22.6	50	22.6	100	50	22.7	100	50
1	26.3	50	25.4	97	50	25.5	97	50
2	28.0	50	27.6	99	50	27.8	99	50
3	29.3	50	28.8	98	50	29.7	101	50
4	30.2	50	29.7	98	50	30.3	100	50
5	31.1	50	30.7	99	50	31.3	101	50
6	31.9	50	31.8	100	50	32.4	102	50
7	32.9	50	32.1	98	50	32.8	100	50
8	32.5	50	32.3	99	50	33.0	102	49
9	33.8	50	33.4	99	50	34.2	101	49
10	34.4	50	33.9	99	50	34.7	101	49
11	35.9	50	35.3	98	50	36.0	100	49
12	35.6	50	35.6	100	50	36.2	102	49
13	36.9	50	36.6	99	50	36.9	100	49
17	39.2	50	39.3	100	50	39.3	100	49
21	40.4	50	40.9	101	50	41.4	102	49
26	41.3	50	41.0	99	50	41.3	100	49
30	42.2	47	41.5	98	50	41.8	99	49
34	42.5	47	41.8	98	49	42.5	100	49
38	43.1	47	42.8	99	49	43.0	100	49
43	44.7	46	43.4	97	49	44.1	99	49
45	44.9	46	43.3	96	49	44.6	99	49
49	45.8	46	42.9	94	49	43.2	94	47
53	45.8	46	44.7	98	49	44.5	97	47
58	46.6	46	44.3	95	49	44.9	96	46
62	47.2	46	45.0	95	47	45.2	96	45
67	47.1	46	45.5	97	46	45.1	96	44
71	48.6	44	45.9	94	45	45.5	94	42
75	47.8	44	45.9	96	44	45.2	95	41
80	47.8	41	45.1	94	44	43.4	91	41
84	47.7	40	44.4	93	43	43.4	91	41
88	46.4	40	43.6	94	42	42.3	91	39
93	45.9	38	42.1	92	38	41.2	90	38
97	45.2	38	41.4	92	34	40.4	89	34
101	44.0	36	41.1	93	28	39.6	90	30
104	--	36	--	--	26	--	--	30
FEMALE								
0	18.7	50	18.8	101	50	18.7	100	50
1	19.7	50	19.7	100	50	19.5	99	50
2	20.9	50	21.4	102	50	21.2	101	50
3	22.4	50	22.2	99	50	22.5	100	50
4	22.8	50	22.5	99	50	22.6	99	50
5	23.4	50	23.4	100	50	23.3	100	50
6	24.1	50	24.0	100	50	24.2	100	50
7	24.9	50	23.3	94	50	24.4	98	50
8	24.6	50	24.1	98	50	24.4	99	50
9	25.1	50	24.6	98	50	25.0	100	50
10	25.2	50	24.8	98	50	25.1	100	50
11	26.2	50	25.7	98	50	26.3	100	50
12	26.3	50	25.6	97	50	26.1	99	50
13	27.5	50	26.9	98	50	27.1	99	50
17	29.4	50	28.7	98	50	28.7	98	50
21	30.7	50	29.6	96	50	30.3	99	50
26	31.5	50	30.4	97	49	31.2	99	50
30	32.0	50	30.8	96	49	31.1	97	50
34	32.5	50	30.9	95	49	31.8	98	50
38	32.8	50	30.9	94	49	32.5	99	50
43	33.7	50	31.8	94	49	32.9	98	49
45	34.3	50	32.6	95	49	34.2	100	49
49	34.4	50	33.1	96	49	33.4	97	49
53	35.3	50	33.9	96	49	34.8	99	48
58	36.6	50	34.8	95	49	36.4	99	48
62	37.1	50	35.3	95	49	37.0	100	48
67	38.3	50	36.0	94	49	37.9	99	48
71	40.0	49	37.4	94	47	39.4	99	48
75	40.3	49	38.0	94	46	39.8	99	48
80	41.6	47	39.3	94	46	41.0	99	45
84	42.7	46	39.3	92	45	42.3	99	43
88	44.2	43	39.1	88	45	42.6	96	42
93	44.2	42	39.0	88	43	41.6	94	42
97	45.1	40	38.7	86	40	40.8	90	42
101	44.4	36	37.5	84	35	41.7	94	35
104	--	35	--	--	32	--	--	35

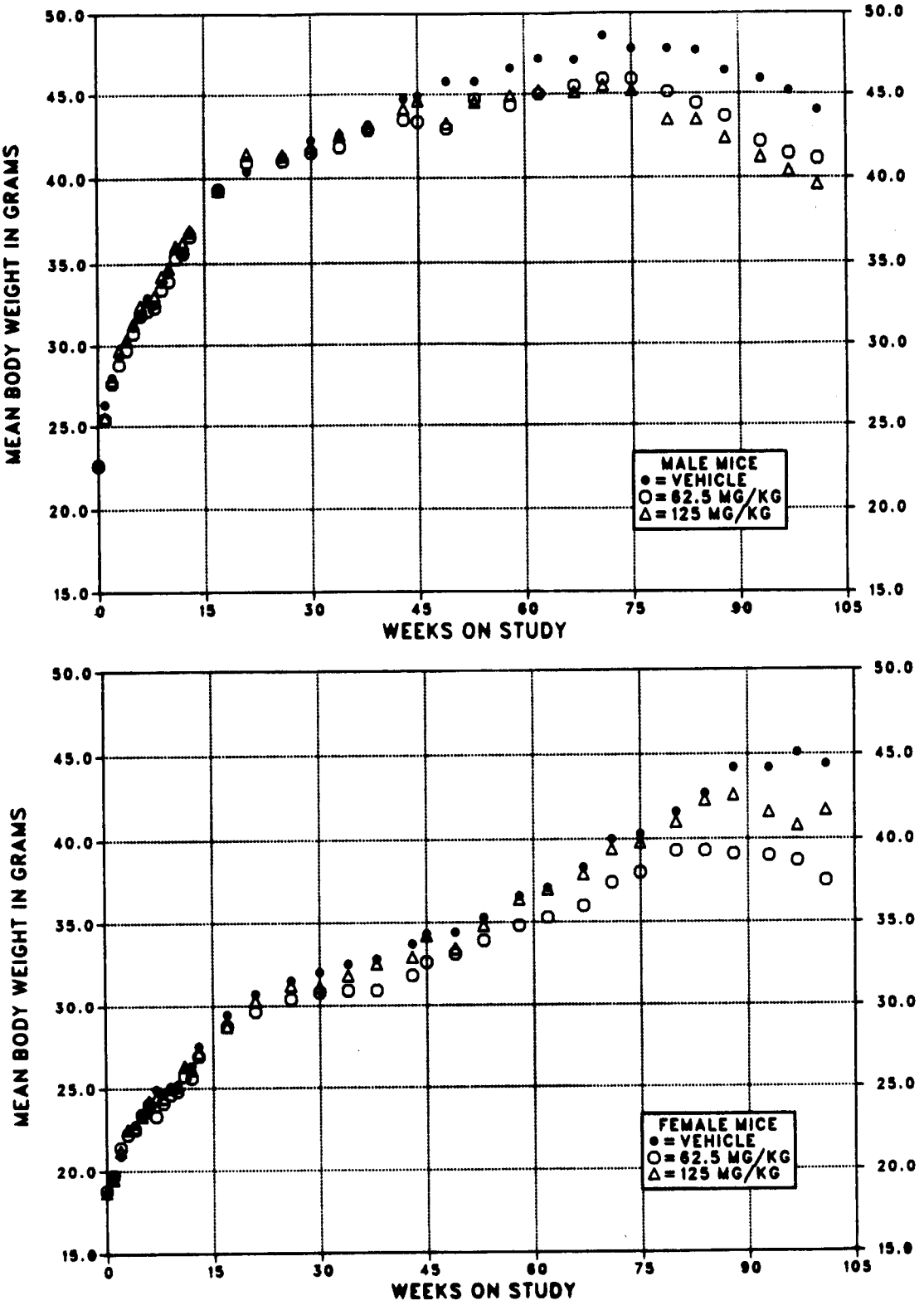


FIGURE 6. GROWTH CURVES FOR MICE ADMINISTERED 4-HEXYLRESORCINOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered 4-hexylresorcinol at the doses used in these studies and for vehicle controls are shown in Table 16 and in the Kaplan and Meier curves in Figure 7. No significant differences in survival were observed between any group of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the adrenal gland, harderian gland, kidney, bone, liver, circulatory system, and lung.

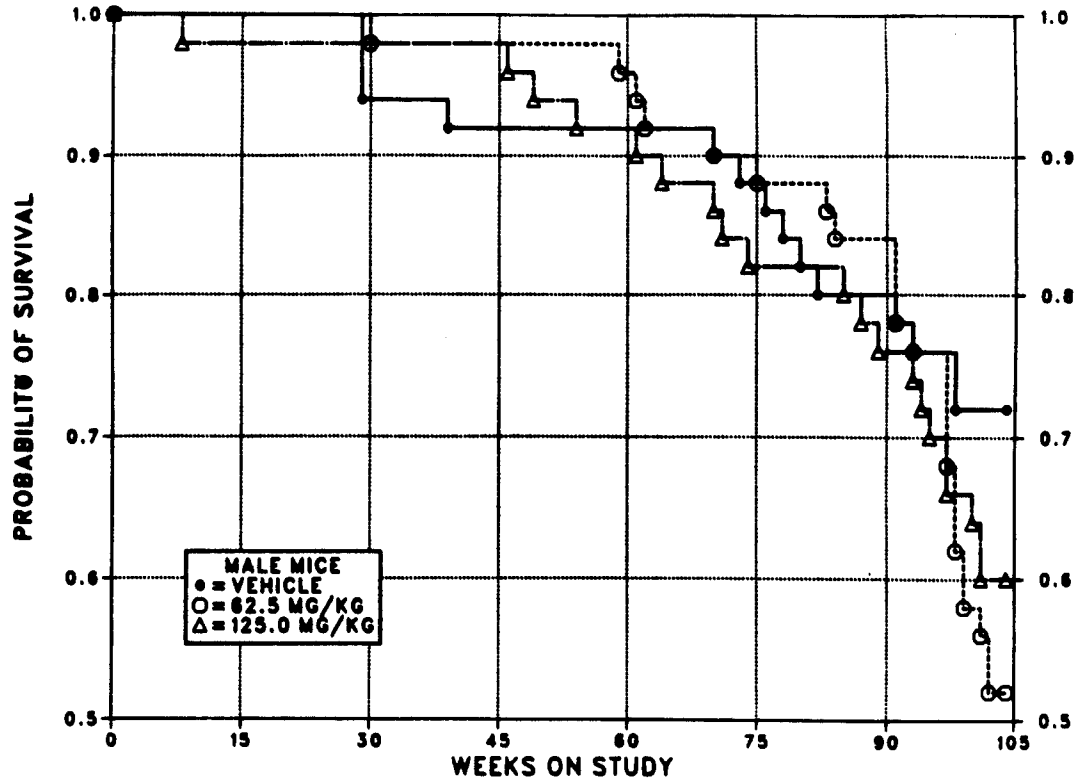
Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in corn oil vehicle control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Historical incidences of tumors in corn oil vehicle control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 16. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	14	24	20
Killed at termination	36	26	30
Survival P values (c)	0.293	0.123	0.333
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	15	18	15
Killed at termination	35	32	35
Survival P values (c)	1.000	0.688	0.955

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.



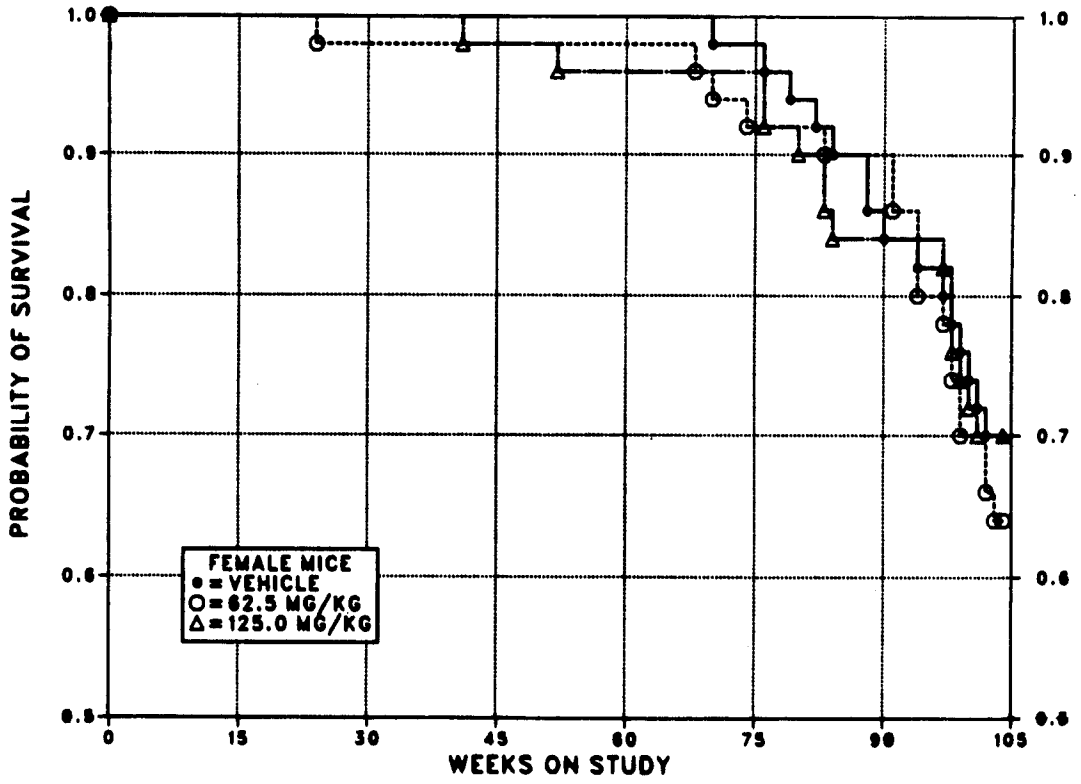


FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 4-HEXYLRESORCINOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Adrenal Gland: Focal hyperplasia of the adrenal medulla was observed at increased incidences in dosed male mice (Table 17). Pheochromocytomas in male mice occurred with a positive trend, but the incidences in the dosed groups were not significantly different from that in the vehicle controls. Hyperplasia and pheochromocytomas comprise a morphologic spectrum of proliferative changes of the adrenal medulla. Foci of hyperplasia consisted of poorly delineated clusters or nests of adrenal medullary cells with more abundant basophilic-staining cytoplasm and enlarged and/or hyperchromatic nuclei as compared with normal medullary cells. Pheochromocytomas were more circumscribed than foci of hyperplasia and showed minimal to moderate compression of adjacent parenchyma and greater cellular atypia.

Harderian Gland: The incidences of carcinomas and adenomas or carcinomas (combined) in low dose male mice were significantly greater than those in the vehicle controls (Table 18). The incidences of adenomas or carcinomas (combined) in female mice were as follows: 2/50 in the vehicle control, 4/49 in the low dose, and 1/50 in the high dose group. Adenomas of the harderian gland are circumscribed masses of tall columnar epithelium arranged in complex papillary formations. The neoplastic epithelium displaces and compresses the adjacent normal tubuloalveolar glands. Carcinomas are more heterogeneous in growth pattern and exhibit greater cellular pleomorphism and atypia.

TABLE 17. ANALYSIS OF ADRENAL GLAND MEDULLARY LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (a)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Focal Hyperplasia			
Overall Rates	5/50 (10%)	16/50 (32%)	10/49 (20%)
Pheochromocytoma (b)			
Overall Rates	1/50 (2%)	(c) 2/50 (4%)	5/49 (10%)
Adjusted Rates	2.8%	4.7%	15.4%
Terminal Rates	1/36 (3%)	0/26 (0%)	3/29 (10%)
Week of First Observation	104	62	93
Life Table Tests	P=0.047	P=0.465	P=0.072
Incidental Tumor Tests	P=0.076	P=0.640	P=0.134

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C, Table C3 (footnotes).
(b) Historical incidence of pheochromocytomas or malignant pheochromocytomas (combined) in NTP studies (mean ± SD): 19/1,443 (1% ± 2%)
(c) A malignant pheochromocytoma was also observed in one of the animals with a benign pheochromocytoma.

TABLE 18. ANALYSIS OF HARDERIAN GLAND TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
Carcinoma			
Overall Rates	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted Rates	0.0%	13.5%	6.7%
Terminal Rates	0/36 (0%)	3/26 (12%)	2/30 (7%)
Week of First Observation		75	104
Life Table Tests	P=0.179	P=0.038	P=0.199
Incidental Tumor Tests	P=0.200	P=0.042	P=0.199
Adenoma or Carcinoma (a)			
Overall Rates	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted Rates	0.0%	13.5%	10.0%
Terminal Rates	0/36 (0%)	3/26 (12%)	3/30 (10%)
Week of First Observation		75	104
Life Table Tests	P=0.089	P=0.038	P=0.090
Incidental Tumor Tests	P=0.101	P=0.042	P=0.090

(a) Historical incidence in NTP studies (mean ± SD): 56/1,497 (4% ± 3%)

Kidney: Nephropathy was observed at increased incidences in dosed male and female mice (male: vehicle control, 39/50; low dose, 43/50; high dose, 47/50; female: 7/50; 40/49; 47/50). The degree of severity of the nephropathy was judged to be greater in dosed groups of male and female mice than in vehicle control groups. Nephropathy in male and female mice varied from mild focal atrophy of tubules in the outer cortex to severe atrophy with dilatation of the tubular lumens and Bowman's space, tubular cysts, tubular regeneration, and variable lymphoplasmocytic inflammatory infiltrates. A tubular cell adenoma was observed in one low dose male; no renal neoplasms were seen in females.

Bone: Osteosclerosis was observed at increased incidences in high dose male and female mice (male: vehicle control, 5/50; low dose, 5/50; high dose, 15/50; female: 21/50; 25/49; 40/50). Osteosclerosis was a focal or multifocal lesion observed primarily in the internal surface of the cortical bone of the femur, the bone selected for histopathologic evaluation. It was characterized by excessive cancellous bone containing immature connective tissue and small numbers of hematopoietic cells.

Liver: Hepatocellular adenomas, carcinomas, and adenomas or carcinomas (combined) in male mice occurred with negative trends; the incidences of hepatocellular adenomas in low dose male mice, of hepatocellular carcinomas in high dose male mice, and of hepatocellular adenomas or carcinomas (combined) in dosed male mice were significantly lower than those in the vehicle controls (Table 19).

Circulatory System: The incidences of hemangiomas and hemangiomas or hemangiosarcomas (combined) in high dose male and female mice were significantly lower than those in the vehicle controls (Table 20).

Lung: The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in low dose female mice was significantly lower than that in the vehicle controls (vehicle control, 5/50; low dose, 0/47 [$P < 0.05$]; high dose, 2/49).

TABLE 19. ANALYSIS OF HEPATOCELLULAR TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Adenoma			
Overall Rates	11/50 (22%)	1/50 (2%)	4/50 (8%)
Adjusted Rates	30.6%	3.8%	12.0%
Terminal Rates	11/36 (31%)	1/26 (4%)	3/30 (10%)
Week of First Observation	104	104	64
Life Table Tests	P=0.038N	P=0.011N	P=0.088N
Incidental Tumor Tests	P=0.035N	P=0.011N	P=0.078N
Carcinoma			
Overall Rates	10/50 (20%)	8/50 (16%)	5/50 (10%)
Adjusted Rates	22.3%	21.7%	13.2%
Terminal Rates	2/36 (6%)	3/26 (12%)	1/30 (3%)
Week of First Observation	70	62	85
Life Table Tests	P=0.165N	P=0.484N	P=0.189N
Incidental Tumor Tests	P=0.023N	P=0.084N	P=0.014N
Adenoma or Carcinoma (a)			
Overall Rates	21/50 (42%)	9/50 (18%)	9/50 (18%)
Adjusted Rates	47.5%	25.1%	23.9%
Terminal Rates	13/36 (36%)	4/26 (15%)	4/30 (13%)
Week of First Observation	70	62	64
Life Table Tests	P=0.022N	P=0.050N	P=0.036N
Incidental Tumor Tests	P=0.002N	P=0.002N	P=0.002N

(a) Historical incidence in NTP studies (mean ± SD): 477/1,490 (32% ± 9%)

TABLE 20. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
MALE			
Hemangioma			
Overall Rates	6/50 (12%)	(a) 1/50 (2%)	0/50 (0%)
Adjusted Rates	16.7%		0.0%
Terminal Rates	6/36 (17%)		0/30 (0%)
Week of First Observation	104		
Life Table Test			P=0.029N
Incidental Tumor Test			P=0.029N
Hemangiosarcoma			
Overall Rates	4/50 (8%)	(a) 3/50 (6%)	2/50 (4%)
Hemangioma or Hemangiosarcoma (b)			
Overall Rates	10/50 (20%)	(a) 4/50 (8%)	2/50 (4%)
Adjusted Rates	26.0%		6.1%
Terminal Rates	8/36 (22%)		1/30 (3%)
Week of First Observation	80		97
Life Table Test			P=0.032N
Incidental Tumor Test			P=0.019N
FEMALE			
Hemangioma			
Overall Rates	4/50 (8%)	(c) 1/49 (2%)	0/50 (0%)
Adjusted Rates	11.4%		0.0%
Terminal Rates	4/35 (11%)		0/35 (0%)
Week of First Observation	104		
Life Table Test			P=0.063N
Incidental Tumor Test			P=0.063N
Hemangiosarcoma			
Overall Rates	2/50 (4%)	(c) 1/49 (2%)	0/50 (0%)
Hemangioma or Hemangiosarcoma (d)			
Overall Rates	6/50 (12%)	(c) 2/49 (4%)	0/50 (0%)
Adjusted Rates	16.4%		0.0%
Terminal Rates	5/35 (14%)		0/35 (0%)
Week of First Observation	97		
Life Table Test			P=0.018N
Incidental Tumor Test			P=0.018N

(a) Only 28 spleens were examined microscopically.
(b) Historical incidence in NTP studies (mean ± SD): 80/1,497 (5% ± 4%)
(c) Only 18 spleens were examined microscopically.
(d) Historical incidence in NTP studies (mean ± SD): 56/1,494 (4% ± 3%)

IV. DISCUSSION AND CONCLUSIONS

Toxicologic Characterization of 4-Hexylresorcinol
Genetic Toxicology of 4-Hexylresorcinol
Carcinogenicity of 4-Hexylresorcinol
Decreased Incidences of Neoplasia
Data Audit
Conclusions

Toxicologic Characterization of 4-Hexylresorcinol

Sixteen-day and 13-week gavage studies of 4-hexylresorcinol in corn oil were performed to characterize the toxicity of the chemical and to select doses for subsequent 2-year toxicology and carcinogenesis studies. The administration of 4-hexylresorcinol in the 16-day studies at doses ranging from 31.3 mg/kg to 500 mg/kg in rats and mice did not produce toxicity other than a 16% reduction in the final mean body weight in male rats at 500 mg/kg. To better characterize the toxicity of this chemical, 1,000 mg/kg was chosen as the highest dose for the 13-week studies for both species. Thus, the range of doses for the 13-week studies was 62.5-1,000 mg/kg.

