NATIONAL TOXICOLOGY PROGRAM
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No. 301

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *ORTHO*-PHENYLPHENOL (CAS NO. 90-43-7) ALONE AND WITH 7,12-DIMETHYLBENZ(*a*)ANTHRACENE (CAS NO. 57-97-6) IN SWISS CD-1 MICE (DERMAL 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 *ORTHO*-PHENYLPHENOL

(CAS NO. 90-43-7)

ALONE AND WITH 7,12-DIMETHYLBENZ(*a*)ANTHRACENE

(CAS NO. 57-97-6)

IN SWISS CD-1 MICE

(DERMAL STUDIES)

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

March 1986

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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NOTE TO THE READER

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 testing in the NTP Carcinogenesis Program 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 test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be 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 Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

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 earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. 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.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, 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. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for 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).

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.

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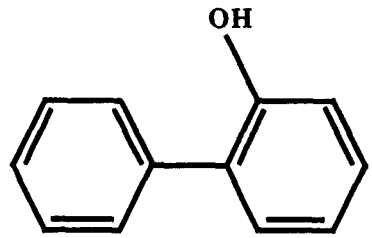

***ORTHO*-PHENYLPHENOL**

CAS NO. 90-43-7

$C_{12}H_{10}O$ Molecular weight 170.2

ABSTRACT

o-Phenylphenol is used primarily as a germicide and fungicide for citrus fruits and vegetables and was selected for carcinogenesis studies because of the potential for human exposure. Four-week studies were conducted in which groups of 10 male and 10 female Swiss Webster mice were given dermal applications to the dorsal interscapular region of 0, 6, 11, 21, 36, or 56 mg of *o*-phenylphenol in 0.1 ml of acetone. Doses were administered 3 days per week for 4 weeks, and animals were monitored for clinical changes. Reductions in body weights of acetone vehicle control male mice were observed, but no compound-related changes in weight or survival occurred in male or female mice administered *o*-phenylphenol. *o*-Phenylphenol caused dose-related ulcerative lesions at the site of application. The severity of these lesions was judged not to be life threatening.

Carcinogenesis studies were conducted to determine whether *o*-phenylphenol was a complete carcinogen for skin or a promoter in a two-stage initiation/promotion skin paint model. Groups of 50 Swiss CD-1 mice of each sex were used for up to 102 weeks. Five dose groups were used: an acetone vehicle control group; a positive control group initiated with 7,12-dimethylbenz(*a*)anthracene (DMBA) and promoted with 12-O-tetradecanoylphorbol-13-acetate (TPA); an initiator control group that received DMBA plus acetone; a group that received repeated applications of *o*-phenylphenol; and a promotion group that was initiated with DMBA and received repeated applications of *o*-phenylphenol. The following doses were applied dermally to a clipped area on the dorsal interscapular region 3 days per week: *o*-phenylphenol--55.5 mg/0.1 ml acetone; or TPA--0.005 mg/0.1 ml acetone. DMBA was administered as a single dose at a concentration of 0.05 mg/0.1 ml acetone to the dorsal interscapular region.

In the 2-year studies, mean body weights of the *o*-phenylphenol, DMBA/*o*-phenylphenol, and DMBA/TPA groups were not markedly different from those of mice that received DMBA/acetone. Similarly, there were no significant group differences in survival except for a decrease in survival in the positive control group (DMBA/TPA).

Skin neoplasms classified as squamous cell papillomas, squamous cell carcinomas, basal cell tumors, basal cell carcinomas, keratoacanthomas, or sebaceous adenomas occurred in mice dosed with DMBA/acetone, DMBA/*o*-phenylphenol, or DMBA/TPA alone. However, the incidence of skin neoplasms in mice dosed with DMBA/acetone (15/100) was similar to that in mice dosed with DMBA/*o*-phenylphenol (17/100). The incidence of skin neoplasms in male and female mice dosed with DMBA/TPA (52/100) was substantially greater than those in mice dosed with either DMBA/acetone or DMBA/*o*-phenylphenol. Similarly, the mean time of appearance of skin papillomas occurred much earlier in the DMBA/TPA groups than in the DMBA/acetone or DMBA/*o*-phenylphenol groups. All groups had

nonneoplastic lesions consisting of inflammation, ulceration, hyperkeratosis, and acanthosis at the site of application. These lesions were present in the acetone vehicle control group and, to a larger extent, in the *o*-phenylphenol, DMBA/*o*-phenylphenol, and DMBA/TPA groups. No skin neoplasms were observed in male or female mice receiving *o*-phenylphenol or in the acetone vehicle control groups. Moreover, a complete histopathologic review revealed no other neoplasms at any other site at significantly increased incidences in the groups receiving *o*-phenylphenol compared with the acetone vehicle controls. There were also no tumor-enhancing (or tumor-inhibiting) effects of *o*-phenylphenol and DMBA given in combination.

o-Phenylphenol was weakly mutagenic in strain TA1535 of *Salmonella typhimurium* only in the absence of rat liver S9; it was not mutagenic in strains TA1537, TA98, or TA100. It was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the presence or absence of Aroclor 1254-induced male F344 rat liver S9. *o*-Phenylphenol did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. *o*-Phenylphenol induced sister-chromatid exchanges in Chinese hamster ovary (CHO) cells only in the absence of rat liver S9. It did not induce chromosomal aberrations in CHO cells in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9.

An audit of the experimental data was conducted for these 2-year studies of *o*-phenylphenol. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year dermal application studies, there was *no evidence of carcinogenicity** in male or female Swiss CD-1 mice administered *o*-phenylphenol alone or as a promoter following initiation with DMBA. *o*-Phenylphenol, however, caused nonneoplastic lesions, which included ulceration, inflammation, and hyperkeratosis, at the site of application.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of *o*-Phenylphenol is based on the 4-week studies that began in June 1979 and ended in July 1979 and on the 2-year studies that began in July 1980 and ended in July 1982 at Battelle Columbus Laboratories.

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The members of the Peer Review Panel who evaluated the draft Technical Report on *o*-Phenylphenol on March 29, 1985, 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 o-PHENYLPHENOL

On March 29, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of *o*-phenylphenol received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Tannenbaum, a principal reviewer, agreed with the conclusions. He wondered if the current categories for strength of evidence of carcinogenicity encompassed findings in studies of chemicals as promoters. Dr. J. Huff, NIEHS, indicated that such specialty categories were not contemplated as yet.

As a second principal reviewer, Dr. Crowley agreed with the conclusions. However, he questioned the use of the fairly recently derived statistical test by Korn and Liu to assess significance of possible synergistic or antagonistic effects of DMBA and *o*-phenylphenol on tumor induction. Given the negative results, the test could be deleted. Dr. J. Haseman, NIEHS, agreed that the interaction test (Korn-Liu) added little to these studies and would be deleted. He said that the NTP was in the process of evaluating the operating characteristics of several procedures recently proposed for assessing possible synergistic effects.

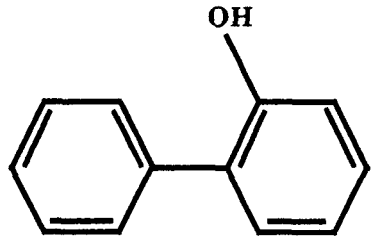
As a third principal reviewer, Dr. Swenberg also agreed with the conclusions. Since the chemical was poorly absorbed from the skin, he questioned the histologic examination of so many tissues. Dr. E. McConnell, NIEHS/NTP, replied that these examinations were routine for all studies, including those by the dermal route, at the time these studies were designed. Currently, the design for histologic examinations would be tailored to whether appreciable absorption was known or expected. Dr. Huff stated that for dermal studies, NTP is considering limiting the amount of pathologic review to the site of application, to known target organs, and to observations and trends from gross pathologic examinations.

In futher discussion, Dr. Purchase said that the current description of the methods used did not allow the reviewer to determine whether the different types of responses to skin carcinogens could have been measured, such as shortening of time to tumor, increases in number of animals with tumors, and increases in multiplicity of tumors. Dr. W. Kluwe, NIEHS, replied that current design incorporates tumor mapping, recording, and tracking and more reliance on microscopic evaluation, procedures that should provide for better interpretation of future data. Dr. Kociba noted the development of ulcerations at the site of chemical application in some of the animals and asked whether, from the standpoint of animal health, more could be done to minimize the development and duration of these lesions. Dr. Huff indicated that this was certainly a primary consideration for all current studies.

Dr. Tannenbaum moved that the Technical Report on the toxicology and carcinogenesis studies of *o*-phenylphenol be accepted with modifications as requested. Dr. Swenberg seconded the motion, and the Report was approved by nine affirmative votes. There was one abstention because of company affiliation (Dr. Kociba).

I. INTRODUCTION

I. INTRODUCTION



***ORTHO*-PHENYLPHENOL**

CAS NO. 90-43-7

$C_{12}H_{10}O$ Molecular weight 170.2

o-Phenylphenol currently is used commercially as a germicide, fungicide, and disinfectant for postharvest treatment of citrus fruits; previously, it was used for treatment of vegetables. It is also used as an intermediate in wear-resistant surface coatings, a dip for crates and hampers, a fungicide in water-based paints, a preservative in adhesives and glues, and a defoamer in paper manufacturing and for impregnation of fruit wraps. Estimated production in the United States was approximately 2×10^9 g per year in 1974 with estimated human exposure being 6.5×10^6 g per year (NCI/SRI estimate).

General Toxicity

Early studies by MacIntosh (1945) and Hodge et al. (1952), which were later repeated by Taniguchi et al. (1981), showed that the acute toxicity of *o*-phenylphenol is low when the chemical is given orally to mice or rats, the acute oral LD_{50} values being between 1 and 3 g/kg body weight. The primary cause of death was congestion and hemorrhage in the lungs (Taniguchi et al., 1981). Cats are more sensitive to *o*-phenylphenol than are other species tested, the acute oral LD_{50} value being 500 mg/kg (MacIntosh, 1945; Oehme, 1971).

Hodge et al. (1952) reported that rats maintained on diets containing *o*-phenylphenol at concentrations up to 0.2% for 2 years had no toxic manifestations. Rats fed diets containing 2% *o*-phenylphenol, however, had retarded growth and renal tubular dilatation. Hiraga and Fugii (1981) reported pyelonephritis in rats fed diets containing sodium *o*-phenylphenate at concentrations of 2% or 4% for 91 weeks.

o-Phenylphenol does not induce changes in immune function in mice following short-term oral administration (Sasaki and Nakao, 1968). This finding was confirmed by Luster et al. (1981) in studies in which $B6C3F_1$ mice were administered oral doses of *o*-phenylphenol (up to 200 mg/kg per day) for 10 days and then examined for a variety of immune functions.

o-Phenylphenol, administered orally to pregnant mice at doses ranging from 1.45 to 2.0 g/kg, produced maternal toxicity and delayed fetal development but not teratogenicity (Ogata et al., 1978). In another study, *o*-phenylphenol was found to be fetotoxic but not teratogenic when administered to pregnant rats in daily doses of 600 mg/kg, on days 6 through 15 of gestation (Kaneda et al., 1978). John et al. (1981) reported that *o*-phenylphenol was not embryotoxic or teratogenic to Sprague-Dawley rats at doses up to 700 mg/kg per day administered on gestation days 6 through 15.

The primary metabolites of sodium *o*-phenylphenate in rat urine are the glucuronic acid conjugates of *o*-phenylphenol and 2,5-dihydroxybiphenyl (Nakao et al., 1983). Dogs and cats also excrete urinary sulfonic acid and glucuronic acid metabolites of *o*-phenylphenol, although the parent compound predominates (Savides and Oehme, 1980).

In humans, *o*-phenylphenol is moderately toxic when ingested or inhaled. It is poorly absorbed through the skin (Harke and Klein, 1981). *o*-Phenylphenol is an irritant when inhaled as a dust or applied to the skin in aqueous solutions above 0.5%, and corneal necrosis may result

from contact with the compound in liquid or dust forms (Gosselin et al., 1976). A fatal oral dose of 10 g was reported (Dreisbach, 1974), and "toxic effects on the urothelium of the bladder" were observed in two humans exposed to *o*-phenylphenol (Gaches, 1975).

Mutagenicity

Shirasu et al. (1978) reported that *o*-phenylphenol was not mutagenic in *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, or TA100) or *Escherichia coli* and did not cause DNA damage in *Bacillus subtilis* or chromosomal aberrations in mouse bone marrow. The authors also indicated that *o*-phenylphenol did not cause dominant lethal mutations in mice. Using the same data but applying different statistical tests, Takahashi (1978) concluded that the results of mutagenicity studies in Salmonella and of dominant lethal assays and chromosomal aberration tests in mice were positive. McMahon et al. (1979) reported that *o*-phenylphenol was mutagenic in strain TA100 of *S. typhimurium*, but no data were provided. The NTP found that *o*-phenylphenol was weakly mutagenic in strain TA1535 of *S. typhimurium* only in the absence of male rat liver S9 (Appendix K, Table K1) and also was weakly mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the presence or absence of Aroclor 1254-induced male rat liver S9 (Tables K2 and K3). *o*-Phenylphenol, however, did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (Table K4). *o*-Phenylphenol induced sister-chromatid exchanges (SCE's) in Chinese hamster ovary (CHO) cells only in the absence of rat liver S9; it did not induce chromosomal aberrations in CHO cells in the presence or absence of S9 (Tables K5 and K6). Tayama-Nawai et al. (1984) showed that *o*-phenylphenol induced SCE's in CHO cells in the absence of S9. In addition, by using doses that were fivefold higher than those used by NTP, these investigators found that *o*-phenylphenol induced chromosomal aberrations in CHO cells in the absence of S9.

Reitz et al. (1983) found that the related compound sodium o-phenylphenate was not mutagenic in Salmonella and did not induce unscheduled DNA synthesis in rat liver hepatocytes in vitro. In addition, covalently bound radioactivity was not detected in DNA isolated from the bladders of F344 male rats that were administered 500 mg/kg of ^{14}C-sodium *o*-phenylphenate by gavage.

Carcinogenicity Studies

Several studies have been conducted to assess the carcinogenicity of *o*-phenylphenol in laboratory animals. Hodge et al. (1952) did not observe an increased incidence of neoplasms in male and female Wistar rats given *o*-phenylphenol at concentrations up to 2% in the diet for 2 years. *o*-Phenylphenol was not carcinogenic in B6C3F$_1$ or B6AKF$_1$ mice that were administered a single subcutaneous dose of 1 g/kg body weight in corn oil and monitored for 18 months or given 100 mg/kg in 0.5% gelatin by gavage at 7-28 days of age followed by diets containing *o*-phenylphenol at a concentration of 280 ppm for 18 months (Innes, 1968).

More recently, Hiraga and Fujii (1981) reported an increased incidence of neoplasms of the urinary bladder in F344/DuCrj rats administered sodium *o*-phenylphenate in the diet. In a 13-week study, urinary bladder papillomas or transitional cell carcinomas developed in 1/10 male rats fed 1% sodium *o*-phenylphenate, 9/10 male rats fed 2%, 1/10 male rats fed 4%, and 2/10 female rats fed 4%. In a 91-week study, transitional cell carcinomas of the urinary bladder, renal pelvis, or renal papilla developed in 1/21, 7/21, 20/21, and 17/21 male rats fed sodium *o*-phenylphenate in the diet at concentrations of 0.5%, 1%, 2%, or 4%, respectively. In contrast, Reitz et al. (1983) did not observe tumors in the urinary tract of rats exposed for 13 weeks to sodium *o*-phenylphenate at a concentration of 2% in the diet. The authors postulated that the different effects reported in the literature may be due to differences in the concentrations of sodium *o*-phenylphenate used, since a reactive metabolite (dihydrobiphenyl) is formed in rats after they were given doses above 500 mg/kg. This dose is equivalent to approximately 1% in the diet. Recently, Hagiwara et al. (1984) reported that male and female B6C3F$_1$ mice administered sodium o-phenylphenate at levels up to 2% in the diet for 76 weeks did not develop compound-related neoplasms of any type.

Boutwell and Bosch (1959) reported that a high incidence of papillomas (greater than 80%) developed in mice within 10 weeks following initiation with 7,12-dimethylbenz(*a*)anthracene (DMBA) and twice weekly skin applications of 2.5 mg phenol in benzene. Carcinomas developed later in these mice and reached a 47% incidence at week 40. When the dose was decreased by half (1.25 mg), a marked decrease in papillomas occurred. In mice administered 2.5 mg of phenol on the same schedule, but without DMBA initiation, 25% developed papillomas by week 36 and none developed carcinomas. *o*-Phenylphenol was also examined in that study as a complete carcinogen (i.e., mice were not dosed first with DMBA). Only 1/21 mice developed papillomas following a 20-week exposure consisting of twice-weekly dermal applications of 4.5 mg *o*-phenylphenol in benzene.

Study Rationale

o-Phenylphenol was selected for carcinogenesis studies because of its widespread use as a fungicide and germicide on fruits. Although primary human exposure occurs orally, results of feeding studies (Hodge et al., 1952; Innes, 1968) in mice and rats gave no evidence of carcinogenicity. Since dermal exposure also occurs in humans, phenolic compounds are weak promoters of skin tumors (Boutwell and Bosch, 1959), and *o*-phenylphenol is a skin irritant, NCI recommended that *o*-phenylphenol be studied to determine if it is a complete carcinogen alone or a promoter in a two-stage skin carcinogenesis study.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *o*-PHENYLPHENOL

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOUR-WEEK STUDIES

TWO-YEAR STUDIES

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

PROCUREMENT AND CHARACTERIZATION OF *o*-PHENYLPHENOL

o-Phenylphenol, manufactured by Dow Chemical USA, was obtained from Callahan Chemical Company in one batch (lot no. MM09157). The identity of *o*-phenylphenol was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of *o*-phenylphenol was determined by elemental analysis, Karl Fischer water analysis, and gas chromatography (Appendix D). The cumulative data indicated that the *o*-phenylphenol test material was greater than 99% pure and that the major impurity identified was water (0.21%).

o-Phenylphenol was stable at temperatures up to 60° C for 2 weeks. *o*-Phenylphenol was stored in the dark at 23° C. Results of periodic analysis of the bulk chemical by infrared spectroscopy and gas chromatography indicated no notable degradation of the chemical throughout the studies (Appendix D).

7,12-Dimethylbenz(*a*)anthracene (DMBA), lot no. C8H, was obtained from Fisher Scientific and purified at Midwest Research Institute by column chromatography and recrystallization (Appendix E). The DMBA was stored at −20° C. 12-O-Tetradecanoylphorbol-13-acetate (TPA) in individual 10-mg flame-sealed vials was obtained from Consolidated Midland Corporation, Brewster, New York. The TPA was stored in brown bottles (wrapped in aluminum foil) at −20° C in portions sufficient for 1 day of dosing.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

The appropriate amount of *o*-phenylphenol was weighed and mixed with acetone (Burdick and Jackson). *o*-Phenylphenol at 840 mg/ml in acetone was stable for at least 2 weeks at room temperature in the dark (Table 1; Appendix F).

Dose mixtures of *o*-phenylphenol in acetone were periodically analyzed at the testing and analytical laboratories (Appendix G). The results of analyses at the testing laboratory indicated that none of the mixtures analyzed differed from the target concentration by more than 10% (Table 2; Appendix H). In the 2-year studies, formulated mixtures of *o*-phenylphenol were stored at room temperature for no longer than 2 weeks.

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE DERMAL STUDIES OF *o*-PHENYLPHENOL

	Four-Week Studies	Two-Year Studies
Preparation	Weighed portions of *o*-phenylphenol mixed with the appropriate volume of technical-grade acetone and placed on a magnetic stirrer for 5-10 min	Weighed portions of *o*-phenylphenol or TPA mixed with the appropriate volume of acetone; mixing column inverted 21 times until the chemical appeared to be in solution, then inverted an additional 21 times
Maximum Storage Time	9 d	2 wk
Storage Conditions	23° C	4° C in foil-wrapped vials

TABLE 2. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

	Concentration of *o*-Phenylphenol in Acetone
Mean (mg/ml)	556
Range (mg/ml)	527-587
Standard deviation	15.7
Coefficient of variation (percent)	2.82
Number of samples	15

FOUR-WEEK STUDIES

Four-week studies were conducted to evaluate the cumulative toxic effects of repeated dermal administration of *o*-phenylphenol and to determine the doses to be used in the 2-year studies.

Seven-week-old male and female Swiss Webster CFW mice (Crl:CFW[SW]BR) were received from Charles River Breeding Laboratories and observed for 18 days before the studies began. Mice were housed individually in polycarbonate cages. Feed and water were available ad libitum. Groups of 10 mice of each sex were given dermal applications to the dorsal interscapular region of 0, 5.95, 11.4, 20.8, 35.7, or 55.5 mg/0.1 ml in acetone, 3 days per week (Wednesday, Friday, and Monday) for 4 weeks. To facilitate the application of the *o*-phenylphenol, the hair on the application site was clipped weekly with an Oster® clipper that had a number 40 clipping head. Further experimental details are summarized in Table 3.

Animals were monitored twice daily for clinical signs of ill health; moribund animals were killed. Animal weights were recorded weekly. At the end of the 4-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 3.

TWO-YEAR STUDIES

Study Design

In contrast to the 4-week studies in which Swiss Webster (Crl:CFW[SW]BR) mice were used, Swiss Crl:CD-1(ICR)BR(Swiss CD-1) were used in the 2-year studies. Groups of 50 Swiss CD-1 mice of each sex were dosed for 74-102 weeks according to five different protocols. Vehicle controls were given dermal applications to the dorsal interscapular region of 0.1 ml acetone 3 days per week. One dose group was given dermal applications of *o*-phenylphenol (55.5 mg/0.1 ml acetone) 3 days per week for 102 weeks. Three additional groups were given a single dermal application to the dorsal interscapular region of 0.1 ml DMBA (0.05 mg/0.1 ml acetone). Starting 1 week later, the latter three groups were given dermal applications of either acetone (vehicle), *o*-phenylphenol (55.5 mg/0.1 ml), or TPA (0.005 mg/0.1 ml) 3 days per week for the remainder of the studies at the original site of DMBA application. A 2-cm^2 area of skin was covered with these materials. All groups were dosed for 102 weeks except the male (85 weeks) and female (74 weeks) DMBA/TPA groups, which were killed before the end of the studies because of the high number of deaths. The exposure regimens are given in Table 3.

Source and Specifications of Animals

The male and female Swiss CD-1 mice used in these studies were obtained from Charles River Breeding Laboratories, Portage, Michigan, from their cesarean-originated, barrier-sustained production colony. Animals were shipped to the testing laboratory at 5 weeks of age and quarantined for 17 days. A complete necropsy was performed on five animals of each sex to assess their health status. The mice were placed on study at 7 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix I).

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DERMAL STUDIES OF *o*-PHENYLPHENOL

	Four-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Test Groups	10 male and 10 female mice	50 male and 50 female mice
Doses	0.1 ml of 0, 5.95, 11.4, 20.8, 35.7, or 55.5 mg *o*-phenylphenol in 0.1 ml of acetone by dermal application	Vehicle control: 0.1 ml acetone 3 × wk; complete carcinogen: 0.1 ml *o*-phenylphenol (55.5 mg/0.1 ml acetone) 3 × wk; promotion test: 0.1 ml 7,12-dimethylbenz(a)anthracene (DMBA) (0.05 mg/0.1 ml acetone), then 0.1 ml *o*-phenylphenol 3 × wk; initiator control: 0.1 ml DMBA, then 0.1 ml acetone 3 × wk; positive control: 0.1 ml DMBA, then 0.1 ml 12-O-tetradecanoylphorbol-13-acetate (TPA) (0.005 mg/0.1 ml acetone) 3 × wk
Date of First Dose	6/20/79	7/28/80
Date of Last Dose	7/16/79	7/12/82
Duration of Dosing	3 d/wk for 4 wk	DMBA--once; *o*-phenylphenol--102 wk; TPA--85 wk (male), 74 wk (female)
Type and Frequency of Observation	Observed 2 × d; clipped 1 × wk, 24 h before topical application	Observed 2 × d for clincal signs of ill health; dermal masses recorded 2 × wk for the first 3 mo and 1 × mo thereafter; clinical observations recorded daily for the first 17 mo and 1 × mo thereafter. Weighed 1 × wk for 13 wk, 1 × mo thereafter
Necropsy and Histologic Examination	Necropsy performed on all animals; histologic examinations were performed on all 55.5 mg *o*-phenylphenol and vehicle control animals; tissues examined microscopically: heart, kidneys, liver, lungs, ovaries, skin, and thyroid gland	Necropsy performed on all animals; histologic examination performed on all animals; the following tissues were examined microscopically: gross lesions and tissue masses (and regional lymph nodes, if possible), mandibular lymph node, salivary gland, femur including marrow, thyroid gland, parathyroids, small intestine, colon, liver, gallbladder, prostate/testes or ovaries/uterus, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, skin (application site and unspecified sites), lungs and mainstem bronchi, kidneys, adrenal glands, urinary bladder, pituitary gland, eyes, and mammary gland
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species	Swiss Webster CFW mice	Swiss CD-1 mice
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Same as 4-wk studies
Testing Laboratory	Battelle Columbus Laboratories	Same as 4-wk studies
Time Held Before Test	18 d	17 d

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DERMAL STUDIES OF *o*-PHENYLPHENOL (Continued)

	Four-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Age When Placed on Study	54 d	52 d
Age When Killed	87-88 d	112 wk
Necropsy Dates	7/23/79-7/24/79	7/27/82-7/28/82
Method of Animal Distribution	Animals randomized from weight classes into cages by a table of random numbers; cages randomized to test and control groups by another table of random numbers	Same as 4-wk studies; animals housed individually after randomization of cages to dose groups
Animal Identification	Toe clipping	Toe clipping
Feed	Purina 5001 Pelleted Lab Chow® (Ralston Purina Co., St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA) (Appendix J); available ad libitum
Bedding	Absorb-Dri® hardwood chips (Absorb-Dri Inc., Garfield, NJ); changed 2 × wk	Heat-treated hardwood chips (Absorb-Dri Inc., Rochelle Park, NJ)
Water	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 4-wk studies
Cages	Polycarbonate (Lab Products Inc., Rochelle Park, NJ); changed 1 × wk	Same as 4-wk studies
Cage Filters	Spun-bonded polyester (DuPont 2024) (Snow Filtration Co., Cincinnati, OH)	Same as 4-wk studies
Animals per Cage	5 for 2 d, then individually	1
Other Chemicals on Test in the Same Room	None	None
Animal Room Environment	Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as 4-wk studies; DMBA administration conducted under yellow light

II. MATERIALS AND METHODS

Animal Maintenance

All animals were clipped with an Oster® clipper once per week, 24 hours before dermal application. The mice were housed individually in polycarbonate cages. Feed and water were available ad libitum. Details of animal maintenance are summarized in Table 3.

Clinical Examinations and Pathology

All animals were observed twice daily; clinical signs were recorded daily for the first 17 months and once per month thereafter. The number of dermal growths per animal and physical descriptions of the growths were recorded. Dermal masses were recorded twice per week for the first 3 months and once per month thereafter. Body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the studies. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. 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 in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 3.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, target tissues, and tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. 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 evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

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 pathologic 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 dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for survival used the method of Cox (1972) for testing two groups for equality. 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 dose groups with the acetone vehicle controls and with DMBA/vehicle controls.

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. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study 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 acetone 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 study, 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). 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 Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and acetone 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 on which a necropsy was actually performed 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 (Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. This test is based on the overall proportion of tumor-bearing animals and does not adjust for survival diferences.

Analysis of Time to Skin Tumor Appearance: Following histopathologic confirmation of skin tumor development, statistical differences in time to first visible appearance of tumor were determined with life table analyses as described above.

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) are included for those tumors appearing to show compound-related effects.

III. RESULTS

FOUR-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FOUR-WEEK STUDIES

All the mice survived to the end of the studies (Table 4). The final mean body weights of the male and female mice were not affected by the chemical.

An ulcerative lesion was present at the site of application in all mice that received 20.8 mg of *o*-phenylphenol or more, in 6/10 males and 9/10 females that received 11.4 mg, in 2/10 males and 7/10 females that received 5.95 mg, and in 1/10 male and 1/10 female acetone vehicle controls. This lesion included one or more of the following: scattered infiltration of neutrophils, round cells, and mast cells; areas of collagen necrosis and activated fibroblasts; occasional necrotic epithelial cells in adnexal structures and necrotic mesenchymal cells in the dermis; occasional multinucleate epithelial cells associated with hair follicles; and aggregations of inflammatory cells around adnexal structures.

Dose Selection Rationale: Since the severity of the skin lesion was minimal and not life threatening, the highest dose in the 4-week studies (55.5 mg/0.1 ml) was selected for the 2-year studies. The chemical at this concentration did not recrystallize following skin application.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of *o*-phenylphenol and DMBA/*o*-phenylphenol male mice were generally 5%-10% lower than those of the acetone vehicle controls after week 44 (Table 5 and Figure 1). Mean body weights of the female DMBA/TPA group were greater than those of the other female groups during the 1st year of the study. The remaining groups had mean body weights similar to those of the corresponding acetone vehicle control groups.

Mean body weights of the DMBA/*o*-phenylphenol and DMBA/TPA groups were not markedly different from those of the DMBA group (Table 6).

