

**NATIONAL TOXICOLOGY PROGRAM**  
**Technical Report Series**  
**No. 330**



**TOXICOLOGY AND CARCINOGENESIS**

**STUDIES OF**

**4-HEXYLRESORCINOL**

**(CAS NO. 136-77-6)**

**IN F344/N RATS AND B6C3F<sub>1</sub> 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<sub>1</sub> MICE  
(GAVAGE STUDIES)**

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Public Health Service  
National Institutes of Health**

## 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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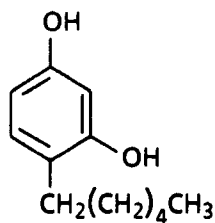
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## 4-HEXYLRESORCINOL

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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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.

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\*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**

<b>Male F344/N Rats</b>	<b>Female F344/N Rats</b>	<b>Male B6C3F<sub>1</sub> Mice</b>	<b>Female B6C3F<sub>1</sub> Mice</b>
<b>Doses</b> 0, 62.5, or 125 mg/kg 4-hexyl-resorcinol in corn oil 5 d/wk			
<b>Survival rates in the 2-year study</b> 30/50; 29/50; 33/50			
<b>Nonneoplastic effects</b> None			
<b>Neoplastic effects</b> None			
<b>Level of evidence of carcinogenic activity</b> No evidence			
<b>Other considerations</b> Decrease in mononuclear cell leukemia			
<b>Genetic toxicology</b> 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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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**

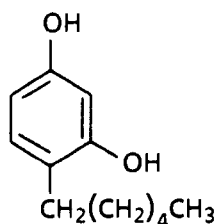
**Toxicity of 4-Hexylresorcinol**

**Genetic Toxicology**

**Carcinogenicity of 4-Hexylresorcinol**

**Study Rationale**

# I. INTRODUCTION



## 4-HEXYLRESORCINOL

CAS No. 136-77-6

C<sub>12</sub>H<sub>18</sub>O<sub>2</sub>

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<sub>50</sub> 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<sub>50</sub> 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 (Boylard 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<sup>+/-</sup> 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  $5 \times 10^{-5}$  M (Morishima et al., 1976a,b). In addition, [<sup>3</sup>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 (Boylard 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.

# I. INTRODUCTION

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## Study Rationale

4-Hexylresorcinol is one of six phenolic anti-septics 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**

**PREPARATION AND CHARACTERIZATION OF  
DOSE MIXTURES**

**SIXTEEN-DAY STUDIES**

**THIRTEEN-WEEK STUDIES**

**TWO-YEAR STUDIES**

**Study Design**

**Source and Specifications of Animals**

**Animal Maintenance**

**Clinical Examinations and Pathology**

**Statistical Methods**

## 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 (Sumnerfield, 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 (Sadler 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  $\mu$ Bondapak C<sub>18</sub> 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,

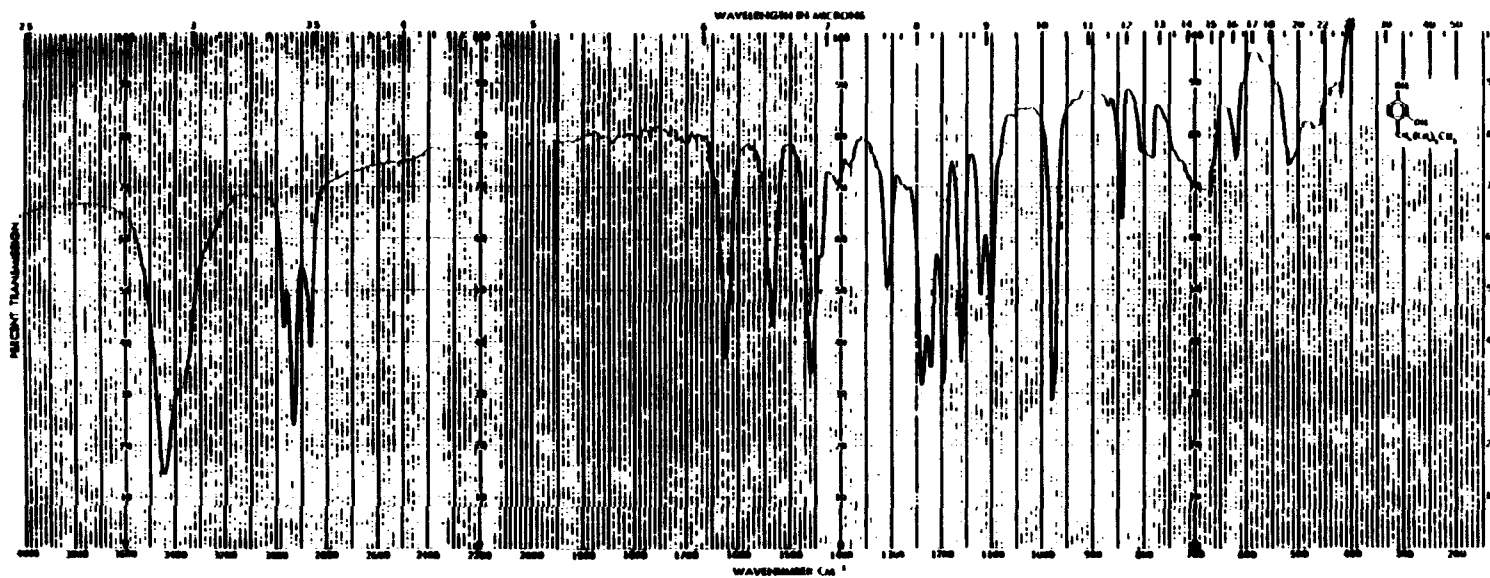


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF 4-HEXYLRESORCINOL (LOT NO. 20818/02)

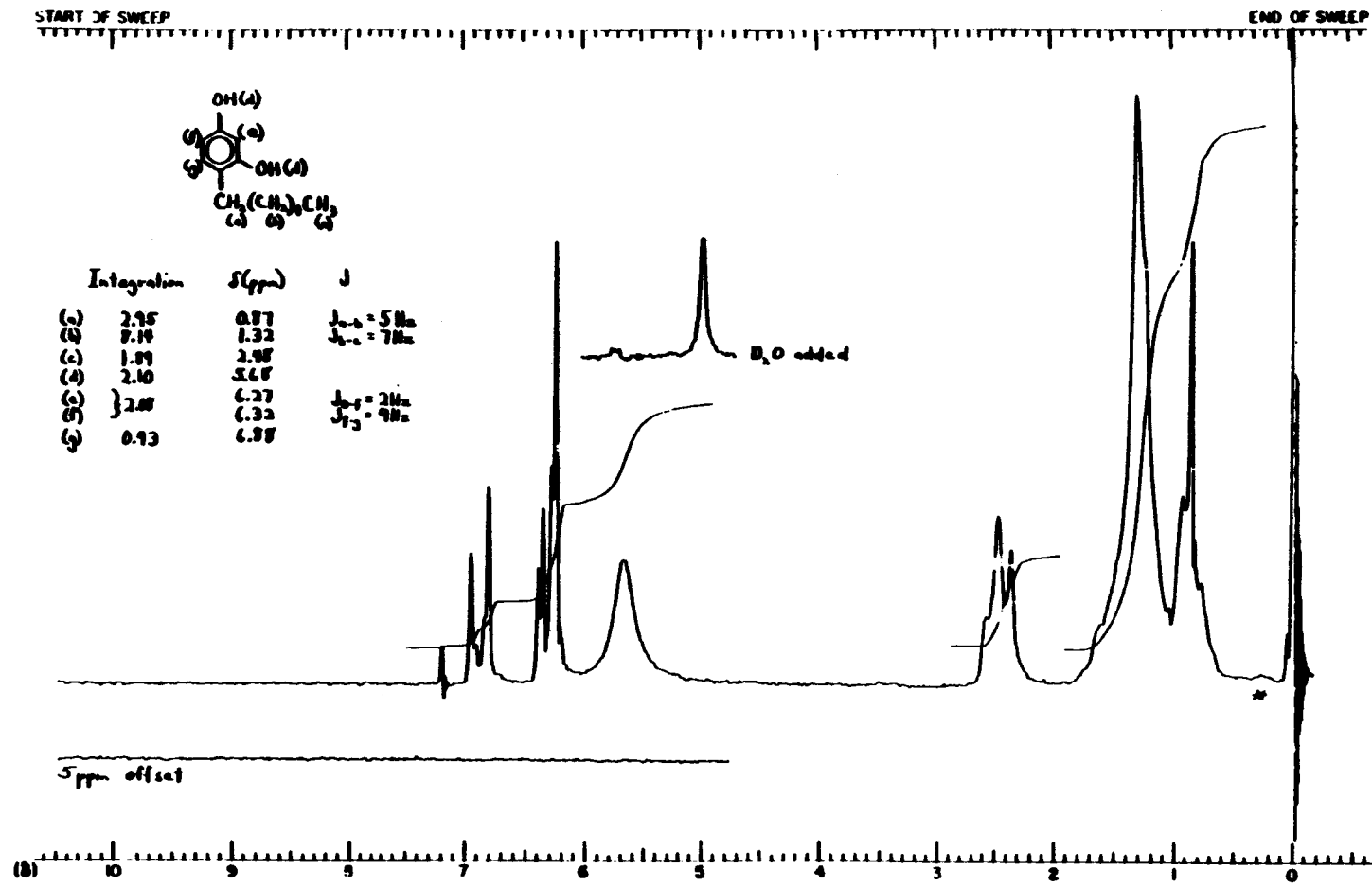


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4-HEXYLRESORCINOL (LOT NO. 20818/02)

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

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
<b>Preparation</b> 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
<b>Maximum Storage Time</b> Not available	1 wk	2 wk
<b>Storage Conditions</b> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> (C57BL/6N, female × C3H/HeN MTV<sup>-</sup>, 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<sub>1</sub> 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**