Body weights at 125 and 250 mg/kg in male rats and at 250 mg/kg in females were reduced markedly compared with those of the vehicle controls. Changes occurring in the testes and seminal vesicles of rats receiving 500 or 1,000 mg/kg of the chemical were considered to be secondary to debilitation in rats dying before the end of the study. Body weights of dosed and vehicle control mice were comparable. The kidney was identified as a target organ in mice.

Many of the rats in the two highest dose groups died during the first 3 weeks of the 13-week studies, and a large number of deaths were observed in mice at 1,000 mg/kg. The deaths observed in rats and mice at doses of 500 and 1,000 mg/kg could be attributed to the acute toxicity of the chemical. However, no deaths were observed at 500 mg/kg in the 16-day studies. This discrepancy cannot be explained, since experimental conditions for the 16-day and 13-week studies were similar.

Chemical-related deaths were also seen in other NCI/NTP short-term studies with resorcinol (NTP unpublished data) and phenol (NCI, 1980), but no target organs were identified. Clinical signs of neurotoxicity in animals exposed to phenolic antiseptics suggest that the central nervous system is affected, and it is not uncommon to see clinical signs of neurotoxicity in the absence of morphologic changes (Norton, 1982). For example, the acute toxicity of phenol has been shown to produce transient central nervous system stimulation followed by central nervous system and cardiovascular depression and death in laboratory animals, but no histopathologic effects on the central nervous system were seen (Goodman et al., 1985; Deichmann and Keplinger, 1981). In contrast, hexachlorophene, another topical antiseptic and a known neurotoxic chemical in laboratory animals and humans (Powell and Lampert, 1977), was found to be neurotoxic in rats that received dietary concentrations of 50-600 ppm over 8 weeks, as shown by clinical signs and neuronal necrosis of the brain (NCI, 1978). In NTP 13-week studies of resorcinol, several animals from high dose groups (rats, 520 mg/kg; mice, 420 mg/kg) died after exhibiting hyperexcitability, tremors, and tachycardia, clinical signs indicating central nervous system involvement (NTP unpublished data). In the present 4-hexylresorcinol studies, hyperexcitability, which could be related to central nervous system stimulation, was observed in the 500 mg/kg groups of rats during the 16-day studies but not in the 13-week or 2-year studies. On the basis of this information only, the association of central nervous system toxicity with 4-hexylresorcinol administration cannot be established.

Chemically related effects in the 2-year study in male rats consisted of reduction in the mean body weights in the high dose group compared with those of the vehicle controls. No untoward clinical signs were observed for rats. In all dosed groups of male and female mice, the body weights were slightly lower than those in the vehicle controls, and these body weight differences were observed primarily in the last 16 weeks of the studies. There were no significant differences in survival, and no clinical signs related to 4-hexylresorcinol administration were observed for mice. However, nephropathy was observed at increased incidences (Tables C5 and D5) and severity in dosed male and female mice. These lesions were also seen during the 13-week studies in mice administered 62.5 mg/kg or more. Osteosclerosis was also moderately increased in dosed mice in the 2-year studies. The reasons for this are not clear.

Genetic Toxicology of 4-Hexylresorcinol

In most assays, 4-hexylresorcinol exhibited little mutagenic activity. Forward mutations were detected at the TK locus of cultured mouse lymphoma cells treated with 4-hexylresorcinol in the presence of metabolic activation; reverse mutations were not induced at the histidine locus of frameshift or base-pair substitution strains of *Salmonella typhimurium* in either the presence or absence of metabolic activation. Further, the chemical did not induce chromosomal aberrations in cultured CHO cells in either the presence or absence of metabolic activation. Treatment of CHO cells in vitro with 4-hexylresorcinol did produce an increase in SCEs in one trial in the absence of metabolic activation at two doses, but the responses were weak.

A structural analog of 4-hexylresorcinol, olivetol (5-pentylresorcinol), has been shown to induce anaphase irregularities in cultured human lymphocytes, possibly by disrupting the assembly of the spindle apparatus (Morishima et al., 1976a,b).

Carcinogenicity of 4-Hexylresorcinol

There was no evidence of carcinogenicity in 4-hexylresorcinol-dosed rats. The only marginally increased pathologic lesions indicative of carcinogenic activity of 4-hexylresorcinol in rats were adenomas and adenomas or carcinomas (combined) of the anterior pituitary gland in female rats (see Table 10). The biologic importance of these results is questionable, since these tumors occur commonly with a relatively wide range of incidences in female F344/N rats (Appendix B, Table B4b). Two astrocytomas and an oligodendroglioma were observed in three high dose male rats, a glioma in one low dose male rat, and an oligodendroglioma in a vehicle control male rat. The incidence of glial cell tumors in brains of high dose male rats was not statistically significant compared with that in the vehicle controls. These neoplasms were detected by microscopic examinations only. Although these tumors are relatively uncommon in historical control male rats (Appendix A, Table A4b), the biologic importance and association of these neoplasms with 4-hexylresorcinol is not clear.

The possible chemically related neoplastic lesions observed in mice were pheochromocytomas of the adrenal medulla and tumors of the harderian gland, both in male mice. The incidence of harderian gland tumors in low dose male mice was statistically significant compared with that in vehicle controls. However, the biologic significance of this finding is lessened by the unusually low incidence in the vehicle control group, compared with that in historical controls (Table C4a). Pheochromocytomas of the adrenal medulla were considered to be possibly related to chemical administration because these neoplasms are relatively uncommon (2% in concurrent controls and 1% in historical controls, Table C4c), and the incidences in low dose (4%) and high dose (10%) male mice were supported by increased incidences of adrenal medullary hyperplasia in these groups.

The results from a previous carcinogenesis study of 4-hexylresorcinol administered by intravaginal instillation to BALB/c mice were also considered equivocal because a single vaginal squamous cell carcinoma was observed in 1/20 mice, and no tumors were seen in the concurrent control group (Boyland et al., 1966). Systemic exposure to phenolic compounds generally does not produce neoplasms in laboratory animals. The studies on structurally related chemicals (phenol administered in drinking water, NCI, 1980; *o*-phenylphenol applied dermally, NTP, 1986) did not show carcinogenicity in either rats or mice. Additionally, hexachlorophene administered in feed to rats was reported not to be carcinogenic (Huff, 1984; NCI, 1978). However, phenol and related compounds are reported to have dermal tumor-promoting activity in mice (Deichmann and Keplinger, 1981).

Decreased Incidences of Neoplasia

The inhibition of mononuclear cell leukemia was found to be dose related in both male and female rats (Table 21). These negative trends were statistically significant. The incidences of thyroid gland C-cell neoplasms in male rats occurred with a marginal negative trend. The incidences of pancreatic islet cell adenomas, fibromas of the mammary gland, and endometrial stromal polyps were also reduced.

TABLE 21. DECREASED INCIDENCES OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Overall rates of tumor reduced			
Male			
Mononuclear cell leukemia (a)	12/49 (24%)	7/50 (14%)	1/50 (2%)
Thyroid gland C-cell adenoma or carcinoma	13/49 (27%)	4/49 (8%)	7/48 (15%)
Pancreatic islet cell adenoma	5/46 (11%)	1/50 (2%)	2/49 (4%)
Female			
Mononuclear cell leukemia (a)	16/50 (32%)	3/50 (6%)	2/50 (4%)
Mammary gland fibroadenoma	15/50 (30%)	12/50 (24%)	8/50 (16%)
Endometrial stromal polyp	14/50 (28%)	11/50 (37%)	7/50 (14%)
Tumor summary for 4-hexylresorcinol 2-year study in male rats			
Total animals with benign tumors	43	44	43
Total benign tumors	102	83	110
Total animals with malignant tumors	20	19	9
Total malignant tumors	22	20	13
Tumor summary for 4-hexylresorcinol 2-year study in female rats			
Total animals with benign tumors	38	36	33
Total benign tumors	67	54	49
Total animals with malignant tumors	23	9	10
Total malignant tumors	25	11	11

(a) $P<0.05$

Decreased incidences of leukemia and mammary gland fibroadenomas have been observed in previous NTP studies in F344/N rats exposed to other chemicals. Mammary gland fibroadenomas in female rats were associated with decreases in body weight, and decreases in incidences of leukemia in both sexes were often associated with increases in liver tumor incidences (Haseman, 1983). The 4-hexylresorcinol-related decreases of the above tumor incidences in rats do not follow this pattern.

In mice, the incidences of hepatocellular neoplasms were reduced in both low and high dose groups, and incidences of hemangiomas and hemangiomas or hemangiosarcomas (combined) were reduced in high dose males and females (Table 22). The incidences of thyroid gland C-cell neoplasms and pancreatic islet cell neoplasms in male rats, mammary gland fibroadenomas in female rats, and hemangiomas or hemangiosarcomas (combined) in male mice are lower than concurrent vehicle control incidences but not much different from the historical control values. However, negative trends for tumors in a number of organs in rats and mice, along with some indications of reduced overall incidences of benign and malignant tumors and delays in the first observation of some tumors in dosed groups, suggest that 4-hexylresorcinol may have some antitumor properties that warrent further investigation. Furthermore, the negative trends occurred without changes in survival or body weights of 4-hexylresorcinol-dosed animals. The chemotherapeutic activity of 4-hexylresorcinol against bacteria, fungi, and parasites is well documented (Goodman et al., 1985), but its chemotherapeutic effect against tumor cells is not known. For these reasons, the NTP has initiated a project to investigate possible inhibiting effects of this chemical in a leukemia transplant model (Dieter et al., 1985, 1987).

TABLE 22. DECREASED INCIDENCES OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Overall rates of tumor reduced			
Male			
Hepatocellular adenoma or carcinoma (a)	21/50 (42%)	9/50 (18%)	9/50 (18%)
Hemangioma or hemangiosarcoma (a)	10/50 (20%)	4/50 (8%)	2/50 (4%)
Female			
Hemangioma or hemangiosarcoma	6/50 (12%)	2/49 (4%)	0/50 (0%)
Tumor summary for 4-hexylresorcinol 2-year study in male mice			
Total animals with benign tumors	21	13	15
Total benign tumors	29	13	19
Total animals with malignant tumors	22	29	21
Total malignant tumors	29	38	24
Tumor summary for 4-hexylresorcinol 2-year study in female mice			
Total animals with benign tumors	23	9	18
Total benign tumors	27	10	24
Total animals with malignant tumors	29	18	21
Total malignant tumors	34	20	23

(a) $P<0.05$

Data Audit

The experimental and tabulated data for the 4-hexylresorcinol studies were examined for accuracy, consistency, and compliance with Good Laboratory Practice requirements. As summarized in Appendix H, the audit revealed no problems with the conduct of the studies or with the collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of 4-hexylresorcinol for male or female F344/N rats given doses of 62.5 or 125 mg/kg. There was *equivocal evidence of carcinogenic activity* of 4-hexylresorcinol for male $B6C3F_1$ mice, as shown by marginally increased incidences of pheochromocytomas (and hyperplasia) of the adrenal medulla and of harderian gland neoplasms. There was *no evidence of carcinogenic activity* for female $B6C3F_1$ mice given doses of 62.5 or 125 mg/kg 4-hexylresorcinol. Decreased incidences of three tumor types were considered related to 4-hexylresorcinol administration: mononuclear cell leukemia in male and female rats, hepatocellular neoplasms in male mice, and circulatory system tumors in male and female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Papilloma, NOS	1 (2%)		
Sebaceous adenoma		1 (2%)	
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(49)	(50)	(50)
Sarcoma, NOS	2 (4%)	1 (2%)	
Fibroma	3 (6%)	3 (6%)	7 (14%)
Fibrosarcoma	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Adenoma, NOS	1 (2%)		1 (2%)
#Lung	(49)	(48)	(50)
Squamous cell carcinoma		1 (2%)	
Alveolar/bronchiolar adenoma	3 (6%)	3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma		3 (6%)	
C-cell carcinoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Leukemia, mononuclear cell	11 (22%)	7 (14%)	1 (2%)
#Spleen	(49)	(50)	(50)
Leukemia, mononuclear cell	1 (2%)		
#Thymus	(30)	(12)	(35)
Thymoma, benign			1 (3%)
CIRCULATORY SYSTEM			
#Spleen	(49)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Lung	(49)	(48)	(50)
Hemangiosarcoma, metastatic			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Neoplastic nodule		1 (2%)	1 (2%)
#Pancreas	(46)	(50)	(49)
Acinar cell adenoma	1 (2%)		1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Undifferentiated carcinoma			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(21)	(47)
Adenoma, NOS	25 (52%)	11 (52%)	22 (47%)
#Adrenal medulla	(48)	(50)	(49)
Pheochromocytoma	19 (40%)	18 (36%)	26 (53%)
Pheochromocytoma, malignant	2 (4%)	5 (10%)	4 (8%)
#Thyroid	(49)	(49)	(48)
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	12 (24%)	3 (6%)	7 (15%)
C-cell carcinoma	1 (2%)	1 (2%)	
#Pancreatic islets	(46)	(50)	(49)
Islet cell adenoma	5 (11%)	1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Fibroadenoma		2 (4%)	1 (2%)
*Preputial gland	(49)	(50)	(50)
Carcinoma, NOS			2 (4%)
Adenoma, NOS		4 (8%)	
#Testis	(49)	(45)	(50)
Interstitial cell tumor	31 (63%)	35 (78%)	39 (78%)
NERVOUS SYSTEM			
#Brain	(49)	(14)	(50)
Glioma, NOS		1 (7%)	
Astrocytoma			1 (2%)
Oligodendroglioma	1 (2%)		1 (2%)
#Cerebellum	(49)	(14)	(50)
Astrocytoma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(49)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	1 (2%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*Muscle hip/thigh	(49)	(50)	(50)
Sarcoma, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Tunica vaginalis	(49)	(50)	(50)
Mesothelioma, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Undifferentiated carcinoma, metastatic			1 (2%)
Sarcoma, NOS, metastatic	1 (2%)		
Hip			
Osteosarcoma			1

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	6	10
Moribund sacrifice	9	9	4
Terminal sacrifice	30	28	33
Dosing accident	2	7	3
TUMOR SUMMARY			
Total animals with primary tumors**	47	45	44
Total primary tumors	125	105	124
Total animals with benign tumors	43	44	43
Total benign tumors	102	83	110
Total animals with malignant tumors	20	19	9
Total malignant tumors	22	20	13
Total animals with secondary tumors##	2		2
Total secondary tumors	2		2
Total animals with tumors uncertain--benign or malignant	1	2	1
Total uncertain tumors	1	2	1

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: VEHICLE CONTROL

ANIMAL NUMBER	1 4 9	1 0 5	1 2 4	1 5 0	1 0 3	1 3 7	1 2 1	1 2 7	1 4 2	1 2 5	1 0 2	1 1 2	1 4 8	1 3 6	1 1 0	1 4 7	1 2 2	1 2 9	1 2 0	1 1 8	1 0 1	1 0 4	1 0 6	1 0 7	1 0 8
WEEKS ON STUDY	0 1 0	0 4 4	0 4 7	0 5 2	0 7 0	0 7 4	0 7 5	0 7 5	0 8 0	0 8 3	0 8 5	0 8 5	0 8 8	0 9 3	0 9 5	0 9 5	0 9 7	0 9 7	0 9 8	1 0 0	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Subcutaneous tissue	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS		X																							
Fibroma													X	X											
Fibrosarcoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
C-cell carcinoma, metastatic																									
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	A	+	−	+	+	+	−	+	−	−	+	+	+	+	+	−	−	+	−	+	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	A	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	A	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	A	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	A	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X		X		X		X	X		X	X		X	X			X			
Adrenal	+	+	A	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X		X				X					
Pheochromocytoma, malignant													X									X			
Thyroid	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma											X									X					
C-cell carcinoma																									
Parathyroid	+	+	A	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	A	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	A	+	N	+	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+
Testis	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor											X			X	X	X	X			X	X	X	X	X	X
Prostate	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma															X										
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	A	N	N	N	N	N	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS															X										
BODY CAVITIES																									
Mediastinum	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic																	X								
Leukemia, mononuclear cell					X		X		X										X	X					

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	109	111	113	114	115	116	117	119	123	126	128	130	131	132	133	134	135	138	139	140	141	143	144	145	146	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Papilloma, NOS						X																				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS																										2
Fibroma																			X							3
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma			X					X																		3
C-cell carcinoma, metastatic																		X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenoma, NOS																									X	1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	–	+	–	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	–	+	–	–	–	–	30
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Acinar cell adenoma																X										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X		X	X				X	X	X				X		X	X		X	X		X	X	X	X	25
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma		X	X	X	X		X	X		X	X	X	X			X	X		X		X	X			X	19
Pheochromocytoma, malignant																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																									X	1
C-cell adenoma		X	X			X					X	X		X	X					X		X	X		12
C-cell carcinoma																		X								1
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	–	+	–	+	+	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma						X			X	X				X						X						5
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X		X	X	X	X	X		31
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Oligodendroglioma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	*49
Carcinoma, NOS													X													1
Adenoma, NOS								X																		1
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Sarcoma, NOS																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Mesothelioma, NOS																				X						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell							X				X							X	X	X				X		11

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: LOW DOSE

ANIMAL NUMBER	0111	0139	0232	0422	0440	0365	0455	0088	0110	0099	0331	0288	0002	0155	0188	0200	0144	0133	0344	0499	0477	0001	0083	0004	0005
WEEKS ON STUDY	0007	0008	0112	0446	0665	0668	0669	0768	0776	0779	0800	0844	0899	0902	0966	0996	0998	1000	1011	1021	1033	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	N	N	N	N	N	N	N	N	N
Sebaceous adenoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																					X				
Fibroma																				X					
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Squamous cell carcinoma																			X						
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	+	–	–	–	–
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	+	–	–	–	–	–	–	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	+	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	–	–	–	–	–	+	–	–	+	–
Adenoma, NOS				X	X				X				X								X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X					X	X		X	X		X	
Pheochromocytoma, malignant																	X						X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	–	+	+	–	+	–	+	+	+	–	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																								X	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N
Fibroadenoma				X										X											
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+
Interstitial cell tumor						X			X	X	X	X			X	X		X	X	X		X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X														X	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Glioma, NOS						X																			
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell											X			X	X	X				X					X

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

ANIMAL NUMBER	006	007	012	016	017	019	021	023	024	025	026	027	029	030	033	035	037	038	041	042	043	044	046	048	050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	N	N	N	N	N	+	N	N	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sebaceous adenoma													X													1
Keratoacanthoma										X																1
Subcutaneous tissue	+	N	N	N	N	N	+	N	N	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Fibroma								X													X					3
Fibrosarcoma																					X					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma																										1
Alveolar/bronchiolar adenoma				X																		X			X	3
Alveolar/bronchiolar carcinoma											X						X									3
Trachea	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	15
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	12
CIRCULATORY SYSTEM																										
Heart	−	−	−	−	−	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	17
DIGESTIVE SYSTEM																										
Salivary gland	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	14
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule													X													1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
Stomach	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	14
Small intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
Large intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−		15
ENDOCRINE SYSTEM																										
Pituitary	−	+	−	+	−	−	−	−	−	−	−	+	+	+	−	−	−	+	−	−	−	−	−	−	+	21
Adenoma, NOS		X		X								X	X	X											X	11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X		X	X		X		X									X		X			X	X	X	X	18
Pheochromocytoma, malignant											X												X		X	5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma		X		X																X						3
C-cell carcinoma					X																					1
Parathyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	9
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibroadenoma																										2
Testis	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	45
Interstitial cell tumor	X	X	X		X	X	X	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X	35
Prostate	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	14
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS									X						X											4
NERVOUS SYSTEM																										
Brain	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	14
Glioma, NOS																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*50
Adenoma, NOS																			X							1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																			X							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell							X																			7

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: HIGH DOSE

ANIMAL NUMBER	083	080	091	097	060	054	098	073	061	078	056	067	071	094	082	099	089	051	052	053	055	057	058	059	062
WEEKS ON STUDY	004	008	011	038	054	072	073	076	078	083	093	093	097	097	098	098	103	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Fibroma											X		X						X		X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Hemangiosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	–	+	–	–	–	+	+	–	+
Thymoma, benign						X																			
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule													X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma																		X							
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X		X		X				X		X	X	X	X	X		X
Adrenal	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma									X	X	X	X	X	X	X		X	X				X		X	X
Pheochromocytoma, malignant												X													
Thyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																		X			X		X	X	
Parathyroid	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma															X			X							
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor						X				X	X	X	X	X	X	X		X	X	X	X	X		X	X
Prostate	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma										X										X					
Oligodendroglioma				X																					
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Undifferentiated carcinoma, metastatic																		X							
Leukemia, mononuclear cell																		X							
Hip, NOS																									
Osteosarcoma																									