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOUR-WEEK DERMAL STUDIES OF *o*-PHENYLPHENOL

Dose (mg/0.1 ml)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	29.1	28.9	− 0.2	--
5.95	10/10	29.4	29.8	+ 0.4	103.1
11.4	10/10	29.3	30.6	+ 1.3	105.9
20.8	10/10	29.4	31.0	+ 1.6	107.3
35.7	10/10	28.7	30.0	+ 1.3	103.8
55.5	10/10	28.8	30.4	+ 1.6	105.2
FEMALE					
0	10/10	23.9	26.5	+ 2.6	--
5.95	10/10	24.1	26.6	+ 2.5	100.4
11.4	10/10	24.2	26.7	+ 2.5	100.8
20.8	10/10	24.9	29.9	+ 5.0	112.8
35.7	10/10	23.9	26.9	+ 3.0	101.5
55.5	10/10	24.7	27.6	+ 2.9	104.2

(a) Number surviving/number in group

TABLE 5. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL RELATIVE TO VEHICLE CONTROLS

Weeks on Study	Veh Control		DMBA (a)			*o*-Phenylphenol			DMBA/*o*-Phenylphenol			DMBA/TPA (b)		
	Av Wt (grams)	No. Survivors	Av Wt (grams)	Wt (% of veh cont)	No. Survivors	Av Wt (grams)	Wt (% of veh cont)	No. Survivors	Av Wt (grams)	Wt (% of veh cont)	No. Survivors	Av Wt (grams)	Wt (% of veh cont)	No. Survivors
MALE														
0	29.3	50	29.9	102	49	29.9	102	50	30.9	105	50	30.1	103	50
1	29.8	50	29.4	99	49	29.6	99	50	30.3	102	50	30.3	102	50
2	30.6	50	30.6	100	49	31.1	102	50	31.5	103	49	31.6	103	50
3	31.8	50	31.5	99	49	31.4	99	49	31.7	100	49	32.6	103	50
4	32.2	50	32.2	100	49	32.1	100	49	32.7	102	49	33.1	103	50
5	32.0	50	32.6	102	49	32.1	100	49	32.9	103	49	33.2	104	50
6	33.3	50	33.2	100	49	32.8	98	49	33.5	101	49	33.7	101	50
7	33.2	50	33.2	100	49	32.9	99	49	33.5	101	49	33.3	100	50
8	33.7	50	33.1	98	49	32.6	97	49	33.8	100	49	33.3	99	50
9	33.9	50	33.6	99	49	33.0	97	49	34.2	101	49	33.2	98	50
10	34.2	50	33.9	99	49	33.3	97	49	34.4	101	49	34.1	100	50
11	34.2	50	34.2	100	49	33.2	97	49	34.6	101	49	33.9	99	50
12	34.8	50	34.4	99	49	34.1	98	49	35.0	101	49	34.8	100	50
13	34.9	50	34.2	98	49	33.9	97	49	35.0	100	49	35.4	101	50
18	36.0	50	35.7	99	49	35.1	98	49	36.0	100	48	35.7	99	49
23	37.5	50	36.5	97	49	35.5	95	49	36.9	98	48	36.2	97	49
27	37.7	50	37.0	98	48	35.6	94	49	37.4	99	46	36.1	96	47
31	37.8	50	37.2	98	48	36.1	96	49	37.2	98	46	37.4	99	45
36	37.8	50	37.2	98	48	36.0	95	49	36.9	98	46	36.5	97	42
40	38.0	49	38.1	100	48	36.5	96	45	38.3	101	43	37.9	100	27
44	38.8	48	38.2	98	48	36.7	95	44	37.5	97	41	36.9	95	27
49	40.2	47	40.2	100	48	38.1	95	41	39.1	97	40	38.8	97	25
53	40.6	45	39.9	98	47	38.3	94	40	39.1	96	38	38.9	96	16
57	39.7	44	38.8	98	45	38.0	96	40	37.6	95	36	39.4	99	13
62	41.2	42	39.4	96	44	38.1	92	37	37.3	91	32	39.6	96	10
66	41.3	42	40.6	98	43	38.4	93	36	40.3	98	32	38.3	93	7
70	40.4	42	40.4	100	43	39.2	97	35	39.8	99	32	37.8	94	6
75	40.9	38	40.3	99	42	39.8	97	28	40.1	98	29	38.8	95	5
79	41.3	38	39.6	96	37	39.1	95	28	39.8	96	28	38.5	93	4
83	40.7	36	38.9	96	35	39.3	97	26	38.7	95	23	34.5	85	4
88	39.4	34	39.8	101	33	38.2	97	25	38.8	98	23	39.0	98	2
93	39.6	29	38.6	97	29	38.6	97	24	38.4	97	18	--	--	--
98	40.0	25	40.9	102	23	38.3	96	22	39.9	100	16	--	--	--
101	38.2	23	41.1	108	21	38.1	100	20	40.1	105	15	--	--	--
103	39.4	20	41.3	105	20	39.0	99	16	39.4	100	15	--	--	--
FEMALE														
0	24.0	50	24.7	103	50	23.9	100	50	24.8	103	50	24.3	101	48
1	24.4	50	24.1	99	50	23.9	98	49	24.2	99	50	24.5	100	48
2	25.0	50	25.7	103	50	25.1	100	49	25.5	102	48	26.1	104	48
3	26.4	50	26.6	101	50	25.1	95	49	26.5	100	48	27.3	103	48
4	26.4	50	26.6	101	50	26.3	100	49	27.0	102	48	27.5	104	48
5	26.8	50	27.2	101	50	26.9	100	49	27.4	102	48	28.2	105	47
6	27.2	50	27.5	101	50	27.3	100	49	27.8	102	48	29.0	107	47
7	27.4	50	27.6	101	50	27.6	101	49	28.0	102	48	28.6	104	47
8	27.6	50	27.6	100	50	27.6	100	49	28.4	103	48	28.8	104	47
9	28.2	50	28.5	101	50	28.2	100	49	28.9	102	48	29.6	105	47
10	28.4	50	28.9	102	50	28.5	100	49	29.0	102	48	30.2	106	47
11	28.6	50	28.8	101	50	28.3	99	49	29.2	102	48	30.2	106	47
12	29.1	50	29.2	100	50	28.8	99	49	29.4	101	48	30.6	105	47
13	29.0	50	29.0	100	50	28.7	99	49	29.4	101	48	30.3	104	47
18	30.1	50	30.5	101	50	30.1	100	49	30.5	101	47	31.8	106	46
23	30.9	49	31.6	102	50	31.0	100	49	31.6	102	47	32.8	106	46
27	31.5	49	32.3	103	50	31.9	101	49	31.8	101	46	34.0	108	42
31	32.5	49	33.6	103	49	32.9	101	47	32.9	101	46	34.3	106	39
36	32.6	49	33.1	102	49	32.8	101	47	33.0	101	46	34.8	107	35
40	32.4	47	34.2	106	48	33.1	102	46	33.3	103	45	34.7	107	29
44	33.4	46	34.9	104	45	34.3	103	46	34.2	102	45	35.3	106	26
49	34.5	45	35.9	104	45	34.6	100	44	35.3	102	43	35.5	103	18
53	35.4	45	36.1	102	44	35.6	101	42	35.4	100	42	36.5	103	16
57	34.2	43	36.4	106	44	35.2	103	40	35.1	103	41	35.5	104	12
62	37.4	40	36.0	96	41	35.2	94	39	36.2	97	36	36.3	97	7
66	36.7	38	37.8	103	41	36.2	99	39	37.7	103	35	32.3	88	4
70	36.7	37	37.7	103	41	36.2	99	39	37.1	101	32	37.5	102	2
75	37.0	31	38.0	103	35	36.8	99	36	37.9	102	26	--	--	--
79	37.8	31	36.6	97	34	35.7	94	35	36.5	97	23	--	--	--
83	36.8	30	35.9	98	32	35.9	98	31	36.5	99	22	--	--	--
88	36.5	29	36.1	99	29	36.4	100	26	37.7	103	17	--	--	--
93	37.5	24	35.7	95	24	36.9	98	19	36.6	98	13	--	--	--
98	35.1	15	37.1	106	17	37.0	105	16	40.1	114	9	--	--	--
101	36.5	14	38.9	107	17	38.5	105	15	40.3	110	7	--	--	--
103	36.2	11	38.1	105	16	38.1	105	15	41.7	115	7	--	--	--

(a) DMBA--7,12-dimethylbenz(*a*)anthracene
(b) TPA--12-O-tetradecanoylphorbol-13-acetate

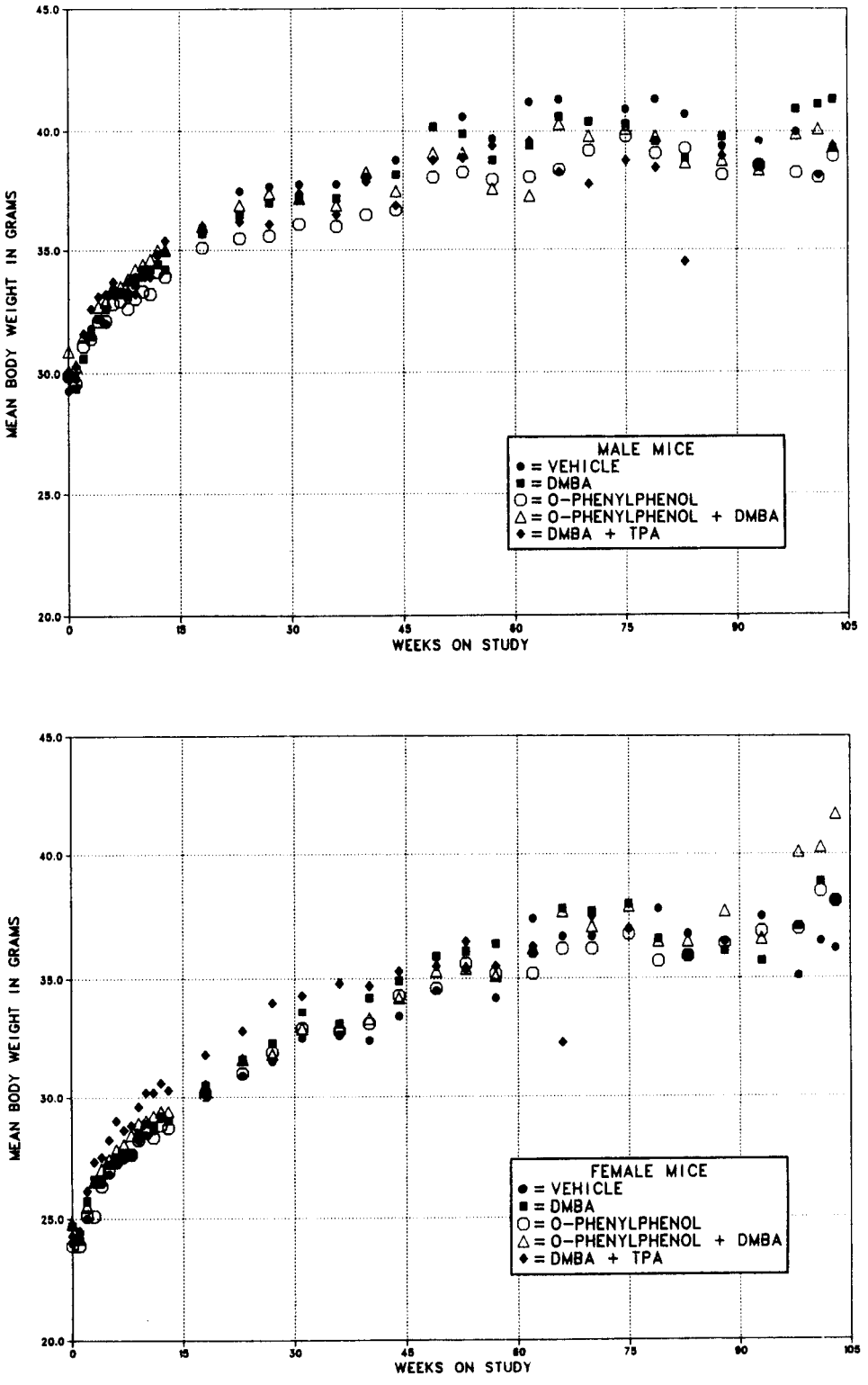


FIGURE 1. GROWTH CURVES FOR MICE ADMINISTERED *o*-PHENYLPHENOL BY DERMAL APPLICATION FOR TWO YEARS

TABLE 6. MEAN BODY WEIGHTS AND SURVIVAL OF MICE ADMINISTERED DMBA IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL (a)

Weeks on Study	DMBA		DMBA/*o*-Phenylphenol			DMBA/TPA (b)		
	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent of DMBA controls)	No. of Survivors	Av Wt (grams)	Wt (percent of DMBA controls)	No. of Survivors
MALE								
0	29.9	49	30.9	103	50	30.1	101	50
1	29.4	49	30.3	103	50	30.3	103	50
2	30.6	49	31.5	103	49	31.6	103	50
3	31.5	49	31.7	101	49	32.6	103	50
4	32.2	49	32.7	102	49	33.1	103	50
5	32.6	49	32.9	101	49	33.2	102	50
6	33.2	49	33.5	101	49	33.7	102	50
7	33.2	49	33.5	101	49	33.3	100	50
8	33.1	49	33.8	102	49	33.3	101	50
9	33.6	49	34.2	102	49	33.2	99	50
10	33.9	49	34.4	101	49	34.1	101	50
11	34.2	49	34.6	101	49	33.9	99	50
12	34.4	49	35.0	102	49	34.8	101	50
13	34.2	49	35.0	102	49	35.4	104	50
18	35.7	49	36.0	101	48	35.7	100	49
23	36.5	49	36.9	101	48	36.2	99	49
27	37.0	48	37.4	101	46	36.1	98	47
31	37.2	48	37.2	100	46	37.4	101	45
36	37.2	48	36.9	99	46	36.5	98	42
40	38.1	48	38.3	101	43	37.9	99	27
44	38.2	48	37.5	98	41	36.9	97	27
49	40.2	48	39.1	97	40	38.8	97	25
53	39.9	47	39.1	98	38	38.9	97	16
57	38.8	45	37.6	97	36	39.4	102	13
62	39.4	44	37.3	95	32	39.6	101	10
66	40.6	43	40.3	99	32	38.3	94	7
70	40.4	43	39.8	99	32	37.8	94	6
75	40.3	42	40.1	100	29	38.8	96	5
79	39.6	37	39.8	101	28	38.5	97	4
83	38.9	35	38.7	99	23	34.5	89	4
88	39.8	33	38.8	97	23	39.0	98	2
93	38.6	29	38.4	99	18	--	--	--
98	40.9	23	39.9	98	16	--	--	--
101	41.1	21	40.1	98	15	--	--	--
103	41.3	20	39.4	95	15	--	--	--
FEMALE								
0	24.7	50	24.8	100	50	24.3	98	48
1	24.1	50	24.2	100	50	24.5	102	48
2	25.7	50	25.5	99	48	26.1	102	48
3	26.6	50	26.5	100	48	27.3	103	48
4	26.6	50	27.0	102	48	27.5	103	48
5	27.2	50	27.4	101	48	28.2	104	47
6	27.5	50	27.8	101	48	29.0	105	47
7	27.6	50	28.0	101	48	28.6	104	47
8	27.6	50	28.4	103	48	28.8	104	47
9	28.5	50	28.9	101	48	29.6	104	47
10	28.9	50	29.0	100	48	30.2	104	47
11	28.8	50	29.2	101	48	30.2	105	47
12	29.2	50	29.4	101	48	30.6	105	47
13	29.0	50	29.4	101	48	30.3	104	47
18	30.5	50	30.5	100	47	31.8	104	46
23	31.6	50	31.6	100	47	32.8	104	46
27	32.3	50	31.8	98	46	34.0	105	42
31	33.6	49	32.9	98	46	34.3	102	39
36	33.1	49	33.0	100	46	34.8	105	35
40	34.2	48	33.3	97	45	34.7	101	29
44	34.9	45	34.2	98	45	35.3	101	26
49	35.9	45	35.3	98	43	35.5	99	18
53	36.1	44	35.4	98	42	36.5	101	16
57	36.4	44	35.1	96	41	35.5	98	12
62	36.0	41	36.2	101	36	36.3	101	7
66	37.8	41	37.7	100	35	32.3	85	4
70	37.7	41	37.1	98	32	37.5	99	2
75	38.0	35	37.9	100	26	--	--	--
79	36.6	34	36.5	100	23	--	--	--
83	35.9	32	36.5	102	22	--	--	--
88	36.1	29	37.7	104	17	--	--	--
93	35.7	24	36.6	103	13	--	--	--
98	37.1	17	40.1	108	9	--	--	--
101	38.9	17	40.3	104	7	--	--	--
103	38.1	16	41.7	109	7	--	--	--

(a) DMBA--7,12-dimethylbenz(a)anthracene
(b) TPA--12-O-tetradecanoylphorbol-13-acetate

Survival

Estimates of the probabilities of the survival for male and female mice of the various dosed groups and the acetone vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the male and female DMBA/TPA groups was significantly ($P < 0.001$) lower than that of the acetone vehicle controls (Table 7). None of the other groups had survival rates significantly different from those of the acetone vehicle controls.

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 skin, kidney, urinary bladder, bone marrow, thyroid gland, adrenal gland/zona fasciculata, liver, and lung. Histopathologic findings on neoplasms in mice are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix B (Tables B1 and B2). Appendix C (Tables C1 and C2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the five groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C (footnotes). Because of increased mortality in the DMBA/TPA groups, there was little overlapping survival between these groups and the corresponding acetone vehicle controls. Consequently, the incidental tumor test has little statistical power for detecting increased tumor incidence and was not carried out for these particular comparisons.

TABLE 7. SURVIVAL OF MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

	Vehicle Control	DMBA (a)	*o*-Phenylphenol (b)	DMBA/ *o*-Phenylphenol (c)	DMBA/ TPA (d)
MALE (e)					
Animals initially in study	50	50	50	50	50
Nonaccidental deaths before termination (f)	31	30	34	35	(g) 50
Killed at termination	18	20	16	14	0
Died during termination period	1	0	0	1	0
Survival P values (h)		0.900	0.325	0.120	< 0.001
FEMALE (e)					
Animals initially in study	50	50	50	50	50
Nonaccidental deaths before termination (f)	39	34	35	43	49
Accidentally killed	0	0	0	0	1
Killed at termination	11	15	15	6	0
Died during termination period	0	1	0	1	0
Survival P values (h)		0.490	0.766	0.089	< 0.001

(a) Administered a single dose of 0.05 mg 7,12-dimethylbenz(*a*)anthracene (DMBA) in acetone
(b) Administered 55.5 mg *o*-phenylphenol in acetone 3 × week
(c) Administered a single dose of DMBA followed by 55.5 mg *o*-phenylphenol in acetone 3 × week
(d) Administered a single dose of DMBA followed by 0.005 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) in acetone 3 × week
(e) Terminal-kill period: week 104
(f) Includes animals killed in a moribund condition
(g) Includes two animals killed at week 90
(h) The results of the life table exact pairwise comparisons with the vehicle controls

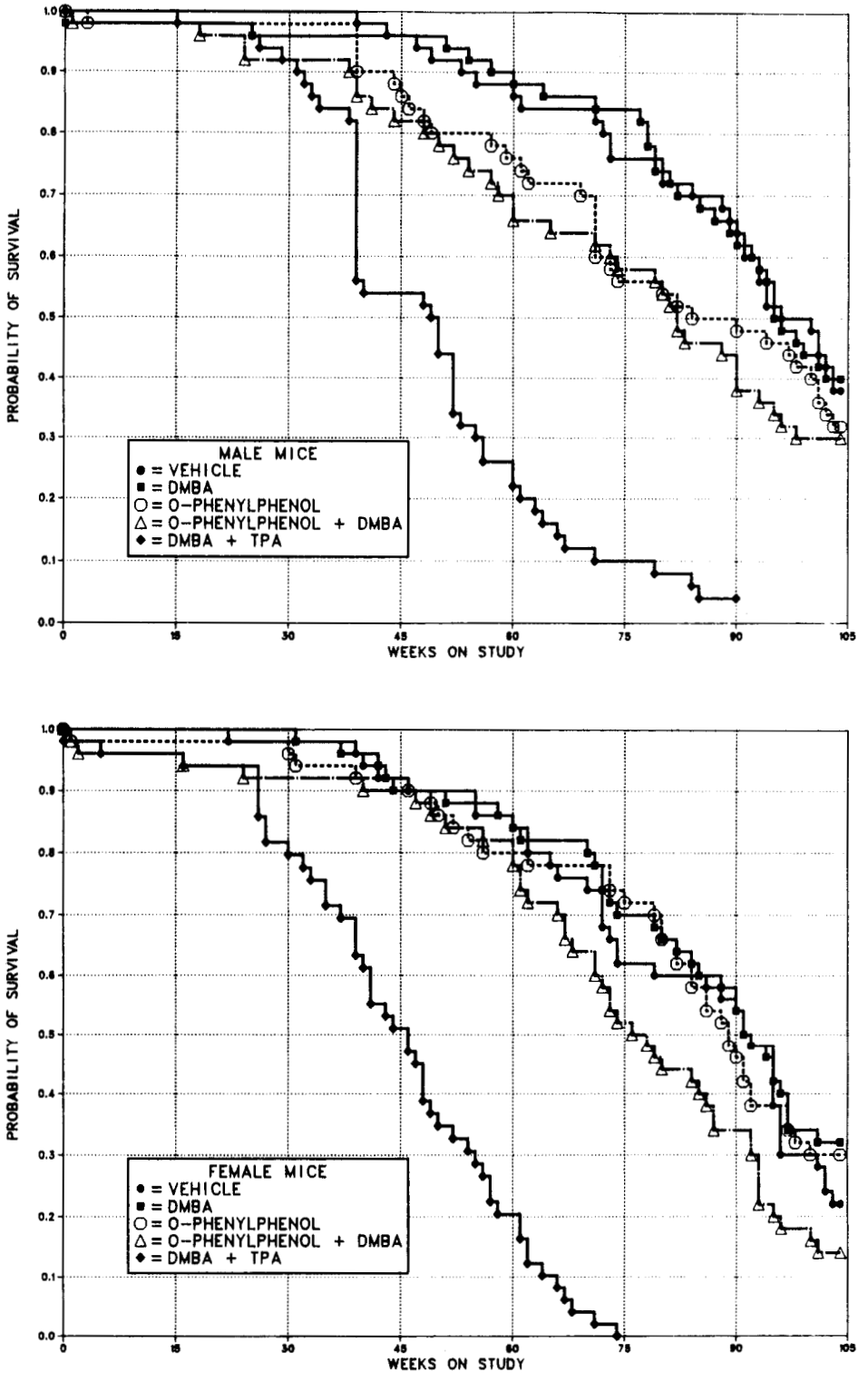


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED o-PHENYLPHENOL BY DERMAL APPLICATION FOR TWO YEARS

Skin: Nonneoplastic lesions, including ulcers, active chronic inflammation, hyperkeratosis, and acanthosis, were observed at the site of application in all groups but at a greater incidence in male and female mice administered *o*-phenylphenol, DMBA/o-phenylphenol, or DMBA/TPA (Table 8).

TABLE 8. NUMBERS OF MICE WITH SKIN LESIONS AT THE APPLICATION SITE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

Lesion	Acetone	*o*-Phenylphenol	DMBA (a)	DMBA/ *o*-Phenylphenol	DMBA/TPA (b)
MALE (c)					
Ulcer	5	19	2	16	15
Active chronic inflammation	10	25	10	25	27
Hyperkeratosis	7	27	8	24	30
Acanthosis	13	44	12	33	44
Squamous cell papilloma	0	0	1	4	7
Squamous cell carcinoma	0	0	4	1	13
Basal cell tumor	0	0	1	2	1
Basal cell carcinoma	0	0	0	2	0
Keratoacanthoma	0	0	0	0	1
Sebaceous adenoma	0	0	1	1	0
Sebaceous adenocarcinoma	0	0	0	0	0
Neoplastic skin lesion (combined) (d)	0	0	6	9	19
FEMALE (c)					
Ulcer	1	11	7	11	12
Active chronic inflammation	7	20	7	27	25
Hyperkeratosis	4	16	4	27	26
Acanthosis	4	36	12	42	41
Squamous cell papilloma	0	0	4	2	17
Squamous cell carcinoma	0	0	3	3	18
Basal cell tumor	0	0	0	0	0
Basal cell carcinoma	0	0	2	3	2
Keratoacanthoma	0	0	0	0	5
Sebaceous adenoma	0	0	1	0	0
Sebaceous adenocarcinoma	0	0	1	0	0
Neoplastic skin lesion (combined) (d)	0	0	9	8	(e) 32

(a) DMBA--7,12-dimethylbenz(a)anthracene
(b) TPA--12-O-tetradecanoylphorbol-13-acetate
(c) 50 animals per group
(d) Some animals had more than one type of neoplastic skin lesion; multiple occurrences of skin tumors in a single animal are counted once only.
(e) Does not include a carcinosarcoma in one animal that had no other skin tumor

The incidences of squamous cell papillomas and squamous cell carcinomas in the male and female DMBA/TPA groups were significantly greater than those in the other DMBA groups (Table 9). The squamous cell carcinomas metastasized to the lung in 5/50 males and 11/50 females in the DMBA/TPA groups. An increased incidence of keratoacanthomas occurred in the female DMBA/TPA group as compared with DMBA groups. In contrast to the DMBA/TPA groups, there was no significant increase in the incidences of squamous cell papillomas or carcinomas in mice dosed with *o*-phenylphenol compared with acetone vehicle controls or in mice dosed with DMBA/*o*-phenylphenol compared with DMBA-dosed controls (Tables 8 and 9). In fact, there were no squamous cell papillomas or carcinomas in mice dosed with *o*-phenylphenol or acetone vehicle.

The incidence of basal cell tumors or basal cell carcinomas (combined) in the male DMBA/*o*-phenylphenol group was significantly greater than that in the acetone vehicle control group but was not significantly increased when compared with the DMBA control group (Table 9). Therefore, the increased incidence was considered to be related to administration of DMBA and not *o*-phenylphenol. No significant increase in the incidence of basal cell tumors or carcinomas (combined) was observed in the female DMBA/*o*-phenylphenol group compared with that in the DMBA group (Tables 8 and 9). There were no basal cell tumors or carcinomas (combined) in either *o*-phenylphenol or vehicle control groups of either sex.

Time to Skin Tumor Appearance: Since data on the time until the first appearance of squamous cell tumors were available from clinical observations, analysis was performed with these data instead with data on the week of death (Table 10). Skin tumors (papillomas and carcinomas) developed earlier in DMBA/TPA groups (8 weeks) than in DMBA groups (60 weeks). In contrast, the time to skin tumor appearance in DMBA/*o*-phenylphenol mice (45 weeks) did not differ markedly from that in DMBA groups.

The following criteria were used to diagnose squamous cell papillomas, keratoacanthomas, basal cell tumors, and basal cell carcinomas:

Squamous cell papilloma is a pedunculated lesion with a narrow stalk or a flat lesion that has a broad base and is elevated above the skin surface. It is characterized by a thick, confluent layer of keratin and hyperplastic stratified squamous epithelium overlying a core of connective tissue and arranged in a papillary configuration. At the base or stalk of the tumor, these layers are continuous with the normal skin epidermis.

Keratoacanthoma is a bud-shaped tumor that may be located entirely in the dermis or extended above the skin surface. The sides and base of the tumor are usually convex and consist of thickened, hyperplastic, stratified squamous epithelium. The body of the tumor consists of similar hyperplastic epithelium overlying a connective tissue core and arranged in a folded or papillary configuration. This hyperplastic epithelium is continuous with the epithelium of the sides and base. The distinction between keratoacanthoma and squamous cell papilloma can be subtle and depends on the structural relationship of the tumor with the subepidermal connective tissue and the normal epidermis. Keratoacanthomas are believed to arise from the epithelium of hair follicles.

Basal cell tumor is a well-demarcated neoplasm originating in the basal cell layer of the epidermis, although the bulk of the neoplasm may extend into the dermis. It consists of thick cords of small uniform basal cells showing little or no squamous differentiation. Transition from the normal basal cell layer of the epidermis to the basal cells of the tumor is sometimes apparent.

Basal cell carcinoma is a malignant counterpart of the basal cell tumor. It comprises similar small basal cells but shows invasion of the adjacent dermis and subcutis. There is necrosis of cells in the center of some cords of neoplastic epithelium. Some components of the tumor may show squamous differentiation and/or anaplasia.

TABLE 9. ANALYSIS OF SKIN TUMORS AT THE APPLICATION SITE IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL AND DMBA (a,b)

	DMBA	DMBA/ *o*-Phenylphenol	DMBA/ TPA (c)
MALE			
Basal Cell Tumor or Carcinoma (d)			
Overall Rates	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates	5.0%	18.2%	2.4%
Terminal Rates	1/20 (5%)	1/15 (7%)	0/0
Life Table Tests		P=0.097	P=0.469
Incidental Tumor Tests		P=0.115	(e)
Fisher Exact Test		P=0.181	P=0.753
Squamous Cell Papilloma			
Overall Rates	1/50 (2%)	4/50 (8%)	7/50 (14%)
Adjusted Rates	5.0%	20.0%	70.4%
Terminal Rates	1/20 (5%)	2/15 (13%)	0/0
Life Table Tests		P=0.100	P<0.001
Incidental Tumor Tests		P=0.144	(e)
Fisher Exact Test		P=0.181	P=0.030
Squamous Cell Carcinoma			
Overall Rates	4/50 (8%)	1/50 (2%)	13/50 (26%)
Adjusted Rates	11.6%	2.9%	76.2%
Terminal Rates	0/20 (0%)	0/15 (0%)	0/0
Life Table Tests		P=0.289	P<0.001
Incidental Tumor Tests		P=0.258	(e)
Fisher Exact Test		(f) P=0.181N	P=0.016
Squamous Cell Papilloma or Carcinoma (d)			
Overall Rates	5/50 (10%)	5/50 (10%)	18/50 (36%)
Adjusted Rates	16.0%	22.3%	91.3%
Terminal Rates	1/20 (5%)	2/15 (13%)	0/0
Life Table Tests		P=0.429	P<0.001
Incidental Tumor Tests		P=0.500	(e)
Fisher Exact Test		P=0.630	P=0.002
All Primary Tumors			
Overall Rates	6/50 (12%)	9/50 (18%)	19/50 (38%)
Adjusted Rates	18.2%	37.3%	91.5%
Terminal Rates	1/20 (5%)	3/15 (20%)	0/0
Life Table Tests		P=0.121	P<0.001
Incidental Tumor Tests		P=0.163	(e)
Fisher Exact Test		P=0.288	P=0.002
FEMALE			
Basal Cell Carcinoma			
Overall Rates	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates	9.2%	19.6%	13.0%
Terminal Rates	1/16 (6%)	1/7 (14%)	0/0
Life Table Tests		P=0.288	P=0.070
Incidental Tumor Tests		P=0.459	(e)
Fisher Exact Test		P=0.500	P=0.691
Squamous Cell Papilloma			
Overall Rates	4/50 (8%)	2/50 (4%)	17/50 (34%)
Adjusted Rates	17.7%	28.6%	70.8%
Terminal Rates	2/16 (13%)	2/7 (29%)	0/0
Life Table Tests		P=0.668	P<0.001
Incidental Tumor Tests		P=0.560	(e)
Fisher Exact Test		P=0.339N	P=0.001

TABLE 9. ANALYSIS OF SKIN TUMORS AT THE APPLICATION SITE IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL AND DMBA (Continued)

	DMBA	DMBA/ *o*-Phenylphenol	DMBA/ TPA
Squamous Cell Carcinoma			
Overall Rates	3/50 (6%)	3/50 (6%)	18/50 (36%)
Adjusted Rates	13.6%	9.5%	83.2%
Terminal Rates	0/16 (0%)	0/7 (0%)	0/0
Life Table Tests		P=0.442	P<0.001
Incidental Tumor Tests		P=0.620N	(e)
Fisher Exact Test		P=0.661N	P<0.001
Squamous Cell Papilloma or Carcinoma (d)			
Overall Rates	7/50 (14%)	5/50 (10%)	31/50 (62%)
Adjusted Rates	28.9%	35.3%	91.0%
Terminal Rates	2/16 (13%)	3/7 (43%)	0/0
Life Table Tests		P=0.463N	P<0.001
Incidental Tumor Tests		P=0.507	(e)
Fisher Exact Test		P=0.380N	P<0.001
Keratoacanthoma			
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	27.0%
Terminal Rates	0/16 (0%)	0/7 (0%)	0/0
Life Table Tests		(g)	P=0.001
Incidental Tumor Tests		(g)	(e)
Fisher Exact Test		(g)	P=0.028
All Primary Tumors			
Overall Rates	9/50 (18%)	8/50 (16%)	(h) 32/50 (64%)
Adjusted Rates	36.0%	51.5%	91.3%
Terminal Rates	3/16 (19%)	3/7 (43%)	0/0
Life Table Tests		P=0.255	P<0.001
Incidental Tumor Tests		P=0.579	(e)
Fisher Exact Test		P=0.500N	P<0.001

(a) DMBA--7,12-dimethylbenz(*a*)anthracene
(b) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C (footnotes).
(c) TPA--12-O-tetradecanoylphorbol-13-acetate
(d) All skin neoplasms (benign and malignant) were combined to determine if there was an effect at the site of application.
(e) Analyses not performed because of poor survival in this group; no dosed animals were alive in the last two time intervals.
(f) A negative trend or lower incidence in a dosed group is indicated by (N).
(g) No P value is presented because no tumors were observed in the DMBA and DMBA/*o*-phenylphenol groups.
(h) One carcinosarcoma was also observed.

TABLE 10. ANALYSIS OF SKIN SQUAMOUS CELL PAPILLOMAS OR CARCINOMAS (COMBINED) IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

	Vehicle Control		DMBA		DMBA/ *o*-Phenylphenol	
	Male	Female	Male	Female	Male	Female
Overall rates	0/50	0/50	5/50 (10%)	7/50 (14%)	5/50 (10%)	5/50 (10%)
Adjusted rates	0%	0%	16.0%	28.9%	22.3%	35.3%
Life table test (a)	--	--	P=0.040	P=0.020	P=0.017	P=0.016
Life table test (b)	--	--	--	--	P=0.289	P=0.463N
Individual week of tumor observation			32	26	22	34
			33	46	31	34
			64	62	50	42
			83	64	61	51
			87	66	62	62
				71		
				92		

(a) P values versus vehicle controls
(b) P values versus DMBA controls

Kidney: The incidences of dilatation of the kidney tubule in male and female groups administered *o*-phenylphenol were slightly increased over those in the acetone vehicle controls, but dilatation was mild and associated with hydronephrosis and nephropathy and did not appear to be compound related (Appendix B, Tables B1 and B2). A kidney tubular cell adenoma was observed in 1/47 males in the *o*-phenylphenol group but not in any other male or female group.

Urinary Bladder: A transitional cell carcinoma was observed in one female in the DMBA/*o*-phenylphenol group but not in any other male or female group. There was a slightly increased incidence of epithelial hyperplasia of the urinary bladder in the male DMBA group over that in the acetone vehicle controls (Table B1).

Bone Marrow: Granulocytic hyperplasia was observed at increased incidences in the male and female DMBA/*o*-phenylphenol and DMBA/TPA groups as compared with those in the acetone vehicle controls or in the DMBA or *o*-phenylphenol groups (male: vehicle control, 9/47; DMBA, 10/47; *o*-phenylphenol, 9/47; DMBA/*o*-phenylphenol, 19/48; DMBA/TPA, 17/47; female: vehicle control, 3/50; DMBA, 6/50; *o*-phenylphenol, 10/48; DMBA/*o*-phenylphenol, 14/49; DMBA/TPA, 15/44). Hyperplasia was directly related to the presence of inflammation and/or tumors on the skin at the site of application.

Thyroid Gland: Although the incidence of thyroid gland follicular cysts was greater in the female *o*-phenylphenol group than in the acetone vehicle controls, the severity of cysts was judged minimal or mild. The follicles near the middle of the gland were somewhat more dilated than adjacent follicles and were lined by flat epithelial cells. This lesion was not considered to be compound related (Table B2).

Adrenal Gland/Zona Fasciculata: Lipoid degeneration was present in 1/49 vehicle control, 7/49 DMBA, 4/45 *o*-phenylphenol, 1/48 DMBA/*o*-phenylphenol, and 0/49 DMBA/TPA male mice and in 4/50 vehicle control, 26/49 DMBA, 24/47 *o*-phenylphenol, 11/50 DMBA/*o*-phenylphenol, and 8/48 DMBA/TPA female mice. The biologic significance of the increase in DMBA or *o*-phenylphenol mice and the apparent antagonistic effect in DMBA/*o*-phenylphenol mice is not known.

Liver: Although focal necrosis of the liver was observed at greater incidences in the male DMBA and *o*-phenylphenol groups than in the acetone vehicle controls (Table B1), the degree of focal necrosis was mostly minimal or mild and was not considered to be compound related.

Lung: The incidence of alveolar/bronchiolar carcinomas in the lungs was increased in DMBA female mice (11/50) compared with that in the acetone vehicle control (3/50) and other dose groups (Appendix C, Table C2).

IV. DISCUSSION AND CONCLUSIONS

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In the 4-week studies, *o*-phenylphenol was administered by dermal application to the dorsal interscapular region of Swiss Webster CFW mice 3 days per week; groups of 10 male and 10 female mice received doses ranging from 5.95 mg to 55.5 mg per mouse in 0.1 ml of acetone. No effects on body weights or survival were observed. An ulcerative lesion was observed at the chemical application site but was not considered severe.

Based on these studies, a dose of 55.5 mg/0.1 ml of acetone was selected for the 2-year studies. Carcinogenesis studies were conducted to determine if *o*-phenylphenol was a promoter in a two-stage initiation/promotion skin paint model in which groups of 50 Swiss CD-1 mice of each sex were dosed for up to 102 weeks. *o*-Phenylphenol was also tested to determine if it is a complete carcinogen in dermal application studies. These studies were not designed to determine toxicity or carcinogenicity by systemic exposure, but all tissues were examined to permit detection of systemic effects. All compounds were administered by dermal application to a clipped area at the dorsal interscapular region.