<b>Sixteen-Day Studies</b>	<b>Thirteen-Week Studies</b>	<b>Two-Year Studies</b>
<b>EXPERIMENTAL DESIGN</b>		
<b>Size of Study Groups</b> 5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
<b>Doses</b> 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
<b>Date of First Dose</b> 9/4/79	3/3/80	Rats--3/10/81; mice--3/24/81
<b>Date of Last Dose</b> 9/19/79	5/29/80	Rats--2/28/83; mice--3/4/83
<b>Duration of Dosing</b> 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)
<b>Type and Frequency of Observation</b> 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
<b>Necropsy and Histologic Examination</b>		
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, sternbrae 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
<b>ANIMALS AND ANIMAL MAINTENANCE</b>		
<b>Strain and Species</b> F344/N rats; B6C3F <sub>1</sub> mice	F344/N rats; B6C3F <sub>1</sub> mice	F344/N rats; B6C3F <sub>1</sub> mice
<b>Animal Source</b> Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
<b>Study Laboratory</b> Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
<b>Method of Animal Identification</b> 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
<b>ANIMALS AND ANIMAL MAINTENANCE (Continued)</b>		
<b>Time Held Before Study</b> 18 d	20 d	14 d
<b>Age When Placed on Study</b> Rats--8 wk; mice--7-9 wk	Rats--7 wk; mice--8-9 wk	Rats--6-7 wk; mice--7-8 wk
<b>Age When Killed</b> Rats--10 wk; mice--9-11 wk	Rats--20 wk; mice--21-23 wk	Rats--110-111 wk; mice--111-112 wk
<b>Necropsy Dates</b> 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
<b>Method of Animal Distribution</b> Animals assigned to groups according to a table of random numbers	Same as 16-d studies	By tables of random numbers
<b>Feed</b> 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
<b>Bedding</b> 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)
<b>Water</b> 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
<b>Cages</b> Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 16-d studies	Same as 16-d studies
<b>Cage Filters</b> Reemay polyester filters (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies
<b>Animals per Cage</b> 5	5	5
<b>Other Chemicals on Study in the Same Room</b> None	None	None
<b>Animal Room Environment</b> 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

## II. MATERIALS AND METHODS

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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<sub>1</sub> mice used in these studies. The influence of the potential genetic non-uniformity 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

## II. MATERIALS AND METHODS

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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**

### III. RESULTS: RATS

#### 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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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
<b>FEMALE</b>					
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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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)
<b>FEMALE</b>					
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.

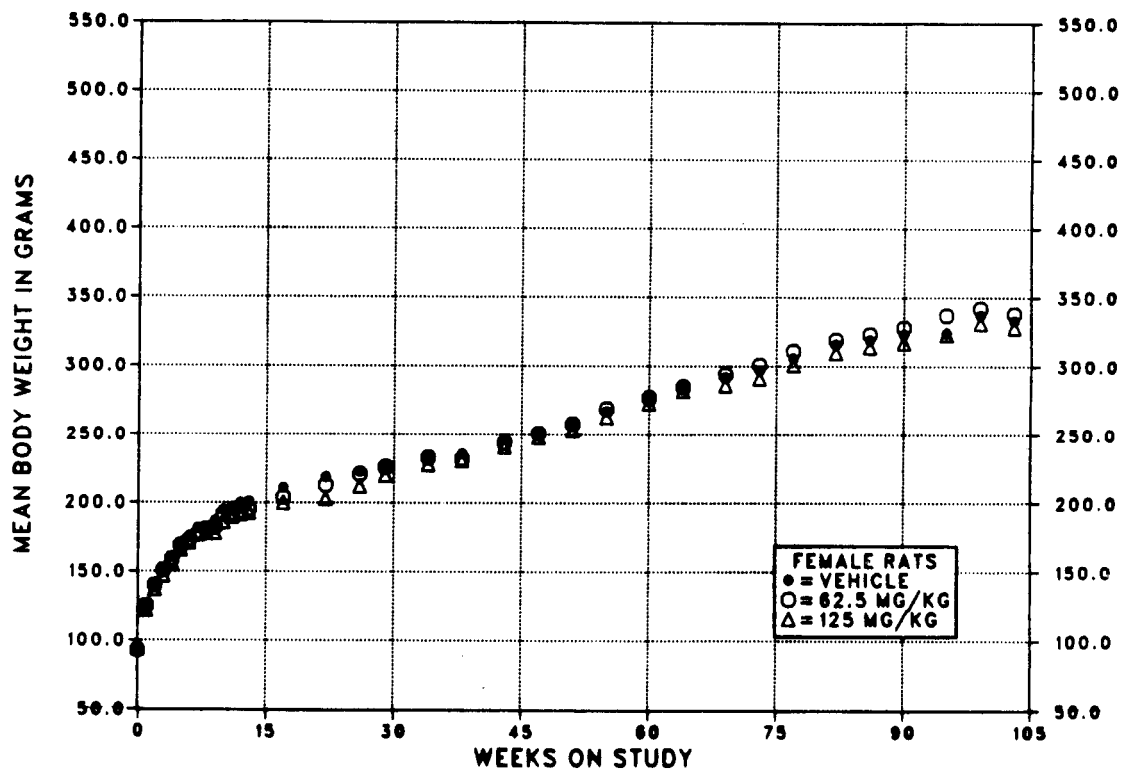
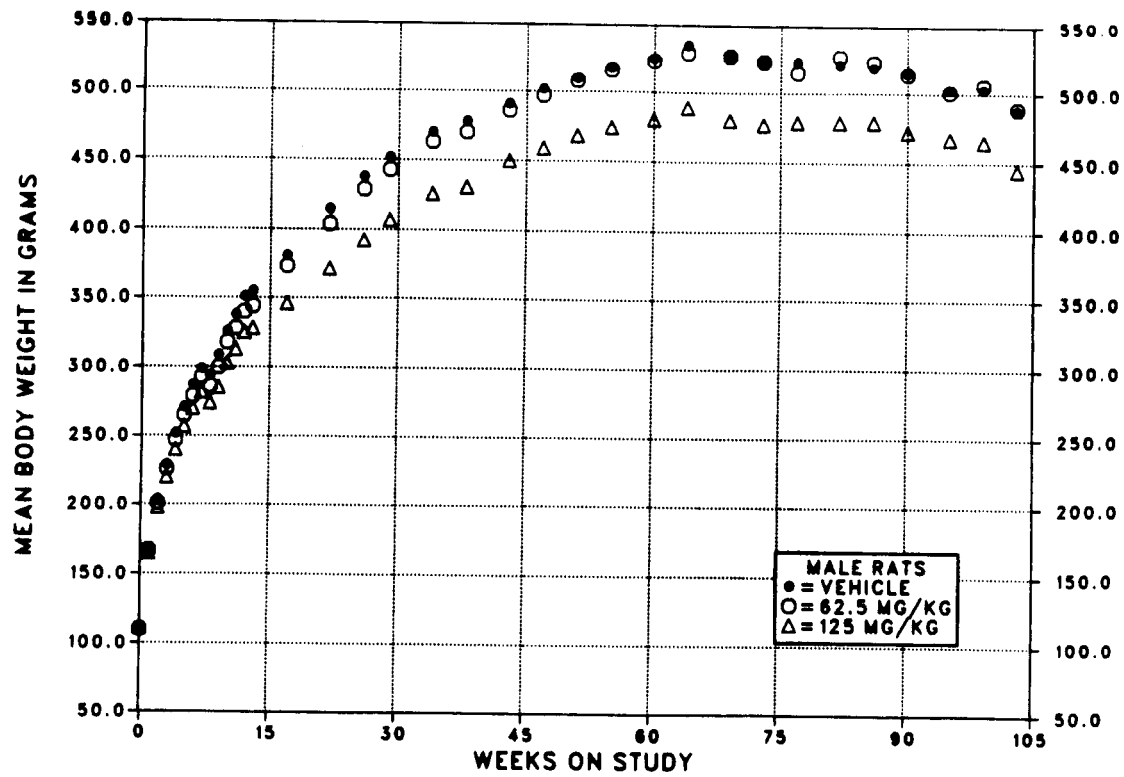
## TWO-YEAR STUDIES

### 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
<b>MALE</b>								
0	111	50	110	99	50	111	100	50
1	168	50	187	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	285	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	528	46	527	100	44	480	91	45
73	528	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
<b>FEMALE</b>								
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	228	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**

