FINAL

Report on Carcinogens Background Document for

Naphthalene

September 19, 2002

Prepared for the:
U.S. Department of Health and Human Services
Public Health Service
National Toxicology Program
Research Triangle Park, NC 27709

Prepared by:
Technology Planning and Management Corporation
Canterbury Hall, Suite 310
4815 Emperor Blvd
Durham, NC 27703
Contract Number N01-ES-85421

FOREWORD

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of all substances (i) that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of Health and Human Services (DHHS) has delegated responsibility for preparation of the RoC to the National Toxicology Program (NTP) who prepares the Report with assistance from other Federal health and regulatory agencies and non-government institutions.

Nominations for listing in or delisting from the RoC are reviewed by a formal process that includes a multi-phased, scientific peer review and multiple opportunities for public comment. The review groups evaluate each nomination according to specific RoC listing criteria. This Background Document was prepared to assist in the review of the nomination of Naphthalene. The scientific information in this document comes from publicly available, peer reviewed sources. Any interpretive conclusions, comments or statistical calculations, etc made by the authors of this document that are not contained in the original citation are identified in brackets [ ]. If any member(s) of the scientific peer review groups feel this Background Document does not adequately capture and present the relevant information they will be asked to write a commentary for this Background Document that will be included as an addendum to the document. In addition, a meeting summary that contains a brief discussion of the respective review group's review and recommendation for the nomination will be added to the Background Document, also as an addendum.

A detailed description of the RoC nomination review process and a list of all nominations under consideration for listing in or delisting from the RoC can be obtained by accessing the NTP Home Page at http://ntp-server.niehs.nih.gov. The most recent RoC, the 9th Edition, was published in May, 2000 and may be obtained by contacting the NIEHS Environmental Health Information Service (EHIS) at http://ehis.niehs.nih.gov (800-315-3010).

CONTRIBUTORS

NIEHS/NTP Staff

C W Jameson, Ph.D.	Head, Report on Carcinogens, Environmental Toxicology Program, NIEHS
Ruth M Lunn, Dr. P.H.	Report on Carcinogens Group, Environmental Toxicology Program, NIEHS
Shawn Jeter, B.S.	Report on Carcinogens Group, Environmental Toxicology Program, NIEHS
AnnaLee Sabella	Report on Carcinogens Group, Environmental Toxicology Program, NIEHS

Support to the National Toxicology Program for the preparation of this background document was provided by Technology Planning and Management Corporation through NIEHS Contract Number NO1-ES-85421

Ronald Thomas, Ph.D., Principal Investigator

Sanford Garner, Ph.D., Co-Principal Investigator

Stanley Atwood, M.S., Senior Scientist

Susan Goldhaber, M.S., Senior Scientist

Greg Pazianos, B.S., Scientist

Ashlee Duncan, M.S., Scientist

Support staff

Angie Fralick, B.S.

Tracy Saunders, B.S.

Consultant

James R. Hailey, Veterinary Pathologist, NIEHS (General Reviewer)

Susan Dakin, Ph.D., Independent Consultant (Scientific Editor)

Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Executive Summary

Introduction

Naphthalene is a polyaromatic hydrocarbon found in coal tar. It was nominated by the National Institute of Environmental Health Sciences based on the results of the National Toxicology Program (NTP) two-year inhalation studies, which concluded that naphthalene was carcinogenic in rats and female mice. Naphthalene was evaluated by the International Agency for Research on Cancer (2000) and classified as possibly carcinogenic to humans (Group 2B) based on sufficient evidence of carcinogenicity in animals.

Human Exposure

Use. The principal use of naphthalene in the United States is as an intermediate in the production of phthalic anhydride, which is an intermediate in the production of phthalate plasticizers, pharmaceuticals, insect repellents, and other materials. Naphthalene also is used as an intermediate in the production of 1-naphthyl-*N*-methylcarbamate insecticides, beta-naphthol and synthetic leather tanning chemicals, and surfactants (e.g. naphthalene sulfonates), and crystalline naphthalene is used as a moth repellent and toilet bowl deodorant.

Production. Naphthalene is produced from either coal tar (of which it is the most *abundant* constituent) or petroleum. Production of naphthalene in 2000 was 235 million pounds, most of which (219 million pounds) was produced from petroleum.

Environmental Exposure. The main source of exposure to naphthalene is through inhalation in ambient and indoor air. The average daily intake of naphthalene from ambient air has been estimated to be 19 μg, based on an average naphthalene concentration of 0.95 $\mu g/m^3$ in urban and suburban air and an inhalation rate of 20 m^3/day. Accidental ingestion of naphthalene-containing household products has been reported, especially in children. Dermal exposure to naphthalene may occur through handling or wearing of clothing stored with naphthalene-containing moth repellents.

Occupational exposure. The National Occupational Exposure Survey, conducted from 1981 to 1983, estimated that 112,702 workers potentially were exposed to naphthalene. Workers identified by the U.S. Environmental Protection Agency (EPA) as potentially exposed to naphthalene include beta-naphthol makers, celluloid makers, coal tar workers, dye chemical makers, fungicide makers, hydronaphthalene makers, moth repellent workers, phthalic anhydride makers, smokeless powder makers, tannery workers, textile chemical workers, and aluminum reduction plant workers. Air concentrations of naphthalene have been measured in many studies and vary with the type of industry. A survey by the National Institute for Occupational Safety and Health (NIOSH) in 1980 reported air concentrations of naphthalene as high as 10.2 $\mu g/m^3$ in an area sample and 19.3 $\mu g/m^3$ in a personal sample.

Regulations. Naphthalene is regulated by the EPA (under the Clean Air Act, Clean Water Act, Safe Drinking Water Act, Resource Conservation and Recovery Act, Superfund Amendments and Reauthorization Act, and Toxic Substances Control Act), the Occupational Safety and Health Administration (OSHA) and the U.S. Food and Drug Administration. OSHA has established an eight-hour time-weighted-average permissible exposure level for naphthalene of 10 ppm (50 mg/m^3), which is consistent with recommendations by NIOSH and the American Conference of Governmental Industrial Hygienists.

Human Cancer Studies

Two case-series studies of cancer occurring in individuals exposed to naphthalene have been reported: laryngeal and other cancers occurring in naphthalene-exposed workers in Germany and colorectal carcinoma occurring among individuals in Africa who had used a naphthalene compound for medicinal reasons. The available data are insufficient for evaluation of the carcinogenicity of naphthalene in humans.

Studies in Experimental Animals

The NTP published two-year carcinogenicity studies of naphthalene administered by inhalation to $B6C3F_1$ mice (NTP 1992) and F344/N rats (NTP 2000). These studies showed no evidence of carcinogenic activity of naphthalene in male $B6C3F_1$ mice; some evidence of carcinogenic activity in female $B6C3F_1$ mice, based on increased incidence of pulmonary alveolar/bronchiolar adenoma; and clear evidence of carcinogenic activity in male and female F344/N rats, based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose. The strain A mouse lung tumor bioassay showed a slight, but not statistically significant, increase in alveolar adenoma in female mice exposed to naphthalene, and the number of tumors per tumor-bearing lung was significantly increased. There was no evidence that naphthalene was carcinogenic in rats by routes of administration other than inhalation; however, these studies are considered inadequate, as the numbers of animals in these experiments were small, and there were no controls.

Genotoxicity

Naphthalene has been tested for genotoxicity in bacterial, non-mammalian, and mammalian systems. In general, naphthalene is not mutagenic in bacteria or in mammalian cell systems. Naphthalene did not induce mutations in bacteria (*Salmonella typhimurium* or *Escherichia coli*) or in human lymphoblastoid cells. In non-mammalian *in vivo* systems, naphthalene induced mutations in fruitflies (*Drosophila melanogaster)* and micronuclei in salamander larvae *(Pleurodeles waltl)*. In mammalian *in vitro* cells systems, naphthalene did not induce cell transformation (in mouse mammary gland cells or rat or mouse embryo cells), DNA strand breaks (in rat hepatocytes), or kinetochore-positive micronuclei (in human lymphoblastoid cells), which are a marker for chromosomal loss. However, positive results were observed for chromosomal aberrations (in Chinese hamster ovary [CHO] cells), sister-chromatid exchange (in CHO cells), and kinetochore-negative micronuclei (in human lymphoblastoid cells), which are a marker for chromosomal breakage. *In vivo* exposure to naphthalene induced oxidative stress and DNA damage in Sprague-Dawley rats.

Other Relevant Data

Absorption, excretion, and metabolism in animals and humans. Naphthalene is rapidly absorbed and metabolized when inhaled or administered dermally or orally to animals. Naphthalene is excreted in the urine as the unchanged parent compound, as metabolites (including 1-naphthol, 2-naphthol, naphthoquinones, and dihydroxynaphthalenes), or as glutathione (GSH), cysteine, glucuronic acid, and sulfate conjugates. Urinary naphthalene metabolites found in workers at a coke plant correlated significantly with naphthalene concentrations in personal air samples, indicating that naphthalene is absorbed in humans. The first step in the metabolism of naphthalene is the formation of naphthalene-1,2-oxide by cytochrome P450 in the presence of NADPH, which is converted to the trans-1,2-diol and other products. The electrophilic naphthalene intermediates are metabolized to naphthoquinones and possibly to free-radical intermediates; *in vivo*, these metabolites contribute to depletion of GSH, and excess metabolites may bind covalently to tissue macromolecules. Higher rates of metabolism in microdissected airways have been reported to occur in mice than in rats or hamsters.

Toxicity. The toxicity of naphthalene is manifested primarily in the hematologic system in humans and dogs (hemolytic anemia), the pulmonary system in rodents (lung injury) and the eye in humans and rodents (lens opacity and cataracts).

Potential mechanisms of carcinogenicity. Naphthalene induced lung neoplasia in female B6C3F$_1$ mice and nasal tumors in male and female F344/N rats. The mechanism of action has not been elucidated. Toxicity of naphthalene to lung and other tissues has been attributed to formation of the 1*R*,2*S*-naphthalene oxide; a strong correlation has been reported between the rates of formation of 1*R*,2*S*-naphthalene oxide in various tissues and tissue-selective toxicity. Naphthalene-induced oxidative damage and DNA breakage, which have been observed in rat liver and brain tissue, may contribute to the toxicity and carcinogenicity of naphthalene. Mice appear to be more susceptible to induction of lung neoplasia by epoxides and epoxide-forming chemicals than are rats. Differences between rats and mice in the metabolism of naphthalene by nasal epithelia and in nasal anatomy may contribute to the species differences in susceptibility to these tumors.

Table of Contents

List of Tables

List of Figures

1 Introduction

Naphthalene is the most abundant constituent of coal tar. Naphthalene is produced by condensation and separation of coal tar from coke-oven gases or from petroleum by dealkylation of methylnaphthalenes. In the United States, most naphthalene is produced from petroleum. The principal use of naphthalene is as an intermediate in the production of phthalic anhydride, which is used as an intermediate in the production of phthalate plasticizers, resins, dyes, insect repellents, and other materials. It also is used in some moth repellents and toilet bowl deodorizers.

Naphthalene was nominated by the National Institute of Environmental Health Sciences for possible listing in the Report on Carcinogens based on the results of National Toxicology Program (NTP) two-year inhalation studies of naphthalene, which concluded that there was clear evidence of carcinogenicity in male and female F344/N rats (respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose) and some evidence of carcinogenicity in female $B6C3F_1$ mice (pulmonary alveolar/bronchiolar adenomas). Naphthalene was also recently evaluated by an IARC Working Group (IARC 2000).

1.1 Chemical identification

Naphthalene ($C_{10}H_8$, mol wt 128.17, CASRN 91-20-3) also is known as naphthalin, naphthene, naphthaline, mothballs, moth flakes, tar camphor, white tar, and camphor tar (NTP 2001). Its RTECS number is QJ0525000, and its DOT number is UN1334, UN2304 (Chemfinder 2002). The structure of naphthalene is illustrated in Figure 1-1.

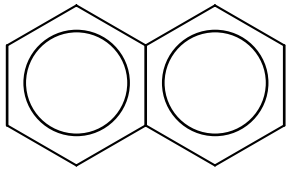


Figure 1-1. Structure of naphthalene

1.2 Physical-chemical properties

Naphthalene occurs as white monoclinic plates, scales, powder, balls, or cakes, with the distinctive odor usually associated with mothballs. It is insoluble in water and soluble in alcohol, benzene, ether, chloroform, carbon tetrachloride, and fixed and volatile oils. It reacts with strong oxidizers and may attack some forms of plastics, rubber, and coatings. Naphthalene is sensitive to heat and volatilizes at room temperature. It sublimes appreciably at temperatures above its melting point and is volatile with steam. It carries two nonequivalent sets of hydrogen atoms; two isomers of every monosubstituted naphthalene are known (HSDB 2002a, NTP 2001). The physical and chemical properties of naphthalene are summarized in Table 1-1.

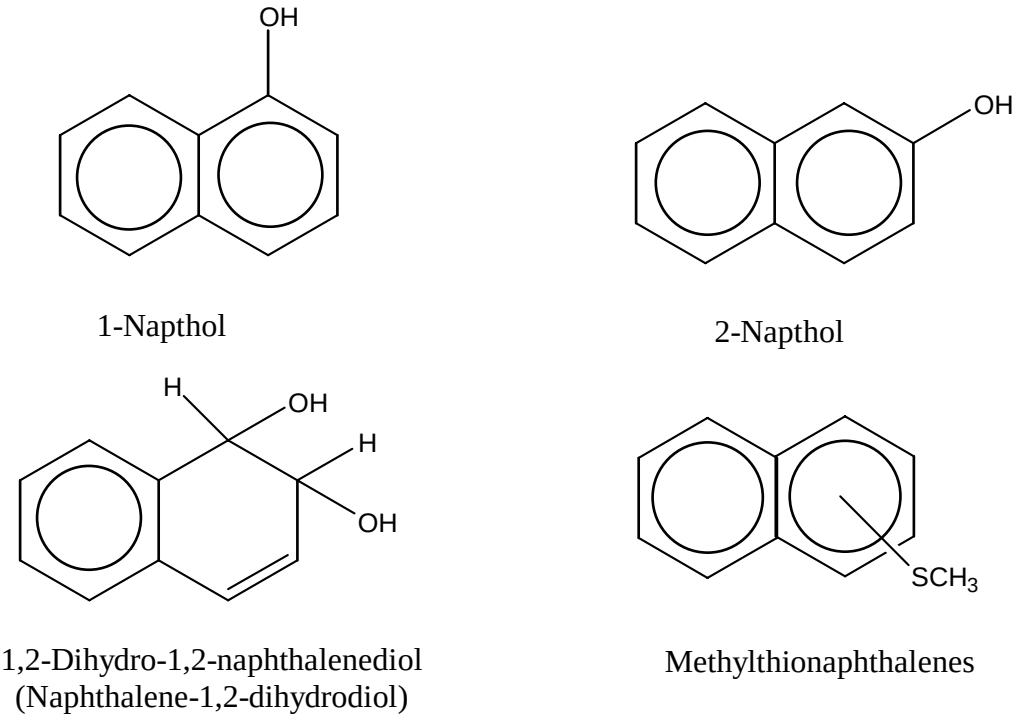
Table 1-1. Physical and chemical properties of naphthalene

Property	Information	Reference
Molecular weight	128.17	Budavari *et al*. 1996
Color	white colorless to brown	Budavari *et al*. 1996 NIOSH 2001
Odor	odor of mothballs	Budavari *et al*. 1996
Physical state	monoclinic prismatic plates, white scales, powder, balls or cakes	Budavari *et al*. 1996
Melting point (°C)	80.2	Budavari *et al*. 1996
Boiling point (°C)	217.9	Budavari *et al*. 1996
Flash point, (°C)	79	Budavari *et al*. 1996
Density at 20°C/4°C (g/cm^3)	1.162	Budavari *et al*. 1996
Vapor pressure (mm Hg)	0.08	NIOSH 2001
Solubility: water benzene chloroform or carbon tetrachloride 95% ethanol ether methanol fixed and volatile oils	 < 1 mg/mL 1 g/3.5 mL 1 g/2 mL 10–50 mg/mL soluble 1 g/13 mL soluble	 NTP 2001 Budavari *et al*. 1996 Budavari *et al*. 1996 NTP 2001 Budavari *et al*. 1996 Budavari *et al*. 1996 Budavari *et al*. 1996
Octanol-water partition coefficient: log K_{ow}	3.30	HSDB 2002a

1.3 Identification of urinary metabolites

The urinary metabolites of naphthalene following oral administration to rats and rabbits and intraperitoneal (i.p.) administration in mice, rats, and guinea pigs were identified. All species excreted 1- and 2-naphthol, 1,2-dihydro-1,2-naphthalenediol, 1-naphthylsulfate, and, except for guinea pigs, 1-naphthylglucuronic acid. Rats and rabbits excreted 1,2-dihydro-2-hydroxy-1-naphthylglucuronic acid, whereas guinea pigs excreted unconjugated 1,2-naphthalenediol (ATSDR 1995).

The structures of four major urinary metabolites of naphthalene are shown in Figure 1-2.



1-Napthol

2-Napthol

1,2-Dihydro-1,2-naphthalenediol
(Naphthalene-1,2-dihydrodiol)

Methylthionaphthalenes

Figure 1-2. Major metabolites of naphthalene

2 Human Exposure

2.1 Uses

The principal use of naphthalene in the United States is as an intermediate in the production of phthalic anhydride. Phthalic anhydride is an intermediate in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellents, and other materials. Naphthalene also is used as an intermediate in the production of 1-naphthyl-*N*-methylcarbamate insecticides, beta-naphthol and synthetic leather tanning chemicals, and surfactants such as naphthalene sulfonates, which are used as dispersants or wetting agents in paint, dye, and paper-coating formulations. It formerly was used as an intermediate in 1-naphthylamine synthesis. Crystalline naphthalene is used as a moth repellent and toilet bowl deodorant. It was used in the early 1900s as an antiseptic, expectorant, and antihelminthic. It was administered for gastrointestinal tract diseases and applied externally for the treatment of skin disorders (ATSDR 1995, HSDB 2002a).

In 1987, the consumption pattern for naphthalene was 60% for production of phthalic anhydride, 10% for production of 1-naphthyl-*N*-methylcarbamate insecticides and related products (tetralin and 1-naphthol), 10% for production of dispersant chemicals, 6% in moth repellents, 5% for production of synthetic tanning agents, 5% for miscellaneous uses, and 4% for exports (HSDB 2002a). In 1999, the consumption pattern had not changed significantly, with 59% used for production of phthalic anhydride, 21% for production of surfactant and dispersant chemicals, 11% for production of 1-naphthyl-*N*-methylcarbamate insecticides, and 9% in moth repellents and for other purposes (ChemExpo 1999). The Chemical Economics Handbook (CEH 2000) also reported consumption patterns for naphthalene for 1995 and 2000 and projected them for 2004. Table 2-1 summarizes naphthalene consumption patterns for those years.

Table 2-1. Naphthalene consumption patterns

Use	Consumption in million pounds (thousand metric tons)		
	1995	2000	2004 (projected)
Phthalic anhydride	145 (66)	146 (66)	147 (67)
Naphthalene sulfonates[a]	47 (21)	59 (27)	65 (29)
Pesticides[b]	38 (17)	30 (14)	10 (5)
Dyestuff intermediates	0 (0)	0 (0)	0 (0)
Other[c]	5 (2)	6 (3)	6 (3)

Source: CEH 2000.

[a]Includes alkylnaphthalene sulfonates and naphthalene sulfonate–formaldehyde condensates, which are used in concrete additives and synthetic tanning agents.

[b]Includes carbaryl and moth repellents.

[c]Includes diisopropyl naphthalene, naphthalene dicarboxylic acid, tetrahydronaphthalene, decahydronaphthalene, and chloronaphthalenes.

2.2 Production

Naphthalene is produced from either coal tar or petroleum (ATSDR 1995) and is the most abundant constituent of coal tar, which contains about 11% naphthalene by dry weight. Naphthalene crystallizes from the middle, or "carbolic oil," fraction of distilled tar and is purified by hot pressing, which may be followed by washing with sulfuric acid, sodium hydroxide, and water, then by fractional distillation or by sublimation (HSDB 2002a). Naphthalene content in crude oil is as follows: 100 to 2,800 mg/kg in oil from coal; 402 to 900 mg/kg in oil from petroleum and 203 to 1,390 mg/kg in oil from shale (WHO 1998).

Since 1960, the most common commercial production process in the United States has been recovery of naphthalene from petroleum. Petroleum is dealkylated of its methyl naphthalenes in the presence of hydrogen at high temperatures and pressure; naphthalene then is recovered by fractionation, decolorized, and purified by crystallization. Naphthalene produced by this process is about 99% pure (ATSDR 1995).

U.S. naphthalene production and production capacity have been estimated by several sources. The Hazardous Substances Data Bank (HSDB 2002a) identified four producers of naphthalene in the United States in 1989: Allied-Signal Inc., in Ohio; Chemical Exchange Industries, Inc., in Texas; Koppers Industries, Inc., in West Virginia; and Texaco Inc., in Delaware. The Chemical Market Reporter (Greenberg 2000) reported production capacities for three U.S. companies that produced naphthalene in 1999; Advanced Aromatics produced naphthalene from aromatic petroleum fractions, whereas Allied-Signal and Koppers recovered naphthalene from coal tar. The respective production capacities of these three companies in 1999 were 40, 100, and 170 million pounds of chemical-grade naphthalene (ChemExpo 1999). In 2000, Koppers was the only U.S. company still producing naphthalene. In March 2000, Recochem Inc., based in Montreal, Canada, purchased Allied-Signal's naphthalene facility in Ohio, and Advanced Aromatics stopped producing naphthalene in order to concentrate on the development and marketing of naphthalene derivatives (Greenberg 2000).

U.S. production of naphthalene peaked in 1968, with the production of 900 million pounds (409,000 metric tons). By 1982, production had significantly decreased to 354 million pounds (161,000 metric tons). Production capacity has remained level in recent years, with an estimated capacity of 349 million pounds (159,000 metric tons) in 1992 (ATSDR 1995). The Chemical Economics Handbook (CEH 2000) has estimated that production of naphthalene in the United States in 2000 was 235 million pounds (107 metric tons) which is 75% of the estimated U.S. production capacity. The CEH also estimated that 241 million pounds (109 metric tons) were consumed in 2000 (CEH 2000). The U.S. International Trade Commission reported production of naphthalene until 1983, and the CEH estimated production levels from 1975 to 2000. Table 2-2 summarizes naphthalene production from coal tars and petroleum.

Table 2-2. Production of naphthalene in the United States

Year	Production (millions of pounds)		
	From Coal Tar	From Petroleum	Total
1965	464	347	811
1970	428	291	719
1975	351	110	461
1976	354	107	461
1977	350	151	501
1978	346	157	503
1979	326	163	489
1980	314	136	450
1981	351	142	493
1982	230	126	356
1983	223	95	318
1984	190	85	275
1985	184	55	239
1986	185	55	240
1987	181	55	236
1988	181	50	231
1989	180	50	230
1990	180	50	230
1991	180	50	230
1992	172	30	202
1993	180	20	200
1994	221	16	237
1995	231	16	247
1996	223	17	240
1997	222	18	240
1998	228	17	245
1999	225	17	242
2000	219	16	235

Source: USITC reported production from coal tar for 1965, 1970, 1981, and 1982 and from petroleum for 1965, 1970, 1975, and 1977-1982. The remaining estimates are from the CEH 2000.

Historically, from 1989 to 1998, naphthalene demand grew 0.5% per year. Future growth is expected to be 1% per year through 2003. Demand for naphthalene sulfonates, used primarily as concrete super-plasticizer additives to increase flow properties, has grown steadily in recent years, but more slowly in the past few years. Demand was 246 million pounds in 1998 and 248 million pounds in 1999, and is projected at 265 million pounds in 2003 (ChemExpo 1999).

2.3 Analysis

Biological samples are analyzed mostly by gas chromatography/mass spectrometry (GC/MS). Naphthalene undergoes short-term bioaccumulation in tissues, but biochemical processes in the body lead to its eventual elimination. New immunological analysis methods are being developed; however, these are not ready for research and clinical practice. Table 2-3 summarizes analytical methods for determining naphthalene in biological samples.

Naphthalene in environmental samples most commonly is detected by GC and high-performance liquid chromatography (HPLC). Table 2-4 summarizes analytical methods determining naphthalene concentrations in environmental samples.

2.4 Environmental occurrence

2.4.1 Air

Most of the naphthalene that enters the environment is discharged to the air (92.2%). The largest amount released (50%) is in fugitive emissions and exhaust from the combustion of wood and fossil fuels. The second-largest source of naphthalene releases is off-gassing from naphthalene-containing moth repellents. Virtually all the naphthalene contained in moth repellents is emitted into the atmosphere at room temperature. In 1989, 12 million pounds of naphthalene was released into the air from moth repellent use. Naphthalene also enters the environment from coal tar pitch fumes, unvented kerosene space heaters, smoke from forest fires, and tobacco fumes. An unfiltered American cigarette contains 2.8 μg of naphthalene, and smoke from a filtered “little cigar” contains 1.2 μg of naphthalene (ATSDR 1995, HSDB 2002a).

The U.S. Environmental Protection Agency’s (EPA’s) Toxic Release Inventory (TRI) reported that in 1999, 2,707,249 lb of naphthalene was released to air from manufacturing and processing facilities in the United States. Because only certain types of facilities are required to report releases, the TRI data are not exhaustive and should be used with caution (TRI99 2001).

Table 2-3. Analytical methods for determining naphthalene in biological samples

Sample matrix	Preparation method	Analytical method	Detection limit	Recovery (%)	Reference
Adipose tissue	extract, bulk lipid removal, Florisil fractionation	high-resolution gas chromatography (HRGC)/MS	9 ng/g	no data	ATSDR 1995
Adipose tissue	extract with hexane, Florisil cleanup	capillary column GC/MS	10 ng/g	90, human	ATSDR 1995
Human milk	purge with helium, desorb thermally	capillary column	no data	no data	ATSDR 1995
Human urine (1-naphthol analysis)	no data	thin-layer chromatography or GC/unspecified spectroscopy	no data	no data	Bieniek 1994
Human urine (naphthalene metabolites)	untreated	LC-MS with pneumatically assisted electrospray interface (ESI)	0.1 mg/L (α-naphthol); 0.02 mg/L (α-naphthylglucuronide); 0.01 mg/L (β-naphthylsulphate)	no data	Andreoli *et al.* 1999
Burned tobacco	extract with methanol/water and cyclohexane, enrich in dimethyl sulfoxide, fractional distillation and evaporation under dry nitrogen	gas-liquid chromatography/MS	no data	85–96	ATSDR 1995

Source: ATSDR 1995, updated with additional references.

Table 2-4. Analytical methods for determining naphthalene in environmental samples

Sample matrix	Preparation method	Analytical method	Detection limit	Recovery (%)	Reference
Air	adsorb (Charcoal or Chromosorb); desorb (carbon disulfide)	GC/flame ionization detector (FID)	1–10 μg/sample; 4 μg/sample	no data	ATSDR 1995
Air	adsorb (solid sorbent); desorb (carbon disulfide)	HPLC/ultraviolet (UV) spectrometry	0.6–13 μg/sample	no data	ATSDR 1995
Air	adsorb (solid sorbent); desorb (carbon disulfide)	GC/FID	0.3–0.5 μg/sample	no data	ATSDR 1995
Air	collect in charcoal tube, extract with acetonitrile	HPLC/fluorescence detection	0.080 μg/filter or 0.070 μg/tube	no data	Hansen *et al.* 1991
Indoor air	medium flow rate samples: extract with methylene chloride, exchange to cyclohexane, clean up, exchange to acetonitrile	HPLC/ultraviolet (UV) spectrometry	250 pg/μL	no data	ATSDR 1995
Indoor air	medium flow rate samples: extract with methylene chloride	GC/MS	no data	no data	ATSDR 1995
Water	purge and trap	HRGC/photoionization detection (PID)	0.06 μg/L	102 ± 6.3	ATSDR 1995
Drinking-, ground- and surface water	purge (inert gas); trap (Chromosorb W); desorb into capillary GC column	GC/MS	0.04 μg/L	no data	ATSDR 1995
Drinking water and raw source water	purge (inert gas); trap (Chromosorb W); desorb into capillary GC column	GC/PID	0.01–0.06 μg/L	no data	ATSDR 1995
Drinking Water	extract in liquid-solid extractor; elute with methylene chloride; dry; concentrate	HPLC/UV/FD	2.20 μg/L	no data	ATSDR 1995
Drinking water	purge and trap	packed column GC/PID	0.01–0.05 μg/L	92	ATSDR 1995

Sample matrix	Preparation method	Analytical method	Detection limit	Recovery (%)	Reference
Drinking water	purge and trap	capillary column GC/MS	0.02–0.2 μg/L	98–104	ATSDR 1995
Drinking water	purge and trap	capillary column GC/PID	no data	102	ATSDR 1995
Wastewater, municipal and industrial	extract with methylene chloride; dry; concentrate	HPLC/UV or GC/FID	0.01–0.06 μg/L	no data	EPA 1996b, 1996f, 1999a
Wastewater, municipal and industrial	extract with methylene chloride; dry; concentrate	GC/MS	1.6 μg/L	no data	EPA 1999b
Wastewater, municipal and industrial	add isotope labeled analogue; extract with methylene chloride; dry over sodium sulfate; concentrate	GC/MS	10 μg/L	no data	EPA 1999c
Wastewater	extract with methylene chloride, exchange to cyclohexane, clean up, exchange to acetonitrile	HPLC/UV	1.8 μg/L	21.5–100	ATSDR 1995
Solid Waste matrices[b]	purge (inert gas); trap (Tenax or Chromosorb W); desorb into capillary GC column	GC/PID	0.06 μg/L	no data	EPA 1996a
Solid Waste matrices[b]	purge (inert gas); trap (Tenax or Chromosorb W); desorption or headspace sampling or direct injection	GC/MS	0.04–0.1 μg/L	no data	EPA 1996c
Air Sampling media, water samples, solid waste matrices, soil samples	liquid-liquid extraction or Soxhlet extraction or ultrasonic extraction or waste dilution or direct injection	GC/MS	10 μg/L (aqueous); 660 μg/kg (soil/sediment) Estimated quantitation limit	no data	EPA 1996d
Soils, sludges, solid wastes	Thermal extraction; concentrate; thermal desportion	TE/GC/MS	0.01–0.5 mg/kg	no data	EPA 1996e
Wastewater, soil, sediment, solid waste	liquid-liquid extraction (water); Soxhlet or ultrasonic extraction (soil/sediment/waste)	GC/FT-IR	20 μg/L	no data	EPA 1996g

Source: ATSDR 1995, updated with additional references.

[a] Identification limit in water. Detection limits for actual samples are several orders of magnitude higher, depending upon the sample matrix and extraction procedure employed.

[b] Includes: groundwater, aqueous sludges, caustic and acid liquors, waste solvents, oily waters, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments.

2.4.2 Water

About 5% of naphthalene entering the environment is released to water. Most of this is from coal tar production and distillation. Other sources of naphthalene in water are oil spills and effluents from the wood-preserving industry (ATSDR 1995).

The Toxic Release Inventory reported that in 1999, 42,067 lb of naphthalene was released to water from manufacturing and processing facilities in the United States. Because the TRI data are not exhaustive, they should be used with caution (TRI99 2001).

2.4.3 Soil

About 2.7% of naphthalene entering the environment is discharged to land. The major source of land releases is coal tar production, with minor contributions from naphthalene production, sludge disposal from sewage treatment facilities, and use of naphthalene-containing organic chemicals (ATSDR 1995).

The Toxic Release Inventory reported that in 1999, 447,129 lb of naphthalene was released to land and 166,064 lb to underground land injection release from manufacturing and processing facilities in the United States. Because the TRI data are not exhaustive, they should be used with caution (TRI99 2001).

2.5 Environmental fate

2.5.1 Air

The most important process by which naphthalene is removed from the atmosphere is degradation through reaction with photochemically produced hydroxyl radicals. The rate of this reaction is 2.17×10^{-11} cm^3/molecule-sec, with a half-life of 3 to 8 hours. The major by-products are 1- and 2-naphthol and 1- and 2-nitronaphthalene. Although photolysis is expected to occur, no experimental data on photolysis of naphthalene were found. In polluted urban air, reaction of naphthalene with NO_3 radicals may result in additional loss from the atmosphere. Naphthalene also will react with N_2O_5, nitrate radical, and ozone in the atmosphere (ATSDR 1995, HSDB 2002a).

2.5.2 Water

Photolysis, volatilization, biodegradation, and adsorption all may be important loss mechanisms for naphthalene discharged into water. The half-life of naphthalene is estimated to be around 71 hours in surface water and 550 days in deeper water (5 meters). Biodegradation of naphthalene is expected to be a dominant fate process in aquatic ecosystems. In oil-contaminated water not exposed to sunlight (because the water is murky or the water depth is great), biodegradation of naphthalene has a half-life of 7 days. In unpolluted water, biodegradation occurs slowly, with a half-life of 1,700 days (ATSDR 1995, HSDB 2002a).

2.5.3 Soil

The sorption of naphthalene to soil will be low to moderate, depending on the soil's organic carbon content, and is not considered to be the major fate process. Naphthalene is expected to biodegrade to carbon dioxide in aerobic soils, with salicylate as an intermediate product. Abiotic degradation of naphthalene is not expected to occur in soil

(ATSDR 1995). Naphthalene's biodegradation rate in soils varies considerably. The estimated half-life of naphthalene in a solid-waste site was 3.6 months. Its half-life was 11 to 18 days in soils with 0.2% to 0.6% organic carbon and 92% to 94% sand and 2 to 3 days in sandy loam with 0.5% to 1% organic carbon (ATSDR 1995). When naphthalene was incubated in two sandy loam soils at concentrations typical of those in waste-disposal sites, 30% of the naphthalene was lost by volatilization in 48 hours, and its half-life in the two soils was 2.1 and 2.2 days (HSDB 2002a).

2.6 Environmental exposure

The main source of exposure to naphthalene is through inhalation in ambient and indoor air. Exposure to small amounts of naphthalene through drinking water also may occur. Naphthalene was detected in 2 of 13,980 samples of food analyzed in six states. Accidental ingestion of naphthalene-containing household products has been reported, especially in children. In 1990, 72 poison control centers in the United States reported 2,400 cases of accidental naphthalene exposure. Dermal exposure to naphthalene may occur through handling or wearing of clothing stored with naphthalene-containing moth repellents (ATSDR 1995).

2.6.1 Air

Exposure of the general public to naphthalene in indoor air most likely occurs through the use of naphthalene-containing moth repellents and smoking. Kerosene heaters may be another source of indoor exposure. Levels of naphthalene in indoor air were measured in various homes at levels ranging from 0.860 to 1,600 $\mu g/m^3$. However, according to the author, the upper range limit may be an error (ATSDR 1995).

The general public is exposed to naphthalene in ambient air, particularly in areas with heavy traffic, near petroleum refineries or coal tar distillation facilities, or where evaporative losses from the storage, transport, transfer, or disposal of fuel oil occurs. The average reported concentration of naphthalene in 67 air samples at several locations in the United States was 0.991 ppb (5.19 $\mu g/m^3$). The median naphthalene level in air at urban sites in 11 U.S. cities was 0.18 ppb (0.94 $\mu g/m^3$) (ATSDR 1995).

An average naphthalene concentration of 170 $\mu g/m^3$ in ambient air was measured in a residential area in Ohio, while a concentration of 3.3 $\mu g/m^3$ was measured in California. Ambient air at five hazardous waste sites and one landfill in New Jersey ranged from 0.42 to 4.6 $\mu g/m^3$ (0.08 to 0.88 ppb), while the average concentration inside cars in commuter traffic was reported at 4.5 $\mu g/m^3$ (ATSDR 1995).

Based on an average naphthalene concentration of 0.95 $\mu g/m^3$ in urban and suburban air and an inhalation rate of 20 m^3/day, daily intake of naphthalene from ambient air has been estimated at 19 μg (ATSDR 1995).

2.6.2 Water

Naphthalene rarely is detected in drinking water. Only one area in the United States reported naphthalene in the drinking water at levels up to 1.4 μg/L. Naphthalene has been detected in the surface water and groundwater in the United States. Data collected from

EPA's water quality storage and retrieval (STORET) database indicate that for 1980 to 1982, 7% of 630 ambient water samples contained naphthalene. The median concentration in these samples was less than 10 μg/L. Naphthalene was detected in 11% of 86 urban runoff samples at concentrations ranging from 0.8 to 2.3 μg/L. Naphthalene also was detected in 35% of groundwater samples at five wood-treatment facilities at an average concentration of 3,312 μg/L (ATSDR 1995).

Based on a concentration range of 0.001 to 2 μg/L, naphthalene exposure from drinking water is estimated at 0.002 to 4 μg per day (ATSDR 1995).

2.6.3 Soil

Naphthalene has been reported at low concentrations in uncontaminated soils, with levels ranging from 0 to 3 μg/kg in untreated agricultural soils. In contaminated soils, naphthalene levels reached 6.1 μg/g in soil contaminated with coal tar, up to 66 μg/kg in sludge-treated soils, and 16.7 mg/kg in soil from a former tar-oil refinery. However, exposure of the general public to naphthalene in soil is not expected (ATSDR 1995).

2.6.4 Other

Naphthalene has rarely been detected in food products in the United States. In a study in six states, naphthalene was detected in two out of 13,980 food samples. Naphthalene concentrations were reported ranging from 5 to 176 ng/g in oysters, 4 to 10 ng/g in mussels, and from less than 1 to 10 ng/g in clams from waters in the United States (ATSDR 1995).

Naphthalene was detected in ash from municipal refuse and hazardous waste incinerators at levels ranging from 6 to 28,000 μg/kg and 0.17 to 41 mg/kg, respectively. The level of naphthalene in smoke from an unfiltered cigarette was 3 μg, while the level in sidestream smoke was 46 μg/cigarette (ATSDR 1995).

2.7 Occupational exposure

EPA has identified these individuals as having potential exposure to naphthalene in the workplace: beta-naphthol makers, celluloid makers, coal tar workers, dye chemical makers, fungicide makers, hydronaphthalene makers, moth repellent workers, phthalic anhydride makers, smokeless powder makers, tannery workers, textile chemical workers, and aluminum reduction plant workers. The highest reported vapor concentrations occurred in an area described as "naphthalene melt present" and ranged from 1,600 to 1,100,000 μg/m^3 (0.3 to 220 ppm) (EPA 1980). Concentrations in other industrial areas were lower. The air concentrations of naphthalene in an aluminum reduction plant were 0.72 to 311.3 μg/m^3 (0.1 to 59.5 ppb) as vapor and 0.090 to 4.00 μg/m^3 as a particulate (Bjørseth *et al.* 1978a). Levels at a coke oven were 11.35 to 1,120 μg/m^3 (2 to 214 ppb) as vapor and 0 to 4.40 μg/m^3 as a particulate (Bjørseth *et al.* 1978b). The air concentrations of naphthalene in work areas of a silicon carbide plant ranged from 1.3 to 58 μg/m^3 (0.2 to 11 ppb) (Dufresne *et al.* 1987). In another study, average naphthalene concentrations were 0.08 μg/m^3 (0.015 ppb) as vapor and 11.43 μg/m^3 as a particulate in paving/roofing/steel/silicon carbide industries, 16.30 μg/m^3 as a particulate in refractory

brick industries [no vapor concentration was reported], 0.01 μg/m^3 (0.002 ppb) as vapor and 75.40 μg/m^3 as a particulate in silicon carbide industries, and 0.52 μg/m^3 (0.1 ppb) as vapor and 1,111 μg/m^3 as a particulate in aluminum refinery industries (Lesage *et al.* 1987).

Hicks (1995) reported average naphthalene concentrations collected from the breathing zones of workers ranging from 2.3 μg/m^3 in hot mix plants to 7.5 μg/m^3 in roofing manufacturing industries. In the same study, dermal wipe samples collected from the back of the hand or forehead of selected workers showed detectable levels in less than 10% of the samples, with concentrations ranging from 5.5 to 520 ng/cm^3.

A survey by the National Institute for Occupational Safety and Health (NIOSH) in 1980 reported air concentrations of naphthalene as high as 10.2 μg/m^3 in an area sample and 19.3 μg/m^3 in a personal sample. The National Occupational Exposure Survey, conducted from 1981 to 1983, estimated that 112,702 workers potentially were exposed to naphthalene (ATSDR 1995).

2.8 Biological indices of exposure

Little information is available about metabolism of naphthalene in humans; however, urinary metabolites in various animal species have been reported (see Sections 1.3 and 6.1). Naphthol (isomer not specified) was found in the urine of a patient four days after naphthalene ingestion. In another study, urine of an 18-month-old child was found to contain 1-naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone nine days after exposure to naphthalene (ATSDR 1995).

1-Naphthol was found in the urine of workers employed in a plant that distilled naphthalene oil with concentrations ranging from 0.4 to 34.6 mg/L. A good statistical correlation was shown between naphthalene exposure between 0.2 and 6 mg/m^3 and urinary excretion of 1-naphthol (Bieniek 1994). Follow up studies show that most naphthalene metabolizes to 1-naphthol, 2-naphthol, and 1,4-naphthoquinone. Significant differences were found between the urine concentrations of 1- and 2-naphthol in workers exposed in a coke plant compared to non-exposed workers. A strong correlation ($r = 0.76$) was also found between the naphthalene in breathing-zone air and concentrations of 1-naphthol and 2-naphthol in post-shift urine. While occupational exposure to naphthalene can be determined by using 1-naphthol as a biomarker; using 1-naphthol to determine general exposure to naphthalene may be misleading because 1-naphthol is also excreted after exposure to the common insecticide carbaryl. Urinary 1-naphthol and 2-naphthol, however, seem to be useful biomarkers to determine naphthalene exposure (Bieniek 1997). A later study showed that smoking should be considered when using 1-naphthol and 2-naphthol as biomarkers for naphthalene exposure. Urinary levels were three and seven-fold higher for 1-naphthol and 2-naphthol, respectively, among smokers than among non-smokers. Genetic polymorphisms of CYP2E1 and GSTM1 also affected urinary levels of these naphthols. Diet and age were not a factor in the use of these urinary metabolites (Yang *et al.* 1999).

Using radiolabeled (^{14}C) naphthalene, *in vivo* percutaneous absorption studies were performed using spiked JP-8, the major jet fuel used by the U.S. Army and Air Force,

and excised pig ear skin and human skin. Naphthalene permeated significantly through both skins, and permeation rates were found to be proportional to its concentration in JP-8 (Kanikkannan *et al.* 2001a). JP-8 + 100 is a new fuel introduced by the U.S. Air Force that contains JP-8 and additives. Permeation of naphthalene in JP-8 + 100 was significantly higher in pig ear skin than that of JP-8 (Kanikkannan *et al.* 2001b).