The experimental design consisted of five dose groups: an acetone vehicle control group; a positive control group that was initiated with 7,12-dimethylbenz(*a*)anthracene (DMBA) and promoted with 12-O-tetradecanoylphorbol-13-acetate (TPA); an initiator control group that received DMBA plus acetone; a complete carcinogen test group that received repeated applications of *o*-phenylphenol; and a promotion group that was initiated with DMBA and exposed to repeated applications of *o*-phenylphenol. The following doses were applied dermally to a clipped area on the dorsal interscapular region 3 days per week: *o*-phenylphenol--55.5 mg/0.1 ml acetone; DMBA--0.05 mg/0.1 ml acetone; and TPA--0.005 mg/0.1 ml acetone. Although chemical application in most two-stage skin carcinogenesis studies is normally completed within 1 year, the present studies were continued for 2 years because *o*-phenylphenol was being tested simultaneously as a potential complete carcinogen, which requires a 2-year exposure.

The time to appearance of skin tumors observed in the DMBA/TPA groups was similar to that seen in previous two-stage carcinogenesis studies that used CD-1 mice (Slaga, 1983; Reiners et al., 1983). Although the incidences of skin neoplasms in the DMBA/TPA groups were only 38% in males and 66% in females, it appeared that these incidences were sufficient for the groups to be used as positive controls. The incidence of carcinomas in SENCAR mice dosed on a similar regimen has been reported to be as high as 100% (Slaga, 1983). The development of skin neoplasms in 6/50 male and 9/50 female mice in the DMBA/acetone control group indicated that a potentially carcinogenic dose of DMBA was administered. The skin tumors, however, did not appear until after approximately 30 weeks of exposure, long after the appearance of tumors in the DMBA/TPA groups.

Chemically related effects on survival occurred only in the DMBA/TPA groups; increased deaths occurred in both male and female groups after 40 weeks of exposure. The surviving male and female mice in these groups were killed at 85 and 74 weeks, respectively, since over 80% of the animals in these groups were moribund. Because of the low survival in these groups, incidental tumor tests comparing these groups with the acetone vehicle controls were not conducted. Mean body weights of all dosed male groups tended to be slightly lower than those of the acetone vehicle controls after week 44; however, mean body weights of the DMBA/*o*-phenylphenol and DMBA/TPA groups were not different from those of the DMBA/acetone groups.

Toxicity

In the 2-year studies, dermal application of DMBA/TPA or *o*-phenylphenol to Swiss CD-1 mice caused nonneoplastic lesions at the site of application; these lesions consisted of inflammation, ulceration, and acanthosis. Increased incidences of these lesions were found in the *o*-phenylphenol, DMBA/*o*-phenylphenol, and DMBA/TPA groups compared with the incidences in the DMBA or acetone vehicle controls. No marked toxicity was observed in dosed groups at areas other than the site of application. No marked effects on the kidney were seen in mice dosed with *o*-phenylphenol or DMBA/*o*-phenylphenol as compared with those in groups dosed with DMBA alone, although male

and female mice dosed with *o*-phenylphenol had slight increases in frequency of dilatation of kidney tubules, and females had a slight increase of lymphocytic infiltration. The kidney was reported to be one of the primary organs affected in rats orally administered *o*-phenylphenol (Hodge et al., 1952; Hiraga and Fujii, 1981).

Increased incidences of granulocytic hyperplasia of the bone marrow and splenic hematopoiesis were observed in DMBA/*o*-phenylphenol and DMBA/TPA groups of each sex. This increase may be related to inflammatory lesions in the dosed animals. Previous studies demonstrated that $B6C3F_1$ mice dosed orally with *o*-phenylphenol for 2 weeks at doses up to 200 mg/kg per day had normal bone marrow and immune functions (Luster et al., 1981). Other notable observations in the current 2-year studies included an increased incidence of follicular cysts (20/46, 43%) in the thyroid gland of female mice dosed with *o*-phenylphenol compared with that in the acetone vehicle controls (6/47, 13%) and increased incidences of lipoid degeneration in the zona fasciculata of the adrenal gland in all dosed groups compared with those in acetone vehicle controls. The slight organ system toxicity observed in *o*-phenylphenol-dosed mice in these studies may be due, in part, to the relatively poor absorption of o-phenylphenol through the skin (less than 1% of the administered dose [approximately 6 mg] is absorbed in humans) (Harke and Klein, 1981). Alternatively, systemic exposure to o-phenylphenol may have occurred as a result of preening.

Mutagenicity

o-Phenylphenol exhibited weak genotoxicity in some short-term tests, including mutagenicity in one strain of *Salmonella typhimurium* and in the mouse lymphoma L5178Y/$TK^{+/-}$ cells and sister-chromatid exchanges in Chinese hamster ovary (CHO) cells (Appendix K). These three positive results were obtained in the absence of exogenous metabolic activation (S9), and the addition of rat liver S9 eliminated the direct-acting genetic toxicity of *o*-phenylphenol in Salmonella and CHO cells. The three positive responses occurred at or near cytotoxic doses. Although S9 did not alter the mutagenicity of *o*-phenylphenol in the mouse lymphoma assay, a second experiment (in the presence of S9 with dimethyl sulfoxide as the solvent) was not conducted to confirm these data. Thus, although *o*-phenylphenol had weak, direct-acting genetic toxicity, this activity was, in general, eliminated by mammalian metabolism. When *o*-phenylphenol-treated CHO cells were given a 42-hour expression period, the frequency of chromosomal aberrations and the frequency of SCE's were reduced to control levels compared with the frequencies obtained after a 27-hour expression period (Tayama-Nawai et al., 1984). These results suggest that *o*-phenylphenol induces SCE's in the first and second S-phase and that the *o*-phenylphenol-induced DNA damage that leads to the formation of SCE's is temporary and is eliminated after an additional round of DNA synthesis.

Neoplastic Effects on the Skin

The combined incidences of squamous cell papillomas and carcinomas of the skin in male and female DMBA/TPA groups (18/50 and 31/50) were greater than those in DMBA groups (5/50 and 7/50). The incidences of squamous cell papillomas or carcinomas (combined) in mice dosed with DMBA/*o*-phenylphenol (male, 5/50; female, 5/50) were similar to those in mice dosed with DMBA alone (male, 5/50; female, 7/50). Squamous cell papillomas or carcinomas (combined) were not detected in mice dosed with acetone or *o*-phenylphenol with acetone.

After chemical exposure was begun, the mean time for appearance of papillomas or carcinomas occurred much later in the DMBA (60 weeks) and DMBA/*o*-phenylphenol (45 weeks) groups than in the DMBA/TPA (8 weeks) groups. There was no significant difference in the mean time to skin tumor development between DMBA and DMBA/*o*-phenylphenol groups.

The combined incidence of basal cell tumors and basal cell carcinomas was significantly greater in male mice (4/50), but not female mice (3/50), administered DMBA/*o*-phenylphenol when compared with vehicle controls (0/50 for both males and females) but not when compared with the DMBA groups (male, 1/50; female, 2/50). An increased incidence of keratoacanthomas (5/50) was seen in the female DMBA/TPA group but not in any other experimental group.

IV. DISCUSSION AND CONCLUSIONS

In summary, no skin tumors developed in mice dosed with *o*-phenylphenol alone. Skin neoplasms classified as squamous cell papillomas, squamous cell carcinomas, basal cell tumors, basal cell carcinomas, keratoacanthomas, or sebaceous adenomas occurred in mice dosed with DMBA, DMBA/*o*-phenylphenol, or DMBA/TPA (see Table 9). These tumors occurred at the site of chemical application. The incidences and the time to appearance of skin tumors in both male and female mice dosed with DMBA (15/100) and with DMBA/*o*-phenylphenol (17/100) were similar. The incidences of male and female mice with skin neoplasms in the DMBA/TPA groups (male, 19/50; female, 33/50) were greater than those in mice dosed with either DMBA or DMBA/*o*-phenylphenol. No skin tumors developed in mice dosed with *o*-phenylphenol alone. All groups developed nonneoplastic lesions, such as inflammation, ulceration, hyperkeratosis, and acanthosis, at the site of application. However, the incidences of nonneoplastic skin lesions were greater in the *o*-phenylphenol, DMBA/*o*-phenylphenol, and DMBA/TPA groups than in the acetone vehicle control or DMBA groups.

Conclusions: Under the conditions of these 2-year dermal application studies, there was *no evidence of carcinogenicity** in male or female Swiss CD-1 mice administered *o*-phenylphenol alone or as a promoter following initiation with DMBA. *o*-Phenylphenol, however, caused nonneoplastic lesions, which included ulceration, inflammation, and hyperkeratosis, at the site of application.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ANIMALS INITIALLY IN STUDY	50	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50	50
ANIMALS EXAMINED HISTOPATH	50	50	50	50	50
INTEGUMENTARY SYSTEM					
*SKIN	(50)	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)		4 (8%)	7 (14%)
SQUAMOUS CELL CARCINOMA		4 (8%)		1 (2%)	13 (26%)
BASAL-CELL TUMOR		1 (2%)		2 (4%)	1 (2%)
BASAL-CELL CARCINOMA				2 (4%)	
SEBACEOUS ADENOMA		1 (2%)		1 (2%)	
KERATOACANTHOMA					1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)	(50)
FIBROSARCOMA				2 (4%)	2 (4%)
RESPIRATORY SYSTEM					
#LUNG	(50)	(50)	(50)	(50)	(50)
SQUAMOUS CELL CAR, META					5 (10%)
ADENOCAR, NOS, METASTATIC		1 (2%)			
ALVEOLAR/BRON ADENOMA	9 (18%)	11 (22%)	10 (20%)	9 (18%)	2 (4%)
ALVEOLAR/BRON CARCINOMA	6 (12%)	5 (10%)	4 (8%)	2 (4%)	
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
MALIG. LYMPHOMA, UNDIF TYPE	1 (2%)				
MALIG. LYMPHOMA, LYMPH TYPE		5 (10%)	1 (2%)	1 (2%)	2 (4%)
MALIG. LYMPHOMA, HISTIO TYPE	5 (10%)	1 (2%)	3 (6%)	1 (2%)	
MALIG. LYMPHOMA, MIXED TYPE	2 (4%)	1 (2%)	1 (2%)	2 (4%)	
#PANCREATIC L. NODE	(37)	(41)	(42)	(40)	(30)
MALIG. LYMPHOMA, HISTIO TYPE		1 (2%)			
#AXILLARY LYMPH NODE	(37)	(41)	(42)	(40)	(30)
SQUAMOUS CELL CAR, METASTA					1 (3%)
#LIVER	(47)	(48)	(48)	(46)	(47)
MALIG. LYMPHOMA, HISTIO TYPE			1 (2%)		
CIRCULATORY SYSTEM					
#SPLEEN	(44)	(49)	(47)	(48)	(48)
HEMANGIOSARCOMA			2 (4%)		
HEMANGIOSARCOMA, UNC PRIM OR MET		1 (2%)			
#LIVER	(47)	(48)	(48)	(46)	(47)
HEMANGIOSARCOMA	2 (4%)	2 (4%)	1 (2%)		
HEMANGIOSARCOMA, UNC PRIM OR MET		1 (2%)			

(a) Administered a single dose (0.05 mg) of dimethylbenz(*a*)anthracene (DMBA) in 0.1 ml acetone then 0.1 ml acetone 3 × week for 2 years
(b) Administered 55.5 mg *o*-phenylphenol (*o*-PP) in 0.1 ml acetone 3 × week for 2 years
(c) Administered a single dose (0.05 mg) of DMBA then 55.5 mg *o*-PP in 0.1 ml acetone 3 × week for 2 years
(d) Administered a single dose (0.05 mg) of DMBA then 0.005 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) in 0.1 ml acetone 3 × week for 2 years

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
DIGESTIVE SYSTEM					
#LIVER	(47)	(48)	(48)	(46)	(47)
HEPATOCELLULAR ADENOMA	7 (15%)	11 (23%)	6 (13%)	3 (7%)	3 (6%)
HEPATOCELLULAR CARCINOMA	4 (9%)	3 (6%)	3 (6%)	5 (11%)	1 (2%)
#FORESTOMACH	(39)	(46)	(44)	(45)	(43)
SQUAMOUS CELL PAPILLOMA	1 (3%)			1 (2%)	
#DUODENUM	(37)	(43)	(42)	(40)	(42)
ADENOCARCINOMA, NOS		1 (2%)			
URINARY SYSTEM					
#KIDNEY	(47)	(49)	(47)	(49)	(48)
TUBULAR-CELL ADENOMA			1 (2%)		
#KIDNEY/CAPSULE	(47)	(49)	(47)	(49)	(48)
ADENOCARCINOMA, NOS, META		1 (2%)			
ENDOCRINE SYSTEM					
#PITUITARY	(38)	(41)	(41)	(43)	(36)
ADENOMA, NOS		1 (2%)			
#ANTERIOR PITUITARY	(38)	(41)	(41)	(43)	(36)
CARCINOMA, NOS		1 (2%)			
#ADRENAL	(49)	(49)	(45)	(48)	(49)
CORTICAL ADENOMA	3 (6%)	2 (4%)		2 (4%)	
#ADRENAL/CAPSULE	(49)	(49)	(45)	(48)	(49)
ADENOMA, NOS		2 (4%)	1 (2%)		
#THYROID	(49)	(46)	(47)	(45)	(41)
FOLLICULAR-CELL ADENOMA				1 (2%)	
REPRODUCTIVE SYSTEM					
*PREPUCE	(50)	(50)	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)			
#TESTIS	(48)	(50)	(49)	(49)	(50)
INTERSTITIAL-CELL TUMOR		1 (2%)	1 (2%)		
#RETE TESTIS	(48)	(50)	(49)	(49)	(50)
ADENOMA, NOS			1 (2%)		
*EPIDIDYMIS	(50)	(50)	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)		
NERVOUS SYSTEM					
#CEREBRUM	(44)	(49)	(48)	(49)	(48)
CARCINOMA, NOS, INVASIVE		1 (2%)			
SPECIAL SENSE ORGANS					
*HARDERIAN GLAND	(50)	(50)	(50)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS	1 (2%)				
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
*MEDIASTINUM	(50)	(50)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, META		2 (4%)			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, META		1 (2%)			1 (2%)
ALVEOLAR/BRONCHIOLAR CA, META	1 (2%)				
LEIOMYOSARCOMA, UNC PRIM OR META		1 (2%)			
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	50	50	50	50	50
NATURAL DEATH	23	17	14	22	23
MORIBUND SACRIFICE	9	13	20	14	25
SCHEDULED SACRIFICE					2
TERMINAL SACRIFICE	18	20	16	14	
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIM TUMORS**	30	40	24	28	23
TOTAL PRIMARY TUMORS	41	59	37	39	32
TOTAL ANIMALS WITH BENIGN TUM	17	23	17	17	12
TOTAL BENIGN TUMORS	21	31	21	23	14
TOTAL ANIMALS WITH MALIG TUMORS	19	24	13	14	17
TOTAL MALIGNANT TUMORS	20	25	16	16	18
TOTAL ANIMALS WITH SEC TUMORS##	1	5			6
TOTAL SECONDARY TUMORS	1	6			7
TOTAL ANIMALS WITH TUM UNCERTAIN-PRIMARY OR METASTATIC		2			
TOTAL UNCERTAIN TUMORS		3			

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ANIMALS INITIALLY IN STUDY	50	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50	50
ANIMALS EXAMINED HISTOPATH	50	50	50	50	50
INTEGUMENTARY SYSTEM					
*SKIN	(50)	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		4 (8%)		2 (4%)	17 (34%)
SQUAMOUS CELL CARCINOMA		3 (6%)		3 (6%)	†18 (36%)
SQUAMOUS CELL CA, UNC PRIM/META					1 (2%)
BASAL-CELL CARCINOMA		2 (4%)		3 (6%)	2 (4%)
SEBACEOUS ADENOMA		1 (2%)			
SEBACEOUS ADENOCARCINOMA		1 (2%)			
KERATOACANTHOMA					†5 (10%)
SARCOMA, NOS, INVASIVE				1 (2%)	
CARCINOSARCOMA					1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)	(50)
BASAL-CELL CARCINOMA, META		†1 (2%)			
SARCOMA, NOS				1 (2%)	
SARCOMA, NOS, UNC PRIM OR META				1 (2%)	
FIBROSARCOMA		2 (4%)			3 (6%)
OSTEOSARCOMA		1 (2%)			
RESPIRATORY SYSTEM					
#LUNG	(50)	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, META					11 (22%)
BASAL-CELL CARCINOMA, META		2 (4%)		1 (2%)	1 (2%)
ADENOCARCINOMA, NOS, META	1 (2%)	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	7 (14%)	7 (14%)	8 (16%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CAR	3 (6%)	11 (22%)	1 (2%)	5 (10%)	1 (2%)
CYSTADENOCARCINOMA, META		1 (2%)			
ADENOCA/SQUAM METAPLASIA, MET	1 (2%)				
LEIOMYOSARCOMA, METASTATIC	1 (2%)				
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
MALIG. LYMPHOMA, UNDIFFER TYPE	1 (2%)			1 (2%)	
MALIG. LYMPHOMA, LYMPHO TYPE	1 (2%)	4 (8%)	3 (6%)	3 (6%)	1 (2%)
MALIG. LYMPHOMA, HISTIO TYPE	4 (8%)		6 (12%)	6 (12%)	2 (4%)
MALIG. LYMPHOMA, MIXED TYPE	4 (8%)	2 (4%)	1 (2%)	3 (6%)	
GRANULOCYTIC LEUKEMIA					1 (2%)
#SPLEEN	(48)	(47)	(47)	(48)	(46)
LEIOMYOSARCOMA, UNC PRIM OR META	1 (2%)				
#LYMPH NODE	(36)	(37)	(41)	(40)	(42)
BASAL-CELL CARCINOMA, META		1 (3%)			
#MEDIASTINAL L. NODE	(36)	(37)	(41)	(40)	(42)
BASAL-CELL CARCINOMA					1 (2%)

(a) Administered a single dose (0.05 mg) of dimethylbenz(*a*)anthracene (DMBA) in 0.1 ml acetone then 0.1 ml acetone 3 × week for 2 years
(b) Administered 55.5 mg *o*-phenylphenol (*o*-PP) in 0.1 ml acetone 3 × week for 2 years
(c) Administered a single dose (0.05 mg) of DMBA then 55.5 mg *o*-phenylphenol (*o*-PP) in 0.1 ml acetone 3 × week for 2 years
(d) Administered a single dose (0.05 mg) of DMBA then 0.005 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) in 0.1 ml acetone 3 × week for 2 years

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
HEMATOPOIETIC SYSTEM (Continued)					
#MESENTERIC L. NODE	(36)	(37)	(41)	(40)	(42)
MALIG. LYMPHOMA, HISTIO TYPE		1 (3%)			
#BRACHIAL LYMPH NODE	(36)	(37)	(41)	(40)	(42)
FIBROSARCOMA, METASTATIC					1 (2%)
#THYMUS	(31)	(34)	(36)	(37)	(27)
SQUAMOUS CELL CARCINOMA, META					1 (4%)
CIRCULATORY SYSTEM					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA, UNC PRIM OR MET				1 (2%)	
#BONE MARROW	(50)	(50)	(48)	(49)	(44)
HEMANGIOMA				1 (2%)	
#SPLEEN	(48)	(47)	(47)	(48)	(46)
HEMANGIOMA			1 (2%)		
HEMANGIOSARCOMA		2 (4%)	2 (4%)		
#BASE OF HEART	(50)	(49)	(49)	(50)	(49)
BASAL-CELL CARCINOMA, META					1 (2%)
#LIVER	(44)	(45)	(44)	(47)	(47)
HEMANGIOMA			1 (2%)		1 (2%)
HEMANGIOSARCOMA	1 (2%)	2 (4%)	2 (5%)		
HEMANGIOSARCOMA, METASTATIC			1 (2%)		
#UTERUS	(49)	(50)	(49)	(49)	(48)
HEMANGIOMA		2 (4%)			
HEMANGIOSARCOMA				2 (4%)	
#OVARY	(49)	(50)	(50)	(49)	(47)
HEMANGIOMA				1 (2%)	
HEMANGIOSARCOMA	1 (2%)				
DIGESTIVE SYSTEM					
#LIVER	(44)	(45)	(44)	(47)	(47)
HEPATOCELLULAR ADENOMA		1 (2%)	3 (7%)	2 (4%)	
HEPATOCELLULAR CARCINOMA			1 (2%)		
*GALLBLADDER	(50)	(50)	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)		
#ESOPHAGUS	(49)	(50)	(49)	(49)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)		
#GLANDULAR STOMACH	(43)	(43)	(43)	(45)	(46)
ADENOCARCINOMA, NOS		1 (2%)			
#FORESTOMACH	(43)	(43)	(43)	(45)	(46)
SQUAMOUS CELL PAPILLOMA	3 (7%)			1 (2%)	
*RECTUM	(50)	(50)	(50)	(50)	(50)
SARCOMA, NOS				1 (2%)	
URINARY SYSTEM					
#URINARY BLADDER	(37)	(39)	(42)	(41)	(43)
TRANSITIONAL-CELL CARCINOMA				1 (2%)	
ENDOCRINE SYSTEM					
#ANTERIOR PITUITARY	(45)	(44)	(37)	(42)	(37)
ADENOMA, NOS		1 (2%)			
#ADRENAL MEDULLA	(50)	(49)	(47)	(50)	(48)
PHEOCHROMOCYTOMA	1 (2%)		1 (2%)	1 (2%)	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(50)	(50)	(50)	(50)	(50)
ADENOCARCINOMA, NOS	2 (4%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)
CYSTADENOCARCINOMA, NOS		1 (2%)			
ADENOCA/SQUAMOUS METAPLASIA	1 (2%)				
#UTERUS	(49)	(50)	(49)	(49)	(48)
FIBROMA	1 (2%)				
LEIOMYOMA	1 (2%)	1 (2%)			
LEIOMYOSARCOMA	2 (4%)			1 (2%)	
LEIOMYOSARC, UNC PRIM OR META	1 (2%)				
ENDOMETRIAL STROMAL POLYP	2 (4%)	6 (12%)	3 (6%)	3 (6%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)	2 (4%)	2 (4%)		
#CERVIX UTERI	(49)	(50)	(49)	(49)	(48)
FIBROMA			1 (2%)		
LEIOMYOSARCOMA		1 (2%)			
#ENDOMETRIAL GLAND	(49)	(50)	(49)	(49)	(48)
CARCINOMA IN SITU, NOS			1 (2%)		
CARCINOMA, NOS		1 (2%)			
ADENOCARCINOMA, NOS		1 (2%)			
PAPILLARY CYSTADENOCARC, NOS		1 (2%)			
#OVARY/PAROVARIAN	(49)	(50)	(50)	(49)	(47)
FIBROMA	1 (2%)				
#OVARY	(49)	(50)	(50)	(49)	(47)
PAPILLARY ADENOMA		1 (2%)			
CYSTADENOMA, NOS				1 (2%)	
LUTEOMA	1 (2%)	2 (4%)	3 (6%)	1 (2%)	
NERVOUS SYSTEM					
NONE					
SPECIAL SENSE ORGANS					
*EYELID	(50)	(50)	(50)	(50)	(50)
SEBACEOUS ADENOMA		1 (2%)			
*HARDERIAN GLAND	(50)	(50)	(50)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS	2 (4%)				
MUSCULOSKELETAL SYSTEM					
*LUMBAR VERTEBRA	(50)	(50)	(50)	(50)	(50)
OSTEOMA			1 (2%)		
*FEMUR	(50)	(50)	(50)	(50)	(50)
OSTEOMA			1 (2%)	1 (2%)	
BODY CAVITIES					
*THORACIC CAVITY	(50)	(50)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, MET		1 (2%)			
*MEDIASTINUM	(50)	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, MET					1 (2%)
ALVEOLAR/BRONCHIOLAR CA, META		1 (2%)			
SARCOMA, NOS, METASTATIC				1 (2%)	
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, META					1 (2%)
LEIOMYOSARCOMA, INVASIVE	1 (2%)				
CARCINOSARCOMA, METASTATIC					1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	50	50	50	50	50
NATURAL DEATH	20	20	20	19	24
MORIBUND SACRIFICE	19	15	15	25	25
TERMINAL SACRIFICE	11	15	15	6	
ACCIDENTALLY KILLED, NOS					1
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUM**	26	34	24	36	36
TOTAL PRIMARY TUMORS	41	68	44	56	60
TOTAL ANIMALS WITH BENIGN TUMORS	13	17	17	18	22
TOTAL BENIGN TUMORS	17	27	23	22	27
TOTAL ANIMALS WITH MALIG. TUM	20	27	16	28	25
TOTAL MALIGNANT TUMORS	22	41	21	32	32
TOTAL ANIMALS WITH SEC TUM##	3	6	1	2	15
TOTAL SECONDARY TUMORS	4	9	1	3	18
TOTAL ANIMALS WITH TUMORS UNCER-PRIMARY OR METASTATIC	1			2	1
TOTAL UNCERTAIN TUMORS	2			2	1

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN TISSUES IS COUNTED ONCE ONLY

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	0048	0118	0223	0450	0112	0033	0224	0220	0211	0114	0006	0445	0440	0447	0441	0334	0333	0117	0116	0337	0001	0111	0266	0038	0039
WEEKS ON STUDY	0339	0443	0447	0449	0553	0555	0600	0611	0711	0712	0713	0733	0800	0808	0844	0888	0899	0900	0911	0913	0913	0933	0944	0944	0966
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X					X					
Alveolar/bronchiolar carcinoma																				X					X
Trachea	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–
Lymph nodes	–	+	–	+	+	+	–	+	+	–	+	–	–	+	–	+	+	+	+	+	+	+	+	+	–
Thymus	+	–	–	–	+	+	–	–	+	–	+	+	+	–	+	+	+	–	+	–	+	+	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X			X						X			X
Hepatocellular carcinoma																									
Hemangiosarcoma																							X		
Bile duct	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	N	N	+	+	+	+	N	+	+	N	N	N	N	N	+	N	N	N	+	+	+	N
Pancreas	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	–	+	–	–	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–
Squamous cell papilloma																									
Small intestine	+	+	–	+	–	+	–	–	+	–	+	+	–	+	+	–	–	+	+	–	–	+	+	+	–
Large intestine	+	+	–	+	+	+	+	–	+	–	+	+	–	+	+	–	–	+	+	–	–	+	+	+	–
URINARY SYSTEM																									
Kidney	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	–	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	–	–	+	–	+	–	–	+	+	–	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	–	–	–	–	+	+	–	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–
NERVOUS SYSTEM																									
Brain	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary cystadenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar ca, metastatic																									
Malig. lymphoma, undifferentiated type						X																			
Malig. lymphoma, histiocytic type					X								X				X		X						
Malignant lymphoma, mixed type																									

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Mis-sexed	B	No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	02 5	01 9	02 9	02 8	00 8	03 5	00 2	00 4	00 5	00 7	00 9	01 0	01 3	01 5	02 2	02 7	03 0	03 1	03 2	03 6	04 2	04 3	04 4	04 6	04 9	TOTAL
WEEKS ON STUDY	10 0	10 1	10 1	10 2	10 3	10 3	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X		X			X				X					X			X			X				9
Alveolar/bronchiolar carcinoma			X		X			X								X										6
Trachea	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph nodes	+	+	+	–	+	+	+	–	–	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	37
Thymus	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular adenoma							X							X											X	7
Hepatocellular carcinoma		X										X	X		X											4
Hemangiosarcoma											X															2
Bile duct	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder & common bile duct	+	+	N	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	50*
Pancreas	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Squamous cell papilloma																X										1
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	37
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY SYSTEM																										
Kidney	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma				X					X															X		3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	–	+	–	–	–	–	–	+	–	–	+	–	+	–	+	–	–	–	+	–	–	+	–	+	+	26
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Testis	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Papillary cystadenoma, NOS																									X	1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Alveolar/bronchiolar ca, metastatic			X																							1
Malig. lymphoma, undifferentiated type																										1
Malig. lymphoma, histiocytic type																					X					5
Malignant lymphoma, mixed type					X																		X			2

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL: DMBA

ANIMAL NUMBER	0035	0014	0039	0029	0007	0033	0024	0002	0041	0034	0044	0001	0003	0019	0010	0036	0048	0005	0006	0030	0045	0012	0004	0037	0040
WEEKS ON STUDY	0000	0025	0051	0054	0057	0060	0064	0071	0077	0078	0078	0079	0079	0081	0082	0085	0087	0089	0090	0092	0093	0094	0095	0095	095
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma					X	X																		X	
Basal cell tumor																									
Sebaceous adenoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																						X			
Alveolar/bronchiolar adenoma																		X						X	
Alveolar/bronchiolar carcinoma											X					X						X			
Trachea	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, uncl prim or metast															X										
Lymph nodes	–	+	–	+	+	–	–	+	–	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+
Malig lymphoma, histiocytic type								X																	
Thymus	+	+	+	+	–	–	+	–	+	+	+	+	–	–	–	–	–	+	–	–	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X														X		X	X
Hepatocellular carcinoma																				X			X		
Hemangiosarcoma																									
Hemangiosarcoma, unc prim or metast															X										
Bile duct	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	N	+	+	+	N	+	N	+	N	+	N	N	N	+	+	N	+	N	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	–	+	+	+	+	+	–	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																						X			
Large intestine	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																						X			
Urinary bladder	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	–	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	–	–	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+
Carcinoma, NOS														X											
Adenoma, NOS																						X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X													
Cortical adenoma																			X						
Thyroid	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive														X											
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metast											X					X									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic					X																				
Leiomyosarcoma, unc prim or metastat																				X					
Malig lymphoma, lymphocytic type		X	X	X																					
Malig lymphoma, histiocytic type																									X
Malignant lymphoma, mixed type																									

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Mis-sexed	B	No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: DMBA (Continued)

ANIMAL NUMBER	047	022	046	027	038	008	009	011	013	015	016	017	018	020	021	023	025	026	028	031	032	042	043	049	050	TOTAL
WEEKS ON STUDY	096	098	099	101	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma													X													1
Squamous cell carcinoma		X																								4
Basal cell tumor													X													1
Sebaceous adenoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma	X			X	X				X		X	X			X		X	X								11
Alveolar/bronchiolar carcinoma							X													X						5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, uncl prim or metast																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	41
Malig lymphoma, histiocytic type																										1
Thymus	–	–	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	–	+	–	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma								X	X	X		X				X	X								X	11
Hepatocellular carcinoma																		X								3
Hemangiosarcoma	X																						X			2
Hemangiosarcoma, uncl prim or metast																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Small intestine	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma, NOS																										1
Large intestine	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Urinary bladder	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	41
Carcinoma, NOS																										1
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																X										2
Cortical adenoma																									X	2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid	+	+	–	–	+	+	+	+	+	–	+	+	–	–	–	–	–	+	+	+	+	+	–	–	–	17
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor			X																							1
Prostate	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Sarcoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, invasive																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Alveolar/bronchiolar carcinoma, metast																										2
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma, metastatic																										1
Leiomyosarcoma, unc prim or metastatic																										1
Malig. lymphoma, lymphocytic type															X									X		5
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																X										1

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF o-PHENYLPHENOL: o-PP

ANIMAL NUMBER	0202	0216	0446	0447	0448	0332	0335	0343	0226	0007	0005	0227	0444	0445	0115	0006	0008	0221	0223	0334	0337	0336	0341	0339	0333
WEEKS ON STUDY	0003	0339	0339	0339	0344	0445	0446	0448	0449	0457	0559	0561	0662	0692	0691	0711	0711	0711	0711	0717	0717	0734	0804	0822	0844
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								X
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	–	+	+	+	–	+	+	–	+	–	+	–	–	+	+	+	+	+	+	+	+	–
Thymus	–	+	+	–	+	+	+	+	–	–	–	–	+	+	–	+	+	–	–	+	+	+	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Hemangiosarcoma																									
Malig. lymphoma, histiocytic type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	N	N	+	N	+	+	N	N	+	+	N	N	N	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+
Small intestine	+	+	+	+	+	–	+	–	+	+	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+
Large intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	–	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+
Adrenal	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+
Parathyroid	+	+	+	+	+	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	+	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Adenoma, NOS																									
Interstitial cell tumor																									X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Epididymis	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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type																	X		X						
Malignant lymphoma, mixed type																				X					

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Mis-sexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: *o*-PP (Continued)

ANIMAL NUMBER	00 09	00 28	00 25	01 18	01 10	01 12	04 49	01 17	01 13	00 01	00 02	00 03	00 04	01 11	01 14	01 19	02 22	02 24	02 29	03 01	03 31	03 38	04 40	04 42	05 50	TOTAL
WEEKS ON STUDY	09 90	09 94	09 97	09 98	10 00	10 11	10 01	10 02	10 03	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X		X				X		X			X	X			X					X					10
Alveolar/bronchiolar carcinoma				X	X				X																X	4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma			X								X															2
Lymph nodes	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Thymus	+	–	–	–	+	–	+	–	–	+	+	–	–	–	+	+	+	+	+	–	+	+	–	–	+	26
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma							X	X											X	X		X			X	6
Hepatocellular carcinoma													X		X									X		3
Hemangiosarcoma											X															1
Malig. lymphoma, histiocytic type															X											1
Bile duct	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	N	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Small intestine	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tubular cell adenoma							X																			1
Urinary bladder	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	41
Adrenal	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS		X																								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	–	+	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	+	–	+	–	–	–	12
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS				X																						1
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Adenoma, NOS													X													1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malig. lymphoma, lymphocytic type														X												1
Malig. lymphoma, histiocytic type																									X	3
Malignant lymphoma, mixed type																										1