### III. RESULTS: RATS

#### 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

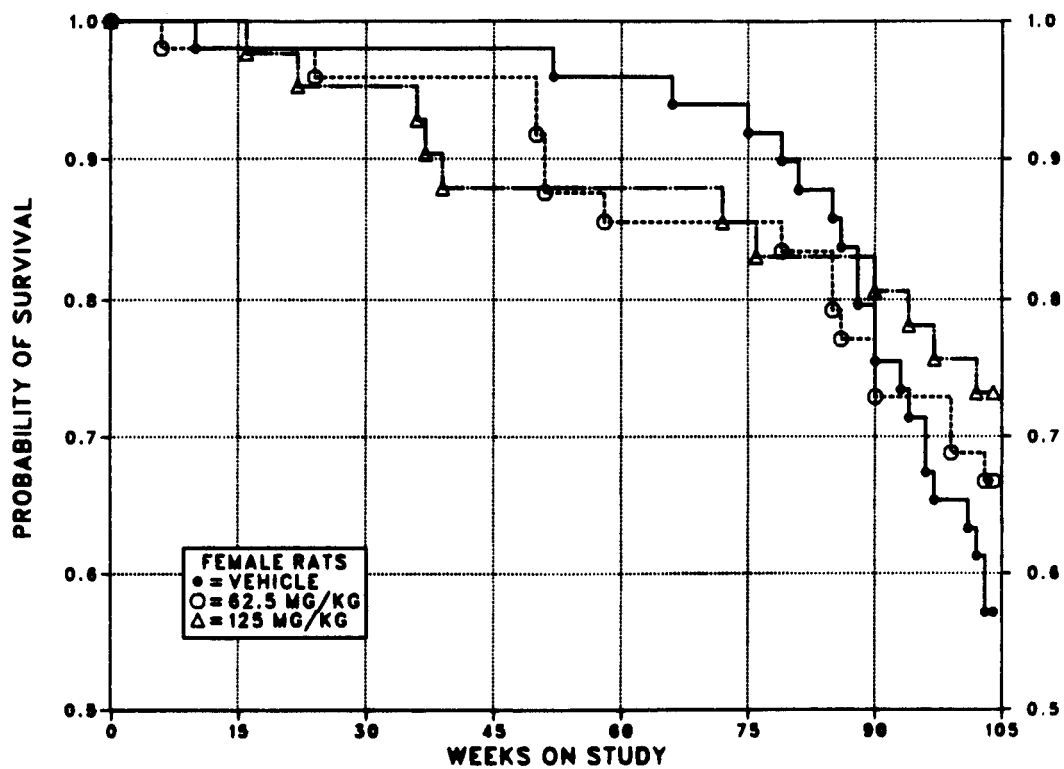
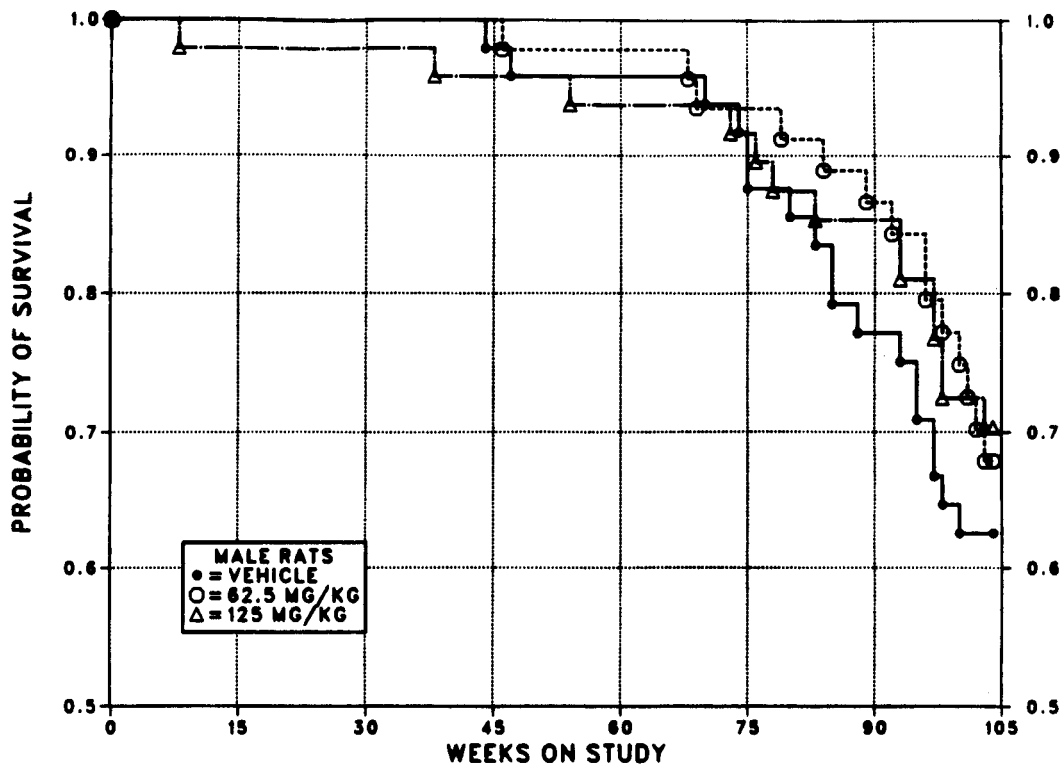
	Vehicle Control	62.5 mg/kg	125 mg/kg
<b>MALE (a)</b>			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	14	14
Accidentally killed (c)	2	7	3
Killed at termination	30	28	33
Died during termination period	0	1	0
Survival P values (d)	0.452	0.602	0.527
<b>FEMALE (a)</b>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

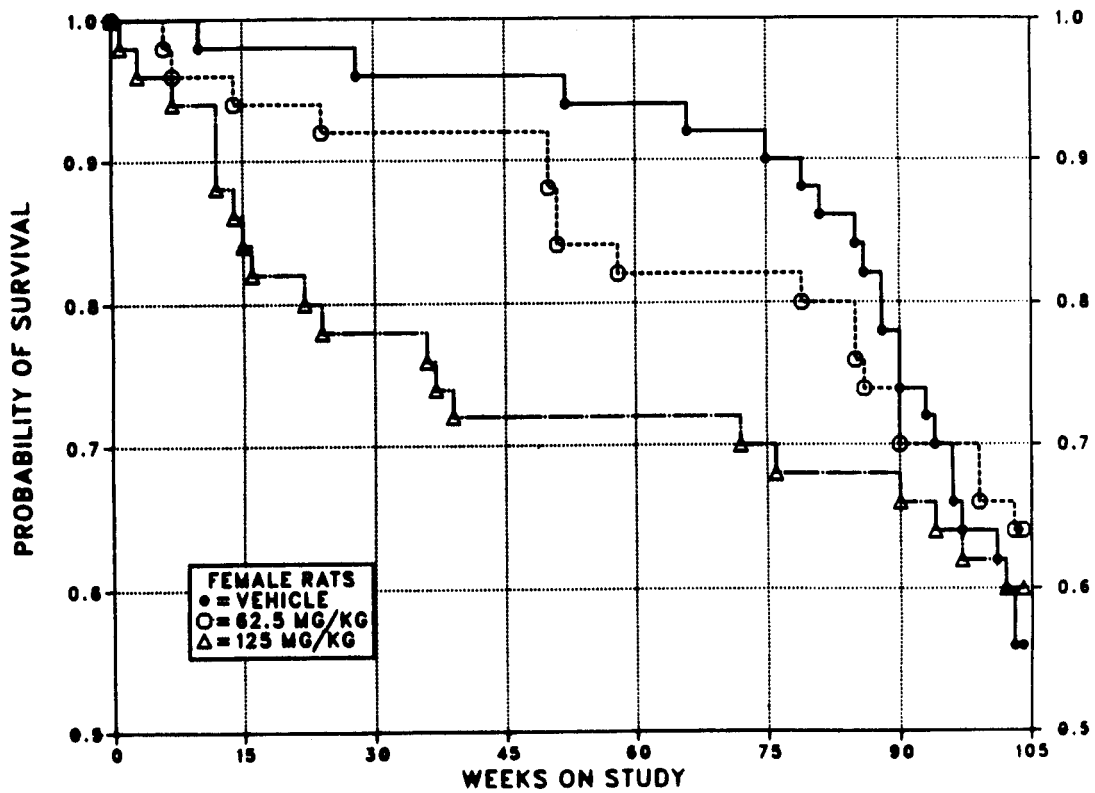
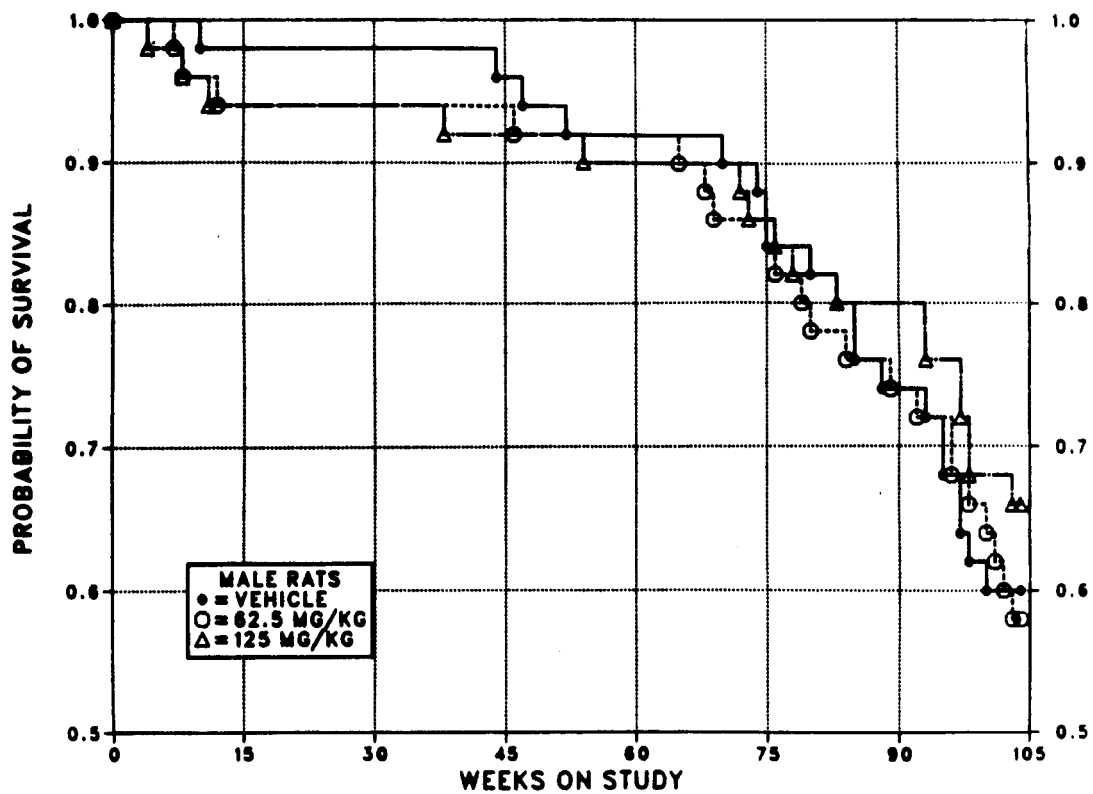
(b) Includes animals killed in a moribund condition