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

ANIMAL NUMBER	063	064	065	066	068	069	070	072	074	075	076	077	079	081	084	085	086	087	088	090	092	093	095	096	100	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma											X								X		X					7
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X							X													2
Hemangiosarcoma, metastatic	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS	X																									1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	−	−	−	+	−	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	35
Thymoma, benign																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma																			X							1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Undifferentiated carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	47
Adenoma, NOS			X	X	X	X	X								X			X	X		X	X	X	X		22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma	X		X			X		X	X		X		X		X	X			X	X		X	X		X	26
Pheochromocytoma, malignant	X			X																	X					4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma	X																				X	X				7
Parathyroid	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma							X																			1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	39
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X																		X					2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										2
Oligodendroglioma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Undiff. carcinoma, metastatic																										1
Leukemia, mononuclear cell																										1
Hip, NOS																										
Osteosarcoma	X																									1

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/49 (6%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	8.4%	9.9%	19.4%
Terminal Rates (c)	1/30 (3%)	2/29 (7%)	5/33 (15%)
Week of First Observation	88	102	93
Life Table Tests (d)	P=0.144	P=0.652	P=0.203
Incidental Tumor Tests (d)	P=0.098	P=0.654	P=0.124
Cochran-Armitage Trend Test (d)	P=0.112		
Fisher Exact Test (d)		P=0.651N	P=0.167
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/49 (8%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	11.6%	9.9%	19.4%
Terminal Rates (c)	2/30 (7%)	2/29 (7%)	5/33 (15%)
Week of First Observation	88	102	93
Life Table Tests (d)	P=0.246	P=0.510N	P=0.319
Incidental Tumor Tests (d)	P=0.186	P=0.510N	P=0.223
Cochran-Armitage Trend Test (d)	P=0.204		
Fisher Exact Test (d)		P=0.489N	P=0.274
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	6/49 (12%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	15.9%	12.9%	19.4%
Terminal Rates (c)	2/30 (7%)	2/29 (7%)	5/33 (15%)
Week of First Observation	44	102	93
Life Table Tests (d)	P=0.500	P=0.385N	P=0.559
Incidental Tumor Tests (d)	P=0.439	P=0.359N	P=0.477
Cochran-Armitage Trend Test (d)	P=0.451		
Fisher Exact Test (d)		P=0.357N	P=0.516
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/49 (6%)	3/48 (6%)	2/50 (4%)
Adjusted Rates (b)	9.4%	10.7%	6.1%
Terminal Rates (c)	2/30 (7%)	3/28 (11%)	2/33 (6%)
Week of First Observation	97	104	104
Life Table Tests (d)	P=0.368N	P=0.636	P=0.455N
Incidental Tumor Tests (d)	P=0.374N	P=0.624	P=0.465N
Cochran-Armitage Trend Test (d)	P=0.403N		
Fisher Exact Test (d)		P=0.651	P=0.490N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/49 (0%)	3/48 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	10.7%	0.0%
Terminal Rates (c)	0/30 (0%)	3/28 (11%)	0/33 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.611N	P=0.108	(e)
Incidental Tumor Tests (d)	P=0.611N	P=0.108	(e)
Cochran-Armitage Trend Test (d)	P=0.633N		
Fisher Exact Test (d)		P=0.117	(e)
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	6/48 (13%)	2/50 (4%)
Adjusted Rates (b)	9.4%	21.4%	6.1%
Terminal Rates (c)	2/30 (7%)	6/28 (21%)	2/33 (6%)
Week of First Observation	97	104	104
Life Table Tests (d)	P=0.371N	P=0.211	P=0.455N
Incidental Tumor Tests (d)	P=0.376N	P=0.203	P=0.465N
Cochran-Armitage Trend Test (d)	P=0.413N		
Fisher Exact Test (d)		P=0.233	P=0.490N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	12/49 (24%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	32.9%	19.3%	3.0%
Terminal Rates (c)	7/30 (23%)	2/29 (7%)	1/33 (3%)
Week of First Observation	70	80	104
Life Table Tests (d)	P=0.001N	P=0.178N	P=0.001N
Incidental Tumor Tests (d)	P=0.001N	P=0.149N	P=0.002N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.142N	P=0.001N
Pituitary Gland: Adenoma			
Overall Rates (a)	25/48 (52%)	(f) 11/21 (52%)	22/47 (47%)
Adjusted Rates (b)	63.3%		62.3%
Terminal Rates (c)	16/30 (53%)		18/31 (58%)
Week of First Observation	74		78
Life Table Test (d)			P=0.295N
Incidental Tumor Test (d)			P=0.509N
Fisher Exact Test (d)			P=0.379N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	19/48 (40%)	18/50 (36%)	26/49 (53%)
Adjusted Rates (b)	57.3%	54.3%	63.2%
Terminal Rates (c)	16/30 (53%)	14/29 (48%)	18/33 (55%)
Week of First Observation	93	89	78
Life Table Tests (d)	P=0.188	P=0.535N	P=0.222
Incidental Tumor Tests (d)	P=0.116	P=0.536N	P=0.144
Cochran-Armitage Trend Test (d)	P=0.106		
Fisher Exact Test (d)		P=0.437N	P=0.130
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	2/48 (4%)	5/50 (10%)	4/49 (8%)
Adjusted Rates (b)	5.9%	16.3%	11.4%
Terminal Rates (c)	1/30 (3%)	4/29 (14%)	3/33 (9%)
Week of First Observation	88	98	93
Life Table Tests (d)	P=0.332	P=0.213	P=0.378
Incidental Tumor Tests (d)	P=0.276	P=0.222	P=0.273
Cochran-Armitage Trend Test (d)	P=0.291		
Fisher Exact Test (d)		P=0.235	P=0.348
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	21/48 (44%)	21/50 (42%)	27/49 (55%)
Adjusted Rates (b)	61.4%	61.5%	65.7%
Terminal Rates (c)	17/30 (57%)	16/29 (55%)	19/33 (58%)
Week of First Observation	88	89	78
Life Table Tests (d)	P=0.261	P=0.546	P=0.294
Incidental Tumor Tests (d)	P=0.154	P=0.559	P=0.170
Cochran-Armitage Trend Test (d)	P=0.153		
Fisher Exact Test (d)		P=0.512N	P=0.180
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	12/49 (24%)	3/49 (6%)	7/48 (15%)
Adjusted Rates (b)	37.1%	10.3%	21.2%
Terminal Rates (c)	10/30 (33%)	3/29 (10%)	7/33 (21%)
Week of First Observation	85	104	104
Life Table Tests (d)	P=0.069N	P=0.013N	P=0.102N
Incidental Tumor Tests (d)	P=0.087N	P=0.014N	P=0.145N
Cochran-Armitage Trend Test (d)	P=0.109N		
Fisher Exact Test (d)		P=0.011N	P=0.165N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	13/49 (27%)	4/49 (8%)	7/48 (15%)
Adjusted Rates (b)	40.2%	13.8%	21.2%
Terminal Rates (c)	11/30 (37%)	4/29 (14%)	7/33 (21%)
Week of First Observation	85	104	104
Life Table Tests (d)	P=0.041N	P=0.017N	P=0.064N
Incidental Tumor Tests (d)	P=0.053N	P=0.018N	P=0.094N
Cochran-Armitage Trend Test (d)	P=0.072N		
Fisher Exact Test (d)		P=0.016N	P=0.115N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	5/46 (11%)	1/50 (2%)	2/49 (4%)
Adjusted Rates (b)	16.7%	3.4%	5.7%
Terminal Rates (c)	5/30 (17%)	1/29 (3%)	1/33 (3%)
Week of First Observation	104	104	98
Life Table Tests (d)	P=0.111N	P=0.108N	P=0.179N
Incidental Tumor Tests (d)	P=0.118N	P=0.108N	P=0.193N
Cochran-Armitage Trend Test (d)	P=0.115N		
Fisher Exact Test (d)		P=0.084N	P=0.192N
Preputial Gland: Adenoma			
Overall Rates (a)	0/49 (0%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	0.0%	12.5%	0.0%
Terminal Rates (c)	0/30 (0%)	3/29 (10%)	0/33 (0%)
Week of First Observation		79	
Life Table Tests (d)	P=0.599N	P=0.060	(e)
Incidental Tumor Tests (d)	P=0.560	P=0.061	(e)
Cochran-Armitage Trend Test (d)	P=0.616N		
Fisher Exact Test (d)		P=0.061	(e)
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	0/49 (0%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	0.0%	12.5%	6.1%
Terminal Rates (c)	0/30 (0%)	3/29 (10%)	2/33 (6%)
Week of First Observation		79	104
Life Table Tests (d)	P=0.249	P=0.060	P=0.259
Incidental Tumor Tests (d)	P=0.188	P=0.061	P=0.259
Cochran-Armitage Trend Test (d)	P=0.228		
Fisher Exact Test (d)		P=0.061	P=0.253
Testis: Interstitial Cell Tumor			
Overall Rates (a)	31/49 (63%)	35/45 (78%)	39/50 (78%)
Adjusted Rates (b)	86.0%	97.1%	95.1%
Terminal Rates (c)	25/30 (83%)	25/26 (96%)	31/33 (94%)
Week of First Observation	85	68	72
Life Table Tests (d)	P=0.178	P=0.080	P=0.196
Incidental Tumor Tests (d)	P=0.021	P=0.015	P=0.045
Cochran-Armitage Trend Test (d)	P=0.063		
Fisher Exact Test (d)		P=0.094	P=0.082
Brain: All Glial Cell Tumors (g)			
Overall Rates (a)	1/49 (2%)	(f) 1/14 (7%)	3/50 (6%)
Adjusted Rates (b)	2.8%		7.4%
Terminal Rates (c)	0/30 (0%)		1/33 (3%)
Week of First Observation	95		38
Life Table Test (d)			P=0.318
Incidental Tumor Test (d)			P=0.216
Fisher Exact Test (d)			P=0.316

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	43/49 (88%)	44/50 (88%)	43/50 (86%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	30/30 (100%)	29/29 (100%)	33/33 (100%)
Week of First Observation	74	46	72
Life Table Tests (d)	P=0.262N	P=0.427	P=0.287N
Incidental Tumor Tests (d)	P=0.589	P=0.449	P=0.695N
Cochran-Armitage Trend Test (d)	P=0.455N		
Fisher Exact Test (d)		P=0.606	P=0.516N
All Sites: Malignant Tumors			
Overall Rates (a)	20/49 (41%)	19/50 (38%)	9/50 (18%)
Adjusted Rates (b)	50.1%	49.5%	23.8%
Terminal Rates (c)	11/30 (37%)	10/29 (34%)	6/33 (18%)
Week of First Observation	44	68	38
Life Table Tests (d)	P=0.012N	P=0.520N	P=0.013N
Incidental Tumor Tests (d)	P=0.015N	P=0.490N	P=0.020N
Cochran-Armitage Trend Test (d)	P=0.010N		
Fisher Exact Test (d)		P=0.468N	P=0.011N
All Sites: All Tumors			
Overall Rates (a)	47/49 (96%)	45/50 (90%)	44/50 (88%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	30/30 (100%)	29/29 (100%)	33/33 (100%)
Week of First Observation	44	46	38
Life Table Tests (d)	P=0.127N	P=0.502N	P=0.144N
Incidental Tumor Tests (d)	P=0.105N	P=0.281N	P=0.160N
Cochran-Armitage Trend Test (d)	P=0.112N		
Fisher Exact Test (d)		P=0.227N	P=0.141N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 125 mg/kg and vehicle control groups.
(f) Incomplete sampling of tissues
(g) Includes one oligodendroglioma in the vehicle controls, one glioma, NOS, in the low dose, and one oligodendroglioma and two astrocytomas in the high dose group

TABLE A4a. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls	
	Leukemia	Lymphoma or Leukemia
No 2-year studies by Physiological Research Laboratories are included in the historical data base.		
Overall Historical Incidence		
TOTAL	202/1,450 (13.9%)	213/1,450 (14.7%)
SD (b)	7.55%	7.62%
Range (c)		
High	14/50	14/50
Low	1/50	1/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF BRAIN GLIAL CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. Examined	No. Tumors	Diagnosis
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
		2	Glioma, NOS
		14	Astrocytoma
TOTAL	1,446	16 (1.1%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks. No more than two glial cell tumors have been observed in any vehicle control group

TABLE A4c. HISTORICAL INCIDENCE OF THYROID GLAND C-CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	125/1,417 (88%)	59/1,417 (4.2%)	181/1,417 (12.8%)
SD (b)	5.55%	3.24%	6.36%
Range (c)			
High	10/49	6/50	12/49
Low	0/50	0/50	2/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Epidermal inclusion cyst	3 (6%)	4 (8%)	1 (2%)
Hyperkeratosis	1 (2%)		
*Subcutaneous tissue	(49)	(50)	(50)
Inflammation, chronic		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Inflammation, active chronic	4 (8%)		7 (14%)
Inflammation, chronic	1 (2%)		
Foreign material, NOS			1 (2%)
Hyperplasia, focal			1 (2%)
Polyp, inflammatory			1 (2%)
#Lung/bronchiole	(49)	(48)	(50)
Fibrosis			2 (4%)
#Lung	(49)	(48)	(50)
Mineralization		1 (2%)	
Emphysema, NOS			1 (2%)
Congestion, NOS	6 (12%)	1 (2%)	7 (14%)
Edema, NOS	6 (12%)	4 (8%)	8 (16%)
Hemorrhage	2 (4%)		
Pneumonia, aspiration		1 (2%)	
Inflammation, acute			1 (2%)
Inflammation, chronic	2 (4%)	2 (4%)	4 (8%)
Granuloma, NOS	1 (2%)		1 (2%)
Perivascular cuffing	4 (8%)	2 (4%)	7 (14%)
Alveolar macrophages	4 (8%)	4 (8%)	11 (22%)
Hyperplasia, adenomatous	1 (2%)	2 (4%)	2 (4%)
Metaplasia, osseous	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(13)	(50)
Atrophy, NOS	2 (4%)		
Hyperplasia, NOS	13 (27%)	1 (8%)	7 (14%)
Myelofibrosis	1 (2%)		
#Spleen	(49)	(50)	(50)
Ectopia	2 (4%)	1 (2%)	
Fibrosis	4 (8%)	4 (8%)	1 (2%)
Hemosiderosis	2 (4%)	1 (2%)	1 (2%)
Hematopoiesis	4 (8%)	2 (4%)	2 (4%)
#Splenic capsule	(49)	(50)	(50)
Fibrosis		1 (2%)	
#Lymph node	(49)	(15)	(49)
Hemorrhage		1 (7%)	
Necrosis, NOS		1 (7%)	
#Mandibular lymph node	(49)	(15)	(49)
Hemorrhage		1 (7%)	1 (2%)
#Mesenteric lymph node	(49)	(15)	(49)
Hemorrhage	1 (2%)	1 (7%)	
Inflammation, acute	1 (2%)		
#Thymus	(30)	(12)	(35)
Cyst, NOS			1 (3%)
Congestion, NOS			1 (3%)
Hemorrhage	2 (7%)		2 (6%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Lymph node	(49)	(15)	(49)
Lymphangiectasis		1 (7%)	
*Nasal cavity	(49)	(50)	(50)
Thrombus, fibrin	1 (2%)		
#Heart	(49)	(17)	(50)
Thrombus, fibrin	1 (2%)		
Fibrosis		1 (6%)	
#Right atrium	(49)	(17)	(50)
Mineralization			1 (2%)
#Left atrium	(49)	(17)	(50)
Mineralization			1 (2%)
Thrombus, organized			1 (2%)
#Myocardium	(49)	(17)	(50)
Inflammation, chronic	7 (14%)	7 (41%)	7 (14%)
Fibrosis	47 (96%)	13 (76%)	47 (94%)
Degeneration, NOS	5 (10%)	3 (18%)	8 (16%)
#Endocardium	(49)	(17)	(50)
Fibrosis	1 (2%)		
*Artery	(49)	(50)	(50)
Mineralization	1 (2%)		
Periarteritis		1 (2%)	1 (2%)
Necrosis, fibrinoid		1 (2%)	
*Aorta	(49)	(50)	(50)
Mineralization			1 (2%)
*Pulmonary artery	(49)	(50)	(50)
Mineralization	2 (4%)	1 (2%)	3 (6%)
*Testicular artery	(49)	(50)	(50)
Inflammation, fibrinoid	1 (2%)		
#Liver	(49)	(50)	(50)
Thrombus, fibrin	1 (2%)		
#Pancreas	(46)	(50)	(49)
Perivasculitis			1 (2%)
#Duodenum	(47)	(13)	(50)
Lymphangiectasis			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(49)	(50)	(50)
Hemorrhage		1 (2%)	
#Salivary gland	(48)	(14)	(49)
Multiple cysts			1 (2%)
Inflammation, chronic	3 (6%)	1 (7%)	
Atrophy, NOS	6 (13%)	1 (7%)	3 (6%)
Hyperplasia, focal			1 (2%)
#Submaxillary duct	(48)	(14)	(49)
Dysplasia, epithelial	18 (38%)		24 (49%)
#Liver	(49)	(50)	(50)
Mineralization		1 (2%)	
Hernia, NOS	1 (2%)	1 (2%)	4 (8%)
Congestion, NOS	1 (2%)		2 (4%)
Granuloma, NOS	10 (20%)	9 (18%)	4 (8%)
Necrosis, NOS	1 (2%)		
Necrosis, coagulative	1 (2%)	3 (6%)	
Metamorphosis, fatty	24 (49%)	24 (48%)	26 (52%)
Cytoplasmic change, NOS	3 (6%)	1 (2%)	1 (2%)
Cytoplasmic vacuolization	9 (18%)	5 (10%)	10 (20%)
Basophilic cyto change	29 (59%)	33 (66%)	35 (70%)
Clear cell change	15 (31%)	20 (40%)	19 (38%)
Angiectasis	5 (10%)	2 (4%)	1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Periportal bile duct	(49)	(50)	(50)
Hyperplasia, NOS	43 (88%)	43 (86%)	43 (86%)
#Liver/centrilobular	(49)	(50)	(50)
Congestion, NOS		1 (2%)	
Necrosis, NOS		2 (4%)	1 (2%)
Metamorphosis, fatty	1 (2%)	1 (2%)	2 (4%)
Cytoplasmic vacuolization		1 (2%)	1 (2%)
Angiectasis		1 (2%)	
#Pancreas	(46)	(50)	(49)
Ectopia	2 (4%)		
Fibrosis	1 (2%)		
#Pancreatic acinus	(46)	(50)	(49)
Atrophy, NOS	7 (15%)	9 (18%)	10 (20%)
Hyperplasia, focal		1 (2%)	1 (2%)
#Esophagus	(49)	(13)	(49)
Hyperkeratosis	2 (4%)		1 (2%)
#Glandular stomach	(49)	(14)	(49)
Multiple cysts	25 (51%)	4 (29%)	26 (53%)
#Forestomach	(49)	(14)	(49)
Edema, NOS		1 (7%)	
Ulcer, NOS	1 (2%)	1 (7%)	
Inflammation, acute		1 (7%)	
Inflammation, active chronic	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)	1 (7%)	2 (4%)
Necrosis, NOS	1 (2%)		
Hyperplasia, epithelial	5 (10%)	1 (7%)	2 (4%)
Hyperkeratosis		1 (7%)	
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Cyst, NOS		2 (4%)	
Pyelonephritis, NOS		1 (2%)	
Pyelonephritis, acute	1 (2%)		
Nephropathy	47 (96%)	48 (96%)	45 (90%)
Hyperplasia, tubular cell		1 (2%)	
#Kidney/tubule	(49)	(50)	(50)
Metamorphosis, fatty	1 (2%)		1 (2%)
Cytoplasmic vacuolization		2 (4%)	
#Urinary bladder	(47)	(15)	(48)
Hemorrhage	1 (2%)		
Polyp, inflammatory		1 (7%)	
#Urinary bladder/mucosa	(47)	(15)	(48)
Inflammation, acute necrotizing	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(21)	(47)
Angiectasis	1 (2%)		
#Anterior pituitary	(48)	(21)	(47)
Cyst, NOS	4 (8%)	2 (10%)	4 (9%)
Hemorrhage	1 (2%)		
Hyperplasia, focal	12 (25%)	7 (33%)	11 (23%)
Angiectasis	1 (2%)		2 (4%)
#Pituitary posterior	(48)	(21)	(47)
Embryonal rest	1 (2%)		
Multiple cysts	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(48)	(50)	(49)
Degeneration, hyaline			1 (2%)
Necrosis, coagulative	1 (2%)		
Metamorphosis, fatty	20 (42%)	16 (32%)	9 (18%)
Hyperplasia, focal	23 (48%)	11 (22%)	18 (37%)
Angiectasis	14 (29%)	8 (16%)	16 (33%)
#Adrenal medulla	(48)	(50)	(49)
Cytomegaly			1 (2%)
Hyperplasia, focal	5 (10%)	6 (12%)	7 (14%)
#Thyroid	(49)	(49)	(48)
Hyperplasia, C-cell	14 (29%)	20 (41%)	17 (35%)
Hyperplasia, follicular cell			1 (2%)
#Pancreatic islets	(46)	(50)	(49)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Galactocele			1 (2%)
Hyperplasia, cystic	19 (39%)	1 (2%)	13 (26%)
*Preputial gland	(49)	(50)	(50)
Distention		1 (2%)	
Abscess, NOS		1 (2%)	
Inflammation, active chronic			1 (2%)
Inflammation, chronic			1 (2%)
Atrophy, NOS	24 (49%)	4 (8%)	36 (72%)
#Prostate	(49)	(14)	(49)
Inflammation, active chronic	33 (67%)	9 (64%)	29 (59%)
Inflammation, chronic	2 (4%)		1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)	2 (14%)	2 (4%)
Hyperplasia, focal			1 (2%)
#Testis	(49)	(45)	(50)
Atrophy, NOS	11 (22%)	15 (33%)	15 (30%)
Hyperplasia, interstitial cell	41 (84%)	33 (73%)	40 (80%)
#Spermia	(49)	(45)	(50)
Degeneration, NOS	15 (31%)	1 (2%)	14 (28%)
#Interstitial cell of Leydig	(49)	(45)	(50)
Hypertrophy, NOS			1 (2%)
*Epididymis	(49)	(50)	(50)
Degeneration, NOS	13 (27%)	2 (4%)	14 (28%)
NERVOUS SYSTEM			
#Brain	(49)	(14)	(50)
Hydrocephalus, NOS			2 (4%)
Hemorrhage		1 (7%)	1 (2%)
Gliosis			1 (2%)
#Cerebellum	(49)	(14)	(50)
Abscess, NOS	1 (2%)		
Necrosis, NOS	1 (2%)		
*Spinal cord	(49)	(50)	(50)
Hemorrhage	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(49)	(50)	(50)
Hemorrhage	4 (8%)	8 (16%)	9 (18%)
*Cornea, substantia propria	(49)	(50)	(50)
Vascularization			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS (Continued)			
*Eye/retina	(49)	(50)	(50)
Atrophy, NOS	33 (67%)	42 (84%)	36 (72%)
*Eye/lens, cortex	(49)	(50)	(50)
Cataract	42 (86%)	45 (90%)	40 (80%)
MUSCULOSKELETAL SYSTEM			
*Fascia	(49)	(50)	(50)
Hemorrhage		1 (2%)	
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Granuloma, NOS			1 (2%)
*Mesentery	(49)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Atrophy, NOS	7 (14%)		3 (6%)
Adipose tissue			
Hemorrhage		1	
Necrosis, fat	8	4	1
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy	1		