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL: DMBA AND *o*-PP

ANIMAL NUMBER	0161	0444	0284	0334	0366	0447	0500	0055	0133	0488	0221	0233	0440	0338	0311	0099	0455	0422	0088	0102	0225	0237	0399	0443	0111
WEEKS ON STUDY	0011	0118	0224	0224	0238	0339	0339	0341	0444	0448	0450	0252	0254	0557	0558	0860	0660	0665	0771	0773	0774	0779	0880	0881	0882
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Squamous cell carcinoma																	X								
Basal cell tumor																									
Basal cell carcinoma																			X						
Sebaceous adenoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																				X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	–	–	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–
Thymus	+	–	+	–	+	–	+	–	+	–	+	–	+	–	+	–	–	+	+	+	–	–	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Hepatocellular carcinoma																					X				
Bile duct	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	N	+	N	N	+	N	+	+	N	+	+	N	+	N	+	N	N	+	N	+	N
Pancreas	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	–	+	–
Large intestine	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	–	+	+	–	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Cortical adenoma														X											
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+
Follicular cell adenoma														X											
Parathyroid	+	–	+	–	+	+	+	–	–	+	+	+	–	–	–	–	–	–	+	+	–	+	–	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type																							X		
Malignant lymphoma, mixed type					X																				

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Mis-sexed	B	No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: DMBA AND *o*-PP (Continued)

ANIMAL NUMBER	0 1 2	0 0 6	0 3 5	0 0 7	0 2 6	0 4 9	0 2 4	0 0 1	0 1 4	0 4 1	0 0 2	0 0 3	0 0 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 2	0 2 7	0 2 9	0 3 0	0 3 2	0 3 4	0 4 6	TOTAL
WEEKS ON STUDY	0 8 2	0 8 3	0 8 8	0 9 0	0 9 0	0 9 0	0 9 3	0 9 5	0 9 6	0 9 8	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma				X											X	X										4
Squamous cell carcinoma																										1
Basal cell tumor							X								X										2
Basal cell carcinoma						X																				2
Sebaceous adenoma																				X						1
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibrosarcoma				X																						2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X			X		X				X	X	X		X	X							9
Alveolar/bronchiolar carcinoma													X													2
Trachea	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+		40
Thymus	–	–	–	+	–	–	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocellular adenoma								X										X								3
Hepatocellular carcinoma			X		X		X																		X	5
Bile duct	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder & common bile duct	+	N	N	+	+	+	N	+	N	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	–	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma											X															1
Small intestine	+	–	–	+	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	40
Large intestine	+	–	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adrenal	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma		X																								2
Thyroid	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma																										1
Parathyroid	+	–	–	+	–	–	+	–	–	–	+	+	+	–	+	–	+	–	+	–	–	–	+	+	+	24
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Testis	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malig. lymphoma, lymphocytic type	X																									1
Malig. lymphoma, histiocytic type																										1
Malig. lymphoma, mixed type							X																			2

*Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL: DMBA AND TPA

ANIMAL NUMBER	01199	02299	03398	04000	02303	01808	04101	03505	03000	01616	01717	02020	02121	02404	02505	02606	02808	03111	03313	04202	04303	05000	03606	03909	01505
WEEKS ON STUDY	01505	02205	02606	02909	03101	03202	03303	03404	03808	03909	03909	03909	03909	03909	03909	03909	03909	03909	03909	03909	03909	03909	04000	04808	04909
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																		X							
Basal cell tumor																					X				
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	–	+	–	–	–	+	+	–	–	+	+	+	–	–	–	+	+	–	+	–	–	+	
Squamous cell carcinoma, metastatic																									
Thymus	–	–	+	+	–	–	–	+	+	–	–	+	–	+	+	–	–	–	+	+	–	–	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Liver	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Gallbladder & common bile duct	N	+	N	N	N	N	+	+	N	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	–	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	–	–	–	+	–	–	–	–	+	–	+	–	–	–	–	–	+	–	–	+	+	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic																									
Malig lymphoma, lymphocytic type									X																

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Mis-sexed	B	No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: DMBA AND TPA (Continued)

ANIMAL NUMBER	0004	0007	0037	0005	0009	0027	0048	0049	0034	0046	0006	0012	0002	0047	0044	0032	0022	0008	0110	0114	0111	0003	0045	0001	0013	TOTAL
WEEKS ON STUDY	0500	0500	0500	0502	0502	0502	0502	0502	0503	0505	0506	0506	0600	0600	0601	0603	0604	0606	0607	0711	0719	0804	0805	0901	0900	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma			X									X	X		X	X		X						X		7
Squamous cell carcinoma	X			X		X		X			X			X	X			X	X	X	X	X				13
Basal cell tumor																										1
Keratoacanthoma														X												1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibrosarcoma						X						X														2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic						X									X				X		X	X				5
Alveolar/bronchiolar adenoma																							X		X	2
Trachea	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	–	–	+	–	+	–	+	+	–	+	–	+	–	+	+	+	+	+	–	+	+	+	30
Squamous cell carcinoma, metastatic						X																				1
Thymus	–	+	+	+	+	–	–	–	–	–	+	+	–	–	+	+	–	+	–	–	–	–	+	+	+	22
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular adenoma													X									X		X		3
Hepatocellular carcinoma																							X			1
Bile duct	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder & common bile duct	N	+	+	+	N	N	N	+	N	+	+	+	N	+	+	N	+	+	+	N	+	N	N	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	–	–	+	+	43
Small intestine	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	–	+	+	–	+	+	–	–	+	+	42
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Urinary bladder	–	+	+	–	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	–	–	–	+	+	+	–	+	–	+	+	+	+	+	–	–	+	+	36
Adrenal	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	–	–	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	41
Parathyroid	–	–	–	+	+	+	–	–	–	+	–	+	+	–	–	–	–	–	–	–	–	–	–	+	–	13
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma, metastatic																				X						1
Malig. lymphoma, lymphocytic type		X																								2

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	0050	0044	0030	0037	0045	0034	0048	0033	0023	0040	0049	0009	0036	0017	0020	0041	0047	0001	0007	0038	0031	0046	0003	0012	0024
WEEKS ON STUDY	0222	0339	0440	0442	0466	0555	0550	0662	0662	0665	0666	0670	0772	0772	0773	0774	0774	0779	0886	0888	0990	0991	0991	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									X
Alveolar/bronchiolar adenoma							X																		
Alveolar/bronchiolar carcinoma																				X		X			
Adenoca/squam metaplasia, metas																X									
Leiomyosarcoma, metastatic																							X		
Trachea	A	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Leiomyosarcoma, unc prim or metastatic											X														
Lymph nodes	+	–	+	–	–	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	–	+	–	+
Thymus	A	–	–	+	+	–	–	–	+	–	+	+	+	–	+	+	+	–	+	–	+	–	–	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
Hemangiosarcoma																									
Bile duct	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	+	N	+	N	+	N	+	+	N	N	+	+	+	+	N	N	+	N	N	N	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Stomach	A	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	–	+	+	+	–
Squamous cell papilloma																X									
Small intestine	A	+	–	+	–	+	–	+	+	+	+	–	+	+	+	+	+	–	–	+	–	–	+	+	–
Large intestine	A	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	–	+	+	–
URINARY SYSTEM																									
Kidney	A	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	+	–	–	–	–	–	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	A	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Parathyroid	A	–	+	+	–	–	+	+	+	–	–	+	+	+	–	–	+	+	–	–	+	+	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	+	+	N	+	N	+	+	+	N	+	+	+	+	+	N	N	+	N	N	N	+
Adenocarcinoma, NOS																									X
Adenoca/squamous metaplasia																X									
Uterus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Leiomyoma																									
Leiomyosarcoma									X															X	
Leiomyosarcoma, unc prim or met											X														
Endometrial stromal polyp							X													X					
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																									
Fibroma															X										
Hemangiosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary cystadenoma, NOS																							X		
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma, invasive																								X	
Malig. lymphoma, undiffer-type							X																		
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type												X								X					
Malignant lymphoma, mixed type													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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0014	0002	0006	0013	0025	0035	0005	0010	0011	0027	0004	0026	0032	0016	0008	0015	0018	0019	0021	0022	0028	0029	0039	0042	0043	TOTAL
WEEKS ON STUDY	0992	0995	0995	0995	0995	0996	0996	0996	0996	1001	1002	1002	1003	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma													X	X					X						X	5
Alveolar/bronchiolar carcinoma																								X		3
Adenoca/squam metaplasia, metastatic																										1
Leiomyosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma, uncl prim or metas																										1
Lymph nodes	+	+	+	–	–	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Thymus	+	–	–	+	–	–	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	44
Hemangiosarcoma				X																						1
Bile duct	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	44
Gallbladder & common bile duct	+	N	+	+	N	N	N	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Squamous cell papilloma													X											X		3
Small intestine	+	–	+	+	–	–	+	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	34
Large intestine	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY SYSTEM																										
Kidney	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	37
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																				X						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	+	+	–	–	+	–	+	+	+	+	+	–	+	–	–	+	–	+	+	+	+	–	+	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	+	+	N	N	+	N	+	N	N	N	+	+	N	+	+	+	+	N	+	+	N	50*
Adenocarcinoma, NOS											X															2
Adenoca/squamous metaplasia																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma																			X							1
Leiomyoma													X													1
Leiomyosarcoma																										2
Leiomyosarcoma, uncl prim or metas																										1
Endometrial stromal polyp																										2
Endometrial stromal sarcoma																								X	X	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Luteoma												X														1
Fibroma																										1
Hemangiosarcoma															X											1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	46
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Papillary cystadenoma, NOS							X																			2
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Leiomyosarcoma, invasive																										1
Malig. lymphoma, undifferentiated type																										1
Malig lymphoma, lymphocytic type	X																									1
Malig. lymphoma, histiocytic type											X									X						4
Malignant lymphoma, mixed type									X					X					X							4

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL: DMBA

ANIMAL NUMBER	00303	00209	00237	00339	00445	00118	00443	00228	00112	00441	00008	00336	00330	00110	00006	00222	00111	00447	00332	00338	00350	00266	00488
WEEKS ON STUDY	03 1	03 7	04 2	04 3	04 4	05 1	05 8	06 0	06 1	07 0	07 1	07 2	07 2	07 3	07 4	07 9	08 0	08 2	08 4	08 5	08 8	09 0	09 0	09 1	09 1
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma													X									X			
Squamous cell carcinoma																					X				
Basal cell carcinoma																			X						
Sebaceous adenoma													X												
Sebaceous adenocarcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic																									
Fibrosarcoma																									
Osteosarcoma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic																			X						
Adenocarcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma	X						X								X							X			
Alveolar/bronchiolar carcinoma						X											X	X		X			X		
Cystadenocarcinoma, metastatic							X																		
Trachea	+	+	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	–	–	–	+	–	–	–	+	–	–	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+
Basal cell carcinoma, metastatic																			X						
Malig lymphoma, histiocytic type															X										
Thymus	+	+	+	–	+	+	–	+	+	–	–	+	+	+	–	+	–	+	–	–	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Liver	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	N	N	N	N	N	+	N	+	+	N	N	+	+	+	N	+	N	N	+	+
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	–	–	–	–	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																							X		
Small intestine	+	+	+	–	–	–	–	–	–	–	+	+	+	+	–	–	+	+	+	–	+	+	–	+	+
Large intestine	+	+	+	+	+	–	–	–	–	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	–	+	–	+	–	–	–	+	+	+	+	–	–	+	+	+	–	+	+	–	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	–	+	–	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal Medulla	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	+	–	+	–	–	–	–	–	–	+	+	+	–	–	–	+	–	+	+	–	+	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	+	+	N	+	N	+	+	N	+	N	+	+	+	N	+	+	+	N	N	N
Adenocarcinoma, NOS																						X			
Cystadenocarcinoma, NOS							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenocarcinoma, NOS																									
Papillary cystadenocarcinoma, NOS																									
Leiomyoma																									
Leiomyosarcoma																									
Endometrial stromal polyp											X				X										
Endometrial stromal sarcoma											X														
Hemangioma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
Luteoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Eye appendages	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
Sebaceous adenoma																									
BODY CAVITIES																									
Pleura	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
Alveolar/bronchiolar ca, metastatic																	X								
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar ca, metastatic						X																			
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig lymphoma, lymphocytic type				X																					
Malignant lymphoma, mixed type																									

+ 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 Performe

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: DMBA (Continued)

ANIMAL NUMBER	0 3 4	0 0 1	0 0 2	0 1 5	0 2 1	0 0 9	0 1 4	0 2 5	0 4 0	0 0 4	0 0 5	0 0 7	0 1 3	0 1 6	0 1 7	0 1 9	0 2 3	0 2 4	0 2 7	0 3 1	0 3 3	0 4 2	0 4 4	0 4 6	0 4 9	TOTAL
WEEKS ON STUDY	0 9 2	0 9 4	0 9 5	0 9 5	0 9 6	0 9 7	0 9 7	0 9 7	1 0 1	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma															X			X								4
Squamous cell carcinoma						X			X																	3
Basal cell carcinoma														X												2
Sebaceous adenoma																										1
Sebaceous adenocarcinoma									X																	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Basal cell carcinoma, metastatic														X@												1
Fibrosarcoma												X		X												2
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma, metastatic														X												2
Adenocarcinoma, NOS, metastatic				X																						1
Alveolar/bronchiolar adenoma									X						X	X										7
Alveolar/bronchiolar carcinoma					X			X			X	X	X	X												11
Cystadenocarcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma		X		X																						2
Lymph nodes	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Basal cell carcinoma, metastatic																										1
Malig lymphoma, histiocytic type																										1
Thymus	+	+	–	–	–	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	45
Hepatocellular adenoma									X																	1
Hemangiosarcoma		X																					X			2
Bile duct	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	45
Gallbladder & common bile duct	N	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50*
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma, NOS																										1
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	39
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS								X																		1
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	–	+	+	+	+	–	+	–	–	+	–	–	+	+	+	–	–	–	–	+	+	+	+	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	N	+	N	+	+	+	+	+	+	+	N	N	N	+	N	+	+	N	+	+	N	50*
Adenocarcinoma, NOS				X																						2
Cystadenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																	X									1
Adenocarcinoma, NOS									X																	1
Papillary cystadenocarcinoma, NOS																									X	1
Leiomyoma																							X			1
Leiomyosarcoma										X																1
Endometrial stromal polyp		X							X				X					X								6
Endometrial stromal sarcoma					X																					2
Hemangioma													X												X	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary adenoma					X																					1
Luteoma							X						X													2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Sebaceous adenoma																X										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Alveolar/bronchiolar ca, metastatic																										1
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Alveolar/bronchiolar ca, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malig. lymphoma, lymphocytic type								X					X									X				4
Malignant lymphoma, mixed type										X				X												2

* Animals Necropsied
@ Multiple Occurrence of Morphology

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL: *o*-PP

ANIMAL NUMBER	02816	01624	02466	04405	04513	01344	03151	05025	02535	03539	00801	00919	02902	00243	01547	00404	02115	00518
WEEKS ON STUDY	00101	00301	00339	00466	00499	00502	00522	00546	00626	00773	00735	00779	00800	00802	00822	00844	00864	00889
RESPIRATORY SYSTEM																		
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X								X				X	
Alveolar/bronchiolar carcinoma																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+
HEMATOPOIETIC SYSTEM																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+
Hemangioma																		
Hemangiosarcoma																	X	
Lymph nodes	–	+	+	+	–	+	+	+	–	+	+	+	–	+	+	–	+	+
Thymus	–	–	+	–	+	–	+	+	+	+	+	–	+	–	+	–	+	+
CIRCULATORY SYSTEM																		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
DIGESTIVE SYSTEM																		
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Liver	–	+	+	+	+	+	+	+	+	–	+	–	+	–	–	+	–	+
Hepatocellular adenoma																		
Hepatocellular carcinoma																		
Hemangioma																		
Hemangiosarcoma										X								
Hemangiosarcoma, metastatic																	X	
Bile duct	–	+	+	+	+	+	+	+	+	–	+	–	+	–	–	+	–	+
Gallbladder & common bile duct	N	N	+	+	N	N	+	N	N	+	N	+	N	+	N	N	+	N
Adenocarcinoma, NOS																		
Pancreas	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		
Stomach	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	–
Small intestine	–	+	+	+	+	+	+	+	–	+	+	–	+	–	–	+	–	+
Large intestine	+	+	+	+	+	+	+	+	+	–	+	–	+	–	–	+	–	+
URINARY SYSTEM																		
Kidney	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+
Urinary bladder	–	+	+	+	+	+	+	+	+	–	+	+	–	+	–	–	+	–
ENDOCRINE SYSTEM																		
Pituitary	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	–	+	+
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+
Pheochromocytoma																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–
Parathyroid	–	–	+	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																		
Mammary gland	N	N	+	N	N	N	+	N	N	+	N	N	N	+	N	N	+	+
Adenocarcinoma, NOS																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Carcinoma in situ, NOS																X		
Fibroma																		
Endometrial stromal polyp														X		X		
Endometrial stromal sarcoma													X					X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma											X							
NERVOUS SYSTEM																		
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
MUSCULOSKELETAL SYSTEM																		
Bone	N	N	N	N	N	N	N	N	N	N	O	N	N	N	N	N	N	N
Osteoma														X				
ALL OTHER SYSTEMS																		
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type		X																
Malig. lymphoma, histiocytic type											X							
Malignant lymphoma, mixed type						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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: o-PP (Continued)

ANIMAL NUMBER	0 1 9	0 3 8	0 1 2	0 2 2	0 2 0	0 2 7	0 1 4	0 3 3	0 2 3	0 0 7	0 0 3	0 0 6	0 1 0	0 1 1	0 1 7	0 2 6	0 3 0	0 3 2	0 3 4	0 3 6	0 3 7	0 4 1	0 4 2	0 4 8	0 4 9	TOTAL
WEEKS ON STUDY	0 8 9	0 9 0	0 9 1	0 9 1	0 9 2	0 9 2	0 9 7	0 9 7	0 9 8	1 0 0	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X													X	X							X	7
Alveolar/bronchiolar carcinoma																			X							1
Trachea	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma				X																						1
Hemangiosarcoma			X																							2
Lymph nodes	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	41
Thymus	–	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Hepatocellular adenoma																		X			X			X		3
Hepatocellular carcinoma																					X					1
Hemangioma																							X			1
Hemangiosarcoma			X																							2
Hemangiosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Gallbladder & common bile duct	N	+	+	+	+	N	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	50*
Adenocarcinoma, NOS																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		46
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Squamous cell papilloma														X												1
Stomach	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		43
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		43
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		42
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	–	+	+	–	+	–	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+		37
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Pheochromocytoma						X																				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Parathyroid	+	–	–	–	–	–	+	–	–	+	–	–	–	–	–	+	–	–	–	–	+	–	+	+		12
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	+	N	N	N	N	N	+	N	+	+	N	N	N	+	N	+	+	N	N	N	+	50*
Adenocarcinoma, NOS																									X	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma in situ, NOS																										1
Fibroma																									X	1
Endometrial stromal polyp							X																			3
Endometrial stromal sarcoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Luteoma																			X				X			3
NERVOUS SYSTEM																										
Brain	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Osteoma							X																			2
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malig. lymphoma, lymphocytic type															X								X			3
Malig. lymphoma, histiocytic type			X				X					X		X					X							6
Malignant lymphoma, mixed type																										1

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF o-PHENYLPHENOL: DMBA AND o-PP

ANIMAL NUMBER	033	034	002	040	031	009	032	020	010	019	026	028	038	047	029	021	048	044	042	041	022	007	049	046	043
WEEKS ON STUDY	001	002	016	024	040	047	049	051	056	060	060	061	061	062	066	067	067	068	071	071	072	073	073	074	076
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma					X																	X			
Basal cell carcinoma																			X	X					
Sarcoma, NOS, invasive																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Sarcoma, NOS, unc prim or metastatic																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic																				X					
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	–	+	+	+	+	+	–	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Lymph nodes	+	+	+	+	–	+	+	+	+	–	–	–	–	+	+	+	+	+	+	+	+	+	–	–	+
Thymus	+	+	+	–	+	–	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Gallbladder & common bile duct	+	+	+	+	N	N	+	N	+	+	N	+	N	N	+	+	N	N	N	+	+	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	–
Squamous cell papilloma																				X					
Small intestine	+	–	+	+	–	–	–	–	+	+	+	+	–	–	+	+	–	–	+	+	+	+	+	+	–
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	–
Rectum	N	N	N	N	N	N	N	N	N	+	N	+	N	N	+	+	N	N	+	+	+	+	+	N	N
Sarcoma, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Urinary bladder	+	+	+	+	–	+	–	+	+	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+
Transitional-cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–
Parathyroid	–	–	–	+	–	+	+	+	+	+	–	+	–	+	–	+	+	+	–	+	+	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	N	+	+	N	N	N	+	N	N	N	N	+	N	N	+	+	N	N	N	N	N
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp																						X			
Hemangiosarcoma									X																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	X	+	+	+	+	+	+	+
Cystadenoma, NOS																									
Luteoma																									
Hemangioma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteoma																									
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic																									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma, unc prim or metas																									
Malig. lymphoma, undiffer-type							X																		
Malig. lymphoma, lymphocytic type			X																X						
Malig. lymphoma, histiocytic type														X									X		
Malignant lymphoma, mixed type																									

\+ : 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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: DMBA AND o-PP (Continued)

ANIMAL NUMBER	01 18	02 27	01 12	01 16	03 30	00 04	00 06	04 42	00 08	03 36	01 11	01 13	01 17	02 23	00 01	05 50	03 37	04 45	00 03	00 05	01 14	01 15	02 25	03 35	03 39	TOTAL
WEEKS ON STUDY	07 78	07 79	08 80	08 84	08 85	08 86	08 87	08 87	09 02	09 21	09 23	09 33	09 33	09 33	09 51	09 55	10 00	10 01	10 04	10 04	10 04	10 04	10 04	10 04	10 04	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma																			X		X					2
Squamous cell carcinoma		X																								3
Basal cell carcinoma																					X					3
Sarcoma, NOS, invasive								X																		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS								X																		1
Sarcoma, NOS, unc prim or metastatic								X																		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma	X					X	X						X				X			X			X		8
Alveolar/bronchiolar carcinoma					X					X	X								X		X					5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	49
Hemangioma															X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	–	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	40
Thymus	+	–	+	+	–	+	+	+	+	+	+	–	+	+	+	+	–	–	+	–	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	47
Hepatocellular adenoma										X											X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	47
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	N	N	N	+	N	+	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	–	–	+	–	+	+	+	+	+	34
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	42
Rectum	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	50*
Sarcoma, NOS																		X								1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	41
Transitional-cell carcinoma																							X			1
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	42
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																X										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	43
Parathyroid	–	+	+	+	+	+	–	–	–	–	–	–	–	–	+	+	–	–	+	–	–	–	+	+	+	26
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	N	N	+	N	N	N	N	+	+	+	N	N	+	+	N	+	+	N	+	50*
Adenocarcinoma, NOS			X																				X			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma		X																								1
Endometrial stromal polyp																		X					X			3
Hemangiosarcoma																									X	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma, NOS																										1
Luteoma																								X		1
Hemangioma										X																1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	47
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Osteoma	X																									1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Sarcoma, NOS, metastatic								X																		1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Hemangiosarcoma, unc prim or metas																					X					1
Malig. lymphoma, undiffer-type														X												1
Malig. lymphoma, lymphocytic type						X				X		X							X			X				3
Malig. lymphoma, histiocytic type				X																				X		6
Malignant lymphoma, mixed type																										3

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF o-PHENYLPHENOL: DMBA AND TPA

ANIMAL NUMBER	00005	00008	00113	00211	00111	00225	00440	00442	00004	00110	00229	00228	00443	00118	00449	00220	00356	00464	00550	00448	00002	00115	00437	00439	00009
WEEKS ON STUDY	00000	00000	00055	00116	00226	00226	00226	00226	00227	00227	00230	00232	00333	00335	00335	00337	00339	00339	00340	00340	00341	00411	00411	00413	00444
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Squamous cell papilloma				X	X	X	X				X		X	X				X		X					X
Squamous cell carcinoma															X						X	X@		X	X
Squamous cell ca, unc prim/metastatic																									
Basal cell carcinoma																						X			
Keratoacanthoma																									
Carcinosarcoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic															X						X	X			X
Basal cell carcinoma, metastatic																							X		
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	–	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Lymph nodes	+	+	+	–	+	+	+	–	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–
Basal cell carcinoma																						X			
Fibrosarcoma, metastatic																									
Thymus	+	+	–	–	+	+	+	–	+	–	+	–	+	+	–	–	+	+	+	–	–	–	–	+	+
Squamous cell carcinoma, metastatic																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic																						X			
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Bile duct	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	N	N	N	N	+	+	+	+	N	N	N	+	N	+	N	N	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	–	+	+	–	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	–	–	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	–	+	–	+
Adrenal Medulla	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	–	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	–
Parathyroid	–	–	–	–	–	–	–	+	+	–	+	–	–	–	+	+	–	+	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	N	+	N	+	N	N	+	+	+	+	+	N	+	N	+	N	N	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic																					X				
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic																									
Carcinosarcoma, metastatic																									
Malig. lymphoma, lymphocytic type													X												
Malig. lymphoma, histiocytic type																									
Granulocytic leukemia																									

+ : 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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: DMBA AND TPA (Continued)

ANIMAL NUMBER	00 07	00 36	03 71	01 66	03 31	03 32	04 45	03 38	04 43	00 03	01 01	01 17	02 23	03 30	04 41	00 06	02 26	01 14	02 22	01 12	03 33	03 34	02 27	02 24	01 19	TOTAL
WEEKS ON STUDY	04 46	04 46	04 47	04 48	04 48	04 48	04 49	05 00	05 52	05 54	05 55	05 56	05 57	05 57	05 58	06 01	06 01	06 02	06 02	06 04	06 06	06 07	06 08	07 11	07 14	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma								X	X		X			X						X	X	X				17
Squamous cell carcinoma	X	X	X	X	X		X		X							X	X		X		X	X	X			18
Squamous cell ca, unc prim/metastatic			X																							1
Basal cell carcinoma																X										2
Keratoacanthoma			X@X					X	X							X										5
Carcinosarcoma																		X								1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibrosarcoma		X											X								X					3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic				X	X				X							X	X		X				X			11
Basal cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma									X															X		2
Alveolar/bronchiolar carcinoma													X													1
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	46
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	42
Basal cell carcinoma																										1
Fibrosarcoma, metastatic													X													1
Thymus	–	–	+	–	–	+	+	+	–	+	–	–	+	+	–	+	+	+	–	+	–	+	+	–	–	27
Squamous cell carcinoma, metastatic																	X									1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	49
Basal cell carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Hemangioma																							X			1
Bile duct	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Gallbladder & common bile duct	+	+	+	N	N	N	+	+	+	N	N	+	+	+	N	+	+	N	N	N	+	+	+	+	N	50*
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
Small intestine	+	+	+	+	–	–	–	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	–	37
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	37
Adrenal Medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	42
Parathyroid	+	–	+	+	–	+	+	+	–	–	+	+	–	–	–	+	–	–	–	–	+	–	–	–	–	16
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	50*
Adenocarcinoma, NOS												X														1
Uterus	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endometrial stromal polyp														X												1
Ovary	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma, metastatic			X																							1
Carcinosarcoma, metastatic																		X								1
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type														X										X		2
Granulocytic leukemia			X																							1

* Animals Necropsied
@ Multiple Occurrence of Morphology

APPENDIX B

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ANIMALS INITIALLY IN STUDY	50	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50	50
ANIMALS EXAMINED HISTOPATH	50	50	50	50	50
INTEGUMENTARY SYSTEM					
*SKIN	(50)	(50)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST					3 (6%)
ULCER, NOS	5 (10%)	2 (4%)	†19 (38%)	†16 (32%)	†15 (30%)
INFLAMMATION, ACTIVE CHRONIC	†10 (20%)	†10 (20%)	†25 (50%)	†25 (50%)	†27 (54%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)		2 (4%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)		
GRANULOMA, NOS					1 (2%)
EROSION		1 (2%)			
FIBROSIS, DIFFUSE			1 (2%)		
HYPERPLASIA, NOS		1 (2%)			
HYPERPLASIA, FOCAL		1 (2%)			
HYPERKERATOSIS	†7 (14%)	†8 (16%)	†27 (54%)	†24 (48%)	†30 (60%)
ACANTHOSIS	†13 (26%)	†12 (24%)	†44 (88%)	†33 (66%)	†44 (88%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE					1 (2%)
GRANULOMA, NOS					1 (2%)
FIBROSIS				1 (2%)	
FIBROSIS, FOCAL				1 (2%)	
FIBROSIS, MULTIFOCAL				1 (2%)	
RESPIRATORY SYSTEM					
#LUNG	(50)	(50)	(50)	(50)	(50)
CONGESTION, NOS				1 (2%)	1 (2%)
CONGESTION, ACUTE	2 (4%)		1 (2%)	3 (6%)	
CONGESTION, ACUTE PASSIVE	1 (2%)				
LYMPHOCYTIC INFLAM INFILTR	6 (12%)	9 (18%)	8 (16%)	5 (10%)	
INFLAMMATION, INTERSTITIAL	4 (8%)	2 (4%)	1 (2%)	2 (4%)	7 (14%)
PNEUMONIA, ASPIRATION				1 (2%)	
INFLAMMATION, ACUTE FOCAL			2 (4%)		
INFLAMMATION, ACUTE DIFFUSE				1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)			
INFLAMMATION, ACTIVE CHRONIC				1 (2%)	
INFLAMMATION, ACUTE/CHRONIC				1 (2%)	
INFLAMMATION, CHRONIC FOCAL					1 (2%)
INFLAMMATION GRAN FOCAL	1 (2%)		3 (6%)		1 (2%)
ALVEOLAR MACROPHAGES			2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, ALVEOL EPITHELIUM	5 (10%)	7 (14%)	3 (6%)	7 (14%)	3 (6%)
METAPLASIA, OSSEOUS				1 (2%)	
HISTIOCYTOSIS	1 (2%)		1 (2%)		
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)				
HEMORRHAGE	2 (4%)		1 (2%)	3 (6%)	

(a) Administered a single dose (0.05 mg) of dimethylbenz(*a*)anthracene (DMBA) in 0.1 ml acetone then 0.1 ml acetone 3 × week for 2 years
(b) Administered 55.5 mg *o*-phenylphenol (o-PP) in 0.1 ml acetone 3 × week for 2 years
(c) Administered a single dose (0.05 mg) of DMBA then 55.5 mg *o*-PP in 0.1 ml acetone 3 × week for 2 years
(d) Administered a single dose (0.05 mg) of DMBA then 0.005 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) in 0.1 ml acetone 3 × week for 2 years