(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
<b>Focal Hyperplasia</b>			
Overall Rates	3/50 (6%)	12/50 (24%)	4/50 (8%)
<b>Adenoma</b>			
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
<b>Carcinoma</b>			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
<b>Adenoma or Carcinoma (b)</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
<b>MALE (a)</b>			
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
<b>FEMALE (b)</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
<b>Hyperplasia</b>			
Overall Rates	14/49 (29%)	20/49 (41%)	17/48 (35%)
<b>Adenoma</b>			
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
<b>Carcinoma</b>			
Overall Rates	1/49 (2%)	1/49 (2%)	0/48 (0%)
<b>Adenoma or Carcinoma (a)</b>			
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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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
<b>FEMALE</b>					
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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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)
<b>FEMALE</b>					
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
<b>MALE</b>								
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	38	41.1	93	28	39.6	90	30
104	--	36	--	--	26	--	--	30
<b>FEMALE</b>								
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

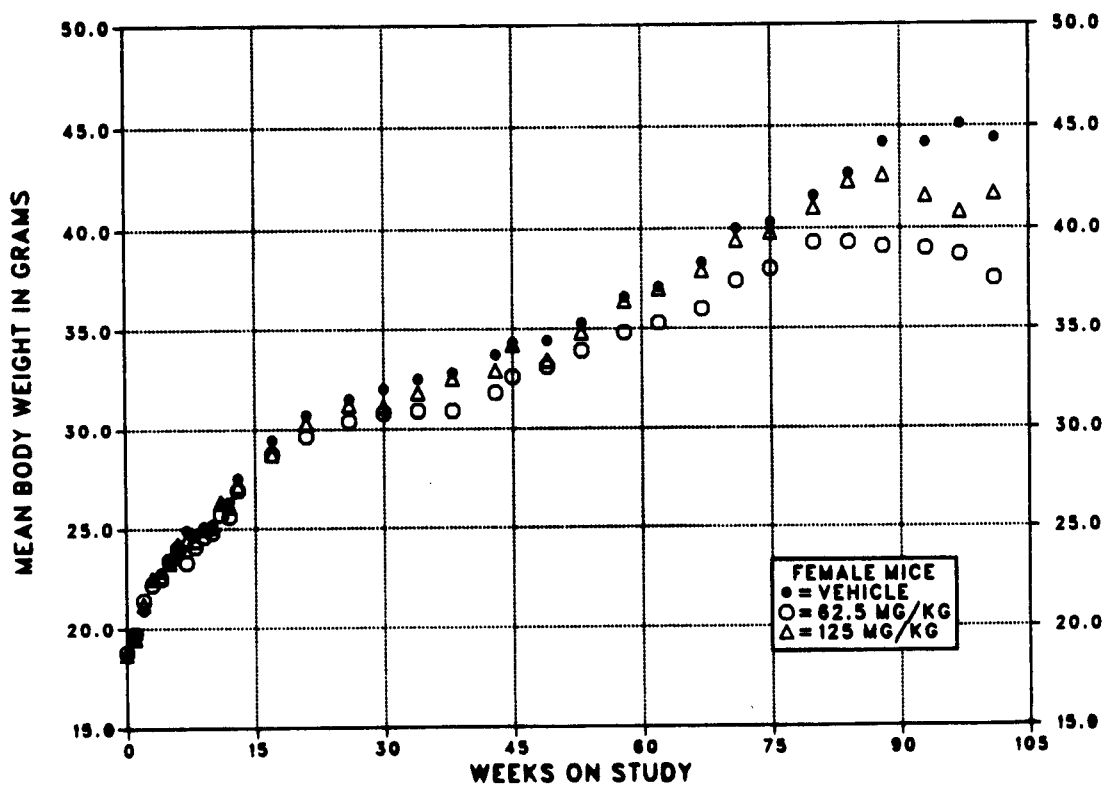
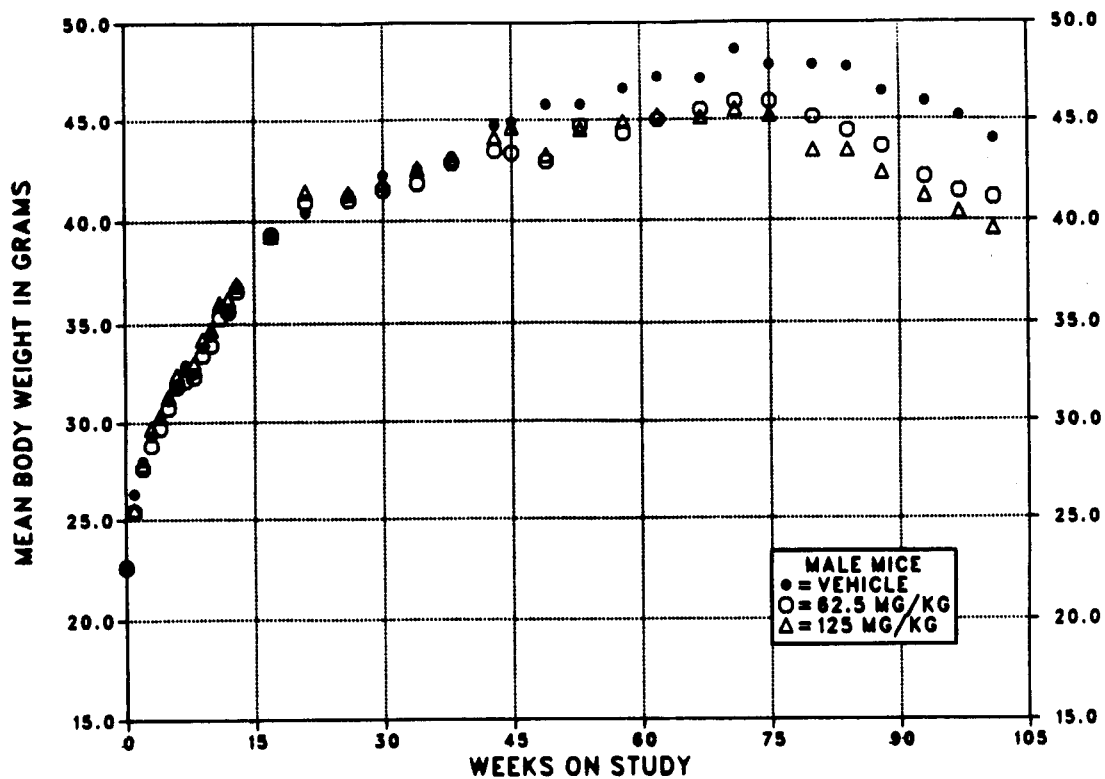


FIGURE 6. GROWTH CURVES FOR MICE ADMINISTERED 4-HEXYLRESORCINOL IN CORN OIL BY GAVAGE FOR TWO YEARS

#### 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.

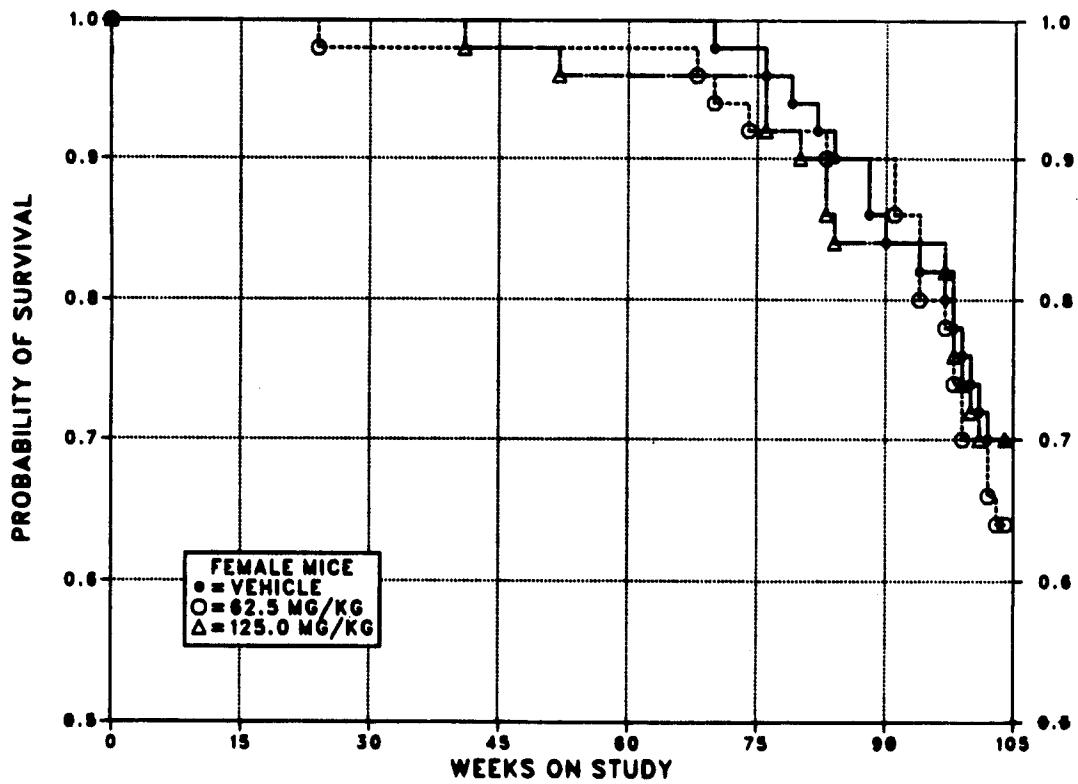
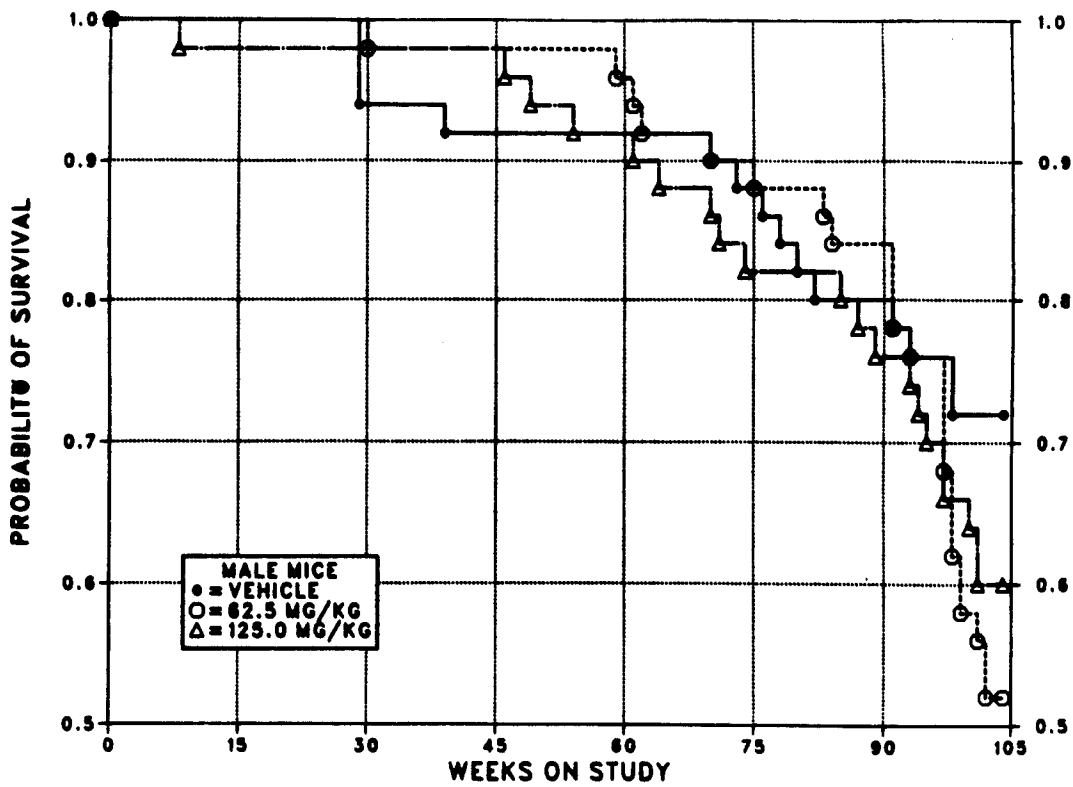
**TABLE 16. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-HEXYLRESORCINOL**