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
Keratoacanthoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
Fibroma	1 (2%)	2 (4%)	2 (4%)
Fibrosarcoma	1 (2%)		
Myxosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
Follicular cell carcinoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, histiocytic type			1 (2%)
Leukemia, mononuclear cell	16 (32%)	3 (6%)	2 (4%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)		1 (2%)
#Pancreas	(50)	(14)	(50)
Acinar cell adenoma	1 (2%)		
#Cecum	(50)	(14)	(50)
Lipoma			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(50)
Carcinoma, NOS			2 (4%)
Adenoma, NOS	21 (42%)	22 (44%)	22 (44%)
#Adrenal	(50)	(14)	(50)
Cortical adenoma	1 (2%)	1 (7%)	
#Adrenal medulla	(50)	(14)	(50)
Pheochromocytoma	5 (10%)		3 (6%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(50)	(16)	(50)
Follicular cell adenoma	1 (2%)		1 (2%)
Follicular cell carcinoma		1 (6%)	1 (2%)
C-cell adenoma	6 (12%)	1 (6%)	2 (4%)
C-cell carcinoma		1 (6%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	15 (30%)	12 (24%)	8 (16%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	3 (6%)	1 (2%)	3 (6%)
Adenoma, NOS	1 (2%)	3 (6%)	2 (4%)
#Uterus	(50)	(30)	(50)
Papillary carcinoma	1 (2%)		
Endometrial stromal polyp	14 (28%)	11 (37%)	7 (14%)
Endometrial stromal sarcoma		3 (10%)	
#Ovary	(50)	(18)	(50)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(15)	(50)
Granular cell tumor, NOS			1 (2%)
#Brain	(50)	(15)	(50)
Granular cell tumor, NOS	1 (2%)		
Oligodendroglioma			1 (2%)
Meningioma		1 (7%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	7	3
Moribund sacrifice	17	9	8
Terminal sacrifice	28	32	30
Dosing accident	1	2	9

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	44	39	35
Total primary tumors	95	65	62
Total animals with benign tumors	38	36	33
Total benign tumors	67	54	49
Total animals with malignant tumors	23	9	10
Total malignant tumors	25	11	11
Total animals with secondary tumors##		1	
Total secondary tumors		1	
Total animals with tumors uncertain--benign or malignant	3		2
Total uncertain tumors	3		2

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: VEHICLE CONTROL

ANIMAL NUMBER	1 4 3	1 2 4	1 1 1	1 0 2	1 4 0	1 4 2	1 4 1	1 4 5	1 1 0	1 0 3	1 1 4	1 3 4	1 3 5	1 0 9	1 0 7	1 1 5	1 3 2	1 2 2	1 4 9	1 3 6	1 0 4	1 4 8	1 0 1	1 0 5	1 0 6
WEEKS ON STUDY	0 1 0	0 2 8	0 5 2	0 6 6	0 7 5	0 7 9	0 8 1	0 8 5	0 8 6	0 8 8	0 8 8	0 9 0	0 9 0	0 9 3	0 9 4	0 9 6	0 9 6	0 9 7	1 0 1	1 0 2	1 0 3	1 0 3	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma												X													
Myxosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	–	+	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule													X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																								X	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X		X		X		X	X	X		X		X	X		X	X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma													X									X			
Pheochromocytoma, malignant					X																				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																X									
Parathyroid	+	–	+	–	–	–	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	–	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																			X						
Fibroadenoma				X								X	X					X		X	X	X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary carcinoma																									
Endometrial stromal polyp				X		X		X	X						X		X		X				X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS			X																						
Leukemia, mononuclear cell						X	X		X	X	X				X		X			X					

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
No tissue information submitted
C: Necropsy, no histology due to protocol
A Autolysis
M: Animal missing
B· No necropsy performed

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

ANIMAL NUMBER	108	112	113	116	117	118	119	120	121	123	125	126	127	128	129	130	131	133	137	138	139	144	146	147	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X																				1
Fibrosarcoma																										1
Myxosarcoma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	−	+	+	−	+	+	+	−	+	+	−	+	+	−	+	−	+	−	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X							X		X				X		X		X			X			X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma											X															1
Pheochromocytoma						X														X		X				5
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma												X														1
C-cell adenoma	X	X						X											X	X						6
Parathyroid	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma		X	X								X		X	X	X		X		X							15
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X												X										X	3
Adenoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary carcinoma																								X		1
Endometrial stromal polyp			X				X						X				X	X						X		14
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																X										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Leukemia, mononuclear cell		X	X					X	X	X						X		X		X						16

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: LOW DOSE

ANIMAL NUMBER	0161	0339	0330	0006	0004	0144	0288	0333	0188	0133	0443	0444	0177	0002	0191	0331	0550	0255	0011	0003	0005	0007	0008	0009	0110
WEEKS ON STUDY	0006	0007	0114	0244	0500	0500	0511	0511	0558	0779	0885	0885	0886	0900	0900	0999	0999	0999	1003	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	+	N	N	+	N	N
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	+	N	N	+	N	N
Fibroma									X				X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma, metastatic																					X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	–	+	+	+	+	+	+	–	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X			X	X		X			X	X		X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Cortical adenoma											X														
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	+	–	–	–	+
Follicular cell carcinoma																					X				
C cell adenoma													X												
C cell carcinoma																									X
Parathyroid	+	+	+	–	+	–	+	–	+	+	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	N	N	+	+	+	N	N
Fibroadenoma										X						X		X			X	X	X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																				X					
Adenoma, NOS																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	+	–	–	+	+	–
Endometrial stromal polyp														X						X			X		
Endometrial stromal sarcoma											X	X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	+	–	–
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	+
Meningioma																									X
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X																				

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

ANIMAL NUMBER	011	012	015	020	021	022	023	024	026	027	029	032	034	035	036	037	038	040	041	042	045	046	047	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																	X									1
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Fibroma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	15
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Esopagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X			X	X	X			X	X	X			X		X		X	X	X				X	X	22
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Cortical adenoma																										1
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	16
Follicular cell carcinoma																										1
C-cell adenoma																										1
C-cell carcinoma																										1
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	N	+	N	+	N	N	N	+	+	N	N	N	N	N	+	N	+	N	N	N	*50
Fibroadenoma	X						X		X				X							X		X				12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS																			X		X					3
Uterus	+	–	–	–	+	+	+	+	–	–	–	+	+	–	+	+	+	+	–	+	–	–	+	–	–	30
Endometrial stromal polyp					X	X	X					X	X				X	X					X			11
Endometrial stromal sarcoma																				X						3
Ovary	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	18
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Meningioma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS								X																		1
Adenoma, NOS															X											1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell								X			X															3

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: HIGH DOSE

ANIMAL NUMBER	0 8 0	0 9 6	0 8 3	0 5 6	0 6 8	0 7 4	0 6 1	0 9 8	0 9 5	0 7 9	1 0 0	0 5 1	0 8 6	0 7 3	0 6 4	0 7 1	0 5 5	0 7 5	0 8 9	0 6 0	0 5 2	0 5 3	0 5 4	0 5 7	0 5 8
WEEKS ON STUDY	0 0 1	0 0 3	0 0 7	0 1 2	0 1 2	0 1 2	0 1 4	0 1 5	0 1 6	0 2 2	0 2 4	0 3 6	0 3 7	0 3 9	0 7 2	0 7 6	0 9 0	0 9 4	0 9 7	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																				X					
Fibroma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																X		X	X		X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Follicular cell carcinoma																									
C cell adenoma																									
Parathyroid	+	−	−	+	+	+	+	+	+	+	+	−	+	−	+	+	−	−	+	−	+	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma															X					X					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																	X								
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp															X								X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																	X								
Oligodendroglioma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type																		X	X						
Leukemia, mononuclear cell																									

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

ANIMAL NUMBER	059	061	062	063	065	066	067	069	070	072	076	077	078	082	084	085	087	088	090	091	092	093	094	097	099	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma																									X	2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	−	+	+	+	+	−	−	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule								X																		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma															X											1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS												X				X										2
Adenoma, NOS	X	X	X	X		X	X			X	X		X		X		X	X	X	X	X			X		22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X																		X						3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Follicular cell carcinoma																							X			1
C-cell adenoma												X												X		2
Parathyroid	+	+	+	+	+	+	+	−	+	−	−	+	−	+	+	−	−	+	−	+	+	+	−	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma			X					X						X	X	X				X						8
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X		X															3
Adenoma, NOS																				X					X	2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp					X					X	X	X					X									7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										1
Oligodendroglioma																X										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, histiocytic type	X																									1
Leukemia, mononuclear cell																										2

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	6.0%	4.9%	9.2%
Terminal Rates (c)	1/28 (4%)	0/32 (0%)	1/30 (3%)
Week of First Observation	90	58	90
Life Table Tests (d)	P=0.371	P=0.680	P=0.488
Incidental Tumor Tests (d)	P=0.120	P=0.592	P=0.141
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.691	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	16/50 (32%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	42.1%	8.3%	6.1%
Terminal Rates (c)	8/28 (29%)	2/32 (6%)	0/30 (0%)
Week of First Observation	79	50	94
Life Table Tests (d)	P<0.001N	P=0.001N	P=0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.002N	P=0.016N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.001N	P<0.001N
Pituitary Gland: Adenoma			
Overall Rates (a)	21/50 (42%)	22/50 (44%)	22/50 (44%)
Adjusted Rates (b)	52.9%	60.8%	66.5%
Terminal Rates (c)	10/28 (36%)	18/32 (56%)	19/30 (63%)
Week of First Observation	79	85	76
Life Table Tests (d)	P=0.487	P=0.518N	P=0.515
Incidental Tumor Tests (d)	P=0.062	P=0.273	P=0.057
Cochran-Armitage Trend Test (d)	P=0.460		
Fisher Exact Test (d)		P=0.500	P=0.500
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	21/50 (42%)	22/50 (44%)	24/50 (48%)
Adjusted Rates (b)	52.9%	60.8%	72.6%
Terminal Rates (c)	10/28 (36%)	18/32 (56%)	21/30 (70%)
Week of First Observation	79	85	76
Life Table Tests (d)	P=0.339	P=0.518N	P=0.373
Incidental Tumor Tests (d)	P=0.023	P=0.273	P=0.021
Cochran-Armitage Trend Test (d)	P=0.308		
Fisher Exact Test (d)		P=0.500	P=0.344
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	(e) 0/14 (0%)	3/50 (6%)
Adjusted Rates (b)	15.9%		10.0%
Terminal Rates (c)	3/28 (11%)		3/30 (10%)
Week of First Observation	90		104
Life Table Test (d)			P=0.338N
Incidental Tumor Test (d)			P=0.511N
Fisher Exact Test (d)			P=0.358N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	6/50 (12%)	(e) 0/14 (0%)	3/50 (6%)
Adjusted Rates (b)	17.7%		10.0%
Terminal Rates (c)	3/28 (11%)		3/30 (10%)
Week of First Observation	75		104
Life Table Test (d)			P=0.245N
Incidental Tumor Test (d)			P=0.368N
Fisher Exact Test (d)			P=0.244N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/50 (12%)	(e,f) 1/16 (6%)	2/50 (4%)
Adjusted Rates (b)	20.2%		6.7%
Terminal Rates (c)	5/28 (18%)		2/30 (7%)
Week of First Observation	96		104
Life Table Test (d)			P=0.118N
Incidental Tumor Test (d)			P=0.150N
Fisher Exact Test (d)			P=0.135N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	15/50 (30%)	12/50 (24%)	8/50 (16%)
Adjusted Rates (b)	41.9%	33.9%	24.7%
Terminal Rates (c)	8/28 (29%)	9/32 (28%)	6/30 (20%)
Week of First Observation	66	79	72
Life Table Tests (d)	P=0.063N	P=0.248N	P=0.085N
Incidental Tumor Tests (d)	P=0.240N	P=0.559N	P=0.267N
Cochran-Armitage Trend Test (d)	P=0.062N		
Fisher Exact Test (d)		P=0.327N	P=0.077N
Clitoral Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	3.6%	9.4%	6.7%
Terminal Rates (c)	1/28 (4%)	3/32 (9%)	2/30 (7%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.424	P=0.353	P=0.524
Incidental Tumor Tests (d)	P=0.424	P=0.353	P=0.524
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.309	P=0.500
Clitoral Gland: Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	10.7%	3.1%	9.4%
Terminal Rates (c)	3/28 (11%)	1/32 (3%)	2/30 (7%)
Week of First Observation	104	104	90
Life Table Tests (d)	P=0.579N	P=0.257N	P=0.647N
Incidental Tumor Tests (d)	P=0.533	P=0.257N	P=0.570
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.309N	P=0.661
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	14.3%	12.5%	15.9%
Terminal Rates (c)	4/28 (14%)	4/32 (13%)	4/30 (13%)
Week of First Observation	104	104	90
Life Table Tests (d)	P=0.459	P=0.570N	P=0.529
Incidental Tumor Tests (d)	P=0.397	P=0.570N	P=0.427
Cochran-Armitage Trend Test (d)	P=0.429		
Fisher Exact Test (d)		P=0.643N	P=0.500
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	14/50 (28%)	(e,g) 11/30 (37%)	7/50 (14%)
Adjusted Rates (b)	37.4%		22.2%
Terminal Rates (c)	7/28 (25%)		6/30 (20%)
Week of First Observation	66		72
Life Table Test (d)			P=0.090N
Incidental Tumor Test (d)			P=0.245N
Fisher Exact Test (d)			P=0.070N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	38/50 (76%)	36/50 (72%)	33/50 (66%)
Adjusted Rates (b)	86.3%	87.8%	91.7%
Terminal Rates (c)	22/28 (79%)	27/32 (84%)	27/30 (90%)
Week of First Observation	66	58	72
Life Table Tests (d)	P=0.177N	P=0.246N	P=0.210N
Incidental Tumor Tests (d)	P=0.076	P=0.288	P=0.111
Cochran-Armitage Trend Test (d)	P=0.160N		
Fisher Exact Test (d)		P=0.410N	P=0.189N
All Sites: Malignant Tumors			
Overall Rates (a)	23/50 (46%)	9/50 (18%)	10/50 (20%)
Adjusted Rates (b)	55.5%	24.5%	29.4%
Terminal Rates (c)	11/28 (39%)	6/32 (19%)	6/30 (20%)
Week of First Observation	52	50	90
Life Table Tests (d)	P=0.007N	P=0.004N	P=0.015N
Incidental Tumor Tests (d)	P=0.047N	P=0.005N	P=0.148N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.003N	P=0.005N
All Sites: All Tumors			
Overall Rates (a)	44/50 (88%)	39/50 (78%)	35/50 (70%)
Adjusted Rates (b)	91.7%	90.7%	97.2%
Terminal Rates (c)	24/28 (86%)	28/32 (88%)	29/30 (97%)
Week of First Observation	52	50	72
Life Table Tests (d)	P=0.058N	P=0.130N	P=0.072N
Incidental Tumor Tests (d)	P=0.371	P=0.585N	P=0.409
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test (d)		P=0.144N	P=0.024N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissue
(f) A C-cell carcinoma was also observed.
(g) Three endometrial stromal sarcomas were also observed.