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
HEMATOPOIESIS					1 (2%)
#BONE MARROW	(47)	(47)	(47)	(48)	(47)
HEMOSIDEROSIS	1 (2%)				
MYELOFIBROSIS	1 (2%)				1 (2%)
HYPERPLASIA, GRANULOCYTIC	9 (19%)	10 (21%)	9 (19%)	19 (40%)	17 (36%)
HYPOPLASIA, HEMATOPOIETIC		2 (4%)			
#SPLEEN	(44)	(49)	(47)	(48)	(48)
DEPLETION, LYMPHOID				1 (2%)	
HEMATOPOIESIS			1 (2%)	1 (2%)	3 (6%)
#SPLENIC FOLLICLES	(44)	(49)	(47)	(48)	(48)
NECROSIS, NOS					1 (2%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	4 (9%)	1 (2%)	3 (6%)
AMYLOIDOSIS	1 (2%)				2 (4%)
DEPLETION, LYMPHOID	6 (14%)	14 (29%)	6 (13%)	10 (21%)	14 (29%)
HYPERPLASIA, LYMPHOID	7 (16%)	15 (31%)	7 (15%)	8 (17%)	1 (2%)
#SPLENIC RED PULP	(44)	(49)	(47)	(48)	(48)
PIGMENTATION, NOS			1 (2%)		
HEMATOPOIESIS	8 (18%)	10 (20%)	8 (17%)	17 (35%)	28 (58%)
#LYMPH NODE	(37)	(41)	(42)	(40)	(30)
INFLAMMATION, ACTIVE CHRONIC					1 (3%)
INFLAMMATION, CHRONIC FOCAL					2 (7%)
HISTIOCYTOSIS	1 (3%)				
PLASMACYTOSIS				1 (3%)	
HEMATOPOIESIS					1 (3%)
#MANDIBULAR L. NODE	(37)	(41)	(42)	(40)	(30)
CYST, NOS			2 (5%)		
HEMORRHAGE	1 (3%)	1 (2%)			
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		
NECROSIS, FOCAL			2 (5%)		
NECROSIS, DIFFUSE				1 (3%)	
DEPLETION, LYMPHOID		2 (5%)		9 (23%)	2 (7%)
HISTIOCYTOSIS	3 (8%)	1 (2%)	3 (7%)		
PLASMACYTOSIS	1 (3%)		4 (10%)	2 (5%)	2 (7%)
HYPERPLASIA, LYMPHOID		3 (7%)		1 (3%)	3 (10%)
HEMATOPOIESIS			2 (5%)		1 (3%)
#CERVICAL LYMPH NODE	(37)	(41)	(42)	(40)	(30)
PLASMACYTOSIS				1 (3%)	
HYPERPLASIA, LYMPHOID				1 (3%)	
#MESENTERIC L. NODE	(37)	(41)	(42)	(40)	(30)
CONGESTION, NOS	1 (3%)				
HEMORRHAGE				1 (3%)	
INFLAMMATION, ACUTE/CHRONIC					1 (3%)
DEPLETION, LYMPHOID				1 (3%)	
HEMATOPOIESIS		2 (5%)		2 (5%)	1 (3%)
#RENAL LYMPH NODE	(37)	(41)	(42)	(40)	(30)
DEPLETION, LYMPHOID				1 (3%)	
ANGIECTASIS	1 (3%)				
HEMATOPOIESIS	1 (3%)				
#AXILLARY LYMPH NODE	(37)	(41)	(42)	(40)	(30)
CYST, NOS	1 (3%)				
MULTIPLE CYSTS			1 (2%)		
HISTIOCYTOSIS	2 (5%)			1 (3%)	
PLASMACYTOSIS		1 (2%)		2 (5%)	
#BRACHIAL LYMPH NODE	(37)	(41)	(42)	(40)	(30)
HISTIOCYTOSIS					1 (3%)
HEMATOPOIESIS					1 (3%)
#SUBSCAPULAR LYMPH NODE	(37)	(41)	(42)	(40)	(30)
PLASMACYTOSIS				2 (5%)	
HYPERPLASIA, LYMPHOID				1 (3%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
HEMATOPOIETIC SYSTEM (Continued)					
#THYMIC LYMPH NODE	(37)	(41)	(42)	(40)	(30)
DEPLETION, LYMPHOID			1 (2%)		
HYPERPLASIA, LYMPHOID			1 (2%)		
#LUNG	(50)	(50)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS					1 (2%)
LEUKOCYTOSIS, NEUTROPHILIC					1 (2%)
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)	(50)
LEUKOCYTOSIS, NEUTROPHILIC					1 (2%)
#SALIVARY GLAND	(50)	(50)	(48)	(48)	(49)
HYPERPLASIA, LYMPHOID					1 (2%)
#LIVER	(47)	(48)	(48)	(46)	(47)
HEMATOPOIESIS	1 (2%)	4 (8%)	4 (8%)	1 (2%)	7 (15%)
#HEPATIC SINUSOID	(47)	(48)	(48)	(46)	(47)
HEMATOPOIESIS					2 (4%)
#LIVER/HEPATOCYTES	(47)	(48)	(48)	(46)	(47)
HEMATOPOIESIS					2 (4%)
#KIDNEY	(47)	(49)	(47)	(49)	(48)
PLASMACYTOSIS	1 (2%)		1 (2%)	1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)		1 (2%)	2 (4%)
HEMATOPOIESIS					3 (6%)
#KIDNEY/CORTEX	(47)	(49)	(47)	(49)	(48)
PLASMACYTOSIS				1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)		
#THYROID	(49)	(46)	(47)	(45)	(41)
DEPLETION, LYMPHOID					1 (2%)
#THYMUS	(34)	(31)	(26)	(29)	(22)
CYST, NOS				1 (3%)	
LYMPHOCYTIC INFLAM INFILTR			1 (4%)		
DEPLETION, LYMPHOID	3 (9%)	7 (23%)	8 (31%)	14 (48%)	9 (41%)
HYPERPLASIA, EPITHELIAL		1 (3%)			
HYPERPLASIA, LYMPHOID	1 (3%)	1 (3%)			
#THYMIC CORTEX	(34)	(31)	(26)	(29)	(22)
DEPLETION, LYMPHOID		1 (3%)		1 (3%)	1 (5%)
#THYMIC LYMPHOCYTES	(34)	(31)	(26)	(29)	(22)
DEGENERATION, NOS					1 (5%)
NECROSIS, NOS			1 (4%)		1 (5%)
NECROSIS, FOCAL	2 (6%)			2 (7%)	
NECROSIS, DIFFUSE			1 (4%)		3 (14%)
CIRCULATORY SYSTEM					
*SUBCUT TISSUE	(50)	(50)	(50)	(50)	(50)
PERIARTERITIS					1 (2%)
#HEART	(49)	(50)	(49)	(50)	(50)
PERIARTERITIS	1 (2%)				
PERIVASCULITIS				2 (4%)	
ANGIECTASIS				1 (2%)	
#HEART/ATRIUM	(49)	(50)	(49)	(50)	(50)
THROMBUS, ORGANIZED	1 (2%)				
#LEFT ATRIUM	(49)	(50)	(49)	(50)	(50)
THROMBUS, ORGANIZED		1 (2%)	1 (2%)		
#MYOCARDIUM	(49)	(50)	(49)	(50)	(50)
MINERALIZATION	1 (2%)				
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)				
INFLAMMATION GRAN FOCAL	1 (2%)				
PERIARTERITIS		2 (4%)			
PERIVASCULITIS		1 (2%)			
DEGENERATION, NOS	7 (14%)	7 (14%)	10 (20%)	7 (14%)	5 (10%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
CIRCULATORY SYSTEM (Continued)					
#MYOCARDIUM/LT. VENTR	(49)	(50)	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL				1 (2%)	
DEGENERATION, NOS					1 (2%)
*ARTERY	(50)	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS			1 (2%)		
*CORONARY VEIN	(50)	(50)	(50)	(50)	(50)
PERIVASCULITIS					1 (2%)
#HEPATIC SINUSOID	(47)	(48)	(48)	(46)	(47)
AMYLOIDOSIS			1 (2%)		
DIGESTIVE SYSTEM					
#SALIVARY GLAND	(50)	(50)	(48)	(48)	(49)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)	1 (2%)	2 (4%)	1 (2%)	
ATROPHY, FOCAL	1 (2%)	1 (2%)			
#LIVER	(47)	(48)	(48)	(46)	(47)
CONGESTION, ACUTE PASSIVE	1 (2%)				
HEMORRHAGIC CYST		1 (2%)			
LYMPHOCYTIC INFLAM INFILTR		2 (4%)		1 (2%)	
INFLAMMATION, ACUTE FOCAL					1 (2%)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	2 (4%)		1 (2%)	
INFLAMMATION GRAN FOCAL	2 (4%)	3 (6%)		1 (2%)	
NECROSIS, FOCAL				1 (2%)	
AMYLOIDOSIS					3 (6%)
BASOPHILIC CYTO CHANGE			2 (4%)		
CLEAR-CELL CHANGE		1 (2%)			
#LIVER/CENTRILOBULAR	(47)	(48)	(48)	(46)	(47)
NECROSIS, FOCAL	1 (2%)				
#LIVER/PERIPORTAL	(47)	(48)	(48)	(46)	(47)
AMYLOIDOSIS					1 (2%)
#LIVER/KUPFFER CELL	(47)	(48)	(48)	(46)	(47)
AMYLOIDOSIS	1 (2%)				1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)		
#LIVER/HEPATOCYTES	(47)	(48)	(48)	(46)	(47)
DEGENERATION, NOS	14 (30%)	26 (54%)	19 (40%)	28 (61%)	10 (21%)
NECROSIS, FOCAL	12 (26%)	25 (52%)	29 (60%)	13 (28%)	15 (32%)
FOCAL CELLULAR CHANGE				1 (2%)	
CELL-SIZE ALTERATION	25 (53%)	17 (35%)	19 (40%)	33 (72%)	17 (36%)
*GALLBLADDER	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS	1 (2%)				
MULTIPLE CYSTS		1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	1 (2%)				
*GALLBLADDER/MUCOSA	(50)	(50)	(50)	(50)	(50)
CYST, NOS		1 (2%)		1 (2%)	1 (2%)
MULTIPLE CYSTS			1 (2%)		
#BILE DUCT	(47)	(48)	(48)	(46)	(47)
CYST, NOS				1 (2%)	
#PANCREAS	(47)	(48)	(47)	(46)	(49)
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		
#PANCREATIC ACINUS	(47)	(48)	(47)	(46)	(49)
ATROPHY, FOCAL			1 (2%)		
#PANCREAS/INTERSTITIU	(47)	(48)	(47)	(46)	(49)
INFLAMMATION, ACUTE DIFFUSE					1 (2%)
#ESOPHAGUS	(50)	(49)	(50)	(50)	(50)
DILATATION, NOS	3 (6%)	1 (2%)	1 (2%)		
HYPERKERATOSIS			1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
DIGESTIVE SYSTEM (Continued)					
#GLANDULAR STOMACH	(39)	(46)	(44)	(45)	(43)
DIVERTICULUM	3 (8%)	6 (13%)	3 (7%)	3 (7%)	
MULTIPLE CYSTS	1 (3%)				
ULCER, NOS	1 (3%)				
LYMPHOCYTIC INFLAM INFILTR		1 (2%)			
ULCER, ACUTE					2 (5%)
INFLAMMATION, ACUTE FOCAL				1 (2%)	
INFLAMMATION, ACTIVE CHRONIC	1 (3%)				
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)	
NECROSIS, FOCAL			2 (5%)	1 (2%)	5 (12%)
HYPERPLASIA, EPITHELIAL				1 (2%)	
DYSPLASIA, NOS	23 (59%)	31 (67%)	18 (41%)	28 (62%)	13 (30%)
#FORESTOMACH	(39)	(46)	(44)	(45)	(43)
EPIDERMAL INCLUSION CYST				1 (2%)	
MULTIPLE CYSTS	1 (3%)				
LYMPHOCYTIC INFLAM INFILTR		1 (2%)			
HYPERKERATOSIS	1 (3%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)
ACANTHOSIS		1 (2%)		2 (4%)	1 (2%)
#JEJUNUM	(37)	(43)	(42)	(40)	(42)
AMYLOIDOSIS	1 (3%)				
#JEJUNAL MUCOSA	(37)	(43)	(42)	(40)	(42)
POLYP, NOS					1 (2%)
#ILEUM	(37)	(43)	(42)	(40)	(42)
INFLAMMATION, ACUTE FOCAL				1 (3%)	
#COLON	(40)	(43)	(46)	(41)	(45)
PARASITISM	6 (15%)	1 (2%)	8 (17%)	2 (5%)	4 (9%)
#COLONIC MUCOSA	(40)	(43)	(46)	(41)	(45)
DEGENERATION, NOS			1 (2%)		
URINARY SYSTEM					
#KIDNEY	(47)	(49)	(47)	(49)	(48)
HYDRONEPHROSIS	2 (4%)		3 (6%)	2 (4%)	1 (2%)
GLOMERULONEPHRITIS, FOCAL			1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAM INFILTR	2 (4%)	9 (18%)	5 (11%)		4 (8%)
GLOMERULONEPHRITIS, ACUTE		1 (2%)			
INFLAMMATION, ACUTE NECROTIZING					1 (2%)
INFLAMMATION, ACTIVE CHRONIC		1 (2%)			
GLOMERULONEPHRITIS, SUBACUTE		2 (4%)	1 (2%)		
PYELONEPHRITIS, ACUTE/CHRONIC					1 (2%)
INFLAMMATION, CHRONIC DIFFUSE					1 (2%)
NEPHROPATHY	32 (68%)	29 (59%)	22 (47%)	21 (43%)	14 (29%)
NEPHROSIS, NOS			1 (2%)		
INFARCT, NOS			1 (2%)		
INFARCT, ACUTE			1 (2%)		
HYPERPLASIA, TUBULAR CELL					1 (2%)
HISTIOCYTOSIS	2 (4%)				
#KIDNEY/CAPSULE	(47)	(49)	(47)	(49)	(48)
HEMORRHAGE		1 (2%)			
#KIDNEY/INTERSTITIUM	(47)	(49)	(47)	(49)	(48)
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)			
#KIDNEY/CORTEX	(47)	(49)	(47)	(49)	(48)
CYST, NOS	1 (2%)	3 (6%)	1 (2%)		
MULTIPLE CYSTS	3 (6%)	1 (2%)	3 (6%)		
HEMORRHAGE		1 (2%)			
NEPHROPATHY				1 (2%)	
INFARCT, FOCAL					1 (2%)
#KIDNEY/MEDULLA	(47)	(49)	(47)	(49)	(48)
HYDRONEPHROSIS	1 (2%)				

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
URINARY SYSTEM (Continued)					
#KIDNEY/GLOMERULUS	(47)	(49)	(47)	(49)	(48)
AMYLOIDOSIS	1 (2%)		1 (2%)		2 (4%)
#BOWMAN'S CAPSULE	(47)	(49)	(47)	(49)	(48)
DILATATION, NOS	5 (11%)	1 (2%)	2 (4%)	3 (6%)	1 (2%)
#KIDNEY/TUBULE	(47)	(49)	(47)	(49)	(48)
MINERALIZATION		1 (2%)			
DILATATION, NOS	1 (2%)	4 (8%)	6 (13%)	3 (6%)	2 (4%)
CYST, NOS		2 (4%)			
MULTIPLE CYSTS					1 (2%)
DEGENERATION, NOS	1 (2%)		1 (2%)	1 (2%)	
NECROSIS, FOCAL		1 (2%)			
REGENERATION, NOS	1 (2%)			1 (2%)	1 (2%)
*URETER	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS				1 (2%)	
LYMPHOCYTIC INFLAM INFILTR		1 (2%)			
INFLAMMATION, ACUTE/CHRONIC				1 (2%)	
#URINARY BLADDER	(41)	(43)	(45)	(46)	(41)
DILATATION, NOS	2 (5%)	3 (7%)	1 (2%)	1 (2%)	
DISTENTION		1 (2%)		1 (2%)	
RETENTION OF CONTENT			1 (2%)		
HEMORRHAGE	1 (2%)	2 (5%)			
LYMPHOCYTIC INFLAM INFILTR	1 (2%)			1 (2%)	
INFLAMMATION, ACUTE					1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)				
INFLAMMATION, ACTIVE CHRONIC	1 (2%)				
HYPERPLASIA, EPITHELIAL	4 (10%)	15 (35%)	7 (16%)	4 (9%)	1 (2%)
#U. BLADDER/MUCOSA	(41)	(43)	(45)	(46)	(41)
DEGENERATION, NOS		2 (5%)			
NECROSIS, CYTODEGENERATIVE					1 (2%)
CYTOPLASMIC VACUOLIZATION				1 (2%)	
#U.BLADDER/SUBMUCOSA	(41)	(43)	(45)	(46)	(41)
EDEMA, NOS	1 (2%)				
*URETHRA	(50)	(50)	(50)	(50)	(50)
CALCULUS,MICROSCOPIC EXAM	3 (6%)				
LYMPHOCYTIC INFLAM INFILTR				1 (2%)	
*PROSTATIC URETHRA	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS		1 (2%)			
RETENTION OF CONTENT		2 (4%)			
RETENTION FLUID			1 (2%)		
OBSTRUCTION, NOS		1 (2%)			
INFLAMMATION, ACUTE DIFFUSE		1 (2%)			
ENDOCRINE SYSTEM					
#PITUITARY	(38)	(41)	(41)	(43)	(36)
CYTOPLASMIC VACUOLIZATION		1 (2%)			
#ANTERIOR PITUITARY	(38)	(41)	(41)	(43)	(36)
EMBRYONAL DUCT CYST		1 (2%)	1 (2%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)			
HYPERPLASIA, FOCAL	1 (3%)				
#ADRENAL/CAPSULE	(49)	(49)	(45)	(48)	(49)
HYPERPLASIA, NOS	1 (2%)				
HYPERPLASIA, FOCAL	12 (24%)	14 (29%)	14 (31%)	5 (10%)	1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ENDOCRINE SYSTEM (Continued)					
#ADRENAL GLAND/ZONA FASCICULATA	(49)	(49)	(45)	(48)	(49)
CONGESTION, ACUTE PASSIVE	1 (2%)				
DEGENERATION, NOS	1 (2%)				
DEGENERATION, LIPOID	1 (2%)	7 (14%)	4 (9%)	1 (2%)	
CYTOPLASMIC CHANGE, NOS	1 (2%)		1 (2%)		
CYTOPLASMIC VACUOLIZATION			1 (2%)	1 (2%)	
FOCAL CELLULAR CHANGE	3 (6%)	12 (24%)	4 (9%)	2 (4%)	
ATROPHY, FOCAL	1 (2%)	3 (6%)	1 (2%)		
HYPERPLASIA, FOCAL	3 (6%)	4 (8%)	2 (4%)	3 (6%)	
#ADRENAL MEDULLA	(49)	(49)	(45)	(48)	(49)
MINERALIZATION	1 (2%)				
HEMORRHAGE	1 (2%)				
NECROSIS, FOCAL	1 (2%)			1 (2%)	
PIGMENTATION, NOS	1 (2%)			1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)		
#THYROID	(49)	(46)	(47)	(45)	(41)
FOLLICULAR CYST, NOS	3 (6%)	8 (17%)	13 (28%)	9 (20%)	2 (5%)
LYMPHOCYTIC INFLAM INFILTR		1 (2%)			
AMYLOIDOSIS	1 (2%)		1 (2%)		1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	1 (2%)	1 (2%)		1 (2%)
#THYROID FOLLICLE	(49)	(46)	(47)	(45)	(41)
DILATATION, NOS		1 (2%)			
MULTIPLE CYSTS	10 (20%)	6 (13%)	6 (13%)	7 (16%)	4 (10%)
#PANCREATIC ISLETS	(47)	(48)	(47)	(46)	(49)
HYPERPLASIA, FOCAL	6 (13%)				
REPRODUCTIVE SYSTEM					
*EPIDIDYMAL LUMEN	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS	2 (4%)				
HEMORRHAGE	1 (2%)				
*PREPUCE	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)	(50)
DILATATION/DUCTS	7 (14%)	5 (10%)	5 (10%)	8 (16%)	6 (12%)
LYMPHOCYTIC INFLAM		1 (2%)			
INFLAMMATION, SUPPURATIVE	2 (4%)				
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		
INFLAMMATION, CHRONIC FOCAL				1 (2%)	
ABSCESS, CHRONIC			1 (2%)		
ATROPHY, FOCAL		3 (6%)	4 (8%)		5 (10%)
METAPLASIA, SQUAMOUS			1 (2%)		
#PROSTATE	(47)	(48)	(46)	(48)	(48)
INFLAMMATION, ACUTE FOCAL					1 (2%)
INFLAMMATION, ACTIVE CHRONIC		1 (2%)			1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS		1 (2%)	1 (2%)		
RETENTION OF CONTENT					1 (2%)
RETENTION FLUID	23 (46%)	26 (52%)	4 (8%)	13 (26%)	2 (4%)
INFLAMMATION, ACUTE	1 (2%)				
INFLAMMATION, ACTIVE CHRONIC			2 (4%)	1 (2%)	
HYPERPLASIA, EPITHELIAL	2 (4%)			2 (4%)	
#PERIPROSTATIC TISSUE	(47)	(48)	(46)	(48)	(48)
LYMPHOCYTIC INFLAM INFILTR				1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)		1 (2%)		
INFLAMMATION, ACTIVE CHRONIC		2 (4%)	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
REPRODUCTIVE SYSTEM (Continued)					
#TESTIS	(48)	(50)	(49)	(49)	(50)
GRANULOMA, SPERMATIC	1 (2%)				
HYPERPLASIA, INTERSTITIAL CELL	11 (23%)	13 (26%)	8 (16%)	5 (10%)	
#TESTIS/TUBULE	(48)	(50)	(49)	(49)	(50)
MINERALIZATION	1 (2%)		1 (2%)		
DEGENERATION, NOS					1 (2%)
ATROPHY, FOCAL			1 (2%)		
#SPERMATOGENIC EPITHELIUM	(48)	(50)	(49)	(49)	(50)
MINERALIZATION		3 (6%)			
DEGENERATION, NOS	1 (2%)	3 (6%)	3 (6%)	6 (12%)	
ATROPHY, FOCAL		1 (2%)			
#SPERMATOGONIA	(48)	(50)	(49)	(49)	(50)
DEGENERATION, NOS	1 (2%)				
#RETE TESTIS	(48)	(50)	(49)	(49)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)		2 (4%)		
*EPIDIDYMIS	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS	1 (2%)				
SPERMATOCELE		1 (2%)		1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)				
INFLAMMATION, ACTIVE CHRONIC	1 (2%)	3 (6%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)				
INFLAMMATION, PYOGRANULO					1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)		
*VAS DEFERENS	(50)	(50)	(50)	(50)	(50)
RETENTION OF CONTENT		1 (2%)			
*VAS DEFERENS/MUCOSA	(50)	(50)	(50)	(50)	(50)
NUCLEAR ENLARGEMENT	1 (2%)				
DYSPLASIA, NOS	1 (2%)				
NERVOUS SYSTEM					
#CEREBRUM	(44)	(49)	(48)	(49)	(48)
ATROPHY, PRESSURE		1 (2%)			
#BRAIN	(44)	(49)	(48)	(49)	(48)
CONGESTION, NOS					1 (2%)
CONGESTION, ACUTE				1 (2%)	
SPECIAL SENSE ORGANS					
*EYE/CORNEA	(50)	(50)	(50)	(50)	(50)
ULCER, NOS			1 (2%)		
INFLAMMATION, ACUTE FOCAL			1 (2%)		
INFLAMMATION, ACTIVE CHRONIC	1 (2%)				1 (2%)
DEGENERATION, NOS				1 (2%)	
*CORNEA, EXTERNAL EPITHELIUM	(50)	(50)	(50)	(50)	(50)
ULCER, NOS					1 (2%)
*EYE/RETINA	(50)	(50)	(50)	(50)	(50)
ATROPHY, NOS			1 (2%)		
ATROPHY, FOCAL				1 (2%)	
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)	(50)	(50)
CATARACT			1 (2%)	1 (2%)	
*EYE/LACRIMAL GLAND	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)			

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
MUSCULOSKELETAL SYSTEM					
*KNEE JOINT	(50)	(50)	(50)	(50)	(50)
EROSION					1 (2%)
*LIGAMENT/KNEE JOINT	(50)	(50)	(50)	(50)	(50)
METAPLASIA, OSSEOUS					1 (2%)
BODY CAVITIES					
*MEDIASTINUM	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC					1 (2%)
*PLEURA	(50)	(50)	(50)	(50)	(50)
FIBROSIS, MULTIFOCAL			1 (2%)		1 (2%)
*PERICARDIUM	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL				1 (2%)	
*EPICARDIUM	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)				1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)		
FIBROSIS, FOCAL					1 (2%)
*MESENTERY	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC					1 (2%)
ALL OTHER SYSTEMS					
KNEE					
INFLAMMATION, ACUTE/CHRONIC					1
ADIPOSE TISSUE					
INFLAMMATION GRANULO FOCAL	1				
SPECIAL MORPHOLOGY SUMMARY					
NONE					

* NUMBER OF ANIMALS NECROPSIED
\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN TISSUES IS COUNTED ONCE ONLY

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ANIMALS INITIALLY IN STUDY	50	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50	50
ANIMALS EXAMINED HISTOPATH	50	50	50	50	50
INTEGUMENTARY SYSTEM					
*SKIN	(50)	(50)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)		2 (4%)
ULCER, NOS	1 (2%)	7 (14%)	†11 (22%)	†11 (22%)	†12 (24%)
INFLAMMATION, ACTIVE CHRONIC	†7 (14%)	†7 (14%)	†20 (40%)	†27 (54%)	†25 (50%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		†1 (2%)	
EROSION	1 (2%)			1 (2%)	
FIBROSIS, MULTIFOCAL			1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)			
HYPERKERATOSIS	4 (8%)	4 (8%)	†16 (32%)	†27 (54%)	†26 (52%)
ACANTHOSIS	4 (8%)	†12 (24%)	†36 (72%)	†42 (84%)	†41 (82%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)	(50)
EDEMA, NOS	1 (2%)			1 (2%)	
INFLAMMATION, ACUTE FOCAL		1 (2%)			
INFLAMMATION, ACTIVE CHRONIC		2 (4%)	1 (2%)	†1 (2%)	†2 (4%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)	
INFLAMMATION GRANULO FOCAL		1 (2%)			
FIBROSIS, MULTIFOCAL				1 (2%)	
FIBROSIS, DIFFUSE					1 (2%)
RESPIRATORY SYSTEM					
#LUNG	(50)	(50)	(50)	(50)	(50)
CONGESTION, NOS				1 (2%)	1 (2%)
CONGESTION, ACUTE	3 (6%)	2 (4%)		1 (2%)	2 (4%)
EDEMA, NOS					1 (2%)
HEMORRHAGE					1 (2%)
LYMPHOCYTIC INFLAM INFILTR	5 (10%)	8 (16%)	8 (16%)	2 (4%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)	4 (8%)	4 (8%)	6 (12%)	3 (6%)
PNEUMONIA, ASPIRATION				1 (2%)	
INFLAMMATION, ACTIVE CHRONIC		1 (2%)			
PNEUMONIA, INTERSTITIAL CHRONIC	1 (2%)	2 (4%)		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)			
INFLAMMATION GRANULO FOCAL			2 (4%)	1 (2%)	2 (4%)
ALVEOLAR MACROPHAGES		1 (2%)		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHEL	3 (6%)	3 (6%)	3 (6%)	1 (2%)	1 (2%)
METAPLASIA, OSSEOUS			1 (2%)		
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)	(50)
EDEMA, NOS			1 (2%)		
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
HEMOSIDEROSIS	1 (2%)				
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
DEPLETION, LYMPHOID				1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)			
HEMATOPOIESIS		1 (2%)			

(a) Administered a single dose (0.05 mg) of dimethylbenz(*a*)anthracene (DMBA) in 0.1 ml acetone then 0.1 ml acetone 3 × week for 2 years
(b) Administered 55.5 mg *o*-phenylphenol (*o*-PP) in 0.1 ml acetone 3 × week for 2 years
(c) Administered a single dose (0.05 mg) of DMBA then 55.5 mg *o*-PP in 0.1 ml acetone 3 × week for 2 years
(d) Administered a single dose (0.05 mg) of DMBA then 0.005 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) in 0.1 ml acetone 3 × week for 2 years