In 1982, the National Human Adipose Tissue Survey detected naphthalene in wet adipose tissue with a frequency of 40%, at a concentration range of less than 9 to 63 ppb. Six of eight samples of mothers' milk from four U.S. urban areas had detectable levels of naphthalene (HSDB 2002a).

2.9 Regulations

EPA regulates naphthalene under the Clean Air Act (CAA) as a hazardous air pollutant and under the Clean Water Act (CWA) and the Safe Drinking Water Act (SWDA) as a water pollutant. EPA also regulates naphthalene under the Resource Conservation and Recovery Act (RCRA) and as a toxic chemical under the Superfund Amendments and Reauthorization Act (SARA) and subjects it to general threshold limits. Naphthalene is subject to reporting and recordkeeping rules under the Toxic Substances Control Act (TSCA). NIOSH has set an eight-hour time-weighted-average (TWA) recommended exposure limit (REL) of 10 ppm (50 mg/m^3), with a short-term exposure limit (STEL) ceiling of 15 ppm (75 mg/m^3). The American Conference of Governmental Industrial Hygienists (ACGIH) has set a threshold limit value of 10 ppm (52 mg/m^3), with a STEL ceiling of 15 ppm (79 mg/m^3). The Occupational Safety and Health Administration (OSHA) regulates naphthalene, with an eight-hour TWA permissible exposure level (PEL) of 10 ppm (50 mg/m^3).

EPA regulations are summarized in Table 2-5, and OSHA regulations in Table 2-6. No U.S. Food and Drug Administration regulations were found for naphthalene, although sodium mono- and di-methyl naphthalene sulfonates are allowed as food additives.

Table 2-5. EPA regulations

Regulatory action	Effect of regulation or other comments
40 CFR 60—PART 60—STANDARDS OF PERFORMANCE FOR NEW STATIONARY SOURCES. Promulgated: 36 FR 24877, 12/23/71. Subparts NNN and RRR.	The intent of these standards is to minimize the emissions of volatile organic compounds like naphthalene through the application of best demonstrated technology.
40 CFR 61—PART 61—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS. Promulgated: 38 FR 8826, 04/06/73. U.S. Code: 7401, 7412, 7414, 7416, and 7601.	This part lists substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants (HAPs). Naphthalene is classified as a hazardous air pollutant.

Regulatory action	Effect of regulation or other comments
40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Code: 7401 *et seq.*	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) air pollutants, such as naphthalene, are listed in this part pursuant to section 112(b) of the CAA. Areas where naphthalene is identified as a HAP are in the polymers and resin industries, wood manufacturing operations, off-site waste and recovery operations, and petroleum refineries.
40 CFR 116—PART 116—DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/78. U.S. Code: 33 U.S.C. 1251 et seq.	This regulation designates hazardous substances under section 311(b)(2)(a) of the FWPCA. The regulation applies to discharge of naphthalene to surface waters.
40 CFR 117—PART 117—DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. U.S. Code: FWPCA 311(b)(2)(A) and 501(a) as amended by the CWA of 1977.	Discharges to water of amounts equal to or greater than the reportable quantity (RQ) must be reported to EPA. The RQ for environmental releases to water of naphthalene is 10 lb (4.54 kg).
40 CFR 141—PART 141—NATIONAL PRIMARY DRINKING WATER REGULATIONS. Promulgated: 40 FR 59570, 12/24/75. U.S. Code: Public Health Service Act sections 1413–1416, 1445, and 1450 as amended by 1974 SDWA; U.S.C. 300.	To protect a safe drinking water supply, community and non-transient, non-community water systems must monitor for naphthalene.
40 CFR 172—PART 172—Subpart B—Table of Hazardous Materials and Special Provisions. Promulgated: 55 FR 52582, 12/21/90. Naphthalene has a UN number of 1334.	The Hazardous Materials Table in this section designates the materials listed therein as hazardous materials for the purpose of transportation of those materials. Naphthalene is identified in the table.
40 CFR 258—PART 258—CRITERIA FOR MUNICIPAL SOLID WASTE LANDFILLS. Promulgated: 56 FR 51016, 10/09/91. U.S. Code: 33 U.S.C. 1345(d) and (e); 42 U.S.C. 6907(a)(3), 6912(a), 6944(a), and 6949a(c).	The provisions of this part establish minimum national criteria under RCRA, as amended, for all municipal solid waste landfill (MSWLF) units and under the CWA, as amended, for MSWLF that are used to dispose of sewage sludge. The criteria ensure the protection of human health and the environment. The practical quantitation limit for naphthalene is 101 mg/L.
40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTE, Appendix VIII—Hazardous Constituents. Promulgated: 45 FR 33119, 05/19/80; 53 FR 13388, 04/22/88. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, 6922, and 6938.	Appendix VIII is a consolidated list of hazardous constituents identified in this part. Solid wastes containing these constituents are subject to notification requirements of RCRA section 3010 and must be disposed of in RCRA-permitted facilities. Naphthalene has a waste number of U165.
40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Code: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	Naphthalene is listed as a hazardous substance with an RQ of 100 lb (45.4 kg).

Regulatory action	Effect of regulation or other comments
40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Code: 42 U.S.C. 11013 and 11028.	This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of SARA (1986). Information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, and to aid in the development of regulations, guidelines, and standards. See section 372.65 for chemicals and chemical categories to which this part applies.
40 CFR 401—PART 401—GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74, as amended at 47 FR 24537, 06/04/82. U.S. Code: 33 U.S.C. 1251 *et seq.*	Regulations promulgated prescribe effluent limitations guidelines for existing sources, standards of performance for new sources, and pretreatment standards for new and existing sources. Naphthalene is considered a toxic pollutant.
40 CFR 704—PART 704—REPORTING AND RECORDKEEPING REQUIREMENTS. Promulgated: 49 FR 33653, 08/24/84; U.S. Code: 15 U.S.C. 2607(a).	This part specifies reporting and recordkeeping procedures under section 8(a) of TSCA for manufacturers, importers, and processors of chemical substances and mixtures such as naphthalene.
40 CFR 716—PART 716—HEALTH AND SAFETY DATA REPORTING. Promulgated: 51 FR 32726, 09/15/86. U.S. Code: 15 U.S.C. 2607(d).	The provisions of this part require the submission of lists and copies of health and safety studies on chemical substances and mixtures selected for priority consideration for testing rules under section 4(a) of TSCA and on naphthalene.

Source: The regulations in this table have been updated through the 2001 Code of Federal Regulations 40 CFR, 1 July 2001.

Table 2-6. OSHA regulations

Regulatory action	Effect of regulation or other comments
29 CFR 1910.1000—Sec. 1910.1000 Air contaminants. Promulgated: 58 FR 40191, 07/27/93. U.S. Code: 5 U.S.C. 553.	OSHA sets the PEL at 10 ppm (50 mg/m^3) as an 8-h TWA.
29 CFR 1915.1000—Sec. 1915.1000 Air contaminants. Promulgated: 61 FR 31430, 06/20/96.	OSHA sets the PEL at 10 ppm (50 mg/m^3) as an 8-h TWA for shipyards.

Source: The regulations in this table have been updated through the 2001 Code of Federal Regulations 29 CFR, 1 July 2001.

3 Human Cancer Studies

Two case-series of cancer occurring in individuals exposed to naphthalene have been reported: laryngeal and other cancers occurring in naphthalene-exposed workers in Germany and colorectal carcinoma occurring among individuals in Africa who had used a naphthalene compound for medicinal reasons. Wolf (1976, 1978, as cited in NTP 1992, 2000) reported a cluster of cancer including four cases of laryngeal and one case each of gastric and colon cancer occurring in 6 of 15 naphthalene distillation plant workers in East Germany (now part of the Federal Republic of Germany). Ajao *et al*. (1988) reported that of 23 cases of colorectal carcinoma diagnosed between June 1982 and 1984, 11 were in patients under 30 years of age. None of the early-onset cases were regarded as cases of familial polyposis. Half of the patients with early-onset colorectal cancer reported consumption of kafura, which is a naphthalene compound used to treat anorectal problems; the other half did not recall whether they had been treated with this compound as a child.

The available data are insufficient for evaluation of the carcinogenicity of naphthalene in humans.

4 Studies of Cancer in Experimental Animals

The NTP conducted two-year inhalation-exposure studies of the carcinogenicity of naphthalene in B6C3F$_1$ mice (NTP 1992, see Appendix A) and F344/N rats (NTP 2000, see Appendix B). Other relevant studies include short-term carcinogenicity tests (Tsuda *et al.* 1980, Adkins *et al.* 1986), an intraperitoneal injection study in mice (LaVoie *et al.* 1988), and a chronic feeding study in rats (Schmahl 1955, cited in NTP 2000). These data are reviewed in this section. The International Agency for Research on Cancer (IARC) reviewed naphthalene in February 2002 and concluded that naphthalene was possibly carcinogenic to humans based on sufficient evidence of carcinogenicity in experimental animals (Group 2B) (IARC 2002).

4.1 Studies in mice

4.1.1 NTP carcinogenicity bioassay

The NTP selected naphthalene for study because there was inadequate information for regulatory decisions and there was potential for chronic human exposure. This study (NTP 1992) also was published by Abdo *et al.* (1992). The purity of the naphthalene used in this study was greater than 99%; samples contained 0.23% water and 0.15% total impurities (NTP 1992).

Groups of 10- to 11-week-old B6C3F$_1$ mice (75 of each sex) were exposed to naphthalene by inhalation at a concentration of 0, 10, or 30 ppm (0, 50, or 150 mg/m^3), six hours/day, five days/week, for 104 weeks (NTP 1992). Two additional groups of mice (75 of each sex) were exposed to naphthalene at 30 ppm, to ensure that a sufficient number of high-dose animals survived to the end of the study. The original study design called for interim sacrifices at 14 days and 3, 6, 12, and 18 months for hematology evaluations. However, the 3-, 6-, 12-, and 18-month interim evaluations were cancelled because of high mortality in the male control group attributed to fighting-related wounds in the group housed mice.

To avoid condensation in the exposure chambers, the high concentration was approximately half of the saturation concentration for naphthalene vapor at 20°C. The low concentration was the ACGIH occupational threshold limit value. The available data indicate that occupational exposure to naphthalene vapor generally is much lower than the threshold limit value (< 0.001 to about 0.2 ppm); however, concentrations ranging from 0.3 to 220 ppm were reported in an industrial area described as “naphthalene melt present” (see Section 2.7).

Naphthalene vapor was generated by direct sublimation from a 500-mL flask and was delivered with nitrogen through metering valves. Average exposure-chamber concentrations were maintained within 20% of the target concentrations throughout the study period, except that during week 4, the average concentration in the low-dose chamber was only 5.5 ppm.

Mice were housed five per cage, with water available *ad libitum* and feed available *ad libitum* except during exposure periods. All animals were observed twice daily and were weighed at the beginning of the study, weekly for the first 13 weeks, and monthly

thereafter. Hematology parameters were measured for up to five mice of each sex from each chamber 14 days after study initiation. All animals were necropsied, and all organs and tissues were examined for grossly visible lesions. A complete histopathologic examination was performed on all control and high-dose animals and on all animals dying or killed moribund before 21 months. For the low-dose group, histopathologic examination was limited to the lungs and nasal cavity.

Naphthalene exposure did not significantly affect survival of female mice. However, in male mice, survival at the end of the study was 37%, 75%, and 89% in the control, low-dose, and high-dose groups, respectively, and increased survival was significantly associated with increasing exposure. Low survival in the control group was attributed to increased fighting in this group (see Appendix A, pp. A-25 and A-26, Table 3 and Figure 3 in NTP 1992). Nonetheless, more than 50% of the male control group survived to week 92, leaving a sufficient number for evaluation of carcinogenicity. Mean body weights of exposed female mice were slightly lower than, but within 10% of, the mean weight of the controls throughout the study. Mean body weights were slightly lower in exposed male mice than in controls for the first 18 months (see Appendix A, pp. A-23 to A-24, Figure 2 in NTP 1992). No clinical findings were attributed to naphthalene exposure.

Naphthalene exposure did not significantly increase the incidences of neoplasms in male mice. The incidences of pulmonary alveolar/bronchiolar adenoma, carcinoma, and alveolar/bronchiolar adenoma or carcinoma combined were similar in exposed and control male mice after adjustment for survival differences (Table 4-1). Tumor incidences generally were within the historical control ranges.

Increased incidences of some lung neoplasms, primarily alveolar/bronchiolar adenoma, were observed in high-dose female mice and attributed to naphthalene exposure (Table 4-1). Papillary adenoma of the nose was observed in two low-dose female mice, but not attributed to naphthalene exposure.

Alveolar/bronchiolar adenoma and carcinoma form a morphologic continuum. Adenomas were locally compressive nodular masses consisting of cords of well-differentiated epithelial cells, whereas carcinomas were composed of ribbons and/or coalescing sheets of smaller, more anaplastic cells, which sometimes extended into adjacent parenchyma (NTP 1992).

In addition to the neoplastic lesions, naphthalene exposure increased the incidences and severity of chronic inflammation of the nose and lungs, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium in the nose (Table 4-2). The more advanced inflammatory lesions were called “granulomatous inflammation” and were characterized by cellular infiltrates with large, foamy macrophages, sometimes accompanied by multinucleated giant cells. Although the severity of the non-neoplastic lesions generally was minimal to mild, they were considered features of an overall inflammatory response that was directly related to naphthalene exposure.

Table 4-1. Incidences of lung tumors in B6C3F$_1$ mice following inhalation exposure to naphthalene for two years

Sex	Conc. (ppm)	N	Lung tumor incidence (%)[a]		
			Adenoma	Carcinoma	Combined
Male	0	70	7 (25.7)	0 (0.0)	7 (25.7)
	10	69	15 (28.8)	3 (5.5)	17 (31.9)
	30	135	27 (22.7)	7 (5.9)	31 (26.0)
	Trend		NS	NS	NS
	HC[b]	478	69 (6–24)	30 (0–14)	94 (10–30)
Female	0	69	5 (8.3)	0 (0.0)	5 (8.3)
	10	65	2 (3.5)	0 (0.0)	2 (3.5)
	30	135	28 (25.6)**	1 (1.0)	29 (26.5)**
	Trend		$P \leq 0.001$	NS	$P \leq 0.001$
	HC[b]	466	27 (0–10)	13 (0–6)	39 (0–12)

Source: NTP 1992.

**$P \leq 0.01$, NS = not significant (logistic regression test).

[a]Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality.

[b]Historical control incidence from all NTP inhalation studies (range %).

Table 4-2. Incidences of non-neoplastic lesions in B6C3F$_1$ mice following inhalation exposure to naphthalene for two years

Sex	Conc. (ppm)	N	Incidence (%)				
			Nose			Lung	
			Chronic inflammation	Metaplasia olfactory epithelium	Hyperplasia respiratory epithelium	Chronic inflammation	Granulomatous inflammation
Male	0	70	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	10	69	67 (97)***	66 (96)***	66 (96)***	21 (30)***	19 (28)***
	30	135	133 (99)***	134 (99)***	134 (99)***	56 (41)***	15 (11)*
	Trend		$P \leq 0.001$	$P \leq 0.001$	$P \leq 0.001$	$P \leq 0.001$	NS
Female	0	69	1 (1)	0 (0)	0 (0)	3 (4)	0 (0)
	10	65	65 (100)***	65 (100)***	65 (100)***	13 (20)**	38 (58)***
	30	135	135 (100)***	135 (100)***	135 (100)***	52 (39)***	42 (31)***
	Trend		$P \leq 0.001$	$P \leq 0.001$	$P \leq 0.001$	$P \leq 0.001$	$P = 0.004$

Source: NTP 1992.

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (logistic regression test).

4.1.2 Strain A mouse lung tumor bioassay

The strain A mouse lung tumor bioassay was investigated as a short-term *in vivo* model for predicting the carcinogenicity of chemicals administered by inhalation (Adkins *et al.* 1986). These mice are highly susceptible to lung cancer and have been used extensively in bioassays for assessing the carcinogenic activity of many chemicals (Stoner *et al.* 1993). Groups of 30 female Strain A/J mice (six to eight weeks old) were exposed to reagent-grade naphthalene (98% to 99% purity) at a concentration of 0, 10, or 30 ppm, six hours/day, five days/week, for six months. The positive-control group of 20 mice received a single i.p. injection of urethane. Food and water were available *ad libitum* during nonexposure periods. The animals were sacrificed after six months, the lungs were removed and fixed for 24 hours, lung nodules were counted by three or more technicians, and sections of lungs with nodules were histopathologically examined. The mean numbers of adenomas per mouse were compared with a one-way analysis of variance (Kruskal-Wallis test).

Survival was not affected by naphthalene exposure. Of the 30 animals in each group, 29 survived in the chamber-control and high-dose groups and 27 in the low-dose group. All mice in the positive control group survived to the end of the study and developed adenomas, an average of 28.9 per mouse. The incidence of alveolar adenoma was slightly higher in the low-dose (29%) and high-dose (30%) groups than in the chamber controls (21%); however, the differences were not statistically significant. The average number of tumors per mouse, 0.21, 0.35, and 0.37 in the control, low-dose, and high-dose groups, respectively, did not differ significantly. The number of tumors per tumor-bearing lung was significantly greater ($P < 0.05$) in the naphthalene-exposed mice than in the chamber controls; however, the number of tumors per tumor-bearing lung was significantly lower

in the chamber controls than in historical controls of this mouse strain (Adkins *et al.* 1986).

4.2 Studies in rats

4.2.1 NTP carcinogenicity bioassay

NTP selected naphthalene for study in rats because of its carcinogenicity in mice (see Section 4.1.1) and because previous studies in rats had not used inhalation exposure and were inadequate. The naphthalene used in this study had total impurities of 0.6% (NTP 2000).

Groups of six-week-old F344/N rats (49 of each sex) were exposed to naphthalene by inhalation at a concentration of 0, 10, 30, or 60 ppm, six hours/day, five days/week, for 105 weeks, resulting in estimated daily doses of 0, 3.6 to 3.9, 10.7 to 11.4, or 20.1 to 20.6 mg/kg body weight (b.w.). The highest exposure level was the highest concentration that can be generated without condensation. For evaluation of toxicokinetic parameters, additional groups of rats (9 of each sex) were exposed to naphthalene at a concentration of 10, 30, or 60 ppm for up to 18 months. The animals were housed individually; water was available *ad libitum*, and feed was available *ad libitum* except during exposure periods. All animals were observed twice daily. Clinical findings were recorded every four weeks to week 92 and every two weeks thereafter. Animals were weighed at the beginning of the study, every four weeks from week 4 to week 92, and every two weeks thereafter. Complete necropsies and microscopic examinations were performed on all core study animals. All tissues and organs were examined for grossly visible lesions, and all major tissues were fixed and preserved for microscopic examination. Blood samples for toxicokinetic evaluation were drawn after 2 weeks and 3, 6, 12, and 18 months. The samples were collected from three males and three females per group at six time points after exposure (0 to 480 minutes for the 10-ppm group, 0 to 720 minutes for the 30-ppm group, and 0 to 960 minutes for the 60-ppm group) and analyzed for naphthalene concentrations.

Naphthalene vapor was generated from a 2-L glass reaction flask surrounded by a heated mantle. Heated nitrogen metered into the flask carried the vaporized naphthalene out of the generator, and the vapor was transported to the exposure room through a heated Teflon line. The vapor was diluted with heated air filtered through a high-efficiency particulate air filter and charcoal before entering a distribution manifold. Average concentrations were maintained within 1% of the target concentrations throughout the study period.

There were no significant differences in survival rates between exposed and control male or female rats (see Appendix B, pp. B-33 and B-34, Table 3 and Figure 2 in NTP 2000). Throughout the study, mean body weights were lower in exposed males than in controls, whereas mean body weights of exposed and control females were generally similar (see Appendix B, pp. B-35 to B-37, Figure 2 and Tables 4 and 5 in NTP 2000). There were no clinical findings related to naphthalene exposure.

Rats exposed to naphthalene had increased incidences of several neoplasms and nonneoplastic lesions of the nose. Lesions occurred in all three levels of the nasal cavity

that are routinely examined in NTP studies. Malignant nasal neoplasms frequently blocked the nasal passages or destroyed the normal architecture of the nasal turbinates and occasionally invaded the brain. Nasal neoplasms included neuroblastoma of the olfactory epithelium and adenoma of the respiratory epithelium (Table 4-3).

Neuroblastoma incidence showed a dose-related trend in both male and female rats, and the incidence in female rats at 60 ppm was significantly higher than that in chamber controls. Nasal adenoma incidence also showed a dose-related trend in male rats and was significantly increased in all exposed groups. The incidence of nasal adenoma was slightly higher in female rats at 30 or 60 ppm than in controls, but the differences were not significant. These types of nasal tumors are extremely rare in F344 rats. Neither neuroblastomas nor nasal adenomas were observed in any animals in historical control groups.

The neuroblastomas were variably sized unilateral or bilateral invasive masses that arose in Level III of the nasal cavity and extended into Levels I and II. Other masses extended along the mucosa and replaced the epithelium of the turbinates and nasal septum. The morphology of the neoplasms varied. Component neoplastic cells were round, polygonal, or spindle-shaped and arranged in variably sized irregular islands, cords, and rosettes separated by fibrovascular stroma. In other masses, component cells were arranged in a glandular pattern. Some cells had scant eosinophilic to amphophilic cytoplasm with pale oval to polygonal vesicular nuclei and prominent central nucleoli; others had abundant cytoplasm and elongate, intensely basophilic nuclei. Small nests of neoplastic cells were present in the lamina propria of the turbinates and nasal septum and in olfactory nerve bundles. A few neoplasms had focal irregular areas of squamous metaplasia, sometimes extensive, with formation of keratin pearls. Variably sized focal areas of coagulative necrosis also were observed in most neoplasms. Mitotic figures were abundant. Neoplams that invaded the cribriform plate extended into the olfactory lobes of the brain (NTP 2000).

Adenomas arose from the respiratory and transitional epithelia of Levels I and II of the nasal cavity along the medial or lateral aspects or tips of the nasoturbinates or the lateral wall. They were irregular exophytic, polypoid, pedunculated or broad-based sessile masses that varied in size and sometimes partially occluded the nasal passages. Component neoplastic cells were well differentiated, simple to cuboidal to columnar and arranged primarily as variably sized glands surrounded by scant fibrovascular stroma with few focal solid areas of cells. In some masses, the epithelium appeared to be pseudostratified. The glands often were variably distended by luminal accumulations of proteinaceous secretory material and cellular debris. A few adenomas were composed of less well differentiated cells that were squamoid in morphology; these cells were large, round to polygonal, with scant to moderate amounts of eosinophilic cytoplasm and large round to oval nuclei containing one or two prominent nucleoli (NTP 2000).

Table 4-3. Nasal tumor incidences in F344/N rats following inhalation exposure to naphthalene for two years

Sex	Conc. (ppm)	N	Tumor incidence (%)[a]

			Adenoma (respiratory epithelium)	Neuroblastoma (olfactory epithelium)	Brain metastasis
Male	0	49	0 (0.0)	0 (0.0)	0
	10	49	6 (15.3)*	0 (0.0)	0
	30	48	8 (20.6)**	4 (10.1)	0
	60	48	15 (38.1)***	3 (7.7)	2
	Trend		$P < 0.001$	$P = 0.027$	
	HC[b]	299	0	0	
Female	0	49	0 (0.0)	0 (0.0)	0
	10	49	0 (0.0)	2 (5.1)	1
	30	49	4 (9.8)	3 (7.2)	0
	60	49	2 (5.2)	12 (28.2)***	4
	Trend		$P = 0.066$	$P < 0.001$	
	HC[b]	299	0	0	

Source: NTP 2000.

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (poly-3 test).

[a]Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

[b]Historical control incidences based on all NTP inhalation studies that used the new NTP 2000 diet. Incidences from studies using the former NIH-07 diet were 0/1,048 males and 0/1,044 females.

Unlike mice (see Section 4.1.1), rats did not show increased incidences of lung neoplasms. Alveolar/bronchiolar adenoma or carcinoma combined occurred in 2/49, 3/49, 1/48, and 0/49 male rats exposed to naphthalene at 0, 10, 30, or 60 ppm, respectively. The only lung neoplasm observed in female rats was in the control group. The only effects in rat lung that may have been related to naphthalene exposure were minimal chronic inflammation (males) and alveolar epithelial hyperplasia (females).

Several non-neoplastic lesions of the nose were significantly more common in exposed rats than in chamber controls (see Appendix B, pp. B-39, Table 6 in NTP 2000). These included epithelial and goblet-cell hyperplasia, squamous metaplasia, and hyaline degeneration of the respiratory epithelium; atrophy, atypical (basal-cell) hyperplasia, inflammation, and hyaline degeneration of the olfactory epithelium; and hyperplasia and squamous metaplasia of the Bowman's glands in the olfactory region of the nose. Based on a severity scale with 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked, the severity of olfactory epithelial and glandular lesions increased in a dose-related manner from mild (1.9 to 2.2) to moderate (2.9 to 3.5) severity. Most of these lesions are commonly observed in inhalation studies with chemical irritants and are adaptive responses. Ward *et al.* (1993) reviewed 19 inhalation bioassays conducted by the NTP and reported that nasal lesions were reported for 5/5 nasal carcinogens and for 12/14 nasal noncarcinogens. They concluded that while cell proliferation may be a factor in multistage carcinogenesis, the association between cell proliferation and carcinogenesis is not always demonstrable.

Olfactory epithelial atypical (basal-cell) hyperplasia was not observed in the control groups, nor were similar lesions reported in other NTP inhalation studies. This lesion occurred in 88% to 98% of the exposed rats and increased in severity with dose. The cells involved in olfactory epithelial atypical hyperplasia and focal areas of intraepithelial hyperplasia or dysplasia appeared to form a continuum with the neuroblastoma. Respiratory epithelial adenoma was not clearly associated with any of the non-neoplastic lesions. Lung lesions that may have been related to naphthalene exposure included chronic inflammation (males) and alveolar epithelial hyperplasia (females) (Table 4-4).

Table 4-4. Incidences of selected non-neoplastic lesions in F344 rats following inhalation exposure to naphthalene for two years

Sex	Conc. (ppm)	N	Incidence (%)		
			Nose	Lung	
			Atypical hyperplasia olfactory epithelium	Chronic inflammation	Alveolar epithelial hyperplasia
Male	0	49	0 (0)	2 (4)	23 (47)
	10	49	48 (98)**	13 (27)*	12 (24)
	30	48	45 (94)**	6 (13)	9 (19)
	60	48	46 (96)**	15 (31)*[a]	16 (33)
Female	0	49	0 (0)	16 (33)	4 (8)
	10	49	48 (98)**	15 (31)	11 (22)*
	30	49	48 (98)**	19 (39)	11 (22)*
	60	49	43 (88)**	22 (45)	9 (18)

Source: NTP 2000.

*$P \leq 0.05$, **$P \leq 0.01$ (poly-3 test)

[a]49 rats examined.

4.2.2 Other studies

Tumors were not observed in rats orally administered naphthalene once daily, six days/week, for 700 days (Schmahl 1955, cited in NTP 2000). The total dose administered was 10 g, or about 41 mg/kg b.w. per day. No controls were reported, and only 28 rats were used. In the same study, rats given 820 mg of naphthalene subcutaneously or intraperitoneally over a 40-week period did not develop tumors.

Tsuda *et al.* (1980) investigated the induction of resistant hepatocytes as a possible short-term *in vivo* test for carcinogenicity by testing 21 carcinogenic chemicals and 7 noncarcinogenic analogs. Naphthalene was included as one of the noncarcinogenic analogs. Following exposure of rats to liver carcinogens, a small number of hepatocytes become resistant to the inhibitory effect of 2-acetylaminofluorene on cell proliferation stimulated by partial hepatectomy or administration of carbon tetrachloride. These resistant hepatocytes, detected by staining for gamma-glutamyl transpeptidase (γ-GT), are presumed to be preneoplastic lesions that can form hepatocytic nodules through clonal expansion. Twelve hours after partial hepatectomy, 8 rats were administered

naphthalene intragastrically at a dose of 100 mg/kg. A control group of 17 rats was administered the solvent vehicle (corn oil). The animals were fed a basal diet containing 0.02% 2-acetylaminofluorene from week 2 to week 4 after hepatectomy and were given carbon tetrachloride intragastrically at a dose of 2.0 mL/kg at the start of week 3. The animals were returned to the basal diet without 2-acetylaminofluorene after week 4, and were sacrificed at week 5. Rats given naphthalene did not differ significantly from controls in the number, area, or size of foci of resistant hepatocytes.

Groups of 31 male and 16 female CD1 mice were injected i.p. with a 0.05 M solution of naphthalene in dimethylsulfoxide (DMSO) at 1, 8, and 15 days of age (for a total dose of about 1.75 µmol) and examined at 52 weeks. Tumor incidence was not significantly higher than in control mice (21 of each sex) injected with DMSO alone (LaVoie *et al.* 1988).

4.3 Summary

The NTP published two-year carcinogenicity studies of naphthalene administered by inhalation to $B6C3F_1$ mice (NTP 1992) and F344/N rats (NTP 2000). These studies showed no evidence of carcinogenic activity of naphthalene in male $B6C3F_1$ mice; some evidence of carcinogenic activity in female $B6C3F_1$ mice, based on increased incidence of pulmonary alveolar/bronchiolar adenoma; and clear evidence of carcinogenic activity in male and female F344/N rats, based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose.

Other studies have shown weak to no evidence that naphthalene is carcinogenic in experimental animals. The strain A mouse lung tumor bioassay showed a slight, but not statistically significant, increase in alveolar adenoma in female mice exposed to naphthalene; however, the number of tumors per tumor-bearing lung was increased ($P < 0.05$). There was no evidence that naphthalene was carcinogenic in rats by routes of administration other than inhalation; however, the numbers of animals in these experiments were small, and there were no controls. In a short-term assay, rats given a partial hepatectomy followed by a single intragastric exposure to naphthalene, two weeks of exposure to 2-acetylaminofluorene in the diet, and a single intragastric dose of carbon tetrachloride did not develop increased numbers of resistant hepatocytes (as indicated by γ-GT activity).

5 Genotoxicity

The available literature on the genotoxicity of naphthalene (Sections 5.1–5.4) and naphthalene-related compounds (Section 5.5) is summarized below.

5.1 Prokaryotic systems

5.1.1 Reverse mutation in Salmonella typhimurium

In studies with *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, naphthalene at exposure levels of 0.3 to 100 μg/plate did not induce reverse mutation, with or without induced rat liver S9 metabolic activation (Mortelmans *et al.* 1986, NTP 1992, 2000). Negative results also were reported in the following studies, with and without S9 metabolic activation: McCann *et al*. (1975) (10 to 1,000 μg/plate), Kaden *et al*. (1979) (2 mM), Florin *et al*. (1980) (0.03 to 30 μmol/plate), Seixas *et al*. (1982) (1.6 mM), Connor *et al*. (1985) (100 to 2,000 μg/plate), Sakai *et al*. (1985) (5 to 250 μg/plate), Bos *et al*. (1988) (1 to 50 μg/plate), and Kangsadalampai *et al*. (1997) (12.64 to 50.56 μg/plate).

5.1.2 Mutation in Escherichia coli

Naphthalene was not genotoxic in the SOS-chromotest with *Escherichia coli* strain PQ37 at concentrations of 0.156 to 10.0 μg/plate, either with or without induced rat liver S9 (Mersch-Sundermann *et al.* 1992, 1993). Naphthalene also did not induce mutations in *Escherichia coli* strains WP2 and WP100 at a concentration of 2000 μg/plate, either with or without metabolic activation (Mamber *et al.* 1983), or in lysogenic strain GY5027 and indicator strain GY4015, with metabolic activation (Mamber *et al*. 1984).

5.2 Eukaryotic systems

5.2.1 Mutagenicity in Drosophila melanogaster

Naphthalene tested at concentrations of 1 to 10 mM in the wing somatic mutation and recombination test in *Drosophila melanogaster* induced mutations in flies from both the standard cross and the high-bioactivation cross (the progeny of which have increased sensitivity to promutagens and procarcinogens). Naphthalene increased the frequency of wing spots in the progeny of both crosses; however, the mutagenic effect was greater in the bioactivated flies (Delgado-Rodriguez *et al.* 1995).

5.3 Mammalian systems

5.3.1 In vitro *assays*

5.3.1.1 Mutation in human B-lymphoblastoid cells

Sasaki *et al.* (1997) and Grosovsky *et al*. (1999) evaluated naphthalene for genotoxicity in the human B-lymphoblastoid cell line MCL-5 at the heterozygous thymidine kinase (*TK*) locus and the hemizygous hypoxanthine phosphoribosyl transferase (*HPRT*) locus. Exposure to naphthalene at 40 μg/mL (0.31 μmol/mL) did not significantly increase mutation frequency at the *TK* locus, but resulted in small increases in mutation frequency at the *HPRT* locus. Because the increases in *TK* and *HPRT* mutation frequency did not differ significantly, and because the types of mutations recoverable at *HPRT* are expected

to be a subset of those recoverable at *TK*, the authors suggested that the small increase in *HPRT* mutations might not be biologically significant.

5.3.1.2 Cell transformation

The cell-transforming ability of naphthalene has been investigated in several cellular systems, including rat embryo cells infected with the Rauscher leukemia virus (0.1 and 0.5 μg/mL) (Freeman *et al.* 1973), mouse embryo cells infected with the AKR leukemia virus (0.1 to 5.0 μg/mL) (Rhim *et al.* 1974), and mouse mammary gland cells (0.001 to 1.0 μg/mL) (Tonelli *et al.* 1979). Naphthalene exposure did not increase the incidence of cell transformation in any of these studies.

5.3.1.3 Cytogenetic effects

Naphthalene at concentrations of 30 to 67.5 μg/mL increased the incidence of chromosomal aberrations in Chinese hamster ovary (CHO) cells, but only in the presence of rat liver S9 metabolic activation (NTP 1992, 2000).

Sasaki *et al*. (1997) and Grosovsky *et al*. (1999) evaluated naphthalene (0.23 μmol/mL) in the CREST modified micronucleus test, which distinguishes chromosomal loss from chromosomal breakage. Exposure to naphthalene (0.23 μmol/mL) resulted in statistically significant increases in CREST-negative micronuclei, indictating chromosomal breakage, but did not in CREST-positive micronuclei (which indicate chromosomal loss) or in total micronuclei.

5.3.1.4 Sister-chromatid exchange

Naphthalene at concentrations of 2.7 to 90 μg/mL induced sister-chromatid exchange in CHO cells, both with and without rat liver S9 metabolic activation NTP (1992, 2000). However, naphthalene at 100 μM did not induce sister-chromatid exchange in human peripheral lymphocytes (Tingle *et al.* 1993).

5.3.1.5 DNA damage/repair test

Naphthalene at concentrations of 0.03 to 3 mM did not induce DNA single-strand breaks in rat hepatocytes (Sina *et al.* 1983).

5.3.2 In vivo *assays*

5.3.2.1 Oxidative stress and DNA damage

Oral administration of naphthalene to Sprague-Dawley rats (120 mg/kg b.w. per day for 120 consecutive days) resulted in oxidative stress (increased lipid peroxidation) and DNA breakage in liver and brain tissue (Bagchi *et al.* 1998). In comparison with results from concurrent controls, liver and brain samples from rats exposed to naphthalene showed 1.2- to 1.4-fold increases in lipid peroxidation and 1.1- to 1.9-fold increases in DNA fragmentation; all increases were noted between treatment days 45 and 105. The authors concluded that these tissue-damaging effects may contribute to the toxicity and carcinogenicity of naphthalene.

A single oral dose of 1,100 mg of naphthalene to female Sprague-Dawley rats resulted in oxidative stress and DNA breakage (Vuchetich *et al.* 1996). In comparison with results

from concurrent controls, naphthalene administration increased lipid peroxidation in liver and brain mitochondria and microsomes 2.0- to 2.2-fold at 24 hours. Treatment with vitamin E succinate (VES) three days before and four days after administration of naphthalene protected rats from oxidative stress and reduced DNA breakage in hepatic tissue. VES treatment reduced lipid peroxidation at 24 hours by 16% to 25% in liver and brain mitochondria and microsomes. Naphthalene administration increased DNA single-strand breaks in liver and brain tissue 3.0- and 2.4-fold, respectively, at 24 hours. Following coadministration of naphthalene and VES, single-strand breaks in liver samples were increased only 1.6-fold at 24 hours, but the frequency of single-strand breaks in brain samples was not reduced.

5.4 Other tests

Naphthalene was tested for its ability to induce micronucleus formation in the erythrocytes of *Pleurodeles waltl* (salamander) larvae exposed *in vivo* (Djomo *et al.* 1995). Naphthalene was genotoxic at 0.50 ppm (the highest concentration tested), weakly genotoxic 0.25 ppm, and not genotoxic at 0.125 ppm (the lowest concentration).

5.5 Naphthalene-related compounds

1,4-Naphthalene diamine, 1-naphthol, 1-methylnaphthalene, 2-methylnaphthalene, and 1,4-dimethylnaphthalene did not induce reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 (McCann *et al.* 1975, Florin *et al.* 1980, Mortelmans *et al.* 1986). However, 1-methylnaphthalene induced mutations in *Salmonella typhimurium* strain TM677 (Kaden *et al.* 1979) and ambient air extracts from an environmental chamber in which naphthalene was reacted with nitrogen-containing reagents induced mutations in *Salmonella typhimurium* strain TA 98 (Arey *et al.* 1992). In *Escherichia coli* strain PQ37, 2,7-dinitronaphthalene and 2-nitronaphthalene were mutagenic; 1-amino-4-nitronaphthalene gave marginally positive results; and 1-nitronaphthalene, 1,5-dinitronaphthalene, and 2-methyl-1-nitronaphthalene were not mutagenic (Mersch-Sundermann *et al.* 1993). Both 1-nitronaphthalene and 1,5-dinitronaphthalene were genotoxic in the wing somatic mutation and recombination test in *Drosophila melanogaster* (Delgado-Rodriguez *et al.* 1995).

In the human B-lymphoblastoid cell line MCL-5, 2-nitronaphthalene significantly increased the mutation frequency at the *TK* locus, but not at the *HPRT* locus. No increases in mutation frequency were observed with 1-nitronaphthalene, 1-hydroxy-2-nitronaphthalene, 2-hydroxy-1-nitronaphthalene, or 1,4-naphthoquinone. In tests of the same five chemicals in the CREST modified micronucleus test, 1,4-naphthoquinone significantly increased the frequency of CREST-positive micronuclei and total micronuclei, but the other four chemicals gave negative results (Sasaki *et al.* 1997, Grosovsky *et al.* 1999). 1-Naphthylamine and 2-naphthylamine induced transformation of mouse mammary gland cells (Tonelli *et al.* 1979).

5.6 Summary

Table 5-1 summarizes the data on naphthalene genotoxicity. The majority of tests have not shown naphthalene to be mutagenic *in vitro*. Naphthalene did not induce reverse mutation in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, TM677, UTH8413, or UTH8414 or in *Escherichia coli* strains PQ37, WP2, WP100,

GY5027, or GY4015. It also did not induce cell transformation in mouse mammary gland cells or rat or mouse embryo cells, mutations or micronuclei in human B-lymphoblastoid MCL-5 cells, or DNA strand breaks in rat hepatocytes. However, naphthalene induced chromosomal aberrations and sister-chromatid exchange in CHO cells, micronuclei indicating chromosomal breakage in human lymphoblastoid cells, and oxidative stress and DNA damage in Sprague-Dawley rats. In non-mammalian test systems, naphthalene induced mutations in *Drosophila melanogaster* and micronuclei in *Pleurodeles waltl* larvae.

Table 5-1. Comparative summary of genetic effects of naphthalene exposure

Test system	End Point	Results[a]		Reference
		without metabolic activation	with metabolic activation	
S. typhimurium TA98, TA100, TA 1535, TA1537	reverse mutation	–	–	McCann *et al*. 1975, Florin *et al*. 1980, Mortelmans *et al*. 1986, NTP 1992, 2000
S. typhimurium TA97, TA98, TA100	reverse mutation	–	–	Sakai *et al.* 1985
S. typhimurium TA98, TA100	reverse mutation	–	–	Bos *et al*. 1988, Kangsadalampai *et al.* 1997
S. typhimurium TA98, TA100, UTH8413, UTH8414	reverse mutation	–	–	Connor *et al.* 1985
S. typhimurium TA1537	reverse mutation	–	–	Seixas *et al*. 1982
S. typhimurium TM677	forward mutation	NR	–	Kaden *et al*. 1979, Seixas *et al*. 1982
Escherichia coli PQ37	DNA damage (β-galactosidase activity)	–	–	Mersch-Sundermann *et al.* 1992, 1993
Escherichia coli WP2, WP100	DNA damage (rec assay)	–	–	Mamber *et al*. 1983
Escherichia coli GY5027, GY4015	prophage induction	NR	–	Mamber *et al.* 1984
Drosophila melanogaster	mutation and mitotic recombination	+	+	Delgado-Rodriguez *et al.* 1995
Pleurodeles waltl larvae	micronuclei	+	NA	Djomo *et al*. 1995
Mouse mammary gland cells	cell transformation	–	NA	Tonelli *et al.* 1979
Rat embryo cells	cell transformation	–	NA	Freeman *et al*. 1973
Mouse embryo cells	cell transformation	–	NA	Rhim *et al*. 1974

Test system	End Point	Results[a]		Reference
		without metabolic activation	with metabolic activation	
Rat hepatocytes	DNA strand breaks	–	NA	Sina *et al*. 1983
CHO cells	chromosomal aberrations	–	+	NTP 1992, 2000
CHO cells	sister-chromatid exchange	+	+	NTP 1992, 2000
Human peripheral lymphocytes	sister-chromatid exchange	NR	–	Tingle *et al*. 1993
Human B-lymphoblastoid MCL-5 cells	mutation at *TK* and *HPRT* loci	–	NA	Sasaki *et al*. 1997, Grosovsky *et al*. 1999
Human B-lymphoblastoid MCL-5 cells	micronuclei	+*, –**	NA	Sasaki *et al*. 1997, Grosovsky *et al.* 1999
Sprague-Dawley rats	DNA fragmentation and breakage	+	NA	Vuchetich *et al.* 1996, Bagchi *et al.* 1998

[a]+ = positive result, – = negative result, NR = not reported, NA = not applicable.

*Positive for CREST-negative micronuclei (chromosomal breakage).