	Vehicle Control	62.5 mg/kg	125 mg/kg
<b>MALE (a)</b>			
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
<b>FEMALE (a)</b>			
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
<b>Focal Hyperplasia</b>			
Overall Rates	5/50 (10%)	16/50 (32%)	10/49 (20%)
<b>Pheochromocytoma (b)</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
<b>Adenoma</b>			
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
<b>Carcinoma</b>			
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
<b>Adenoma or Carcinoma (a)</b>			
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  $\pm$  SD): 56/1,497 (4%  $\pm$  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.



### III. RESULTS: MICE

*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
<b>Adenoma</b>			
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
<b>Carcinoma</b>			
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
<b>Adenoma or Carcinoma (a)</b>			
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
<b>MALE</b>			
<b>Hemangioma</b>			
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
<b>Hemangiosarcoma</b>			
Overall Rates	4/50 (8%)	(a) 3/50 (6%)	2/50 (4%)
<b>Hemangioma or Hemangiosarcoma (b)</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
<b>FEMALE</b>			
<b>Hemangioma</b>			
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
<b>Hemangiosarcoma</b>			
Overall Rates	2/50 (4%)	(c) 1/49 (2%)	0/50 (0%)
<b>Hemangioma or Hemangiosarcoma (d)</b>			
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**

## IV. DISCUSSION AND CONCLUSIONS

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### 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 Kepingler, 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
<b>Overall rates of tumor reduced</b>			
<b>Male</b>			
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%)
<b>Female</b>			
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%)
<b>Tumor summary for 4-hexylresorcinol 2-year study in male rats</b>			
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
<b>Tumor summary for 4-hexylresorcinol 2-year study in female rats</b>			
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 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 warrant 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
<b>Overall rates of tumor reduced</b>			
<b>Male</b>			
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%)
<b>Female</b>			
Hemangioma or hemangiosarcoma	6/50 (12%)	2/49 (4%)	0/50 (0%)
<b>Tumor summary for 4-hexylresorcinol 2-year study in male mice</b>			
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
<b>Tumor summary for 4-hexylresorcinol 2-year study in female mice</b>			
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<sub>1</sub> 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<sub>1</sub> 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.





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## APPENDIX A

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

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**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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)	
<b>RESPIRATORY SYSTEM</b>			
*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%)		
<b>HEMATOPOIETIC SYSTEM</b>			
*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%)
<b>CIRCULATORY SYSTEM</b>			
#Spleen	(49)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Lung	(49)	(48)	(50)
Hemangiosarcoma, metastatic			1 (2%)
<b>DIGESTIVE SYSTEM</b>			
#Liver	(49)	(50)	(50)
Neoplastic nodule		1 (2%)	1 (2%)
#Pancreas	(46)	(50)	(49)
Acinar cell adenoma	1 (2%)		1 (2%)
<b>URINARY SYSTEM</b>			
#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
<b>ENDOCRINE SYSTEM</b>			
#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%)
<b>REPRODUCTIVE SYSTEM</b>			
*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%)
<b>NERVOUS SYSTEM</b>			
#Brain	(49)	(14)	(50)
Glioma, NOS		1 (7%)	
Astrocytoma			1 (2%)
Oligodendroglioma	1 (2%)		1 (2%)
#Cerebellum	(49)	(14)	(50)
Astrocytoma			1 (2%)
<b>SPECIAL SENSE ORGANS</b>			
*Zymbal gland	(49)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	1 (2%)	1 (2%)	1 (2%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Muscle hip/thigh	(49)	(50)	(50)
Sarcoma, NOS	1 (2%)		
<b>BODY CAVITIES</b>			
*Mediastinum	(49)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Tunica vaginalis	(49)	(50)	(50)
Mesothelioma, NOS		1 (2%)	
<b>ALL OTHER SYSTEMS</b>			
*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
<b>ANIMAL DISPOSITION SUMMARY</b>			
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
<b>TUMOR SUMMARY</b>			
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 0 2	1 1 4	1 4 3	1 1 6	1 1 0	1 1 7	1 2 2	1 2 9	1 0 0	1 1 8	1 0 4	1 0 6	1 0 7	1 1 0	1 0 8	
WEEKS ON STUDY	0 1 0	0 4 4	0 7 7	0 2 2	0 0 4	0 7 4	0 7 5	0 7 5	0 0 0	0 0 3	0 0 5	0 0 5	0 0 8	0 0 8	0 0 8	0 0 9	0 0 9	0 0 9	0 0 9	0 0 9	0 0 9	0 0 8	0 0 4	0 0 4	0 0 4	0 0 4	0 0 4
<b>INTEGUMENTARY SYSTEM</b>																											
Skin	+																										
Papilloma, NOS	+																										
Subcutaneous tissue	+																										
Sarcoma, NOS	+																										
Fibroma	+																										
Fibrosarcoma	+																										
<b>RESPIRATORY SYSTEM</b>																											
Lungs and bronchi	+																										
Alveolar/bronchiolar adenoma	+																										
C-cell carcinoma, metastatic	+																										
Trachea	+																										
Nasal cavity	+																										
Adenoma, NOS	+																										
<b>HEMATOPOIETIC SYSTEM</b>																											
Bone marrow	+																										
Spleen	+																										
Leukemia, mononuclear cell	+																										
Lymph nodes	+																										
Thymus	+																										
<b>CIRCULATORY SYSTEM</b>																											
Heart	+																										
<b>DIGESTIVE SYSTEM</b>																											
Salivary gland	+																										
Liver	+																										
Bile duct	+																										
Pancreas	+																										
Acinar cell adenoma	+																										
Esophagus	+																										
Stomach	+																										
Small intestine	+																										
Large intestine	+																										
<b>URINARY SYSTEM</b>																											
Kidney	+																										
Urinary bladder	+																										
<b>ENDOCRINE SYSTEM</b>																											
Pituitary	+																										
Adenoma, NOS	+																										
Adrenal	+																										
Pheochromocytoma	+																										
Pheochromocytoma, malignant	+																										
Thyroid	+																										
Follicular cell carcinoma	+																										
C-cell adenoma	+																										
C-cell carcinoma	+																										
Parathyroid	+																										
Pancreatic islets	+																										
Islet cell adenoma	+																										
<b>REPRODUCTIVE SYSTEM</b>																											
Mammary gland	+																										
Testis	+																										
Interstitial cell tumor	+																										
Prostate	+																										
<b>NERVOUS SYSTEM</b>																											
Brain	+																										
Oligodendroglioma	+																										
<b>SPECIAL SENSE ORGANS</b>																											
Zymbal gland	N																										
Carcinoma, NOS	N																										
Adenoma, NOS	N																										
<b>MUSCULOSKELETAL SYSTEM</b>																											
Muscle	N																										
Sarcoma, NOS	N																										
<b>BODY CAVITIES</b>																											
Mediastinum	N																										
Mesothelioma, NOS	N																										
<b>ALL OTHER SYSTEMS</b>																											
Multiple organs, NOS	N																										
Sarcoma, NOS, metastatic	N																										
Leukemia, mononuclear cell	N																										

+: 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: LOW DOSE**  
(Continued)