TABLE B4a. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls	
	Leukemia	Lymphoma or Leukemia
No 2-year studies by Physiological Research Laboratories are included in the historical data base.		
Overall Historical Incidence		
TOTAL	271/1,450 (18.7%)	283/1,450 (19.5%)
SD (b)	8.52%	8.70%
Range (c)		
High	21/50	22/50
Low	2/50	2/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B4b. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 520/1,407 (37.0%)	(c) 43/1,407 (3.1%)	(b,c) 561/1,407 (39.9%)
SD (d)	8.35%	2.90%	8.47%
Range (e)			
High	27/49	5/47	30/49
Low	9/50	0/50	11/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes 72 chromophobe adenomas
(c) Includes four chromophobe carcinomas and six adenocarcinomas, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)	1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Inflammation, active chronic	4 (8%)		7 (14%)
Inflammation, chronic			1 (2%)
Hyperplasia, focal	1 (2%)		
Metaplasia, squamous			1 (2%)
#Lung/bronchiole	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Fibrosis		1 (2%)	6 (12%)
Hyperplasia, epithelial			1 (2%)
#Lung	(50)	(50)	(50)
Emphysema, NOS		1 (2%)	5 (10%)
Congestion, NOS	2 (4%)	3 (6%)	6 (12%)
Edema, NOS	3 (6%)	3 (6%)	6 (12%)
Hemorrhage	3 (6%)	2 (4%)	2 (4%)
Pneumonia, aspiration	1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)		1 (2%)
Pneumonia, interstitial chronic		1 (2%)	
Inflammation, granulomatous	1 (2%)		
Perivascular cuffing	9 (18%)	15 (30%)	8 (16%)
Alveolar macrophages	4 (8%)		12 (24%)
Hyperplasia, adenomatous	1 (2%)		3 (6%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(14)	(50)
Granuloma, NOS		1 (7%)	1 (2%)
Hyperplasia, NOS	19 (38%)	6 (43%)	9 (18%)
Myelofibrosis	2 (4%)		1 (2%)
#Spleen	(50)	(50)	(50)
Fibrosis	2 (4%)		
Necrosis, diffuse	1 (2%)		
Hemosiderosis	3 (6%)	5 (10%)	8 (16%)
Hyperplasia, reticulum cell	1 (2%)		
Hematopoiesis	7 (14%)	8 (16%)	5 (10%)
#Splenic capsule	(50)	(50)	(50)
Fibrosis	2 (4%)		
#Mandibular lymph node	(50)	(14)	(50)
Hyperplasia, lymphoid			1 (2%)
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(38)	(14)	(44)
Cyst, NOS	1 (3%)	1 (7%)	3 (7%)
Hemorrhage	2 (5%)	3 (21%)	1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Myocardium	(50)	(15)	(50)
Inflammation, chronic	10 (20%)	2 (13%)	9 (18%)
Fibrosis	34 (68%)	5 (33%)	30 (60%)
Degeneration, NOS	11 (22%)		5 (10%)
Necrosis, NOS	1 (2%)		
*Artery	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic		1 (2%)	
*Aorta	(50)	(50)	(50)
Mineralization	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Mineralization	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(14)	(50)
Inflammation, chronic	1 (2%)		
Atrophy, NOS	12 (24%)		5 (10%)
Hypertrophy, focal			1 (2%)
Hyperplasia, focal			1 (2%)
#Submaxillary duct	(49)	(14)	(50)
Dysplasia, epithelial	20 (41%)		15 (30%)
#Liver	(50)	(50)	(50)
Hernia, NOS	8 (16%)	1 (2%)	4 (8%)
Congestion, NOS	1 (2%)		
Granuloma, NOS	12 (24%)	20 (40%)	14 (28%)
Necrosis, NOS		3 (6%)	
Necrosis, focal	1 (2%)		
Necrosis, coagulative	4 (8%)	2 (4%)	
Metamorphosis, fatty	15 (30%)	12 (24%)	4 (8%)
Nuclear alteration	2 (4%)		1 (2%)
Cytoplasmic change, NOS	1 (2%)	1 (2%)	5 (10%)
Cytoplasmic vacuolization	16 (32%)	2 (4%)	7 (14%)
Basophilic cyto change	33 (66%)	41 (82%)	33 (66%)
Clear cell change	3 (6%)	8 (16%)	8 (16%)
Angiectasis	1 (2%)	1 (2%)	2 (4%)
#Periportal bile duct	(50)	(50)	(50)
Hyperplasia, NOS	34 (68%)	29 (58%)	23 (46%)
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, coagulative	1 (2%)		
Metamorphosis, fatty		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	1 (2%)
#Pancreas	(50)	(14)	(50)
Ectopia			1 (2%)
#Pancreatic acinus	(50)	(14)	(50)
Atrophy, NOS	12 (24%)	2 (14%)	7 (14%)
#Esophagus	(50)	(14)	(49)
Hemorrhage			1 (2%)
Hyperkeratosis	2 (4%)		1 (2%)
#Glandular stomach	(49)	(13)	(50)
Multiple cysts	37 (76%)	5 (38%)	23 (46%)
#Forestomach	(49)	(13)	(50)
Edema, NOS	3 (6%)		2 (4%)
Ulcer, NOS			2 (4%)
Inflammation, active chronic	3 (6%)		2 (4%)
Inflammation, chronic	1 (2%)		
Hyperplasia, epithelial	4 (8%)		2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS		2 (4%)	
Nephropathy	32 (64%)	36 (72%)	33 (66%)
#Kidney/tubule	(50)	(50)	(50)
Degeneration, hyaline	1 (2%)		
Metamorphosis, fatty	3 (6%)		1 (2%)
Pigmentation, NOS	1 (2%)	1 (2%)	
#Urinary bladder	(50)	(11)	(50)
Multiple cysts	1 (2%)		
Hyperplasia, epithelial	2 (4%)		1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
#Anterior pituitary	(50)	(50)	(50)
Cyst, NOS	21 (42%)	16 (32%)	12 (24%)
Hyperplasia, focal	3 (6%)	12 (24%)	4 (8%)
Angiectasis	5 (10%)	5 (10%)	
#Pituitary posterior	(50)	(50)	(50)
Cyst, NOS	2 (4%)		
#Adrenal	(50)	(14)	(50)
Congestion, NOS			1 (2%)
#Adrenal cortex	(50)	(14)	(50)
Hemorrhage		1 (7%)	
Degeneration, lipoid			1 (2%)
Necrosis, coagulative	1 (2%)	1 (7%)	1 (2%)
Metamorphosis, fatty	6 (12%)		1 (2%)
Cytomegaly			1 (2%)
Hyperplasia, focal	21 (42%)	1 (7%)	15 (30%)
Angiectasis	27 (54%)	1 (7%)	35 (70%)
#Adrenal medulla	(50)	(14)	(50)
Hyperplasia, focal			2 (4%)
#Thyroid	(50)	(16)	(50)
Hyperplasia, C-cell	20 (40%)	4 (25%)	18 (36%)
#Thyroid follicle	(50)	(16)	(50)
Metaplasia, squamous		1 (6%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, cystic	33 (66%)	5 (10%)	31 (62%)
*Clitoral gland	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
Atrophy, NOS	11 (22%)		4 (8%)
#Uterus	(50)	(30)	(50)
Mineralization	1 (2%)		
Hydrometra	1 (2%)	4 (13%)	5 (10%)
Hematometra			1 (2%)
Inflammation, active chronic	2 (4%)		
Hyperplasia, epithelial			1 (2%)
#Uterus/endometrium	(50)	(30)	(50)
Hyperplasia, NOS			1 (2%)
#Endometrial gland	(50)	(30)	(50)
Cyst, NOS	6 (12%)	4 (13%)	8 (16%)
#Ovary	(50)	(18)	(50)
Mineralization	1 (2%)		
Cyst, NOS	2 (4%)	3 (17%)	3 (6%)
Necrosis, NOS	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
*Choroid plexus	(50)	(50)	(50)
Mineralization	1 (2%)		
#Brain	(50)	(15)	(50)
Hydrocephalus, NOS	1 (2%)		2 (4%)
Hemorrhage			1 (2%)
#Cerebellum	(50)	(15)	(50)
Hemorrhage	1 (2%)		
Abscess, NOS			1 (2%)
Necrosis, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)	7 (14%)	
*Eye/cornea	(50)	(50)	(50)
Epidermal inclusion cyst			1 (2%)
Synechia, anterior			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	35 (70%)	40 (80%)	34 (68%)
*Eye/lens, cortex	(50)	(50)	(50)
Cataract	32 (64%)	40 (80%)	34 (68%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Epicardium	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	9	4	4
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
\# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		1 (2%)	
Fibrosarcoma	3 (6%)	7 (14%)	4 (8%)
Rhabdomyosarcoma			1 (2%)
Neurilemoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	7 (14%)	6 (12%)	3 (6%)
Alveolar/bronchiolar carcinoma	4 (8%)	3 (6%)	2 (4%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	
Malignant lymphoma, histiocytic type		1 (2%)	1 (2%)
Malignant lymphoma, mixed type	5 (10%)	3 (6%)	4 (8%)
#Spleen	(50)	(28)	(50)
Malignant lymphoma, mixed type		1 (4%)	
#Mesenteric lymph node	(50)	(18)	(47)
Malignant lymphoma, mixed type		2 (11%)	1 (2%)
#Small intestine	(50)	(12)	(45)
Malignant lymphoma, mixed type			1 (2%)
#Peyer's patch	(50)	(12)	(45)
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	1 (2%)
*Axilla	(50)	(50)	(50)
Hemangioma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Spleen	(50)	(28)	(50)
Hemangioma	2 (4%)	1 (4%)	
Hemangiosarcoma	1 (2%)		
#Mesenteric lymph node	(50)	(18)	(47)
Hemangioma	1 (2%)		
*Bone	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Heart	(50)	(12)	(50)
Hemangioma	1 (2%)		
#Liver	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)
#Urinary bladder	(48)	(12)	(48)
Hemangioma	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	11 (22%)	1 (2%)	4 (8%)
Hepatocellular carcinoma	10 (20%)	8 (16%)	5 (10%)
Pheochromocytoma, metastatic		1 (2%)	
#Forestomach	(50)	(11)	(49)
Squamous cell carcinoma		1 (9%)	
#Small intestine	(50)	(12)	(45)
Carcinoma, NOS	1 (2%)		
#Duodenum	(50)	(12)	(45)
Papillary carcinoma	1 (2%)		
#Jejunum	(50)	(12)	(45)
Adenocarcinoma, NOS		1 (8%)	
Mucinous adenocarcinoma		1 (8%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(11)	(50)
Adenoma, NOS	2 (4%)		
#Adrenal/capsule	(50)	(50)	(49)
Neoplasm, NOS			1 (2%)
Adenoma, NOS			1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	1 (2%)	2 (4%)	5 (10%)
Pheochromocytoma, malignant		1 (2%)	
#Thyroid	(49)	(10)	(50)
Follicular cell adenoma	1 (2%)		1 (2%)
#Parathyroid	(38)	(7)	(36)
Adenoma, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS		4 (8%)	2 (4%)
Adenoma, NOS		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Neurilemoma, malignant	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	6	7
Moribund sacrifice	9	18	13
Terminal sacrifice	36	26	30
TUMOR SUMMARY			
Total animals with primary tumors**	36	34	30
Total primary tumors	58	51	44
Total animals with benign tumors	21	13	15
Total benign tumors	29	13	19
Total animals with malignant tumors	22	29	21
Total malignant tumors	29	38	24
Total animals with secondary tumors##		3	
Total secondary tumors		3	
Total animals with tumors uncertain-- benign or malignant			1
Total uncertain tumors			1

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: VEHICLE CONTROL

ANIMAL NUMBER	112	120	128	141	132	222	107	146	134	143	131	116	108	145	101	102	103	104	105	106	109	110	111	113	114
WEEKS ON STUDY	029	029	029	039	070	073	076	078	080	082	091	093	098	098	104	044	044	044	044	044	044	044	044	044	044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Fibrosarcoma								X						X											
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X		X								X						X
Alveolar/bronchiolar carcinoma						X					X														
Trachea	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thymus	+	+	+	+	+	+	+	–	–	+	+	+	–	+	–	+	+	+	+	–	–	–	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X			X		X	X				
Hepatocellular carcinoma					X	X	X	X		X		X	X	X											
Hemangioma																									
Hemangiosarcoma									X		X														
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Papillary carcinoma																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, malignant												X													
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																									
Axilla, NOS																									
Hemangioma																						X			

+ Tissue examined microscopically
– Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed
No tissue information submitted
C Necropsy, no histology due to protocol
A. Autolysis
M Animal missing
B No necropsy performed

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

ANIMAL NUMBER	115	117	118	119	121	123	124	125	126	127	129	130	133	135	136	137	138	139	140	142	144	147	148	149	150	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																					X					3
Hemangiosarcoma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X	X			X								7
Alveolar/bronchiolar carcinoma		X			X																					4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma															X	X										2
Hemangiosarcoma		X																								1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma													X													1
Thymus	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																X										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X				X			X			X			X	X	X							11
Hepatocellular carcinoma																X					X					10
Hemangioma																	X									1
Hemangiosarcoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																			X							1
Papillary carcinoma	X																									1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma																				X						1
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS														X	X											2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																					X					1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma													X													1
Parathyroid	−	−	+	+	−	+	−	+	+	+	−	−	+	+	−	−	+	+	+	+	+	+	+	+	−	38
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type			X						X		X				X							X				5
Axilla, NOS																										
Hemangioma																										1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: LOW DOSE

ANIMAL NUMBER	00009	00466	00077	00188	00006	00133	00311	00377	00355	00441	00477	00366	00002	00177	00322	00455	00088	00161	00334	00110	00550	00211	00277	00433	00001
WEEKS ON STUDY	03000	05909	06101	06202	07000	07505	08303	08404	09101	09901	09901	09903	09907	09707	09907	09707	09808	09908	09808	09909	09909	10101	10202	10202	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	N	+	N	N	N	+	N	N
Fibroma																									
Fibrosarcoma							X					X	X	X		X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic										X															
Alveolar/bronchiolar adenoma		X															X								
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic							X																		
Trachea	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	−	+	−	+	+	−
Hemangioma																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	−	−	−	−	−	−	−	−	+
Malignant lymphoma, mixed type																									
Thymus	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma				X	X					X				X		X									
Pheochromocytoma, metastatic																X									
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Esophagus	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Adenocarcinoma, NOS																									
Mucinous adenocarcinoma																						X			
Large intestine	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	−	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X												X									
Pheochromocytoma, malignant																X									
Thyroid	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Parathyroid	−	+	+	−	+	+	+	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−
Prostate	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS						X																			
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																	X								
Malignant lymphoma, NOS								X																	
Malignant lymphoma, histiocytic type															X										
Malignant lymphoma, mixed type										X													X		X

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

ANIMAL NUMBER	00003	00004	00005	00111	00112	00114	00115	00119	00200	00222	00233	00244	00255	00266	00288	00299	00300	00333	00383	00399	00400	00411	00422	00488	00499	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	+	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibroma							X																			1
Fibrosarcoma							X		X																	7
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma				X													X		X	X						6
Alveolar/bronchiolar carcinoma									X						X						X					3
Fibrosarcoma, metastatic													•													1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Spleen	–	–	–	–	–	–	–	–	+	+	–	+	–	+	+	–	+	+	–	–	+	–	–	–	–	28
Hemangioma														X												1
Malignant lymphoma, mixed type												X														1
Lymph nodes	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	+	–	18
Malignant lymphoma, mixed type							X																	X		2
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X																							1
Hepatocellular carcinoma		X			X						X															8
Pheochromocytoma, metastatic																										1
Hemangiosarcoma								X																		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	11
Squamous cell carcinoma																				X						1
Small intestine	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Adenocarcinoma, NOS									X																	1
Mucinous adenocarcinoma																										1
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma											X															1
Urinary bladder	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	12
ENDOCRINE SYSTEM																										
Pituitary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										2
Pheochromocytoma, malignant																										1
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS											X								X							4
Adenoma, NOS																						X				1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																	X									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																										3

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: HIGH DOSE

ANIMAL NUMBER	059	086	060	056	057	058	078	063	090	084	087	055	071	065	074	080	096	093	072	073	051	052	053	054	061
WEEKS ON STUDY	008	046	049	054	061	064	070	071	074	085	087	089	093	094	095	097	097	100	101	101	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS													X												
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X										X	X					
Rhabdomyosarcoma															X										
Neurilemoma																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	−	+	+	−	+	+	+	+	+	+	−	−	+	−	−	−	+	−	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X																			
Hepatocellular carcinoma										X		X			X		X								
Hemangiosarcoma																X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	+	+	+	+	+	+	+	+	−	+	+	−	−	+	−	+	+	+	+	+	+	+
Malignant lymphoma, mixed type														X											
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS																									
Adenoma, NOS																									
Pheochromocytoma													X							X					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	−	+	−	−
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																								X	
Malignant lymphoma, histiocytic type																								X	
Malignant lymphoma, mixed type											X														

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

ANIMAL NUMBER	062	064	066	067	068	069	070	075	076	077	079	081	082	083	085	088	089	091	092	094	095	097	098	099	100	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																			X							4
Rhabdomyosarcoma																										1
Neurilemoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X	X											3
Alveolar/bronchiolar carcinoma				X						X																2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, mixed type		X																								1
Thymus	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS									X																	1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X		X												X								4
Hepatocellular carcinoma							X																			5
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Malignant lymphoma, mixed type																		X								2
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplasm, NOS					X																					1
Adenoma, NOS																			X							1
Pheochromocytoma								X			X			X												5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma	X																									1
Parathyroid	−	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	−	−	−	+	+	+	−	+	+	36
Adenoma, NOS											X															1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X		X																					2
Adenoma, NOS																		X								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type											X		X						X							4

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	62.5 mg/kg	125 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	(b) 7/50 (14%)	4/50 (8%)
Adjusted Rates (c)	7.5%	19.0%	11.5%
Terminal Rates (d)	1/36 (3%)	2/26 (8%)	1/30 (3%)
Week of First Observation	78	83	74
Life Table Tests (e)	P=0.372	P=0.132	P=0.437
Incidental Tumor Tests (e)	P=0.506N	P=0.500	P=0.570N
Cochran-Armitage Trend Test (e)	P=0.432		
Fisher Exact Test (e)		P=0.159	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	7/50 (14%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (c)	18.0%	19.5%	10.0%
Terminal Rates (d)	5/36 (14%)	4/26 (15%)	3/30 (10%)
Week of First Observation	80	59	104
Life Table Tests (e)	P=0.203N	P=0.567	P=0.229N
Incidental Tumor Tests (e)	P=0.161N	P=0.526N	P=0.220N
Cochran-Armitage Trend Test (e)	P=0.128N		
Fisher Exact Test (e)		P=0.500N	P=0.159N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (c)	10.0%	11.5%	6.7%
Terminal Rates (d)	2/36 (6%)	3/26 (12%)	2/30 (7%)
Week of First Observation	73	104	104
Life Table Tests (e)	P=0.341N	P=0.620N	P=0.405N
Incidental Tumor Tests (e)	P=0.313N	P=0.569N	P=0.364N
Cochran-Armitage Trend Test (e)	P=0.264N		
Fisher Exact Test (e)		P=0.500N	P=0.339N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (c)	25.0%	30.5%	16.7%
Terminal Rates (d)	7/36 (19%)	7/26 (27%)	5/30 (17%)
Week of First Observation	73	59	104
Life Table Tests (e)	P=0.200N	P=0.476	P=0.215N
Incidental Tumor Tests (e)	P=0.154N	P=0.594N	P=0.189N
Cochran-Armitage Trend Test (e)	P=0.110N		
Fisher Exact Test (e)		P=0.500N	P=0.131N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	5/50 (10%)	(f) 6/50 (12%)	7/50 (14%)
Adjusted Rates (c)	13.9%		20.9%
Terminal Rates (d)	5/36 (14%)		5/30 (17%)
Week of First Observation	104		87
Life Table Test (e)			P=0.277
Incidental Tumor Test (e)			P=0.325
Fisher Exact Test (e)			P=0.380
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/50 (10%)	(f) 8/50 (16%)	8/50 (16%)
Adjusted Rates (c)	13.9%		24.1%
Terminal Rates (d)	5/36 (14%)		6/30 (20%)
Week of First Observation	104		87
Life Table Test (e)			P=0.184
Incidental Tumor Test (e)			P=0.222
Fisher Exact Test (e)			P=0.277

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Circulatory System: Hemangioma			
Overall Rates (a)	6/50 (12%)	(f) 1/50 (2%)	0/50 (0%)
Adjusted Rates (c)	16.7%		0.0%
Terminal Rates (d)	6/36 (17%)		0/30 (0%)
Week of First Observation	104		
Life Table Test (e)			P=0.029N
Incidental Tumor Test (e)			P=0.029N
Fisher Exact Test (e)			P=0.014N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	(f) 3/50 (6%)	2/50 (4%)
Adjusted Rates (c)	10.1%		6.1%
Terminal Rates (d)	2/36 (6%)		1/30 (3%)
Week of First Observation	80		97
Life Table Test (e)			P=0.395N
Incidental Tumor Test (e)			P=0.303N
Fisher Exact Test (e)			P=0.339N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	10/50 (20%)	(f) 4/50 (8%)	2/50 (4%)
Adjusted Rates (c)	26.0%		6.1%
Terminal Rates (d)	8/36 (22%)		1/30 (3%)
Week of First Observation	80		97
Life Table Test (e)			P=0.032N
Incidental Tumor Test (e)			P=0.019N
Fisher Exact Test (e)			P=0.014N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	11/50 (22%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (c)	30.6%	3.8%	12.0%
Terminal Rates (d)	11/36 (31%)	1/26 (4%)	3/30 (10%)
Week of First Observation	104	104	64
Life Table Test (e)	P=0.038N	P=0.011N	P=0.088N
Incidental Tumor Test (e)	P=0.035N	P=0.011N	P=0.078N
Cochran-Armitage Trend Test (e)	P=0.018N		
Fisher Exact Test (e)		P=0.002N	P=0.045N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	10/50 (20%)	8/50 (16%)	5/50 (10%)
Adjusted Rates (c)	22.3%	21.7%	13.2%
Terminal Rates (d)	2/36 (6%)	3/26 (12%)	1/30 (3%)
Week of First Observation	70	62	85
Life Table Tests (e)	P=0.165N	P=0.484N	P=0.189N
Incidental Tumor Tests (e)	P=0.023N	P=0.084N	P=0.014N
Cochran-Armitage Trend Test (e)	P=0.106N		
Fisher Exact Test (e)		P=0.398N	P=0.131N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	21/50 (42%)	9/50 (18%)	9/50 (18%)
Adjusted Rates (c)	47.5%	25.1%	23.9%
Terminal Rates (d)	13/36 (36%)	4/26 (15%)	4/30 (13%)
Week of First Observation	70	62	64
Life Table Tests (e)	P=0.022N	P=0.050N	P=0.036N
Incidental Tumor Tests (e)	P=0.002N	P=0.002N	P=0.002N
Cochran-Armitage Trend Test (e)	P=0.004N		
Fisher Exact Test (e)		P=0.008N	P=0.008N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	(g) 2/50 (4%)	5/49 (10%)
Adjusted Rates (c)	2.8%	4.7%	15.4%
Terminal Rates (d)	1/36 (3%)	0/26 (0%)	3/29 (10%)
Week of First Observation	104	62	93
Life Table Tests (e)	P=0.047	P=0.465	P=0.072
Incidental Tumor Tests (e)	P=0.076	P=0.640	P=0.134
Cochran-Armitage Trend Test (e)	P=0.057		
Fisher Exact Test (e)		P=0.500	P=0.098
Harderian Gland: Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (c)	0.0%	13.5%	6.7%
Terminal Rates (d)	0/36 (0%)	3/26 (12%)	2/30 (7%)
Week of First Observation		75	104
Life Table Tests (e)	P=0.179	P=0.038	P=0.199
Incidental Tumor Tests (e)	P=0.200	P=0.042	P=0.199
Cochran-Armitage Trend Test (e)	P=0.222		
Fisher Exact Test (e)		P=0.059	P=0.247
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (c)	0.0%	13.5%	10.0%
Terminal Rates (d)	0/36 (0%)	3/26 (12%)	3/30 (10%)
Week of First Observation		75	104
Life Table Tests (e)	P=0.089	P=0.038	P=0.090
Incidental Tumor Tests (e)	P=0.101	P=0.042	P=0.090
Cochran-Armitage Trend Test (e)	P=0.118		
Fisher Exact Test (e)		P=0.059	P=0.121
All Sites: Benign Tumors			
Overall Rates (a)	21/50 (42%)	13/50 (26%)	15/50 (30%)
Adjusted Rates (c)	55.1%	40.8%	43.3%
Terminal Rates (d)	19/36 (53%)	9/26 (35%)	11/30 (37%)
Week of First Observation	80	59	64
Life Table Tests (e)	P=0.281N	P=0.292N	P=0.328N
Incidental Tumor Tests (e)	P=0.166N	P=0.158N	P=0.201N
Cochran-Armitage Trend Test (e)	P=0.120N		
Fisher Exact Test (e)		P=0.070N	P=0.149N
All Sites: Malignant Tumors			
Overall Rates (a)	22/50 (44%)	29/50 (58%)	21/50 (42%)
Adjusted Rates (c)	47.8%	70.9%	52.1%
Terminal Rates (d)	12/36 (33%)	15/26 (58%)	11/30 (37%)
Week of First Observation	70	62	74
Life Table Tests (e)	P=0.393	P=0.045	P=0.455
Incidental Tumor Tests (e)	P=0.287N	P=0.396	P=0.247N
Cochran-Armitage Trend Test (e)	P=0.460N		
Fisher Exact Test (e)		P=0.115	P=0.500N
All Sites: All Tumors			
Overall Rates (a)	36/50 (72%)	34/50 (68%)	30/50 (60%)
Adjusted Rates (c)	78.3%	81.9%	71.2%
Terminal Rates (d)	26/36 (72%)	19/26 (73%)	18/30 (60%)
Week of First Observation	70	59	64
Life Table Tests (e)	P=0.457N	P=0.234	P=0.473N
Incidental Tumor Tests (e)	P=0.072N	P=0.233N	P=0.057N
Cochran-Armitage Trend Test (e)	P=0.122N		
Fisher Exact Test (e)		P=0.414N	P=0.146N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) A fibroma was also observed in an animal bearing a fibrosarcoma.
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(f) Only 28 spleens and 18 lymph nodes were examined microscopically.
(g) A malignant pheochromocytoma was also observed in an animal bearing a benign pheochromocytoma.