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
HEMATOPOIETIC SYSTEM (Continued)					
*BLOOD	(50)	(50)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS					2 (4%)
LEUKOCYTOSIS, NEUTROPHILIC				1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)	(50)
MASTOCYTOSIS			1 (2%)		
#BONE MARROW	(50)	(50)	(48)	(49)	(44)
NECROSIS, FOCAL				1 (2%)	
NECROSIS, DIFFUSE					2 (5%)
METAMORPHOSIS, FATTY		1 (2%)			
HISTIOCYTOSIS		1 (2%)			
MYELOFIBROSIS	1 (2%)	2 (4%)	1 (2%)		
HYPERPLASIA, GRANULOCYTIC	3 (6%)	6 (12%)	10 (21%)	14 (29%)	15 (34%)
HYPOPLASIA, HEMATOPOIETIC			2 (4%)		
HYPOPLASIA, GRANULOCYTIC			1 (2%)		
APLASIA, HEMATOPOIETIC	1 (2%)				
#SPLEEN	(48)	(47)	(47)	(48)	(46)
NECROSIS, FOCAL	1 (2%)				
DEPLETION, LYMPHOID			3 (6%)	5 (10%)	6 (13%)
HEMATOPOIESIS					1 (2%)
#SPLENIC FOLLICLES	(48)	(47)	(47)	(48)	(46)
NECROSIS, FOCAL	2 (4%)	1 (2%)	1 (2%)		
AMYLOIDOSIS				2 (4%)	3 (7%)
DEPLETION, LYMPHOID	9 (19%)	7 (15%)	8 (17%)	6 (13%)	7 (15%)
HYPERPLASIA, LYMPHOID	5 (10%)	7 (15%)	9 (19%)		
#SPLENIC RED PULP	(48)	(47)	(47)	(48)	(46)
FIBROSIS, FOCAL	1 (2%)				
PIGMENTATION, NOS				1 (2%)	
HEMOSIDEROSIS			1 (2%)		
HEMATOPOIESIS	8 (17%)	17 (36%)	12 (26%)	19 (40%)	26 (57%)
#LYMPH NODE	(36)	(37)	(41)	(40)	(42)
PLASMACYTOSIS					1 (2%)
#MANDIBULAR L. NODE	(36)	(37)	(41)	(40)	(42)
CYST, NOS			1 (2%)		1 (2%)
HEMORRHAGE	1 (3%)			3 (8%)	
INFLAMMATION, ACUTE			1 (2%)		
INFLAMMATION, ACUTE FOCAL					1 (2%)
INFLAMMATION, ACUTE DIFFUSE					1 (2%)
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (3%)	1 (3%)			1 (2%)
NECROSIS, FOCAL			1 (2%)	1 (3%)	
NECROSIS, DIFFUSE					1 (2%)
PIGMENTATION, NOS		1 (3%)	2 (5%)	1 (3%)	
DEPLETION, LYMPHOID	2 (6%)	6 (16%)			1 (2%)
HISTIOCYTOSIS	4 (11%)			1 (3%)	4 (10%)
PLASMACYTOSIS	1 (3%)	1 (3%)	4 (10%)	1 (3%)	2 (5%)
HYPERPLASIA, LYMPHOID	2 (6%)	5 (14%)	4 (10%)	2 (5%)	2 (5%)
HEMATOPOIESIS				2 (5%)	3 (7%)
#THORACIC LYMPH NODE	(36)	(37)	(41)	(40)	(42)
DEPLETION, LYMPHOID		1 (3%)			
#PANCREATIC L. NODE	(36)	(37)	(41)	(40)	(42)
HEMORRHAGE				1 (3%)	
HEMATOPOIESIS				1 (3%)	1 (2%)
#LUMBAR LYMPH NODE	(36)	(37)	(41)	(40)	(42)
PLASMACYTOSIS			1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
HEMATOPOIETIC SYSTEM (Continued)					
#MESENTERIC L. NODE	(36)	(37)	(41)	(40)	(42)
CONGESTION, NOS	1 (3%)				
HEMORRHAGE				1 (3%)	
INFLAMMATION, MULTIFOCAL	1 (3%)				
ANGIECTASIS	1 (3%)	2 (5%)	1 (2%)		
HYPERPLASIA, LYMPHOID		1 (3%)			
HEMATOPOIESIS		2 (5%)	1 (2%)	1 (3%)	
#RENAL LYMPH NODE	(36)	(37)	(41)	(40)	(42)
INFLAMMATION, ACTIVE CHRONIC					1 (2%)
HYPERPLASIA, LYMPHOID		1 (3%)			
HEMATOPOIESIS				1 (3%)	
#AXILLARY LYMPH NODE	(36)	(37)	(41)	(40)	(42)
INFLAMMATION, ACTIVE CHRONIC					2 (5%)
NECROSIS, FOCAL				1 (3%)	
PLASMACYTOSIS				1 (3%)	1 (2%)
HEMATOPOIESIS					1 (2%)
#THYMIC LYMPH NODE	(36)	(37)	(41)	(40)	(42)
MINERALIZATION	1 (3%)				
HEMATOPOIESIS					1 (2%)
#LUNG	(50)	(50)	(50)	(50)	(50)
LEUKOCYTOSIS, NEUTROPHILIC				1 (2%)	
HYPERPLASIA, LYMPHOID				1 (2%)	
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)	(50)
LEUKOCYTOSIS, NEUTROPHILIC					3 (6%)
#SALIVARY GLAND	(50)	(49)	(47)	(47)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)		1 (2%)	
#LIVER	(44)	(45)	(44)	(47)	(47)
HEMATOPOIESIS		3 (7%)	4 (9%)	4 (9%)	8 (17%)
#HEPATIC SINUSOID	(44)	(45)	(44)	(47)	(47)
LEUKOCYTOSIS, NOS					1 (2%)
#KIDNEY	(47)	(49)	(47)	(49)	(48)
PLASMACYTOSIS		1 (2%)	1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)			3 (6%)
HEMATOPOIESIS				1 (2%)	
#U. BLADDER/SUBMUCOSA	(37)	(39)	(42)	(41)	(43)
HYPERPLASIA, LYMPHOID					1 (2%)
#ZONA FASCICULATA	(50)	(49)	(47)	(50)	(48)
HEMATOPOIESIS					1 (2%)
#THYMUS	(31)	(34)	(36)	(37)	(27)
EMBRYONAL DUCT CYST					1 (4%)
CONGESTION, NOS				1 (3%)	
HEMORRHAGE		1 (3%)	1 (3%)		
INFLAMMATION, ACUTE/CHRONIC				1 (3%)	
DEPLETION, LYMPHOID	6 (19%)	14 (41%)	12 (33%)	7 (19%)	10 (37%)
HYPERPLASIA, LYMPHOID	5 (16%)	7 (21%)	3 (8%)	5 (14%)	
#THYMIC CORTEX	(31)	(34)	(36)	(37)	(27)
DEPLETION, LYMPHOID	2 (6%)		1 (3%)		3 (11%)
#THYMIC LYMPHOCYTES	(31)	(34)	(36)	(37)	(27)
NECROSIS, FOCAL		1 (3%)	1 (3%)	2 (5%)	2 (7%)
NECROSIS, DIFFUSE		1 (3%)			
LEUKOCYTOSIS, NOS		1 (3%)			
CIRCULATORY SYSTEM					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
PERIARTERITIS				1 (2%)	
#MANDIBULAR L. NODE	(36)	(37)	(41)	(40)	(42)
LYMPHANGIECTASIS		1 (3%)	1 (2%)		1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
CIRCULATORY SYSTEM (Continued)					
#LUNG	(50)	(50)	(50)	(50)	(50)
THROMBUS, FIBRIN		1 (2%)			
#HEART	(50)	(49)	(49)	(50)	(49)
INFLAMMATION, ACTIVE CHRONIC				1 (2%)	
BACTERIAL SEPTICEMIA					1 (2%)
#BASE OF HEART	(50)	(49)	(49)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL					1 (2%)
#LEFT VENTRICLE	(50)	(49)	(49)	(50)	(49)
DILATATION, NOS		1 (2%)			
#MYOCARDIUM	(50)	(49)	(49)	(50)	(49)
MINERALIZATION	2 (4%)	1 (2%)	1 (2%)		
LYMPHOCYTIC INFLAM INFILTR	1 (2%)				
INFLAMMATION, ACUTE FOCAL					1 (2%)
INFLAMMATION, ACTIVE CHRONIC	1 (2%)				
ABSCESS, CHRONIC					1 (2%)
INFLAMMATION GRANULO FOCAL					1 (2%)
PERIARTERITIS	1 (2%)		1 (2%)		
PERIVASCULITIS			1 (2%)		
DEGENERATION, NOS	4 (8%)	3 (6%)	7 (14%)	3 (6%)	1 (2%)
NECROSIS, FOCAL					1 (2%)
#MYOCARDIUM/RT. VENTR	(50)	(49)	(49)	(50)	(49)
HEMORRHAGE				1 (2%)	
INFLAMMATION, ACUTE FOCAL				1 (2%)	
*PERIAORTIC TISSUE	(50)	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)				
*CEREBRAL ARTERY	(50)	(50)	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)			
*UTERINE ARTERY	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS		1 (2%)			
NECROSIS, FIBRINOID		1 (2%)			
*OVARIAN ARTERY	(50)	(50)	(50)	(50)	(50)
NECROSIS, FIBRINOID		1 (2%)			
#SALIVARY GLAND	(50)	(49)	(47)	(47)	(50)
PERIVASCULITIS		1 (2%)			
#HEPATIC SINUSOID	(44)	(45)	(44)	(47)	(47)
DILATATION, NOS		1 (2%)			
AMYLOIDOSIS			1 (2%)		2 (4%)
#UTERUS	(49)	(50)	(49)	(49)	(48)
THROMBUS, ORGANIZED		2 (4%)			
#OVARY	(49)	(50)	(50)	(49)	(47)
THROMBUS, ORGANIZED		2 (4%)			
#ZONA FASCICULATA	(50)	(49)	(47)	(50)	(48)
PERIVASCULITIS		1 (2%)			
DIGESTIVE SYSTEM					
*TONGUE	(50)	(50)	(50)	(50)	(50)
EDEMA, NOS		1 (2%)			
#SALIVARY GLAND	(50)	(49)	(47)	(47)	(50)
HEMORRHAGE				1 (2%)	
ATROPHY, FOCAL					1 (2%)
#LIVER	(44)	(45)	(44)	(47)	(47)
HEMORRHAGE				1 (2%)	
LYMPHOCYTIC INFLAM INFILTR	1 (2%)	5 (11%)		1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)	1 (2%)			1 (2%)
INFLAMMATION, ACUTE/CHRONIC					1 (2%)
INFLAMMATION GRANULO FOCAL	5 (11%)	3 (7%)	4 (9%)	2 (4%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
DIGESTIVE SYSTEM					
#LIVER (Continued)	(44)	(45)	(44)	(47)	(47)
NECROSIS, FOCAL			2 (5%)		
AMYLOIDOSIS			1 (2%)		4 (9%)
PIGMENTATION, NOS	2 (5%)	1 (2%)			
BASOPHILIC CYTO CHANGE		1 (2%)			
EOSINOPHILIC CYTO CHANGE	1 (2%)		1 (2%)		
CELL-SIZE ALTERATION					1 (2%)
#PORTAL TRACT	(44)	(45)	(44)	(47)	(47)
AMYLOIDOSIS			1 (2%)		
PIGMENTATION, NOS		1 (2%)			
#LIVER/CENTRILOBULAR	(44)	(45)	(44)	(47)	(47)
INFLAMMATION, ACTIVE CHRONIC				1 (2%)	
NECROSIS, FOCAL				1 (2%)	1 (2%)
#LIVER/KUPFFER CELL	(44)	(45)	(44)	(47)	(47)
AMYLOIDOSIS				2 (4%)	
#LIVER/HEPATOCYTES	(44)	(45)	(44)	(47)	(47)
DEGENERATION, NOS	9 (20%)	17 (38%)	8 (18%)	7 (15%)	1 (2%)
NECROSIS, FOCAL	8 (18%)	8 (18%)	13 (30%)	7 (15%)	13 (28%)
CYTOPLASMIC VACUOLIZATION				2 (4%)	
CELL-SIZE ALTERATION	11 (25%)	6 (13%)	6 (14%)	7 (15%)	1 (2%)
*GALLBLADDER	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS	1 (2%)			1 (2%)	
DISTENTION			2 (4%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)				
*GALLBLADDER/MUCOSA	(50)	(50)	(50)	(50)	(50)
HYPERPLASIA, CYSTIC			1 (2%)		
#BILE DUCT	(44)	(45)	(44)	(47)	(47)
CYST, NOS	1 (2%)	1 (2%)			
MULTIPLE CYSTS		2 (4%)			
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)		
#PANCREAS	(50)	(48)	(46)	(46)	(48)
DILATATION/DUCTS	1 (2%)				
HEMORRHAGE	1 (2%)				
INFLAMMATION, ACUTE FOCAL					1 (2%)
FIBROSIS, FOCAL				1 (2%)	
#PANCREATIC ACINUS	(50)	(48)	(46)	(46)	(48)
NECROSIS, FOCAL					1 (2%)
ATROPHY, NOS				1 (2%)	
ATROPHY, FOCAL	1 (2%)		1 (2%)		
#ESOPHAGUS	(49)	(50)	(49)	(49)	(49)
DILATATION, NOS			1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)		1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)		
#GLANDULAR STOMACH	(43)	(43)	(43)	(45)	(46)
MINERALIZATION					1 (2%)
DIVERTICULUM		1 (2%)	1 (2%)	2 (4%)	
LYMPHOCYTIC INFLAM INFILTR	1 (2%)	2 (5%)			
ULCER, ACUTE			1 (2%)		
NECROSIS, FOCAL					1 (2%)
DYSPLASIA, NOS	28 (65%)	35 (81%)	11 (26%)	25 (56%)	12 (26%)
#FORESTOMACH	(43)	(43)	(43)	(45)	(46)
EPIDERMAL INCLUSION CYST			2 (5%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)			
HYPERKERATOSIS	2 (5%)	4 (9%)		1 (2%)	2 (4%)
ACANTHOSIS	1 (2%)	2 (5%)	1 (2%)		
DYSPLASIA, NOS				1 (2%)	
#JEJUNUM	(34)	(38)	(43)	(34)	(37)
AMYLOIDOSIS			1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
DIGESTIVE SYSTEM (Continued)					
#JEJUNAL SUBMUCOSA	(34)	(38)	(43)	(34)	(37)
EDEMA, NOS		1 (3%)			
AMYLOIDOSIS		1 (3%)	1 (2%)		
#COLON	(40)	(43)	(44)	(42)	(45)
CAST, NOS					1 (2%)
INFLAMMATION, ACUTE FOCAL					1 (2%)
PARASITISM	6 (15%)	4 (9%)	8 (18%)	8 (19%)	7 (16%)
AMYLOIDOSIS		1 (2%)			
#COLONIC SUBMUCOSA	(40)	(43)	(44)	(42)	(45)
NECROSIS, NOS				1 (2%)	
#CECUM	(40)	(43)	(44)	(42)	(45)
EDEMA, NOS		1 (2%)			
URINARY SYSTEM					
#KIDNEY	(47)	(49)	(47)	(49)	(48)
HYDRONEPHROSIS	1 (2%)	1 (2%)	2 (4%)	1 (2%)	
GLOMERULONEPHRITIS, FOCAL				1 (2%)	1 (2%)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)	4 (8%)	7 (15%)	1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE					1 (2%)
GLOMERULONEPHRITIS, SUBACUTE				2 (4%)	1 (2%)
GLOMERULONEPHRITIS, CHRONIC				1 (2%)	1 (2%)
PYELONEPHRITIS, CHRONIC					1 (2%)
PLASMA-CELL INFILTRATE					1 (2%)
NEPHROPATHY	20 (43%)	30 (61%)	23 (49%)	18 (37%)	11 (23%)
BACTERIAL SEPTICEMIA					1 (2%)
DEGENERATION, NOS				1 (2%)	
GLOMERULOSCLEROSIS, NOS		1 (2%)			1 (2%)
INFARCT, FOCAL					1 (2%)
INFARCT, ACUTE					1 (2%)
AMYLOIDOSIS					1 (2%)
HYPERPLASIA, TUBULAR CELL					1 (2%)
HISTIOCYTOSIS	1 (2%)				
#KIDNEY/INTERSTITIUM	(47)	(49)	(47)	(49)	(48)
INFLAMMATION, ACTIVE CHRONIC	1 (2%)		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC					2 (4%)
INFLAMMATION, CHRONIC FOCAL					1 (2%)
#KIDNEY/CORTEX	(47)	(49)	(47)	(49)	(48)
CYST, NOS	1 (2%)		2 (4%)	1 (2%)	
MULTIPLE CYSTS	1 (2%)		1 (2%)		
INFARCT, FOCAL	1 (2%)				1 (2%)
#KIDNEY/MEDULLA	(47)	(49)	(47)	(49)	(48)
INFLAMMATION, INTERSTITIAL				1 (2%)	
GRANULOMA, NOS		1 (2%)			
#KIDNEY/GLOMERULUS	(47)	(49)	(47)	(49)	(48)
AMYLOIDOSIS	1 (2%)		4 (9%)		1 (2%)
#BOWMAN'S CAPSULE	(47)	(49)	(47)	(49)	(48)
DILATATION, NOS			2 (4%)	1 (2%)	
#KIDNEY/TUBULE	(47)	(49)	(47)	(49)	(48)
MINERALIZATION					4 (8%)
DILATATION, NOS	3 (6%)	3 (6%)	10 (21%)	6 (12%)	6 (13%)
CAST, NOS				1 (2%)	
CYST, NOS		1 (2%)			
MULTIPLE CYSTS				1 (2%)	
DEGENERATION, NOS			1 (2%)		1 (2%)
PIGMENTATION, NOS	1 (2%)			1 (2%)	
REGENERATION, NOS			1 (2%)	1 (2%)	
#HENLES LOOP/DESCEND.	(47)	(49)	(47)	(49)	(48)
CAST, NOS					1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF o-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	o-PP (b)	DMBA/ o-PP (c)	DMBA/ TPA (d)
URINARY SYSTEM (Continued)					
#CONVOLUTED TUBULES	(47)	(49)	(47)	(49)	(48)
DILATATION, NOS					1 (2%)
*URETER	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC				1 (2%)	
#URINARY BLADDER	(37)	(39)	(42)	(41)	(43)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)		
INFLAMMATION, ACUTE/CHRONIC					1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (3%)			
HYPERPLASIA, EPITHELIAL		4 (10%)			
#U. BLADDER/MUCOSA	(37)	(39)	(42)	(41)	(43)
DEGENERATION, BALLOONING			1 (2%)		
NECROSIS, CYTODEGENERATIVE			1 (2%)		
#U. BLADDER/SUBMUCOSA	(37)	(39)	(42)	(41)	(43)
EDEMA, NOS			1 (2%)		
ENDOCRINE SYSTEM					
#PITUITARY	(45)	(44)	(37)	(42)	(37)
HYPERPLASIA, FOCAL			1 (3%)	1 (2%)	
#ANTERIOR PITUITARY	(45)	(44)	(37)	(42)	(37)
CONGESTION, NOS			1 (3%)		
#ADRENAL	(50)	(49)	(47)	(50)	(48)
CONGESTION, NOS		1 (2%)			
#ADRENAL/CAPSULE	(50)	(49)	(47)	(50)	(48)
NECROSIS, FOCAL				1 (2%)	
HYPERPLASIA, FOCAL	25 (50%)	36 (73%)	30 (64%)	24 (48%)	8 (17%)
#ZONA FASCICULATA	(50)	(49)	(47)	(50)	(48)
CONGESTION, NOS		1 (2%)	1 (2%)	1 (2%)	
HEMORRHAGE	1 (2%)				
DEGENERATION, NOS	7 (14%)				
DEGENERATION, LIPOID	4 (8%)	26 (53%)	24 (51%)	11 (22%)	8 (17%)
NECROSIS, FOCAL	1 (2%)				
CYTOPLASMIC CHANGE, NOS	1 (2%)			1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)				
FOCAL CELLULAR CHANGE		2 (4%)	1 (2%)		
CELL-SIZE ALTERATION				2 (4%)	
ATROPHY, NOS				1 (2%)	
HYPERTROPHY, FOCAL	1 (2%)				
HYPERPLASIA, FOCAL	2 (4%)				
#ADRENAL MEDULLA	(50)	(49)	(47)	(50)	(48)
MINERALIZATION			1 (2%)		
DEGENERATION, NOS	1 (2%)				
DEGENERATION, LIPOID			2 (4%)		
NECROSIS, FOCAL	1 (2%)				
PIGMENTATION, NOS		1 (2%)			
PHAGOCYTIC CELL				1 (2%)	
HYPERPLASIA, NOS			1 (2%)		
HYPERPLASIA, FOCAL			3 (6%)		
#THYROID	(47)	(47)	(46)	(43)	(42)
EMBRYONAL DUCT CYST	1 (2%)				
FOLLICULAR CYST, NOS	2 (4%)	6 (13%)	12 (26%)	4 (9%)	3 (7%)
LYMPHOCYTIC INFLAM INFILTR			1 (2%)		
INFLAMMATION GRANULO FOCAL			1 (2%)		
AMYLOIDOSIS			2 (4%)		
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)	2 (4%)	1 (2%)	1 (2%)	
#THYROID FOLLICLE	(47)	(47)	(46)	(43)	(42)
DILATATION, NOS		1 (2%)			
RETENTION OF CONTENT		1 (2%)			
MULTIPLE CYSTS	4 (9%)	8 (17%)	8 (17%)	3 (7%)	2 (5%)
CRYSTALS, NOS			1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
ENDOCRINE SYSTEM (Continued)					
#THYROID PARAFOLLICULAR CELLS	(47)	(47)	(46)	(43)	(42)
AMYLOIDOSIS				1 (2%)	
#PARATHYROID	(30)	(25)	(12)	(26)	(16)
HYPERPLASIA, FOCAL		1 (4%)			
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(50)	(50)	(50)	(50)	(50)
DILATATION/DUCTS	3 (6%)		1 (2%)	3 (6%)	
MULTIPLE CYSTS					1 (2%)
INFLAMMATION, ACUTE FOCAL					2 (4%)
INFLAMMATION, ACTIVE CHRONIC		1 (2%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)		
FIBROSIS, MULTIFOCAL					1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)			
HYPERPLASIA, FOCAL	1 (2%)			1 (2%)	
HYPERPLASIA, CYSTIC	1 (2%)				
*MAMMARY ACINUS	(50)	(50)	(50)	(50)	(50)
DILATATION, NOS				1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)			
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)	3 (6%)	1 (2%)
HYPERPLASIA, CYSTIC		3 (6%)	1 (2%)	1 (2%)	4 (8%)
*CLITORAL GLAND	(50)	(50)	(50)	(50)	(50)
DILATATION/DUCTS		1 (2%)			
#UTERUS	(49)	(50)	(49)	(49)	(48)
DILATATION, NOS	2 (4%)	2 (4%)		2 (4%)	
HEMORRHAGE	2 (4%)				
HEMATOMA, ORGANIZED	1 (2%)				
HEMORRHAGE, CHRONIC			2 (4%)		
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)				
INFLAMMATION, CHRONIC		1 (2%)			
FIBROSIS, MULTIFOCAL					1 (2%)
ANGIECTASIS		1 (2%)	1 (2%)		
#CERVIX UTERI	(49)	(50)	(49)	(49)	(48)
INFLAMMATION, CHRONIC FOCAL			1 (2%)		
#ENDOMETRIAL GLAND	(49)	(50)	(49)	(49)	(48)
MULTIPLE CYSTS	4 (8%)	1 (2%)			2 (4%)
HYPERPLASIA, FOCAL					2 (4%)
HYPERPLASIA, CYSTIC	36 (73%)	37 (74%)	39 (80%)	33 (67%)	19 (40%)
METAPLASIA, SQUAMOUS	1 (2%)	2 (4%)	2 (4%)		
#ENDOMETRIAL STROMA	(49)	(50)	(49)	(49)	(48)
HYPERPLASIA, DIFFUSE			1 (2%)		
#FALLOPIAN TUBE	(49)	(50)	(49)	(49)	(48)
INFLAMMATION, ACUTE FOCAL	1 (2%)				
INFLAMMATION, CHRONIC FOCAL				1 (2%)	
#OVARY	(49)	(50)	(50)	(49)	(47)
MINERALIZATION			1 (2%)		
FOLLICULAR CYST, NOS	17 (35%)	29 (58%)	32 (64%)	27 (55%)	20 (43%)
PAROVARIAN CYST	3 (6%)	3 (6%)	4 (8%)	1 (2%)	
HEMORRHAGIC CYST		2 (4%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)			

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
REPRODUCTIVE SYSTEM					
#OVARY (Continued)	(49)	(50)	(50)	(49)	(47)
DEGENERATION, NOS		2 (4%)	1 (2%)		
NECROSIS, FOCAL		1 (2%)			
AMYLOIDOSIS					1 (2%)
PIGMENTATION, NOS		4 (8%)		1 (2%)	
ATROPHY, SENILE	1 (2%)				
HYPERPLASIA, TUBULAR CELL		1 (2%)			
HYPERPLASIA, EPITHELIAL			1 (2%)		
ANGIECTASIS				1 (2%)	
#OVARY/CAPSULE	(49)	(50)	(50)	(49)	(47)
MULTIPLE CYSTS		2 (4%)			
#OVARY/FOLLICLE	(49)	(50)	(50)	(49)	(47)
MULTIPLE CYSTS	23 (47%)	11 (22%)	8 (16%)	7 (14%)	5 (11%)
HEMORRHAGE	1 (2%)				
HEMORRHAGIC CYST	3 (6%)			3 (6%)	
INFLAMMATION, ACTIVE CHRONIC					1 (2%)
NECROSIS, FOCAL	9 (18%)	2 (4%)	11 (22%)	6 (12%)	14 (30%)
HYPERPLASIA, EPITHELIAL	3 (6%)				
NERVOUS SYSTEM					
#CEREBRUM	(46)	(48)	(47)	(47)	(50)
INFLAMMATION, MULTIFOCAL					1 (2%)
PERIVASCULAR CUFFING					1 (2%)
ATROPHY, PRESSURE		1 (2%)			
#BRAIN	(46)	(48)	(47)	(47)	(50)
HYDROCEPHALUS, NOS			1 (2%)		
CONGESTION, NOS	1 (2%)				
#PREOPTIC AREA	(46)	(48)	(47)	(47)	(50)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)				
SPECIAL SENSE ORGANS					
*EYE	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC	1 (2%)				
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)			
*HARDERIAN GLAND	(50)	(50)	(50)	(50)	(50)
RETENTION OF CONTENT				1 (2%)	
LYMPHOCYTIC INFLAM INFILTR				1 (2%)	
MUSCULOSKELETAL SYSTEM					
*FEMUR	(50)	(50)	(50)	(50)	(50)
OSTEOSCLEROSIS		4 (8%)			
*KNEE JOINT	(50)	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL				1 (2%)	
*ABDOMINAL MUSCLE	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL					1 (2%)
BODY CAVITIES					
*THORACIC CAVITY	(50)	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAM INFILTR			1 (2%)		
*MEDIASTINUM	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC		2 (4%)			

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-PP (b)	DMBA/ *o*-PP (c)	DMBA/ TPA (d)
BODY CAVITIES (Continued)					
*PERITONEUM	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC			1 (2%)		
*PLEURA	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC	2 (4%)				
FIBROSIS, MULTIFOCAL			1 (2%)		
*PERICARDIUM	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACTIVE CHRONIC	1 (2%)	1 (2%)			
*EPICARDIUM	(50)	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL					1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)	1 (2%)	
HYPERPLASIA, MESOTHELIAL				1 (2%)	
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAM INFILTR		1 (2%)			
NECROSIS, FOCAL	1 (2%)				
AMYLOIDOSIS	2 (4%)	3 (6%)		2 (4%)	1 (2%)
SPECIAL MORPHOLOGY SUMMARY					
NO LESION REPORTED					1
AUTO/NECROPSY/HISTO PERF	1				

* NUMBER OF ANIMALS NECROPSIED
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN TISSUES IS COUNTED ONCE ONLY

APPENDIX C

ANALYSES OF PRIMARY TUMORS IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

TABLE C1. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL

	Vehicle Control	DMBA (a)	*o*-Phenyl-phenol (b)	DMBA/ *o*-Phenyl-phenol (c)	DMBA/ TPA (d)
Skin: Basal Cell Tumor or Carcinoma					
Overall Rates (e)	0/50 (0%)	1/50 (2%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (f)	0.0%	5.0%	0.0%	18.2%	2.4%
Terminal Rates (g)	0/19 (0%)	1/20 (5%)	0/16 (0%)	1/15 (7%)	0/0
Life Table Test (h)		P=0.510	(i)	P=0.031	P=0.460
Incidental Tumor Test (h)		P=0.510	(i)	P=0.039	(j)
Fisher Exact Test (h)		P=0.500	(i)	P=0.059	P=0.500
Skin: Squamous Cell Papilloma					
Overall Rates (e)	0/50 (0%)	1/50 (2%)	0/50 (0%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (f)	0.0%	5.0%	0.0%	20.0%	70.4%
Terminal Rates (g)	0/19 (0%)	1/20 (5%)	0/16 (0%)	2/15 (13%)	0/0
Life Table Test (h)		P=0.510	(i)	P=0.035	P<0.001
Incidental Tumor Test (h)		P=0.510	(i)	P=0.060	(j)
Fisher Exact Test (h)		P=0.500	(i)	P=0.059	P=0.006
Skin: Squamous Cell Carcinoma					
Overall Rates (e)	0/50 (0%)	4/50 (8%)	0/50 (0%)	1/50 (2%)	13/50 (26%)
Adjusted Rates (f)	0.0%	11.6%	0.0%	2.9%	76.2%
Terminal Rates (g)	0/19 (0%)	0/20 (0%)	0/16 (0%)	0/15 (0%)	0/0
Life Table Test (h)		P=0.070	(i)	P=0.454	P<0.001
Incidental Tumor Test (h)		P=0.055	(i)	P=0.523	(j)
Fisher Exact Test (h)		P=0.059	(i)	P=0.500	P<0.001
Skin: Squamous Cell Papilloma or Carcinoma					
Overall Rates (e)	0/50 (0%)	5/50 (10%)	0/50 (0%)	5/50 (10%)	18/50 (36%)
Adjusted Rates (f)	0.0%	16.0%	0.0%	22.3%	91.3%
Terminal Rates (g)	0/19 (0%)	1/20 (5%)	0/16 (0%)	2/15 (13%)	0/0
Life Table Test (h)		P=0.040	(i)	P=0.017	P<0.001
Incidental Tumor Test (h)		P=0.031	(i)	P=0.033	(j)
Fisher Exact Test (h)		P=0.028	(i)	P=0.028	P<0.001
Skin: All Primary Tumors					
Overall Rates (e)	0/50 (0%)	6/50 (12%)	0/50 (0%)	9/50 (18%)	19/50 (38%)
Adjusted Rates (f)	0.0%	18.2%	0.0%	37.3%	91.5%
Terminal Rates (g)	0/19 (0%)	1/20 (5%)	0/16 (0%)	3/15 (20%)	0/0
Life Table Tests (h)	P<0.001	P=0.022	(h)	P<0.001	P<0.001
Incidental Tumor Tests (h)	P<0.001	P=0.018	(h)	P=0.001	(j)
Fisher Exact Test (h)		P=0.013	(h)	P=0.001	P<0.001
Lung: Alveolar/Bronchiolar Adenoma					
Overall Rates (e)	9/50 (18%)	11/50 (22%)	10/50 (20%)	9/50 (18%)	2/50 (4%)
Adjusted Rates (f)	36.5%	42.9%	42.5%	45.7%	66.7%
Terminal Rates (g)	5/19 (26%)	6/20 (30%)	4/16 (25%)	5/15 (33%)	0/0
Life Table Test (h)		P=0.416	P=0.321	P=0.319	P=0.003
Incidental Tumor Test (h)		P=0.416	P=0.237	P=0.328	(j)
Fisher Exact Test (h)		P=0.402	P=0.500	P=0.602	P=0.026N
Lung: Alveolar/Bronchiolar Carcinoma					
Overall Rates (e)	6/50 (12%)	5/50 (10%)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (f)	23.9%	17.6%	19.8%	9.7%	0.0%
Terminal Rates (g)	2/19 (11%)	2/20 (10%)	1/16 (6%)	1/15 (7%)	0/0
Life Table Test (h)		P=0.493N	P=0.489N	P=0.273N	(k)
Incidental Tumor Test (h)		P=0.496N	P=0.576N	P=0.293N	(j)
Fisher Exact Test (h)		P=0.500N	P=0.370N	P=0.134N	P=0.013N

TABLE C1. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-Phenyl-phenol (b)	DMBA/ *o*-Phenyl-phenol (c)	DMBA/ TPA (d)
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma					
Overall Rates (e)	13/50 (26%)	16/50 (32%)	13/50 (26%)	11/50 (22%)	2/50 (4%)
Adjusted Rates (f)	48.4%	55.2%	52.1%	52.7%	66.7%
Terminal Rates (g)	6/19 (32%)	8/20 (40%)	5/16 (31%)	6/15 (40%)	0/0
Life Table Test (h)		P=0.354	P=0.377	P=0.429	P=0.003
Incidental Tumor Test (h)		P=0.333	P=0.254	P=0.382	(j)
Fisher Exact Test (h)		P=0.330	P=0.590	P=0.408N	P=0.002N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type					
Overall Rates (e)	0/50 (0%)	5/50 (10%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (f)	0.0%	15.5%	6.3%	3.8%	6.3%
Terminal Rates (g)	0/19 (0%)	2/20 (10%)	1/16 (6%)	0/15 (0%)	0/0
Life Table Test (h)		P=0.039	P=0.466	P=0.435	P=0.158
Incidental Tumor Test (h)		P=0.024	P=0.466	P=0.545	(j)
Fisher Exact Test (h)		P=0.028	P=0.500	P=0.500	P=0.247
Hematopoietic System: Malignant Lymphoma, Histiocytic Type					
Overall Rates (e)	5/50 (10%)	2/50 (4%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (f)	15.2%	5.8%	17.5%	3.6%	0.0%
Terminal Rates (g)	1/19 (5%)	0/20 (0%)	2/16 (13%)	0/15 (0%)	0/0
Life Table Test (h)		P=0.220N	P=0.627N	P=0.201N	P=0.554N
Incidental Tumor Test (h)		P=0.199N	P=0.594N	P=0.069N	(j)
Fisher Exact Test (h)		P=0.218N	P=0.500N	P=0.102N	P=0.028N
Hematopoietic System: Lymphoma, All Malignant					
Overall Rates (e)	(l)8/50 (16%)	8/50 (16%)	6/50 (12%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (f)	25.4%	24.8%	25.7%	14.1%	6.3%
Terminal Rates (g)	2/19 (11%)	3/20 (15%)	3/16 (19%)	0/15 (0%)	0/0
Life Table Test (h)		P=0.584N	P=0.542N	P=0.362N	P=0.497N
Incidental Tumor Test (h)		P=0.598N	P=0.451	P=0.168N	(j)
Fisher Exact Test (h)		P=0.607	P=0.387N	P=0.178N	P=0.046N
Circulatory System: Hemangiosarcoma					
Overall Rates (e)	2/50 (4%)	(m) 3/50 (6%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (f)	8.6%	11.3%	10.3%	0.0%	0.0%
Terminal Rates (g)	1/19 (5%)	1/20 (5%)	1/16 (6%)	0/15 (0%)	0/0
Life Table Test (h)		P=0.509	P=0.640	P=0.316	(k)
Incidental Tumor Test (h)		P=0.503	P=0.604	P=0.377	(j)
Fisher Exact Test (h)		P=0.500	P=0.691	P=0.247N	P=0.247N
Liver: Hepatocellular Adenoma					
Overall Rates (e)	7/47 (15%)	11/48 (23%)	6/48 (13%)	3/46 (7%)	3/47 (6%)
Adjusted Rates (f)	26.0%	43.1%	32.7%	14.9%	65.4%
Terminal Rates (g)	3/19 (16%)	7/20 (35%)	4/16 (25%)	1/15 (7%)	0/0
Life Table Test (h)		P=0.247	P=0.588	P=0.321	P=0.002
Incidental Tumor Test (h)		P=0.251	P=0.529	P=0.315	(j)
Fisher Exact Test (h)		P=0.231	P=0.483N	P=0.167N	P=0.158N
Adrenal: Adenoma					
Overall Rates (e)	3/49 (6%)	4/49 (8%)	1/45 (2%)	2/48 (4%)	0/49 (0%)
Adjusted Rates (f)	14.6%	15.1%	4.2%	6.8%	0.0%
Terminal Rates (g)	2/19 (11%)	2/20 (10%)	0/16 (0%)	0/15 (0%)	0/0
Life Table Test (h)		P=0.510N	P=0.371	P=0.627N	(i)
Incidental Tumor Test (h)		P=0.516N	P=0.432	P=0.610N	(j)
Fisher Exact Test (h)		P=0.500	P=0.341N	P=0.510N	P=0.121N

TABLE C1. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-Phenyl-phenol (b)	DMBA/ *o*-Phenyl-phenol (c)	DMBA/ TPA (d)
Liver: Hepatocellular Carcinoma					
Overall Rates (e)	4/47 (9%)	3/48 (6%)	3/48 (6%)	5/46 (11%)	1/47 (2%)
Adjusted Rates (f)	19.5%	11.3%	18.8%	21.9%	33.3%
Terminal Rates (g)	3/19 (16%)	1/20 (5%)	3/16 (19%)	1/15 (7%)	0/0
Life Table Test (h)		P=0.479	P=0.594N	P=0.310N	P=0.059
Incidental Tumor Test (h)		P=0.468	P=0.602N	P=0.319N	(j)
Fisher Exact Test (h)		P=0.488N	P=0.488N	P=0.486	P=0.181N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall Rates (e)	11/47 (23%)	14/48 (29%)	9/48 (19%)	8/46 (17%)	4/47 (9%)
Adjusted Rates (f)	42.5%	51.1%	49.5%	33.8%	76.9%
Terminal Rates (g)	6/19 (32%)	8/20 (40%)	7/16 (44%)	2/15 (13%)	0/0
Life Table Test (h)		P=0.363	P=0.583N	P=0.595N	P<0.001
Incidental Tumor Test (h)		P=0.374	P=0.564	P=0.603	(j)
Fisher Exact Test (h)		P=0.343	P=0.380N	P=0.323N	P=0.044N
Adrenal: Cortical Adenoma					
Overall Rates (e)	3/49 (6%)	2/49 (4%)	0/45 (0%)	2/48 (4%)	0/49 (0%)
Adjusted Rates (f)	14.6%	8.0%	0.0%	6.8%	0.0%
Terminal Rates (g)	2/19 (11%)	1/20 (5%)	0/16 (0%)	0/15 (0%)	0/0
Life Table Test (h)		P=0.493N	P=0.156N	P=0.627N	(k)
Incidental Tumor Test (h)		P=0.486N	P=0.175N	P=0.610N	(j)
Fisher Exact Test (h)		P=0.500N	P=0.137N	P=0.510N	P=0.121N

(a) Administered a single dose of 0.05 mg 7,12-dimethylbenz(*a*)anthracene (DMBA) in acetone
(b) Administered 55.5 mg *o*-phenylphenol in acetone 3 × week
(c) Administered a single dose of DMBA and 55.5 mg *o*-phenylphenol in acetone 3 × week
(d) Administered a single dose of DMBA and 0.005 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) in acetone 3 × week
(e) Number of tumor-bearing animals/number of animals examined at the site
(f) Kaplan-Meier tumor incidences at the end of the study after adjusting for intercurrent mortality
(g) Observed tumor incidence at terminal kill
(h) 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 Fisher exact test compares directly the overall incidence rates. A lower incidence in a dosed group is indicated by (N).
(i) No P value is reported because no tumors were observed in the vehicle control and dosed groups.
(j) Analysis not performed because of poor survival in this group; no dosed animals were alive in the last two time intervals.
(k) Analysis not performed; all dosed animals died before first tumor was observed in the vehicle controls.
(l) Includes five histiocytic, two mixed types, and one undifferentiated
(m) Includes one hemangiosarcoma, uncertain primary or metastatic