**Negative for CREST-positive micronuclei (chromosomal loss) and total micronuclei.

6 Other Relevant Data

Naphthalene is rapidly absorbed and metabolized when inhaled or administered dermally or orally. In its reports of mouse and rat carcinogenicity bioassays, the NTP also reviewed the literature pertaining to naphthalene's absorption, distribution, metabolism, excretion, and mechanism of action (NTP 1992, 2000) and developed a model to estimate its uptake, distribution, and metabolism in rats and mice, using chronic toxicity data from the two-year studies and data from single six-hour inhalation exposures. The NTP did not conduct or review any subchronic studies of naphthalene or propose a mechanism of action for the carcinogenicity of naphthalene in animals or humans (NTP 1992, 2000). In its recent review of naphthalene, IARC (2002) also reviewed data relevant to naphthalene's absorption, distribution, metabolism, and mechanism of action; naphthalene was classified as *possibly carcinogenic to humans* (Group 2B).

6.1 Mammalian absorption, distribution, and excretion

The NTP (2000) reviewed the literature pertaining to the absorption of naphthalene. Orally administered naphthalene is readily absorbed by a variety of animal species, including rats (strain not specified), laying pullets, swine, and dairy cattle. Once absorbed, naphthalene is metabolized quickly regardless of the route of administration. After dermal or i.p. administration, naphthalene is absorbed, metabolized, and excreted primarily in the urine.

6.1.1 Human studies

Limited information was found pertaining to the absorption, distribution, or excretion of naphthalene by humans. The NTP (2000) literature review reported that absorption of naphthalene has been demonstrated by observation of signs and symptoms of toxicity in infants accidentally exposed to naphthalene vapors in clothes. Transplacental transport of naphthalene and/or its metabolites is evidenced by hemolytic anemia in newborns whose mothers ingested naphthalene during the last trimester of pregnancy. A study conducted by the Centers for Disease Control and Prevention found 1-naphthol in 86% of 983 urine samples from human participants, with an average concentration of 17 μg/L; 2-naphthol was detected in 81% of 977 samples, with an average concentration of 7.8 μg/L. Although 1-naphthol may be produced by the cleavage of carbaryl, a 1-naphthyl-*N*-methylcarbamate insecticide, as well as from the oxidation of naphthalene, the study investigators concluded that these results reflected naphthalene exposure.

Studies by Bieniek (1994, 1997) on industrial workers exposed to naphthalene provided additional evidence for absorption of naphthalene by humans. Urine samples were collected from workers exposed to naphthalene and other phenolic compounds through distillation of naphthalene oil or employment in a coke plant, and personal air samples were collected during the workday. The highest values (7.48 ± 2.187 mg/L; geometric mean ± geometric standard deviation; N = 75) for urinary 1-naphthol, a urinary metabolite of naphthalene, were observed for naphthalene oil distillation operators. The urinary excretion of 1-naphthol varied for cokers at two different coke plants based on the technology used in the plants. In a coke plant using older technology the urinary 1-naphthol values were 4.86 ± 2.465 mg/L (N = 57), while in a plant using more modern

technology the mean excretion was 0.89 ± 1.783 mg/L (N = 66). Subjects who were not occupationally exposed to naphthalene had urinary 1-naphthol levels of 0.13 ± 1.868 mg/L (N = 24). Urinary 1-naphthol concentrations of coke oven workers were highly correlated (r = 0.80) with naphthalene concentration in breathing zone air (personal air samples) (Bieniek 1994). In a later report, Bieniek (1997) identified 1-naphthol, 2-naphthol, and 1,4-naphthoquinone in urine samples collected from coke plant-workers exposed to naphthalene as tar distillation process operators or naphthalene oil distillation operators. Significant correlations were reported for urinary 1-naphthol in breathing-zone air for both tar distillation operators ($r^2 = 0.46$, $P < 0.001$; N = 69) and naphthalene oil distillation operators ($r^2 = 0.55$, $P < 0.001$; N = 33). Correlation coefficients were slightly lower for urinary 2-naphthol; however, they were still highly significant ($P < 0.001$) for both work categories. The author concluded that urinary 1-naphthol and 2-naphthol seemed to be useful biomarkers in assessing exposure of coke plant workers to naphthalene.

Kanikkannan *et al.* (2001a, 2001b) investigated the percutaneous permeation of JP-8 (2001a) or JP-8+100 (2001b) jet fuels across human skin *in vitro*. JP-8, which is the major jet fuel used by the U.S. Army and Air Force, is a kerosene-based petroleum distillate with variable composition from batch to batch; however, its general composition is 18% aromatic hydrocarbons with the remainder as aliphatic hydrocarbons (C_8 to C_{17}). The JP-8+100 jet fuel is a recently introduced product used by the U.S. Air Force and consists of JP-8 plus three performance additives (butylated hydroxytoluene antioxidant, metal deactivator MDA, and 8Q405 detergent/dispersant). The concentration of naphthalene was 0.26% (w/w) in the batches of both JP-8 and JP-8+100 tested by Kanikkannan *et al.* (2001a, 2001b). The steady state flux value for naphthalene across human skin was significantly ($P < 0.01$, Student's t-test) higher (0.451 ± 0.022 μg/cm^2 per hour) than the corresponding value for pig skin (See Section 6.1.2, below) (Kanikkannan *et al.* 2001a). The authors concluded that naphthalene permeated through human skin without any apparent lag time.

6.1.2 Animal studies

Chen and Dorough (1979) found that within 48 hours of an i.p. injection of 100 mg/kg of [^{14}C]naphthalene in female Sprague-Dawley rats, 23% to 41% of the label was excreted in the urine and 5% to 10% in the bile. Of the label excreted in the urine, 5% to 20% was unconjugated, and 80% to 95% was sulfate, glucuronide, and mercapturic acid conjugates.

At 48 hours after dermal administration of 43 μg of [^{14}C]naphthalene to Sprague-Dawley rats, 70% of the label had been excreted in the urine, 14% in the expired air, and 4% in the feces (Turkall *et al.* 1994). Metabolites identified in the urine were 2,7- and 1,2-dihydroxynaphthalene, 1,2-naphthoquinone, and 1- and 2-naphthol. Less than 0.5% of the parent compound was excreted in the urine. The plasma half-life was 2.1 hours for the absorption phase and 12 hours for the elimination phase.

After a single 20-mg/kg i.p. dose of [ring-U-^{3}H]naphthalene was administered to male Wistar rats, more than 88% of the compound was excreted in urine and feces within 72 hours. No significant naphthalene deposits formed in the tissues, and only minor amounts

(5% of the dose) remained in the muscles at 72 hours after administration (Kilanowicz *et al.* 1999). Four naphthalene urinary metabolites (see Figure 1-2) were identified by GC/MS; the primary urinary metabolites were 1- and 2-naphthol (approximately 33% and 9%, respectively). Unchanged parent compound accounted for approximately 46% of total urinary excretion. Radioactivity in plasma reached a maximum at 2 hours after administration, with biphasic half-lives for clearance of 0.8 h (phase I) and 99 h (phase II). The half-life of radioactive naphthalene in erythrocytes was approximately 9 hours (monophasic). The authors reported that one hour after administration, the tritium concentrations were highest in fat, liver, and kidneys; however, no data were provided. Total balance data for 24, 48, and 72 hours after administration are shown in Table 6-1. Quantitative evaluation at 72 hours showed approximately 46% of the administered naphthalene was eliminated as unchanged parent compound, while approximately 48% of the metabolites contained oxygen obtained through ring hydroxylation, hydration, and glutathione conjugation. No explanation was given for the much higher percentage (46%) of unmetabolized naphthalene excreted in the urine by Wistar rats in this study compared to the earlier study by Turkall *et al.* (1994) (see above) in which less than 0.5% of dermally administered naphthalene was excreted unchanged in the urine of Sprague-Dawley rats.

The penetration of naphthalene from complex mixtures across skin preparations *in vitro* also has been studied. Sartorelli *et al.* (1999) applied a mixture of 13 polycyclic aromatic hydrocarbons (PAHs), including naphthalene, in solution in either a lubricating oil or acetone (with artificial sweat) to full-thickness skin prepared from the abdomen of monkeys (*Cercopithecus aetiops*). They reported that the passage of naphthalene across the skin preparations was significantly slower when the PAHs were applied in the oil matrix compared to the acetone solution with artificial sweat. Steady state flux rates for naphthalene were the highest among the 13 PAHs; 0.2740 ± 0.2189 nmol/cm^2 per hour for lubricating oil medium and 1.0107 ± 0.3981 nmol/cm^2 per hour for acetone with artificial sweat. Naphthalene also had the shortest lag time for absorption from either vehicle, 4.86 ± 7.99 hour from lubricating oil and 1.18 ± 0.01 hour from acetone with artificial sweat.

Kanikkannan *et al.* (2001a, 2001b) (see Section 6.1.1, above) also investigated the percutaneous permeation of JP-8 (2001a) or JP-8+100 (2001b) jet fuels across pig ear skin *in vitro*. The permeation of [^{14}C]naphthalene tracer across pig skin *in vitro* was slightly, but significantly ($P < 0.05$, Student's t-test), lower for JP-8 than for JP-8+100 (steady state flux values of 0.376 ± 0.017 and 0.419 ± 0.033 μg/cm^2 per hour, respectively) (Kanikkannan *et al.* 2001b). The authors concluded that naphthalene permeated through pig ear skin without any apparent lag time.

6.1.3 Pharmacokinetic modeling

The NTP developed a physiologically based pharmacokinetic (PBPK) model to estimate the uptake, distribution, and metabolism of naphthalene in rats and mice (NTP 2000, Willems *et al.* 2001) based on data obtained from the NTP chronic toxicity studies of naphthalene and from single six-hour inhalation exposures to the same concentrations used in the chronic studies (NTP 1992, 2000 [TR Appendix D], Abdo *et al.* 1992). A diffusion-limited PBPK model was used to predict naphthalene metabolism and tissue

distribution in F344/N rats and B6C3F$_1$ mice exposed to naphthalene at concentrations of 0, 10, or 30 ppm for mice and 0, 10, 30, or 60 ppm for rats, six hours/day, five days/week, for 104 to 105 weeks. Whole-blood samples from rats were analyzed for naphthalene at 2 weeks and 3, 6, 12, and 18 months (see Appendix B, Tables D1 and D2 and Figures D2 and D3, pp. B-150 to B-155). Additional groups of rats and mice were evaluated after single six-hour inhalation exposures to naphthalene at the same concentrations used in the two-year studies (see Appendix B, Table D3 and Figure D4, pp. B-154 and B-156).

Table 6-1. Total balance of [ring-U-^{3}H]naphthalene in 6 male rats following a single 20-mg/kg i.p. dose (mean ± SEM)

Medium	Percent of administered dose		
	24 h	48 h	72 h
Urine	55.53 ± 7.35	64.40 ± 10.15	68.15 ± 8.79
Feces	10.42 ± 2.68	17.20 ± 1.55	19.75 ± 1.17
Erythrocytes + plasma[a]	0.74 ± 0.08	0.65 ± 0.04	0.65 ± 0.06
Fat tissue[b]	0.40 ± 0.06	0.12 ± 0.05	0.10 ± 0.05
Muscle[c]	1.67 ± 0.37	1.85 ± 0.19	5.00 ± 0.37
Liver	0.40 ± 0.02	0.47 ± 0.05	0.28 ± 0.04
Total	69.16	84.69	93.93

Source: Kilanowicz *et al.* 1999.

[a]Estimate based on 7 mL blood/100 g rat body weight.

[b]Estimate based on 12% of the total body weight as fat.

[c]Estimate based on 40% of the total body weight as muscle.

Data from the NTP PBPK model indicate rapid absorption of naphthalene, with metabolism of almost all of the naphthalene absorbed by rats and mice, estimates from the model are 88% to 96% metabolized by rats and 96% to 98% metabolized by mice (Willems *et al.* 2001). These high rates of metabolism indicate that once naphthalene is absorbed into the general circulation, very little parent compound is eliminated via exhalation. The species difference observed for absorption may be attributed to the greater metabolic capacity of mice. Total naphthalene metabolized (i.e., the internalized dose) was nearly equal for the mice exposed at 10 ppm and the rats exposed at 60 ppm, a finding that may be attributed to the higher ventilation rates and greater naphthalene metabolism in mice.

The NTP (2000) PBPK results revealed several gender- and species-related differences. Metabolic capacity in the lungs of rats and mice was similar between the sexes. The lung metabolic saturation level was equal in male and female rats; however, in mice, metabolic saturation occurred at lower naphthalene blood concentrations in females than in males. The liver metabolic pathway represented by the Michaelis-Menten equation

predicted equivalent metabolic capacity and saturation level in male and female rats. However, both the metabolic capacity and saturation level were lower in female mice than in male mice. The second liver metabolic pathway, characterized by a Hill equation with a Hill exponent of 2, also predicted similar metabolic capacity and saturation level in male and female rats. In mice, the Hill interpretation predicted equivalent metabolic capacity in males and females, but a lower saturation level in females.

In the lungs, the estimated steady-state concentration of naphthalene was fairly similar in rats and mice exposed to equivalent concentrations; however, the rates of metabolism and the cumulative metabolism in the lung were significantly greater in mice than in rats. Increased rates of metabolism were not proportional to increased exposure, suggesting metabolic saturation in the lung; further, saturation was more apparent in the rat than in the mouse. Metabolism was higher in mouse than rat liver, but the species difference was less pronounced than in the lung. Metabolic saturation was evident only in the liver of rats exposed to naphthalene at 60 ppm. In both species, 65% to 75% of the metabolic clearance occurred during the six-hour exposure. However, metabolic clearance in rats exposed at 60 ppm accounted for only about half of the total inhaled dose; this finding was attributed to metabolic saturation in the liver, which resulted in greater storage of parent compound in the fat in this exposure group (NTP 2000).

6.2 Metabolism

6.2.1 Human studies

Little information was found regarding the metabolism of naphthalene in humans. The NTP (2000) reported that glutathione conjugation of naphthalene metabolites plays an important role in naphthalene's elimination in rodents but not in primates, including humans. The Agency for Toxic Substances and Disease Registry (1995) reviewed the literature and reported that naphthol (isomer not specified) was detected in the urine of patients four days after naphthalene ingestion; naphthalene was not identified in the urine after day five. 1-Naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone were identified in the urine of an 18-month-old child approximately nine days after exposure. All of these metabolites except 1,4-naphthoquinone still were present at day 13. The route of exposure could not be established conclusively (ATSDR 1995).

Metabolism of naphthalene by human microsomal preparations *in vitro* has been reported. Microsomal fractions from human lung tissue in the presence of glutathione and glutathione transferases metabolized naphthalene to naphthalene dihydrodiol and three glutathione conjugates (Buckpitt and Bahnson 1986). Human liver microsomes isolated from six histologically normal livers produced 1,2-dihydro-1,2-naphthalenediol (naphthalene-1,2-dihydrodiol), the principal stable metabolite, and 1-naphthol. For human and induced mouse microsomes, the ratios of *trans*-1,2-dihydrodiol to 1-naphthol were 8.6 and 0.4, respectively. Naphthalene-1,2-dihydrodiol was the product of sequential 1,2-epoxidation and hydrolysis, whereas 1-naphthol was formed by spontaneous re-arrangement of the 1,2-epoxide. More than one cytochrome P450 enzyme mediated the metabolism of naphthalene, as demonstrated by its incomplete inhibition by a series of selective P450 inhibitors (Tingle *et al.* 1993). Lanza *et al.* (1999) characterized the epoxidation of naphthalene by recombinant CYP2F1 expressed in lymphoblastoid cells to evaluate the hypothesis that this human enzyme could bioactivate naphthalene.

The CYP2F1 enzyme is the human ortholog of the mouse enzyme CYP2F2 (see Section 6.3.2.3 below). The metabolites of naphthalene formed by incubation of microsomes prepared from human lymphoblastoid cells expressing CYP2F1 were identified as glutathione conjugates separated by HPLC. Glutathione conjugates 1 and 3 are formed from naphthalene 1*S*,2*R*-oxide, and conjugate 2 is formed from the naphthalene 1*R*,2*S*-oxide enantiomer (see Figure 6-1). Quantities of conjugates 1 and 3 were >3-fold and 4-fold greater, respectively, than that of conjugate 2. Thus, the authors concluded that the human enzyme (CYP2F1) might predominantly form a different enantiomeric epoxide of naphthalene compared to the mouse (CYP2F2) enzyme.

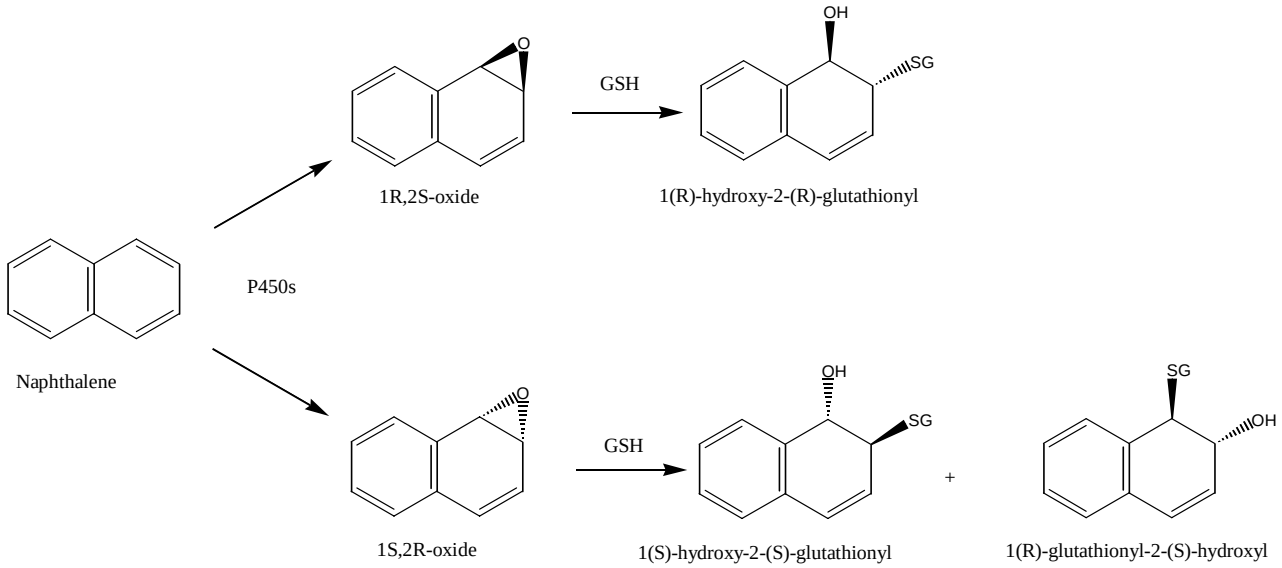
Polymorphisms of human cytochromes P450 and other metabolic enzymes have been studied for their involvement in naphthalene metabolism as measured by urinary excretion of 1-naphthol and 2-naphthol. Yang *et al.* (1999) observed a relationship between urinary naphthalene metabolites and polymorphisms of CYP1A1, CYP2E1, or glutathione S-transferase M1 (GSTM1) in a Japanese population. No differences in metabolism were reported for CYP1A1 exon 7 polymorphism; however, smokers with a C to T transition (c2) in one (c1/c2) or both (c2/c2) alleles of the 5'-flanking region of the CYP2E1 gene had higher concentrations of urinary 2-naphthol than did individuals with two wild-type (c1/c1) alleles. Genetic deficiency of GSTM1 was also correlated with higher concentrations of urinary 1-naphthol and 2-naphthol compared to individuals expressing normal levels of the enzyme.

Nan *et al.* (2001) carried out a similar study of excretion of the naphthalene metabolite 2-naphthol among Korean coke oven workers and university students in which they compared the effects of occupation, lifestyle, and genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and glutathione S-transferase θ1 (GSTT1). Urinary 2-naphthol concentrations were significantly higher in the coke oven workers compared to the students. Among coke oven workers, CYP2E1 and GSTM1 were significant factors in the univariate analysis of urinary 2-naphthol levels. GSTM1 and smoking were significant factors for the university students. The authors concluded that CYP2E1 and GSTM1 are important enzymes in the metabolism of naphthalene.

6.2.2 Animal studies

The metabolism of naphthalene is complex, with formation of multiple oxygenated metabolites and their stereoisomers (see Appendix B, p. B-16 and Figure 1, p. B-18). In a review of the literature, the NTP (2000) reported the first step in naphthalene metabolism to be the formation of naphthalene-1,2-oxide (Figure 6-1) by oxygen and the NADPH-dependent microsomal monooxygenase system, with subsequent conversion to the trans-1,2-diol and other products (Figure 6-2). The two stereoisomers of naphthalene epoxide (naphathalene-1,2-oxide) are shown in Figure 6-1. The stereoselective epoxidation of naphthalene in various animal species and tissues has been proposed as an important factor in the acute toxicity of naphthalene (Buckpitt *et al.* 1987). Buckpitt and Franklin (1989) reported a strong correlation between the rates of formation of 1*R*-2*S*-naphthalene oxide in various tissues and tissue-selective toxicity. They further stated that microsomal metabolism of naphthalene in rabbit and rat liver results in the formation of 1,2-dihydro-1,2-naphthalenediol (dihydrodiol) and 1-naphthol. The 1,2-epoxide is an obligate intermediate in the *in vitro* formation of 1-naphthol, dihydrodiol (Figure 6-2), and

glutathione (GSH) conjugates (Figure 6-1). These reactive epoxide intermediates may undergo further metabolism by three major metabolic pathways, including hydration by epoxide hydrolases, conjugation by glutathione transferases (GSTs), and, in *in vitro* systems, spontaneous rearrangement of the epoxide to 1-naphthol (95%) and 2-naphthol (5%). Four diastereomeric GSH conjugates are possible from naphthalene-1,2-oxides, and three have been isolated and identified, including 1-(R)-hydroxy-2-(R)-glutathionyl, 1-(S)-hydroxy-2-(S)-glutathionyl, and 1-(R)-glutathionyl-2(S)-hydroxyl (Buckpitt *et al.* 1987) (Figure 6-1).



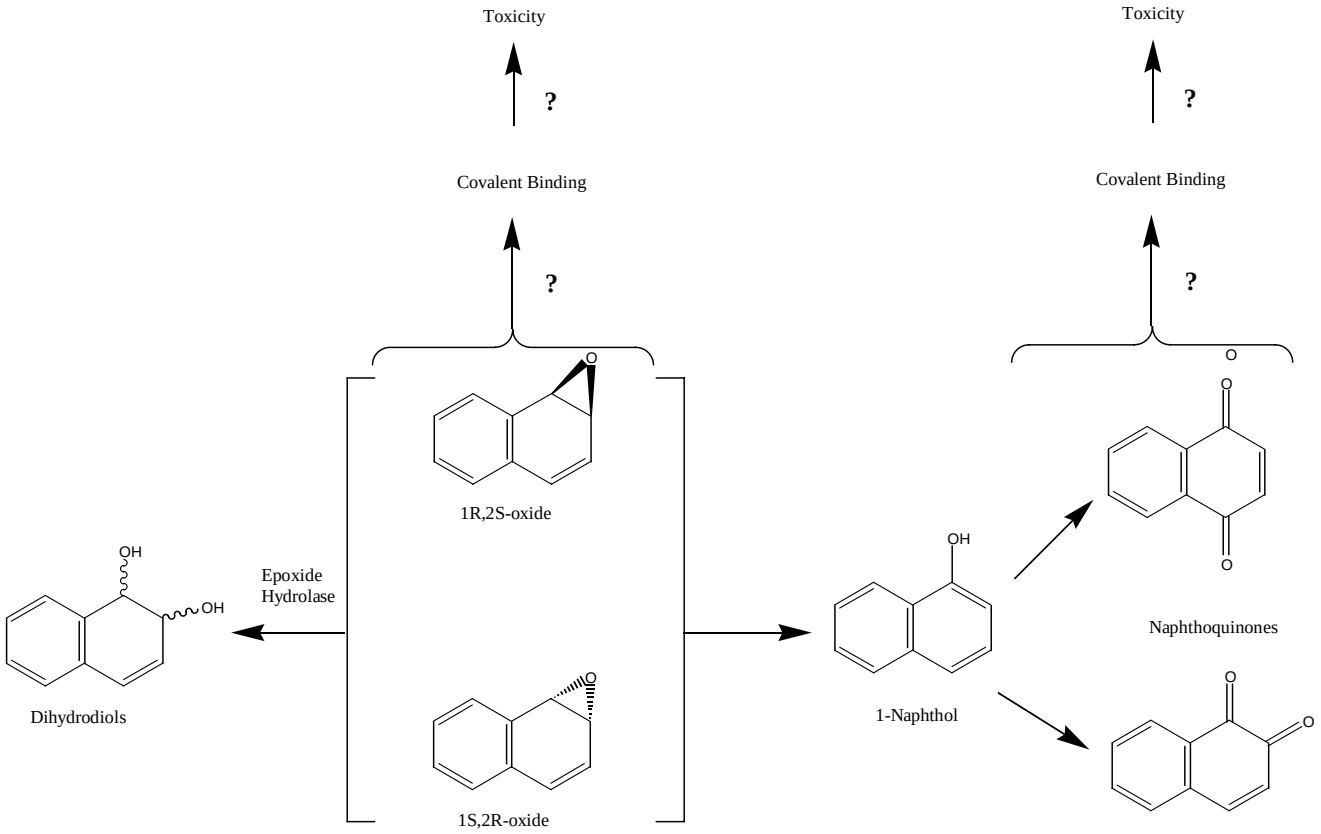
Adapted from Shultz *et al.* 1999.

Figure 6-1. Metabolism of naphthalene to reactive epoxides and their GSH conjugates

Using microdissected airways, Buckpitt *et al.* (1985) found that the rate of naphthalene metabolism was higher in mice than in rats or hamsters. Additionally, metabolism in the distal airways was higher than in the trachea in all three species. At all airway levels, mouse and hamster postmitochondrial supernatants, prepared from the dissected airways, metabolized naphthalene oxide to diol and three GSH conjugates at rates 8- to 10-fold higher than rat tissues.

The rate of naphthalene metabolism by microsomal preparations from rat, hamster, and monkey lungs was considerably lower than that by similar preparations from mouse lung (12%, 37%, and 1% of the rate in mouse lung microsomes, respectively) (Buckpitt *et al.* 1992). The mouse lung microsomal preparation favored the formation of the 1*R*,2*S*-epoxide over the 1*S*,2*R*-epoxide, whereas in the nonsensitive species (rats and hamsters), the 1*S*,2*R*-oxide dominated (Buckpitt *et al.* 1992). Supporting evidence for the preferential metabolism through the 1*R*,2*S*-epoxide pathway in mice *in vivo* was reported by Pakenham *et al.* (2002). They showed that the ratio of urinary mercapturates derived from the 1*R*,2*S*-epoxide to those formed from the 1*S*,2*R*-epoxide was 1:1 or greater in

Swiss-Webster mice (ratios as high as 6:1 were observed at low concentrations of inhaled naphthalene), while the ratio was less than 1:1 at all doses in Sprague-Dawley rats. Lanza *et al.* (1999) reported that the human CYP2F1 also predominantly formed naphthalene 1*S*,2*R*-oxide, the opposite enantiomeric epoxide from the mouse enzyme. Buckpitt *et al* (1992) pointed out that the rate of metabolism by primate lung microsomal enzymes was similar to that of human lung enzymes. Thus, the rate of metabolism in mouse lung microsomes is approximately 10-times greater than for rat lung and 100 times greater than for human. They concluded that the correlation between the rate and stereochemistry of the epoxidation of naphthalene and the toxicity of naphthalene in rodents may suggest that the airways of primates could be less susceptible to naphthalene injury if cytotoxicity is dependent on the stereochemistry and rate of epoxidation.



Adapted from Chichester *et al.* 1994.

Figure 6-2. Potential reactive intermediates in naphthalene metabolism

Buckpitt *et al.* (1992) also compared the rates of metabolism of naphthalene by three different segments of nasal mucosa from mouse, rat, and hamster. Tissue was sampled from lateral wall, septum, and olfactory regions and homogenized. Postmitochondrial supernatants were prepared and used to assess metabolism of naphthalene to the diol and three different glutathione conjugates. The highest rate of metabolism was observed with mouse olfactory epithelium; rat olfactory epithelium metabolized naphthalene at approximately half the rate of the mouse tissue; and the metabolic rate of hamster

olfactory epithelium was less than 5% of that of the mouse. The other two nasal regions, i.e., the lateral and septal regions, had metabolic rates that were less than half those of the olfactory region. The glutathione conjugates were formed predominantly from 1*R*,2*S*-naphthalene oxide in all three species. In rat olfactory epithelium the ratio of conjugate 2 (derived from 1*R*,2*S*-naphthalene oxide) to conjugates 1 and 3 (derived from 1*S*,2*R*-naphthalene oxide) was greater than 36.Although considerable interspecies similarities in naphthalene metabolites have been observed, some notable exceptions exist, as shown in Table 6-2. 1,2-Dihydroxynaphthalene is formed only in guinea pigs, and no glucuronides were detected in that species. GSH conjugation of naphthalene metabolites plays an important role in the elimination pathway in rodents but not in primates, including humans. It was reported by the NTP (2000) that single gavage doses of naphthalene at 30, 75, or 200 mg/kg b.w. administered to male Wistar rats resulted in a dose-related increase in thioether excretion in the urine. In contrast, this increase was not seen in similarly treated male or female chimpanzees. Based on the spectrum of naphthalene metabolites found in mammals, a metabolic pathway was proposed (NTP 2000, Figure 1, p. B-18).

Table 6-2. Metabolites of naphthalene identified in the urine of various species[a]

Metabolite	Rat	Mouse	Rabbit	Guinea Pig
1-Naphthol	+	+	+	+
1-Naphthyl sulfate	+	+	+	+
1-Naphthyl glucuronide	+	+	+	–
2-Naphthol	+	+	+	+
1,2-Dihydroxynaphthalene	–	–	–	+
1,2-Dihydro-1,2-dihydroxynaphthalene	+	+	+	+
1,2-Dihydro-2-hydroxy-1-naphthyl glucuronide	+	–	+	–
1-Naphthyl mercapturic acid	+	+	+	+

Source: NTP 2000.

[a]+ = metabolite present; – = metabolite not present.

Naphthalene or naphthol metabolites injected i.p. into male C57BL/6 and DBA/2 mice were bioactivated by cytochrome P450 to an electrophilic epoxide intermediate, which was further metabolized to naphthoquinones and possibly to a free-radical intermediate (Wells *et al.* 1989).

Naphthalene was shown to be bioactivated in a dose-dependent manner by a reconstituted cytochrome P450 system *in vitro* (Doherty *et al.* 1985) to electrophilic intermediates (naphthalene-1,2-oxides), which were metabolized to naphthoquinones (1,2-naphthoquinone and 1,4-naphthoquinone) and possibly to free-radical intermediates (Figure 6-2); *in vivo*, these metabolites subsequently deplete GSH and become covalently bound to tissue macromolecules (Buckpitt and Warren 1983, Warren *et al.* 1982).

Microsomal preparations from liver, lungs, and kidneys are able to transform naphthalene metabolites. Human liver microsomal preparations metabolized naphthalene to 1-naphthol and naphthalene 1,2-dihydrodiol (Tingle *et al.* 1993) (Figure 6-2). Similar preparations from either human (Buckpitt and Bahnson 1986) or mouse (Buckpitt *et al.* 1984) lung tissue metabolized naphthalene to 1,2-naphthalenediol and three different glutathione conjugates, which were identified as trans-1*S*-hydroxy-2*S*-glutathionyl-1,2-dihydronaphthalene; trans-1*R*-hydroxy-2*R*-glutathionyl-1,2-dihydronaphthalene, and trans-1*R*-glutathionyl-2*R*-hydroxy-1,2-dihydronaphthalene (Buonarati *et al.* 1990) (Figure 6-1). Lung, liver, and kidney microsomal preparations from rats, mice, or hamsters converted naphthalene to these conjugates in the presence of GSH and GSTs (Buckpitt *et al.* 1987). It should be noted that the rate and stereoselectivity of naphthalene metabolism in human lung microsomes differs substantially from that in mouse lung microsomes. In human lung microsomes, metabolism by the intermediate epoxide pathway occurred at less than 3% of the rate in mouse lung microsomes (Buckpitt and Bahnson 1986). In a recent *in vitro* study with mouse lung Clara cells exposed to naphthalene, Zheng *et al*. (1997) found 1,2-naphthoquinone to be covalently bound to the cysteine residues of proteins.

Naphthalene is excreted primarily in the urine (Figure 6-1) as unchanged parent compound or as glutathione, cysteine, glucuronic acid, and sulfate conjugates (see Section 1.3) (Kilanowicz *et al.* 1999).

Intraperitoneal injection of naphthalene to male rats resulted in urinary excretion of 20% to 30% of the administered dose in the first 24 hours and 3% to 11% in the second 24 hours (Horning *et al.* 1980). Acidic conjugates accounted for 80% to 95% of the total metabolites excreted. Enzymatic hydrolysis to neutral metabolites revealed that 20% to 40% of the total radioactivity represented glucuronides and sulfates, indicating that the remainder of the acidic conjugates included thioethers. Two methylthio metabolites, 1α,4β-di(methylthio)-2β,3α-dihydroxynaphthalene and 1α-methylthio-2β,3α,4β-trihydroxynaphthalene, were identified, and the authors stated that numerous other methylthio metabolites were formed. The initial reaction of naphthalene metabolism results in the production of an epoxide intermediate, which undergoes oxidation to form di-, tri-, and tetra-hydroxylated compounds. The major metabolites identified include the neutral forms and acidic (glucuronide and sulfate) conjugates of the following: 1-naphthol, 2-naphthol, 1,2-naphthalenediol, 1,2-dihydro-1,2-naphthalenediol (cis and trans), 1,4-dihydro-1,4-naphthalenediol (cis and trans), and 1,1-, 2,7-, and 2,6-naphthalenediol (ATSDR 1995).

Intraperitoneal injection of naphthalene to male mice resulted in urinary excretion of 65% of the administered dose in the first 24 hours and 3% in the second 24 hours. As in rats, the majority of the excreted metabolites (96%) were conjugates. The major naphthalene metabolites recovered after hydrolysis were 1-naphthol, *trans*-1,2-dihydrodiol, *trans*-1-hydroxy-2-methylthio-1,2-dihydronaphthalene, 1-methylthionaphthalene, and 2-naphthol. Seven sulfur-containing derivatives were identified as (1-hydroxy-1,2-dihydro-2-naphthalenylthio)acetic acid, 2-hydroxy-3-(1-hydroxy-1,2-dihydro-2-naphthalenylthio)propanoic acid, 1,2,3-trihydroxy-1,2,3,4-tetrahydro-4-naphthalenylthio)acetic acid, 1-(naphthalenylthio)acetic acid, 2-hydroxy-3-(1-naphthalenylthio)propanoic acid, *N*-acetyl-*S*-(1-naphthalenyl)-L-cysteine, and the major

sulfur-containing derivative *N*-acetyl-*S*-(1-hydroxy-1,2-dihydro-2-naphthalenyl)-L-cysteine. The sulfur metabolites were produced by conjugation with glutathione followed by removal of the glycyl and glutamyl moieties and modification of cysteine. Nine methylthio derivatives, including 1-methylnaphthalene and *trans*-1-hydroxy-2-methylthio-1,2-dihydronaphthalene, also were identified in the urine. Compared to rats administered equivalent doses, mice excreted more naphthalene as bivalent sulfur metabolites than as glucuronides of hydroxylated naphthalene (Stillwell *et al.* 1982).

6.3 Toxicity

6.3.1 Human studies

The NTP report (2000) provided a detailed account of naphthalene's toxicity to humans. Naphthalene inhalation causes headache, confusion, eye irritation, nausea, and profuse perspiration, with vomiting, optic neuritis, hematuria, and edema. Toxicity and death have been reported in newborn infants exposed to naphthalene vapors in clothes. Naphthalene ingestion results in abdominal pain, nausea, vomiting, diarrhea, darkening of the urine, irritation of the bladder, jaundice, anemia, and hypothermia. Cataract formation, retinal hemorrhage, chorioretinitis, optic nerve atrophy, and blindness have been reported in humans exposed to naphthalene. Naphthalene poisoning has produced hemolytic anemia in children and adults. Santucci and Shah (2000) reviewed the hospital charts of 24 children identified with hemolysis and subsequently diagnosed as glucose-6-phosphate dehydrogenase deficient. They reported that 14 of the 24 children had naphthalene-associated hemolysis while the remaining 10 had infection-associated hemolysis.

6.3.2 Animal studies

The NTP (2000) reported the median lethal doses (LD_{50}s) for rats and mice (strains not specified), respectively, to be 1,110 to 9,430 and 350 to 710 mg/kg b.w. for oral administration, 2,500 and 969 mg/kg b.w. for dermal administration, and 1,000 and 350 mg/kg b.w. for i.p. administration (NTP 2000). These values suggest that mice are more sensitive than rats to the acute effects of naphthalene. The reported median lethal concentration for rats exposed to naphthalene vapors for eight hours was 500 mg/m^3 (NTP 2000). The major sites affected by naphthalene toxicity are the hematologic and pulmonary systems and the eye.

6.3.2.1 Hematological effects

The NTP (2000) literature review reported several hematological effects of naphthalene exposure. In CD-1 mice administered naphthalene at 267 mg/kg b.w. per day by gavage for 14 days, hematologic parameters were only slightly altered; no hemolytic anemia was observed. However, dogs receiving naphthalene mixed in feed for a dose of 263 or 1,525 mg/kg b.w. per day for seven days developed hemolytic anemia, suggesting that mice are less sensitive than dogs to the hemolytic effects of naphthalene.

6.3.2.2 Ocular effects

In its review, the NTP (2000) reported several ocular effects of naphthalene exposure. Lens opacity was reported in black-hooded and brown Norway rats given naphthalene at 700 or 5,000 mg/kg b.w. per day for 79 to 102 days. Cataracts involving the whole lens

occurred in pigmented and albino rabbits within two weeks of daily oral administration of naphthalene at 1 g/kg b.w.; the incidence was greater in the albino strain. van Heyningen and Pirie (1967) reported that tissues of the eye in rabbits enzymatically converted naphthalene metabolites, including 1,2-dihydro-1,2-dihydroxynaphthalene, 2-hydroxy-1-naphthyl sulfate, and (1,2-dihydro-2-hydroxy-1-naphthyl glucosid)uronic acid, to 1,2-dihydroxynaphthalene. They concluded that 1,2-dihydroxynaphthalene was the primary toxic agent in cataractogenesis through its autoxidation to 1,2-naphthoquinone, which bound to lens proteins. A study with male C57BL/6J mice suggested that naphthalene cataractogenesis requires P450 (CYP1A and CYP2A) bioactivation to a reactive metabolite (possibly a naphthoquinone), a free-radical derivative, or a combination of both (Wells *et al.* 1989). In these studies, pretreatment of mice with the cytochrome P450 inhibitor SKF-525A or the spin-trapping agent α-phenyl-*N*-butylnitrone in addition to treatment with vitamin E or caffeic acid inhibited naphthalene cataractogenicity. L-Cysteine prodrugs also were effective in preventing naphthalene-induced cataracts in mice, apparently by maintaining hepatic glutathione concentrations (Rathbun *et al.* 1996).

6.3.2.3 Respiratory tract toxicity

The respiratory tract has been identified as a site of naphthalene toxicity in rats and mice. In mice, lung injury induced by naphthalene exposure is related to the degree of monooxygenase activity, covalent binding to tissue macromolecules, depletion of the pulmonary GSH stores, and stereoselectivity of the metabolism (Plopper *et al.* 1992, Chichester *et al.* 1994, Cho *et al.* 1994, Höke and Zellerhoff 1998). The relative quantities of reactive naphthalene metabolites covalently bound intra- or extra-cellularly may depend on the saturation of intracellular detoxification pathways, such as hydrolysis or enzymatic attack (Richieri and Buckpitt 1987).

Intraperitoneal administration of naphthalene produced a highly organ-selective and species-selective lesion of the pulmonary bronchiolar epithelium in mice, but no such lesion was detected in rats or hamsters. In its review, the NTP reported that a single i.p. injection of naphthalene at 0.05 mmol/kg b.w. (6 mg/kg) or 2 mmol/kg b.w. (256 mg/kg) induced necrosis of the bronchial/bronchiolar epithelium in C57BL/6J mice (NTP 2000). This lesion was reversible, and regeneration occurred after seven days. Necrosis of the bronchial epithelial (Clara) cells occurred in the lungs of C57BL/6J mice given a single i.p. injection of naphthalene at 125 or 250 mg/kg b.w. An i.p. injection of 400 or 600 mg/kg in Swiss TO mice damaged the Clara cells of the lung and proximal tubule epithelial cells of the kidney. In contrast, an i.p. injection of 1,600 mg/kg in Wistar-derived rats did not produce any damage in the lung or the kidney. The NTP review stated that these results suggested that rats were less susceptible to naphthalene toxicity than mice and that the difference in susceptibility was due to differences in the rate of naphthalene metabolism.

Plopper *et al.* (1992) studied histopathologic changes in the respiratory tract 24 hours after parenteral administration of a single oral dose of naphthalene to Swiss Webster mice (0 to 400 mg/kg b.w.), Sprague-Dawley rats (0 to 1,600 mg/kg b.w.), and Golden Syrian hamsters (0 to 800 mg/kg b.w.). Naphthalene injury (swelling, vacuolization, exfoliation, or necrosis) to the tracheobronchial epithelium in the mice was specific to Clara cells.

Dose-related injury occurred in the terminal bronchioles and involved proximal airways, at dose levels well below the mouse LD_{50}. Clara cells in the rat were refractory to injury, and proximal airways were more susceptible than distal airways in the hamster. Naphthalene was cytotoxic to the olfactory epithelium in rats and mice, with the effect seen at a higher dose in mice (400 mg/kg b.w.) than in rats (200 mg/kg b.w.). Recent studies with adult and neonatal Swiss Webster mice showed that Clara cells in the neonates were more susceptible than adult cells to injury following exposure to naphthalene *in vivo* (Fanucchi *et al.* 1997).

Buckpitt *et al.* (1985) reported that immunohistochemical analysis of airway explants from a sensitive species (mice) and nonsensitive species (rats and hamsters) indicated that the cells from mice contain a unique P450 (CYP2F, a family of microsomal enzymes uniquely expressed in the lung and olfactory mucosal cells (Lakritz *et al.* 1996, Shultz *et al.* 1999)). This enzyme catalyzes the high degree of metabolic stereoselectivity to 1*R*-2*S*-naphthalene oxide over the 1*S*-2*R*-oxide (66:1 enantiomeric ratio) in mice (Shultz *et al.* 1999). The orthologs of CYP2F2 in the rat and primate are designated CYP2F4 and CYP2F1, respectively (Shultz *et al.* 2001). The rates of metabolism of naphthalene by the enzymes of these species differ widely.