ANIMAL NUMBER	WEEKS ON STUDY																				TOTAL TISSUES TUMORS		
	0/6	0/7	0/1	0/2	0/6	0/7	0/1	0/2	0/2	0/2	0/2	0/2	0/3	0/3	0/3	0/3	0/4	0/4	0/4	0/4		0/4	0/5
<b>INTEGUMENTARY SYSTEM</b>																							
Skin																							
Sebaceous adenoma																							
Keratoacanthoma																							
Subcutaneous tissue																							
Sarcoma, NOS																							
Fibroma																							
Fibrosarcoma																							
<b>RESPIRATORY SYSTEM</b>																							
Lungs and bronchi																							
Squamous cell carcinoma																							
Alveolar/bronchiolar adenoma																							
Alveolar/bronchiolar carcinoma																							
Trachea																							
<b>HEMATOPOIETIC SYSTEM</b>																							
Bone marrow																							
Spleen																							
Lymph nodes																							
Thymus																							
<b>CIRCULATORY SYSTEM</b>																							
Heart																							
<b>DIGESTIVE SYSTEM</b>																							
Salivary gland																							
Liver																							
Neoplastic nodule																							
Bile duct																							
Pancreas																							
Esophagus																							
Stomach																							
Small intestine																							
Large intestine																							
<b>URINARY SYSTEM</b>																							
Kidney																							
Urinary bladder																							
<b>ENDOCRINE SYSTEM</b>																							
Pituitary																							
Adenoma, NOS																							
Adrenal																							
Pheochromocytoma																							
Pheochromocytoma, malignant																							
Thyroid																							
C-cell adenoma																							
C-cell carcinoma																							
Parathyroid																							
Pancreatic islets																							
Islet cell adenoma																							
<b>REPRODUCTIVE SYSTEM</b>																							
Mammary gland																							
Fibroadenoma																							
Testis																							
Interstitial cell tumor																							
Prostate																							
Preputial/clitoral gland																							
Adenoma, NOS																							
<b>NERVOUS SYSTEM</b>																							
Brain																							
Glioma, NOS																							
<b>SPECIAL SENSE ORGANS</b>																							
Zymbal gland																							
Adenoma, NOS																							
<b>BODY CAVITIES</b>																							
Tunica vaginalis																							
Mesothelioma, NOS																							
<b>ALL OTHER SYSTEMS</b>																							
Multiple organs, NOS																							
Leukemia, mononuclear cell																							

\* 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
<b>Subcutaneous Tissue: Fibroma</b>			
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
<b>Subcutaneous Tissue: Fibroma or Fibrosarcoma</b>			
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
<b>Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Carcinoma</b>			
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)
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>			
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
<b>Hematopoietic System: Mononuclear Cell Leukemia</b>			
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
<b>Pituitary Gland: Adenoma</b>			
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
<b>Adrenal Gland: Pheochromocytoma</b>			
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
<b>Adrenal Gland: Malignant Pheochromocytoma</b>			
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
<b>Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma</b>			
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
<b>Thyroid Gland: C-Cell Adenoma</b>			
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
<b>Thyroid Gland: C-Cell Adenoma or Carcinoma</b>			
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
<b>Pancreatic Islets: Islet Cell Adenoma</b>			
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
<b>Preputial Gland: Adenoma</b>			
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)
<b>Preputial Gland: Adenoma or Carcinoma</b>			
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
<b>Testis: Interstitial Cell Tumor</b>			
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
<b>Brain: All Glial Cell Tumors (g)</b>			
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
<b>All Sites: Benign Tumors</b>			
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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.		
<b>Overall Historical Incidence</b>		
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.			
<b>Overall Historical Incidence</b>			
		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.			
<b>Overall Historical Incidence</b>			
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
<b>ANIMALS INITIALLY IN STUDY</b>	50	50	50
<b>ANIMALS NECROPSIED</b>	49	50	50
<b>ANIMALS EXAMINED HISTOPATHOLOGICALLY</b>	49	50	50
<b>INTEGUMENTARY SYSTEM</b>			
*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%)	
<b>RESPIRATORY SYSTEM</b>			
*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%)
<b>HEMATOPOIETIC SYSTEM</b>			
#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
<b>CIRCULATORY SYSTEM</b>			
#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%)
<b>DIGESTIVE SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM (Continued)</b>			
#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%)	
<b>URINARY SYSTEM</b>			
#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%)		
<b>ENDOCRINE SYSTEM</b>			
#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
<b>ENDOCRINE SYSTEM (Continued)</b>			
#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%)	
<b>REPRODUCTIVE SYSTEM</b>			
*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%)
<b>NERVOUS SYSTEM</b>			
#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%)		
<b>SPECIAL SENSE ORGANS</b>			
*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
<b>SPECIAL SENSE ORGANS (Continued)</b>			
*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%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Fascia	(49)	(50)	(50)
Hemorrhage		1 (2%)	
<b>BODY CAVITIES</b>			
*Mediastinum	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Granuloma, NOS			1 (2%)
*Mesentery	(49)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
<b>ALL OTHER SYSTEMS</b>			
*Multiple organs	(49)	(50)	(50)
Atrophy, NOS	7 (14%)		3 (6%)
Adipose tissue			
Hemorrhage		1	
Necrosis, fat	8	4	1
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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

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**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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)		
<b>RESPIRATORY SYSTEM</b>			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
Follicular cell carcinoma, metastatic		1 (2%)	
<b>HEMATOPOIETIC SYSTEM</b>			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, histiocytic type			1 (2%)
Leukemia, mononuclear cell	16 (32%)	3 (6%)	2 (4%)
<b>CIRCULATORY SYSTEM</b>			
None			
<b>DIGESTIVE SYSTEM</b>			
#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%)
<b>URINARY SYSTEM</b>			
None			
<b>ENDOCRINE SYSTEM</b>			
#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
<b>REPRODUCTIVE SYSTEM</b>			
*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%)		
<b>NERVOUS SYSTEM</b>			
#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%)	
<b>SPECIAL SENSE ORGANS</b>			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS		1 (2%)	
<b>MUSCULOSKELETAL SYSTEM</b>			
None			
<b>BODY CAVITIES</b>			
None			
<b>ALL OTHER SYSTEMS</b>			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
<b>ANIMAL DISPOSITION SUMMARY</b>			
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
<b>TUMOR SUMMARY</b>			
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	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	4	2	1	0	4	4	4	1	0	1	3	3	0	0	1	3	2	4	3	0	4	0	0	0	0		
WEEKS ON STUDY	3	4	1	2	0	2	1	5	0	3	4	4	5	9	7	5	2	2	9	6	4	8	1	1	1		
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1		
	1	2	5	6	7	7	8	8	8	8	8	9	9	9	9	9	9	9	0	0	0	0	0	0	0		
	0	8	2	6	5	9	1	5	6	8	8	0	0	3	4	6	6	7	1	2	3	3	4	4			
<b>INTEGUMENTARY SYSTEM</b>																											
Subcutaneous tissue																											
Fibroma																											
Fibrosarcoma																											
Myxosarcoma																											
X																											
<b>RESPIRATORY SYSTEM</b>																											
Lungs and bronchi																											
Alveolar/bronchiolar adenoma																											
Trachea																											
-																											
<b>HEMATOPOIETIC SYSTEM</b>																											
Bone marrow																											
Spleen																											
Lymph nodes																											
Thymus																											
-																											
<b>CIRCULATORY SYSTEM</b>																											
Heart																											
+																											
<b>DIGESTIVE SYSTEM</b>																											
Salivary gland																											
Liver																											
Neoplastic nodule																											
Bile duct																											
Pancreas																											
Acinar cell adenoma																											
Esophagus																											
Stomach																											
Small intestine																											
Large intestine																											
X																											
<b>URINARY SYSTEM</b>																											
Kidney																											
Urinary bladder																											
+																											
<b>ENDOCRINE SYSTEM</b>																											
Pituitary																											
Adenoma, NOS																											
Adrenal																											
Cortical adenoma																											
Pheochromocytoma																											
Pheochromocytoma, malignant																											
Thyroid																											
Follicular cell adenoma																											
C-cell adenoma																											
Parathyroid																											
X																											
<b>REPRODUCTIVE SYSTEM</b>																											
Mammary gland																											
Adenocarcinoma, NOS																											
Fibroadenoma																											
Preputial/clitoral gland																											
Carcinoma, NOS																											
Adenoma, NOS																											
Uterus																											
Papillary carcinoma																											
Endometrial stromal polyp																											
Ovary																											
Granulosa cell tumor																											
X																											
<b>NERVOUS SYSTEM</b>																											
Brain																											
Granular cell tumor, NOS																											
X																											
<b>ALL OTHER SYSTEMS</b>																											
Multiple organs, NOS																											
Sarcoma, NOS																											
Leukemia, mononuclear cell																											
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 IN THE TWO-YEAR GAVAGE STUDY OF 4-HEXYLRESORCINOL: HIGH DOSE**

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



**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
<b>Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma</b>			
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
<b>Hematopoietic System: Mononuclear Cell Leukemia</b>			
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
<b>Pituitary Gland: Adenoma</b>			
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
<b>Pituitary Gland: Adenoma or Carcinoma</b>			
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
<b>Adrenal Gland: Pheochromocytoma</b>			
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
<b>Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma</b>			
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
<b>Thyroid Gland: C-Cell Adenoma</b>			
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
<b>Mammary Gland: Fibroadenoma</b>			
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
<b>Clitoral Gland: Adenoma</b>			
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
<b>Clitoral Gland: Carcinoma</b>			
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
<b>Clitoral Gland: Adenoma or Carcinoma</b>			
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
<b>Uterus: Endometrial Stromal Polyp</b>			
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
<b>All Sites: Benign Tumors</b>			
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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.		
<b>Overall Historical Incidence</b>		
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.			
<b>Overall Historical Incidence</b>			
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
<b>INTEGUMENTARY SYSTEM</b>			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)	1 (2%)	2 (4%)
<b>RESPIRATORY SYSTEM</b>			
*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%)
<b>HEMATOPOIETIC SYSTEM</b>			
#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
<b>CIRCULATORY SYSTEM</b>			
#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%)		
<b>DIGESTIVE SYSTEM</b>			
#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
<b>URINARY SYSTEM</b>			
#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%)
<b>ENDOCRINE SYSTEM</b>			
#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%)	
<b>REPRODUCTIVE SYSTEM</b>			
*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
<b>NERVOUS SYSTEM</b>			
*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%)		
<b>SPECIAL SENSE ORGANS</b>			
*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%)
<b>MUSCULOSKELETAL SYSTEM</b>			
None			
<b>BODY CAVITIES</b>			
*Epicardium	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
<b>ALL OTHER SYSTEMS</b>			
Adipose tissue			
Necrosis, fat	9	4	4
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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