TABLE C4a. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 52/1,497 (3.5%)	4/1,497 (0.3%)	(b) 56/1,497 (3.7%)
SD (c)	2.92%	0.70%	3.15%
Range (d)			
High	5/50	1/49	5/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes three papillary adenomas, one cystadenoma, and one papillary cystadenoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	10/1,497 (0.7%)	72/1,497 (4.8%)	80/1,497 (5.3%)
SD (b)	1.21%	4.19%	4.27%
Range (c)			
High	2/50	7/50	8/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4c. HISTORICAL INCIDENCE OF ADRENAL GLAND PHEOCHROMOCYTOMAS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
No 2-year studies by Physiological Research Laboratories are included in the historical data base.	
Overall Historical Incidence	
TOTAL	(b) 19/1,443 (1.3%)
SD (c)	2.43%
Range (d)	
High	(b) 5/49
Low	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes one malignant pheochromocytoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE C4d. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	201/1,490 (13.5%)	306/1,490 (20.5%)	477/1,490 (32.0%)
SD (b)	6.45%	7.70%	8.99%
Range (c)			
High	14/50	19/50	25/50
Low	0/50	3/49	7/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation chronic necrotizing		1 (2%)	
Inflammation with fibrosis		1 (2%)	
Calcification, NOS	1 (2%)	1 (2%)	
Hyperkeratosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic		1 (2%)	1 (2%)
Plasma cell infiltrate			1 (2%)
Inflammation, granulomatous	1 (2%)		
Fibrosis		1 (2%)	
Pigmentation, NOS		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	2 (4%)		
Inflammation, suppurative	5 (10%)	1 (2%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic focal	2 (4%)	1 (2%)	1 (2%)
Reaction, foreign body	1 (2%)		
*Nasal mucosa	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Degeneration, hyaline			1 (2%)
#Bronchial mucosa	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
#Lung	(50)	(50)	(50)
Atelectasis	2 (4%)	1 (2%)	2 (4%)
Congestion, NOS	7 (14%)	5 (10%)	7 (14%)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)
Perivascular cuffing	1 (2%)	4 (8%)	3 (6%)
Pigmentation, NOS		1 (2%)	
Alveolar macrophages	2 (4%)		
Hyperplasia, adenomatous	1 (2%)	1 (2%)	
#Lung/alveoli	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, chronic focal	1 (2%)		1 (2%)
Crystals, NOS	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	4 (8%)		3 (6%)
#Bone marrow	(50)	(10)	(50)
Fibrosis	1 (2%)		1 (2%)
Hyperplasia, NOS	6 (12%)	1 (10%)	2 (4%)
Angiectasis	1 (2%)	1 (10%)	3 (6%)
Hyperplasia, granulocytic	15 (30%)	6 (60%)	24 (48%)
Hyperplasia, lymphoid	1 (2%)		
#Spleen	(50)	(28)	(50)
Mineralization		1 (4%)	
Inflammation, acute focal			1 (2%)
Necrosis, focal		1 (4%)	
Amyloidosis		1 (4%)	
Atrophy, NOS		2 (7%)	1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
#Spleen (Continued)	(50)	(28)	(50)
Hyperplasia, granulocytic	1 (2%)		
Hyperplasia, reticulum cell	6 (12%)	5 (18%)	1 (2%)
Hyperplasia, lymphoid	16 (32%)	6 (21%)	14 (28%)
Hematopoiesis	13 (26%)	10 (36%)	12 (24%)
#Splenic capsule	(50)	(28)	(50)
Fibrosis	1 (2%)		
#Splenic follicles	(50)	(28)	(50)
Necrosis, NOS	1 (2%)	1 (4%)	
Atrophy, NOS	1 (2%)		1 (2%)
#Lymph node	(50)	(18)	(47)
Hemorrhage		1 (6%)	
Hemosiderosis	1 (2%)		
Angiectasis			1 (2%)
Histiocytosis			1 (2%)
Plasmacytosis		1 (6%)	
Erythrophagocytosis			1 (2%)
#Mandibular lymph node	(50)	(18)	(47)
Hemorrhage			2 (4%)
Plasmacytosis	1 (2%)		
#Lumbar lymph node	(50)	(18)	(47)
Plasmacytosis			1 (2%)
#Mesenteric lymph node	(50)	(18)	(47)
Hemorrhage	4 (8%)	1 (6%)	8 (17%)
Inflammation, acute		1 (6%)	1 (2%)
Inflammation, granulomatous			1 (2%)
Amyloidosis			1 (2%)
Cytomegaly	6 (12%)		2 (4%)
Atrophy, NOS			1 (2%)
Angiectasis	14 (28%)	4 (22%)	6 (13%)
Hyperplasia, lymphoid	7 (14%)	1 (6%)	
#Renal lymph node	(50)	(18)	(47)
Plasmacytosis			1 (2%)
#Lung	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		
Hyperplasia, lymphoid			3 (6%)
#Salivary gland	(50)	(10)	(50)
Hyperplasia, lymphoid	9 (18%)		3 (6%)
#Liver	(50)	(50)	(50)
Hematopoiesis	1 (2%)	2 (4%)	2 (4%)
#Peyer's patch	(50)	(12)	(45)
Hyperplasia, lymphoid			1 (2%)
#Ileum	(50)	(12)	(45)
Hyperplasia, lymphoid	1 (2%)		
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	3 (6%)	3 (6%)	3 (6%)
#Urinary bladder	(48)	(12)	(48)
Hyperplasia, lymphoid	3 (6%)		5 (10%)
#Prostate	(50)	(11)	(49)
Hyperplasia, lymphoid	9 (18%)		6 (12%)
#Thymus	(37)	(6)	(34)
Cyst, NOS	7 (19%)		5 (15%)
Multiple cysts	3 (8%)		3 (9%)
Inflammation, suppurative	1 (3%)		
Necrosis, NOS	1 (3%)	1 (17%)	1 (3%)
Atrophy, NOS		2 (33%)	6 (18%)
Hyperplasia, epithelial	1 (3%)		2 (6%)
Hyperplasia, lymphoid	1 (3%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Lymph node	(50)	(18)	(47)
Thrombosis, NOS			1 (2%)
#Mesenteric lymph node	(50)	(18)	(47)
Lymphangiectasis		1 (6%)	
#Heart	(50)	(12)	(50)
Perivasculitis			1 (2%)
#Left atrium	(50)	(12)	(50)
Inflammation, acute/chronic	1 (2%)		
#Myocardium	(50)	(12)	(50)
Inflammation, chronic	1 (2%)		
Fibrosis			1 (2%)
Degeneration, NOS	1 (2%)		
Necrosis, focal			1 (2%)
Calcification, focal			2 (4%)
*Artery	(50)	(50)	(50)
Perivasculitis			1 (2%)
*Aorta	(50)	(50)	(50)
Calcification, NOS			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Calcification, NOS		1 (2%)	
*Vein	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
#Kidney	(50)	(50)	(50)
Perivasculitis		1 (2%)	
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	7 (14%)	1 (2%)	1 (2%)
*Pulp of tooth	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
*Gingival mucous membrane	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Liver	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Hemorrhage		1 (2%)	
Fibrosis	1 (2%)		
Perivascular cuffing	2 (4%)		
Degeneration, NOS	1 (2%)		
Necrosis, focal	4 (8%)	1 (2%)	
Necrosis, coagulative	2 (4%)	1 (2%)	2 (4%)
Infarct, NOS	1 (2%)	2 (4%)	
Amyloidosis		1 (2%)	
Metamorphosis, fatty	3 (6%)	1 (2%)	2 (4%)
Calcification, focal			1 (2%)
Focal cellular change	2 (4%)		2 (4%)
Clear cell change	1 (2%)		
Hepatocytomegaly			4 (8%)
#Liver/Kupffer cell	(50)	(50)	(50)
Hyperplasia, diffuse			1 (2%)
#Liver/hepatocytes	(50)	(50)	(50)
Nuclear alteration			1 (2%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS	2 (4%)		1 (2%)
Multiple cysts		1 (2%)	
Inflammation, chronic	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
*Gallbladder/mucosa	(50)	(50)	(50)
Degeneration, hyaline	1 (2%)		
#Pancreas	(50)	(13)	(50)
Cyst, NOS		2 (15%)	1 (2%)
Atrophy, focal	1 (2%)		
#Pancreatic acinus	(50)	(13)	(50)
Cytoplasmic vacuolization			2 (4%)
Atrophy, NOS			1 (2%)
Atrophy, focal	1 (2%)		
Hypertrophy, focal	1 (2%)		3 (6%)
#Esophagus	(49)	(10)	(50)
Ulcer, NOS			1 (2%)
Hyperkeratosis		1 (10%)	
#Glandular stomach	(50)	(11)	(49)
Cyst, NOS			1 (2%)
Multiple cysts			1 (2%)
Inflammation, chronic focal	1 (2%)		
Degeneration, NOS			1 (2%)
Calcification, NOS	2 (4%)		
#Forestomach	(50)	(11)	(49)
Ulcer, NOS			1 (2%)
Inflammation, acute/chronic	3 (6%)		1 (2%)
Inflammation, chronic	1 (2%)		
Erosion	1 (2%)		
Hyperplasia, epithelial	1 (2%)		1 (2%)
Hyperkeratosis	1 (2%)		
#Small intestinal crypt of Lieberkuhn	(50)	(12)	(45)
Deposit, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis			1 (2%)
Cyst, NOS	1 (2%)	2 (4%)	
Multiple cysts	1 (2%)	3 (6%)	5 (10%)
Glomerulonephritis, NOS		2 (4%)	
Pyelonephritis, NOS		1 (2%)	1 (2%)
Pyelonephritis, chronic		1 (2%)	1 (2%)
Inflammation with fibrosis			1 (2%)
Nephropathy	39 (78%)	43 (86%)	47 (94%)
Calcification, NOS	4 (8%)	2 (4%)	1 (2%)
Metaplasia, osseous	1 (2%)	3 (6%)	4 (8%)
#Kidney/glomerulus	(50)	(50)	(50)
Deposit, NOS	1 (2%)		
#Convoluted tubules	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Degeneration, hyaline			1 (2%)
Pigmentation, NOS	1 (2%)		
#Urinary bladder	(48)	(12)	(48)
Calculus, gross observation only	1 (2%)		1 (2%)
Hemorrhage		1 (8%)	
Inflammation, necrotizing		1 (8%)	
Inflammation, acute/chronic		1 (8%)	
Necrosis, NOS		1 (8%)	
Hyperplasia, epithelial	1 (2%)		1 (2%)
#Urinary bladder/serosa	(48)	(12)	(48)
Inflammation, acute/chronic			1 (2%)
Perivascular cuffing	1 (2%)		
*Urethra	(50)	(50)	(50)
Inflammation, acute			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(11)	(50)
Cyst, NOS	5 (10%)		3 (6%)
Multiple cysts	1 (2%)		3 (6%)
Hyperplasia, focal	1 (2%)		2 (4%)
#Adrenal/capsule	(50)	(50)	(49)
Hyperplasia, stromal	31 (62%)	34 (68%)	37 (76%)
#Adrenal cortex	(50)	(50)	(49)
Ectopia	3 (6%)	1 (2%)	2 (4%)
Degeneration, lipoid	1 (2%)	3 (6%)	
Cytomegaly	1 (2%)		
Hypertrophy, NOS			1 (2%)
Hypertrophy, focal	7 (14%)	7 (14%)	6 (12%)
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
Angiectasis		1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Multiple cysts		1 (2%)	
Hyperplasia, focal	5 (10%)	16 (32%)	10 (20%)
Angiectasis			1 (2%)
#Thyroid	(49)	(10)	(50)
Follicular cyst, NOS	1 (2%)		1 (2%)
Degeneration, NOS	1 (2%)		
#Thyroid follicle	(49)	(10)	(50)
Multiple cysts	1 (2%)	1 (10%)	1 (2%)
Hyperplasia, papillary	1 (2%)		1 (2%)
#Parathyroid	(38)	(7)	(36)
Ectopia			1 (3%)
Angiectasis	1 (3%)		
#Pancreatic islets	(50)	(13)	(50)
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Ulcer, NOS			2 (4%)
Inflammation, acute			1 (2%)
*Prepuce	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)	
Abscess, NOS	4 (8%)	1 (2%)	7 (14%)
Inflammation, acute/chronic	7 (14%)	4 (8%)	4 (8%)
Inflammation, chronic	5 (10%)	2 (4%)	8 (16%)
Inflammation, granulomatous	1 (2%)		
Inflammation, pyogranulomatous	1 (2%)		
Calcification, NOS			2 (4%)
Metaplasia, squamous	17 (34%)	8 (16%)	19 (38%)
#Prostate	(50)	(11)	(49)
Hemorrhage			1 (2%)
Inflammation, chronic	2 (4%)	3 (27%)	2 (4%)
Hyperplasia, papillary	1 (2%)		
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	2 (4%)		2 (4%)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic	1 (2%)		
Fibrosis	1 (2%)	2 (4%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Testis	(50)	(11)	(49)
Multiple cysts	1 (2%)		
Edema, NOS			2 (4%)
Degeneration, NOS	1 (2%)		1 (2%)
Calcification, NOS	9 (18%)	1 (9%)	3 (6%)
Cytomegaly			1 (2%)
Atrophy, NOS	2 (4%)	2 (18%)	1 (2%)
Atrophy, focal	1 (2%)	1 (9%)	
*Epididymis	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, granulomatous	1 (2%)		
Granuloma, spermatic	1 (2%)		
Degeneration, NOS			1 (2%)
Cytomegaly			3 (6%)
*Scrotum	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
Inflammation, pyogranulomatous			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(11)	(50)
Hemorrhage	1 (2%)		
Perivascular cuffing			1 (2%)
#Brain/thalamus	(50)	(11)	(50)
Calcification, NOS	22 (44%)	4 (36%)	28 (56%)
*Spinal cord	(50)	(50)	(50)
Demyelinization			1 (2%)
SPECIAL SENSE ORGANS			
*Cornea, external epithelium	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
*Eye/lacrimal gland	(50)	(50)	(50)
Inflammation, necrotizing			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	1 (2%)
Angiectasis	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Granuloma, foreign body			1 (2%)
Osteosclerosis	5 (10%)	5 (10%)	15 (30%)
*Skull	(50)	(50)	(50)
Hyperostosis			1 (2%)
*Ankle joint	(50)	(50)	(50)
Ankylosis	12 (24%)	16 (32%)	19 (38%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute			1 (2%)
*Inguinal region	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, necrotizing			1 (2%)
Inflammation, acute/chronic	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Pericardium	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		
ALL OTHER SYSTEMS			
Knee			
Dyschondroplasia	13	15	13
Exostosis	1		
Adipose tissue			
Necrosis, fat	3	3	3
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Basal cell tumor			1 (2%)
Basal cell carcinoma	1 (2%)		
*Subcutaneous tissue	(50)	(49)	(50)
Malignant melanoma	1 (2%)		
Sarcoma, NOS			1 (2%)
Fibrosarcoma	2 (4%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Trachea	(50)	(6)	(49)
Fibrosarcoma, metastatic	1 (2%)		
#Lung	(50)	(47)	(49)
Neoplasm, NOS, metastatic			1 (2%)
Carcinoma, NOS, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	4 (8%)		2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Malignant lymphoma, undifferentiated type	1 (2%)		1 (2%)
Malignant lymphoma, lymphocytic type	1 (2%)		
Malignant lymphoma, histiocytic type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, mixed type	18 (36%)	8 (16%)	17 (34%)
Mast cell sarcoma		1 (2%)	
Leukemia, NOS	1 (2%)		
Granulocytic leukemia		1 (2%)	
#Spleen	(50)	(18)	(50)
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type	1 (2%)		
#Lung	(50)	(47)	(49)
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, mixed type		1 (2%)	
#Uterus	(50)	(40)	(50)
Malignant lymphoma, histiocytic type			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)	
#Spleen	(50)	(18)	(50)
Hemangioma	3 (6%)		
Angioma			1 (2%)
#Salivary gland	(50)	(7)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
#Uterus	(50)	(40)	(50)
Hemangioma		1 (3%)	
#Uterus/endometrium	(50)	(40)	(50)
Hemangioma	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	3 (6%)		1 (2%)
#Duodenum	(50)	(7)	(49)
Adenomatous polyp, NOS			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(15)	(49)
Carcinoma, NOS	1 (2%)	1 (7%)	
Adenoma, NOS	12 (24%)	6 (40%)	9 (18%)
#Thyroid	(50)	(48)	(50)
Follicular cell adenoma	1 (2%)	2 (4%)	4 (8%)
Follicular cell carcinoma			1 (2%)
#Pancreatic islets	(49)	(8)	(50)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Vagina	(50)	(49)	(50)
Leiomyosarcoma	1 (2%)		
#Uterus	(50)	(40)	(50)
Endometrial stromal polyp	2 (4%)		3 (6%)
#Ovary	(50)	(13)	(45)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(50)
Carcinoma, NOS	1 (2%)	3 (6%)	
Adenoma, NOS	1 (2%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Squamous cell carcinoma		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	1	5	5
Moribund sacrifice	14	13	10
Terminal sacrifice	35	32	35

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	39	22	30
Total primary tumors	62	30	47
Total animals with benign tumors	23	9	18
Total benign tumors	27	10	24
Total animals with malignant tumors	29	18	21
Total malignant tumors	34	20	23
Total animals with secondary tumors##	1	1	1
Total secondary tumors	1	1	1
Total animals with tumors uncertain--benign or malignant	1		
Total uncertain tumors	1		

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: VEHICLE CONTROL

ANIMAL NUMBER	12 9	11 1	13 1	10 8	14 1	10 1	11 6	11 0	12 2	13 4	12 6	10 5	14 5	10 3	12 8	10 2	10 4	10 6	10 7	10 9	11 2	11 3	11 4	11 5	11 7
WEEKS ON STUDY	07 0	07 6	07 9	08 2	08 4	08 8	08 8	09 0	09 4	09 7	09 8	09 9	10 0	10 1	10 2	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma											X														
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant melanoma																									X
Fibrosarcoma								X				X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic								X																	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Malignant lymphoma, histiocytic type																					X				
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	+	–	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X																
Hemangiosarcoma																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS															X										
Adenoma, NOS											X	X		X			X	X		X	X	X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	–	–	–	+	+	+	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma																					X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																						X			
Hemangioma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor														X											
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type	X																								
Malignant lymphoma, lymphocytic type														X											
Malignant lymphoma, histiocytic type							X																		
Malignant lymphoma, mixed type				X	X										X	X	X		X	X	X	X	X	X	
Leukemia, NOS													X												

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	118	119	120	121	123	124	125	127	130	132	133	135	136	137	138	139	140	142	143	144	146	147	148	149	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Malignant melanoma																										1
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X													X					X							4
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma									X										X				X			3
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																							X			1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma												X					X									3
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS											X				X							X		X		12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma					X																					1
Parathyroid	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	39
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp											X															2
Hemangioma									X																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS															X											1
Adenoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type				X		X		X							X			X						X	X	18
Leukemia, NOS																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: LOW DOSE

ANIMAL NUMBER	0363	0613	0634	0641	0740	0826	0847	0902	0909	0919	0908	0927	0937	0928	0929	0930	0931	0925	1001	1003	1004	1005	1006	1007	1010
WEEKS ON STUDY	0244	0688	0710	0744	0883	0991	0991	0944	0944	0944	0997	0998	0998	0999	0999	1002	1002	1003	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N
Fibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									
Trachea	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	−	+	−	−	−	+	−	−	+	+	A	−	+	−	−	+	−	−
Lymph nodes	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−	−	+	A	−	−	−	−	−	−	−
Thymus	+	+	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	−	A	−	−	−	−	−	−	−
Esophagus	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
Small intestine	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
Large intestine	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	−	−	A	+	−	−	+	−	−	−
Carcinoma, NOS																									
Adenoma, NOS											X	X	X						X						
Adrenal	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	−	−	+	+	−	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	−	−	−	+	−	+	+	+	A	+	+	+	+	+	+	−
Hemangioma			X																						
Ovary	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	+	−	A	−	−	−	−	−	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	A	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N
Carcinoma, NOS										X															
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N
Squamous cell carcinoma								X																	
Hemangiosarcoma									X																
Malignant lymphoma, histiocytic type														X											
Malignant lymphoma, mixed type									X			X				X							X		
Mast cell sarcoma					X																				
Granulocytic leukemia											X														

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

ANIMAL NUMBER	0111	0112	0114	0115	0116	0117	0118	0120	0121	0122	0123	0124	0132	0133	0135	0138	0139	0142	0143	0144	0145	0146	0148	0149	0150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
Carcinoma, NOS, metastatic																				X						1
Malignant lymphoma, lymphocytic type																		X								1
Malignant lymphoma, mixed type																			X							1
Trachea	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	8
Spleen	−	−	−	−	+	−	+	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−	+	−	18
Lymph nodes	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	+	−	12
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	5
CIRCULATORY SYSTEM																										
Heart	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	7
DIGESTIVE SYSTEM																										
Salivary gland	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	7
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Pancreas	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	8
Esophagus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
Stomach	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	8
Small intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	7
Large intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
ENDOCRINE SYSTEM																										
Pituitary	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	+	−	15
Carcinoma, NOS																			X							1
Adenoma, NOS																				X				X		6
Adrenal	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	7
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																			X	X						2
Parathyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	3
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Uterus	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	−	+	40
Hemangioma																										1
Ovary	−	−	+	−	−	−	−	+	−	+	−	−	−	+	−	−	−	−	+	−	−	−	−	−	+	13
NERVOUS SYSTEM																										
Brain	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	7
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Carcinoma, NOS	X																			X						3
Adenoma, NOS																							X			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Squamous cell carcinoma																										1
Hemangiosarcoma																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type														X	X	X								X		8
Mast cell sarcoma																										1
Granulocytic leukemia																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: HIGH DOSE

ANIMAL NUMBER	057	073	085	096	098	056	059	078	097	054	070	100	094	051	075	052	053	055	058	060	061	062	063	064	065
WEEKS ON STUDY	041	052	076	076	080	083	083	084	097	098	098	098	099	100	101	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																			X						
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, metastatic																									
Alveolar/bronchiolar adenoma																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Angioma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	+	+	+	–	–	+	–	+	–	+	+	–	–	+	–	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X	X							X		X		X									X
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma					X						X														
Follicular cell carcinoma																							X		
Parathyroid	–	+	+	+	–	–	–	–	+	+	–	–	+	+	+	+	+	–	+	–	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									X
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp															X	X									
Malignant lymphoma, histiocytic type																									
Ovary	+	+	–	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, histiocytic type											X														
Malignant lymphoma, mixed type								X		X		X		X									X	X	