TABLE C2. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL

	Vehicle Control	DMBA (a)	*o*-Phenyl-phenol (b)	DMBA/ *o*-Phenyl-phenol (c)	DMBA/ TPA (d)
Skin: Basal Cell Carcinoma					
Overall Rates (e)	0/50 (0%)	2/50 (4%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (f)	0.0%	9.2%	0.0%	19.6 %	13.0%
Terminal Rates (g)	0/11 (0%)	1/16 (6%)	0/15 (0%)	1/7 (14%)	0/0
Life Table Tests (h)		P=0.288	(i)	P=0.083	P=0.072
Incidental Tumor Tests (h)		P=0.334	(i)	P=0.122	(j)
Fisher Exact Test (h)		P=0.247	(i)	P=0.121	P=0.247
Skin: Squamous Cell Papilloma					
Overall Rates (e)	0/50 (0%)	4/50 (8%)	0/50 (0%)	2/50 (4%)	17/50 (34%)
Adjusted Rates (f)	0.0%	17.7%	0.0%	28.6%	70.8%
Terminal Rates (g)	0/11 (0%)	2/16 (13%)	0/15 (0%)	2/7 (29%)	0/0
Life Table Test (h)		P=0.094	(i)	P=0.140	P<0.001
Incidental Tumor Tests (h)		P=0.088	(i)	P=0.140	(j)
Fisher Exact Test (h)		P=0.059	(i)	P=0.247	P<0.001
Skin: Squamous Cell Carcinoma					
Overall Rates (e)	0/50 (0%)	3/50 (6%)	0/50 (0%)	3/50 (6%)	18/50 (36%)
Adjusted Rates (f)	0.0%	13.6%	0.0%	9.5%	83.2%
Terminal Rates (g)	0/11 (0%)	0/16 (0%)	0/15 (0%)	0/7 (0%)	0/0
Life Table Test (h)		P=0.151	(i)	P=0.098	P<0.001
Incidental Tumor Tests (h)		P=0.087	(i)	P=0.187	(j)
Fisher Exact Test (h)		P=0.121	(i)	P=0.121	P<0.001
Skin: Squamous Cell Papilloma or Carcinoma					
Overall Rates (e)	0/50 (0%)	7/50 (14%)	0/50 (0%)	5/50 (10%)	31/50 (62%)
Adjusted Rates (f)	0.0%	28.9%	0.0%	35.3%	66.0%
Terminal Rates (g)	0/11 (0%)	2/16 (13%)	0/15 (0%)	2/7 (29%)	0/0
Life Table Test (h)		P=0.020	(i)	P=0.016	P<0.001
Incidental Tumor Tests (h)		P=0.010	(i)	P=0.034	(j)
Fisher Exact Test (h)		P=0.006	(i)	P=0.028	P<0.001
Skin: Keratoacanthoma					
Overall Rates (e)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (f)	0.0%	0.0%	0.0%	0.0%	27.0%
Terminal Rates (g)	0/11 (0%)	0/16 (0%)	0/15 (0%)	0/7 (0%)	0/0
Life Table Test (h)		(i)	(i)	(i)	P=0.001
Incidental Tumor Test (h)		(i)	(i)	(i)	(j)
Fisher Exact Test (h)		(i)	(i)	(i)	P=0.028
Skin: All Primary Tumors					
Overall Rates (e)	0/50 (0%)	9/50 (18%)	0/50 (0%)	8/50 (16%)	(k) 32/50 (64%)
Adjusted Rates (f)	0.0%	36.0%	0.0%	51.5%	91.3%
Terminal Rates (g)	0/11 (0%)	3/16 (19%)	0/15 (0%)	3/7 (43%)	0/0
Life Table Tests (h)	P<0.001	P=0.008	(h)	P=0.002	P<0.001
Incidental Tumor Tests (h)	P<0.001	P=0.004	(h)	P=0.005	(j)
Fisher Exact Test (h)		P=0.001	(h)	P=0.003	P<0.001
Subcutaneous Tissue: Fibrosarcoma					
Overall Rates (e)	0/50 (0%)	2/50 (4%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (f)	0.0%	12.5%	0.0%	0.0%	29.1%
Terminal Rates (g)	0/11 (0%)	2/16 (13%)	0/15 (0%)	0/7 (0%)	0/0
Life Table Test (h)		P=0.322	(i)	(i)	P=0.006
Incidental Tumor Test (h)		P=0.322	(i)	(i)	(j)
Fisher Exact Test (h)		P=0.247	(i)	(i)	P=0.121

TABLE C2. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-Phenyl-phenol (b)	DMBA/ *o*-Phenyl-phenol (c)	DMBA/ TPA (d)
Lung: Alveolar/Bronchiolar Adenoma					
Overall Rates (e)	5/50 (10%)	7/50 (14%)	7/50 (14%)	8/50 (16%)	2/50 (4%)
Adjusted Rates (f)	31.9%	26.0%	30.0%	50.8%	52.9%
Terminal Rates (g)	2/11 (18%)	2/16 (13%)	3/15 (20%)	2/7 (29%)	0/0
Life Table Test (h)		P=0.509	P=0.480	P=0.089	P=0.081
Incidental Tumor Test (h)		P=0.343	P=0.473	P=0.165	(j)
Fisher Exact Test (h)		P=0.380	P=0.380	P=0.277	P=0.218N
Lung: Alveolar/Bronchiolar Carcinoma					
Overall Rates (e)	3/50 (6%)	11/50 (22%)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (f)	15.3%	41.7%	6.7%	40.2%	7.7%
Terminal Rates (g)	1/11 (9%)	4/16 (25%)	1/15 (7%)	2/7 (29%)	0/0
Life Table Test (h)		P=0.056	P=0.269N	P=0.158N	P=0.263
Incidental Tumor Test (h)		P=0.060	P=0.125N	P=0.292N	(j)
Fisher Exact Test (h)		P=0.020	P=0.309N	P=0.357	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma					
Overall Rates (e)	8/50 (16%)	18/50 (36%)	8/50 (16%)	13/50 (26%)	3/50 (6%)
Adjusted Rates (f)	43.6%	58.9%	35.8%	75.4%	56.6%
Terminal Rates (g)	3/11 (27%)	6/16 (38%)	4/15 (27%)	4/7 (57%)	0/0
Life Table Test (h)		P=0.082	P=0.495N	P=0.024N	P=0.015
Incidental Tumor Test (h)		P=0.042	P=0.393N	P=0.072N	(j)
Fisher Exact Test (h)		P=0.020	P=0.607N	P=0.163	P=0.100N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type					
Overall Rates (e)	1/50 (2%)	4/50 (8%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (f)	4.0%	18.6%	15.1%	11.4%	2.6%
Terminal Rates (g)	0/11 (0%)	2/16 (13%)	2/15 (13%)	0/7 (0%)	0/0
Life Table Test (h)		P=0.251	P=0.346	P=0.222	P=0.449
Incidental Tumor Test (h)		P=0.238	P=0.491	P=0.350	(j)
Fisher Exact Test (h)		P=0.181	P=0.309	P=0.309	P=0.753
Hematopoietic System: Malignant Lymphoma, Histiocytic Type					
Overall Rates (e)	4/50 (8%)	1/50 (2%)	6/50 (12%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (f)	20.0%	2.8%	29.4%	32.8%	53.8%
Terminal Rates (g)	1/11 (9%)	0/16 (0%)	3/15 (20%)	1/7 (14%)	0/0
Life Table Test (h)		P=0.143N	P=0.474	P=0.193	P=0.027
Incidental Tumor Test (h)		P=0.211N	P=0.309	P=0.347	(j)
Fisher Exact Test (h)		P=0.181N	P=0.370	P=0.370	P=0.339N
Hematopoietic System: Malignant Lymphoma, Mixed Type					
Overall Rates (e)	4/50 (8%)	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (f)	23.1%	12.5%	2.3%	31.8%	0.0%
Terminal Rates (g)	1/11 (9%)	2/16 (13%)	0/15 (0%)	2/7 (29%)	0/0
Life Table Test (h)		P=0.226N	P=0.154N	P=0.582N	P=0.981
Incidental Tumor Test (h)		P=0.356N	P=0.324N	P=0.639N	(j)
Fisher Exact Test (h)		P=0.339N	P=0.181N	P=0.500N	P=0.059N
Hematopoietic System: Lymphoma, All Malignant					
Overall Rates (e)	(l)10/50 (20%)	7/50 (14%)	10/50 (20%)	13/50 (26%)	3/50 (6%)
Adjusted Rates (f)	42.8%	32.2%	43.6%	63.2%	55.1%
Terminal Rates (g)	2/11 (18%)	4/16 (25%)	5/15 (33%)	3/7 (43%)	0/0
Life Table Test (h)		P=0.176N	P=0.478N	P=0.106N	P=0.064
Incidental Tumor Test (h)		P=0.313	P=0.507N	P=0.279	(j)
Fisher Exact Test (h)		P=0.298N	P=0.598N	P=0.318	P=0.036N

TABLE C2. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-Phenyl-phenol (b)	DMBA/ *o*-Phenyl-phenol (c)	DMBA/ TPA (d)
Hematopoietic System: Lymphoma or Leukemia					
Overall Rates (e)	10/50 (20%)	7/50 (14%)	10/50 (20%)	13/50 (26%)	4/50 (8%)
Adjusted Rates (f)	42.8%	32.2%	43.6%	63.2%	57.0%
Terminal Rates (g)	2/11 (18%)	4/16 (25%)	5/15 (33%)	3/7 (43%)	0/0
Life Table Test (h)		P=0.176N	P=0.478N	P=0.106N	P=0.023
Incidental Tumor Test (h)		P=0.313	P=0.507N	P=0.279	(j)
Fisher Exact Test (h)		P=0.298N	P=0.598N	P=0.318	P=0.074N
Circulatory System: Hemangiosarcoma					
Overall Rates (e)	2/50 (4%)	3/50 (6%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (f)	12.9%	14.1%	10.0%	16.3%	0.0%
Terminal Rates (g)	1/11 (9%)	1/16 (6%)	0/15 (0%)	1/7 (14%)	0/0
Life Table Test (h)		P=0.559	P=0.502	P=0.536	(m)
Incidental Tumor Test (h)		P=0.435	P=0.511	P=0.591	(j)
Fisher Exact Test (h)		P=0.500	P=0.500	P=0.691	P=0.247N
Circulatory System: Hemangioma or Hemangiosarcoma					
Overall Rates (e)	2/50 (4%)	5/50 (10%)	5/50 (10%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (f)	12.9%	25.5%	19.8%	28.4%	33.3%
Terminal Rates (g)	1/11 (9%)	3/16 (19%)	1/15 (7%)	1/7 (14%)	0/0
Life Table Test (h)		P=0.303	P=0.231	P=0.152	P=0.051
Incidental Tumor Test (h)		P=0.210	P=0.283	P=0.239	(j)
Fisher Exact Test (h)		P=0.218	P=0.218	P=0.339	P=0.500N
Liver: Hepatocellular Adenoma					
Overall Rates (e)	0/44 (0%)	1/45 (2%)	(n) 3/44 (7%)	2/47 (4%)	0/47 (0%)
Adjusted Rates (f)	0.0%	5.9%	20.0%	19.3%	0.0%
Terminal Rates (g)	0/11 (0%)	0/15 (0%)	3/15 (20%)	1/7 (14%)	0/0
Life Table Test (h)		P=0.525	P=0.174	P=0.154	(i)
Incidental Tumor Test (h)		P=0.429	P=0.174	P=0.215	(i)
Fisher Exact Test (h)		P=0.506	P=0.121	P=0.264	(i)
Forestomach: Squamous Cell Papilloma					
Overall Rates (e)	3/43 (7%)	0/43 (0%)	0/43 (0%)	1/45 (2%)	0/45 (0%)
Adjusted Rates (f)	17.9%	0.0%	0.0%	3.1%	0.0%
Terminal Rates (g)	1/11 (9%)	0/16 (0%)	0/15 (0%)	0/7 (0%)	0/0
Life Table Test (h)		P=0.093N	P=0.100N	P=0.446N	P=0.998N
Incidental Tumor Test (h)		P=0.183N	P=0.217N	P=0.344N	(j)
Fisher Exact Test (h)		P=0.121N	P=0.121N	P=0.291N	P=0.112N
Mammary Gland: All Adenocarcinoma					
Overall Rates (e)	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (f)	12.6%	9.7%	6.7%	18.0%	7.1%
Terminal Rates (g)	0/11 (0%)	0/16 (0%)	1/15 (7%)	1/7 (14%)	0/0
Life Table Test (h)		P=0.644N	P=0.290N	P=0.675N	P=0.310N
Incidental Tumor Test (h)		P=0.591	P=0.363N	P=0.516N	(j)
Fisher Exact Test (h)		P=0.661N	P=0.309N	P=0.500N	P=0.309N
Uterus: Leiomyosarcoma					
Overall Rates (e)	3/49 (6%)	1/50 (2%)	0/49 (0%)	1/49 (2%)	0/48 (0%)
Adjusted Rates (f)	8.3%	6.3%	0.0%	4.2%	0.0%
Terminal Rates (g)	0/11 (0%)	1/16 (6%)	0/15 (0%)	0/7 (0%)	0/0
Life Table Test (h)		P=0.276N	P=0.138N	P=0.397N	P=0.682N
Incidental Tumor Test (h)		P=0.307N	P=0.166N	P=0.228N	(j)
Fisher Exact Test (h)		P=0.301N	P=0.121N	P=0.309N	P=0.125N

TABLE C2. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF *o*-PHENYLPHENOL (Continued)

	Vehicle Control	DMBA (a)	*o*-Phenyl-phenol (b)	DMBA/ *o*-Phenyl-phenol (c)	DMBA/ TPA (d)
Uterus: Leiomyoma or Leiomyosarcoma					
Overall Rates (e)	4/49 (8%)	2/50 (4%)	0/49 (0%)	1/49 (2%)	0/48 (0%)
Adjusted Rates (f)	14.9%	12.5%	0.0%	4.2%	0.0%
Terminal Rates (g)	0/11 (0%)	2/16 (13%)	0/15 (0%)	0/7 (0%)	0/0
Life Table Test (h)		P=0.276N	P=0.072N	P=0.295N	P=0.682N
Incidental Tumor Test (h)		P=0.348N	P=0.132N	P=0.154N	(j)
Fisher Exact Test (h)		P=0.329N	P=0.059N	P=0.181N	P=0.061N
Uterus: Endometrial Stromal Polyp					
Overall Rates (e)	2/49 (4%)	6/50 (12%)	3/49 (6%)	3/49 (6%)	1/48 (2%)
Adjusted Rates (f)	5.4%	25.2%	11.1%	27.5%	7.7%
Terminal Rates (g)	0/11 (0%)	2/16 (13%)	0/15 (0%)	1/7 (14%)	0/0
Life Table Test (h)		P=0.192	P=0.537	P=0.359	P=0.488
Incidental Tumor Test (h)		P=0.094	P=0.551	P=0.474	(j)
Fisher Exact Test (h)		P=0.141	P=0.500	P=0.500	P=0.508N
Endometrial Gland: Adenocarcinoma or Carcinoma					
Overall Rates (e)	0/49 (0%)	3/50 (6%)	1/49 (2%)	0/49 (0%)	0/48 (0%)
Adjusted Rates (f)	0.0%	17.6%	3.4%	0.0%	0.0%
Terminal Rates (g)	0/11 (0%)	2/16 (13%)	0/15 (0%)	0/7 (0%)	0/0
Life Table Test (h)		P=0.177N	P=0.493	(i)	(i)
Incidental Tumor Test (h)		P=0.132N	P=0.677	(i)	(i)
Fisher Exact Test (h)		P=0.125	P=0.500	(i)	(i)
Ovary: Luetoma					
Overall Rates (e)	1/49 (2%)	2/50 (4%)	3/50 (6%)	1/49 (2%)	0/47 (0%)
Adjusted Rates (f)	7.1%	10.9%	15.6%	14.3%	0.0%
Terminal Rates (g)	0/11 (0%)	1/16 (6%)	2/15 (13%)	1/7 (14%)	0/0
Life Table Test (h)		P=0.591	P=0.382	P=0.628	(m)
Incidental Tumor Test (h)		P=0.430	P=0.191	P=0.653	(j)
Fisher Exact Test (h)		P=0.508	P=0.316	P=0.753	P=0.510N

(a) Administered a single dose of 0.05 mg 7,12-dimethylbenz(*a*)anthracene (DMBA) in acetone
(b) Administered 55.5 mg *o*-phenylphenol in acetone 3 × week
(c) Administered a single dose of DMBA and 55.5 mg *o*-phenylphenol in acetone 3 × week
(d) Administered a single dose of DMBA and 0.005 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) in acetone 3 × week
(e) Number of tumor-bearing animals/number of animals examined at the site
(f) Kaplan-Meier tumor incidences at the end of the study after adjusting for intercurrent mortality
(g) Observed tumor incidence at terminal kill
(h) 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 Fisher exact test compares directly the overall incidence rates. A lower incidence in a dosed group is indicated by (N).
(i) No P value is reported because no tumors were observed in the vehicle control and dosed groups.
(j) Analysis not reported because of poor survival in this group; no dosed animals were alive in the last two time intervals.
(k) One carcinosarcoma also observed.
(l) Includes four histiocytic, four mixed, and two undifferentiated
(m) Analysis not performed; all dosed animals died before the first tumor was observed in the vehicle controls.
(n) Hepatocellular adenoma and carcinoma observed in one animal

TABLE C3. ANALYSIS OF SKIN TUMORS AT THE APPLICATION SITE IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL AS COMPARED WITH THOSE IN THE DMBA GROUP (a,b)

	DMBA	DMBA/ *o*-Phenylphenol	DMBA/ TPA (c)
MALE			
Basal Cell Tumor or Carcinoma (d)			
Overall Rates	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates	5.0%	18.2%	2.4%
Terminal Rates	1/20 (5%)	1/15 (7%)	0/0
Life Table Tests		P=0.097	P=0.469
Incidental Tumor Tests		P=0.115	(e)
Fisher Exact Test		P=0.181	P=0.753
Squamous Cell Papilloma			
Overall Rates	1/50 (2%)	4/50 (8%)	7/50 (14%)
Adjusted Rates	5.0%	20.0%	70.4%
Terminal Rates	1/20 (5%)	2/15 (13%)	0/0
Life Table Tests		P=0.100	P<0.001
Incidental Tumor Tests		P=0.144	(e)
Fisher Exact Test		P=0.181	P=0.030
Squamous Cell Carcinoma			
Overall Rates	4/50 (8%)	1/50 (2%)	13/50 (26%)
Adjusted Rates	11.6%	2.9%	76.2%
Terminal Rates	0/20 (0%)	0/15 (0%)	0/0
Life Table Tests		P=0.289	P<0.001
Incidental Tumor Tests		P=0.258	(e)
Fisher Exact Test		(f) P=0.181N	P=0.016
Squamous Cell Papilloma or Carcinoma (d)			
Overall Rates	5/50 (10%)	5/50 (10%)	18/50 (36%)
Adjusted Rates	16.0%	22.3%	91.3%
Terminal Rates	1/20 (5%)	2/15 (13%)	0/0
Life Table Tests		P=0.429	P<0.001
Incidental Tumor Tests		P=0.500	(e)
Fisher Exact Test		P=0.630	P=0.002
All Primary Tumors			
Overall Rates	6/50 (12%)	9/50 (18%)	19/50 (38%)
Adjusted Rates	18.2%	37.3%	91.5%
Terminal Rates	1/20 (5%)	3/15 (20%)	0/0
Life Table Tests		P=0.121	P<0.001
Incidental Tumor Tests		P=0.163	(e)
Fisher Exact Test		P=0.288	P=0.002
FEMALE			
Basal Cell Carcinoma			
Overall Rates	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates	9.2%	19.6%	13.0%
Terminal Rates	1/16 (6%)	1/7 (14%)	0/0
Life Table Tests		P=0.288	P=0.070
Incidental Tumor Tests		P=0.459	(e)
Fisher Exact Test		P=0.500	P=0.691
Squamous Cell Papilloma			
Overall Rates	4/50 (8%)	2/50 (4%)	17/50 (34%)
Adjusted Rates	17.7%	28.6%	70.8%
Terminal Rates	2/16 (13%)	2/7 (29%)	0/0
Life Table Tests		P=0.668	P<0.001
Incidental Tumor Tests		P=0.560	(e)
Fisher Exact Test		P=0.339N	P=0.001

TABLE C3. ANALYSIS OF SKIN TUMORS AT THE APPLICATION SITE IN MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL AS COMPARED WITH THOSE IN THE DMBA GROUP (Continued)

	DMBA	DMBA/ *o*-Phenylphenol	DMBA/ TPA
Squamous Cell Carcinoma			
Overall Rates	3/50 (6%)	3/50 (6%)	18/50 (36%)
Adjusted Rates	13.6%	9.5%	83.2%
Terminal Rates	0/16 (0%)	0/7 (0%)	0/0
Life Table Tests		P=0.442	P<0.001
Incidental Tumor Tests		P=0.620N	(e)
Fisher Exact Test		P=0.661N	P<0.001
Squamous Cell Papilloma or Carcinoma (d)			
Overall Rates	7/50 (14%)	5/50 (10%)	31/50 (62%)
Adjusted Rates	28.9%	35.3%	91.0%
Terminal Rates	2/16 (13%)	3/7 (43%)	0/0
Life Table Tests		P=0.463N	P<0.001
Incidental Tumor Tests		P=0.507	(e)
Fisher Exact Test		P=0.380N	P<0.001
Keratoacanthoma			
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	27.0%
Terminal Rates	0/16 (0%)	0/7 (0%)	0/0
Life Table Tests		(g)	P=0.001
Incidental Tumor Tests		(g)	(e)
Fisher Exact Test		(g)	P=0.028
All Primary Tumors			
Overall Rates	9/50 (18%)	8/50 (16%)	(h) 32/50 (64%)
Adjusted Rates	36.0%	51.5%	91.3%
Terminal Rates	3/16 (19%)	3/7 (43%)	0/0
Life Table Tests		P=0.255	P<0.001
Incidental Tumor Tests		P=0.579	(e)
Fisher Exact Test		P=0.500N	P<0.001

(a) DMBA--7,12-dimethylbenz(*a*)anthracene
(b) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Tables C1 and C2 (footnotes).
(c) TPA--12-O-tetradecanoylphorbol-13-acetate
(d) All skin neoplasms (benign and malignant) were combined to determine if there was an effect at the site of application.
(e) Analyses not performed because of poor survival in this group; no dosed animals were alive in the last two time intervals.
(f) A negative trend or lower incidence in a dosed group is indicated by (N).
(g) No P value is reported because no tumors were observed in the DMBA and DMBA/*o*-phenylphenol groups.
(h) One carcinosarcoma was also observed.

APPENDIX D

CHEMICAL CHARACTERIZATION OF

o-PHENYLPHENOL

APPENDIX D. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of o-Phenylphenol (Lot No. MM09157) Performed by the Analytical Chemistry Laboratory

A. Physical Properties

	Determined	Literature Values
1. Appearance:	Pinkish flakes	
	Determined	**Literature Values**
2. Melting Point:	55.5°-58° C (visual, capillary) 52.5°-55° C (Dupont 900 DTA)	55.5°-57.5° C (Merck Index, 1976)

B. Spectral Data

1. Infrared	**Determined**	**Literature Values**
a. Instrument:	Beckman IR-12	
b. Phase:	5% potassium bromide pellet	
c. Results:	See Figure 3	Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible	**Determined**	**Literature Values**
a. Instrument:	Cary 118	
b. Solvent:	Methanol	Methanol
c. Results:	λ_{max} (nm) $\varepsilon \times 10^{-3}$	λ_{max} (nm) $\varepsilon \times 10^{-3}$
	287.5 4.973 ± 0.087 (δ) 246 11.108 ± 0.204	287 2.47 245.5 5.56
	A gradually increasing absorbance was seen in the visible region from 380 to 350 nm for a 1 mg/ml solution. There is a twofold difference between the ε_{max} values obtained at Midwest Research Institute (MRI) and the literature values. The same results were obtained on a repeat analysis; therefore, the literature values appear to be in error.	Not consistent with literature values (Sadtler Standard Spectra).

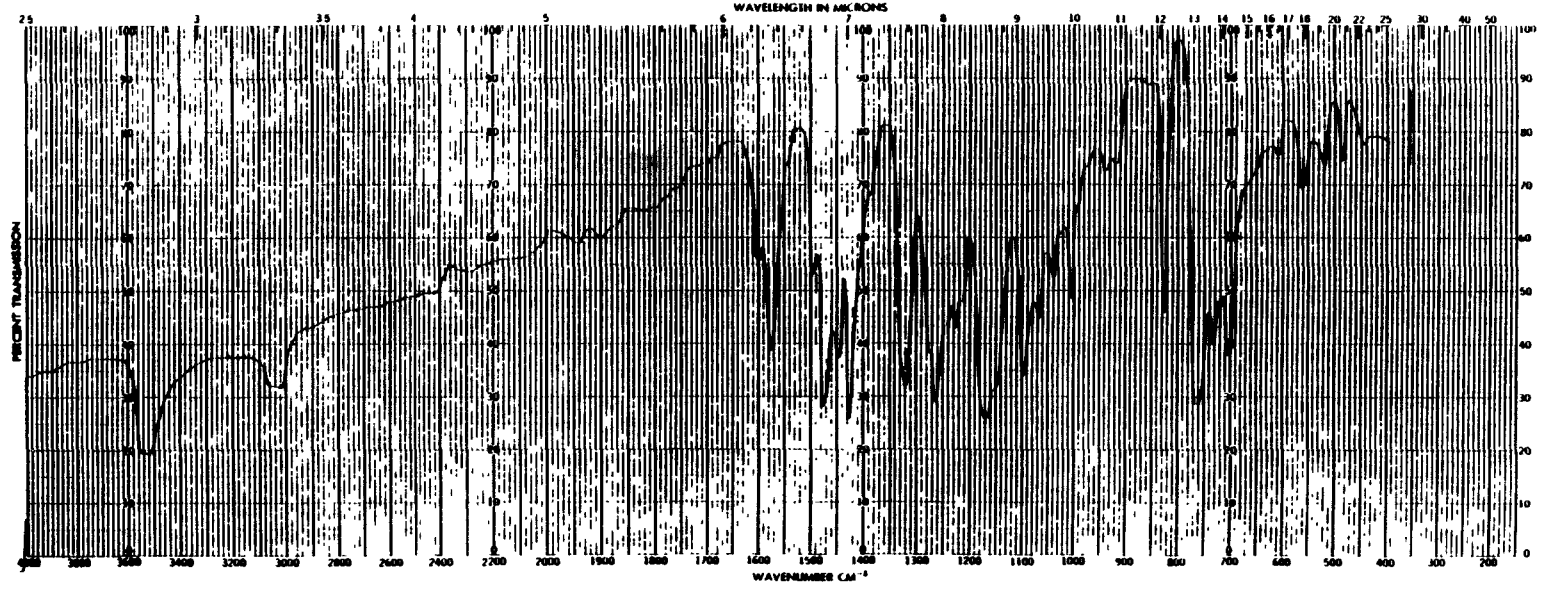

FIGURE 3. INFRARED ABSORPTION SPECTRUM OF *o*-PHENYLPHENOL (LOT NO. MM09157)

3. **Nuclear Magnetic Resonance**

	Determined	Literature Values
a. Instrument:	Varian EM 360-A	
b. Solvent:	Chloroform-d with internal tetramethyl-silane	
c. Assignments:	See Figure 4	Consistent with literature spectrum (Sadtler Standard Spectra)
d. Chemical Shift (δ):	a s, 5.47 ppm b m, 6.03-7.48 ppm c 7.25 ppm	
e. Integration Ratios:	a 1.04 b, c } 9.03	

C. Water Analysis (Karl Fischer): 0.21% ± 0.01 (δ)%

D. Titration: Titration of the phenol group using various nonaqueous methods was not successful

E. Elemental Analysis

Element	C	H
Theory (T)	84.68	5.92
Determined (D)	84.05	6.01
	85.05	6.01
Percent D/T	100.38	101.52

F. Chromatographic Analysis

1. **Thin-Layer Chromatography**

Plates: Silica Gel 60 F-254, 0.25 mm layer
Reference Standard: α-napthol (1 µl of a 10 µg/µl solution in acetone)
Amount Spotted: 100 and 300 µg (10 and 30 µl of 10 µg/µl solution in acetone)
Visualization: Ultraviolet (254 nm) and ferricyanide (potassium)-ferric chloride (Stahl, 1969)

a. System 1: Toluene:methanol (95:5)

R_f: 0.54
R_{st}: 1.43

b. System 2: Chloroform (100%)

R_f: 0.68
R_{st}: 2.34

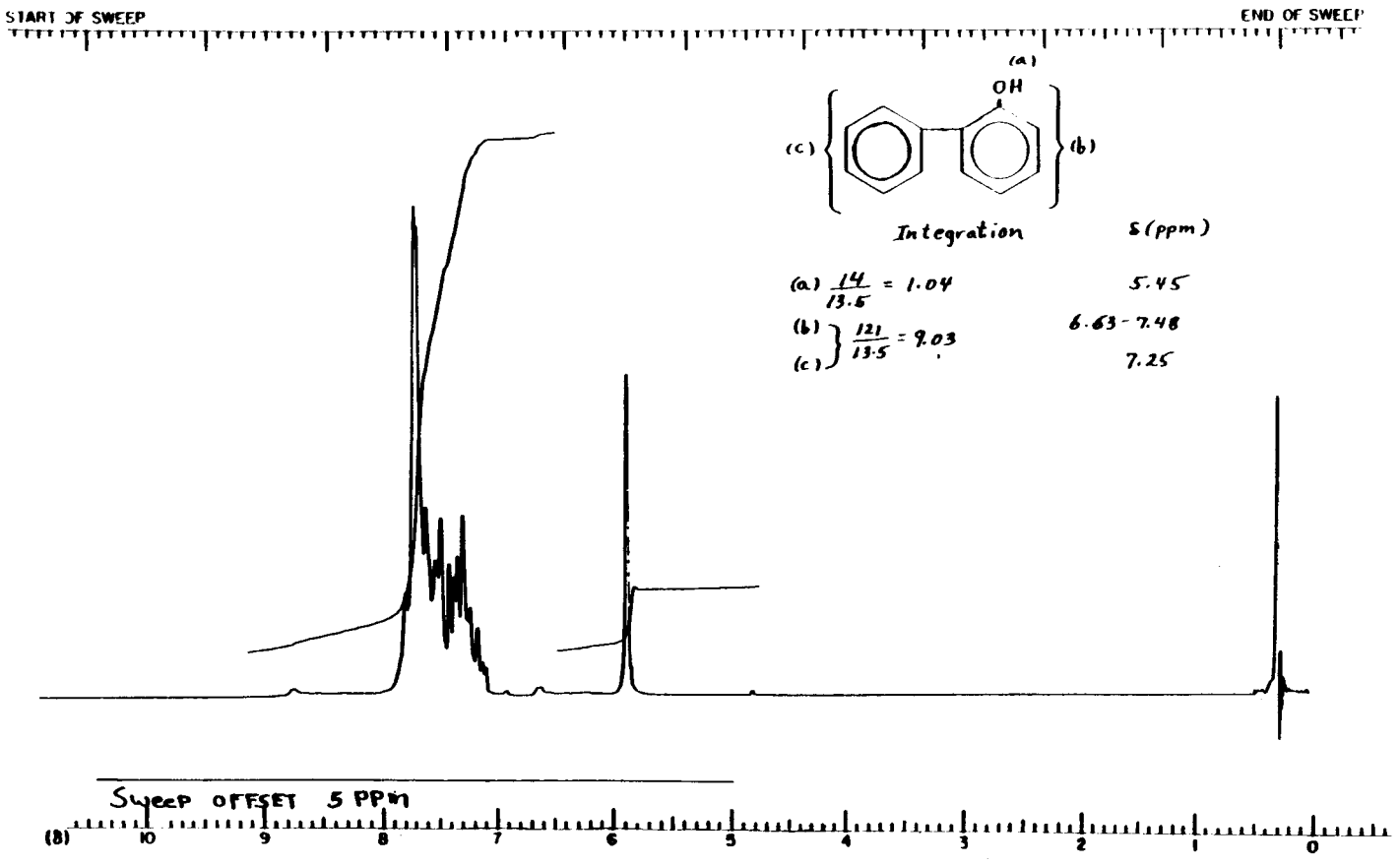

FIGURE 4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF *o*-PHENYLPHENOL (LOT NO. MM09157)

2. Gas Chromatography

Instrument: Varian 3740
Detector: Flame ionization
Carrier gas: Nitrogen
Carrier flow rate: 70 cc/min

System 1

Column: 3% SP-2100 on 100/120 Supelcoport, 1.8 m×4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 250° C
Oven temperature program: 5 min at 50° C, then 50°-250° at 10° C/min
Sample injected: 5 µl of a 10 mg/ml solution in methylene chloride to quantitate impurities and 5 µl of a 5 mg/ml solution in methylene chloride to check for detector overloading

Results: Major peak and three small impurities (one in front of and two following the major peak) with a combined area of 0.05% that of the major peak area

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	2.3	0.22	0.03
2	10.3	1.00	100
3	12.3	1.19	0.01
4	13.1	1.27	0.01

System 2

Column: 1% SP-1240 on 100/120 Supelcoport, 1.8 m×4 mm ID, glass
Inlet temperature: 180° C
Detector temperature: 230° C
Oven temperature program: 5 min at 50° C, then 50°-180° at 10° C/min
Sample injected: 4 µl of 200 and 10 mg/ml solutions in methanol to quantitate impurities and 4 µl of a 5 mg/ml solution in methanol to check for detector overloading

Results: Major peak and five impurities (all in front of the major peak) with a combined area 0.17% that of the major peak; the largest impurity had an area 0.13% that of the major peak. Three unresolved impurities had a combined area 0.03% that of the major peak; the remaining impurity had an area of 0.01% that of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	12.9	0.70	0.01
2	14.5	0.79	0.13
3	17.0	0.92	
4	17.3	0.94	0.03 (combined)
5	17.4	0.95	
6	18.4	1.00	100

G. Conclusions: Results of elemental analysis for carbon and hydrogen were in agreement with the theoretical values. Thin-layer chromatography on two systems indicated only the major component. Gas chromatography on one system indicated three small impurities with a combined area of 0.05% that of the major peak; a second gas chromatographic system indicated five impurities, the largest of which had an area of 0.13% that of the major peak. The remaining four impurities had a combined area of 0.04% that of the major peak. Titration with Karl Fischer reagent indicated 0.21% ± 0.01 (δ)% water. The extinction coefficients in the ultraviolet region were not in agreement with the literature values. Since the values obtained at MRI were one-half the literature values and the analysis was repeated with the same results, the literature values were considered to be in error. The infrared and nuclear magnetic resonance spectra were consistent with the literature spectra.

II. Stability Study of o-Phenylphenol Performed by the Analytical Chemistry Laboratory

A. Sample Storage: Samples of *o*-phenylphenol were stored for 2 weeks at −20°, 5°, 25°, and 60° C in glass tubes with Teflon®-lined lids.