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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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)
<b>RESPIRATORY SYSTEM</b>			
#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%)	
<b>HEMATOPOIETIC SYSTEM</b>			
*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%)
<b>CIRCULATORY SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM</b>			
*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%)	
<b>URINARY SYSTEM</b>			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	
<b>ENDOCRINE SYSTEM</b>			
#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%)
<b>REPRODUCTIVE SYSTEM</b>			
*Preputial gland	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
<b>NERVOUS SYSTEM</b>			
None			
<b>SPECIAL SENSE ORGANS</b>			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS		4 (8%)	2 (4%)
Adenoma, NOS		1 (2%)	1 (2%)
<b>MUSCULOSKELETAL SYSTEM</b>			
None			
<b>BODY CAVITIES</b>			
*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
<b>ALL OTHER SYSTEMS</b>			
None			
<b>ANIMAL DISPOSITION SUMMARY</b>			
Animals initially in study	50	50	50
Natural death	5	6	7
Moribund sacrifice	9	18	13
Terminal sacrifice	36	26	30
<b>TUMOR SUMMARY</b>			
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: HIGH DOSE**

ANIMAL NUMBER	0959	0860	0855	0855	0855	0878	0888	0893	0893	0893	0895	0897	0897	0898	0899	0899	0899	0899	0902	0903	0903	0905	0905	0905	0905	0906	0906	
WEEKS ON STUDY	08	04	04	05	06	06	07	07	08	08	08	09	09	09	09	09	09	09	09	10	11	11	11	11	11	11	11	
<b>INTEGUMENTARY SYSTEM</b>																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Papilloma, NOS																												
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrosarcoma																												
Rhabdomyosarcoma																												
Neurilemoma																												
<b>RESPIRATORY SYSTEM</b>																												
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																												
Alveolar/bronchiolar carcinoma																												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>HEMATOPOIETIC SYSTEM</b>																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Malignant lymphoma, mixed type																												
Thymus	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>CIRCULATORY SYSTEM</b>																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>DIGESTIVE SYSTEM</b>																												
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	N	N	
Papilloma, NOS																												
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma																												
Hepatocellular carcinoma																												
Hemangiosarcoma																												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	N	+	+	+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Small intestine	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Malignant lymphoma, mixed type																												
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>URINARY SYSTEM</b>																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>ENDOCRINE SYSTEM</b>																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Neoplasm, NOS																												
Adenoma, NOS																												
Pheochromocytoma																												
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell adenoma																												
Parathyroid	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS																												
<b>REPRODUCTIVE SYSTEM</b>																												
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	N	N	
Testis	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>NERVOUS SYSTEM</b>																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>SPECIAL SENSE ORGANS</b>																												
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	N	N	
Carcinoma, NOS																												
Adenoma, NOS																												
<b>ALL OTHER SYSTEMS</b>																												
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	N	N	
Hemangiosarcoma																												
Malignant lymphoma, histiocytic type																												
Malignant lymphoma, mixed type																												





**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
<b>Subcutaneous Tissue: Fibrosarcoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Carcinoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Mixed Type</b>			
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
<b>Hematopoietic System: Lymphoma, All Malignant</b>			
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
<b>Circulatory System: Hemangioma</b>			
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
<b>Circulatory System: Hemangiosarcoma</b>			
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
<b>Circulatory System: Hemangioma or Hemangiosarcoma</b>			
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
<b>Liver: Hepatocellular Adenoma</b>			
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
<b>Liver: Hepatocellular Carcinoma</b>			
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
<b>Liver: Hepatocellular Adenoma or Carcinoma</b>			
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
<b>Adrenal Gland: Pheochromocytoma</b>			
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
<b>Harderian Gland: Carcinoma</b>			
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
<b>Harderian Gland: Adenoma or Carcinoma</b>			
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
<b>All Sites: Benign Tumors</b>			
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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)**

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- (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<sub>1</sub> 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.			
<b>Overall Historical Incidence</b>			
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<sub>1</sub> 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.			
<b>Overall Historical Incidence</b>			
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<sub>1</sub> 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.	
<b>Overall Historical Incidence</b>	
TOTAL SD (c)	(b) 19/1,443 (1.3%) 2.43%
Range (d) High Low	(b) 5/49 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<sub>1</sub> 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.			
<b>Overall Historical Incidence</b>			
TOTAL SD (b)	201/1,490 (13.5%) 6.45%	306/1,490 (20.5%) 7.70%	477/1,490 (32.0%) 8.99%
Range (c) High Low	14/50 0/50	19/50 3/49	25/50 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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)	
<b>RESPIRATORY SYSTEM</b>			
*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%)
<b>HEMATOPOIETIC SYSTEM</b>			
*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
<b>HEMATOPOIETIC SYSTEM</b>			
#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
<b>CIRCULATORY SYSTEM</b>			
#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%)	
<b>DIGESTIVE SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM (Continued)</b>			
*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%)
<b>URINARY SYSTEM</b>			
#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%)		
#Convolute 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
<b>ENDOCRINE SYSTEM</b>			
#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%)		
<b>REPRODUCTIVE SYSTEM</b>			
*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
<b>REPRODUCTIVE SYSTEM (Continued)</b>			
#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%)
<b>NERVOUS SYSTEM</b>			
#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)
Demyelination			1 (2%)
<b>SPECIAL SENSE ORGANS</b>			
*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%)		
<b>MUSCULOSKELETAL SYSTEM</b>			
*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%)
<b>BODY CAVITIES</b>			
*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
<b>BODY CAVITIES (Continued)</b>			
*Pericardium	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		
<b>ALL OTHER SYSTEMS</b>			
Knee			
Dyschondroplasia	13	15	13
Exostosis	1		
Adipose tissue			
Necrosis, fat	3	3	3
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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

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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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)
<b>RESPIRATORY SYSTEM</b>			
#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%)		
<b>HEMATOPOIETIC SYSTEM</b>			
*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%)
<b>CIRCULATORY SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM</b>			
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	3 (6%)		1 (2%)
#Duodenum	(50)	(7)	(49)
Adenomatous polyp, NOS			1 (2%)
<b>URINARY SYSTEM</b>			
None			
<b>ENDOCRINE SYSTEM</b>			
#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%)
<b>REPRODUCTIVE SYSTEM</b>			
*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%)		
<b>NERVOUS SYSTEM</b>			
None			
<b>SPECIAL SENSE ORGANS</b>			
*Harderian gland	(50)	(49)	(50)
Carcinoma, NOS	1 (2%)	3 (6%)	
Adenoma, NOS	1 (2%)	1 (2%)	1 (2%)
<b>MUSCULOSKELETAL SYSTEM</b>			
None			
<b>BODY CAVITIES</b>			
None			
<b>ALL OTHER SYSTEMS</b>			
*Multiple organs	(50)	(49)	(50)
Squamous cell carcinoma		1 (2%)	
<b>ANIMAL DISPOSITION SUMMARY</b>			
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
<b>TUMOR SUMMARY</b>			
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: LOW DOSE**

ANIMAL NUMBER	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	051	052	053	054	055	056	057	058	059	060
WEEKS ON STUDY	24	26	27	27	28	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29
<b>INTEGUMENTARY SYSTEM</b>																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma				X																A					
<b>RESPIRATORY SYSTEM</b>																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																				A					
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									
Trachea	+	-	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>HEMATOPOIETIC SYSTEM</b>																									
Bone marrow	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Spleen	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Lymph nodes	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Thymus	+	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>CIRCULATORY SYSTEM</b>																									
Heart	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>DIGESTIVE SYSTEM</b>																									
Salivary gland	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Esophagus	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Stomach	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Small intestine	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
Large intestine	+	+	+	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>URINARY SYSTEM</b>																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Urinary bladder	-	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>ENDOCRINE SYSTEM</b>																									
Pituitary	+	+	+	+	+	+	+	-	-	-	-	+	+	+	-	-	-	-	-	A	+	-	-	+	-
Carcinoma, NOS																									
Adenoma, NOS												X	X	X						X					
Adrenal	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	+	+	+	+	+
Thyroid	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	-	-	-	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>REPRODUCTIVE SYSTEM</b>																									
Mammary gland	+	+	+	N	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Hemangioma				X																					
Ovary	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>NERVOUS SYSTEM</b>																									
Brain	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-
<b>SPECIAL SENSE ORGANS</b>																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
<b>ALL OTHER SYSTEMS</b>																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N
Squamous cell carcinoma								X																	
Hemangiosarcoma									X																
Malignant lymphoma, histiocytic type										X															
Malignant lymphoma, mixed type													X							X					
Mast cell sarcoma						X																		X	
Granulocytic leukemia													X												



**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	099	055	056	077	078	079	045	077	000	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025		
WEEKS ON STUDY	41	42	46	46	00	03	03	04	07	08	08	00	00	00	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	
<b>INTEGUMENTARY SYSTEM</b>																																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Basal cell tumor																																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma, NOS																																									
Fibrosarcoma																																									
<b>RESPIRATORY SYSTEM</b>																																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, metastatic																																									
Alveolar/bronchiolar adenoma																																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>HEMATOPOIETIC SYSTEM</b>																																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Angioma																																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	-	+	+	+	+	-	-	+	-	+	-	+	+	-	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	
<b>CIRCULATORY SYSTEM</b>																																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>DIGESTIVE SYSTEM</b>																																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>URINARY SYSTEM</b>																																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>ENDOCRINE SYSTEM</b>																																									
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	
<b>REPRODUCTIVE SYSTEM</b>																																									
Mammary gland	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																																									
Malignant lymphoma, histiocytic type																																									
Ovary	+	+	-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>NERVOUS SYSTEM</b>																																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>SPECIAL SENSE ORGANS</b>																																									
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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Adenoma, NOS																																									
<b>ALL OTHER SYSTEMS</b>																																									
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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Malignant lymphoma, undifferentiated type																																									
Malignant lymphoma, histiocytic type																																									
Malignant lymphoma, mixed type									X	X			X		X																							X	X		