Severe bronchiolar epithelial cell necrosis in male Swiss Webster mice was observed following a single i.p. dose of 200 mg/kg of [^{14}C]naphthalene; however, no renal or hepatic necrosis was noted (Warren *et al.* 1982). Pretreatment with piperonyl butoxide substantially reduced the bronchiolar necrosis, confirming the involvement of cytochrome P450–mediated metabolism in the lung. Reactive metabolites bound covalently to tissue macromolecules in a dose-dependent manner, and binding was consistently increased in tissues with higher cytochrome P450 levels, such as lung, liver, and kidney. Covalent binding in the liver, a non-target tissue, was as high as binding in the lung; binding demonstrated a significant dose threshold that depended on the substantial depletion of tissue GSH reserves. Pretreatment of mice with diethyl maleate resulted in a dose-related reduction in GSH levels and increased severity of the lung lesion, indicating pulmonary metabolic activation and production of reactive naphthalene metabolites. GSH levels and covalent binding were inversely related, suggesting that GSH is important in the detoxification of reactive naphthalene metabolites. West *et al*. (2000) found GSH to be critical in the development of resistance to naphthalene injury by murine Clara cells.

6.3.2.4 Other Effects

The NTP Technical Report (2000) reported additional effects observed following naphthalene exposure. In rats, a single i.p. injection of naphthalene (1 g/kg b.w.) caused accumulation of ammonia in the brain, which correlated positively with naphthalene's lethality. Naphthalene inhibited aryl hydrocarbon hydroxylase activity in liver homogenates and microsomal preparations obtained from rats receiving 40-mg/kg i.p. injections for three days. A single 250-mg/kg i.p. dose of naphthalene to C57BL/6J mice depressed microsomal monooxygenase enzyme activity in the lung by 30% to 70%; enzyme activity was not affected in the liver.

Evaluation of the cytotoxicity of naphthalene and several of its metabolites to human liver microsomes indicated that the parent compound and the alcohol (1-naphthol) were

metabolized to species that were cytotoxic to resting human mononuclear leukocytes (Wilson *et al.* 1996). 1-Naphthol was more cytotoxic than naphthalene, and the dihydrodiol was not cytotoxic. The cytotoxicity of naphthalene and 1-naphthol increased with increasing concentration of liver microsomal protein, but 1-naphthol was activated at a much lower microsomal protein concentration than the parent compound.

6.4 Potential mechanisms of carcinogenicity

In two-year inhalation exposure studies (NTP 1992, 2000, Abdo *et al.* 1992), exposure to naphthalene induced lung neoplasms in female $B6C3F_1$ mice and nasal tumors in male and female F344/N rats (see Section 4.1). The difference in the sites of neoplasms between rats and mice may be related to differences in the anatomy of the nasal passages and in the metabolic activation of naphthalene in these two species. The NTP (2000) discussed the difference in the sites of neoplasms in rats and mice and the potential explanations for these differences. The distribution of potential carcinogens to the nasal passages of different species may contribute to this effect and the rates of production and clearance of carcinogenic metabolites of naphthalene may be different. Based on this discussion, the NTP speculated that activation and deactivation of naphthalene and accumulation of carcinogenic metabolite(s) could be greater in the nasal passages of rats than of mice; conversely the metabolism and accumulation of carcinogenic metabolites may be greater in the lungs of mice than of rats (see pp. B-47 to B-50). The high rate of metabolism of naphthalene in mouse lung and in rat nasal epithelium could be related to site-specific tissue damage. However, others have suggested that the presence of unique cytochromes P450 in the rat nasal mucosa could play a protective role in reducing the lung toxicity of some inhaled chemicals (Thornton-Manning and Dahl 1997).

6.4.1 Pulmonary carcinogenesis

The NTP report provided information on the metabolism and tissue distribution of inhaled naphthalene but did not propose a potential mechanism of naphthalene carcinogenicity. The results from the NTP PBPK model indicate that tissue dosimetry alone does not explain naphthalene's carcinogenic potential in the mouse lung but not in the rat lung (NTP 2000). The higher rate of metabolism in the mouse lung may be a contributing factor; however, because the model does not include detoxification rates for potentially carcinogenic naphthalene metabolites, lung concentrations of reactive intermediates cannot be compared with the naphthalene exposure concentrations. If detoxification processes are faster in mice than in rats, then rates of metabolic activation alone cannot reliably predict lung cancer risk. Naphthalene oxide is the primary metabolite formed by cytochrome P450–mediated oxidation of naphthalene. However, the metabolism of naphthalene oxide was not included in the NTP PBPK model. Further, no data were available on the blood concentrations of 1*R*-2*S*- and 1*S*-2*R*-naphthalene oxide.

Vuchetich *et al.* (1996) and Bagchi *et al.* (1998) proposed that oxidative stress induced by chronic oral administration of naphthalene to rats (see Section 5.3.2) could damage tissue and might contribute to the toxicity and carcinogenicity of this compound. The possible role of oxidative stress in naphthalene toxicity was supported by the ability of an antioxidant, vitamin E succinate, to significantly decrease the urinary excretion of lipid metabolites in rats exposed to naphthalene. The authors proposed that quinone

derivatives of naphthalene, including 1,2- and 1,4-naphthoquinone, could undergo redox cycling reactions that would produce reactive oxygen species and semiquinone anion radicals. Their reports, however, did not directly establish a role for these potentially reactive naphthalene metabolites in naphthalene toxicity. Thus, the chemical mechanism underlying any potential carcinogenicity of naphthalene remains to be elucidated.

6.4.1.1 Species differences in sensitivity to epoxides

Mice appear to be more susceptible to lung neoplasm induction by epoxides and epoxide-forming chemicals than are rats (Melnick and Huff 1993). Melnick and Sills (2001) reviewed the carcinogenicity of the epoxide-forming chemicals 1,3-butadiene, isoprene, and chloroprene in rats and mice together with that of the epoxide, ethylene oxide. The authors reported that all four chemicals induced lung tumors in mice, but only chloroprene induced lung tumors in rats (female). The NTP (2000) stated that if naphthalene oxide is the sole agent responsible for induction of lung neoplasms in mice exposed to naphthalene, then the species difference in response in the lung may be attributed to a combination of higher rates of naphthalene oxide production in the mouse lung and, possibly, a greater susceptibility of the mouse lung to epoxide-induced carcinogenesis.

The metabolism of chemicals to epoxides may differ among species, among strains, and even within the airways of individual animals. Forkert *et al.* (2001) demonstrated that CYP2E1-mediated formation of 1,1-dichloroethylene epoxide and other reactive intermediates and the severity of lung cytotoxicity both were correlated with the levels of CYP2E1 in the lungs of three strains of mice. The species difference in bioactivation and detoxication of 1,3-butadiene between B6C3F_1 mice and Sprague-Dawley rats has also been proposed to result from differences in cytochrome P450 activity. Buckpitt *et al.* (1995) examined the metabolism of naphthalene by specific subcompartments of microdissected airways from mice, rats, and hamsters. They reported that naphthalene was converted to its epoxide more rapidly in the tracheobronchial airways of susceptible than nonsusceptible species, and that expression of the cytochrome P450 isoform CYP2F2 correlated with the conversion rates.

6.4.1.2 Toxicity of naphthalene to Clara cells of the lung in mice and rats

Gram (1997) reviewed a number of studies on species differences in naphthalene lung toxicity. Clara cells in the lungs of mice were much more susceptible to naphthalene toxicity than were these cells in the lungs of rats or hamsters. In one study, naphthalene (i.p. administration) caused Clara cell toxicity at 50 mg/kg in mice, minor alterations in Clara cells at 800 mg/kg in hamsters, and no effects in rats at naphthalene levels up to 1,600 mg/kg. West *et al*. (2001) reported injury in Clara cells in the lungs from inhalation exposures as low as 2 ppm in mice, while no toxicity was reported in rats at concentrations as high as 110 ppm.

Several studies have examined the pattern of events in the Clara cells that result in naphthalene-induced acute toxicity. One study showed a pattern of focal swelling of the Clara cells, followed by changes in Clara cell ultrastructure, including the rearrangement of cytoskeletal filaments, and finally, loss of cell membrane permeability (Van Winkle *et al.* 1999). Another study showed that glutathione levels decreased by 50% in the first

hour after the injection of 200 mg/kg naphthalene in mice. This decrease occurred before the first signs of cellular damage (cytoplasmic vacuolization), showing that the loss of intracellular glutathione is an early event that precedes signs of cellular damage (Plopper *et al.* 2001). It has been proposed that the species differences in Clara cell toxicity (see above) are caused by naphthalene's ability to deplete glutathione more severely in the mouse lung, as compared to the hamster or rat (Gram 1997).

Naphthalene administration (i.p. injection of 200 mg/kg b.w.) to Swiss Webster mice resulted in exfoliation of Clara cells two days after treatment (Van Winkle *et al.* 1995). Over the same time course that the volume fraction of Clara cells decreased, i.e., one to two days after exposure to naphthalene, the proliferation of cells in the epithelium and interstitium also was increasing. Cell proliferation was maximal at two days post treatment, and Clara cell differentiation markers had returned to control levels by day five. Stripp *et al*. (1995) also followed the re-expression of Clara cell differentiation markers in FVB/n mice injected i.p. with naphthalene. They observed a re-population of the naphthalene-injured airways by proliferation of immature epithelial cells preferentially at airway bifurcations.

6.4.1.3 Pulmonary neuroendocrine cell hyperplasia after naphthalene toxicity

Pulmonary airway epithelial cells include a population of pulmonary neuroendocrine cells (PNECs) that are scattered throughout the bronchial tree and are able to secrete a variety of neuropeptides. Since these cells and the peptides that they secrete may play a role in fetal lung development, some researchers have postulated a role for these cells in recovery from chemical toxicity and have examined their number and activity in lungs of mice expose to naphthalene. Stevens *et al.* (1997) and Peake *et al.* (2000) reported that PNEC hyperplasia could be detected in the lungs of FVB/n mice five days after i.p. injection with 300 mg/kg b.w. naphthalene in corn oil. Increased cell proliferation was involved in this hyperplasia as evidenced by an increase in [^{3}H]thymidine labeling in clusters of PNECs in neuroepithelial bodies (NEBs). The number of PNECs per mm^2 was threefold higher in the lungs of naphthalene-treated mice compared to those of control mice. The authors concluded that proliferation of PNECs could play a key role in the renewal of airway epithelial cells after toxic injury by naphthalene. They also suggested that further research is needed to elucidate the relationship between injury and repair of Clara cells and the proliferation of PNECs after toxic injury.

6.4.2 Nasal and olfactory epithelia as targets for chemical carcinogenesis

Pino *et al.* (1999) were able to identify only one report of a spontaneous tumor of the olfactory epithelium in rodents. However, they questioned the spontaneous nature of even that one tumor since it was observed in a "low-dose group of rats in a two-year carcinogenicity feeding study, in which no carcinogenicity for rats had been determined (Shibuya *et al.* 1996)." [The agent being tested was not identified by Shibuya *et al.* (1996).] Brown *et al.* (1991) reviewed the literature on proliferative lesions of the rodent nasal cavity. The authors drew several general conclusions from their review, including a statement that rodents rarely develop spontaneous nasal tumors. The conclusions that specifically related to nasal tumors of rats are summarized here. They found that rats were more susceptible than were mice to the induction of nasal cavity epithelial tumors. Olfactory epithelial tumors were described as almost uniformly malignant and invasive.

Additionally, they pointed out that tumors of the olfactory region induced by exposure to chemicals could result from targeting to the region even with systemic administration; thus, an inhalational route of exposure was not required to demonstrate carcinogenesis.

6.4.2.1 Metabolism of naphthalene by nasal epithelia

The metabolism of naphthalene by nasal mucosal postmitochondrial supernatants varied among species (mouse, rat, and hamster) (see Section 6.2.2, above), but the relative rates of metabolism did not correlate well with the relative sensitivity of the olfactory mucosa of these species to naphthalene toxicity (Buckpitt *et al.* 1992). The rat nasal mucosal tissue was the most sensitive to the toxic effects of naphthalene and was the only site of tumors in rats in the two-year bioassay (NTP 2000 and Section 4.2, above). The highest rate of metabolism, however, was two-fold higher for mouse olfactory epithelium compared to that of the rat. Buckpitt *et al.* (1992) suggested that the differences in sensitivity of rat versus mouse or hamster olfactory epithelium could be related to other metabolic factors such as epoxide hydrolase or glutathione S-transferase activity or the levels of reduce glutathione in tissues of the different species.

6.4.2.2 Chemicals that produce nasal tumors

Haseman and Hailey (1997) summarized the incidence of nasal tumors in almost 500 rodent carcinogenicity studies included in the NTP database at that time. They identified 12 chemicals that produced nasal tumors in rats (Table 6-3). Two additional chemicals that were subjects of two-year NTP bioassay studies subsequent to their review also are included in Table 6-3.

6.4.2.3 Species differences in nasal anatomy

Although the nasal airways of animals and humans have some similarities, the anatomy of the upper respiratory tract differs among species of experimental animals used to study carcinogenicity and between these animal species and humans. Reznik (1990) and Ménache *et al*. (1997) reviewed the comparative anatomy, physiology, and function of the upper airways of humans and of laboratory animals used in toxicology studies. One important distinction is that the human nose has a relatively simple structure necessary to perform its primary function of breathing (respiration) while other mammals tend to have more complex noses to support their primary function of olfaction. However, even within species of laboratory animals, differences in the ratio of respiratory to olfactory epithelium exist. For example, the respiratory epithelium per unit volume of nasal cavity is greater in mice than in rats.

The differences in anatomy may affect the way in which inhaled materials distribute to and are cleared from specific cell types of the nasal cavities. Morgan and Monticello (1990) reviewed the literature on the site specificity of nasal lesions induced by inhalational exposure of laboratory animals to a variety of chemicals. They concluded that the combined effects of airflow and tissue sensitivity determined the nature and distribution of nasal lesions resulting from a number of xenobiotic chemicals. The differences in nasal anatomy have been invoked in discussions of differential toxicity of chemicals across species; however, these differences may be more relevant to risk assessments than to the potential carcinogenicity of chemicals such as naphthalene.

Table 6-3. Chemicals that produced nasal tumors in rats in NTP/NCI studies (Adapted from Haseman and Hailey 1997).

Chemical	Technical report	Nasal carcinogenicity	Sex	Route of administration	Tumor types
Allyl glycidol ether	376	E	M	Inhalation	(a)
		–	F		Adenoma
p-Cresidine	142	+	M	Feed	Neuroblastoma
		+	F		Neuroblastoma
1,2-Dibromo-3-chloropropane	206	+	M	Inhalation	(b)
		+	F		(b)
1,2-Dibromethane	210	+	M	Inhalation	(b)
		+	F		(b)
2,3-Dibromo-1-propanol	400	+	M	Skin paint	Adenoma
		+	F		Adenoma
Dimethylvinyl chloride	316	+	M	Gavage	(c)
		+	F		(c)
1,4-Dioxane	080	+	M	Water	(c)
		+	F		(c)
1,2-Epoxybutane	329	+	M	Inhalation	Adenoma
		E	F		Adenoma
Furfuryl alcohol[1]	482	+	M	Inhalation	(d)
		E	F		Adenoma
Iodinated glycerol	340	E	M	Gavage	Adenoma
		-	F		Adenoma
Pentachlorophenol, purified[2]	483	+	M	Feed	Carcinoma
		-	F		-
Procarbazine	019	+	M	IP injection	Neuroblastoma
		+	F		Neuroblastoma
Propylene oxide	267	+	M	Inhalation	Adenoma
		+	F		Adenoma
2,6-Xylidine	278	+	M	Feed	(b)
		+	F		(b)

E = Equivocal evidence; - negative; + positive
(a)- One papillary adenoma, one squamous cell carcinonma, one poorly differentiated adenocarcinomas
(b)- Carcinoma, squamous cell papilloma, squamous cell carcinoma, adenoma, adenocarcinoma, adenomatous polyp, or carcinosarcoma
(c)- Carcinoma, squamous cell carcinoma, or adenocarcinoma
(d)- Two adenomas, one carcinoma, and three squamous cell carcinomas
[1]NTP Technical Report 482 (1999a).
[2]NTP Technical Report 483 (1999b).

6.4.2.4 Epithelial cell proliferation in nasal carcinogenesis

An increase in the rate of cell proliferation has been considered to be a contributing factor in carcinogenesis as it may provide an increased opportunity for somatic mutations during DNA replication. Formaldehyde, which is a weakly genotoxic carcinogen, has been studied extensively, and its effect on target cell proliferation correlates with tumor incidence (Monticello and Morgan 1997). The same authors, however, have pointed out that other inhaled irritant gases that induce severe nasal cytotoxicity and other non-neoplastic effects do not induce nasal tumors with chronic exposure (Monticello *et al.* 1993). Ward *et al.* (1993) reviewed the association between cell proliferation and nasal carcinogenesis in rodent bioassays sponsored by the NTP. They reported that of the 19 chemicals that were subjects of inhalation bioassays, 5 were nasal carcinogens, while the remaining 14 were nasal noncarcinogens. When the nasal lesions observed with the 19 chemicals were summarized by species/sex experiments, nasal lesions, including epithelial hyperplasia and metaplasia, were present in 15/15 experiments with the 5 nasal carcinogens, while 36/59 experiments with nasal noncarcinogens were positive for these lesions. The authors of this review concluded that, "Although cell proliferation may contribute to multistage carcinogenesis, cell proliferation is not necessarily a tumor promoter or cocarcinogen."

6.5 Naphthalene-related compounds

No data on the carcinogenicity of the naphthalene metabolites 1-naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone (see Figures 1-2, 1-3, and 6-2) were found. The carcinogenicity of a number of naphthalene-related compounds has been reviewed by the NTP and IARC. Table 6-4 summarizes the data available on the carcinogenicity and mutagenicity of these naphthalene derivatives; studies of the mutagenicity of naphthalene-related compounds are discussed in Section 5.5.

Table 6-4. Carcinogenicity and mutagenicity data for some naphthalene derivatives

Naphthalene derivative	CAS#	Carcinogenicity and mutagenicity data
1-Naphthylamine	134–32–7	IARC (1987) Group 3 (not classifiable as to its carcinogenicity to humans). Positive for mutation in *Salmonella typhimurium*, chromosomal aberrations in cultured rodent cells, and aneuploidy in yeast; negative for mutation in *Drosophila*, cell transformation in Syrian hamster embryo cells, and mutation in yeast (IARC 1987).
2-Naphthylamine	91–59–8	*Known to be a human carcinogen* (NTP 2001) based on sufficient evidence in humans (bladder cancer in workers) and in animals (urinary bladder carcinoma in hamsters, dogs, nonhuman primates, and mice). Positive for mutation in *Salmonella typhimurium*, *Drosophila*, and Chinese hamster ovary cells (HSDB 2002b).
N-phenyl-2-naphthylamine	135–88–6	No evidence in male or female F344 rats or male B6C3F_1 mice. Equivocal evidence in B6C3F_1 female mice (two rare kidney neoplasms) (NTP 1988). Weakly positive for sister-chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells; negative for mutation in *Salmonella typhimurium* (NTP 2002a).
1,5-Naphthalenediamine	2243–62–1	Negative in male F344 rats and positive in female F344 rats (clitoral and uterine neoplasms). Positive in male B6C3F_1 mice (thyroid neoplasms) and female B6C3F_1 mice (thyroid, liver, and lung neoplasms) (NTP 1978a). IARC (1982) Group 3 (not classifiable as to its carcinogenicity to humans). Positive for mutation in *Salmonella typhimurium* (IARC 1982).
1-Nitronaphthalene	86–57–7	Negative in male and female F344 rats and male and female B6C3F_1 mice (NTP 1978b). IARC (1981) Group 3 (not classifiable as to its carcinogenicity to humans). Positive for mutation in *Salmonella typhimurium;* weakly positive for chromosomal aberrations and negative for sister chromatid exchange *in vitro* (cell line not specified);and negative for sex-linked recessive lethal/reciprocal translocation in *Drosophila* (NTP 2002b).

6.6 Summary

Naphthalene is rapidly absorbed and metabolized when inhaled or administered dermally or orally to animals. Naphthalene is excreted in the urine as the unchanged parent compound, as metabolites (including 1-naphthol, 2-naphthol, naphthoquinones, and dihydroxynapthalenes), or as glutathione (GSH), cysteine, glucuronic acid, and sulfate conjugates. Urinary naphthalene metabolites found in workers at a coke plant correlated significantly with naphthalene concentrations in personal air samples, indicating that naphthalene is absorbed in humans. The first step in the metabolism of naphthalene is the formation of naphthalene-1,2-oxide by cytochrome P450 in the presence of NADPH, which is converted to the trans-1,2-diol and other products. The electrophilic naphthalene intermediates are metabolized to naphthoquinones and possibly to free-radical intermediates; *in vivo*, these metabolites contribute to depletion of GSH, and excess metabolites may bind covalently to tissue macromolecules. Higher rates of metabolism in microdissected airways have been reported to occur in mice than in rats or hamsters.

The toxicity of naphthalene is manifested primarily in the hematologic system in humans and dogs (hemolytic anemia), the pulmonary system in rodents (lung injury) and the eye in humans and rodents (lens opacity and cataracts).

Naphthalene induced lung neoplasia in female B6C3F$_1$ mice and nasal tumors in male and female F344/N rats. The mechanism of action has not been elucidated. Toxicity of naphthalene to lung and other tissues has been attributed to formation of the 1*R*,2*S*-naphthalene oxide; a strong correlation has been reported between the rates of formation of 1*R*,2*S*-naphthalene oxide in various tissues and tissue-selective toxicity. Naphthalene-induced oxidative damage and DNA breakage, which have been observed in rat liver and brain tissue, may contribute to the toxicity and carcinogenicity of naphthalene. Mice appear to be more susceptible to induction of lung neoplasia by epoxides and epoxide-forming chemicals than are rats. Differences between rats and mice in the metabolism of naphthalene by nasal epithelia and in nasal anatomy may contribute to the species differences in susceptibility to these tumors.

7 References

1. Abdo, K.M., S.L. Eustis, M. McDonald, M.P. Jokinen, B. Adkins, Jr., and J.K. Haseman. 1992. Naphthalene: a respiratory tract toxicant and carcinogen for mice. *Inhal Toxicol* 4:393-409.

2. Adkins, B., E.W. Van Stee, J.E. Simmons, and S.L. Eustis. 1986. Oncogenic response of strain A/J mice to inhaled chemicals. *J Toxicol Environ Health* 17:311-322.

3. Ajao, O.G., M.O. Adenuga, and J.K. Ladipo. 1988. Colorectal carcinoma in patients under the age of 30 years: a review of 11 cases. *J R Coll Surg Edinb* 33:277-279.

4. Andreoli, R., P. Manini, E. Bergamaschi, A. Mutti, I. Franchini, and W.M. Niessen. 1999. Determination of naphthalene metabolites in human urine by liquid chromatography-mass spectrometry with electrospray ionization. *J Chromatogr A* 847:9-17.

5. Arey, J., W.P. Harger, D. Helmig, and R. Atkinson. 1992. Bioassay-directed fractionation of mutagenic PAH atmospheric photooxidation products and ambient particulate extracts. *Mutat Res* 281:67-76.

6. ATSDR. 1995. Toxicological profile for naphthalene. U.S. Public Health Service. Available at http://www.atsdr.cdc.gov/toxprofiles/tp67.html.

7. Bagchi, D., M. Bagchi, J. Balmoori, P.J. Vuchetich, and S.J. Stohs. 1998. Induction of oxidative stress and DNA damage by chronic administration of naphthalene to rats. *Res Commun Mol Pathol Pharmacol* 101:249-257.

8. Bieniek, G. 1994. The presence of 1-naphthol in the urine of industrial workers exposed to naphthalene. *Occup Environ Med* 51:357-359.

9. Bieniek, G. 1997. Urinary naphthols as an indicator of exposure to naphthalene. *Scand J Work Environ Health* 23:414-420.

10. Bjørseth, A., O. Bjørseth, and P.E. Fjeldstad. 1978a. Polycyclic aromatic hydrocarbons in the work atmosphere. I. Determination in an aluminum reduction plant. *Scand J Work Environ Health* 4:212-223.

11. Bjørseth, A., O. Bjørseth, and P.E. Fjeldstad. 1978b. Polycyclic aromatic hydrocarbons in the work atmosphere. II. Determination in a coke plant. *Scand J Work Environ Health* 4:224-236.

12. Bos, R.P., J.G. Theuws, F.J. Jongeneelen, and P.T. Henderson. 1988. Mutagenicity of bi-, tri- and tetra-cyclic aromatic hydrocarbons in the taped-plate assay and in the conventional Salmonella mutagenicity assay. *Mutat Res* 204:203-206.

13. Brown, H.R., T.M. Monticello, R.R. Maronpot, H.W. Randall, J.R. Hotchkiss, and K.T. Morgan. 1991. Proliferative and neoplastic lesions in the rodent nasal cavity. *Toxicol Pathol* 19:358-372.

14. Buckpitt, A., M. Buonarati, L.B. Avey, A.M. Chang, D. Morin, and C.G. Plopper. 1992. Relationship of cytochrome P450 activity to Clara cell cytotoxicity. II. Comparison of stereoselectivity of naphthalene epoxidation in lung and nasal mucosa of mouse, hamster, rat and rhesus monkey. *J Pharmacol Exp Ther* 261:364-372.

15. Buckpitt, A., A.M. Chang, A. Weir, L. Van Winkle, X. Duan, R. Philpot, and C. Plopper. 1995. Relationship of cytochrome P450 activity to Clara cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. *Mol Pharmacol* 47:74-81.

16. Buckpitt, A.R. and D.L. Warren. 1983. Evidence for hepatic formation, export and covalent binding of reactive naphthalene metabolites in extrahepatic tissues *in vivo*. *J Pharmacol Exp Ther* 225:8-16.

17. Buckpitt, A.R., L.S. Bahnson, and R.B. Franklin. 1984. Hepatic and pulmonary microsomal metabolism of naphthalene to glutathione adducts: factors affecting the relative rates of conjugate formation. *J Pharmacol Exp Ther* 231:291-300.

18. Buckpitt, A.R., L.S. Bahnson, and R.B. Franklin. 1985. Evidence that 1-naphthol is not an obligate intermediate in the covalent binding and the pulmonary bronchiolar necrosis by naphthalene. *Biochem Biophys Res Commun* 126:1097-1103.

19. Buckpitt, A.R. and L.S. Bahnson. 1986. Naphthalene metabolism by human lung microsomal-enzymes. *Toxicology* 41:333-341.

20. Buckpitt, A.R., N. Castagnoli, S.D. Nelson, A.D. Jones, and L.S. Bahnson. 1987. Stereoselectivity of naphthalene epoxidation by mouse, rat, and hamster pulmonary, hepatic, and renal microsomal enzymes. *Drug Metab Dispos* 15:491-498.

21. Buckpitt, A.R. and R.B. Franklin. 1989. Relationship of naphthalene and 2-methylnaphthalene metabolism to pulmonary bronchiolar epithelial cell necrosis. *Pharmacol Ther* 41:393-410.

22. Budavari, S., M.J. O'Neil, A. Smith, and P.E. Heckelman. 1996. The Merck Index. Budavari, S., M.J. O'Neil, A. Smith and P.E. Heckelman eds. Merck & Company, Whitehouse Station, NJ. pp. 1094.

23. Buonarati, M., A.D. Jones, and A. Buckpitt. 1990. *In vivo* metabolism of isomeric naphthalene oxide glutathione conjugates. *Drug Metab Dispos* 18:183-189.

24. CEH. 2000. Chemical Economics Handbook, V. 27. SRI International, Menlo Park, CA.

25. ChemExpo. 1999. Naphthalene. Available at http://www.chemexpo.com/news/PROFILE990531.cfm.

26. Chemfinder. 2002. Naphthalene. CambridgeSoft Corporation. Available at http://www.chemfinder.camsoft.com (and search 91-20-3).

27. Chen, K.C. and H.W. Dorough. 1979. Glutathione and mercapturic acid conjugations in the metabolism of naphthalene and 1-naphthyl N-methylcarbamate (carbaryl). *Drug Chem Toxicol* 2:331-354.

28. Chichester, C.H., A.R. Buckpitt, A. Chang, and C.G. Plopper. 1994. Metabolism and cytotoxicity of naphthalene and its metabolites in isolated murine Clara cells. *Mol Pharmacol* 45:664-672.

29. Cho, M., C. Chichester, D. Morin, C. Plopper, and A. Buckpitt. 1994. Covalent interactions of reactive naphthalene metabolites with proteins. *J Pharmacol Exp Ther* 269:881-889.

30. Connor, T.H., J.C. Theiss, H.A. Hanna, D.K. Monteith, and T.S. Matney. 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol Lett* 25:33-40.

31. Delgado-Rodriguez, A., R. Ortíz-Marttelo, U. Graf, R. Villalobos-Pietrini, and S. Gäomez-Arroyo. 1995. Genotoxic activity of environmentally important polycyclic aromatic hydrocarbons and their nitro derivatives in the wing spot test of *Drosophila melanogaster*. *Mutat Res* 341:235-247.

32. Djomo, J.E., V. Ferrier, L. Gauthier, C. Zoll-Moreux, and J. Marty. 1995. Amphibian micronucleus test *in vivo*: evaluation of the genotoxicity of some major polycyclic aromatic hydrocarbons found in a crude oil. *Mutagenesis* 10:223-226.

33. Doherty, M.A., R. Makowski, G.G. Gibson, and G.M. Cohen. 1985. Cytochrome P-450 dependent metabolic activation of 1-naphthol to naphthoquinones and covalent binding species. *Biochem Pharmacol* 34:2261-2267.

34. Dufresne, A., J. Lesage, and G. Perrault. 1987. Evaluation of occupational exposure to mixed dusts and polycyclic aromatic hydrocarbons in silicon carbide plants. *Am Ind Hyg Assoc J* 48:160-166.

35. EPA. 1980. Ambient Water Quality Criteria for Naphthalene, EPA 440-5-80-059. Office of Water, Regulations and Standards, Criteria and Standards Division, Washington, D.C.

36. EPA. 1996a. Method 802IB Aromatic and haloginated volatiles by gas chromatography using photoionizatin and/or electrolytic conductivity detectors [Rev. 2]. Test Methods for Evaluating Solid Waste - Physical/Chemical Methods (US EPA No SW-846). Office of Solid Waste, Washington, D.C.

37. EPA. 1996b. Method 8100 Polynuclear aromatic hydrocarbons. In Test Methods for Evaluating Solid Waste - Physical/Chemical Methods (US EPA No SW-846). Office of Solid Waste, Washington, D.C.

38. EPA. 1996c. Method 8260B Volatile organic compounds by gas chromatography/mass spectrometry (GC/MS) [Rev. 2]. In Test Methods for Evaluating Solid Waste - Physical/Chemical Methods (US EPA No SW-846). Office of Solid Waste, Washington, D.C.

39. EPA. 1996d. Method 8270C Semivolatile organic compounds by gas chromatography/mass spectrometry (GC/MS) [Rev. 3]. In Test Methods for Evaluating Solid Waste - Physical/Chemical Methods (US EPA No SW-846). Office of Solid Waste, Washington, D.C.

40. EPA. 1996e. Method 8275A Semivolatile organic compounds (PAHs and PCBs) in soils/sludges and solid wastes using thermal extraction/gas chromatography/mass spectrometry (TE/GC/MS) [Rev. 1]. In Test Methods for Evaluating Solid Waste - Physical/Chemical Methods (US EPA No SW-846). Office of Solid Waste, Washington, D.C.

41. EPA. 1996f. Method 8310 Polynuclear aromatic hydrocarbons. In Test Methods for Evaluating Solid Waste - Physical/Chemical Methods (US EPA No SW-846). Office of Solid Waste, Washington, DC.

42. EPA. 1996g. Method 8410 Gas chromatography/Fourier transform infrared (gc/ft-ir) spectrometry for semivolatile organics: capillary column. In Test Methods for Evaluating Solid Waste - Physical/Chemical Methods (US EPA No SW-846). Office of Solid Waste, Washington, DC.

43. EPA. 1999a. Methods for organic chemical analysis of municipal and industrial wastewater. Method 610 - Polynuclear aromatic hydrocarbons. In US Code Fed Regul, Title 40, Part 136, App A. Office of Solid Waste, Washington, DC. pp. 145-157.

44. EPA. 1999b. Methods for organic chemical analysis of municipal and industrial wastewater. Method 625 - Base neutrals and acids. In US Code Fed Regul, Title 40, Part 136, App A. Office of Solid Waste, Washington, DC. pp. 202-225.

45. EPA. 1999c. Methods for organic chemical analysis of municipal and industrial wastewater. Method 1625B - Base neutrals and acids. In US Code Fed Regul, Title 40, Part 136, App A. Office of Solid Waste, Washington, DC. pp. 286-306.

46. Fanucchi, M.V., A.R. Buckpitt, M.E. Murphy, and C.G. Plopper. 1997. Naphthalene cytotoxicity of differentiating Clara cells in neonatal mice. *Toxicol Appl Pharmacol* 144:96-104.

47. Florin, I., L. Rutberg, M. Curvall, and C.R. Enzel. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology* 15:219-232.

48. Forkert, P.G., S.M. Boyd, and J.B. Ulreich. 2001. Pulmonary bioactivation of 1,1-dichloroethylene is associated with CYP2E1 levels in A/J, CD-1, and C57BL/6 mice. *J Pharmacol Exp Ther* 297:1193-1200.

49. Freeman, A.E., E.K. Weisburger, J.H. Weisburger, R.G. Wolford, J.M. Maryak, and R.J. Huebner. 1973. Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. *J Natl Cancer Inst* 51:799-808.

50. Gram, T.E. 1997. Chemically reactive intermediates and pulmonary xenobiotic toxicity. *Pharmacol Rev* 49:297-341.

51. Greenberg, K. 2000. North American Naphthalene Market Tightens Through Consolidation. Chemical Market Reporter 257(20):14.

52. Grosovsky, A.J., J.C. Sasaki, J. Arey, D.A. Eastmond, K.K. Parks, and R. Atkinson. 1999. Evaluation of the potential health effects of the atmospheric reaction products of polycyclic aromatic hydrocarbons. *Res Rep Health Eff Inst* 84:1-22.

53. Hansen, A.M., I.L. Olsen, E. Holst, and O.M. Poulsen. 1991. Validation of a high-performance liquid chromatography/fluorescence detection method for the simultaneous quantification of fifteen polycyclic aromatic hydrocarbons. *Ann Occup Hyg* 35:603-611.

54. Haseman, J.K. and J.R. Hailey. 1997. An update of the National Toxicology Program database on nasal carcinogens. *Mutat Res* 380:3-11.

55. Hicks, J.B. 1995. Asphalt industry cross-sectional exposure assessment study. *Appl Occup Environ Hyg* 10:840-848.

56. Höke, H. and R. Zellerhoff. 1998. Metabolism and toxicity of diisopropylnaphthalene as compared to naphthalene and monoalkyl naphthalenes: a minireview. *Toxicology* 126:1-7.

57. Horning, M.G., W.G. Stillwell, G.W. Griffin, and W.S. Tsang. 1980. Epoxide intermediates in the metabolism of naphthalene by the rat. *Drug Metab Dispos* 8:404-414.

58. HSDB. 2002a. Naphthalene. Revised January 18, 2002. Last reviewed November 7, 1991. National Library of Medicine, Hazardous Substance Data Bank. Available at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search CAS No. 91-20-3 and select Naphthalene.

59. HSDB. 2002b. 2-Naphthylamine. Revised January 14, 2002. Last reviewed May 25, 1986. National Library of Medicine, Hazardous Substance Data Bank. Available at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search CAS No. 91-20-3 and select Naphthalene.

60. IARC. 1981. Some Antineoplastic and Immunosuppressive Agen. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 26. World Health Organization, International Agency for Research on Cancer, Lyon, France.

61. IARC. 1982. Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking Water and Dental Preparations. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 27. World Health Organization, International Agency for Research on Cancer, Lyon, France.

62. IARC. 1987. 1-Naphthylamine. In Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7. World Health Organization, International Agency for Research on Cancer, Lyon, France.

63. IARC. 2002. Traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 82. World Health Organization, International Agency for Research on Cancer, Lyon, France.

64. Kaden, D.A., R.A. Hites, and W.G. Thilly. 1979. Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to *Salmonella typhimurium*. *Cancer Res* 39:4152-4159.

65. Kangsadalampai, K., C. Butryee, and K. Manoonphol. 1997. Direct mutagenicity of the polycylic aromatic hydrocarbon-containing fraction of smoked and charcoal-broiled foods treated with nitrite in acid solution. *Food Chem Toxicol* 35:213-218.

66. Kanikkannan, N., R. Patel, T. Jackson, M.S. Shaik, and M. Singh. 2001a. Percutaneous absorption and skin irritation of JP-8 (jet fuel). *Toxicology* 161:1-11.

67. Kanikkannan, N., S. Burton, R. Patel, T. Jackson, M.S. Shaik, and M. Singh. 2001b. Percutaneous permeation and skin irritation of JP-8+100 jet fuel in a porcine model. *Toxicol Lett* 119:133-142.

68. Kilanowicz, A., B. Czerski, and A. Sapota. 1999. The disposition and metabolism of naphthalene in rats. *Int J Occup Med Environ Health* 12:209-219.

69. Lakritz, J., A. Chang, A. Weir, S. Nishio, D. Hyde, R. Philpot, A. Buckpitt, and C. Plopper. 1996. Cellular and metabolic basis of Clara cell tolerance to multiple doses of cytochrome P450-activated cytotoxicants. I: Bronchiolar epithelial reorganization and expression of cytochrome P450 monooxygenases in mice exposed to multiple doses of naphthalene. *J Pharmacol Exp Ther* 278:1408-1418.

70. Lanza, D.L., E. Code, C.L. Crespi, F.J. Gonzalez, and G.S. Yost. 1999. Specific dehydrogenation of 3-methylindole and epoxidation of naphthalene by recombinant human CYP2F1 expressed in lymphoblastoid cells. *Drug Metab Dispos* 27:798-803.

71. LaVoie, E.J., S. Dolan, P. Little, C.X. Wang, S. Sugie, and A. Rivenson. 1988. Carcinogenicity of quinoline, 4- and 8-methylquinoline and benzoquinolines in newborn mice and rats. *Food Chem Toxicol* 26:625-629.

72. Lesage, J., G. Perrault, and P. Durand. 1987. Evaluation of worker exposure to polycyclic aromatic hydrocarbons. *Am Ind Hyg Assoc J* 48:753-759.

73. Mamber, S.W., V. Bryson, and S.E. Katz. 1983. The *Escherichia coli* WP2/WP100 rec assay for detection of potential chemical carcinogens. *Mutat Res* 119:135-144.

74. Mamber, S.W., V. Bryson, and S.E. Katz. 1984. Evaluation of the *Escherichia coli* K12 inductest for detection of potential chemical carcinogens. *Mutat Res* 130:141-151.

75. McCann, J., E. Choi, E. Yamasaki, and B.N. Ames. 1975. Detection of carcinogens as mutagens in the *Salmonella*/microsome test: assay of 300 chemicals. *Proc Natl Acad Sci Usa* 72:5135-5139.

76. Melnick, R.L. and J.E. Huff. 1993. 1,3-Butadiene induces cancer in experimental animals at all concentrations from 6.25 to 8000 parts per million. *IARC Sci Publ* 127:309-322.

77. Melnick, R.L. and R.C. Sills. 2001. Comparative carcinogenicity of 1,3-butadiene, isoprene, and chloroprene in rats and mice. *Chem Biol Interact* 135-136:27-42.

78. Ménache, M.G., L.M. Hanna, E.A. Gross, S.R. Lou, S.J. Zinreich, D.A. Leopold, A.M. Jarabek, and F.J. Miller. 1997. Upper respiratory tract surface areas and volumes of laboratory animals and humans: considerations for dosimetry models. *J Toxicol Environ Health* 50:475-506.

79. Mersch-Sundermann, V., S. Mochayedi, and S. Kevekordes. 1992. Genotoxicity of polycyclic aromatic hydrocarbons in *Escherichia coli* PQ37. *Mutat Res* 278:1-9.

80. Mersch-Sundermann, V., S. Mochayedi, S. Kevekordes, S. Kern, and F. Wintermann. 1993. The genotoxicity of unsubstituted and nitrated polycyclic aromatic hydrocarbons. *Anticancer Res* 13:2037-2043.

81. Monticello, T.M., E.A. Gross, and K.T. Morgan. 1993. Cell proliferation and nasal carcinogenesis. *Environ Health Perspect* 101 Suppl 5:121-124.

82. Monticello, T.M. and K.T. Morgan. 1997. Chemically-induced nasal carcinogenesis and epithelial cell proliferation: a brief review. *Mutat Res* 380:33-41.

83. Morgan, K.T. and T.M. Monticello. 1990. Airflow, gas deposition, and lesion distribution in the nasal passages. *Environ Health Perspect* 85:209-218.

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

85. Nan, H.M., H. Kim, H.S. Lim, J.K. Choi, T. Kawamoto, J.W. Kang, C.H. Lee, Y.D. Kim, and E.H. Kwon. 2001. Effects of occupation, lifestyle and genetic polymorphisms of CYP1A1, CYP2E1, GSTM1 and GSTT1 on urinary 1-hydroxypyrene and 2-naphthol concentrations. *Carcinogenesis* 22:787-793.

86. NIOSH. 2001. Naphthalene. NIOSH Pocket Guide to Chemical Hazards. Available at http://www.cdc.gov/niosh/npg/npgd0439.html.

87. NTP. 1978a. Bioassy of 1,5-Naphthalenediamine for Possible Carcinogenicity (CAS No. 2243-62-1). NTP Technical Report Series No 143. National Toxicology Program, Research Triangle Park, NC.

88. NTP. 1978b. Bioassy of 1-Nitronaphthalene for Possible Carcinogenicity (CAS No. 86-57-7). NTP Technical Report Series No 64. National Toxicology Program, Research Triangle Park, NC.

89. NTP. 1988. Toxicology and Carcinogenesis Studies of *N*-Phenyl-2-naphthylamine (CAS No. 135-88-6) in F344/N Rats and B6C3F_1 Mice (Feed Studies). NTP Technical Report Series No 333. National Toxicology Program, Research Triangle Park, NC.

90. NTP. 1992. Toxicology and Carcinogenesis Studies of Naphthalene in B6C3F_1 mice (Inhalation Studies). NTP Technical Report Series No 410. National Toxicology Program, Research Triangle Park, NC.

91. NTP. 1999a. Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N Rats and B6C3F_1 (Inhalation Studies). National Toxicology Program Technical Report Series No 482.

92. NTP. 1999b. Toxicology and Carcinogenesis Studies of Pentachlorophenol (CAS No. 87-86-5) in F344/N Rats (Feed Studies). National Toxicology Program Technical Report Series No 483.

93. NTP. 2000. Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in F344/N Rats (Inhalation Studies). National Toxicology Program Technical Report Series No 500.