B. Analytical Method: Gas chromatography

1. **Instrument:** Varian 3700 with auto-injector
2. **Detector:** Flame ionization
3. **Column:** 1% SP-1240 on 100/120 Supelcoport
4. **Inlet temperature:** 200°
5. **Detector temperature:** 300° C
6. **Carrier gas:** Nitrogen
7. **Carrier flow rate:** 70 cc/min
8. **Oven temperature program:** 170° C, isothermal
9. **Samples injected:** Solutions of *o*-phenylphenol (0.05%) from each storage temperature in methylene chloride containing 0.7% docasane internal standard
10. **Retention times:** Docasane--1.8 min; *o*-phenylphenol--3.0 min

A previously determined compound-to-standard relative response ratio was used to compare the known concentration in the peak areas of the docasane standard with that in the sample. The concentrations of *o*-phenylphenol in the sample peaks thus obtained were normalized to the −20° C concentration.

C. Results

Storage Temperature (degrees centigrade)	o-Phenylphenol (percent of −20° C sample)
−20	100.0 ± 1.9
5	99.0 ± 1.9
25	99.4 ± 1.9
60	99.9 ± 1.9

D. Conclusion: *o*-Phenylphenol is stable as the bulk chemical when stored for 2 weeks at temperatures up to 60° C.

III. Stability Study of *o*-Phenylphenol Performed by the Testing Laboratory

A. Storage Conditions

Bulk chemical: Room temperature
Reference chemical: −20° C

B. Analytical Methods

1. Gas Chromatography

Column: 1% 1240DA on 100/120 Supelcoport in glass column
Detector temperature: 230° C
Injector temperature: 180° C
Oven temperature program: 50° C for 6 min, then 50°-180° at 10° C/min
Carrier gas: Nitrogen
Sample size: 6 µl of 10 mg/ml *o*-phenylphenol in methanol

a. Analyses performed 11/1/79-6/3/81

Instrument: Aerograph 2100--Gas chromatograph with CDS 111L Data System
Carrier flow rate: 70 cc/min

b. Analyses performed 9/22/81-8/24/82

Instrument: Hewlett-Packard 5840A--Gas Chromatograph with reporting integrator
Carrier flow rate: 35 cc/min (25 cc/min on 5/26/82)

2. Infrared Spectroscopy

Instrument: Digilab FTS 10 (Fourier Transform IR System)
Samples run in potassium bromide pellet

C. Results

1. Gas Chromatography

Date	Percent Purity of *o*-Phenylphenol	
	Bulk	Reference
11/1/79	99.83	99.77
2/19/80	99.79	99.73
6/30/80	99.81	99.85
9/30/80	99.93	99.81
2/6/81	99.77	99.70
6/3/81	99.88	99.83
9/22/81	99.88	99.88
1/28/82	99.88	99.84
5/26/82	99.90	99.89
8/24/82	99.87	99.86

2. Infrared Spectroscopy: All spectra were consistent with those supplied by the analytical testing laboratory

D. Conclusion: No degradation of the test material occurred during the studies.

APPENDIX E

PURIFICATION AND ANALYSIS OF 7,12-DIMETHYLBENZ(a)ANTHRACENE

APPENDIX E. PURIFICATION AND ANALYSIS

I. Purification and Analysis of 7,12-Dimethylbenz(a)anthracene (DMBA) at the Analytical Chemistry Laboratory

A. Purification

1. Method

Two 5-g samples were mixed together and then purified in two separate batches. Each batch was dissolved in as little benzene as possible and loaded onto a neutral alumina column (Activity I), 40 cm × 2.5 cm. The compound was eluted from the column with 300 ml benzene; the 100- to 300-ml fraction was taken. This eluate was reduced to one-half the original volume by evaporation; an equal amount of isopropanol was added. This solution was allowed to stand overnight at room temperature. The resulting pale yellow crystalline flakes were washed four times with 25 ml isopropanol. Two subsequent recrystallizations were made by heating the solvent, adding more isopropanol, and cooling to room temperature. The crystallized material was washed with four 25-ml volumes of isopropanol. All of the recrystallized material was dried overnight in vacuo at 40° C and mixed before being analyzed.

2. Results

A yield of 6.5 g of DMBA was obtained.

3. Conclusion

Purification of DMBA was accomplished by column cleanup and subsequent recrystallization. A 65% recovery was obtained.

B. Analysis of Purified Material

1. Gas Chromatography

Instrument: Perkin-Elmer 3920
Detector: Flame ionization
Inlet temperature: 275° C
Detector temperature: 300° C
Carrier gas: Nitrogen

a. System 1

Column: 2.5% SP-301 on 100/120 Supelcoport, 1.8 m × 2 mm ID, glass
Carrier flow rate: 25 ml/min
Oven temperature: 275° C, isothermal
Samples injected: 3 µl of a 1% (w/v) solution in chloroform to search for impurities

Results: A major peak (retention time, 10 minutes) and no impurities (limit of detection ≃0.1% by relative area)

b. System 2

Column: 3% SP-2100 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Carrier flow rate: 55 ml/min
Oven temperature program: 1 min at 100° C, then 16° C/min to 275° C; held at 275° C for 16 min
Samples injected: 3 µl of a 10% (w/v) solution in chloroform to detect impurities, and 1.7-3.6 µl of a 1% (w/v) solution in chloroform to determine the area of the major peak for quantitation purposes and to establish linearity of detector response

Results: A major peak followed by two impurities

Peak No.	Retention Time (minutes)	Retention Time (relative to major peak)	Area (percent of major peak)
1	15.6	1.00	100.0
2	17.4	1.12	0.03
3	18.1	1.16	0.04

2. High-Performance Liquid Chromatography

Instrument system
Pump(s): Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K

Detection: Ultraviolet at 254 nm
Column: µ Bondapak C_{18}, 300 × 3.9 mm ID
Guard column: CO:PELL ODS 72 × 2.3 mm ID
Solvent system: Acetonitrile in water
Program: From 38% to 62% acetonitrile in 1 hour
Flow rate: 1 ml/minute
Samples injected: 100 µl of a 0.32 mg/ml solution in methanol and 100 µl of a 0.08 mg/ml solution

Results: A major peak preceded by one impurity

Peak No.	Retention Time (minutes)	Retention Time (relative to major peak)	Area (percent of major peak)
1	59.4	0.58	0.35
2	101.7	1.00	100.0

II. Analysis of 7,12-Dimethylbenz(a)anthracene (DMBA) at the Testing Laboratory

A. Storage Conditions

Bulk sample was stored in resealable brown glass sample vials under nitrogen at −20° C. At the time of analysis, aliquots were removed and added to screw-capped sample vials that were wrapped in tinfoil. Acetone was added, and samples were flushed with nitrogen, sealed, and stored at −20° C. After each analysis, the sample was flushed with nitrogen, sealed, and kept at −20° C.

B. Analytical Method

High-Performance Liquid Chromatography

Instrument: DuPont 830 Liquid Chromatograph with 838 Programmable Gradient
Detection: Ultraviolet at 254 nm
Column: μ Bondapak C_{18}, 300 × 4.1 mm ID
Guard column: CO:PELL ODS 72 × 2.3 mm ID
Solvent system: A--62% water, 38% acetonitrile; B--38% water, 62% acetonitrile
Program: Hold A for 5 minutes, then A to B in 20 minutes
Flow rate: 1 ml/minute
Sample size: 50 μl
Concentrations: 0.025, 0.050, and 0.25 mg/ml solutions in acetone
Chart Speed: 0.1 in/minute

C. Results

Acetone alone gave six peaks that were also present in the chromatograms of DMBA at an attenuation of 32. The high concentration DMBA sample (0.25 mg/ml) showed one major peak and one impurity that represented 0.30% of the major peak (calculated from the 0.25 mg/ml sample).

Sample (mg/ml)	Retention Time (minutes)	Area (cm^2)	Area (percent of major peak)
0.25	(a)	(b) 4003.80	100.0
	42.0	12.00	0.30
0.025	51.4	400.38	100.0
0.050	50.8	908.80	100.0

(a) Top of peak off chromatogram
(b) Calculated from 0.025 mg/ml concentration

D. Conclusions

Results of the high-performance chromatographic analyses of DMBA were consistent with those reported by the analytical chemistry laboratory.

APPENDIX F

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX F. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Purpose

These studies were conducted to determine the maximum solubility of *o*-phenylphenol in acetone and to test the stability of the chemical formulated into a dose solution for dermal application with acetone at a concentration of 90% maximum solubility.

B. Determination of Maximum Solubility

1. Procedure

o-Phenylphenol (approximately 30 g) was stirred with approximately 20 ml of acetone for 15 minutes in a 125-ml Erlenmeyer flask. The solution was allowed to stand a few minutes to allow the undissolved chemical to settle out; then three 2-ml aliquots were transferred to tared 50-ml beakers.

Acetone was removed by evaporation in a hood, and the beakers with residue were reweighed. The mean of the triplicate deteminations gave a maximum solubility of 928 ± 2 mg/ml.

2. Conclusion

The maximum solubility of *o*-phenylphenol in acetone at room temperature was determined to be 928 ± 2 mg/ml.

C. Two-Year Studies--Dose Mixture Stability

1. Stability Test Parameters

a. Concentration: 835 mg/ml
b. Vehicle: Acetone
c. Duration: 14 d
d. Storage and Sampling Schedule: At 25° C--d 0, 0 + 3 h, 1, 7, 11, and 14 d; at 5° C--0, 7, and 14 d

2. Sample Preparation

Solutions of *o*-phenylphenol in acetone were prepared in duplicate on five different days over a 14-day period. The days were chosen so that the solutions, when analyzed on the 14th day, represented samples that had been stored 0, 0 + 3 hours open to air and light, 1, 7, 11, and 14 d at room temperature, and 0, 7, and 14 days at 5° C. All samples, except the 3-hour stability sample, were stored in the dark after preparation.

The solutions were prepared by transferring accurately weighed quantities (approximately 2.8 g) of *o*-phenylphenol into 5-ml septum vials and adding 1 ml of acetone (total volume, 3.3 ml; displacement volume of *o*-phenylphenol, 0.85 ml/g). The vials were sealed, shaken for 30 seconds, and stored for the stability study. The concentration of *o*-phenylphenol in the acetone solutions was approximately 840 mg/ml.

3. Analysis Procedure

The contents of each septum vial was quantitatively transferred into 100-ml volumetric flasks and diluted to 100 ml with acetone. A 5-ml aliquot of each solution was further diluted to 100 ml in a 100-ml volumetric flask containing 5 ml of an internal standard solution (*n*-tetradecane, 22.4 mg/ml in acetone). The *o*-phenylphenol content of the solutions was determined by the gas chromatographic system described below:

a. Instrument: Varian 3700 gas chromatograph equipped with an autosampler and CDS-111 data system
b. Column: Glass, 1.8 m × 2 mm ID packed with 3% SP-2100 on 100/120 mesh Supelcoport
c. Detector: Flame ionization
d. Temperatures
Injection: 170° C
Oven: 130° C, isothermal
Detector: 220° C
e. Carrier gas: Nitrogen
f. Carrier flow rate: 30 ml/min
g. Injection volume: 3 µl
h. Retention times
o-Phenylphenol: 3.1 min
Internal standard: 4.5 min

The instrument was calibrated by using two independently prepared stock standard solutions of *o*-phenylphenol (approximately 1.4 mg/ml in acetone) which were injected after every third sample.

4. Quality Assurance Measures

All stability samples were prepared and tested in duplicate. The chemical analyses were performed by making duplicate injections of extracts from each stability sample following a randomized order for the standards and samples. Instrument calibration was maintained by making duplicate injections of a standard after every third sample. All determinations were related to an internal standard incorporated into the solutions. Results were calculated from relative response factors (RRF) computed from electronically integrated peak areas of the calibration standards using the following equations:

$$RRF = \frac{\text{Milligrams per milliliter test chemical} \times \text{peak area of internal standard}}{\text{Peak area of test chemical} \times \text{milligrams per milliliter of internal standard}}$$

The total milligrams of chemical in the sample was calculated according to the following equation:

$$\text{Milligrams of chemical} = \frac{RRF \times \text{sample peak area} \times \text{milligrams per millilliter of internal standard} \times DF}{\text{Peak area of test chemical} \times \text{milligrams per milliliter of internal standard}}$$

where DF = dilution factor = 2,000. Then the milligrams per milliliter chemical = chemical/total sample volume, where the total sample volume = volume of acetone + grams of chemical × displacement volume (0.85 ml/g).

The linearity of the gas chromatographic system was evaluated with standard solutions of *o*-phenylphenol in acetone at concentrations of approximately 0.84, 1.4, and 1.68 mg/ml. The correlation coefficient calculated from the linear regression equation with the standard curve data was 0.99971. Special care was exercised in handling the sample and standard solutions to prevent errors caused by evaporation of the acetone.

5. Results of the 14-Day Stability Study

Storage (days)	Storage Temperature	Milligrams *o*-PP (a)/Milliliter Acetone Determined	Target	Determined (mg/ml) / Target (mg/ml) × 100
0		837 836	835 835	100.2 100.1 (b) Mean = 100.2 ± 0.1
0 + 3 h, open to air and light	Ambient	835 836	835 836	100.0 100.0 Mean = 100.0 ± 0
1	Ambient	835 835	835 835	100.0 100.0 Mean = 100.0 ± 0
7	Ambient	835 834	836 836	99.9 99.8 Mean = 99.9 ± 0.1
7	5° C	835 836	835 835	99.9 100.1 Mean = 100.0 ± 0.1
11	Ambient	835 835	836 835	99.8 99.9 Mean = 99.9 ± 0.1
14	Ambient	835 835	835 835	100.0 100.0 Mean = 100.0 ± 0
14	5° C	835 835	835 835	100.0 99.6 Mean = 99.8 ± 0.2

(a) *o*-PP: *o*-phenylphenol
(b) Mean ± standard deviation

6. Conclusion

o-Phenylphenol formulated into 840-mg/ml dose solutions with acetone showed no measurable loss of stability after 2 weeks' storage in the dark at room temperature. The solutions that were exposed for 3 hours, open to air and light, also showed no loss of chemical but did lose a significant amount of acetone by evaporation. Special care was recommended to minimize evaporation loss.

II. Preparation of Dose Mixtures at the Testing Laboratory

o-Phenylphenol was prepared for application with high-grade acetone (produced by Burdick and Jackson, Muskegon, Michigan) as the delivery vehicle. The dose batches were prepared weekly at a concentration of 55.5 mg/100 µl by adding weighed portions of *o*-phenylphenol to the appropriate volume of acetone in a mixing column and inverting the column 21 times and an additional 21 times beyond achievement of solution. The 12-O-tetradecanoylphorbol-13-acetate solution was prepared in a similar manner at a concentration of 5 µg/100 µl of acetone. The 7,12-dimethylbenz(*a*)anthracene solution was prepared for the single application on July 26, 1980, by diluting 25 mg with enough acetone to obtain a volume of 50 ml with a concentration of 50 µg/100 µl. The solution was prepared under yellow light.

APPENDIX G

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX G. METHODS OF ANALYSIS

I. Procedures Conducted at the Analytical Testing Laboratory

A. Preparation of Spiked Acetone Standard

Standard solutions of *o*-phenylphenol in methanol were prepared independently at two concentrations. These solutions were diluted with methanol to prepare standards at four additional concentrations. The six standard solutions bracketed the specified dose range of the referee sample. Undosed acetone was diluted with methanol for use as a blank. An aliquot of each standard and acetone blank solution was further diluted with methanol/water (1:1) and used in the analysis procedure described below.

B. Preparation of the Referee Samples

Three portions of the three referee dose mixtures (two samples for mixing date 5/7/82) were pipetted into individual volumetric flasks and diluted with methanol to the appropriate volume. An aliquot of each diluted sample was further diluted with methanol/water (1:1). The samples were then analyzed following the procedure described below.

C. Analysis Procedure

A 5-ml aliquot of each spiked standard, blank, and referee sample solution prepared as described above was diluted to 100 ml with methanol/water (1:1). After the solutions were mixed, the absorbance of the solutions was measured versus methanol/water (1:1) in 1-cm quartz cells at 244-246 nm on Cary 219 or 118 spectrophotometers.

The total amount of *o*-phenylphenol in the referee dose mixtures was determined for the linear regression equation obtained from the standard data, relating the absorbance of each standard to the amount of chemical in the respective standard.

D. Quality Assurance Measures

The referee dose mixtures were each analyzed in triplicate (duplicate for mixing date 5/7/82), and the undosed acetone sample was analyzed once. Individually spiked portions of undosed acetone (six concentrations bracketing the specified dose range of the referee sample) were prepared from two independently weighed standards and were treated like the referee dose mixtures for obtaining standard data.

II. Procedures Conducted at the Testing Laboratory

Standards were prepared by serial dilution of three concentrations of *o*-phenylphenol in acetone. The stock solution was made by dissolving a weighed quantity of *o*-phenylphenol in the required volume of acetone. Test and standard samples were diluted 150 µl to 10 ml with methanol, 150 µl to 10 ml with methanol/water (1:1) and finally 500 µl to 10 ml with methanol/water (1:1). Samples were then read on a Gilford 2400 S spectrophotometer at 243 nm. Concentrations were determined from the linear regression standard curve, and analyses were done in duplicate.

APPENDIX H

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE H1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

Date Mixed	Concentration (a) of *o*-Phenylphenol in Acetone (g/ml)	Percent Target (b)
8/8/80	0.587	105.8
9/12/80	0.548	98.7
11/7/80	0.535	96.4
1/16/81	0.555	100.0
2/27/81	0.574	103.4
4/24/81	0.527	95.0
6/19/81	0.552	99.5
8/14/81	0.572	103.1
8/20/81	0.564	101.6
10/13/81	0.562	101.3
12/4/81	0.549	98.9
2/12/82	0.568	102.3
4/16/82	0.558	100.5
5/7/82	0.540	97.3
6/11/82	0.554	99.8
Mean (g/ml)	0.556	
Range (g/ml)	0.527-0.587	
Standard deviation	0.0157	
Coefficient of variation (percent)	2.82	
Number of samples	15	

(a) Results of duplicate analysis
(b) Target concentration = 0.555 g/ml

TABLE H2. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL

Date Mixed	Determined Concentration (g/ml) (a)	
	Testing Laboratory (b)	Referee Laboratory (b)
9/12/80	0.548	0.539
2/27/81	0.574	0.503
8/20/81	0.564	0.552
2/12/82	0.568	0.458
5/7/82	0.540	0.560

(a) Target concentration = 0.555 g/ml
(b) Results of duplicate analysis

APPENDIX I

SENTINEL ANIMAL PROGRAM

APPENDIX I. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Studies of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect test 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 test rooms. These animals are untreated, and these animals and the test 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.

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

Hemagglutination Inhibition	Complement Fixation	ELISA
PVM (pneumonia virus of mice)	M.Ad. (mouse adenovirus)	MHV (18 and 24 mo)
Reo 3 (reovirus type 3)	LCM (lymphocytic choriomeningitis virus)	
GDVII (Theiler's encephalomyelitis virus)	Sendai (24 mo)	
Poly (polyoma virus)	MHV (mouse hepatitis virus) (12 mo)	
MVM (minute virus of mice)		
Ectro (infectious ectromelia)		
Sendai (12 and 18 mo)		

II. Results

Results are presented in Table I1.

TABLE I1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR MICE IN THE TWO-YEAR DERMAL STUDIES OF *o*-PHENYLPHENOL (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
12	6/9	MVM
	1/9	Reo 3
18	2/8	MVM
	1/9	PVM
	5/9	MHV
24	3/10	MVM
	4/10	PVM
	7/10	MHV

(a) Blood samples were taken from sentinel animals at 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, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX J

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

Pelleted Diet: June 1980 to July 1982

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

TABLE J1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

(a) Prepared according to NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen #16 before mixing.
(c) Details given in Table J2

TABLE J2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE J3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.04 ± 0.75	22.7 - 25.1	24
Crude fat (percent by weight)	4.84 ± 0.80	4.1 - 5.7	24
Crude fiber (percent by weight)	3.40 ± 0.29	2.9 - 4.3	24
Ash (percent by weight)	6.56 ± 0.50	5.7 - 7.43	24
Vitamins			
Vitamin A (IU/kg)	11,146 ± 2,291	7,200 - 17,000	24
Vitamin D (IU/kg)	6,300		1
α-tocopherol (ppm)	37.6	31.1 - 44.0	2
Thiamine (ppm)	17.3 ± 3.3	7.4 - 27.0	(c) 23
Riboflavin (ppm)	6.9	6.1 - 7.4	2
Niacin (ppm)	75	65 - 85	2
Pantothenic acid (ppb)	30.2	29.8 - 30.5	2
Pyridoxine (ppm)	7.2	5.6 - 8.8	2
Folic acid (ppm)	2.1	1.8 - 2.4	2
Biotin (ppm)	0.24	0.21 - 0.27	2
Vitamin B_{12} (ppb)	12.8	10.6 - 15.0	2
Choline (ppm)	3,315	3,200 - 3,430	2
Minerals			
Calcium (percent of total diet)	1.29 ± 0.21	0.81 - 1.69	24
Phosphorous (percent of total diet)	1.00 ± 0.07	0.86 - 1.10	24
Potassium (percent of total diet)	0.809	0.772 - 0.846	2
Chloride (percent of total diet)	0.557	0.479 - 0.635	2
Sodium (percent of total diet)	0.304	0.258 - 0.349	2
Magnesium (percent of total diet)	0.172	0.166 - 0.177	2
Sulfur (percent of total diet)	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
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21 - 1.31	2
Cystine	0.395	0.39 - 0.40	2
Glycine	1.175	1.15 - 1.20	2
Histidine	0.553	0.530 - 0.576	2
Isoleucine	0.908	0.881 - 0.934	2
Leucine	1.905	1.85 - 1.96	2
Lysine	1.250	1.20 - 1.30	2
Methionine	0.310	0.306 - 0.314	2
Phenylalanine	0.967	0.960 - 0.974	2
Threonine	0.834	0.827 - 0.840	2
Tryptophan	0.175	0.171 - 0.178	2
Tyrosine	0.587	0.566 - 0.607	2
Valine	1.085	1.05 - 1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1

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

TABLE J4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.42 ± 0.21	<0.05 - 1.06	24
Cadmium (ppm)	0.09 ± 0.2	<0.05 - 0.10	24
Lead (ppm)	0.99 ± 0.72	0.42 - 3.37	24
Mercury (ppm)	(a) <0.05		24
Selenium (ppm)	0.31 ± 0.08	0.14 - 0.52	24
Aflatoxins (ppb)	(a)(b) <10	<5.0 - <10.0	24
Nitrate nitrogen (ppm) (c)	8.15 ± 3.65	2.1 - 17.0	24
Nitrite nitrogen (ppm) (c)	2.23 ± 1.59	0.4 - 6.9	24
BHA (ppm) (d)	4.55 ± 3.59	(e) <0.4 - 13.0	24
BHT (ppm) (d)	2.55 ± 1.40	0.8 - 5.9	24
Aerobic plate count (CFU/g)	40,592 ± 32,056	4,900 - 120,000	24
Coliform (MPN/g) (f)	(g) 30.3 ± 53.2	<3 - 240	23
	(h) 74.8 ± 224.5	<3 - 1,100	24
E. coli (MPN/g)	(i) <3		24
Total nitrosamines (ppb)	(j) 7.20 ± 7.04	<0.8 - 24.5	21
	(k) 29.40 ± 64.76	<0.8 - 273.2	24
N-Nitrosodimethylamine (ppb)	(j) 5.67 ± 6.49	0.8 - 20.0	21
	(k) 27.67 ± 64.38	0.8 - 272	24
N-Nitrosopyrrolidine (ppb)	1.35 ± 0.92	0.0 - 3.5	24
Pesticides (ppm)			
Alpha BHC (l)	(a) <0.01		24
Beta BHC	(a) <0.02		24
Gamma BHC-Lindane	(a) <0.01		24
Delta 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	(a) <0.05	(m) 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 PCB's	(a) <0.2		24
Ronnel	(a) <0.01		24
Ethion	(a) <0.02		24
Trithion	(a) <0.05		24
Diazinon	(a) <0.1	(m) 0.2 (4/27/81)	24
Methyl parathion	(a) <0.02		24
Ethyl parathion	(a) <0.02		24
Malathion	0.09 ± 0.06	(n) <0.05-0.27	24
Endosulfan I	(a) <0.01		24
Endosulfan II	(a) <0.01		24
Endosulfan sulfate	(a) <0.03		24

(a) All values were less than the detection limit (mean) given.
(b) Detection limit 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) Two batches contained less than 0.5 ppm.
(f) MPN = most probable number
(g) Excludes one value of 1,100 obtained for batch produced on 12/16/80
(h) Includes the high value listed in (g)
(i) All values were less than 3 MPN/g.
(j) All values were corrected for percent recovery; mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb in batches produced on 1/26/81, 2/23/81, and 4/27/81.
(k) All values were corrected for percent recovery; mean, standard deviation, and range include the very high values given in (j).
(l) BHC is hexachlorocyclohexane or benzene hexachloride.
(m) The value of the one observation above the detection limit and the date it was obtained
(n) Eleven batches contained more than 0.05 ppm.

APPENDIX K

GENETIC TOXICOLOGY OF *o*-PHENYLPHENOL

TABLE K1. MUTAGENICITY OF *o*-PHENYLPHENOL IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	139 ± 5.4	147 ± 16.8	142 ± 0.9
	3.3	128 ± 4.0	150 ± 11.1	149 ± 6.3
	10	117 ± 9.5	149 ± 8.6	148 ± 3.7
	33	150 ± 8.8	141 ± 7.0	145 ± 2.6
	100	152 ± 8.0	145 ± 9.5	134 ± 8.3
	150	Toxic	--	--
	200	--	143 ± 2.2	124 ± 8.0
TA1535	0	21 ± 4.5	12 ± 1.7	12 ± 0.3
	3.3	--	11 ± 1.2	13 ± 3.8
	10	33 ± 1.5	13 ± 3.3	14 ± 3.4
	33	--	6 ± 1.2	12 ± 1.3
	40	33 ± 5.5	--	--
	60	52 ± 1.5	--	--
	80	47 ± 0.6	--	--
	100	60 ± 4.0	10 ± 0.9	9 ± 1.2
	120	47 ± 6.4	--	--
	140	43 ± 2.0	--	--
	200	--	10 ± 1.5	10 ± 2.5
TA1537	0	4 ± 0.9	10 ± 1.8	11 ± 2.0
	3.3	5 ± 1.0	7 ± 0.7	6 ± 0.3
	10	6 ± 0.7	9 ± 0.9	8 ± 2.4
	33	6 ± 0.3	10 ± 1.2	7 ± 0.3
	100	7 ± 0.0	7 ± 1.5	6 ± 1.0
	150	Toxic	--	--
	200	--	8 ± 1.2	6 ± 0.3
TA98	0	20 ± 2.0	31 ± 3.2	33 ± 1.8
	3.3	17 ± 1.9	26 ± 1.2	27 ± 3.5
	10	15 ± 3.8	27 ± 3.2	25 ± 0.3
	33	17 ± 0.3	30 ± 4.7	27 ± 2.3
	100	14 ± 3.3	31 ± 4.9	28 ± 3.6
	150	15 ± 1.2	--	--
	200	--	16 ± 2.1	25 ± 0.3

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and test compound or solvent (DMSO) were incubated for 20 min at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 h (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

TABLE K2. MUTAGENICITY OF *o*-PHENYLPHENOL IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9 (a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO		225	76	100	99
		141	65	100	72
		172	70	100	82
		176	66	100	90
3-Methylcholanthrene	2.5	577	27	26	712
		645	47	34	454
o-Phenylphenol	0.32	112	73	106	51
		167	71	82	79
	0.63	87	53	90	55
		86	60	85	48
	1.25	156	73	78	71
		105	60	72	58
	2.50	166	63	19	87
		149	46	25	108
	5.00	247	38	4	216
		192	29	4	222

(a) Experiment was performed once, and all doses were tested in duplicate. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 h at 37° C in medium, washed, resuspended in medium, and incubated for 48 h at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells. S9 was prepared from the livers of Aroclor 1254-induced male F344 rats.

TABLE K3. MUTAGENICITY OF *o*-PHENYLPHENOL IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Water					
		91	57	100	53
		76	77	100	33
		64	54	100	40
		95	57	100	56
Ethyl methanesulfonate					
	250	751	78	74	323
		759	92	83	275
o-Phenylphenol					
	20	127	86	80	49
		86	73	70	39
		82	66	69	42
	30	108	97	76	37
		115	94	77	41
		145	118	78	41
	40	121	84	56	48
		178	107	53	56
		214	108	61	66
	50	195	95	39	68
		245	81	26	102
		201	79	34	84
	60	397	103	16	128

(a) Experiments were performed twice, all doses were tested in triplicate, except the solvent control (water), which was tested in quadruplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 h at 37° C in medium, washed, resuspended in medium, and incubated for 48 h at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

TABLE K4. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY *o*-PHENYLPHENOL

Route of Exposure	Dose (ppm)	No. of Lethals/No. of X Chromosomes Tested (a)			
		Mating 1	Mating 2	Mating 3	Total (percent)
Feeding	0	3/2,691	1/2,578	1/2,367	5/7,636 (0.07)
	250	3/3,278	2/3,170	1/2,774	6/9,222 (0.07)
Injection	0	2/3,364	1/3,157	3/2,640	6/9,161 (0.07)
	500	2/2,424	0/2,238	5/2,072	7/6,734 (0.10)

(a) The sex-linked recessive lethal assay was performed essentially as described by Abrahamson and Lewis (1971). Exposure by feeding was done by allowing 24-h-old Canton-S males to feed for 3 d on a solution of the test chemical dissolved in 5% sucrose. Exposure by injection was done by injecting 72-h-old adult males at the base of the halteres with enough of the test chemical dissolved in 0.7% sodium chloride to distend the abdomen (approximately 0.3 µl). Injected flies were allowed to recover for 24 h before being mated. Exposed males were mated to three *Basc* females for 3 d and given fresh females at 2-d intervals to produce three broods of 3, 2, and 2 d, after which the parents were discarded. F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental males were kept together to identify clusters; none were found. After 17 d, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. The z-values, calculated according to Margolin et al. (1983), were −0.0105 for feeding and 0.8380 for injection and were not significant at the 5% level of significance.

TABLE K5. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *o*-PHENYLPHENOL (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	SCE/Cell	Dose (µg/ml)	SCE/Cell
DMSO (10 µl)	8.9	DMSO (10 µl)	9.1
o-Phenylphenol		*o*-Phenylphenol	
14.9	9.9	24.9	9.9
20.0	10.4	49.8	10.1
29.9	11.4	75.4	10.8
Mitomycin C		Cyclophosphamide	
0.01	27.8	2.0	34.5
0.0015	13.4	0.4	13.6

(a) Sister-chromatid exahange, SCE; Chinese hamster ovary, CHO.
(b) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation continued for 24 hours. Cells were washed, fresh medium containing BrdU (10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours. Cells were then collected by mitotic shake-off, treated for 3 minutes with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978).
(c) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 µM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE K6. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS CELLS BY *o*-PHENYLPHENOL (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
DMSO (10 µl)	0 (0)	DMSO (10 µl)	2 (2)
o-Phenylphenol		*o*-Phenylphenol	
60.0	2 (1)	70.2	3 (3)
70.2	3 (3)	80.0	2 (2)
80.0	2 (2)	90.0	5 (4)
Mitomycin C		Cyclophosphamide	
0.0625	56 (28)	37.5	64 (36)
0.025	15 (13)	5.0	17 (14)

(a) Aberration, Abs; Chinese hamster ovary, CHO.
(b) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(c) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation; then cells were harvested and fixed as above. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

APPENDIX L

DATA AUDIT SUMMARY

APPENDIX L. DATA AUDIT SUMMARY

The experimental data and tables of the NTP Technical Report on the toxicology and carcinogenesis studies of *o*-phenylphenol alone and with 7,12-dimethylbenz(*a*)anthracene in Swiss CD-1 mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was performed by personnel of ImmuQuest Laboratories and Pathology Associates during October and November 1984 at the National Toxicology Program Archives, Rockville, Maryland. The audit team comprised the following members: P. Errico, M.A., K. Witkin, Ph.D., L. Brennecke, D.V.M., C. Reese, M.S., and S. Corson, HT (ASCP). The 2-year carcinogenesis studies on *o*-phenylphenol were conducted at Battelle Columbus Laboratories from July 1980 to July 1982.

The audit was reviewed by the National Toxicology Program. The full report of the audit is on file at NIEHS, Research Triangle Park, North Carolina. The audit involved a review of data for 10% of the animals. These data included body weight, clinical observations (including tumor observations), gross and microscopic observations, animal identification, and wet tissue examination. All Individual Animal Data Reports (IADR's), chemistry, and environmental and mortality records were reviewed. Slide and block matches were performed for groups T (DMBA/*o*-phenylphenol), V (acetone vehicle), and Z (*o*-phenylphenol).

The audit revealed that some inattention to detail occurred during the studies. Watering system malfunctions resulted in animal weight fluctuations. The clinical observation and mortality data indicated some confusion about animal identification, as indicated by corrections in log books, but this did not influence the final interpretation of the results.

There was generally good correlation between gross and microscopic diagnoses. Four cases were found involving potential tumors in nontarget organs, each in a different dose group. These involved the liver or lung. The auditing pathologist examined the slides and wet tissues for each of the discrepancies and did not find the lesions described on the IADR. In addition, even if these did represent untrimmed tumors, the statistical significance of the data would not change.

In many cases, the wet tissue bags did not contain the feet, and thus animal identification could not be confirmed in these instances. However, the audit did not detect any misidentified animals.

Any discrepancies that might have influenced the final interpretation of these studies of *o*-phenylphenol were resolved. Minor problems not mentioned here which were not considered to have affected the outcome of the studies were not necessarily pursued to final resolution but are identified in the NTP audit report. In summary, the data examined in this audit are considered adequate to meet the objectives of these studies.

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