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

ANIMAL NUMBER	0666	0667	0668	0669	0671	0672	0674	0676	0677	0679	0680	0681	0682	0683	0684	0686	0687	0688	0689	0690	0691	0692	0693	0695	0699	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor	X																									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplasm, NOS, metastatic				X																						1
Alveolar/bronchiolar adenoma					X																					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Angioma															X											1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma														X												1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenomatous polyp, NOS								X																		1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Adenoma, NOS			X		X								X													9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma													X							X						4
Follicular cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	–	–	+	–	–	+	+	+	+	+	+	+	–	+	+	+	–	+		35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp					X																					3
Malignant lymphoma, histiocytic type																								X		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	45
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																	X									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type			X																							1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type	X	X					X			X	X		X	X		X	X			X				X		17

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control		62.5 mg/kg	125 mg/kg
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	4/50 (8%)		0/47 (0%)	2/49 (4%)
Adjusted Rates (b)	11.4%		0.0%	5.7%
Terminal Rates (c)	4/35 (11%)		0/31 (0%)	2/35 (6%)
Week of First Observation	104			104
Life Table Tests (d)	P=0.225N		P=0.079N	P=0.336N
Incidental Tumor Tests (d)	P=0.225N		P=0.079N	P=0.336N
Cochran-Armitage Trend Test (d)	P=0.230N			
Fisher Exact Test (d)			P=0.066N	P=0.349N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	5/50 (10%)		0/47 (0%)	2/49 (4%)
Adjusted Rates (b)	13.5%		0.0%	5.7%
Terminal Rates (c)	4/35 (11%)		0/31 (0%)	2/35 (6%)
Week of First Observation	94			104
Life Table Tests (d)	P=0.122N		P=0.043N	P=0.218N
Incidental Tumor Tests (d)	P=0.125N		P=0.038N	P=0.226N
Cochran-Armitage Trend Test (d)	P=0.124N			
Fisher Exact Test (d)			P=0.033N	P=0.226N
Hematopoietic System: Malignant Lymphoma, Mixed Type				
Overall Rates (a)	19/50 (38%)	(e,f)	9/49 (18%)	17/50 (34%)
Adjusted Rates (b)	49.5%			43.2%
Terminal Rates (c)	16/35 (46%)			13/35 (37%)
Week of First Observation	82			84
Life Table Test (d)				P=0.427N
Incidental Tumor Test (d)				P=0.466N
Fisher Exact Test (d)				P=0.418N
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	22/50 (44%)	(e,f)	11/49 (22%)	19/50 (38%)
Adjusted Rates (b)	52.9%			47.2%
Terminal Rates (c)	16/35 (46%)			14/35 (40%)
Week of First Observation	70			84
Life Table Test (d)				P=0.364N
Incidental Tumor Test (d)				P=0.404N
Fisher Exact Test (d)				P=0.343N
Hematopoietic System: Lymphoma or Leukemia				
Overall Rates (a)	23/50 (46%)	(e,f)	12/49 (24%)	19/50 (38%)
Adjusted Rates (b)	54.1%			47.2%
Terminal Rates (c)	16/35 (46%)			14/35 (40%)
Week of First Observation	70			84
Life Table Test (d)				P=0.300N
Incidental Tumor Test (d)				P=0.329N
Fisher Exact Test (d)				P=0.272N
Circulatory System: Hemangioma				
Overall Rates (a)	4/50 (8%)	(e,f)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	11.4%			0.0%
Terminal Rates (c)	4/35 (11%)			0/35 (0%)
Week of First Observation	104			
Life Table Test (d)				P=0.063N
Incidental Tumor Test (d)				P=0.063N
Fisher Exact Test (d)				P=0.059N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	6/50 (12%)	(e) 2/49 (4%)	0/50 (0%)
Adjusted Rates (b)	16.4%		0.0%
Terminal Rates (c)	5/35 (14%)		0/35 (0%)
Week of First Observation	97		
Life Table Test (d)			P=0.018N
Incidental Tumor Test (d)			P=0.018N
Fisher Exact Test (d)			P=0.014N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/50 (6%)	0/49 (0%)	1/50 (2%)
Adjusted Rates (b)	8.0%	0.0%	2.9%
Terminal Rates (c)	2/35 (6%)	0/32 (0%)	1/35 (3%)
Week of First Observation	94		104
Life Table Tests (d)	P=0.180N	P=0.132N	P=0.307N
Incidental Tumor Tests (d)	P=0.176N	P=0.112N	P=0.307N
Cochran-Armitage Trend Test (d)	P=0.177N		
Fisher Exact Test (d)		P=0.125N	P=0.309N
Pituitary Gland: Adenoma			
Overall Rates (a)	12/49 (24%)	(f) 6/15 (40%)	9/49 (18%)
Adjusted Rates (b)	32.0%		22.4%
Terminal Rates (c)	9/34 (26%)		5/34 (15%)
Week of First Observation	98		76
Life Table Test (d)			P=0.323N
Incidental Tumor Test (d)			P=0.330N
Fisher Exact Test (d)			P=0.312N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	13/49 (27%)	(f) 7/15 (47%)	9/49 (18%)
Adjusted Rates (b)	33.9%		22.4%
Terminal Rates (c)	9/34 (26%)		5/34 (15%)
Week of First Observation	98		76
Life Table Test (d)			P=0.251N
Incidental Tumor Test (d)			P=0.248N
Fisher Exact Test (d)			P=0.234N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	1/50 (2%)	2/48 (4%)	4/50 (8%)
Adjusted Rates (b)	2.9%	6.3%	10.0%
Terminal Rates (c)	1/35 (3%)	2/32 (6%)	2/35 (6%)
Week of First Observation	104	104	80
Life Table Tests (d)	P=0.123	P=0.469	P=0.184
Incidental Tumor Tests (d)	P=0.109	P=0.469	P=0.159
Cochran-Armitage Trend Test (d)	P=0.119		
Fisher Exact Test (d)		P=0.485	P=0.181
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	2/48 (4%)	5/50 (10%)
Adjusted Rates (b)	2.9%	6.3%	12.7%
Terminal Rates (c)	1/35 (3%)	2/32 (6%)	3/35 (9%)
Week of First Observation	104	104	80
Life Table Tests (d)	P=0.064	P=0.469	P=0.107
Incidental Tumor Tests (d)	P=0.055	P=0.469	P=0.092
Cochran-Armitage Trend Test (d)	P=0.061		
Fisher Exact Test (d)		P=0.485	P=0.102

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	62.5 mg/kg	125 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	2/50 (4%)	(f) 0/40 (0%)	3/50 (6%)
Adjusted Rates (b)	5.7%		8.3%
Terminal Rates (c)	2/35 (6%)		2/35 (6%)
Week of First Observation	104		101
Life Table Test (d)			P=0.498
Incidental Tumor Test (d)			P=0.500
Fisher Exact Test (d)			P=0.500
Harderian Gland: Carcinoma			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	0/50 (0%)
Adjusted Rates (b)	2.9%	8.4%	0.0%
Terminal Rates (c)	1/35 (3%)	2/32 (6%)	0/35 (0%)
Week of First Observation	104	94	
Life Table Tests (d)	P=0.380N	P=0.285	P=0.500N
Incidental Tumor Tests (d)	P=0.378N	P=0.313	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.379N		
Fisher Exact Test (d)		P=0.301	P=0.500N
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	5.7%	11.5%	2.9%
Terminal Rates (c)	2/35 (6%)	3/32 (9%)	1/35 (3%)
Week of First Observation	104	94	104
Life Table Tests (d)	P=0.408N	P=0.306	P=0.500N
Incidental Tumor Tests (d)	P=0.407N	P=0.330	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.329	P=0.500N
All Sites: Benign Tumors			
Overall Rates (a)	23/50 (46%)	9/49 (18%)	18/50 (36%)
Adjusted Rates (b)	58.8%	23.6%	43.4%
Terminal Rates (c)	19/35 (54%)	5/32 (16%)	12/35 (34%)
Week of First Observation	94	70	76
Life Table Tests (d)	P=0.187N	P=0.007N	P=0.225N
Incidental Tumor Tests (d)	P=0.174N	P=0.002N	P=0.215N
Cochran-Armitage Trend Test (d)	P=0.170N		
Fisher Exact Test (d)		P=0.003N	P=0.208N
All Sites: Malignant Tumors			
Overall Rates (a)	29/50 (58%)	18/49 (37%)	21/50 (42%)
Adjusted Rates (b)	61.6%	42.6%	52.2%
Terminal Rates (c)	17/35 (49%)	9/32 (28%)	16/35 (46%)
Week of First Observation	70	83	84
Life Table Tests (d)	P=0.104N	P=0.076N	P=0.122N
Incidental Tumor Tests (d)	P=0.090N	P=0.020N	P=0.110N
Cochran-Armitage Trend Test (d)	P=0.066N		
Fisher Exact Test (d)		P=0.027N	P=0.081N
All Sites: All Tumors			
Overall Rates (a)	39/50 (78%)	22/49 (45%)	30/50 (60%)
Adjusted Rates (b)	82.9%	50.0%	69.5%
Terminal Rates (c)	27/35 (77%)	11/32 (34%)	22/35 (63%)
Week of First Observation	70	70	76
Life Table Tests (d)	P=0.086N	P=0.012N	P=0.093N
Incidental Tumor Tests (d)	P=0.064N	P<0.001N	P=0.067N
Cochran-Armitage Trend Test (d)	P=0.041N		
Fisher Exact Test (d)		P<0.001N	P=0.042N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Only 18 spleens and 12 lymph nodes were examined microscopically.
(f) Incomplete sampling of tissues

TABLE D4a. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	22/1,494 (1.5%)	34/1,494 (2.3%)	56/1,494 (3.7%)
SD (b)	1.96%	2.29%	2.77%
Range (c)			
High	4/50	3/49	5/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D4b. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	63/1,485 (4.2%)	23/1,485 (1.5%)	86/1,485 (5.8%)
SD (b)	2.85%	1.73%	3.30%
Range (c)			
High	5/50	2/48	6/50
Low	0/50	0/50	0/49

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Erosion		1 (2%)	
Hyperkeratosis			1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(49)	(50)
Hemorrhage	1 (2%)		
Inflammation, suppurative	5 (10%)		1 (2%)
Inflammation, acute	1 (2%)		
Deposit, NOS			1 (2%)
*Tracheal lumen	(50)	(49)	(50)
Hemorrhage	1 (2%)		
*Nasal mucosa	(50)	(49)	(50)
Degeneration, hyaline	1 (2%)		
#Tracheal gland	(50)	(6)	(49)
Multiple cysts		1 (17%)	
#Lung/bronchus	(50)	(47)	(49)
Hemorrhage	1 (2%)		
#Lung/bronchiole	(50)	(47)	(49)
Hyperplasia, epithelial			1 (2%)
#Lung	(50)	(47)	(49)
Congestion, NOS		2 (4%)	1 (2%)
Hemorrhage	1 (2%)	2 (4%)	
Inflammation, acute/chronic			1 (2%)
Perivascular cuffing	1 (2%)	6 (13%)	1 (2%)
Necrosis, focal			1 (2%)
Calcification, NOS	1 (2%)		1 (2%)
Alveolar macrophages	2 (4%)		
Hyperplasia, adenomatous			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Hyperplasia, lymphoid	13 (26%)	5 (10%)	13 (26%)
*Blood	(50)	(49)	(50)
Leukocytosis, neutrophilic			1 (2%)
#Bone marrow	(50)	(8)	(50)
Fibrosis, focal			1 (2%)
Hyperplasia, NOS	4 (8%)	1 (13%)	4 (8%)
Angiectasis			1 (2%)
Hyperplasia, granulocytic	16 (32%)	2 (25%)	9 (18%)
Hyperplasia, reticulum cell	1 (2%)		
#Spleen	(50)	(18)	(50)
Hematoma, NOS			1 (2%)
Necrosis, focal			1 (2%)
Necrosis, diffuse			1 (2%)
Russell body			1 (2%)
Hyperplasia, reticulum cell	2 (4%)	1 (6%)	2 (4%)
Hyperplasia, lymphoid	8 (16%)	2 (11%)	7 (14%)
Hematopoiesis	15 (30%)	5 (28%)	14 (28%)
#Lymph node	(49)	(12)	(50)
Histiocytosis			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(49)	(12)	(50)
Congestion, NOS		1 (8%)	
Erythrophagocytosis	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
#Mesenteric lymph node	(49)	(12)	(50)
Angiectasis	2 (4%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)		
#Renal lymph node	(49)	(12)	(50)
Erythrophagocytosis	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
#Lung	(50)	(47)	(49)
Leukocytosis, NOS			1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
#Salivary gland	(50)	(7)	(50)
Hyperplasia, lymphoid	4 (8%)		
#Liver	(50)	(49)	(50)
Hyperplasia, lymphoid		4 (8%)	
Hematopoiesis	2 (4%)	1 (2%)	2 (4%)
#Omentum	(50)	(8)	(50)
Hyperplasia, lymphoid			1 (2%)
#Cecum	(50)	(6)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Kidney	(50)	(49)	(50)
Hyperplasia, lymphoid		5 (10%)	2 (4%)
#Urinary bladder	(47)	(6)	(48)
Hyperplasia, lymphoid	3 (6%)		1 (2%)
#Mesovarium	(50)	(13)	(45)
Hyperplasia, lymphoid	1 (2%)		
#Adrenal cortex	(50)	(7)	(48)
Hematopoiesis			1 (2%)
#Thymus	(44)	(5)	(37)
Cyst, NOS	2 (5%)	1 (20%)	1 (3%)
Multiple cysts	1 (2%)		1 (3%)
Atrophy, NOS	5 (11%)	2 (40%)	3 (8%)
Hyperplasia, lymphoid	1 (2%)		3 (8%)
CIRCULATORY SYSTEM			
#Mandibular lymph node	(49)	(12)	(50)
Lymphangiectasis			1 (2%)
#Heart	(50)	(7)	(50)
Endocarditis, bacterial			1 (2%)
Inflammation, acute focal	1 (2%)		
#Heart/atrium	(50)	(7)	(50)
Thrombosis, NOS		1 (14%)	
#Myocardium	(50)	(7)	(50)
Inflammation, necrotizing		1 (14%)	
Fibrosis			1 (2%)
Degeneration, NOS			1 (2%)
*Uterine artery	(50)	(49)	(50)
Amyloidosis	1 (2%)		
*Tunica intima of vein	(50)	(49)	(50)
Hyperplasia, NOS	1 (2%)		
#Uterus	(50)	(40)	(50)
Thrombosis, NOS		1 (3%)	
#Ovary	(50)	(13)	(45)
Thrombosis, NOS	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Tooth	(50)	(49)	(50)
Dysplasia, NOS	2 (4%)		
#Salivary gland	(50)	(7)	(50)
Degeneration, NOS	1 (2%)		1 (2%)
#Liver	(50)	(49)	(50)
Fibrosis, focal			1 (2%)
Perivascular cuffing	1 (2%)		
Necrosis, focal	5 (10%)	7 (14%)	8 (16%)
Necrosis, diffuse	1 (2%)		
Necrosis, coagulative	1 (2%)	1 (2%)	1 (2%)
Metamorphosis, fatty	1 (2%)	6 (12%)	1 (2%)
Focal cellular change	4 (8%)	1 (2%)	1 (2%)
Hepatocytomegaly	1 (2%)		2 (4%)
Angiectasis	1 (2%)		1 (2%)
#Liver/centrilobular	(50)	(49)	(50)
Metamorphosis, fatty	1 (2%)	1 (2%)	
*Gallbladder	(50)	(49)	(50)
Degeneration, hyaline	1 (2%)		
*Gallbladder/mucosa	(50)	(49)	(50)
Multiple cysts			1 (2%)
#Pancreas	(49)	(8)	(50)
Multiple cysts			1 (2%)
Cystic ducts			1 (2%)
Edema, NOS		1 (13%)	
Inflammation with fibrosis			1 (2%)
Atrophy, NOS	1 (2%)		2 (4%)
#Pancreatic acinus	(49)	(8)	(50)
Degeneration, NOS			1 (2%)
Hypertrophy, focal		1 (13%)	
#Esophagus	(50)	(6)	(50)
Foreign body, NOS		1 (17%)	
Inflammation, chronic	1 (2%)		
#Glandular stomach	(50)	(8)	(50)
Cyst, NOS	3 (6%)		
Inflammation, acute	1 (2%)		
Inflammation, chronic			1 (2%)
Calcification, NOS	2 (4%)		2 (4%)
#Forestomach	(50)	(8)	(50)
Multiple cysts	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)		
Erosion			1 (2%)
Hyperkeratosis			1 (2%)
#Ileal submucosa	(50)	(7)	(49)
Amyloidosis	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Glomerulonephritis, acute	1 (2%)		
Pyelonephritis, acute			1 (2%)
Glomerulonephritis, chronic	1 (2%)		
Nephropathy	7 (14%)	40 (82%)	47 (94%)
Amyloidosis		1 (2%)	
Calcification, focal			1 (2%)
Metaplasia, osseous	2 (4%)		5 (10%)
#Kidney/cortex	(50)	(49)	(50)
Atrophy, focal	1 (2%)		
#Perirenal tissue	(50)	(49)	(50)
Perivascular cuffing		1 (2%)	
#Kidney/glomerulus	(50)	(49)	(50)
Degeneration, hyaline			1 (2%)
Amyloidosis	2 (4%)		1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Convoluted tubules	(50)	(49)	(50)
Degeneration, hyaline	1 (2%)		5 (10%)
#Urinary bladder	(47)	(6)	(48)
Congestion, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(15)	(49)
Cyst, NOS	3 (6%)		5 (10%)
Focal cellular change	1 (2%)		
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	17 (35%)	2 (13%)	15 (31%)
Angiectasis	2 (4%)	1 (7%)	1 (2%)
#Adrenal/capsule	(50)	(7)	(48)
Cyst, NOS			1 (2%)
Hyperplasia, stromal	49 (98%)	5 (71%)	46 (96%)
Metaplasia, osseous	1 (2%)		
#Adrenal cortex	(50)	(7)	(48)
Ectopia	3 (6%)		2 (4%)
Focal cellular change	1 (2%)		
Hypertrophy, focal	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)		
Hyperplasia, stromal	1 (2%)		
#Adrenal medulla	(50)	(7)	(48)
Focal cellular change	1 (2%)		
Hyperplasia, focal			2 (4%)
#Thyroid	(50)	(48)	(50)
Granuloma, NOS			1 (2%)
#Thyroid follicle	(50)	(48)	(50)
Follicular cyst, NOS		1 (2%)	3 (6%)
Multiple cysts	1 (2%)	3 (6%)	
Degeneration, NOS	1 (2%)		
Hyperplasia, papillary	1 (2%)	3 (6%)	2 (4%)
#Parathyroid	(39)	(3)	(35)
Hyperplasia, focal			1 (3%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Dilatation/ducts	9 (18%)		11 (22%)
Cyst, NOS			1 (2%)
Inflammation, acute	1 (2%)		
Hyperplasia, NOS	3 (6%)		
*Clitoral gland	(50)	(49)	(50)
Inflammation, acute/chronic	1 (2%)		
#Uterus	(50)	(40)	(50)
Dilatation, NOS	3 (6%)	2 (5%)	3 (6%)
Inflammation, acute		1 (3%)	
Inflammation, acute necrotizing		1 (3%)	
Abscess, NOS			2 (4%)
Inflammation, pyogranulomatous	1 (2%)		
Necrosis, NOS		1 (3%)	
Angiectasis		1 (3%)	
#Uterus/endometrium	(50)	(40)	(50)
Cyst, NOS		2 (5%)	1 (2%)
Multiple cysts	3 (6%)	1 (3%)	1 (2%)
Inflammation, suppurative		1 (3%)	1 (2%)
Pyometra	1 (2%)		
Inflammation, acute	1 (2%)		
Hyperplasia, cystic	41 (82%)	34 (85%)	42 (84%)
Angiectasis	4 (8%)	1 (3%)	2 (4%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Fallopian tube	(50)	(40)	(50)
Calcification, NOS			1 (2%)
Hyperplasia, epithelial			1 (2%)
#Ovary	(50)	(13)	(45)
Cyst, NOS	9 (18%)	6 (46%)	9 (20%)
Multiple cysts	3 (6%)	1 (8%)	1 (2%)
Hemorrhagic cyst	5 (10%)	1 (8%)	4 (9%)
Abscess, NOS	2 (4%)		1 (2%)
Calcification, NOS	1 (2%)		1 (2%)
Hyperplasia, granulosa cell			1 (2%)
Angiectasis			1 (2%)
#Mesovarium	(50)	(13)	(45)
Calcification, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(7)	(50)
Hydrocephalus, NOS			1 (2%)
Epidermal inclusion cyst	1 (2%)		
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate	3 (6%)	1 (14%)	2 (4%)
Perivascular cuffing			1 (2%)
#Corpus callosum	(50)	(7)	(50)
Epidermal inclusion cyst	1 (2%)		
#Brain/thalamus	(50)	(7)	(50)
Calcification, NOS	24 (48%)	4 (57%)	25 (50%)
#Cerebellum	(50)	(7)	(50)
Perivascular cuffing		1 (14%)	
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(49)	(50)
Hemorrhage			1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, chronic	2 (4%)		
Inflammation, chronic focal			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(49)	(50)
Osteosclerosis	21 (42%)	25 (51%)	40 (80%)
BODY CAVITIES			
*Mediastinum	(50)	(49)	(50)
Inflammation, chronic			1 (2%)
Necrosis, fat			1 (2%)
*Pleura	(50)	(49)	(50)
Inflammation, acute			1 (2%)
*Mesentery	(50)	(49)	(50)
Abscess, NOS	1 (2%)		1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Hemorrhage			1 (2%)
Inflammation, granulomatous	1 (2%)		
Knee			
Dyschondroplasia	3	4	6
Adipose tissue			
Necrosis, fat	2		3