94. NTP. 2001. 2-Naphthylamine, 9th Report on Caricongens. National Toxicology Program. Available at http://ehp.niehs.nih.gov/roc/.

95. NTP. 2002a. N-Phenyl-2-Naphthylamine. Revised May 10, 2002. Available at http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html and search 86-57-7.

96. NTP. 2002b. 1-Nitronaphthalene. Revised May 10, 2002. Available at http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html and search 86-57-7.

97. NTP Chemical Repository. 2001. Naphthalene. Revised August 13, 2001. National Toxicology Program. Available at http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html and search 91-20-3 and select H&S:NAPHTHALENE 91-20-3.

98. Pakenham, G., J. Lango, M. Buonarati, D. Morin, and A. Buckpitt. 2002. Urinary naphthalene mercapturates as biomarkers of exposure and stereoselectivity of naphthalene epoxidation. *Drug Metab Dispos* 30:247-253.

99. Peake, J.L., S.D. Reynolds, B.R. Stripp, K.E. Stephens, and K.E. Pinkerton. 2000. Alteration of pulmonary neuroendocrine cells during epithelial repair of naphthalene-induced airway injury. *Am J Pathol* 156:279-286.

100. Pino, M.V., M.G. Valerio, G.K. Miller, J.L. Larson, D.L. Rosolia, Z. Jayyosi, C.N. Crouch, J.Q. Trojanowski, and L.E. Geiger. 1999. Toxicologic and carcinogenic effects of the type IV phosphodiesterase inhibitor RP 73401 on the nasal olfactory tissue in rats. *Toxicol Pathol* 27:383-394.

101. Plopper, C.G., C. Suverkropp, D. Morin, S. Nishio, and A. Buckpitt. 1992. Relationship of cytochrome P-450 activity to Clara cell cytotoxicity. I. Histopathologic comparison of the respiratory tract of mice, rats and hamsters after parenteral administration of naphthalene. *J Pharmacol Exp Ther* 261:353-363.

102. Plopper, C.G., L.S. Van Winkle, M.V. Fanucchi, S.R. Malburg, S.J. Nishio, A. Chang, and A.R. Buckpitt. 2001. Early events in naphthalene-induced acute Clara cell toxicity. II. Comparison of glutathione depletion and histopathology by airway location. *Am J Respir Cell Mol Biol* 24:272-281.

103. Rathbun, W.B., H.T. Nagasawa, and C.E. Killen. 1996. Prevention of naphthalene-induced cataract and hepatic glutathione loss by the L-cysteine prodrugs, MTCA and PTCA. *Exp Eye Res* 62:433-441.

104. Reznik, G.K. 1990. Comparative anatomy, physiology, and function of the upper respiratory tract. *Environ Health Perspect* 85:171-176.

105. Rhim, J.S., D.K. Park, E.K. Weisburger, and J.H. Weisburger. 1974. Evaluation of an in vitro assay system for carcinogens based on prior infection of rodent cells with nontransforming RNA tumor virus. *J Natl Cancer Inst* 52:1167-1173.

106. Richieri, P.R. and A.R. Buckpitt. 1987. Efflux of naphthalene oxide and reactive naphthalene metabolites from isolated hepatocytes. *J Pharmacol Exp Ther* 242:485-492.

107. Sakai, M., D. Yoshida, and S. Mizusaki. 1985. Mutagenicity of polycyclic aromatic hydrocarbons and quinones on *Salmonella typhimurium* TA97. *Mutat Res* 156:61-67.

108. Santucci, K. and B. Shah. 2000. Association of naphthalene with acute hemolytic anemia. *Acad Emerg Med* 7:42-47.

109. Sartorelli, P., A. Cenni, G. Matteucci, L. Montomoli, M.T. Novelli, and S. Palmi. 1999. Dermal exposure assessment of polycyclic aromatic hydrocarbons: in vitro percutaneous penetration from lubricating oil. *Int Arch Occup Environ Health* 72:528-532.

110. Sasaki, J.C., J. Arey, D.A. Eastmond, K.K. Parks, and A.J. Grosovsky. 1997. Genotoxicity induced in human lymphoblasts by atmospheric reaction products of naphthalene and phenanthrene. *Mutat Res* 393:23-35.

111. Seixas, G.M., B.M. Andon, P.G. Hollingshead, and W.G. Thilly. 1982. The aza-arenes as mutagens for *Salmonella typhimurium*. *Mutat Res* 102:201-212.

112. Shibuya, K., M. Tajima, and T. Nunoya. 1996. Olfactory undifferentiated carcinoma with endocranial extension in a Fischer-344 rat. *Toxicol Pathol* 24:361-364.

113. Shultz, M.A., P.V. Choudary, and A.R. Buckpitt. 1999. Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. *J Pharmacol Exp Ther* 290:281-288.

114. Shultz, M.A., D. Morin, A.M. Chang, and A. Buckpitt. 2001. Metabolic capabilities of CYP2F2 with various pulmonary toxicants and its relative abundance in mouse lung subcompartments. *J Pharmacol Exp Ther* 296:510-519.

115. Sina, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor, and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat Res* 113:357-391.

116. Stevens, T.P., J.T. McBride, J.L. Peake, K.E. Pinkerton, and B.R. Stripp. 1997. Cell proliferation contributes to PNEC hyperplasia after acute airway injury. *Am J Physiol* 272:L486-493.

117. Stillwell, W.G., M.G. Horning, G.W. Griffin, and W.S. Tsang. 1982. Identification of new sulfur-containing metabolites of naphthalene in mouse urine. *Drug Metab Dispos* 10:624-631.

118. Stoner, G.D., G. Adam-Rodwell, and M.A. Morse. 1993. Lung tumors in strain A mice: application for studies in cancer chemoprevention. *J Cell Biochem Suppl* 17F:95-103.

119. Stripp, B.R., K. Maxson, R. Mera, and G. Singh. 1995. Plasticity of airway cell proliferation and gene expression after acute naphthalene injury. *Am J Physiol* 269:L791-799.

120. Thornton-Manning, J.R. and A.R. Dahl. 1997. Metabolic capacity of nasal tissue interspecies comparisons of xenobiotic-metabolizing enzymes. *Mutat Res* 380:43-59.

121. Tingle, M.D., M. Pirmohamed, E. Templeton, A.S. Wilson, S. Madden, N.R. Kitteringham, and B.K. Park. 1993. An investigation of the formation of cytotoxic, genotoxic, protein-reactive and stable metabolites from naphthalene by human liver microsomes. *Biochem Pharmacol* 46:1529-1538.

122. Tonelli, Q.J., R.P. Custer, and S. Sorof. 1979. Transformation of cultured mouse mammary glands by aromatic amines and amides and their derivatives. *Cancer Res* 39:1784-1792.

123. TRI99. 2001. Data contained in the Toxic Chemical Release Inventory (TRI). Available from the U.S. Environmental Protection Agency Office of Environmental Information. Available at http://www.epa.gov/triexplorer/chemical.htm.

124. Tsuda, H., G. Lee, and E. Farber. 1980. Induction of resistant hepatocytes as a new principle for a possible short-term *in vivo* test for carcinogens. *Cancer Res* 40:1157-1164.

125. Turkall, R.M., G.A. Skowronski, A.M. Kadry, and M.S. Abdel-Rahman. 1994. A comparative study of the kinetics and bioavailability of pure and soil-adsorbed naphthalene in dermally exposed male rats. *Arch Environ Contam Toxicol* 26:504-509.

126. van Heyningen, R. and A. Pirie. 1967. The metabolism of naphthalene and its toxic effect on the eye. 102:842-852.

127. Van Winkle, L.S., A.R. Buckpitt, S.J. Nishio, J.M. Isaac, and C.G. Plopper. 1995. Cellular response in naphthalene-induced Clara cell injury and bronchiolar epithelial repair in mice. Am J Physiol 269:L800-818.

128. Van Winkle, L.S., Z.A. Johnson, S.J. Nishio, C.D. Brown, and C.G. Plopper. 1999. Early events in naphthalene-induced acute Clara cell toxicity: comparison of membrane permeability and ultrastructure. *Am J Respir Cell Mol Biol* 21:44-53.

129. Vuchetich, P.J., D. Bagchi, M. Bagchi, E.A. Hassoun, L. Tang, and S.J. Stohs. 1996. Naphthalene-induced oxidative stress in rats and the protective effects of vitamin E succinate. *Free Radic Biol Med* 21:577-590.

130. Ward, J.M., H. Uno, Y. Kurata, C.M. Weghorst, and J.J. Jang. 1993. Cell proliferation not associated with carcinogenesis in rodents and humans. *Environ Health Perspect* 101 Suppl 5:125-135.

131. Warren, D.L., D.L. Brown, and A.R. Buckpitt. 1982. Evidence for cytochrome *P*-450 mediated metabolism in the bronchiolar damage by naphthalene. *Chem-Biol Interact* 40:287-303.

132. Wells, P.G., B. Wilson, and B.M. Lubek. 1989. *In vivo* murine studies on the biochemical mechanism of naphthalene cataractogenesis. *Toxicol Appl Pharmacol* 99:466-473.

133. West, J.A., G. Pakehham, D. Morin, C.A. Fleschner, A.R. Buckpitt, and C.G. Plopper. 2001. Inhaled naphthalene causes dose dependent Clara cell cytotoxicity in mice but not in rats. *Toxicol Appl Pharmacol* 173:114-119.

134. West, J.A.A., A.R. Buckpitt, and C.G. Plopper. 2000. Elevated airway GSH resynthesis confers protection to Clara cells from naphthalene injury in mice made tolerant by repeated exposures. *J Pharmacol Exp Ther* 294:516-523.

135. WHO. 1998. Selected Non-heterocyclic Polycyclic Aromatic Hydrocarbons,. World Health Organization. Available at http://www.inchem.org/documents/ehc/ehc/ehc202.htm.

136. Willems, B.A., R.L. Melnick, M.C. Kohn, and C.J. Portier. 2001. A physiologically based pharmacokinetic model for inhalation and intravenous administration of naphthalene in rats and mice. *Toxicol Appl Pharmacol* 176:81-91.

137. Wilson, A.S., C.D. Davis, D.P. Williams, A.R. Buckpitt, M. Pirmohamed, and B.K. Park. 1996. Characterisation of the toxic metabolite(s) of naphthalene. *Toxicology* 114:233-242.

138. Yang, M., M. Koga, T. Katoh, and T. Kawamoto. 1999. A study for the proper application of urinary naphthols, new biomarkers for airborne polycyclic aromatic hydrocarbons. *Arch Environ Contam Toxicol* 36:99-108.

139. Zheng, J., M. Cho, A.D. Jones, and B.D. Hammock. 1997. Evidence of quinone metabolites of naphthalene covalently bound to sulfur nucleophiles of proteins of murine Clara cells after exposure to naphthalene. *Chem Res Toxicol* 10:1008-1014.

Appendix A: NTP (1992). Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in B6C3F$_1$ Mice (Inhalation Studies). TR 410. PP A-1 – A-173.

NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 410

TOXICOLOGY AND CARCINOGENESIS STUDIES OF NAPHTHALENE

(CAS NO. 91-20-3)

IN B6C3F$_1$ MICE

(INHALATION STUDIES)

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

FOREWORD

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

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

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

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

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 while supplies last from the NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-1371).

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF NAPHTHALENE

(CAS NO. 91-20-3)

IN B6C3F$_1$ MICE

(INHALATION STUDIES)

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

April 1992

NTP TR 410

NIH Publication No. 92-3141

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

CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

K.M. Abdo, Ph.D.
C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.W. Bristol, Ph.D.
S.L. Eustis, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
R.A. Griesemer, D.V.M., Ph.D.
J.K. Haseman, Ph.D.
R.D. Irwin, Ph.D.
M.M. McDonald, D.V.M., Ph.D.
G.N. Rao, D.V.M., Ph.D.
M.B. Thompson, D.V.M., PhD.
K.L. Witt, M.S., Oak Ridge Associated Universities

Northrop Services, Inc.

Conducted studies, evaluated pathology findings

B. Adkins, Jr., Ph.D., Principal Investigator
R.L. Peiffer, Jr., D.V.M., Ph.D., Veterinary Ophthalmology Consultant

Experimental Pathology Laboratories, Inc.

Provided pathology quality assessment

J.F. Hardisty, D.V.M., Principal Investigator
K. Yoshitomi, D.V.M., Ph.D.

Integrated Laboratory Systems

Performed quality assurance audits

J.C. Bhandari, D.V.M., Ph.D., Principal Investigator

NTP Pathology Working Group

Evaluated slides, prepared pathology report for mice (3 April 90)

P.K. Hildebrandt, D.V.M., Chair
PATHCO, Inc.
G. Burger, D.V.M.
RJR Nabisco
M.P. Jokinen, D.V.M.
National Toxicology Program
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program
K.T. Morgan, B.V.Sc., M.R.C.V.S., Ph.D.
CIIT
D. Singh, D.V.M., Ph.D.
Environmental Protection Agency (observer)
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

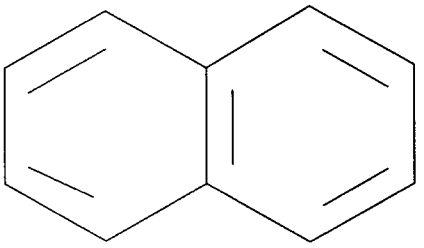
Biotechnical Services, Inc.

Prepared Technical Report

L.G. Cockerham, Ph.D., Principal Investigator
P. Chaffin, M.S.
G.F. Corley, D.V.M.
J.A. Gregan, M.A.

CONTENTS

ABSTRACT



NAPHTHALENE

CAS No. 91-20-3

Chemical Formula: $C_{10}H_8$ Molecular Weight: 128.16

Synonyms: Naphthalin, Naphthene, Tar Camphor

Naphthalene, a white, crystalline powder, is used as a moth repellent and in the manufacture of phthalic and anthranilic acids, naphthylamines, and synthetic resins. The 2-year studies were conducted by exposing groups of male and female B6C3F$_1$ mice to naphthalene (>99% pure) vapor for 6 hours daily, 5 days per week, for 104 weeks. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary cells.

2-Year Studies

Groups of male and female mice were exposed to atmospheres containing 0 (75 mice per group), 10 (75 mice per group), or 30 ppm (150 mice per group) naphthalene. Mice from each group were included for 14-day hematology evaluations (male: 0 ppm, 5 animals; 10 ppm, 4; 30 ppm, 10; female: 0 ppm, 4; 10 ppm, 5; 30 ppm, 10). Mean body weights of exposed mice were slightly lower than those of controls throughout the studies. Survival of male control mice was significantly less than that of exposed mice; the lower survival was the result of wound trauma and secondary infections related to fighting among the group-housed mice (0 ppm, 26/70, 37%; 10 ppm, 52/69, 75%; 30 ppm, 118/133, 89%). Survival of exposed female mice was similar to that of controls (59/69, 86%; 57/65, 88%; 102/135, 76%).

Neoplastic and Nonneoplastic Effects in the 2-Year Studies

No increase in tumor incidence related to naphthalene administration was observed in male mice. In females, the incidence of pulmonary alveolar/bronchiolar adenomas was significantly greater in the high-dose group than in the controls (5/69, 7%; 2/65, 3%; 28/135, 21%). One other high-dose female had an alveolar/bronchiolar carcinoma. The combined incidence of alveolar/bronchiolar adenomas and carcinomas in the high-dose females was above those for control female B6C3F$_1$ mice from NTP feed, water, and inhalation studies (91/1,166, 7.8%, range 0%-16%). These lung tumors were attributed to naphthalene exposure.

Nonneoplastic lesions attributed to naphthalene exposure were observed in the nose and lungs of mice of both sexes. In the nose, naphthalene exposure was associated with an increase in the incidence and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of respiratory epithelium. Chronic inflammation in the lung was associated with chemical exposure.

Genetic Toxicology

Naphthalene was negative for the induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 with and without exogenous metabolic activation (S9). In cytogenetic tests with Chinese hamster ovary cells, naphthalene induced sister chromatid exchanges with and without S9 activation. Exposure to naphthalene induced a significant increase in chromosomal aberrations in Chinese hamster ovary cells in the presence of S9.

Conclusions

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of naphthalene in male B6C3F$_1$ mice exposed to 10 or 30 ppm. There was *some evidence of carcinogenic activity* of naphthalene in female B6C3F$_1$ mice, based on increased incidences of pulmonary alveolar/bronchiolar adenomas.

In both male and female mice, naphthalene caused increased incidences and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium in the nose and chronic inflammation in the lungs.

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

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

	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses	0, 10, or 30 ppm in the air for 6 hours daily, 5 days a week, for 104 weeks	0, 10, or 30 ppm in the air for 6 hours daily, 5 days a week, for 104 weeks
Body weights	Exposed slightly lower than controls	Exposed slightly lower than controls
2-Year survival rates	26/70, 37%; 52/69, 75%; 118/135, 87%	59/69, 86%; 57/65, 88%; 102/135, 76%
Nonneoplastic effects	Nose: chronic inflammation (0/70, 67/69, 133/135), metaplasia of the olfactory epithelium (0/70, 66/69, 134/135), hyperplasia of respiratory epithelium (0/70, 66/69, 134/135)	Nose: chronic inflammation (1/69, 65/65, 135/135), metaplasia of the olfactory epithelium (0/69, 65/65, 135/135), hyperplasia of respiratory epithelium (0/69, 65/65, 135/135)
	Lung: chronic inflammation (0/70, 21/69, 56/135)	Lung: chronic inflammation (3/69, 13/65, 52/135)
Neoplastic effects	None	Lung: alveolar/bronchiolar adenomas (5/69, 2/65, 28/135) and alveolar/bronchiolar carcinomas (0/69, 0/65, 1/135)
Level of evidence of carcinogenic activity	No evidence	Some evidence
Genetic toxicology		
Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA100, TA1535, TA1537, and TA98	
Sister chromatid exchange		
Chinese hamster ovary cells *in vitro*:	Positive with and without S9	
Chromosomal aberrations		
Chinese hamster ovary cells *in vitro*:	Positive with S9	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on the inhalation studies on naphthalene on March 11, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities:

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

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Daniel S. Longnecker, M.D., Chair
Department of Pathology
Dartmouth Medical School
Hanover, NH

Paul T. Bailey, Ph.D., Principal Reviewer
Toxicology Division
Mobil Oil Corporation
Princeton, NJ

Jay I. Goodman, Ph.D.
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

Ellen K. Silbergeld, Ph.D.*
University of Maryland Medical School
Environmental Defense Fund
Baltimore, MD

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, M.S., M.P.H.
Department of Industrial Hygiene
United Rubber Workers International Union
Akron, OH

Gary P. Carlson, Ph.D., Principal Reviewer
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Harold Davis, D.V.M., Ph.D., Principal Reviewer
School of Aerospace Medicine
Brooks Air Force Base, TX

Robert H. Garman, D.V.M.
Consultants in Veterinary Pathology
Murrysville, PA

David W. Hayden, D.V.M, Ph.D.
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

Curtis D. Klaassen, Ph.D.
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Barbara McKnight, Ph.D.
Department of Biostatistics
University of Washington
Seattle, WA

Lauren Zeise, Ph.D.
California Department of Health Services/RCHAS
Berkeley, CA

* Did not attend

SUMMARY OF PEER REVIEW COMMENTS

On March 11, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of naphthalene received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of naphthalene by discussing the chemical and rationale for the study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in mice. The proposed conclusions were *no evidence of carcinogenic activity* in male $B6C3F_1$ mice and *some evidence of carcinogenic activity* in female $B6C3F_1$ mice.

Dr. Carlson, a principal reviewer, agreed with the conclusions. He asked for clarification of the incidence of inflammation. Dr. M.M. McDonald, NIEHS, explained that there were animals with inflammation and other animals characterized with a more extensive inflammatory response called granulomatous inflammation; therefore, there was no real overlap. Dr. Carlson suggested that the extensive work of Alan Buckpitt and coworkers on naphthalene metabolism and toxicity should be reviewed and mentioned since these studies may help in understanding any tie between metabolism and inflammation in the lung. Dr. Abdo said he was familiar with some of this work and would cite it (page 12).

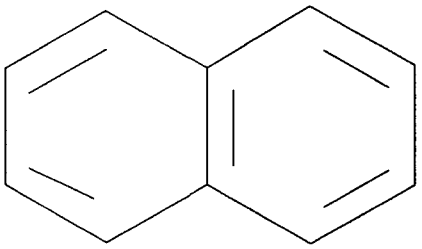
Dr. Davis, the second principal reviewer, agreed with the conclusions, but asked why the conclusion in female mice was not *clear evidence*. Dr. Abdo said the level of *some evidence* was chosen in part because all but one of the lung tumors were benign. Dr. Davis asked whether there was information on metabolites of naphthalene in humans. Dr. Abdo said he would cite information on human metabolism in the report (page 12).

Dr. Bailey, the third principal reviewer, agreed with the conclusions. He said that an explanation should be given for the absence of cataractogenesis in view of background information indicating such effects in mice. Dr. G.N. Rao, NIEHS, said $B6C3F_1$ mice were responsive at the Ah locus. (A report in the literature with nine inbred mouse strains exposed to naphthalene indicated cataracts developed only in responsive strains.) Dr. Rao commented that in the current studies exposure may not have been adequate for a cataractogenic effect since the animals often closed their eyes during exposure periods.

Dr. Hayden said inhalation exposure seemed to be appropriate based on types of human exposure. Thus, since previous studies with naphthalene in rats have been by other routes of administration, he proposed that a future study in rats by inhalation could be useful. Dr. Zeise said she disagreed with discounting the relationship of hemangiosarcomas in females to naphthalene exposure because they occurred at various sites. Dr. J.K. Haseman, NIEHS, noted that the main reason for discounting them was that the incidence in the high-dose group (4%) was similar to the mean historical control value.

Dr. Carlson moved that the Technical Report on naphthalene be accepted with the revisions discussed and the conclusions as written for male mice, *no evidence of carcinogenic activity*, and for female mice, *some evidence of carcinogenic activity*. Dr. Davis seconded the motion, which was accepted unanimously with 10 votes.

INTRODUCTION



NAPHTHALENE

CAS No. 91-20-3

Chemical Formula: $C_{10}H_8$ Molecular Weight: 128.16

Synonyms: Naphthalin, Naphthene, Tar Camphor

PHYSICAL AND CHEMICAL PROPERTIES

Naphthalene is a white, crystalline powder with a characteristic odor. Naphthalene has a boiling point of 217.9° C, a melting point of 80.2° C, a specific gravity of 1.14 at 4° C, a vapor pressure of 1 mm at 52.5° C, and vapor density of 4.4. It is insoluble in water (3 mg/100 mL), slightly soluble in methanol and ethanol (4.2 g/100 mL), soluble in benzene (40.2 g/100 mL), and very soluble in ether, chloroform, and carbon disulfide (50 g/100 mL). Naphthalene is commercially prepared from coal tar by fractional distillation or by sublimation (*Merck Index*, 1983).

PRODUCTION, USE, AND HUMAN EXPOSURE

United States production of naphthalene in 1984 was 280 million pounds (RTECS, 1990). Naphthalene is used in the manufacture of phthalic and anthranilic acids, naphthols, naphthylamines, sulfonic acid, synthetic resins, celluloid, lampblack, smokeless powder, and hydronaphthalenes. It is used as an insecticide, antiseptic, and vermicide (*Merck Index*, 1983). It is also an ingredient in various commercial moth repellents and toilet bowl cleaners (Gosselin *et al.*, 1976). A 0.2% solution in combination veterinary topical antiseptic is used for irrigating wounds; 1% solutions are used on neglected wounds. Naphthalene is also used externally on livestock and poultry to control lice (Rossoff, 1974).

From a survey conducted between 1981-1983, NIOSH estimated 112,696 workers, about 4.6% females, in 31 major industrial groups were potentially exposed to naphthalene. The top six industries, by total workers, accounted for over 50% of the total workers potentially exposed to naphthalene. Also, the petroleum and coal products and oil and gas extraction industries were among the top three industries and comprised about 21.4% of the workers potentially exposed to naphthalene. An estimated 1,838 agricultural services workers were exposed to naphthalene; over 87% were females (NIOSH, 1990).

ENVIRONMENTAL OCCURRENCE

Naphthalene has frequently been detected in water samples from the United States (Shackelford and Keith, 1976). A concentration of 1 ng/L was detected in tap water from the District of Columbia in 1974 (Scheiman *et al.*, 1974). The highest concentration detected in potable water by the Environmental Protection Agency was 1 μg/L (EPA, 1975). Naphthalene has also been detected in tap water from Waterloo, Iowa, although no levels were reported (Burnham *et al.*, 1973). The EPA has detected naphthalene in industrial effluent discharges from pesticide manufacture, petroleum refining, and nylon production; the level detected in petroleum refining effluent was 53 μg/L (Keith and Hercules, 1973; Webb *et al.*, 1973). Concentrations from 0.1 to 3.4 μg/kg were detected in tissue of fish from the Charles River in Boston (Hites and Biemann, 1972) and an unspecified concentration was detected in fish tissue from the Escambra River in Florida (Keith and Hercules, 1973).

The current Occupational Health and Safety Administration (OSHA) limit for naphthalene is 10 ppm in the air per 8-hour work shift (NIOSH, 1981). The American Conference of Governmental Hygienists reports that the odor threshold for naphthalene is at least as low as 0.3 ppm (ACGIH, 1989).

ABSORPTION AND METABOLISM

Naphthalene is readily absorbed when inhaled (Clayton and Clayton, 1982); it is also absorbed orally. This compound was readily absorbed by tissues of laying pullets (0.443 mg), swine (2.46 mg), and dairy cattle (30.69 mg) after oral intubation of a single dose or 31 daily doses (0.036, 0.112, and 5.115 mg). The adipose tissue, kidney, liver, and lung of pullets had the highest naphthalene levels after a single dose, and the kidney had the highest level after 31 daily doses. In swine, adipose tissue had the highest level of naphthalene after a single dose and lung tissue had the highest level after 31 daily doses. In cattle, the liver had the highest levels after both treatments (Eisele, 1985).

Thirty minutes after instillation of 100 nmol of ^{14}C-naphthalene into a closed rat intestinal loop, 84% was recovered unmetabolized from portal blood and only 1% was found in the luminal contents (Bock *et al.*, 1979). After an intraperitoneal injection of 100 mg/kg of naphthalene in rats, 20% to 30% was excreted in the urine and 5% to 10% in the bile. Of these excretions, 70% to 90% were in the form of acid conjugates (Clayton and Clayton, 1982). Naphthalene was not detected in fecal excretion of rats given 535 or 770 mg of the compound in the feed or 100 mg by stomach tube (Chang, 1943), suggesting that the compound was readily absorbed by rats.

An epoxide intermediate was postulated as the initial metabolite, with subsequent conversion to the trans-1,2-diol and other products (Sims and Grover, 1974). Support for this mechanism was first provided by Jerina *et al.* (1970) who demonstrated the formation of 1,2-naphthalene oxide from naphthalene in a microsomal system. Naphthalene was shown to be bioactivated by cytochrome P_{450} to electrophilic intermediates, which were subsequently metabolized to naphthoquinones and possibly to free radical intermediates (Buckpitt and Warren, 1983; Doherty *et al.*, 1985). In more recent studies, naphthalene was found to be biotransformed to dihydrodiol and 3-glutathinone conjugates by a human lung microsomal fraction in the presence of glutathiase and glutathione transferase (Buckpitt and Bahnson, 1986). Table 1 shows some of the metabolites identified in the urine of various species (Williams, 1959). The metabolic pathway for naphthalene suggested by Bock *et al.* (1976) is presented in Figure 1.

TABLE 1
Metabolites of Naphthalene Identified in the Urine of Various Species[a]

	Rat	Mouse	Rabbit	Guinea Pig
1-Naphthol	+	+	+	+
1-Naphthylsulfuric acid	+	+	+	+
1-Naphthylglucuronide	+	-	+	+
2-Naphthol	+	+	+	+
1,2-Dihydroxynaphthalene	+	-	-	+
2-Hydroxy-1-naphthyl-sulfuric acid	NT	NT	+	NT
1:2-Dihydronaphthalene-1:2-diol	+	+	+	+
1,2-Dihydro-2-hydroxy-1-naphthylglucuronide	+	-	+	-
1:2-Dihydro-1-naphthyl-glucuronide	+	NT	+	NT
1-Naphthylmercapturic acid	+	-	+	-

[a] + = metabolite present; - = metabolite not present; NT = species not tested for this metabolite; Williams, 1959

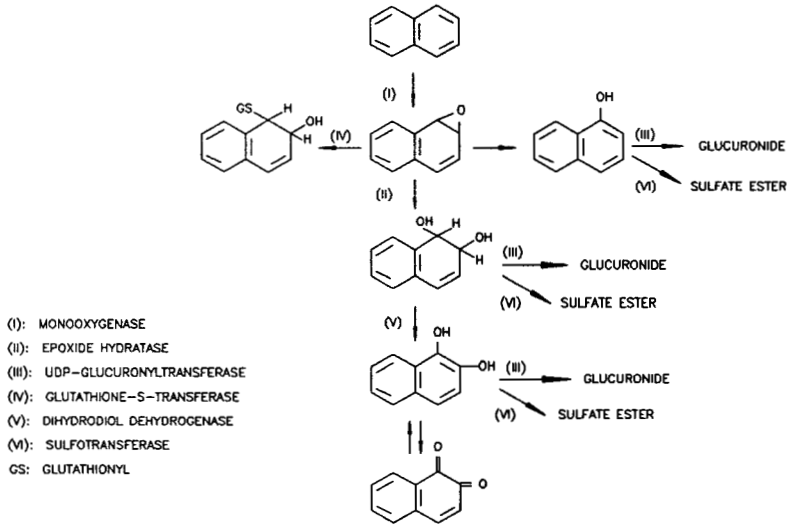


FIGURE 1
Metabolism of Naphthalene in Hepatocytes (from Bock *et al.*, 1976)

TOXICITY

Human Toxicity

Effects of naphthalene inhalation in humans include headache, confusion, eye irritation, nausea, profuse perspiration with vomiting, optic neuritis, hematuria, and edema. Naphthalene ingestion has resulted in abdominal pain, nausea, vomiting, diarrhea, darkening of the urine, irritation of the bladder, jaundice, anemia, and hyperthermia (Gerarde, 1960).

A pharmacist ingesting 5 g of naphthalene developed blindness and bilateral cataracts (Lezenius, 1902). Occupational exposure to powdered naphthalene resulted in cataracts, retinal hemorrhage, and chorioretinitis in two workers (Van der Hoeve, 1906). Cataracts were diagnosed in 8 of 29 chemical plant workers exposed to naphthalene for 5 years, with a greater incidence noted among younger workers (Ghetti and Mariani, 1956).

Naphthalene poisoning has produced hemolytic anemia in children (Zuelzer and Apt, 1949; Dawson *et al.*, 1958; Zinkham and Childs, 1958; Santhanakrishnan *et al.*, 1973) and adults (Taylor and Russell, 1932; Konar *et al.*, 1939). Individuals with decreased glucose-6-phosphate dehydrogenase activity are particularly susceptible to this effect (Haddad and Winchester, 1983; Melzer-Lange and Walsh-Kelly, 1989). Notable features of the hemolytic anemia included Heinz-body formation, hemoglobinuria, and decreases in hemoglobin, hematocrit, and red blood cell count. The hemolytic anemia was followed by renal failure (MacGregor, 1954; Gidron and Leurer, 1956). A case of aplastic anemia was reported in a woman exposed to vapors of dichlorobenzene and naphthalene, but the association is uncertain due to the lack of other substantiating reports (Harden and Baetjer, 1978).

Animal Toxicity

The oral LD_{50} value for naphthalene is 490 mg/kg for rats. LD_{50} values for mice are 533 mg/kg (oral), 969 mg/kg (subcutaneous), 100 mg/kg (intravenous), and 100 mg/kg (inhalation) (Union Carbide, 1969; RTECS, 1983).

Daily oral administration of 1 g/kg to rabbits led to degenerative changes in the lens of the eye, initially observed as swelling of the peripheral portion of the lens. Within 2 weeks the whole lens became cataractous (Potts, 1986). Van Heyningen and Pirie (1976) reviewed cataract formation in rats and rabbits resulting from naphthalene administration and concluded that, although the toxic agent in both species is the liver metabolite 1,2-dihydroxynaphthalene, different metabolic routes are involved: phenol oxidase in rats and catechol oxidase in rabbits. This is consistent with the observations that the pigmented strain of rats was more susceptible to cataract formation than the albino strain since polyphenol oxidase is found only in the pigmented strain. Albino and pigmented rabbits responded similarly to naphthalene (Koch and Doldi, 1975). The strain difference observed in rats also appears to occur in mice. Shichi *et al.* (1980) have reported correlations between the Ah^b allele and cataract formation in nine inbred mouse strains (four responsive at the Ah locus and five nonresponsive), with cataracts developing only in the responsive strains. Animals were exposed concomitantly to β-naphthoflavone for the induction of total body cytochrome P_{450} during daily administration of 60 to 120 mg/kg in a 60-day study. A study conducted with biochemical probes on male C57BL/6J mice suggests naphthalene cataractogenesis requires P_{450} bioactivation to a reactive metabolite (possibly a naphthoquinone), a free radical derivative, or a combination of both (Wells *et al.*, 1989). In these studies, a pretreatment of mice with SKF-525A or α-phenyl-N-butylnitrone in addition to treatment with vitamin E or caffeic acid inhibited naphthalene cataractogenicity, while pretreatment with phenobarbital or with diethyl-maleate enhanced naphthalene cataractogenicity.

Hemolytic anemia was observed in dogs given oral doses of 3 to 9 g of naphthalene (Zuelzer and Apt, 1949). All hematological values returned to normal 50 days after administration.

Pulmonary necrosis was observed in rats and mice given intraperitoneal injections of naphthalene. Naphthalene accumulated in the lungs of rats and mice after a single intraperitoneal injection (Reid *et al.*, 1973). Mice given a single intraperitoneal injection of 0.5, 1, or 2 mmol/kg showed dose-related necrosis of the bronchiolar epithelium (Mahvi *et al.*, 1977). This lesion was reversible and regeneration occurred after 7 days. Necrosis of the bronchial epithelial (Clara) cells occurred in the lungs of mice given a single intraperitoneal injection of 125 or 250 mg/kg naphthalene (Tong *et al.*, 1981).

Rats are more tolerant to naphthalene toxicity than mice. An intraperitoneal injection of 400 or 600 mg/kg in mice damaged the Clara cells in the lung and proximal tubule epithelial cells of the kidney. In contrast, an intraperitoneal injection of 1,600 mg/kg to rats did not produce any damage in the lung or the kidney (O'Brien *et al.*, 1985). The difference in susceptibility was attributed to the variation in the metabolic rate of the two species. It was found that the covalent binding and metabolism of naphthalene were 10% greater in microsomes prepared from mouse lung than those prepared from rats.

In vivo studies with target cell explants from sensitive species (mice) and nonsensitive species (rats and hamsters) showed that the cells obtained from mice contain a unique P_{450} enzyme capable of stereospecific metabolism of naphthalene to 1R,2S-naphthalene oxide; 1R,2S-naphthalene epoxide was not detected. Cells from rats and hamsters metabolized naphthalene to these two metabolites with the latter metabolite predominant (Chang *et al.*, 1991). Tolerance to pulmonary toxicity was observed in mice upon repeated dosing with naphthalene. Mice given a single intraperitoneal injection of 50, 100, or 200 mg/kg showed swelling of Clara cells with some exfoliation of epithelial cells, necrosis, and swollen cells with pyknotic nuclei. The severity of these lesions was dose dependent. Airways of mice receiving the same doses once a day for 7 days were essentially similar to controls. The increased tolerance resulting from multiple dosing was attributed to the selective decrease in the formation of 1R,2S-naphthalene oxide by mouse lung but not liver microsomal enzymes (O'Brien *et al.*, 1989).

Other Effects

A single intraperitoneal injection of naphthalene (1 g/kg) caused ammonia accumulation in the brains of rats. The accumulation of ammonia correlated positively with the lethality of the compound (Bolonova, 1967). Brain ammonia reacts with glutamic acid, with glutamine dehydrogenase as a catalyst, to form glutamine (DeBruin, 1976). This suggests glutamine dehydrogenase activity is inhibited by naphthalene. Naphthalene inhibited aryl hydrocarbon hydroxylase activity in liver homogenates and microsomal preparations obtained from rats given 40 mg/kg intraperitoneal injections for 3 days (Alexandrov and Frayssinet, 1973). A single 250 mg/kg intraperitoneal dose of naphthalene to C57BL/6J mice depressed the enzyme activity of microsomal monooxygenase in the lung by 30% to 70%; enzyme activity was not affected in the liver (Tong *et al.*, 1982).

Carcinogenic Activity

Possible Evidence in Humans

In East Germany, four cases of laryngeal carcinoma, a case of gastric carcinoma, a case of colon carcinoma, and a case of lupus erythematosus of the cheek were reported among 7 of 15 employees involved in naphthalene manufacture (Wolf, 1976). Seven tumor-free workers suffered various degrees of rhinopharyngo-laryngitis, an inflammation possibly conducive to prodromal carcinogenesis. Laryngeal cancer developed in 4 of 15 naphthalene distillation workers (Wolf, 1978). The incidence of laryngeal cancer in these distillation workers is approximately four thousand times greater than the general incidence of laryngeal cancer in East Germany. Kup (1978) studied 15 patients: 12 with laryngeal carcinomas, two with epipharyngeal cancer, and one with nasal carcinoma. He observed that four of the laryngeal cancer patients were exposed to naphthalene, but suggested that most of the cancers were not work related; most of the workers were smokers as well.

Possible Evidence in Animals

Daily 6-hour exposures to atmospheres of 30 ppm naphthalene for 6 months did not elicit a significant increase in lung adenomas among Strain A/J mice. Histopathologic examination of lungs from the animals, however, revealed an increased incidence of multiple alveolar adenomas relative to concurrent controls. However, the number of tumors per tumor-bearing lung in the concurrent controls was significantly lower than that observed in unexposed controls for this strain of mice (Adkins *et al.*, 1986). Negative results were reported in early naphthalene dermal studies, but experimental details were unavailable (Kennaway, 1930). A rat dermal study with 1,4-naphthoquinone, a naphthalene metabolite, resulted in skin papilloma incidences of 15% to 20%, with some leading to malignant epitheliomas (Takizawa, 1940). Levels of naphthalene producing systemic toxicity in a rabbit dermal study did not cause any carcinogenic activity (Bogdat'eva and Bid, 1955). Tumors occurred in 9 of 25 black mice

receiving naphthalene in benzene and in 3 of 21 black mice receiving the benzene control in a lifetime (5 days/week) dermal study (Knake, 1956). In the exposed mice, four had lymphocytic leukemia, three had lung adenomas, one had lymphosarcoma, and one had a nonspecified tumor; in the benzene controls, one had lymphosarcoma, one had lung adenoma, and one had a nonspecified tumor. A group of 40 rats administered seven subcutaneous biweekly doses of 500 mg/kg of naphthalene in benzene and then observed for 18 months had a tumor incidence of 15% (five animals with lymphosarcomas and one with fibroadenoma), while tumor incidences of 5% and 2% occurred in vehicle controls and unexposed controls, respectively (Knake, 1956). No carcinogenic activity or toxic effects were observed either in rats given a total of 10 g of naphthalene orally over a 700-day period or in rats given 820 mg subcutaneously or intraperitoneally over a 40-week period (Schmal, 1955). No controls were used in these studies, but a concurrent study with anthracene administered subcutaneously did produce tumors. Boyland *et al.* (1964) examined the effects of implanting naphthalene in the urinary bladder of mice and found a 4% incidence of carcinomas after 30 weeks which was similar to the effect of implanting inert substances such as glass.

Genetic Toxicology

Data from numerous genotoxicity studies indicate that naphthalene is nonmutagenic in *Salmonella typhimurium*, with or without metabolic activation (Anderson and Styles, 1978; Connor *et al.*, 1985; Nohmi *et al.*, 1985; Sakai *et al.*, 1985; Mortelmans *et al.*, 1986; Narbonne *et al.*, 1987; Bos *et al.*, 1988). In addition, the halogenated structural analogue 1-chloronaphthalene and the metabolites 1-naphthol and 2-naphthol showed no mutagenic activity in *S. typhimurium*, with or without metabolic activation (Anderson and Styles, 1978; Florin *et al.*, 1980; De Flora, 1981; Gocke *et al.*, 1981; Probst *et al.*, 1981; Lofroth *et al.*, 1985; Narbonne *et al.*, 1987). Testing of viscosity changes *in vitro* showed little binding of naphthalene to bacterial DNA (Lerman, 1965). Naphthalene can be bound, but only weakly, to nucleic acid (denatured and native calf thymus DNA) *in vitro* (Ts'o and Lu, 1964). Naphthalene was reported to be negative for the induction of single-strand breaks in rat hepatocytes *in vitro* when assayed by alkaline elution (Sina *et al.*, 1983). Brookes and Lawley (1964) found no binding to mouse skin proteins *in vivo* and noted that binding of naphthalene to DNA and RNA was insignificant.

Although the metabolite 1-naphthol was negative in several *S. typhimurium* gene mutation studies, it did cause differential growth inhibition in some strains of *Escherichia coli* (Suter and Jaeger, 1982) and *Bacillus subtilis* (Tanooka, 1977; Kawachi *et al.*, 1980), presumably as a result of DNA damage. It was negative in a variety of other genotoxicity tests, including assays for induction of sex-linked recessive lethal mutations in male Berlin K *Drosophila melanogaster* (Gocke *et al.*, 1981), unscheduled DNA synthesis in rat hepatocytes *in vitro* (Probst and Hill, 1980), and gene mutations in mouse L5178Y cells (Amacher and Turner, 1982). 1-Naphthol was also reported to be negative for induction of micronuclei in rat (Hossack and Richardson, 1977) and mouse (Gocke *et al.*, 1981) bone marrow cells following acute exposure *in vivo*.

Study Rationale

Naphthalene was nominated by NIOSH, OSHA, and EPA for carcinogenic evaluation because evidence in the literature was inadequate for reaching a regulatory decision, and because of the potential for chronic exposure to humans through the use of mothballs in the home. Potential chronic exposure can also occur on the job or through cigarette smoke (3 μg naphthalene/cigarette; Schweltz *et al.*, 1978). The inhalation route of administration was chosen because it is the primary route of human exposure. The decision to conduct the chronic studies in mice instead of rats was based on the negative results obtained by Schmal (1955) in a gavage study of naphthalene in rats. In that study, 28 animals were dosed once daily, 6 times per week, until each rat was administered a total of 10 g over 700 days. The study alone would be considered inadequate as a full carcinogenicity bioassay by today's standards.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF NAPHTHALENE

Naphthalene (scintillation grade) was obtained from Fisher Scientific Company (Fair Lawn, NJ) in two lots (lot numbers 775379 and 735773). Identity, purity, and stability analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). The methods and results of these studies are detailed in Appendix E.