**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
<b>Lung: Alveolar/Bronchiolar Adenoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Mixed Type</b>			
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
<b>Hematopoietic System: Lymphoma, All Malignant</b>			
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
<b>Hematopoietic System: Lymphoma or Leukemia</b>			
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
<b>Circulatory System: Hemangioma</b>			
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
<b>Circulatory System: Hemangioma or Hemangiosarcoma</b>			
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
<b>Liver: Hepatocellular Adenoma</b>			
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
<b>Pituitary Gland: Adenoma</b>			
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
<b>Pituitary Gland: Adenoma or Carcinoma</b>			
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
<b>Thyroid Gland: Follicular Cell Adenoma</b>			
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
<b>Thyroid Gland: Follicular Cell Adenoma or Carcinoma</b>			
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
<b>Uterus: Endometrial Stromal Polyp</b>			
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
<b>Harderian Gland: Carcinoma</b>			
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
<b>Harderian Gland: Adenoma or Carcinoma</b>			
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
<b>All Sites: Benign Tumors</b>			
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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)**

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- (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<sub>1</sub> MICE ADMINISTERED CORN OIL BY GAVAGE (a)**

	<u>Incidence in Vehicle Controls</u>		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
<b>Overall Historical Incidence</b>			
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<sub>1</sub> MICE ADMINISTERED CORN OIL BY GAVAGE (a)**

	<u>Incidence in Vehicle Controls</u>		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
<b>Overall Historical Incidence</b>			
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
<b>INTEGUMENTARY SYSTEM</b>			
*Skin	(50)	(49)	(50)
Erosion		1 (2%)	
Hyperkeratosis			1 (2%)
<b>RESPIRATORY SYSTEM</b>			
*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%)
<b>HEMATOPOIETIC SYSTEM</b>			
*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
<b>HEMATOPOIETIC SYSTEM (Continued)</b>			
#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%)
<b>CIRCULATORY SYSTEM</b>			
#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
<b>DIGESTIVE SYSTEM</b>			
*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%)		
<b>URINARY SYSTEM</b>			
#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
<b>URINARY SYSTEM (Continued)</b>			
#Convoluted tubules	(50)	(49)	(50)
Degeneration, hyaline	1 (2%)		5 (10%)
#Urinary bladder	(47)	(6)	(48)
Congestion, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)		
<b>ENDOCRINE SYSTEM</b>			
#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%)
<b>REPRODUCTIVE SYSTEM</b>			
*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
<b>REPRODUCTIVE SYSTEM (Continued)</b>			
#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%)
<b>NERVOUS SYSTEM</b>			
#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%)	
<b>SPECIAL SENSE ORGANS</b>			
*Nasolacrimal duct	(50)	(49)	(50)
Hemorrhage			1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, chronic	2 (4%)		
Inflammation, chronic focal			1 (2%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Bone	(50)	(49)	(50)
Osteosclerosis	21 (42%)	25 (51%)	40 (80%)
<b>BODY CAVITIES</b>			
*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%)
<b>ALL OTHER SYSTEMS</b>			
*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
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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**

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

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

(b) Revertants are presented as mean  $\pm$  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)
<b>-S9</b>					
<b>Trial 1</b>					
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
<b>Trial 2</b>					
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
<b>+S9 (h)</b>					
<b>Trial 1</b>					
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
<b>Trial 2</b>					
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 ( $6 \times 10^5$ /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,  $3 \times 10^6$  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  $\pm$  standard error of replicate trials for approximately  $3 \times 10^6$  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  $1 \times 10^6$  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 Chromosomes	No. of SCEs	SCEs/Chromosome	SCEs/Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
<b>- S9 (c)--Summary: Positive</b>								
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
<b>+ S9 (d)--Summary: Negative</b>								
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

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# APPENDIX F. SENTINEL ANIMAL PROGRAM

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## 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<sub>1</sub> 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:

	<u>Hemagglutination Inhibition</u>	<u>Complement Fixation</u>	<u>ELISA</u>
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
<b>RATS</b>		
6	8/10	RCV
12	--	None positive
18	1/10	RCV
24	2/10	RCV
<b>MICE</b>		
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)**

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**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
<b>Vitamin</b>		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D <sub>3</sub>	4,600,000 IU	D-activated animal sterol
K <sub>3</sub>	2.8 g	Menadione activity
d- $\alpha$ -Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	d-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B <sub>12</sub>	4,000 $\mu$ g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	d-Biotin
<b>Mineral</b>		
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 $\pm$ Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.85 $\pm$ 0.78	22.7-25.3	24
Crude fat (percent by weight)	5.02 $\pm$ 0.44	4.2-5.7	24
Crude fiber (percent by weight)	3.31 $\pm$ 0.23	2.9-3.8	24
Ash (percent by weight)	6.44 $\pm$ 0.44	5.7-7.43	24
<b>Essential Amino Acid (percent of total diet)</b>			
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
<b>Essential Fatty Acid (percent of total diet)</b>			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
<b>Vitamin</b>			
Vitamin A (IU/kg)	10,917 $\pm$ 1,876	8,210-15,000	24
Vitamin D (IU/kg)	6,300		1
$\alpha$ -Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.8 $\pm$ 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 <sub>12</sub> (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
<b>Mineral</b>			
Calcium (percent)	1.25 $\pm$ 0.15	1.08-1.69	24
Phosphorus (percent)	0.98 $\pm$ 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
<i>E. coli</i> (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
<i>N</i> -Nitrosodimethylamine (ppb) (k,l)	3.43 ± 3.96	0.8-16.5	21
<i>N</i> -Nitrosodimethylamine (ppb) (k,m)	25.71 ± 64.90	0.8-272	24
<i>N</i> -Nitrosopyrrolidine (ppb)	1.05 ± 0.49	0.3-2.9	24
<b>Pesticide (ppm)</b>			
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)**

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- (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

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The archival records and pathology materials for the 2-year gavage studies of 4-hexylresorcinol in F344/N rats and B6C3F<sub>1</sub> 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.



NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS  
PUBLISHED AS OF APRIL 1988

TR No.	CHEMICAL	TR No.	CHEMICAL
200	2,6-Toluenediamine Dihydrochloride	263	1,2-Dichloropropane
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)	267	Propylene Oxide
202	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Dermal)	269	Telone II®
203	Phenol	271	HC Blue No. 1
204	Benzoin	272	Propylene
205	4,4'-Oxydianiline	273	Trichloroethylene (Four strains of rats)
206	Dibromochloropropane	274	Tris(2-ethylhexyl)phosphate
207	Cytembena	275	2-Chloroethanol
208	FD & C Yellow No. 6	276	8-Hydroxyquinoline
209	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Gavage)	281	H.C. Red No. 3
210	1,2-Dibromoethane (Inhalation)	282	Chlorodibromomethane
211	C.I. Acid Orange 10	284	Diallylphthalate (Rats)
212	Di(2-ethylhexyl)adipate	285	C.I. Basic Red 9 Monohydrochloride
213	Butylbenzyl Phthalate	287	Dimethyl Hydrogen Phosphite
214	Caprolactam	288	1,3-Butadiene
215	Bisphenol A	289	Benzene
216	11-Aminoundecanoic Acid	291	Isophorone
217	Di(2-ethylhexyl)phthalate	293	HC Blue No. 2
219	2,6-Dichloro-p-phenylenediamine	294	Chlorinated Trisodium Phosphate
220	C.I. Acid Red 14	295	Chrysotile Asbestos (Rats)
221	Locust Bean Gum	296	Tetrakis(hydroxymethyl)phosphonium Sulfate and Tetrakis(hydroxymethyl)phosphonium Chloride
222	C.I. Disperse Yellow 3	298	Dimethyl Morpholinophosphoramidate
223	Eugenol	299	C.I. Disperse Blue 1
224	Tara Gum	300	3-Chloro-2-methylpropene
225	D & C Red No. 9	301	o-Phenylphenol
226	C.I. Solvent Yellow 14	303	4-Vinylcyclohexene
227	Gum Arabic	304	Chlorendic Acid
228	Vinylidene Chloride	305	Chlorinated Paraffins (C <sub>23</sub> , 43% chlorine)
229	Guar Gum	306	Dichloromethane
230	Agar	307	Ephedrine Sulfate
231	Stannous Chloride	308	Chlorinated Paraffins (C <sub>12</sub> , 60% chlorine)
232	Pentachloroethane	309	Decabromodiphenyl Oxide
233	2-Biphenylamine Hydrochloride	310	Marine Diesel Fuel and JP-5 Navy Fuel
234	Allyl Isothiocyanate	311	Tetrachloroethylene (Inhalation)
235	Zearalenone	312	n-Butyl Chloride
236	D-Mannitol	314	Methyl Methacrylate
237	1,1,1,2-Tetrachloroethane	315	Oxytetracycline Hydrochloride
238	Ziram	316	1-Chloro-2-methylpropene
239	Bis(2-chloro-1-methylethyl)ether	317	Chlorpheniramine Maleate
240	Propyl Gallate	318	Ampicillin Trihydrate
242	Diallyl Phthalate (Mice)	319	1,4-Dichlorobenzene
244	Polybrominated Biphenyl Mixture	320	Rotenone
245	Melamine	321	Bromodichloromethane
247	L-Ascorbic Acid	322	Phenylephrine Hydrochloride
248	4,4'-Methylenedianiline Dihydrochloride	323	Dimethyl Methylphosphonate
249	Amosite Asbestos	324	Boric Acid
250	Benzyl Acetate	325	Pentachloronitrobenzene
251	Toluene Diisocyanate	326	Ethylene Oxide
252	Geranyl Acetate	327	Xylenes (Mixed)
253	Allyl Isovalerate	328	Methyl Carbamate
255	1,2-Dichlorobenzene	329	1,2-Epoxybutane
257	Diglycidyl Resorcinol Ether	333	N-Phenyl-2-naphthylamine
259	Ethyl Acrylate	334	2-Amino-5-nitrophenol
261	Chlorobenzene		

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.