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy		1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

GENETIC TOXICOLOGY OF 4-HEXYLRESORCINOL

TABLE E1. MUTAGENICITY OF 4-HEXYLRESORCINOL IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
Study Performed at EG&G Mason Research Institute							
TA100	0	95 ± 3.9	121 ± 14.6	122 ± 4.7	138 ± 7.7	111 ± 6.8	107 ± 1.3
	0.3	127 ± 1.5	124 ± 3.0	--	--	--	--
	1	107 ± 4.8	133 ± 9.8	--	130 ± 11.1	--	121 ± 11.7
	3.3	99 ± 1.7	120 ± 0.9	101 ± 11.2	120 ± 7.2	112 ± 8.2	115 ± 3.7
	10	113 ± 4.7	121 ± 2.3	136 ± 2.2	135 ± 5.4	131 ± 5.2	133 ± 8.7
	22	(c) 91 ± 6.0	(c) 104 ± 14.0	--	--	--	--
	33	--	--	127 ± 5.7	121 ± 9.6	110 ± 4.2	138 ± 2.1
	100	--	--	(c) 133 ± 6.1	(c) 132 ± 5.5	Toxic	(c) 95 ± 2.0
	220	--	--	Toxic	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Equivocal
	Positive control (d)	1,395 ±113.0	1,015 ± 44.7	1,146 ± 28.6	918 ± 21.8	1,025 ± 30.8	859 ± 4.0
TA1535	0	21 ± 1.5	19 ± 0.9	11 ± 1.9	11 ± 1.2	10 ± 2.5	8 ± 1.5
	0.3	23 ± 1.5	18 ± 2.9	--	--	--	--
	1	18 ± 0.0	19 ± 5.0	--	11 ± 0.6	--	10 ± 1.8
	3.3	17 ± 3.2	19 ± 0.0	13 ± 1.0	14 ± 0.3	14 ± 1.2	12 ± 1.9
	10	19 ± 1.9	24 ± 1.2	10 ± 1.8	11 ± 1.2	9 ± 1.5	13 ± 0.9
	22	(c) 13 ± 1.5	(c) 15 ± 1.5	--	--	--	--
	33	--	--	11 ± 0.7	13 ± 2.4	12 ± 1.5	11 ± 0.6
	100	--	--	(c) 12 ± 0.9	(c) 6 ± 1.2	(c) 4 ± 0.5	(c) 6 ± 0.9
	220	--	--	Toxic	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	907 ± 12.4	836 ± 12.5	74 ± 7.2	94 ± 1.5	82 ± 6.5	76 ± 2.0
TA1537	0	3 ± 0.7	6 ± 0.3	3 ± 1.2	6 ± 0.7	7 ± 0.7	8 ± 1.2
	0.3	4 ± 0.9	3 ± 0.3	--	--	--	--
	1	7 ± 2.3	6 ± 1.9	--	6 ± 1.3	--	9 ± 1.2
	3.3	3 ± 1.2	4 ± 1.0	7 ± 1.5	12 ± 1.8	5 ± 0.9	8 ± 1.8
	10	6 ± 1.2	9 ± 1.7	6 ± 1.0	8 ± 0.7	7 ± 2.2	6 ± 1.2
	22	(c) 3 ± 0.7	(c) 5 ± 0.9	--	--	--	--
	33	--	--	6 ± 0.9	7 ± 2.3	6 ± 1.8	8 ± 1.2
	100	--	--	(c) 4 ± 0.6	(c) 6 ± 1.8	(c) 2 ± 0.3	(c) 7 ± 1.2
	220	--	--	Toxic	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	153 ± 27.2	428 ± 23.7	136 ± 8.7	81 ± 7.8	119 ± 3.0	61 ± 5.0
TA98	0	10 ± 0.7	17 ± 0.9	16 ± 2.7	30 ± 4.1	19 ± 1.5	22 ± 1.5
	0.3	14 ± 2.7	20 ± 2.5	--	--	--	--
	1	12 ± 1.2	17 ± 1.0	--	26 ± 2.6	--	22 ± 1.8
	3.3	14 ± 3.7	18 ± 1.9	20 ± 1.7	34 ± 1.5	17 ± 1.0	27 ± 1.2
	10	11 ± 2.3	21 ± 0.7	28 ± 3.5	31 ± 4.6	21 ± 4.3	31 ± 2.4
	22	(c) 13 ± 0.9	(c) 17 ± 2.7	--	--	--	--
	33	--	--	24 ± 0.9	31 ± 1.5	19 ± 0.3	21 ± 1.9
	100	--	--	(c) 21 ± 0.6	(c) 27 ± 1.3	Toxic	(c) 21 ± 1.5
	220	--	--	Toxic	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	1,037 ± 44.2	1,463 ± 36.5	1,202 ± 7.6	1,035 ± 19.2	1,333 ± 50.9	836 ± 36.7

TABLE E1. MUTAGENICITY OF 4-HEXYLRESORCINOL IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
Study Performed at SRI International							
TA100	0	104 ± 4.6	98 ± 6.7	117 ± 5.3	113 ± 5.9	133 ± 10.4	105 ± 4.0
	1	--	105 ± 9.0	--	132 ± 10.8	--	115 ± 0.7
	3	144 ± 9.6	92 ± 11.8	142 ± 13.1	128 ± 10.3	136 ± 13.0	113 ± 3.8
	10	150 ± 2.0	95 ± 5.9	127 ± 13.1	120 ± 11.9	141 ± 18.8	110 ± 8.8
	33	(c) 15 ± 14.7	(c) 0 ± 0.0	140 ± 12.7	110 ± 22.1	130 ± 3.5	123 ± 7.8
	100	Toxic	Toxic	126 ± 11.2	108 ± 12.1	82 ± 42.2	(c) 0 ± 0.0
	333	Toxic	--	Toxic	--	Toxic	--
	Trial summary	Equivocal	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	419 ± 12.6	336 ± 7.9	778 ± 10.2	991 ± 7.8	495 ± 23.2	392 ± 5.5
TA1535	0	32 ± 1.8	21 ± 3.2	35 ± 4.3	28 ± 1.5	24 ± 1.3	28 ± 0.7
	1	--	9 ± 2.7	--	24 ± 6.2	--	29 ± 1.8
	3	22 ± 2.4	4 ± 1.2	26 ± 1.0	12 ± 2.2	35 ± 4.4	22 ± 2.8
	10	20 ± 3.5	5 ± 2.1	34 ± 6.9	21 ± 4.3	28 ± 0.7	25 ± 3.7
	33	10 ± 3.8	(c) 0 ± 0.0	22 ± 3.4	18 ± 3.8	27 ± 1.7	24 ± 6.7
	100	(c) 0 ± 0.0	Toxic	Toxic	(c) 0 ± 0.0	7 ± 4.4	(c) 0 ± 0.0
	333	Toxic	--	Toxic	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	379 ± 22.3	334 ± 14.3	356 ± 53.3	337 ± 24.8	120 ± 13.2	232 ± 8.0
TA1537	0	6 ± 0.6	7 ± 1.3	7 ± 0.7	7 ± 1.5	15 ± 1.2	11 ± 2.5
	1	--	3 ± 0.9	--	11 ± 1.8	--	14 ± 1.2
	3	5 ± 1.3	5 ± 0.9	6 ± 1.2	8 ± 2.3	15 ± 1.5	13 ± 4.1
	10	5 ± 2.2	5 ± 1.0	6 ± 0.9	6 ± 0.9	13 ± 2.1	12 ± 1.8
	33	5 ± 2.6	(c) 0 ± 0.0	6 ± 1.9	8 ± 2.5	16 ± 1.0	8 ± 1.0
	100	6 ± 6.0	Toxic	7 ± 0.9	(c) 0 ± 0.0	(c) 2 ± 2.0	(c) 0 ± 0.0
	333	Toxic	--	Toxic	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	277 ± 25.1	177 ± 7.0	454 ± 17.6	248 ± 2.3	204 ± 14.8	121 ± 12.5
TA98	0	18 ± 3.8	15 ± 0.7	26 ± 2.9	31 ± 3.4	33 ± 4.0	38 ± 3.2
	1	--	14 ± 1.2	--	25 ± 2.7	--	37 ± 2.1
	3	17 ± 6.0	13 ± 3.0	32 ± 4.9	26 ± 1.2	56 ± 0.9	36 ± 2.3
	10	20 ± 3.0	10 ± 2.4	33 ± 3.0	28 ± 4.7	39 ± 5.0	37 ± 2.4
	33	(c) 1 ± 0.7	(c) 0 ± 0.0	36 ± 4.3	31 ± 3.4	41 ± 4.7	42 ± 5.1
	100	Toxic	Toxic	42 ± 2.2	(c) 0 ± 0.0	(c) 5 ± 5.3	(c) 0 ± 0.0
	333	Toxic	--	Toxic	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Equivocal	Negative
	Positive control (d)	730 ± 18.6	693 ± 16.6	477 ± 29.8	858 ± 48.1	401 ± 33.1	236 ± 16.8

(a) The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (EG&G study: dimethyl sulfoxide; SRI study: 95% ethanol) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE E2. MUTAGENICITY OF 4-HEXYLRESORCINOL IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
-S9					
Trial 1					
Ethyl alcohol (d)		69.3 ± 8.3	99.7 ± 13.1	89.0 ± 3.6	44.0 ± 4.5
4-Hexylresorcinol	1.25	68.0 ± 5.7	102.0 ± 13.1	51.3 ± 3.3	25.7 ± 2.9
	2.5	78.0 ± 11.2	98.0 ± 17.1	67.0 ± 1.0	30.0 ± 5.1
	5	67.0 ± 2.0	114.5 ± 9.5	60.0 ± 13.0	30.5 ± 7.5
	10	66.7 ± 6.1	101.0 ± 10.2	52.3 ± 4.6	27.0 ± 4.0
	15	75.7 ± 8.4	36.7 ± 7.4	79.7 ± 5.8	36.3 ± 6.1
	20	(e) 81	105	64	27
	30	Lethal	--	--	--
Methyl methanesulfonate	5	65.0 ± 13.1	79.3 ± 3.8	440.3 ± 44.8	(f) 235.7 ± 28.6
Trial 2					
Ethyl alcohol (d)		81.5 ± 7.9	99.8 ± 19.6	98.5 ± 8.3	40.5 ± 2.4
4-Hexylresorcinol	2.5	95.7 ± 3.0	120.0 ± 6.0	83.0 ± 4.0	29.0 ± 2.1
	5	87.7 ± 10.1	130.7 ± 5.0	88.7 ± 18.0	33.7 ± 4.4
	7.5	85.0 ± 5.0	121.5 ± 4.5	80.5 ± 9.5	31.5 ± 1.5
	10	87.7 ± 2.8	119.3 ± 10.5	106.3 ± 11.6	40.3 ± 3.3
	15	88.0 ± 3.2	82.3 ± 13.9	97.7 ± 11.4	37.7 ± 5.2
	20	(g) 80.0 ± 1.0	31.0 ± 17.0	136.0 ± 29.0	57.0 ± 13.0
	25	Lethal	--	--	--
Methyl methanesulfonate	5	71.7 ± 7.5	65.3 ± 7.5	613.3 ± 29.6	(f) 288.3 ± 18.0
+S9 (h)					
Trial 1					
Ethyl alcohol (d)		100.8 ± 2.8	100.0 ± 4.3	278.0 ± 10.4	92.3 ± 4.9
4-Hexylresorcinol	2.5	61.3 ± 5.5	62.7 ± 2.3	142.7 ± 8.1	77.7 ± 2.7
	5	64.0 ± 4.2	48.0 ± 0.6	204.7 ± 35.2	109.7 ± 26.3
	10	77.7 ± 4.3	33.0 ± 2.5	378.0 ± 59.1	(f) 161.0 ± 17.2
	15	71.0 ± 2.0	36.3 ± 5.6	315.0 ± 10.7	(f) 148.7 ± 5.8
	20	90.7 ± 8.5	25.7 ± 2.9	346.7 ± 25.9	(f) 128.7 ± 10.9
	30	84.0 ± 6.1	18.3 ± 0.9	390.3 ± 91.7	(f) 151.3 ± 24.4
Methylcholanthrene	2.5	100.0 ± 2.9	95.7 ± 9.9	514.3 ± 33.6	(f) 172.3 ± 13.3
Trial 2					
Ethyl alcohol (d)		97.0 ± 7.2	100.0 ± 5.7	266.5 ± 29.1	90.8 ± 5.0
4-Hexylresorcinol	2.5	71.7 ± 3.9	75.3 ± 4.4	184.7 ± 17.9	85.7 ± 3.8
	5	85.0 ± 5.6	72.3 ± 6.4	368.3 ± 32.3	(f) 144.7 ± 9.4
	10	72.7 ± 0.7	50.7 ± 1.8	319.0 ± 20.5	(f) 147.0 ± 10.1
	15	91.7 ± 6.2	38.7 ± 4.4	398.3 ± 42.8	(f) 144.7 ± 13.9
	20	80.7 ± 5.7	29.0 ± 8.2	443.3 ± 41.6	(f) 186.7 ± 28.2
	30	71.0 ± 11.7	9.7 ± 2.3	409.3 ± 77.4	(f) 201.0 ± 48.1
	40	Lethal	--	--	--
Methylcholanthrene	2.5	84.0 ± 7.0	81.0 ± 24.1	544.7 ± 93.8	(f) 225.0 ± 57.7

TABLE E2. MUTAGENICITY OF 4-HEXYLRESORCINOL IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

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

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 4-HEXYLRESORCINOL (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)--Summary: Positive								
Dimethyl sulfoxide		50	1,049	399	0.38	8.0	26.0	--
4-Hexylresorcinol	16	50	1,045	453	0.43	9.1	26.0	113.8
	18	50	1,030	488	0.47	9.8	26.0	122.5
	20	50	1,048	508	0.48	10.2	26.0	127.5
Mitomycin C	0.005	25	524	735	1.40	29.4	26.0	367.5
+S9 (d)--Summary: Negative								
Dimethyl sulfoxide		50	1,046	448	0.43	9.0	26.0	--
4-Hexylresorcinol	5	50	1,046	428	0.41	8.6	26.0	95.6
	16	50	1,045	466	0.45	9.3	26.0	103.3
	50	50	1,049	488	0.47	9.8	26.0	108.9
Cyclophosphamide	1	50	1,049	912	0.87	18.2	26.0	202.2

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

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 4-HEXYLRESORCINOL (a)

	−S9 (b)					+S9 (c)			
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time 13.0 h					Harvest time 12.0 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	4	0.04	4		100	5	0.05	4
4-Hexylresorcinol					4-Hexylresorcinol				
5	100	3	0.03	3	1.6	100	7	0.07	6
16	100	4	0.04	4	5	100	6	0.06	6
50	100	3	0.03	3	16	100	7	0.07	7
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.150	50	13	0.26	24	15	50	19	0.38	30

(a) Study performed at Columbia University. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (mouse hepatitis virus) (6 mo)	MHV (12, 18, 24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	

II. Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	8/10	RCV
12	--	None positive
18	1/10	RCV
24	2/10	RCV
MICE		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX G

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

Pelleted Diet: December 1980 to January 1983

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

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

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried 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) NIH, 1978; NCI, 1976
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

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

	Amount	Source
Vitamin		
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 activity
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
Mineral		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.85 ± 0.78	22.7-25.3	24
Crude fat (percent by weight)	5.02 ± 0.44	4.2-5.7	24
Crude fiber (percent by weight)	3.31 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.44 ± 0.44	5.7-7.43	24
Essential Amino Acid (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acid (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamin			
Vitamin A (IU/kg)	10,917 ± 1,876	8,210-15,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.8 ± 2.0	14.0-21.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Mineral			
Calcium (percent)	1.25 ± 0.15	1.08-1.69	24
Phosphorus (percent)	0.98 ± 0.06	0.88-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.48 ± 0.17	<0.29-1.06	24
Cadmium (ppm) (a)	<0.10		24
Lead (ppm)	1.00 ± 0.74	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	9.22 ± 3.62	3.8-17.0	24
Nitrite nitrogen (ppm) (c)	2.16 ± 1.53	0.4-6.9	24
BHA (ppm) (d,e)	6.68 ± 4.95	<0.4-17.0	24
BHT (ppm) (d)	3.45 ± 2.56	0.9-12.0	24
Aerobic plate count (CFU/g) (f)	40,557 ± 29,431	4,900-88,000	23
Aerobic plate count (CFU/g) (g)	77,617 ± 183,824	4,900-930,000	24
Coliform (MPN/g) (h)	16.6 ± 22.9	<3-93	22
Coliform (MPN/g) (i)	80.20 ± 236.3	<3-1,100	24
E. coli (MPN/g) (j)	<3		24
Total nitrosamines (ppb) (k,l)	4.63 ± 4.19	<0.8-18.5	21
Total nitrosamines (ppb) (k,m)	27.15 ± 64.35	0.8-273.2	24
N-Nitrosodimethylamine (ppb) (k,l)	3.43 ± 3.96	0.8-16.5	21
N-Nitrosodimethylamine (ppb) (k,m)	25.71 ± 64.90	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.05 ± 0.49	0.3-2.9	24
Pesticide (ppm)			
α-BHC (a,n)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (o)	<0.05	0.09; 8/26/81	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (o)	<0.1	0.2; 4/27/81	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (p)	0.10 ± 0.07	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

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

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: Alfalfa, grains, and fish meal
(d) Source of contamination: Soy oil and fish meal
(e) One batch contained less than 0.1 ppm.
(f) Mean, standard deviation, and range exclude one very high value of 930,000 obtained for the batch produced on 12/22/82.
(g) Mean, standard deviation, and range include the high value listed in footnote (f).
(h) Mean, standard deviation, and range exclude one very high value of 1,100 obtained for the batch produced on 12/16/80 and one high value of 460 obtained in the batch produced on 9/23/82 (MPN = most probable number).
(i) Mean, standard deviation, and range include the high values listed in footnote (h).
(j) All values were less than 3 MPN/g.
(k) All values were corrected for percent recovery.
(l) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in footnote (l).
(n) BHC = hexachlorocyclohexane or benzene hexachloride.
(o) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(p) Thirteen batches contained more than 0.05 ppm.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The archival records and pathology materials for the 2-year gavage studies of 4-hexylresorcinol in F344/N rats and B6C3F$_1$ mice were audited for accuracy, completeness, and procedures consistent with the FDA Good Laboratory Practice (GLP) regulations for nonclinical laboratory studies. The studies were conducted at Physiological Research Laboratories, Minneapolis, Minnesota, under a subcontract with Tracor Jitco, Inc., for the National Toxicology Program (NTP). Rats were exposed to 4-hexylresorcinol for 103 weeks from March 10, 1981, to February 28, 1983, and mice, from March 24, 1981, to March 14, 1983. The studies commenced 7 months before the date (October 1, 1981) when the NTP required studies to be conducted in full compliance with the GLP regulations.

The audit was conducted at the NTP Archives, Research Triangle Park, North Carolina, from April 21 to April 29, 1986, by the following personnel of the Product Safety Assessment Division of Dynamac Corporation: T.E. Arledge, D.V.M.; J.C. Bhandari, D.V.M., Ph.D.; A.D. Bridge, B.S.; R.J. Egsegian, B.S.; S.K. Hall, B.S.; C.C. McGhee, D.V.M., Ph.D.; D.J. Mull, B.S.; S.P. Shrivastava, Ph.D.; S.B. Singh, D.V.M., Ph.D. The audit consisted of an indepth review of the data collected during the conduct of the studies, pathology materials, correspondence, and the NTP Technical Report (Staff Review I Draft) dated September 1986. The full report of the audit is on file at the NIEHS. The audit included a review of:

(1) The inlife toxicology data for all records pertaining to study design, animal identification, palpable mass observations, mortality, and diagnostic serology; special studies on eye examinations and light intensity surveys; and body weight data and clinical observations for 50% of the cages and a 10% randomly selected sample of animals, respectively.

(2) The correspondence and records of chemical shipment and receipt; Midwest Research Institute (MRI) identity, purity, and stability data; MRI recommendations for analytical methods, dose preparation, and storage conditions; records for bulk chemical reanalysis; chemical/vehicle, referee, feed, and water analyses; and chemical use and dose preparation logs.

(3) All Individual Animal Data Records (IADRs) for correlation of gross observations with microscopic diagnoses, microscopic description vs. diagnosis, disposition codes, and condition codes vs. hours until necropsy.

(4) Wet tissue bag count (100%) and wet tissue (10% random sample plus any noncorrelations between gross observations with microscopic diagnoses or gross observations with clinical observations) examination for untrimmed potential lesions and carcass identification; slide/block matching for 100% of vehicle control and high dose groups.

(5) Data entry errors on IADR forms for 10% of the study animals.

(6) Quality assessment report and Individual Animal Tumor Pathology Tables for tissue accountability (100%).

The audit showed that the records for the studies were complete, except for some of the records for gavage dosing, room air flow testing, and balance calibration. All pathology materials were available with the exception that the right ear, which indicated the 100's digit of the animal number for low dose animals, was not preserved. The audit findings indicated that the inlife and chemistry portions of the studies were conducted and documented adequately. Examination of more than 4,000 wet tissues from 87 animals indicated that, with the exception of the missing right ear for low dose animals, animals were identified properly and there were a few untrimmed potential lesions; most of the untrimmed potential lesions were not in target organs, represented minor, inconsequential lesions, or were distributed across the study groups, and therefore, did not influence the interpretation of the data. Thus, the records and materials at the NTP archives support the data and results presented in the Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PUBLISHED AS OF APRIL 1988

TR No.	CHEMICAL
200	2,6-Toluenediamine Dihydrochloride
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
202	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Dermal)
203	Phenol
204	Benzoin
205	4,4'-Oxydianiline
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl 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)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. 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(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
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
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol

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