The study chemical, a white, crystalline powder, was identified as naphthalene by appearance, melting point determination, and infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lot number 775379 was found to be greater than 99% by elemental analysis, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Stability studies indicated that naphthalene was stable as a bulk chemical for 2 weeks at temperatures up to 60° C.

GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

In each of three Hinners-type inhalation chambers, naphthalene vapor was generated by direct sublimation from a 500 mL flask and was delivered through metering valves using nitrogen. Naphthalene chamber concentrations were monitored with a Miran Model 80 infrared analyzer and computer-adjusted to the desired concentration by a software feedback arrangement. Individual monitors were used for each of the exposure chambers. Calibration was performed daily using a closed loop system.

During the 2-year studies, weekly average concentrations in the 10 ppm chamber were within 20% of the target concentration except for one week when the mean was 5.5 ppm. Concentrations in the two 30 ppm chambers were within 20% of the target concentration throughout the studies. A summary of weekly average exposure concentrations for the 2-year studies is presented in Table E1.

Study Design

Groups of 75 mice of each sex were exposed by inhalation to naphthalene at target concentrations of 0 (chamber controls), 10, or 30 ppm. These dose levels were equivalent to 0, 50, or 150 mg/m^3. Two additional groups of 75 male mice and 75 female mice were exposed to 30 ppm in a fourth chamber. Twice as many animals received the high dose because of the lack of information on the long-term toxicity of inhaled naphthalene and to ensure that a sufficient number of animals lived to study termination. Exposures were for 6 hours daily, 5 days weekly, for 104 weeks.

In each chamber, 50 animals per sex were designated for the 2-year studies; 5 animals per sex were designated for 14-day and 3, 6, 12, and 18-month interim hematology evaluations. However, because of the high mortality in the male control group, the 3-, 6-, 12-, and 18-month interim evaluations were cancelled and all surviving interim animals were incorporated into the 2-year studies.

The high dose, 30 ppm, is equal to approximately one half of the saturating concentration for naphthalene at 20° C. Higher levels were not selected to ensure that condensation did not occur in the exposure chambers. The low dose, 10 ppm, is the threshold limit value established for the compound by the American Conference of Governmental Industrial Hygienists (ACGIH, 1989).

Source and Specification of Animals

Male and female B6C3F$_1$ mice were obtained from Simonsen Labs (Gilroy, CA). Mice were held 28 or 35 days before study initiation. The study began when the mice were 10 to 11 weeks old. Animal health was to be monitored by serologic analyses performed at 6-month intervals according to the protocols of the NTP Sentinel Animal Program; these were not conducted due to deaths among study animals. All mice were vaccinated for Sendai virus before study initiation and at week 31.

Animal Maintenance

Mice were housed five per cage with feed and water available *ad libitum* during nonexposure periods. All exposure cages were rotated weekly in the exposure chambers during the studies. Further details of animal maintenance are given in Table 2.

Clinical Examinations and Pathology

All animals were observed twice daily, 7 days a week. Each group of five mice was weighed by cage initially, weekly for the first 13 weeks of the study, and monthly thereafter. Hematology parameters were measured on up to five mice of each sex from each chamber 14 days after study initiation. Serial slit-lamp biomicroscopy and indirect ophthalmoscopic examinations were performed on five animals of each sex from each dose group at 6-month intervals during the studies. Table 2 contains the complete list of the analyses and studies performed on animals in the 2-year inhalation studies of naphthalene.

A necropsy was performed on all animals. During necropsy, all organs and tissues were examined for grossly visible lesions. A complete histopathologic examination inclusive of gross lesions was performed on all control and high-dose animals and on all animals dying or killed moribund prior to 21 months. Histopathologic examinations of the lungs and nasal cavities were performed on all low-dose mice. Tissues for microscopic examination were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin.

Pathology evaluations were completed by the study laboratory pathologist and the pathology data were entered into the Toxicology Data Management System (TDMS). The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. A quality assessment pathologist reviewed all lung and nose sections from all male and female mice for accuracy and consistency of neoplastic and nonneoplastic lesion diagnosis.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG), which reviewed tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms of the nose and lungs and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were selected by the PWG chair for review by the PWG. The PWG included the quality assessment pathologist as well as other pathologists experienced in rodent toxicologic pathology, who examined these tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

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

Calculation of Incidence

The incidence of neoplasms or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which 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) before tissue

sampling for histopathology, or when lesions could have appeared at multiple sites (e.g., mononuclear cell leukemia), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence

The majority of tumors in these studies was considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and, thus, did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals. Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. For further discussion of these methods, see Haseman (1984).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of tumor incidence. NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for tumors appearing to show compound-related effects.

Analysis of Continuous Variables

Hematology data, which typically have skewed distributions, were analyzed using the multiple comparison methods of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-response trends and to determine whether a trend-sensitive test (Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunn's test).

Quality Assurance Methods

Study records were submitted to the NTP Archives and audited by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by the NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of naphthalene was assessed by testing its ability to induce mutations in *Salmonella typhimurium* (strains TA100, TA1535, TA1537, and TA98) and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The protocols and results for these studies are given in Appendix C.

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Naphthalene

Study Laboratory
Northrop Services, Incorporated (Research Triangle Park, NC)

Strain and Species
B6C3F$_1$ Mice

Animal Source
Simonsen Labs (Gilroy, CA)

Time Held Before Study Initiation
28 and 35 days

Age When Placed on Studies
10-11 weeks

Date of First Dose
31 August 1982

Duration of Dosing
6 hours daily, 5 days a week, for 104 weeks

Date of Last Dose
24 August 1984

Age When Killed
116-118 weeks

Size of Study Groups
75 males and 75 females in 0 and 10 ppm groups; 150 males and 150 females in 30 ppm dose group

Animals per Cage
5

Method of Animal Identification
Ear punch

Diet
NIH-31 diet (Zeigler Brothers, Gardners, PA), available *ad libitum* during nonexposure periods

Maximum Storage Time for Feed
90 days

Water
Deionized water, available *ad libitum* during nonexposure periods, in new polypropylene/polyethylene bottles (Girton Manufacturing, Millville, PA), changed weekly

Cages
Stainless steel wire mesh cages (Lab Products, Inc., Maywood, NJ), changed weekly

Chambers
Stainless steel and glass Rochester-type chambers (Young and Bertke Company, Cincinnati, OH)

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Naphthalene
(continued)

Bedding
BetaChips®, hardwood laboratory bedding (Northeastern Products, Warrensburg, NY) and Sanichip (P.J. Murphy Forest Products Corp., Rochelle Park, NJ), changed twice weekly

Cage Filters
Semi-permanent, spun-bonded polyester (Lab Products, Inc., Maywood, NJ), changed monthly

Racks
Stainless steel, changed twice weekly

Animal Room Environment
Fluorescent light: 12 hours/day
Room air changes: 10 changes/hour

Doses
0, 10, or 30 ppm by inhalation

Type and Frequency of Observation
Observed twice daily; body weights taken initially, weekly through week 13, monthly thereafter, and at scheduled sacrifice or death

Necropsy
Necropsy performed on all animals.

Histopathology
Complete histopathologic examination performed on all mice dying early or killed moribund prior to 21 months, and all control and high-dose animals. In addition to tissue masses, gross lesions, and associated regional lymph nodes, the following organs and/or tissues were examined: adrenal gland, bone (femur including marrow), brain, epididymis, esophagus, gallbladder, heart, kidney, large intestine (cecum, colon, rectum), larynx, liver, lung, lymph node (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach (glandular and forestomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Low-dose animals had lungs and nasal cavities examined microscopically.

Hematology
Blood samples were collected from 5 mice of each sex from each chamber (except 4 control female mice) for hematology determinations: hematocrit, hemoglobin, erythrocytes, mean cell volume, reticulocytes, and leukocytes at day 14.

Supplemental Studies
Serial ophthalmoscopic examinations by slit-lamp biomicroscopy and indirect ophthalmoscopy were performed at 6-month intervals throughout the studies on 5 mice at each dose.

RESULTS

As detailed in the Materials and Methods section, the 30 ppm groups were housed in two chambers, each containing 75 animals of each sex. For comparative purposes, the incidences of neoplasms and nonneoplastic lesions for males and females in the two 30 ppm chambers are given separately in Appendixes A and B.

Survival and body weights of male and female mice in one 30 ppm exposure chamber were similar to those of male and female mice in the other 30 ppm chamber. With three exceptions, tumor incidences of males and females in one 30 ppm chamber were also similar to those of males and females in the other 30 ppm chamber. These exceptions were subcutaneous mesenchymal tumors in males (0/67 or 0% vs. 8/68 or 12%), hepatocellular tumors in males (7/67 or 10% vs. 16/68 or 24%), and hemangiomas and hemangiosarcomas in females (0/68 or 0% vs. 5/67 or 8%). Application of permutation tests (Farrar and Crump, 1988) revealed that the latter two tumor incidences might be due to chance, but that the difference in integumentary system mesenchymal tumors in males remained significant ($P \leq 0.05$) even after adjusting for multiple comparisons. The reason for this variation in integumentary system tumors between chambers is unknown, but since this was the only strong evidence of a difference (the incidences of most nonneoplastic lesions were similar in the two chambers), the incidences from the two chambers were pooled in subsequent statistical analyses.

BODY WEIGHTS AND CLINICAL FINDINGS

Mean body weights of female mice exposed to naphthalene were slightly lower than but within 10% of those of the controls throughout the study. Mean body weights of exposed male mice were slightly lower than but within 10% of those of the controls the first 18 months (Figure 2).

No clinical findings attributed directly to naphthalene exposure were observed. In general, exposed mice tended to huddle in the cage corners during exposure periods, therefore, fighting was observed less frequently among the exposed males than among control males. No treatment-related ocular lesions were observed in selected control and exposed mice subjected to serial slit-lamp biomicroscopy and indirect ophthalmoscopic examination at 6-month intervals throughout the studies. There were no biologically significant changes in hematology parameters for exposed mice at day 14 of the study (Table D1).

SURVIVAL

Table 3 and Figure 3 show that survival was significantly decreased in the male controls compared to the exposed males, while survival of the females did not vary significantly among groups. The lower survival in control males was related to wound trauma and secondary lesions resulting from increased fighting in the group.

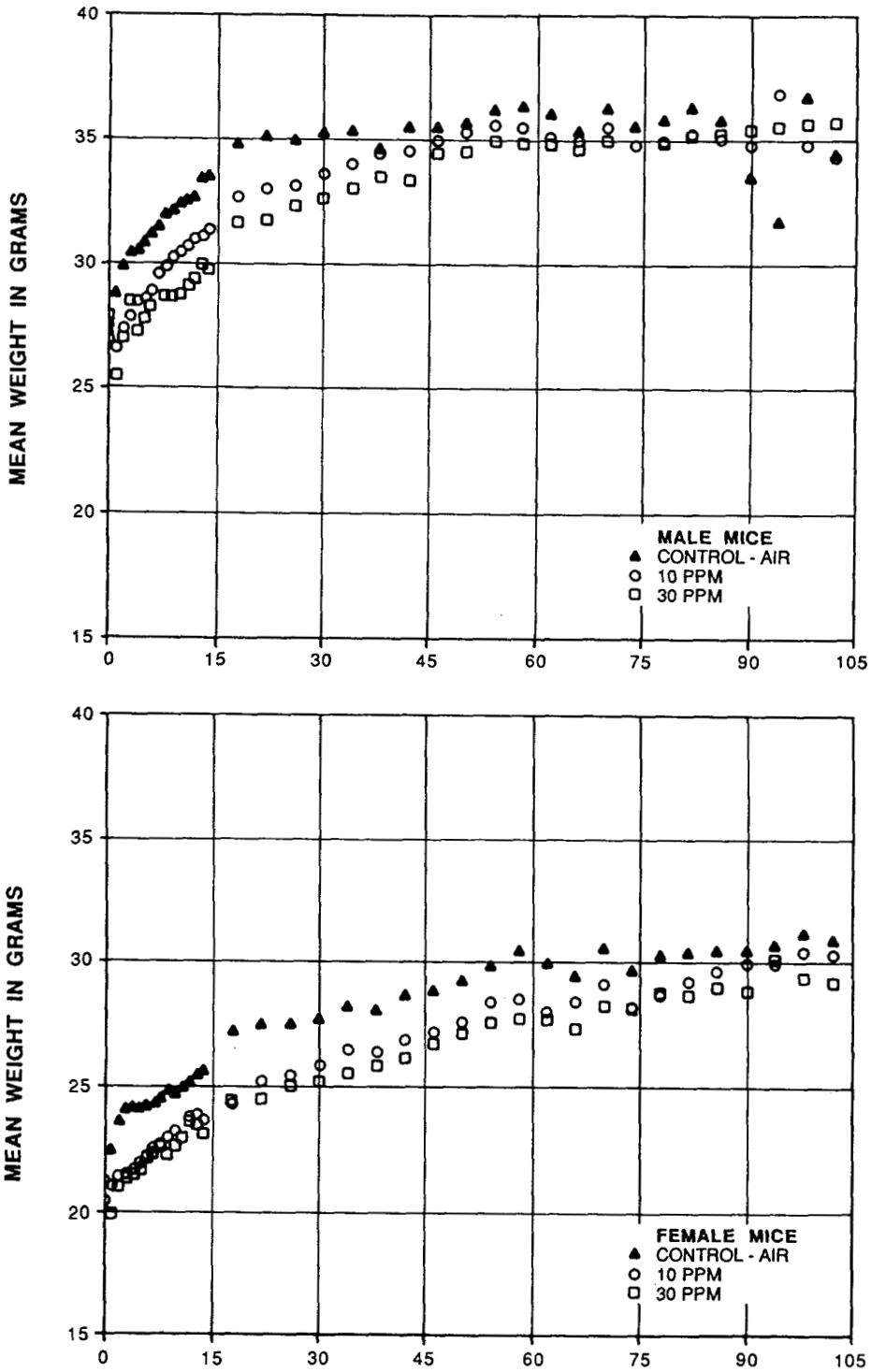


FIGURE 2
Growth Curves for Male and Female Mice Administered Naphthalene by Inhalation for 2 Years

TABLE 3
Survival of Mice in the 2-Year Inhalation Studies of Naphthalene

	0 ppm	10 ppm	30 ppm
Male			
Animals initially in study	75	75	150
Special study animals[a,b]	5	5	13
Natural deaths	31	10	7
Moribund kills	13	7	8
Accidental deaths[a]			2
Missing[a]		1	2
Animals surviving to study termination[c]	26	52	118
Percent survival at end of study[d]	37	75	89
Mean survival (days)[e]	525	648	701
Survival analysis[f]	P≤0.001N	P≤0.001N	P≤0.001N
Female			
Animals initially in study	75	75	150
Special study animals[a,b]	5	7	12
Natural deaths	8	6	17
Moribund kills	2	2	16
Accidental deaths[a]	1		
Missing[a]		3	3
Animals surviving to study termination[c]	59	57	102
Percent survival at end of study[d]	86	88	76
Mean survival (days)[e]	707	692	696
Survival analysis[f]	P=0.025	P=0.673N	P=0.125

[a] Censored from survival analysis.
[b] These mice not examined microscopically; includes mice from the 14-day interim evaluation and mice found dead or killed moribund before the study began
[c] Includes animals that died the last week of the study
[d] Kaplan-Meier determinations
[e] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[f] The entry in the control column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972). A negative trend or lower mortality is indicated by N.

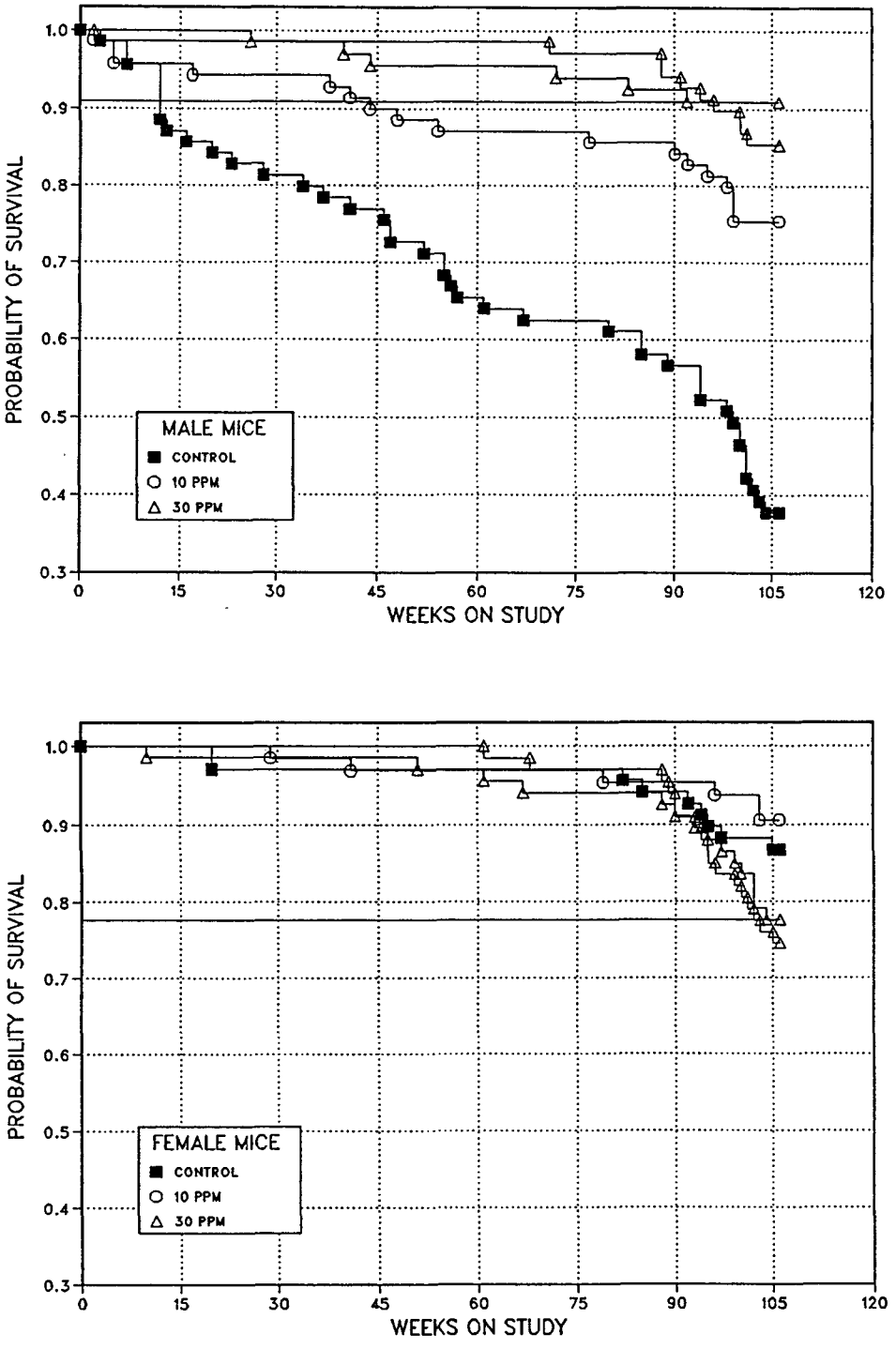


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Naphthalene by Inhalation for 2 Years

PATHOLOGY AND STATISTICAL ANALYSIS OF RESULTS

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplastic or nonneoplastic lesions of the lung, nose, and skin, as well as hemangiosarcomas at various hematopoietic sites (bone marrow and spleen).

Summaries of the incidences of neoplastic and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred at an incidence of at least 5% in at least one study group, and historical incidences for the neoplasms mentioned in this section are presented in Appendixes A and B.

Lung: The high-dose females had significantly increased incidences of alveolar/bronchiolar adenomas, and one carcinoma occurred in a high-dose female (Table 4). The combined incidence of alveolar/bronchiolar adenomas and carcinomas in control female B6C3F$_1$ mice from NTP inhalation studies is 39/466 (8.4%, range 0%-12%) (Table B4a). In control female B6C3F$_1$ mice from NTP feed, water, and inhalation studies, the combined incidence of alveolar/bronchiolar adenomas and carcinomas is 91/1,166 (7.8%, range 0%-16%). Because increased incidences of these neoplasms in exposed females were statistically significant and well above historical control ranges, they were considered to be directly related to naphthalene exposure.

Compared to control males, exposed males had marginally increased incidences of alveolar/bronchiolar adenomas and carcinomas. In control male B6C3F$_1$ mice from NTP inhalation studies, the combined incidence of alveolar/bronchiolar adenomas and carcinomas is 94/478 (19.7%, range 10%-30%) (Table A4). In control male B6C3F$_1$ mice from NTP feed, water, and inhalation studies, the combined incidence of alveolar/bronchiolar adenomas and carcinomas is 229/1,172 (19.5%, range 6%-42%). Because the incidences of these neoplasms in exposed animals were not statistically significant and were within historical control ranges, they were considered unlikely to be directly related to naphthalene exposure. The marginally increased incidences were likely related to the greater survival in the exposed groups than in the controls.

Alveolar/bronchiolar adenomas and carcinomas constitute a morphologic continuum. Adenomas were locally compressive nodular masses consisting of cords of well-differentiated epithelial cells (Plate 1), while carcinomas were composed of ribbons and/or coalescing sheets of smaller, more anaplastic, cells which sometimes extended into adjacent parenchyma.

Several spontaneous nonneoplastic lung lesions occurred in controls but were more frequent and severe in exposed mice of both sexes, while other lesions were seen only in exposed mice. Lesions were generally minimal to mild. Collectively, these were considered features of an overall inflammatory response directly related to naphthalene exposure. Accumulations of intra-alveolar foamy macrophages (histiocyte infiltration) (Plate 2) or interstitial lymphocytes (lymphocyte infiltration) were present in some controls, but were more frequent and extensive in exposed mice. Inflammation and granulomatous inflammation were diagnostic terms used to describe progressive morphologic stages of an overall response. In many exposed mice, focal intra-alveolar mixed inflammatory cell exudates and interstitial fibrosis were collectively termed "inflammation." In similar but more advanced lesions, the cellular infiltrate consisted primarily of large foamy macrophages, sometimes accompanied by multinucleated giant cells, a condition termed "granulomatous inflammation" (Plate 3). Usually only one of these terms was used to describe the overall response in any given mouse. Bronchial submucosal gland distension by mixed inflammatory cell exudates (inflammation) was in many cases also accompanied by the aforementioned lesions. Foci of alveolar epithelial hyperplasia generally occurred distant to areas of inflammation.

TABLE 4
Incidence of Lung Lesions in Mice in the 2-Year Inhalation Studies of Naphthalene

	0 ppm	10 ppm	30 ppm
Male			
Neoplasms			
Alveolar/bronchiolar Adenoma[a]			
Overall rates[b]	7/70 (10%)	15/69 (22%)	27/135 (20%)
Adjusted rates[c]	25.7%	28.8%	22.7%
Terminal rates[d]	6/26 (23%)	15/52 (29%)	26/118 (22%)
First incidence (days)	714	736 (T)	656
Logistic regression tests[e]	P=0.411N	P=0.450	P=0.541
Alveolar/bronchiolar Carcinoma[f]			
Overall rates	0/70 (0%)	3/69 (4%)	7/135 (5%)
Adjusted rates	0.0%	5.5%	5.9%
Terminal rates	0/26 (0%)	2/52 (4%)	7/118 (6%)
First incidence (days)	–[g]	629	736 (T)
Logistic regression tests	P=0.180	P=0.176	P=0.222
Alveolar/bronchiolar Adenoma or Carcinoma[h]			
Overall rates	7/70 (10%)	17/69 (25%)	31/135 (23%)
Adjusted rates	25.7%	31.9%	26.0%
Terminal rates	6/26 (23%)	16/52 (31%)	30/118 (25%)
First incidence (days)	714	629	656
Logistic regression tests	P=0.530	P=0.212	P=0.394
Nonneoplastic Lesions			
Infiltration Cellular, Lymphocyte			
Overall rates	3/70 (4%)	0/69 (0%)	8/135 (6%)
Logistic regression tests	P=0.143	P=0.201N	P=0.407
Average severity grade[i]	1.7	0	2.3
Infiltration Cellular, Histiocyte			
Overall rates	1/70 (1%)	12/69 (17%)	16/135 (12%)
Logistic regression tests	P=0.083	P=0.003	P=0.009
Average severity grade	3.0	1.8	1.6
Inflammation			
Overall rates	0/70 (0%)	21/69 (30%)	56/135 (41%)
Logistic regression tests	P≤0.001	P≤0.001	P≤0.001
Average severity grade	0	2.3	2.1
Inflammation, Granulomatous			
Overall rates	0/70 (0%)	19/69 (28%)	15/135 (11%)
Logistic regression tests	P=0.495N	P≤0.001	P=0.021
Average severity grade	0	2.2	2.6
Alveolar Epithelium, Hyperplasia			
Overall rates	2/70 (3%)	7/69 (10%)	12/135 (9%)
Logistic regression tests	P=0.482	P=0.354	P=0.323
Average severity grade	1.5	1.7	1.7
Glands, Inflammation			
Overall rates	7/70 (10%)	14/69 (20%)	22/135 (16%)
Logistic regression tests	P=0.265N	P=0.500	P=0.519N
Average severity grade	1.4	2.1	2.0

TABLE 4
Incidence of Lung Lesions in Mice in the 2-Year Inhalation Studies of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm
Female			
Neoplasms			
Alveolar/bronchiolar Adenoma[j]			
Overall rates	5/69 (7%)	2/65 (3%)	28/135 (21%)
Adjusted rates	8.3%	3.5%	25.6%
Terminal rates	4/59 (7%)	2/57 (4%)	22/102 (22%)
First incidence (days)	729	736 (T)	471
Logistic regression tests	P≤0.001	P=0.233N	P=0.010
Alveolar/bronchiolar Carcinoma[k]			
Overall rates	0/69 (0%)	0/65 (0%)	1/135 (1%)
Alveolar/bronchiolar Adenoma or Carcinoma[l]			
Overall rates	5/69 (7%)	2/65 (3%)	29/135 (22%)
Adjusted rates	8.3%	3.5%	26.5%
Terminal rates	4/59 (7%)	2/57 (4%)	23/102 (23%)
First incidence (days)	729	736 (T)	471
Logistic regression tests	P≤0.001	P=0.233N	P=0.007
Nonneoplastic Lesions			
Infiltration Cellular, Lymphocyte			
Overall rates	11/69 (16%)	21/65 (33%)	46/135 (34%)
Logistic regression tests	P=0.007	P=0.024	P=0.003
Average severity grade	2.2	2.1	2.2
Infiltration Cellular, Histiocyte			
Overall rates	1/69 (1%)	5/65 (8%)	4/135 (3%)
Logistic regression tests	P=0.537N	P=0.096	P=0.430
Average severity grade	2.0	1.6	2.0
Inflammation			
Overall rates	3/69 (4%)	13/65 (20%)	52/135 (39%)
Logistic regression tests	P≤0.001	P=0.006	P≤0.001
Average severity grade	1.7	2.2	2.1
Inflammation, Granulomatous			
Overall rates	0/69 (0%)	38/65 (58%)	42/135 (31%)
Logistic regression tests	P=0.004	P≤0.001	P≤0.001
Average severity grade	0	2.1	2.3
Alveolar Epithelium, Hyperplasia			
Overall rates	3/69 (4%)	6/65 (9%)	12/135 (9%)
Logistic regression tests	P=0.222	P=0.215	P=0.187
Average severity grade	2.3	1.5	1.2
Glands, Inflammation			
Overall rates	1/69 (1%)	3/65 (5%)	15/135 (11%)
Logistic regression tests	P=0.002	P=0.294	P=0.009
Average severity grade	2.0	2.0	2.0

TABLE 4
Incidence of Lung Lesions in Mice in the 2-Year Inhalation Studies of Naphthalene (continued)

(T)Terminal sacrifice
[a] Historical incidence for 2-year NTP inhalation studies with unexposed control groups (mean ± standard deviation): 69/478 (14% ± 5.5%); range 6%-24%
[b] Incidence expressed as number of animals with lesion/total number of animals examined microscopically
[c] Kaplan-Meier estimated tumor incidence at the end of the studies after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[f] Historical incidence: 30/478 (6% ± 5.5%); range 0%-14%
[g] Not applicable; no tumors in animal group
[h] Historical incidence: 94/478 (20% ± 8.1%); range 10%-30%
[i] Average severity grade based on 1=minimal, 2=mild, 3=moderate, and 4=marked
[j] Historical incidence: 27/466 (6% ± 3.2%); range 0%-10%
[k] Historical incidence: 13/466 (3% ± 2.7%); range 0%-6%
[l] Historical incidence: 39/466 (8% ± 3.5%); range 0%-12%

Nose: Several nonneoplastic lesions of the nose occurred in virtually all exposed mice of each sex (Table 5). These lesions included inflammation, metaplasia of the olfactory epithelium (Plate 4), and respiratory epithelial hyperplasia. These focal or multifocal lesions occurred mainly in the posterior nasal cavity and were minimal to mild in severity. Inflammation was characterized by substantia propria edema, congestion, mixed inflammatory cell infiltrates, and occasional fibroplasia as well as intraluminal serous to fibrinopurulent exudate and necrotic debris. Respiratory epithelium hyperplasia, characterized by increased cell layers of respiratory epithelium, resulted in a thickened, folded, irregular mucosal surface. In many cases, the usual olfactory cell layer was replaced by ciliated columnar or pseudo-columnar respiratory-like epithelial cells (olfactory epithelium metaplasia). Collectively, these lesions were considered features of a generalized inflammatory and regenerative process. The dose-related increased incidences of these lesions were considered directly related to naphthalene exposure in both sexes.

Nasal adenomas occurred in the anterior nasal cavities of two females receiving 10 ppm. The incidence of nasal adenomas was not statistically significant and did not occur with a dose-related increased incidence. Therefore, it is unlikely that the occurrence of these neoplasms was directly related to naphthalene exposure.

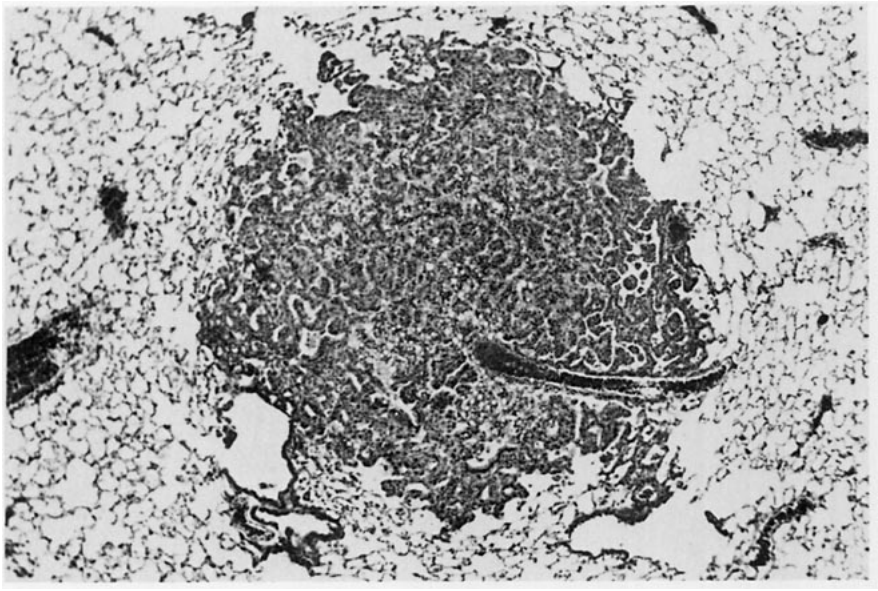


Plate 1
Lung: Alveolar/bronchiolar adenoma in the lung of a male B6C3F$_1$ mouse from 30 ppm exposure group in the 2-year inhalation studies of naphthalene. H&E, ×48

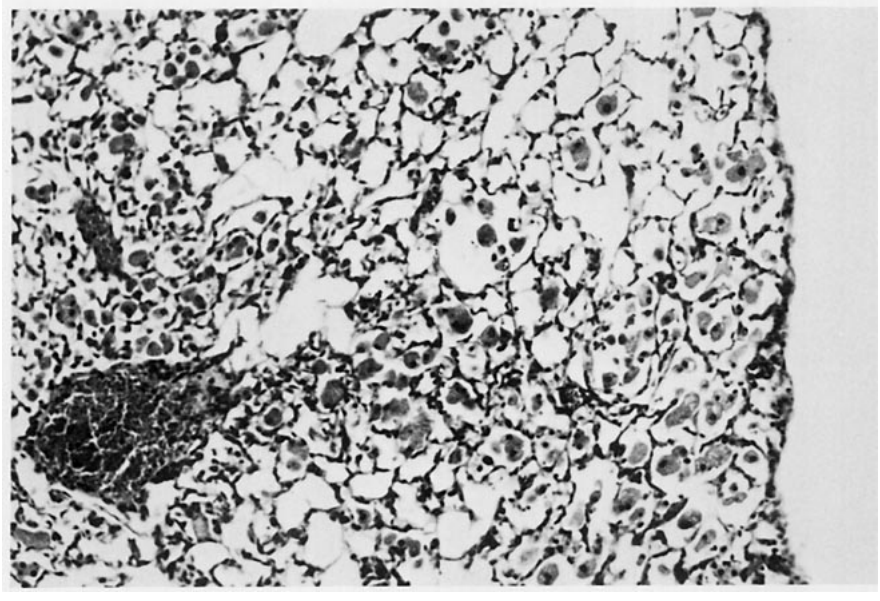


Plate 2
Lung: Mild histiocyte infiltration in alveolar lumens of the lung of a male B6C3F$_1$ mouse from the 10 ppm exposure group in the 2-year inhalation studies of naphthalene. Compare to Plate 3. H&E, ×120

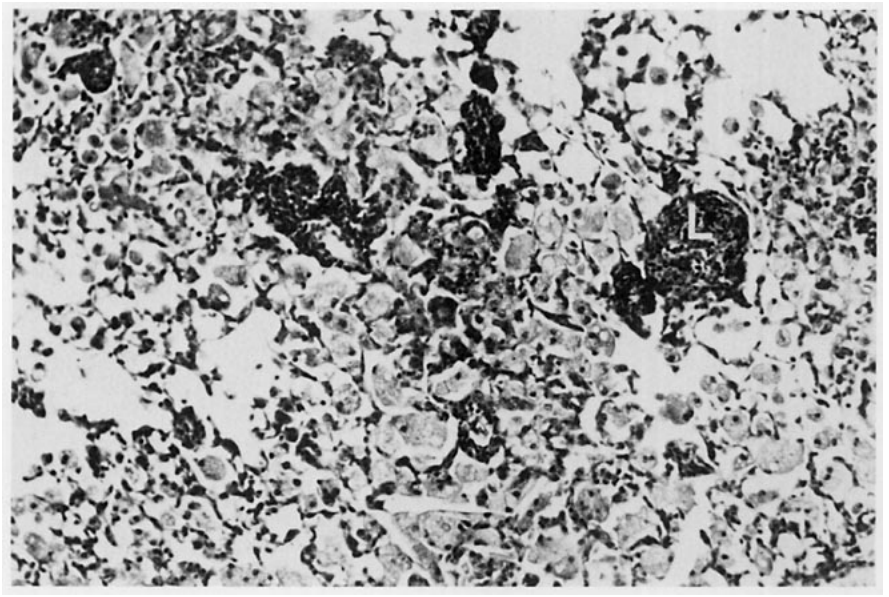


Plate 3
Lung: Moderate granulomatous inflammation in the lung of a female B6C3F$_1$ mouse from the 10 ppm exposure group in the 2-year inhalation studies of naphthalene. Abundant foamy histiocytes are present in alveolar lumens. Note lymphocytic infiltration (L). Compare to Plate 2. H&E, ×120

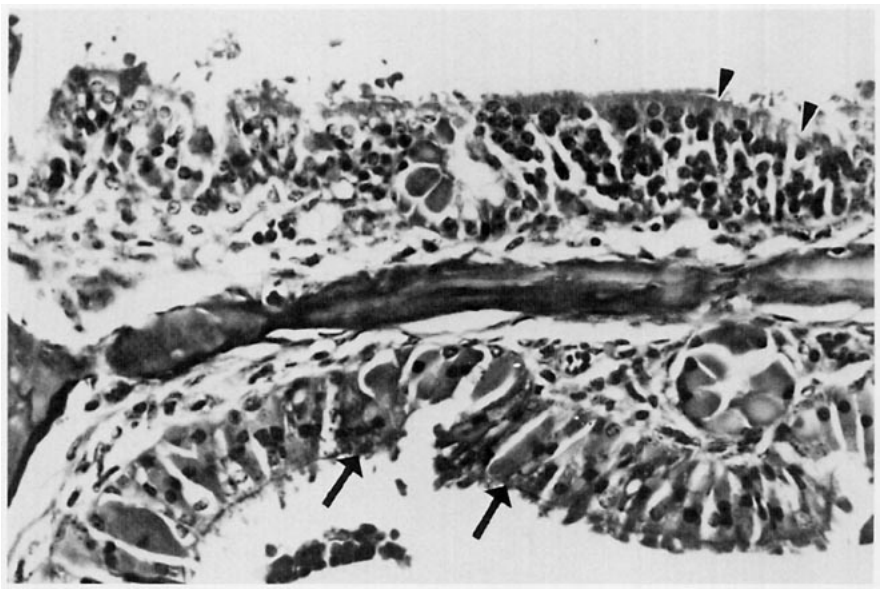


Plate 4
Nose: Nasal turbinate from a B6C3F$_1$ male mouse from the 30 ppm exposure group in the 2-year inhalation studies of naphthalene. Metaplasia of olfactory epithelium (arrows) is present; compare to adjacent relatively unaffected olfactory epithelium (arrowheads). H&E, ×30

TABLE 5
Incidence of Nonneoplastic Nasal Lesions in Mice in the 2-Year Inhalation Studies of Naphthalene

	0 ppm	10 ppm	30 ppm
Male			
Inflammation			
Overall rates[a]	0/70 (0%)	67/69 (97%)	133/135 (99%)
Logistic regression tests[b]	P≤0.001	P≤0.001	P≤0.001
Average severity grade[c]	0	2.2	2.6
Olfactory Epithelium, Metaplasia			
Overall rates	0/70 (0%)	66/69 (96%)	134/135 (99%)
Logistic regression tests	P≤0.001	P≤0.001	P≤0.001
Average severity grade	0	2.5	2.6
Respiratory Epithelium, Hyperplasia			
Overall rates	0/70 (0%)	66/69 (96%)	134/135 (99%)
Logistic regression tests	P≤0.001	P≤0.001	P≤0.001
Average severity grade	0	2.6	2.8
Female			
Inflammation			
Overall rates	1/69 (1%)	65/65 (100%)	135/135 (100%)
Logistic regression tests	P≤0.001	P≤0.001	P≤0.001
Average severity grade	2.0	2.3	2.4
Olfactory Epithelium, Metaplasia			
Overall rates	0/69 (0%)	65/65 (100%)	135/135 (100%)
Logistic regression tests	P≤0.001	P≤0.001	P≤0.001
Average severity grade	0	2.5	2.4
Respiratory Epithelium, Hyperplasia			
Overall rates	0/69 (0%)	65/65 (100%)	135/135 (100%)
Logistic regression tests	P≤0.001	P≤0.001	P≤0.001
Average severity grade	0	2.5	2.7

[a] Incidence expressed as number of animals with lesion/total number of animals examined microscopically
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.
[c] Average severity grade based on 1=minimal, 2=mild, 3=moderate, and 4=marked

Hemangiosarcomas: Hemangiosarcomas (all sites combined) occurred in five high-dose female mice (Table 6). Hemangiomas and hemangiosarcomas are neoplasms of the vascular endothelium that form a morphologic continuum and can occur in any vascularized site in the body. The combined incidence of hemangiomas and hemangiosarcomas in control female B6C3F$_1$ mice from NTP inhalation studies is 17/467 (3.6%, range 0%-8%) (Table B4b). In control female B6C3F$_1$ mice from NTP feed, water, and inhalation studies, the incidence of hemangiomas and hemangiosarcomas (combined) was 47/1,167 (4.0%, range 0%-10%). Because the incidence of these neoplasms was well within the historical control ranges and because the neoplasms occurred at various sites, they were not considered directly related to naphthalene exposure.

TABLE 6
Incidence of Hemangiosarcomas in Female Mice in the 2-Year Inhalation Study of Naphthalene[a]

	0 ppm	10 ppm	30 ppm
Overall rates[b]	0/69 (0%)	0/65 (0%)	5/135 (4%)
Adjusted rates[c]	0.0%	0.0%	4.4%
Terminal rates[d]	0/59 (0%)	0/57 (0%)	2/102 (2%)
First incidence (days)	-[e]	-	648
Logistic regression tests[f]	P=0.034	-	P=0.127

[a] Historical incidence for 2-year NTP inhalation studies with unexposed control groups (mean ± standard deviation): 12/467 (3% ± 2.2%); range 0%-6%
[b] Incidence expressed as number of animals with lesion/total number of animals necropsied
[c] Kaplan-Meier estimated tumor incidence at the end of the studies after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Not applicable; no tumors in animal group
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.

Skin: There was a decreased incidence of combined subcutaneous mesenchymal neoplasms (fibroma, fibrosarcoma, neurofibrosarcoma, sarcoma, and multiple sarcoma) in exposed males compared to controls (Table 7). Multiple fibroma occurred in a single control male. The incidence of combined subcutaneous neoplasms in control males in NTP inhalation studies is 25/479 (5.2%, range 0%-33%) (Table A4b). In control male B6C3F$_1$ mice from recent NTP feed, water, and inhalation studies, the incidence of combined subcutaneous neoplasms was 111/1,177 (9.4%, range 0%-41%). In group-housed male mice, incidences of such neoplasms are variable, and their relationship to fighting is uncertain. It is unlikely that the decreased incidence of combined subcutaneous mesenchymal neoplasms in exposed males was a direct effect of naphthalene exposure. This conclusion is supported by the fact that the two groups of male mice exposed to 30 ppm naphthalene housed in different chambers had significantly different incidences of subcutaneous mesenchymal tumors (0/67 or 0% vs. 8/68 or 12%; Table A2).

Miscellaneous lesions: In exposed male mice versus controls, there were decreased incidences of several nonneoplastic integumentary and genitourinary lesions including skin inflammation and ulcers, preputial ulcers, prostate inflammation, urinary bladder inflammation, and renal pelvis inflammation (Table A5). These lesions were probably associated with fight wound trauma and/or possible secondary ascending genitourinary bacterial infections and may have contributed to the decreased survival of male controls.

TABLE 7
Incidence of Subcutaneous Skin Tumors in Male Mice in the 2-Year Inhalation Study of Naphthalene

	0 ppm	10 ppm	30 ppm
Fibroma			
Overall rates[a]	4/70 (6%)	3/69 (4%)	1/135 (1%)
Adjusted rates[b]	15.4%	5.8%	0.8%
Terminal rates[c]	4/26 (15%)	3/52 (6%)	1/118 (1%)
First incidence (days)	736 (T)	736 (T)	736 (T)
Logistic regression tests[d]	P=0.002N	P=0.165N	P=0.001N
Fibrosarcoma			
Overall rates	11/70 (16%)	6/69 (9%)	4/135 (3%)
Adjusted rates	31.0%	10.4%	3.2%
Terminal rates	4/26 (15%)	2/52 (4%)	2/118 (2%)
First incidence (days)	558	536	611
Logistic regression tests	P≤0.001N	P=0.055N	P≤0.001N
Neurofibrosarcoma			
Overall rates	2/70 (3%)	0/69 (0%)	1/135 (1%)
Adjusted rates	5.5%	0.0%	0.8%
Terminal rates	0/26 (0%)	0/52 (0%)	0/118 (0%)
First incidence (days)	589	-[e]	493
Logistic regression tests	P=0.347N	P=0.199N	P=0.331N
Sarcoma			
Overall rates	6/70 (9%)	2/69 (3%)	3/135 (2%)
Adjusted rates	17.7%	3.7%	2.5%
Terminal rates	2/26 (8%)	1/52 (2%)	2/118 (2%)
First incidence (days)	652	692	696
Logistic regression tests	P=0.013N	P=0.054N	P=0.006N
Fibroma, Fibrosarcoma, Neurofibrosarcoma, or Sarcoma[f]			
Overall rates	23/70 (33%)	11/69 (16%)	8/135 (6%)
Adjusted rates	57.8%	19.1%	6.4%
Terminal rates	10/26 (38%)	6/52 (12%)	4/118 (3%)
First incidence (days)	558	536	493
Logistic regression tests	P≤0.001N	P≤0.001N	P≤0.001N

(T)Terminal sacrifice
[a] Incidence expressed as number of animals with lesion/total number of animals necropsied
[b] Kaplan-Meier estimated tumor incidence at the end of the studies after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group
[f] Historical incidence for 2-year NTP inhalation studies with unexposed control groups (mean ± standard deviation): 25/479 (5.2% ± 7.0%); range 0%-33%

GENETIC TOXICITY

Naphthalene (0.3-100 μg/plate) was negative for the induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 when tested in a preincubation protocol in the presence and the absence of Aroclor 1254induced male Sprague-Dawley rat or Syrian hamster liver S9 (Mortelmans *et al.*, 1986) (Table C1). In cytogenetic tests with Chinese hamster ovary cells, naphthalene induced both sister chromatid exchanges and chromosomal aberrations. Sister chromatid exchanges were induced both in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table C2). The positive responses in the chromosomal aberration test were obtained only in the presence of S9, within a dose range of 30 to 67.5 μg/mL naphthalene (Table C3); a delayed harvest protocol was employed to offset naphthalene-induced cell cycle delay and allow accumulation of sufficient metaphases for scoring.

DISCUSSION AND CONCLUSIONS

Naphthalene, a white, crystalline powder, is widely used as a moth repellant. Naphthalene is also used in the manufacture of phthalic and anthranilic acids, naphthol, naphthylamines, and synthetic resins. This chemical was nominated for toxicology and carcinogenicity studies by NIOSH, OSHA, and EPA because of the potential exposure of millions of people through its use as a moth repellant. Carcinogenicity studies were conducted in mice because no long-term information in mice was available. Inhalation studies were conducted because results of epidemiological studies showed limited evidence for laryngeal cancer in workers exposed to naphthalene (Wolf, 1978) and because human exposure usually occurs via this route. Long-term studies were not conducted in rats because the results of carcinogenicity studies conducted by Schmal (1955) were negative. In those studies, groups of 28 rats were given either 10 g orally over a 700-day period or 820 g given intraperitoneally or intravenously over a 40-week period.

The high dose used for the 2-year studies was 30 ppm. This dose is equal to approximately one-half of the saturating concentration for naphthalene at 20° C and would minimize the condensation of naphthalene in the exposure chambers. The low dose, 10 ppm, represents the threshold limit value established for this compound by the American Conference of Governmental Industrial Hygienists (ACGIH, 1989).

Mean body weights of mice receiving naphthalene were slightly lower than, but within 10% of those of the controls for 18 months of the studies. Survival of control male mice was significantly lower than the survival of the exposed groups (0 ppm, 26/70, 37%; 10 ppm, 52/69, 75%; 30 ppm, 118/133, 89%) due to fighting and wound trauma. However, since over 50% of the animals survived to week 92, a sufficient number of control animals was available for evaluation of carcinogenic potential. Thus the study was considered adequate. Because nasal hyperplasia and metaplasia were seen in virtually all exposed animals, but not in the controls, the doses chosen offered a sufficient challenge for determining the carcinogenic potential of naphthalene.

No biologically significant changes in hematologic parameters in male or female mice were attributable to naphthalene after 14 days of exposure. Naphthalene poisoning in humans was reported to cause hemolytic anemia characterized by Heinz-bodies formation, hemoglobinuria, leukocytosis, and decreases in hemoglobin, hematocrit, and red blood cell count (Melzer-Lange and Walsh-Kelly, 1989). Hemolytic anemia was also observed in dogs given oral doses of 3 to 9 g of naphthalene (Zuelzer and Apt, 1949). The contrast between the effects of naphthalene on mice and its effects on humans and dogs may be attributed to the differences in susceptibility to hemolytic agents (methemoglobin formers) by the species. Humans and dogs were reported to be the most sensitive to such agents, and rats and mice were among the least susceptible (Beard and Noe, 1981). These differences may be due to inherent differences in methemoglobin reductase activity in erythrocytes of the various species. Reductase activity in the less susceptible species was two- to four-fold greater than that of humans (Robin and Harley, 1966).

No increased incidences of neoplastic lesions were attributable to naphthalene exposure in males. The incidence of subcutaneous tissue tumors (fibroma, fibrosarcoma, neurofibrosarcoma, and sarcoma) individually or combined occurred with a negative trend. The decreased incidence in the male high-dose group was significant when compared to the incidence in the control group (Table 7). The overall NTP historical rate for these tumors (combined) in recent inhalation studies is 25/479 (5.2%, range 0%-33%). Differences in survival between the control and exposed male mice cannot be considered as a contributing factor for this negative trend, because subcutaneous tissue tumors are late-appearing tumors, and survival of controls was lower than that of exposed mice. The negative trend for subcutaneous tissue tumors observed in males may be related to the reduced fighting among males exposed to naphthalene. Exposed male mice huddled in the corners of the cages during the 6 hours of exposure and, thus, were less inclined to fight than controls. Negative trends for subcutaneous tissue tumors were not seen in females.

The incidences of pulmonary alveolar/bronchiolar adenomas (7/70, 10%; 15/69, 22%; 27/135, 20%), carcinomas (0/70, 0%; 3/69, 4%; 7/135, 5%), and combined alveolar/bronchiolar adenomas and carcinomas (7/70, 10%; 17/69, 25%; 31/135, 23%) were marginally increased in exposed male mice. The low survival rate of controls, however, accounts for the numerical increase of pulmonary tumors in the exposed males which lived longer. The marginal increase was not statistically significant. Additionally, the incidences of lung neoplasms in the exposed groups of males were within the historical range of 10% to 30%. In female mice, the incidence of these lung neoplasms (principally alveolar/bronchiolar adenoma) in the high-dose group was significantly greater than that of the control (5/69, 7%; 2/65, 3%; 29/135, 22%). The historical incidence of lung tumors in female mice in recent NTP inhalation studies is 39/466 (8.4%, range 0%-12%). These lung neoplasms have also been seen in female mice exposed to structurally related chemicals such as 1,5-naphthalenediamine (NCI, 1978a) and several other aromatic compounds including benzene (NTP, 1986), benzofuran (NTP, 1989), and phenesterin (NCI, 1978b). Accordingly, the increased incidence in lung tumors in this study was considered to be related to naphthalene exposure. Papillary adenomas of the nose were observed in two low-dose female mice. Because these lesions occurred only in the low-dose group, they were not considered to be related to naphthalene exposure.

Compound-related, minimal to mild nonneoplastic lesions were observed in the nose and lung of male and female mice. The nasal lesions observed included chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium (Table 5). These lesions were generally slightly more severe in the high-dose mice. Inflammation was also observed in the lung of exposed mice (Table 4). This inflammation was characterized by focal accumulation of large histiocytes and varying degrees of lymphocytic infiltration, primarily perivascular and peribronchiolar. Alveolar epithelial hyperplasia occurred primarily distant from areas of inflammation. Occasionally, multinucleated giant cells were present in the center of large foci of histiocytes. The lung has been previously identified as the site of naphthalene toxicity in mice. A single intraperitoneal injection of 125 or 250 mg/kg caused necrosis of bronchial and bronchiolar epithelium (Mahvi *et al.*, 1977; Tong *et al.*, 1981). Similar, though more severe pulmonary lesions have occurred in female $B6C3F_1$ mice administered methylnaphthalene by dermal application (Emi and Konishi, 1985).

Conclusions

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of naphthalene in male $B6C3F_1$ mice exposed to 10 or 30 ppm. There was *some evidence of carcinogenic activity* of naphthalene in female $B6C3F_1$ mice, based on increased incidences of pulmonary alveolar/bronchiolar adenomas.

In both male and female mice, naphthalene caused increased incidences and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium in the nose and chronic inflammation in the lungs.

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

REFERENCES

Adkins, B., Jr., Van Stee, E.W., Simmons, J.E., and Eustis, S.L. (1986). Oncogenic response of strain A/J mice to inhaled chemicals. *J. Toxicol. Environ. Health* **17**, 311-322.

Alexandrov, K., and Frayssinet, C. (1973). In vivo effect of some naphthalene-related compounds on aryl hydrocarbon (benzo[a]pyrene) hydroxylase. *J. Natl. Cancer Inst.* **51**, 1067-1069.

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

American Conference of Governmental Industrial Hygienists (ACGIH) (1989). Threshold limit values and biological exposure indices for 1988-1989, p. 116. Cincinnati, OH.

Anderson, D., and Styles, J.A. (1978). An evaluation of 6 short-term tests for detecting organic chemical carcinogens. II. The bacterial mutation test. *Br. J. Cancer* **37**, 924-930.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Beard, R.R., and Noe, J.T. (1981). Aromatic nitro and amino compounds. In *Patty's Industrial Hygiene and Toxicology*, ed. 3, Vol. 2A, p. 2413. (G.D. Clayton and F.E. Clayton, Eds.), John Wiley and Sons, New York.

Bock, K.W., Van Ackeren, G., Lorch, F., and Birke, F.W. (1976). Metabolism of naphthalene to naphthalene dihydrodiol glucuronide in isolated hepatocytes and in liver microsomes. *Biochem. Pharmacol.* **25**, 2351-2356.

Bock, K.W., Von Clausbruch, U.C., and Winne, D. (1979). Absorption and metabolism of naphthalene and benzo(a)pyrene in the rat jejunum *in situ*. *Med. Biol.* **57**, 262-264.

Bogdat'eva, A.G., and Bid, D.Y. (1955). Effect of high molecular weight products of pyrolysis of petroleum on the animal organism. *Gig. Sanit.* **7**, 21.

Bolonova, L.N. (1967). Effect of naphthalene and its methyl derivatives on the content of ammonia in the brain of rats. *Farmakol. Toksikol.* **30**, 484-486.

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

Bos, R.P., Theuws, J.L.G., Jongeneelen, F.J., and Henderson, P.T. (1988). Mutagenicity of bi-, tri-, and tetra-cyclic aromatic hydrocarbons in the "taped-plate assay" and in the conventional Salmonella mutagenicity assay. *Mutat. Res.* **204**, 203-206.

Boyland, E., Busby, E.R., Dukes, C.E., Grover, P.L., and Manson, D. (1964). Further experiments on implantation of materials into the urinary bladder of mice. *Br. J. Cancer* **18**, 575-581.

Brookes, P., and Lawley, P.D. (1964). Evidence for the binding of polynuclear aromatic hydrocarbons to the nucleic acids of mouse skin: Relation between carcinogenic power of hydrocarbons and their binding to deoxyribonucleic acid. *Nature (London)* **202**, 781-784.

Buckpitt, A.R., and Bahnson, L.S. (1986). Naphthalene metabolism by human lung microsomal enzymes. *Toxicology* **41**, 333-341.

Buckpitt, A.R., and Warren, D.L. (1983). Evidence for hepatic formation, export and covalent binding of reactive naphthalene metabolites in extrahepatic tissues *in vivo*. *J. Pharmacol. Exp. Ther.* **225**, 8-16.

Burnham, A.K., Calder, G.V., Fritz, J.S., Junk, G.A., Svek, H.J., and Vick, R. (1973). Trace organics in water: Their isolations and identifications. *J. Amer. Water Works Assoc.* **65**, 722.

Chang, A., Plopper, C., Weir, A., Sassme, H., and Buckpitt, A. (1991). Correlation of species selective pulmonary toxicity to naphthalene (NA) with immuno-histochemical localization of cytochrome P450MN and the stereoselective epoxidation of NA in airway explant incubations. *Toxicologist* **11**, 59 (Abstr.).

Chang, L.H. (1943). The fecal excretion of polycyclic hydrocarbons following their administration to the rat. *J. Biol. Chem.* **151**, 93-99.

Clayton, G.D., and Clayton, F.E., (Eds.). (1982). *Patty's Industrial Hygiene and Toxicology*, ed. 3, Vol. 2B, pp. 3340-3341. John Wiley and Sons, New York.

Connor, T.H., Theiss, J.C., Hanna, H.A., Monteith, D.K., and Matney, T.S. (1985). Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol. Lett.* **25**, 33-40.

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

Dawson, J.P., Thayer, W.W., and Desforges, J.F. (1958). Acute hemolytic anemia in the newborn infant due to naphthalene poisoning: Report of two cases, with investigations into the mechanism of the disease. *Blood* **13**, 1113-1125.

DeBruin, A. (1976). *Biochemical Toxicology of Environmental Agents*, p. 1544. Elsevier, Amsterdam.

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

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

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumor prevalence data. *Appl. Statist.* **32**, 236-248.

Doherty, M.D., Makowski, R., Gibson, G.G., and Cohen, G.M. (1985). Cytochrome P-450 dependent metabolic activation of 1-naphthol to naphthoquinones and covalent binding species. *Biochem. Pharmacol.* **34**, 2261-2267.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

Eisele, G.R. (1985). Naphthalene distribution in tissues of laying pullets, swine, and dairy cattle. *Bull. Environ. Contam. Toxicol.* **34**, 549-556.

Emi, Y., and Konishi, Y. (1985). Endogenous lipid pneumonia in female $B_6C_3F_1$ mice. In *Respiratory System Monographs on the Pathology of Laboratory Animals* (T.C. Jones, V. Mohr, and R.D. Hunt, Eds.), pp 166-168. International Life Science Institute, Springer-Verlag, Berlin.

Farrar, D.B., and Crump, K.S. (1988). Exact statistical tests for any carcinogenic effect in animal bioassays. *Fundam. Appl. Toxicol.* **11**, 652-663.

Florin, I., Rutberg, L., Curvall, M., and Enzell, C.R. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames test. *Toxicology* **15**, 219-232.

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

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

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

Gerarde, H.W. (1960). *Toxicology and Biochemistry of Aromatic Hydrocarbons*, pp. 225-232. Elsevier, Amsterdam.

Ghetti, G., and Mariani, L. (1956). Eye changes due to naphthalene. *Med. Lav.* **47**, 524.

Gidron, E., and Leurer, J. (1956). Naphthalene poisoning. *Lancet* **1**, 228-231.

Gocke, E., King, M.-T., Eckhardt, K., and Wild, D. (1981). Mutagenicity of cosmetics ingredients licensed by the European communities. *Mutat. Res.* **90**, 91-109.

Gosselin, R.E., Hodge, H.C., Smith, R.P., and Gleason, M.N. (1976). *Clinical Toxicology of Commercial Products,* ed. 4, p. III-242. Williams and Wilkins, Baltimore.

Haddad, L.M., and Winchester, J.F. (1983). *Clinical Management of Poisoning and Drug Overdose*, p. 888. Saunders, Philadelphia.

Harden, R.A., and Baetjer, A.M. (1978). Aplastic anemia following exposure to paradichlorobenzene and naphthalene. *J. Occup. Med.* **20**, 820-822.

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

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

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

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagen.* **5** (Suppl. 1), 3-142.

Hites, R.A. and Biemann, K. (1972). Water pollution: Organic compounds in the Charles River, Boston. *Science* **178**, 158.

Hossack, D.J.N., and Richardson, J.C. (1977). Examination of the potential mutagenicity of hair dye constituents using the micronucleus test. *Experientia* **33**, 377-378.

Jerina, D.M., Daly, J.W., Witkop, B., Zaltzman-Nirenberg, P., and Udenfriend, S. (1970). 1,2-Naphthalene oxide as an intermediate in the microsomal hydroxylation of naphthalene. *Biochemistry* **9**, 147-156.

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

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

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M., and Sugiyama, T. (1980). Cooperative program on short-term assays for carcinogenicity in Japan. *Int. Agency Res. Cancer (IARC) Sci. Publ.* **27**, 323-330.

Keith, L.H., and Hercules, S.H. (1973). Environmental applications of advanced instrumental analyses. Environmental Protection Technical Series, EPA-R2-73-155. Environmental Protection Agency, Washington, DC.

Kennaway, E.L. (1930). Further experiments on cancer-producing substances. *Biochem. J.* **24**, 497-504.

Knake, E. (1956). Über schwache geschwulsterzeugende Wirkung von Naphthalin und Benzol. *Virchows Archiv. Pathol. Anat. Physiol.* **329**, 141-176.

Koch, H.-R., and Doldi, K. (1975). Naphthalene cataracts in rats of differently pigmented strains. *Exp. Eye Res.* **20**, 180 (Abstr.).

Konar, N.R., Roy, H.K., and De, M.N. (1939). Naphthalene poisoning. *Indian Med. Gaz.* **74**, 723-725.

Kup, W. (1978). Work-related origin of cancer in the nose, mouth, throat, larynx. *Akad. Wiss.* **2**, 20-25.

Lerman, L.S. (1965). The combination of DNA with polycyclic aromatic hydrocarbons. *Nat. Cancer Conf. Proc. 5th* (1964), 39-48.

Lezenius, A. (1902). Ein Fall von Naphthalincataract am Menschen. *Klin. Monatsbl. Augenheilkd.* **40**, 129-140.

Löfroth, G., Nilsson, L., Agurell, E., and Sugiyama, T. (1985). Salmonella/microsome mutagenicity of monochloro derivatives of some di-, tri-, and tetracyclic aromatic hydrocarbons. *Mutat. Res.* **155**, 91-94.

MacGregor, R.R. (1954). Naphthalene poisoning from the ingestion of moth balls. *Can. Med. Assoc. J.* **70**, 313-314.

Mahvi, D., Bank, H., and Harley, R. (1977). Morphology of a naphthalene-induced bronchiolar lesion. *Am. J. Pathol.* **86**, 559-572.

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

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

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

Melzer-Lange, M., and Walsh-Kelly, C. (1989). Naphthalene-induced hemolysis in a black female toddler deficient in glucose-6-phosphate dehydrogenase. *Pediatr. Emerg. Care* **5**, 24-26.

The Merck Index. (1976). 9th ed. (M. Windholz, Ed.), p. 828. Merck and Co., Rahway, NJ.

The Merck Index. (1983). 10th ed. (M. Windholz, Ed.), p. 914. Merck and Co., Rahway, NJ.

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

Narbonne, J.F., Cassand, P., Alzieu, P., Grolier, P., Mrlina, G., and Calmon, J.P. (1987). Structure-activity relationships of the *N*-methylcarbamate series in *Salmonella typhimurium*. *Mutat. Res.* **191**, 21-27.

National Cancer Institute (NCI) (1978a). Bioassay of 1,5-Naphthalenediamine for Possible Carcinogenicity (CAS No. 2243-62-1). Technical Report Series No. 143. NIH Publication No. 78-1398. National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1978b). Bioassay of Phenesterin for Possible Carcinogenicity (CAS No. 3546-10-9). Technical Report Series No. 60. NIH Publication No. 78-1310. National Institutes of Health, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH) (1981). Occupational Health Guidelines for Naphthalene. In *Occupational Health Guidelines for Chemical Hazards*. NIOSH and Occupational Health and Safety Administration. U.S. Department of Health and Human Services and U.S. Department of Labor, Washington, DC.

National Institutes of Occupational Safety and Health (NIOSH) (1990). National Occupational Exposure Survey (NOES) (1981-1983), unpublished provisional data as of July 1, 1990.

National Toxicology Program (NTP) (1986). Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 289. NIH Publication No. 86-2545. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989). Toxicology and Carcinogenesis Studies of Benzofuran (CAS No. 271-89-6) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 370. NIH Publication No. 90-2825. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nohmi, T., Miyata, R., Yoshikawa, K., and Ishidate, M., Jr. (1985). Mutagenicity tests on organic chemical contaminants in city water and related compounds. I. Bacterial mutagenicity tests. *Eisei Shikenjo Hokoku* **103**, 60-64.

O'Brien, K.A.F., Smith, L.L., and Cohen, G.M. (1985). Differences in naphthalene-induced toxicity in the mouse and rat. *Chem.-Biol. Interact.* **55**, 109-122.

O'Brien, K.A.F., Suverkropp, C., Kanekal, S., Plopper, C.G., and Buckpitt, A.R. (1989). Tolerance to multiple doses of the pulmonary toxicant, naphthalene. *Toxicol. Appl. Pharmacol.* **99**, 487-500.

Potts, A.M. (1986). Toxic Responses of the Eye. In *Casarett and Doull's Toxicology*, (C.D. Klaassen, M. D. Amdur, and J. Doull, Eds.), ed. 3, p. 492. MacMillan, New York.

Probst, G.S., and Hill, L.E. (1980). Chemically-induced DNA repair synthesis in primary rat hepatocytes: A correlation with bacterial mutagenicity. *Ann. N.Y. Acad. Sci.* **349**, 405-406.

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

Registry of Toxic Effects of Chemical Substances (RTECS) (1983), Vol. 2, p. 78. (R.L. Totken and J.R. Lewis, Eds.) Published by National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services.

RTECS [database online] (1990). Bethesda, MD. National Institute for Occupational Safety and Health; 1971- . Updated quarterly. Available from National Library of Medicine, Bethesda, MD.

Reid, W.D., Ilett, K.F., Glick, J.M., and Krishna, G. (1973). Metabolism and binding of aromatic hydrocarbons in the lung: Relationship to experimental bronchiolar necrosis. *Am. Rev. Respir. Dis.* **107**, 539-551.

Robin, H., and Harley, J.D. (1966). Factors influencing response of mammalian species to the methemoglobin reduction test. *Aust. J. Exp. Biol. Med. Sci.* **44**, 519-526.

Rossoff, I.S. (1974). *Handbook of Veterinary Drugs*, p. 377. Springer Publishing, New York.

Sadtler Standard Spectra. Sadtler Research Laboratories, Philadelphia, PA.

Sakai, M., Yoshida, D., and Mizusaki, S. (1985). Mutagenicity of polycyclic aromatic hydrocarbons and quinones on *Salmonella typhimurium* TA97. *Mutat. Res.* **156**, 61-67.

Santhanakrishnan, B.R., Ranganathan, G., and Raju, V.B. (1973). Naphthalene induced haemolytic anaemia with haemoglobinuria. *Indian J. Pediatr.* **40**, 195-197.

Scheiman, M.A., Saunders, R.A., and Saalfeld, F.E. (1974). Organic contaminants in the District of Columbia water supply. *Biomed. Environ. Mass Spectrom.* **1**, 209.

Schmahl, D. (1955). Prüfung von Naphthalin und anthracen auf cancerogene Wirkung an Ratten. *Zeit. Krebsforsch.* **60**, 697-710.

Schweltz, I., Tosk, J., Hilfrich, J., Horita, N., Hoffmann, D., and Wynder, E.L. (1978). Bioassays of naphthalene and alkylnaphthalenes for co-carcinogenic activity: Relation to tobacco carcinogenesis. In *Carcinogenesis - A Comprehensive Survey*, (P.W. Jones and R.I. Freudenthal, Eds.), Vol. 3, pp. 47-60. Raven, New York.

Shackelford, W.M., and Keith, L.H. (1976). *Frequency of Organic Compounds Identified in Water.* Environmental Protection Agency, Athens, GA.

Shichi, H., Tanaka, M., Jensen, N.M., and Nebert, D.W. (1980). Genetic differences in cataract and other ocular abnormalities induced by paracetamol and naphthalene. *Pharmacology* **20**, 229-241.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Sims, P., and Grover, P.L. (1974). Epoxides in polycyclic aromatic hydrocarbon metabolism and carcinogenesis. *Adv. Cancer Res.* **20**, 165-274.

Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I., and Bradley, M.O. (1983). Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat. Res.* **113**, 357-391.

Suter, W., and Jaeger, I. (1982). Comparative evaluation of different pairs of DNA repair-deficient and DNA repair-proficient bacterial tester strains for rapid detection of chemical mutagens and carcinogens. *Mutat. Res.* **97**, 1-18.

Takizawa, N. (1940). Carcinogenic action of quinones. *Proc. Imp. Acad. (Tokyo)* **16**, 309.

Tanooka, H. (1977). Development and applications of *Bacillus subtilis* test systems for mutagens involving DNA-repair deficiency and suppressible auxotrophic mutations. *Mutat. Res.* **42**, 19-32.

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

Taylor, C.J.S.O., and Russell, H. (1932). Blackwater fever and naphthalene poisoning. *W. African Med. J.* **5**, 48-49.

Tong, S.S., Hirokata, Y., Trush, M.A., Mimnaugh, E.G., Ginsburg, E., Lowe, M.C., and Gram, T.E. (1981). Clara cell damage and inhibition of pulmonary mixed-function oxidase activity by naphthalene. *Biochem. Biophys. Res. Commun.* **100**, 944-950.

Tong, S.S., Lowe, M.C., Trush, M.A., Mimnaugh, E.G., Ginsburg, E., Hirokata, Y., and Gram, T.E. (1982). Bronchiolar epithelial damage and impairment of pulmonary microsomal monooxygenase activity in mice by naphthalene. *Exp. Mol. Pathol.* **37**, 358-369.

Ts'o, P.O.P., and Lu, P. (1964). Interaction of nucleic acids. I. Physical binding of thymine, adenine, steroids, and aromatic hydrocarbons to nucleic acids. *Proc. Natl. Acad. Sci. USA* **51**, 17-24.

Union Carbide Corporation (1969). *Naphthalene Safety Data Sheet.* New York.

U.S. Environmental Protection Agency (EPA) (1975). Report to Congress on Preliminary Assessment of Suspected Carcinogens in Drinking Water. U.S. EPA, Washington, DC.

Van der Hoeve, J. (1906). Choreoretinitis bein Menschen durch die Einwirking von Naphthalin. *Arch. Augenheilkd* **56**, 259.

Van Heyningen, R., and Pirie, A. (1976). Naphthalene cataract in pigmented and albino rabbits. *Exp. Eye Res.* **22**, 393-394.

Webb, R.G., Garrison, A.W., Keith, L.H., and McGuire, J.M. (1973). Analysis of organics in water. Environmental Protection Technical Series, EPA-R2-73-277. Environmental Protection Agency, Washington.

Wells, P.G., Wilson, B., and Lubek, B.M. (1989). *In vivo* murine studies on the biochemical mechanism of naphthalene cataractogenesis. *Toxicol. Appl. Pharmacol.* **99**, 466-473.

Williams, R.T. (1959). *Detoxication Mechanisms*, pp. 207-211. Wiley and Sons, New York.

Wolf, O. (1976). Cancer among chemical workers of a naphthalene cleaning plant. *Dtsch. Gesundheitsw.* **31**, 996-999.

Wolf, O. (1978). Carcinoma of the larynx in naphthalene distillation workers. *Z. Gesamte Hyg.* **24**, 737-739.

Zinkham, W.H., and Childs, B. (1958). A defect of glutathione metabolism in erythrocytes from patients with a naphthalene-induced hemolytic anemia. *Pediatrics* **22**, 461-471.

Zuelzer, W.W., and Apt, L. (1949). Acute hemolytic anemia due to naphthalene poisoning. *J. Am. Med. Assoc.* **141**, 185-190.

APPENDIX A
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF NAPHTHALENE

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Naphthalene[a]

	0 ppm	10 ppm	30 ppm	30 ppm
Disposition Summary				
Animals initially in study	75	75	75	75
Special study animals[b]	5	5	6	7
Early deaths				
Natural death	31	10	2	5
Moribund	13	7	3	5
Accidental deaths			2	
Survivors				
Died last week of study		2	1	
Terminal sacrifice	26	50	59	58
Missing		1	2	
Animals examined microscopically	70	69	67	68
Alimentary System				
Gallbladder	(57)	(7)	(61)	(65)
Intestine large, cecum	(56)	(5)	(65)	(65)
Intestine small, duodenum	(49)	(5)	(64)	(66)
Adenocarcinoma			1 (2%)	1 (2%)
Liver	(70)	(33)	(67)	(68)
Hemangiosarcoma				1 (1%)
Hepatocellular carcinoma	6 (9%)	4 (12%)	4 (6%)	3 (4%)
Hepatocellular adenoma	3 (4%)	8 (24%)	3 (4%)	12 (18%)
Hepatocellular adenoma, multiple		2 (6%)		1 (1%)
Mesentery	(1)			(1)
Pancreas	(67)	(10)	(66)	(68)
Salivary glands	(69)	(11)	(67)	(68)
Stomach, forestomach	(63)	(10)	(65)	(68)
Stomach, glandular	(62)	(10)	(65)	(68)
Cardiovascular System				
Heart	(70)	(10)	(67)	(68)
Endocrine System				
Adrenal gland, cortex	(66)	(9)	(65)	(68)
Adenoma			2 (3%)	
Adrenal gland, medulla	(66)	(11)	(64)	(66)
Pheochromocytoma benign	2 (3%)	1 (9%)		1 (2%)
Islets, pancreatic	(67)	(9)	(66)	(68)
Pituitary gland	(52)	(5)	(58)	(55)
Pars distalis, adenoma			1 (2%)	
Thyroid gland	(67)	(8)	(66)	(68)
Follicular cell, adenoma	1 (1%)			
General Body System				
None				

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Genital System				
Epididymis	(69)	(11)	(67)	(68)
Penis	(2)	(2)		(1)
Prostate	(65)	(11)	(67)	(66)
Testes	(69)	(12)	(67)	(68)
Fibrosarcoma, metastatic, skin		1 (8%)		
Hematopoietic System				
Bone marrow	(70)	(10)	(67)	(68)
Lymph node	(67)	(14)	(67)	(68)
Lymph node, bronchial	(38)	(5)	(57)	(43)
Lymph node, mandibular	(61)	(8)	(59)	(66)
Lymph node, mediastinal	(37)	(4)	(43)	(47)
Lymph node, mesenteric	(57)	(4)	(66)	(63)
Spleen	(69)	(18)	(67)	(68)
Thymus	(47)	(1)	(63)	(63)
Integumentary System				
Skin	(69)	(21)	(67)	(68)
Subcutaneous tissue, fibroma	3 (4%)	3 (14%)		1 (1%)
Subcutaneous tissue, fibroma, multiple	1 (1%)			
Subcutaneous tissue, fibrosarcoma	11 (16%)	6 (29%)		4 (6%)
Subcutaneous tissue, fibrous histiocytoma	1 (1%)			1 (1%)
Subcutaneous tissue, neurofibrosarcoma	2 (3%)			1 (1%)
Subcutaneous tissue, sarcoma	6 (9%)	2 (10%)		2 (3%)
Subcutaneous tissue, sarcoma, multiple				1 (1%)
Musculoskeletal System				
Skeletal muscle		(4)		
Sarcoma, metastatic, skin		1 (25%)		
Nervous System				
Brain	(70)	(10)	(67)	(68)
Respiratory System				
Lung	(70)	(69)	(67)	(68)
Alveolar/bronchiolar adenoma	7 (10%)	13 (19%)	12 (18%)	7 (10%)
Alveolar/bronchiolar adenoma, multiple		2 (3%)	3 (4%)	5 (7%)
Alveolar/bronchiolar carcinoma		3 (4%)	4 (6%)	3 (4%)
Fibrosarcoma, metastatic		1 (1%)		
Fibrosarcoma, metastatic, skin		1 (1%)		
Hepatocellular carcinoma, metastatic, liver	3 (4%)			
Sarcoma, metastatic, skin	1 (1%)	1 (1%)		
Sarcoma, metastatic, uncertain primary site			1 (1%)	
Nose	(70)	(69)	(67)	(68)
Special Senses System				
Harderian gland	(1)	(1)	(1)	(1)
Adenoma	1 (100%)	1 (100%)	1 (100%)	1 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Urinary System				
Kidney	(70)	(16)	(67)	(68)
Adenoma	1 (1%)			
Carcinoma				1 (1%)
Urinary bladder	(60)	(16)	(66)	(68)
Systemic Lesions				
Multiple organs[c]	(70)	(69)	(67)	(68)
Leukemia granulocytic				1 (1%)
Lymphoma malignant histiocytic	1 (1%)	1 (1%)		
Lymphoma malignant lymphocytic	3 (4%)	2 (3%)	3 (4%)	1 (1%)
Tumor Summary				
Total animals with primary neoplasms[d]	36	36	27	39
Total primary neoplasms	49	48	34	48
Total animals with benign neoplasms	15	24	19	25
Total benign neoplasms	19	30	22	28
Total animals with malignant neoplasms	26	16	12	19
Total malignant neoplasms	30	18	12	20
Total animals with secondary neoplasms[e]	4	3	1	
Total secondary neoplasms	4	5	1	
Total animals with malignant neoplasms uncertain primary site			1	

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Animals from the hematology group that were sacrificed or died prior to becoming part of the 2-year studies; these animals were not examined microscopically.
[c] Number of animals with any tissues examined microscopically
[d] Primary tumors: all tumors except metastatic tumors
[e] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 0 0 5 1	0 0 5 2	0 0 5 5	0 0 6 4	0 0 7 1	0 0 7 5	0 0 8 2	0 0 8 5	0 0 9 1	0 0 9 2	0 0 9 3	0 0 9 4	0 0 9 5	0 1 3	0 2 3	0 2 3	0 2 4	0 2 5	0 2 5	0 2 5	**Total Tissues/ Tumors**	
Alimentary System																						
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	66	
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58	
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70	
Hepatocellular carcinoma							X								X						6	
Hepatocellular adenoma															X						3	
Mesentery																					1	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62	
Cardiovascular System																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70	
Endocrine System																						
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	66	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	66	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	66	
Pheochromocytoma benign															X						2	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64	
Pituitary gland	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	52	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Follicular cell, adenoma																					1	
General Body System																						
None																						

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	0 1 5	0 4 8	0 4 8	0 8 3	0 8 3	0 8 3	0 8 3	0 8 4	0 8 8	0 8 2	1 1 4	1 3 5	1 5 8	1 8 3	1 9 6	2 3 5	2 5 5	2 8 2	3 2 0	3 2 6	3 2 7	3 6 1	3 8 2	3 8 3	3 8 9	3 9 6
Carcass ID Number	0 2 4 2	0 0 6 2	0 2 3 1	0 0 8 3	1 1 0 2	1 1 0 4	1 2 0 5	2 2 0 2	1 0 0 1	0 0 7 2	0 0 4 5	0 0 7 3	0 0 5 4	0 0 3 4	0 2 3 4	0 0 6 1	0 2 5 4	0 0 2 1	0 0 7 4	0 2 5 2	0 0 6 3	0 0 6 5	0 0 4 2	0 0 2 3	0 0 3 2	0 0 1 2
Genital System																										
Epididymis	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	+																	+								
Preputial gland					+						+			+		+	M									
Prostate	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Testes	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																										
Blood																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, bronchial	M	M	M	M	M	M	+	M	+	M	M	M	M	+	+	+	M	M	M	M	+	M	+	+	M	
Lymph node, mandibular	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	
Lymph node, mediastinal	+	M	M	M	M	M	M	M	M	M	M	M	+	+	+	M	+	M	+	+	+	M	M	+	M	
Lymph node, mesenteric	+	+	+	+	+	+	M	M	M	M	+	M	+	M	+	+	M	+	+	M	+	+	M	+	M	
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	M	M	M	M	+	M	M	M	M	+	+	M	+	M	+	M	+	+	+	+	M	+	M	
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																										
Subcutaneous tissue, fibroma, multiple																										
Subcutaneous tissue, fibrosarcoma																										
Subcutaneous tissue, fibrous histiocytoma																										
Subcutaneous tissue, neurofibrosarcoma																										
Subcutaneous tissue, sarcoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	4 2 1	4 6 5	5 5 8	5 8 9	5 9 0	6 2 0	6 5 2	6 5 4	6 5 5	6 5 1	6 8 8	6 8 7	6 9 0	7 0 4	7 0 6	7 0 6	7 1 4	7 1 5	7 2 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 0 8 1	0 0 8 1	0 0 1 3	0 2 2 4	0 2 2 1	0 0 4 3	0 0 1 1	0 2 4 4	0 2 3 2	0 2 4 3	0 0 4 1	0 0 2 5	0 0 4 4	0 2 2 5	0 0 1 5	0 0 5 3	0 0 3 1	0 2 3 5	0 2 4 1	0 0 1 4	0 0 2 2	0 0 0 4	0 0 3 3	0 0 3 4	0 0 3 5
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland																									
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood								+					+				+								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	M	M	M	+	+	M	+	+	+	M	+	+	+	M	M	+	M	+	M	+	+	M	+	M
Lymph node, mandibular	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	M	M	+	+	M	+	+	+	+	+	+	M	M	M	M	+	+	M	M	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	M	+	+	M	M	M	+	M	M	M	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	+	M	+	+	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																								X	
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma			X		X	X			X		X							X	X						
Subcutaneous tissue, fibrous histiocytoma																						X			
Subcutaneous tissue, neurofibrosarcoma				X											X										
Subcutaneous tissue, sarcoma							X	X					X	X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 0 5 1	0 0 5 2	0 0 5 5	0 0 6 4	0 0 7 1	0 0 7 5	0 0 8 2	0 0 8 5	0 0 9 1	0 0 9 2	0 0 9 3	0 0 9 4	0 0 9 5	0 1 0 3	0 2 2 3	0 2 3 3	0 2 4 5	0 2 5 1	0 2 5 3	0 2 5 5		**Total Tissues/ Tumors**
Genital System																						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		69
Penis																						2
Preputial gland																						4
Prostate	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		65
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		66
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		69
Hematopoietic System																						
Blood																						3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		70
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Lymph node, bronchial	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	M		38
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		61
Lymph node, mediastinal	+	+	+	M	M	M	+	M	+	M	+	+	+	+	+	M	+	+	+	+		37
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+		57
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		69
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		47
Integumentary System																						
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		69
Subcutaneous tissue, fibroma	X		X																			3
Subcutaneous tissue, fibroma, multiple																			X			1
Subcutaneous tissue, fibrosarcoma				X					X							X				X		11
Subcutaneous tissue, fibrous histiocytoma																						1
Subcutaneous tissue, neurofibrosarcoma																						2
Subcutaneous tissue, sarcoma		X													X							6
Musculoskeletal System																						
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		70
Nervous System																						
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		70

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	0	0	0	0	0	0	0	0	0	1	1	1	1	1	2	2	2	3	3	3	3	3	3	3	3
	1	4	4	8	8	8	8	8	8	1	3	5	8	9	3	5	8	2	2	2	6	8	8	8	9
	5	8	8	3	3	3	3	4	8	2	4	8	3	6	5	5	2	0	6	7	1	2	3	9	6
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	2	0	1	1	1	2	1	0	0	0	0	2	0	2	0	0	2	0	0	0	0	0	0
	4	6	3	8	0	0	0	2	0	7	4	7	5	3	6	5	2	7	5	6	6	4	2	3	1
	2	2	1	3	2	4	5	2	1	2	5	3	4	4	1	4	1	4	2	3	5	2	3	2	2
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Hepatocellular carcinoma, metastatic, liver																									
Sarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear								+																	
Eye							+				+		+												
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Urethra																									
Urinary bladder	+	A	A	+	+	+	M	+	A	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																	X								

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	4 2 1	4 6 5	5 5 8	5 8 9	5 9 0	6 2 0	6 5 2	6 5 4	6 5 5	6 8 1	6 8 8	6 9 7	7 0 0	7 0 4	7 0 6	7 0 6	7 1 4	7 1 5	7 2 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 0 8 1	0 0 8 1	0 0 1 3	2 2 2 4	2 2 1 1	0 4 1 3	0 1 1 1	2 4 4 4	2 3 3 2	2 4 4 3	0 4 1 1	0 2 4 5	0 4 4 4	2 2 4 5	0 1 5 5	0 5 3 3	0 3 1 1	2 3 5 5	2 4 1 5	0 1 4 6	0 2 2 4	0 2 2 4	0 3 3 3	0 3 4 6	0 3 5 6
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X						X	X	
Hepatocellular carcinoma, metastatic, liver												X			X										
Sarcoma, metastatic, skin								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Urethra										+															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																	X								
Lymphoma malignant lymphocytic																						X			

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 0 5 1	0 0 5 2	0 0 5 5	0 0 6 4	0 0 7 1	0 0 7 5	0 0 8 2	0 0 8 5	0 0 9 1	0 0 9 2	0 0 9 3	0 0 9 4	0 0 9 5	0 1 0 3	0 2 2 3	0 2 3 3	0 2 4 5	0 2 5 1	0 2 5 3	0 2 5 5	**Total Tissues/ Tumors**	
Respiratory System																						
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70	
Alveolar/bronchiolar adenoma				X					X	X		X									7	
Hepatocellular carcinoma, metastatic, liver															X						3	
Sarcoma, metastatic, skin																					1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70	
Special Senses System																						
Ear			+																		2	
Eye																					3	
Harderian gland													+								1	
Adenoma													X								1	
Urinary System																						
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70	
Adenoma	X																				1	
Urethra																					1	
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	60	
Systemic Lesions																						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70	
Lymphoma malignant histiocytic																					1	
Lymphoma malignant lymphocytic							X														3	

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	
Carcass ID Number	1 2 6 2	1 2 6 3	1 2 7 1	1 2 8 1	1 2 8 2	1 2 8 3	1 2 8 4	1 2 8 5	1 2 9 1	1 2 9 2	1 2 9 3	1 3 0 1	1 3 0 2	1 3 0 3	1 3 1 1	1 3 1 2	1 3 1 3	1 3 1 4	1 3 1 7	1 3 1 9	**Total Tissues/ Tumors**
Alimentary System																					
Esophagus																					7
Gallbladder																					7
Intestine large																					7
Intestine large, cecum																					5
Intestine large, colon																					7
Intestine large, rectum																					5
Intestine small																					8
Intestine small, duodenum																					5
Intestine small, ileum																					6
Intestine small, jejunum																					5
Liver	+	+				+		+		+				+		+				+	33
Hepatocellular carcinoma	X																				4
Hepatocellular adenoma		X												X						X	8
Hepatocellular adenoma, multiple						X															2
Pancreas																	+				10
Salivary glands																					11
Stomach							+														10
Stomach, forestomach							+														10
Stomach, glandular							+														10
Cardiovascular System																					
Heart																					10
Endocrine System																					
Adrenal gland																					11
Adrenal gland, cortex																					9
Adrenal gland, medulla																					11
Pheochromocytoma benign																					1
Islets, pancreatic																					9
Parathyroid gland																					6
Pituitary gland																					5
Thyroid gland																					8
General Body System																					
None																					

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	0 1 4	0 3 0	0 3 1	1 1 9	1 4 7	2 6 5	2 8 7	3 0 3	3 3 0	3 7 2	5 3 6	6 2 9	6 4 0	6 5 9	6 8 0	6 9 0	6 9 2	7 3 3	7 3 7	7 4 8	7 4 4	7 4 4	7 4 4	7 4 4
Carcass ID Number	0 9 1 1	0 9 4 1	0 9 7 1	0 9 3 1	1 0 9 1	0 9 3 2	0 9 2 1	0 9 3 3	0 9 3 4	0 9 5 1	0 9 4 2	1 0 8 5	0 9 2 2	1 1 0 5	1 3 1 1	1 1 9 5	0 9 1 1	0 9 3 2	1 1 9 1	0 9 0 2	0 9 6 1	0 9 6 2	0 9 6 3	0 9 6 4	1 0 8 1
Genital System																								
Ductus deferens																+								
Epididymis	+	+	+	+		+	+	+	+	+	+					+								
Penis						+	+																	
Preputial gland																								
Prostate	+	+	+	+		+	+	+	+	M	+					+								
Seminal vesicle	+	+	+	+		+	+	M	+	+	+			+	+	+								
Testes	+	+	+	+		+	+	+	+	+	+			+			+							
Fibrosarcoma, metastatic, skin														X										
Hematopoietic System																								
Bone marrow	+	+	+	+		+	+	+	+	+	+													
Lymph node	+	+	+	+		+	+	+	+	+	+													
Lymph node, bronchial	M	M	M	M		+	+	+	M	M	M													
Lymph node, mandibular	+	+	M	+		+	M	+	+	+	+													
Lymph node, mediastinal	+	M	+	M		M	M	M	M	+	M													
Lymph node, mesenteric	A	M	M	+		+	M	M	M	M	+													
Spleen	+	+	+	+		+	+	+	+	A	+				+	+								
Thymus	M	M	M	M		+	M	M	M	M	M													
Integumentary System																								
Mammary gland	M	M	M	M		M	M	M	M	M	M													
Skin	+	+	+	+		+	+	+	+	+	+		+	+			+	+		+				
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, fibrosarcoma											X		X	X				X		X				
Subcutaneous tissue, sarcoma																X								
Musculoskeletal System																								
Bone	+	+	+	+		+	+	+	+	+	+							+						
Skeletal muscle		+	+																					
Sarcoma, metastatic, skin																								
Nervous System																								
Brain	+	+	+	+		+	+	+	+	+	+													

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 5
Carcass ID Number	1 0 8 2	1 0 8 3	1 0 8 4	1 1 0 2	1 1 0 3	1 1 0 4	1 1 1 1	1 1 1 2	1 1 1 3	1 1 1 4	1 1 8 1	1 1 8 2	1 1 8 3	1 1 8 4	1 1 9 1	1 1 9 2	1 2 0 1	1 2 0 2	1 2 0 3	1 2 3 1	1 2 3 2	1 2 4 1	1 2 4 2	1 2 4 3	1 2 6 1
Genital System																									
Ductus deferens																									
Epididymis																									
Penis																									
Preputial gland																									
Prostate																									
Seminal vesicle						+												+							
Testes																									
Fibrosarcoma, metastatic, skin																									
Hematopoietic System																									
Bone marrow																									
Lymph node			+															+							
Lymph node, bronchial																									
Lymph node, mandibular																									
Lymph node, mediastinal																		+							
Lymph node, mesenteric			+																						
Spleen					+					+								+			+				
Thymus																									
Integumentary System																									
Mammary gland																									
Skin			+															+							
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma																		X							
Musculoskeletal System																									
Bone																									
Skeletal muscle			+															+							
Sarcoma, metastatic, skin																		X							
Nervous System																									
Brain																									

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	
Carcass ID Number	1 2 6 2	1 2 6 3	1 2 7 1	1 2 8 1	1 2 8 2	1 2 8 3	1 2 8 4	1 2 8 5	1 2 9 1	1 2 9 2	1 2 9 3	1 3 0 1	1 3 0 2	1 3 0 3	1 3 1 1	1 3 1 2	1 3 1 3	1 4 1 1	1 7 1 1	1 9 1 3	**Total Tissues/ Tumors**
Genital System																					
Ductus deferens																					1
Epididymis																					11
Penis																					2
Preputial gland					+																1
Prostate										+											11
Seminal vesicle													+				+				16
Testes																					12
Fibrosarcoma, metastatic, skin																					1
Hematopoietic System																					
Bone marrow																					10
Lymph node		+					+														14
Lymph node, bronchial		+					+														5
Lymph node, mandibular																					8
Lymph node, mediastinal																					4
Lymph node, mesenteric																					4
Spleen		+									+					+					18
Thymus																					1
Integumentary System																					
Mammary gland																					
Skin						+			+	+		+									21
Subcutaneous tissue, fibroma									X	X		X									3
Subcutaneous tissue, fibrosarcoma						X															6
Subcutaneous tissue, sarcoma																					2
Musculoskeletal System																					
Bone																					11
Skeletal muscle																					4
Sarcoma, metastatic, skin																					1
Nervous System																					
Brain																					10

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	0	0	0	1	1	2	2	3	3	3	5	6	6	6	6	6	6	7	7	7	7	7	7	7
	1	3	3	1	4	6	8	0	3	7	3	2	4	5	8	9	9	9	3	3	4	4	4	4
	4	0	1	9	7	5	7	3	0	2	6	9	0	9	0	0	2	3	7	8	4	4	4	4
Carcass ID Number	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	0	0	1	1	0	0	0	0
	9	9	9	9	0	9	9	9	9	9	9	0	9	1	3	1	9	9	3	1	9	9	9	9
	1	4	7	3	9	3	2	3	3	5	4	8	2	0	9	1	6	8	9	0	6	6	6	6
	1	1	1	1	1	2	1	3	4	1	2	5	2	5	1	5	1	1	2	1	2	3	4	5
Respiratory System																								
Larynx	+	+	+	+		+	+	+	+	A	+													
Lung	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma												X									X			
Fibrosarcoma, metastatic											X													
Fibrosarcoma, metastatic, skin														X										
Sarcoma, metastatic, skin																								
Nose	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+		+	+	M	+	+	+													
Special Senses System																								
Eye		+	+			+																		
Harderian gland																								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+		+	+	+	+	+	+			+	+			+						
Urinary bladder	+	+	+	+		+	+	A	+	M	+				+	+								
Systemic Lesions																								
Multiple organs	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																								
Lymphoma malignant lymphocytic																								

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 5
Carcass ID Number	1 0 8 2	1 0 8 3	1 0 8 4	1 1 0 2	1 1 0 3	1 1 0 4	1 1 1 1	1 1 1 2	1 1 1 3	1 1 1 4	1 1 8 1	1 1 8 2	1 1 8 3	1 1 8 4	1 1 9 1	1 1 9 2	1 2 0 1	1 2 0 2	1 2 0 3	1 2 3 1	1 2 3 2	1 2 4 1	1 2 4 2	1 2 4 3	1 2 6 1
Respiratory System																									
Larynx																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X		X			X				X			X								X	X	X	X
Alveolar/bronchiolar adenoma, multiple												X													
Alveolar/bronchiolar carcinoma							X																		
Fibrosarcoma, metastatic																									
Fibrosarcoma, metastatic, skin																									
Sarcoma, metastatic, skin																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea																									
Special Senses System																									
Eye									+																
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney						+																+			
Urinary bladder																				+			+		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic										X															

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	
Carcass ID Number	1 2 6 2	1 2 6 3	1 2 7 1	1 2 8 1	1 2 8 2	1 2 8 3	1 2 8 4	1 2 8 5	1 2 9 1	1 2 9 2	1 2 9 3	1 3 0 1	1 3 0 2	1 3 0 3	1 3 1 1	1 3 1 2	1 3 1 3	1 3 4 1	1 3 7 1	1 3 9 3		**Total Tissues/ Tumors**
Respiratory System																						
Larynx																						9
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		69
Alveolar/bronchiolar adenoma			X							X									X	X		13
Alveolar/bronchiolar adenoma, multiple									X													2
Alveolar/bronchiolar carcinoma																						3
Fibrosarcoma, metastatic																						1
Fibrosarcoma, metastatic, skin																						1
Sarcoma, metastatic, skin																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		69
Trachea																						9
Special Senses System																						
Eye																						4
Harderian gland																			+			1
Adenoma																			X			1
Urinary System																						
Kidney										+												16
Urinary bladder				+	+					+						+						16
Systemic Lesions																						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		69
Lymphoma malignant histiocytic																						1
Lymphoma malignant lymphocytic			X																			2

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 3 8	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	0 4 0 5	0 5 2 1	0 5 2 2	0 5 2 3	0 5 2 4	0 5 3 1	0 5 3 2	0 5 3 3	0 5 3 4	0 5 4 1	0 5 4 2	0 5 4 3	0 5 4 4	0 5 4 5	0 5 5 1	0 5 5 2	0 5 5 3	0 5 5 4	0 5 5 5	0 5 5 5	**Total Tissues/ Tumors**
Alimentary System																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	61
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Adenocarcinoma																					1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Hepatocellular carcinoma																					4
Hepatocellular adenoma											X					X					3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Cardiovascular System																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	65
Adrenal gland, cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	65
Adenoma				X																	2
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	64
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	62
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	58
Pars distalis, adenoma																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
General Body System																					
None																					

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	1 8 2	1 8 2	1 9 6	2 8 0	3 0 2	5 0 4	5 4 7	5 7 8	6 4 4	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	0 3 1 5	0 5 3 5	0 3 5 4	0 3 2 1	0 3 2 5	0 3 4 5	0 3 5 5	0 3 7 3	0 3 3 1	0 3 1 1	0 3 1 2	0 3 1 3	0 3 1 4	0 3 2 2	0 3 2 3	0 3 2 4	0 3 3 2	0 3 3 3	0 3 3 4	0 3 3 5	0 3 4 1	0 3 4 2	0 3 4 3	0 3 4 4	0 3 4 1	0 3 5 1
Genital System																										
Epididymis	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																										
Bone marrow	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mandibular	+		+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M
Lymph node, mediastinal	+		M	+	M	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+		+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+		M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	M		M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																										
Bone	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Larynx	+		+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lung	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X	X									
Alveolar/bronchiolar adenoma, multiple									X																	
Alveolar/bronchiolar carcinoma											X															X
Sarcoma, metastatic, uncertain primary site	X																									
Nose	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	0 3 5 2	0 3 5 3	0 3 6 1	0 3 6 2	0 3 6 3	0 3 6 4	0 3 6 5	0 3 7 1	0 3 7 2	0 3 7 4	0 3 7 5	0 3 8 1	0 3 8 2	0 3 8 3	0 3 8 4	0 3 8 5	0 3 9 1	0 3 9 2	0 3 9 3	0 3 9 4	0 3 9 5	0 4 0 1	0 4 0 2	0 4 0 3	0 4 0 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	M	M	M	+	+	+	+	+	M	M	+	M	M	+	+	M	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X			X													X			X				X
Alveolar/bronchiolar adenoma, multiple														X									X		
Alveolar/bronchiolar carcinoma									X																
Sarcoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 3 8	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	0 4 0 5	0 5 2 1	0 5 2 2	0 5 2 3	0 5 2 4	0 5 3 1	0 5 3 2	0 5 3 3	0 5 3 4	0 5 4 1	0 5 4 2	0 5 4 3	0 5 4 4	0 5 4 5	0 5 5 1	0 5 5 2	0 5 5 3	0 5 5 4	0 5 5 5	**Total Tissues/ Tumors**
Genital System																				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Hematopoietic System																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Lymph node, bronchial	+	+	M	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M	57
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	59
Lymph node, mediastinal	+	+	+	+	+	+	+	M	M	M	M	+	+	M	M	M	M	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	63
Integumentary System																				
Mammary gland	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Musculoskeletal System																				
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Nervous System																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Respiratory System																				
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Alveolar/bronchiolar adenoma									X			X				X	X	X		12
Alveolar/bronchiolar adenoma, multiple																				3
Alveolar/bronchiolar carcinoma												X								4
Sarcoma, metastatic, uncertain primary site																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 3 8	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	0 4 0 5	0 5 2 1	0 5 2 2	0 5 2 3	0 5 2 4	0 5 3 1	0 5 3 2	0 5 3 3	0 5 3 4	0 5 4 1	0 5 4 2	0 5 4 3	0 5 4 4	0 5 4 5	0 5 5 1	0 5 5 2	0 5 5 3	0 5 5 4	0 5 5 5	0 5 5 5	**Total Tissues/ Tumors**
Special Senses System																					
Ear																					1
Eye						+															4
Harderian gland																					1
Adenoma																					1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Lymphoma malignant lymphocytic																					3

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	0 7 0 5	0 8 2 1	0 8 2 3	0 8 2 5	0 8 3 1	0 8 3 2	0 8 3 3	0 8 3 4	0 8 3 5	0 8 4 1	0 8 4 2	0 8 4 3	0 8 4 4	0 8 4 5	0 8 5 1	0 8 5 2	0 8 5 3	0 8 5 4	**Total Tissues/ Tumors**
Alimentary System																			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Adenocarcinoma																			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Hemangiosarcoma		X																	1
Hepatocellular carcinoma				X								X							3
Hepatocellular adenoma	X						X		X	X							X		12
Hepatocellular adenoma, multiple																		X	1
Mesentery																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Cardiovascular System																			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Endocrine System																			
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	66
Pheochromocytoma benign																			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	55
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
General Body System																			
None																			

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	0 1 4	4 9 3	6 1 1	6 1 6	6 3 1	6 5 6	6 7 2	6 9 6	7 0 0	7 0 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2
Carcass ID Number	0 6 9 1	0 6 1 4	0 6 8 2	0 6 7 1	0 7 0 1	0 6 3 5	0 6 2 2	0 6 7 2	0 6 2 3	0 8 5 5	0 6 1 1	0 6 1 2	0 6 1 3	0 6 1 5	0 6 2 1	0 6 2 4	0 6 2 5	0 6 3 1	0 6 3 2	0 6 3 3	0 6 3 4	0 6 4 1	0 6 4 2	0 6 4 3	0 6 4 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis					+																				
Preputial gland							+																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood								+																	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	+	M	+	+	+	M	+	M	+	M	+	+	M	+	M	+	+	+	+	M	+	M	M	M
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma			X	X																					
Subcutaneous tissue, fibrous histiocytoma									X																
Subcutaneous tissue, neurofibrosarcoma		X																							
Subcutaneous tissue, sarcoma								X							X										
Subcutaneous tissue, sarcoma, multiple																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 6 4 5	0 6 5 1	0 6 5 2	0 6 5 3	0 6 5 4	0 6 5 5	0 6 6 1	0 6 6 2	0 6 6 3	0 6 6 4	0 6 6 5	0 6 7 4	0 6 7 3	0 6 7 5	0 6 8 1	0 6 8 3	0 6 8 4	0 6 8 5	0 6 9 2	0 6 9 3	0 6 9 4	0 6 9 5	0 7 0 2	0 7 0 3	0 7 0 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+		+																						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mediastinal	+	+	+	M	M	M	+	M	M	M	+	+	+	+	+	+	+	M	+	+	M	M	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																		X							
Subcutaneous tissue, fibrosarcoma														X				X							
Subcutaneous tissue, fibrous histiocytoma																									
Subcutaneous tissue, neurofibrosarcoma																									
Subcutaneous tissue, sarcoma																									
Subcutaneous tissue, sarcoma, multiple												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	0 7 0 5	0 8 2 1	0 8 2 3	0 8 2 5	0 8 3 1	0 8 3 2	0 8 3 3	0 8 3 4	0 8 3 5	0 8 4 1	0 8 4 2	0 8 4 3	0 8 4 4	0 8 4 5	0 8 5 1	0 8 5 2	0 8 5 3	0 8 5 4	**Total Tissues/ Tumors**
Genital System																			
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Penis																			1
Preputial gland																			3
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Hematopoietic System																			
Blood																			1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Lymph node, bronchial	M	+	+	M	+	+	+	+	+	+	M	M	M	+	+	M	M	+	43
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Lymph node, mediastinal	+	+	+	M	M	M	+	+	M	+	+	M	+	+	+	+	+	M	47
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	63
Integumentary System																			
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Subcutaneous tissue, fibroma																			1
Subcutaneous tissue, fibrosarcoma																			4
Subcutaneous tissue, fibrous histiocytoma																			1
Subcutaneous tissue, neurofibrosarcoma																			1
Subcutaneous tissue, sarcoma																			2
Subcutaneous tissue, sarcoma, multiple																			1
Musculoskeletal System																			
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Nervous System																			
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	0 1 4	4 9 3	6 1 1	6 1 6	6 3 1	6 5 6	6 7 2	6 9 6	7 0 0	7 0 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2
Carcass ID Number	0 6 9 1	0 6 1 4	0 6 8 2	0 6 7 1	0 7 0 1	0 6 3 5	0 6 2 2	0 6 7 2	0 6 2 3	0 8 5 5	0 6 1 1	0 6 1 2	0 6 1 3	0 6 1 5	0 6 2 1	0 6 2 4	0 6 2 5	0 6 3 1	0 6 3 2	0 6 3 3	0 6 3 4	0 6 4 1	0 6 4 2	0 6 4 3	0 6 4 4
Respiratory System																									
Larynx	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X					X						
Alveolar/bronchiolar adenoma, multiple						X																			
Alveolar/bronchiolar carcinoma														X				X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear					+																				
Eye	+																								
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic					X																				
Lymphoma malignant lymphocytic										X															

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 6 4 5	0 6 5 1	0 6 5 2	0 6 5 3	0 6 5 4	0 6 5 5	0 6 6 1	0 6 6 2	0 6 6 3	0 6 6 4	0 6 6 5	0 6 7 4	0 6 7 3	0 6 7 5	0 6 8 1	0 6 8 3	0 6 8 4	0 6 8 5	0 6 9 2	0 6 9 3	0 6 9 4	0 6 9 5	0 7 0 2	0 7 0 3	0 7 0 4
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X						X					X						
Alveolar/bronchiolar adenoma, multiple										X			X												
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic																									
Lymphoma malignant lymphocytic																									

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	0 7 0 5	0 8 2 1	0 8 2 3	0 8 2 5	0 8 3 1	0 8 3 2	0 8 3 3	0 8 3 4	0 8 3 5	0 8 4 1	0 8 4 2	0 8 4 3	0 8 4 4	0 8 4 5	0 8 5 1	0 8 5 2	0 8 5 3	0 8 5 4	**Total Tissues/ Tumors**	
Respiratory System																				
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68	
Alveolar/bronchiolar adenoma		X	X																7	
Alveolar/bronchiolar adenoma, multiple															X		X		5	
Alveolar/bronchiolar carcinoma		X																	3	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Special Senses System																				
Ear																			1	
Eye						+	+												3	
Harderian gland	+																		1	
Adenoma	X																		1	
Urinary System																				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68	
Carcinoma																			1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68	
Systemic Lesions																				
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68	
Leukemia granulocytic																			1	
Lymphoma malignant lymphocytic																			1	

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Naphthalene

	0 ppm	10 ppm	30 ppm
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	2/66 (3%)	1/11 (9%)[e]	1/130 (1%)
Adjusted rates[b]	6.0%		0.9%
Terminal rates[c]	1/25 (4%)		1/115 (1%)
First incidence (days)	389		736 (T)
Life table tests[d]			P=0.104N
Logistic regression tests[d]			P=0.291N
Fisher exact test[d]			P=0.263N
Liver: Hepatocellular Adenoma			
Overall rates	3/70 (4%)	10/33 (30%)[e]	16/135 (12%)
Adjusted rates	9.3%		13.6%
Terminal rates	1/26 (4%)		16/118 (14%)
First incidence (days)	382		736 (T)
Life table tests			P=0.493
Logistic regression tests			P=0.232
Fisher exact test			P=0.059
Liver: Hepatocellular Carcinoma			
Overall rates	6/70 (9%)	4/33 (12%)[e]	7/135 (5%)
Adjusted rates	19.2%		5.9%
Terminal rates	3/26 (12%)		7/118 (6%)
First incidence (days)	655		736 (T)
Life table tests			P=0.014N
Logistic regression tests			P=0.048N
Fisher exact test			P=0.256N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	8/70 (11%)	14/33 (42%)[e]	23/135 (17%)
Adjusted rates	23.7%		19.5%
Terminal rates	3/26 (12%)		23/118 (19%)
First incidence (days)	382		736 (T)
Life table tests			P=0.201N
Logistic regression tests			P=0.530N
Fisher exact test			P=0.197
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	7/70 (10%)	15/69 (22%)	27/135 (20%)
Adjusted rates	25.7%	28.8%	22.7%
Terminal rates	6/26 (23%)	15/52 (29%)	26/118 (22%)
First incidence (days)	714	736 (T)	656
Life table tests	P=0.274N	P=0.529	P=0.441N
Logistic regression tests	P=0.411N	P=0.450	P=0.541
Cochran-Armitage test[d]	P=0.108		
Fisher exact test		P=0.047	P=0.049

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	0/70 (0%)	3/69 (4%)	7/135 (5%)
Adjusted rates	0.0%	5.5%	5.9%
Terminal rates	0/26 (0%)	2/52 (4%)	7/118 (6%)
First incidence (days)	-[f]	629	736 (T)
Life table tests	P=0.256	P=0.246	P=0.222
Logistic regression tests	P=0.180	P=0.176	P=0.222
Cochran-Armitage test	P=0.079		
Fisher exact test		P=0.120	P=0.051
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	7/70 (10%)	17/69 (25%)	31/135 (23%)
Adjusted rates	25.7%	31.9%	26.0%
Terminal rates	6/26 (23%)	16/52 (31%)	30/118 (25%)
First incidence (days)	714	629	656
Life table tests	P=0.363N	P=0.384	P=0.580N
Logistic regression tests	P=0.530	P=0.212	P=0.394
Cochran-Armitage test	P=0.054		
Fisher exact test		P=0.019	P=0.016
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	4/70 (6%)	3/69 (4%)	1/135 (1%)
Adjusted rates	15.4%	5.8%	0.8%
Terminal rates	4/26 (15%)	3/52 (6%)	1/118 (1%)
First incidence (days)	736 (T)	736 (T)	736 (T)
Life table tests	P=0.002N	P=0.165N	P=0.001N
Logistic regression tests	P=0.002N	P=0.165N	P=0.001N
Cochran-Armitage test	P=0.030N		
Fisher exact test		P=0.508N	P=0.047N
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rates	11/70 (16%)	6/69 (9%)	4/135 (3%)
Adjusted rates	31.0%	10.4%	3.2%
Terminal rates	4/26 (15%)	2/52 (4%)	2/118 (2%)
First incidence (days)	558	536	611
Life table tests	P≤0.001N	P=0.016N	P≤0.001N
Logistic regression tests	P≤0.001N	P=0.055N	P≤0.001N
Cochran-Armitage test	P=0.001N		
Fisher exact test		P=0.158N	P=0.002N
Skin (Subcutaneous Tissue): Neurofibrosarcoma, Fibrosarcoma, or Sarcoma			
Overall rates	19/70 (27%)	8/69 (12%)	8/135 (6%)
Adjusted rates	47.2%	13.8%	6.4%
Terminal rates	6/26 (23%)	3/52 (6%)	4/118 (3%)
First incidence (days)	558	536	493
Life table tests	P≤0.001N	P≤0.001N	P≤0.001N
Logistic regression tests	P≤0.001N	P=0.001N	P≤0.001N
Cochran-Armitage test	P≤0.001N		
Fisher exact test		P=0.017N	P≤0.001N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, Neurofibrosarcoma, or Sarcoma			
Overall rates	23/70 (33%)	11/69 (16%)	8/135 (6%)
Adjusted rates	57.8%	19.1%	6.4%
Terminal rates	10/26 (38%)	6/52 (12%)	4/118 (3%)
First incidence (days)	558	536	493
Life table tests	P≤0.001N	P≤0.001N	P≤0.001N
Logistic regression tests	P≤0.001N	P≤0.001N	P≤0.001N
Cochran-Armitage test	P≤0.001N		
Fisher exact test		P=0.016N	P≤0.001N
Skin (Subcutaneous Tissue): Sarcoma			
Overall rates	6/70 (9%)	2/69 (3%)	3/135 (2%)
Adjusted rates	17.7%	3.7%	2.5%
Terminal rates	2/26 (8%)	1/52 (2%)	2/118 (2%)
First incidence (days)	652	692	696
Life table tests	P=0.005N	P=0.031N	P=0.001N
Logistic regression tests	P=0.013N	P=0.054N	P=0.006N
Cochran-Armitage test	P=0.048N		
Fisher exact test		P=0.142N	P=0.044N
All Organs: Malignant Lymphoma (Histiocytic or Lymphocytic)			
Overall rates	4/70 (6%)	3/69 (4%)	4/135 (3%)
Adjusted rates	12.5%	5.8%	3.3%
Terminal rates	2/26 (8%)	3/52 (6%)	2/118 (2%)
First incidence (days)	282	736 (T)	280
Life table tests	P=0.057N	P=0.205N	P=0.059N
Logistic regression tests	P=0.218N	P=0.389N	P=0.332N
Cochran-Armitage test	P=0.237N		
Fisher exact test		P=0.508N	P=0.272N
All Organs: Benign Tumors			
Overall rates	15/70 (21%)	24/69 (35%)	44/135 (33%)
Adjusted rates	48.6%	45.2%	36.6%
Terminal rates	11/26 (42%)	23/52 (44%)	42/118 (36%)
First incidence (days)	382	536	504
Life table tests	P=0.052N	P=0.310N	P=0.075N
Logistic regression tests	P=0.346N	P=0.393	P=0.534N
Cochran-Armitage test	P=0.124		
Fisher exact test		P=0.059	P=0.064
All Organs: Malignant Tumors			
Overall rates	26/70 (37%)	16/69 (23%)	32/135 (24%)
Adjusted rates	60.1%	27.4%	25.1%
Terminal rates	9/26 (35%)	10/52 (19%)	23/118 (19%)
First incidence (days)	282	536	182
Life table tests	P≤0.001N	P≤0.001N	P≤0.001N
Logistic regression tests	P=0.006N	P=0.002N	P=0.001N
Cochran-Armitage test	P=0.058N		
Fisher exact test		P=0.054N	P=0.032N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm
All Organs: Benign and Malignant Tumors			
Overall rates	36/70 (51%)	36/69 (52%)	67/135 (50%)
Adjusted rates	79.7%	62.0%	51.9%
Terminal rates	17/26 (65%)	30/52 (58%)	56/118 (47%)
First incidence (days)	282	536	182
Life table tests	P≤0.001N	P≤0.001N	P≤0.001N
Logistic regression tests	P=0.011N	P=0.036N	P=0.014N
Cochran-Armitage test	P=0.410N		
Fisher exact test		P=0.533	P=0.461N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; in other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, no statistical analyses are provided.
[f] Not applicable; no tumors in animal group

TABLE A4a
Historical Incidence of Lung Alveolar/bronchiolar Tumors in Male B6C3F$_1$ Mice in Inhalation Studies[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	69/478 (14.4%)	30/478 (6.3%)	94/478 (19.7%)
Standard deviation	5.5	5.5	8.1
Range	6%-24%	0%-14%	10%-30%

[a] Data as of 15 September 1990

TABLE A4b
Historical Incidence of Subcutaneous Mesenchymal Tumors in Male B6C3F$_1$ Mice in Inhalation Studies[a]

	Incidence in Controls		
	Neurofibrosarcoma	Fibroma, Fibrosarcoma or Sarcoma	Fibroma, Fibrosarcoma, Neurofibrosarcoma or Sarcoma
Overall Historical Incidence			
Total	2/479 (0.4%)	23/479 (4.8%)	25/479 (5.2%)
Standard deviation	1.0%	9.9%	7.0%
Range	0%-3%	0%-30%	0%-33%

[a] Data as of 15 September 1990

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Naphthalene[a]

	0 ppm	10 ppm	30 ppm	30 ppm
Disposition Summary				
Animals initially in study	75	75	75	75
Special study animals[b]	5	5	6	7
Early deaths				
Natural death	31	10	2	5
Moribund	13	7	3	5
Accidental deaths			2	
Survivors				
Died last week of study		2	1	
Terminal sacrifice	26	50	59	58
Missing		1	2	
Animals examined microscopically	70	69	67	68
Alimentary System				
Gallbladder	(57)	(7)	(61)	(65)
Dilatation		1 (14%)		
Hemorrhage, focal				1 (2%)
Epithelium, hyperplasia, papillary, focal			1 (2%)	
Intestine large, cecum	(56)	(5)	(65)	(65)
Hyperplasia, lymphoid, focal			1 (2%)	1 (2%)
Inflammation, diffuse	1 (2%)			
Intestine large, colon	(56)	(7)	(65)	(68)
Parasite metazoan			4 (6%)	3 (4%)
Intestine large, rectum	(58)	(5)	(64)	(66)
Diverticulum	1 (2%)			
Hemorrhage, focal				1 (2%)
Inflammation, diffuse	1 (2%)			
Parasite metazoan			1 (2%)	
Prolapse				1 (2%)
Intestine small	(57)	(8)	(65)	(66)
Serosa, fibrosis		1 (13%)		
Intestine small, duodenum	(49)	(5)	(64)	(66)
Submucosa, dilatation, focal			1 (2%)	
Intestine small, ileum	(51)	(6)	(64)	(66)
Inflammation, multifocal	1 (2%)			
Intestine small, jejunum	(51)	(5)	(64)	(66)
Hyperplasia, lymphoid, focal				2 (3%)
Liver	(70)	(33)	(67)	(68)
Basophilic focus	2 (3%)		5 (7%)	
Basophilic focus, multifocal			1 (1%)	
Clear cell focus			1 (1%)	2 (3%)
Clear cell focus, multifocal				1 (1%)
Cyst, focal				1 (1%)
Cytoplasmic alteration, focal				1 (1%)
Degeneration, focal		1 (3%)		1 (1%)
Eosinophilic focus				1 (1%)
Fatty change, focal	2 (3%)			
Fibrosis, focal			1 (1%)	
Hematopoietic cell proliferation, focal	1 (1%)		2 (3%)	2 (3%)
Hematopoietic cell proliferation, multifocal	1 (1%)		1 (1%)	1 (1%)
Hematopoietic cell proliferation granulocytic	1 (1%)			
Hemorrhage, focal				1 (1%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Alimentary System (continued)				
Liver (continued)				
Infarct, focal				1 (1%)
Infiltration cellular, lymphocyte, focal			1 (1%)	2 (3%)
Infiltration cellular, lymphocyte, multifocal			3 (4%)	1 (1%)
Mineralization, focal			1 (1%)	
Mixed cell focus			2 (3%)	1 (1%)
Necrosis, focal		2 (6%)		
Necrosis, multifocal	4 (6%)	2 (6%)		1 (1%)
Thrombus, multifocal				1 (1%)
Hepatocyte, cytomegaly, focal				1 (1%)
Serosa, fibrosis		1 (3%)		
Sinusoid, ectasia, focal	1 (1%)			1 (1%)
Mesentery	(1)			(1)
Fat, necrosis, focal	1 (100%)			
Pancreas	(67)	(10)	(66)	(68)
Atrophy	3 (4%)		1 (2%)	4 (6%)
Infiltration cellular, lymphocyte, focal	3 (4%)		1 (2%)	1 (1%)
Infiltration cellular, lymphocyte, multifocal	3 (4%)		3 (5%)	3 (4%)
Infiltration cellular, polymorphonuclear	1 (1%)			
Inflammation, chronic active, diffuse		1 (10%)		
Inflammation, focal			1 (2%)	1 (1%)
Salivary glands	(69)	(11)	(67)	(68)
Atrophy, multifocal				1 (1%)
Infiltration cellular, lymphocyte, focal	1 (1%)		8 (12%)	4 (6%)
Infiltration cellular, lymphocyte, multifocal	13 (19%)	1 (9%)	14 (21%)	16 (24%)
Infiltration cellular, polymorphonuclear	1 (1%)			
Stomach, forestomach	(63)	(10)	(65)	(68)
Hyperplasia, focal			1 (2%)	1 (1%)
Inflammation, focal	1 (2%)			
Stomach, glandular	(62)	(10)	(65)	(68)
Cyst, focal				1 (1%)
Infiltration cellular, polymorphonuclear	1 (2%)			
Inflammation, acute, focal	1 (2%)		1 (2%)	
Mineralization, focal			1 (2%)	
Cardiovascular System				
Heart	(70)	(10)	(67)	(68)
Infiltration cellular, polymorphonuclear	1 (1%)			
Myocardium, inflammation, multifocal	1 (1%)			1 (1%)
Valve, pigmentation, focal	5 (7%)		7 (10%)	5 (7%)
Valve, pigmentation, multifocal	4 (6%)		3 (4%)	3 (4%)
Ventricle, thrombus, focal				1 (1%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Endocrine System				
Adrenal gland	(66)	(11)	(65)	(68)
Capsule, hyperplasia, focal			3 (5%)	2 (3%)
Capsule, hyperplasia, multifocal	45 (68%)	2 (18%)	49 (75%)	49 (72%)
Adrenal gland, cortex	(66)	(9)	(65)	(68)
Atrophy, focal	1 (2%)			
Atypical cells, focal				1 (1%)
Clear cell focus	1 (2%)			
Cyst			1 (2%)	
Focal cellular change	1 (2%)		3 (5%)	
Giant cell, multifocal				1 (1%)
Hyperplasia, focal				1 (1%)
Hypertrophy, focal	2 (3%)		4 (6%)	1 (1%)
Adrenal gland, medulla	(66)	(11)	(64)	(66)
Hyperplasia	1 (2%)	1 (9%)		
Islets, pancreatic	(67)	(9)	(66)	(68)
Infiltration cellular, polymorphonuclear	1 (1%)			
Infiltration cellular, polymorphonuclear, focal			1 (2%)	
Parathyroid gland	(64)	(6)	(62)	(66)
Cyst, focal	1 (2%)		4 (6%)	2 (3%)
Ectopic tissue				1 (2%)
Pituitary gland	(52)	(5)	(58)	(55)
Cyst			1 (2%)	
Pars distalis, congestion	1 (2%)			
Thyroid gland	(67)	(8)	(66)	(68)
Cyst			1 (2%)	
Infiltration cellular, lymphocyte, focal				1 (1%)
C-cell, hyperplasia	1 (1%)			
Follicle, dilatation, focal				3 (4%)
Follicular cell, hyperplasia, focal	1 (1%)		1 (2%)	2 (3%)
General Body System				
None				
Genital System				
Ductus deferens		(1)		
Serosa, inflammation, chronic		1 (100%)		
Epididymis	(69)	(11)	(67)	(68)
Granuloma sperm			2 (3%)	1 (1%)
Infiltration cellular, lymphocyte, focal			1 (1%)	
Infiltration cellular, polymorphonuclear	1 (1%)			
Inflammation, focal				1 (1%)
Spermatocele, focal	1 (1%)			1 (1%)
Duct, dilatation, focal			2 (3%)	
Serosa, inflammation, chronic		1 (9%)		
Penis	(2)	(2)		(1)
Inflammation, multifocal	1 (50%)			
Preputial gland	(4)	(1)		(3)
Hyperplasia				1 (33%)
Inflammation	1 (25%)			1 (33%)
Duct, dilatation	3 (75%)	1 (100%)		1 (33%)
Prostate	(65)	(11)	(67)	(66)
Infiltration cellular, lymphocyte	1 (2%)	1 (9%)		1 (2%)
Infiltration cellular, polymorphonuclear	1 (2%)			
Inflammation, acute	8 (12%)	2 (18%)		1 (2%)
Serosa, inflammation, chronic		1 (9%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Genital System (continued)				
Seminal vesicle	(66)	(16)	(67)	(68)
Dilatation	3 (5%)	2 (13%)		1 (1%)
Inflammation, focal	2 (3%)			1 (1%)
Serosa, inflammation, chronic		2 (13%)		
Testes	(69)	(12)	(67)	(68)
Angiectasis, focal			1 (1%)	
Atrophy		1 (8%)	1 (1%)	2 (3%)
Mineralization, focal	4 (6%)		2 (3%)	4 (6%)
Thrombus, focal			1 (1%)	
Bilateral, atrophy	1 (1%)			1 (1%)
Interstitial cell, hyperplasia, multifocal			1 (1%)	
Hematopoietic System				
Blood	(3)			(1)
Leukocytosis	3 (100%)			1 (100%)
Bone marrow	(70)	(10)	(67)	(68)
Angiectasis, focal			1 (1%)	
Congestion				1 (1%)
Hemorrhage, focal			1 (1%)	1 (1%)
Hyperplasia	9 (13%)		1 (1%)	5 (7%)
Myelofibrosis, focal			1 (1%)	
Thrombus	1 (1%)			
Myeloid cell, hyperplasia	1 (1%)			
Lymph node, bronchial	(38)	(5)	(57)	(43)
Giant cell, multifocal			2 (4%)	1 (2%)
Hyperplasia, lymphoid	1 (3%)	1 (20%)	2 (4%)	
Infiltration cellular, polymorphonuclear	1 (3%)			
Pigmentation	3 (8%)		2 (4%)	3 (7%)
Lymphocyte, necrosis		1 (20%)		
Lymph node, mandibular	(61)	(8)	(59)	(66)
Angiectasis	1 (2%)			
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid			2 (3%)	
Infiltration cellular, polymorphonuclear	1 (2%)			
Pigmentation	12 (20%)	1 (13%)	5 (8%)	11 (17%)
Lymphocyte, necrosis, multifocal	1 (2%)			
Lymph node, mediastinal	(37)	(4)	(43)	(47)
Hyperplasia, lymphoid		1 (25%)	1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear	1 (3%)			
Inflammation, acute		1 (25%)		
Pigmentation	2 (5%)		1 (2%)	3 (6%)
Lymph node, mesenteric	(57)	(4)	(66)	(63)
Angiectasis	1 (2%)			
Erythrophagocytosis	7 (12%)		13 (20%)	13 (21%)
Giant cell, multifocal	11 (19%)		24 (36%)	16 (25%)
Hematopoietic cell proliferation granulocytic	3 (5%)			
Hemorrhage	12 (21%)		16 (24%)	13 (21%)
Hyperplasia, lymphoid	1 (2%)		4 (6%)	4 (6%)
Hyperplasia, plasma cell	1 (2%)			
Infiltration cellular, polymorphonuclear	1 (2%)			
Inflammation, acute	3 (5%)			
Lymphocyte, necrosis, multifocal	1 (2%)		1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Hematopoietic System (continued)				
Spleen	(69)	(18)	(67)	(68)
Congestion	1 (1%)			1 (1%)
Depletion lymphoid		1 (6%)		
Hematopoietic cell proliferation	20 (29%)	5 (28%)		13 (19%)
Hematopoietic cell proliferation granulocytic	1 (1%)			
Hyperplasia, lymphoid	1 (1%)	1 (6%)	2 (3%)	5 (7%)
Capsule, fibrosis		1 (6%)		
Lymphocyte, necrosis	2 (3%)		1 (1%)	
Thymus	(47)	(1)	(63)	(63)
Cyst	2 (4%)		4 (6%)	2 (3%)
Cyst, multifocal			2 (3%)	2 (3%)
Depletion lymphoid, diffuse	1 (2%)			
Ectopic parathyroid gland, focal				1 (2%)
Hyperplasia, lymphoid, multifocal	1 (2%)			
Epithelial cell, cytoplasmic alteration, focal				1 (2%)
Thymocyte, necrosis	8 (17%)	1 (100%)	1 (2%)	
Integumentary System				
Skin	(69)	(21)	(67)	(68)
Acanthosis, focal	2 (3%)		1 (1%)	
Cyst epithelial inclusion	1 (1%)			
Infiltration cellular, polymorphonuclear	1 (1%)			
Inflammation, focal	5 (7%)	2 (10%)	1 (1%)	2 (3%)
Ulcer	4 (6%)	2 (10%)		
Lymphatic, dilatation				2 (3%)
Prepuce, inflammation, chronic active	1 (1%)			
Prepuce, ulcer	3 (4%)			
Subcutaneous tissue, angiectasis				1 (1%)
Subcutaneous tissue, edema, diffuse	1 (1%)			
Subcutaneous tissue, fibrosis, multifocal	1 (1%)			1 (1%)
Subcutaneous tissue, hemorrhage	1 (1%)			
Sweat gland, ectasia, multifocal			1 (1%)	
Tail, inflammation, necrotizing, multifocal	1 (1%)			
Musculoskeletal System				
Bone	(70)	(11)	(67)	(68)
Vertebra, developmental malformation	1 (1%)			
Vertebra, fracture healed		1 (9%)		
Skeletal muscle		(4)		
Inflammation, chronic		3 (75%)		
Nervous System				
Brain	(70)	(10)	(67)	(68)
Mineralization, focal	1 (1%)		7 (10%)	4 (6%)
Mineralization, multifocal	18 (26%)	1 (10%)	25 (37%)	25 (37%)
Olfactory lobe, hemorrhage, focal			1 (1%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Respiratory System				
Larynx	(69)	(9)	(64)	(67)
Infiltration cellular, lymphocyte, focal			1 (2%)	
Inflammation, focal	1 (1%)			2 (3%)
Epithelium, hyperplasia, focal	2 (3%)			
Lung	(70)	(69)	(67)	(68)
Congestion	9 (13%)	1 (1%)		
Hemorrhage	4 (6%)	3 (4%)	5 (7%)	
Infiltration cellular, lymphocyte	3 (4%)		4 (6%)	4 (6%)
Infiltration cellular, polymorphonuclear	1 (1%)			
Infiltration cellular, histiocyte	1 (1%)	12 (17%)	11 (16%)	5 (7%)
Inflammation		21 (30%)	28 (42%)	28 (41%)
Inflammation, granulomatous		19 (28%)	3 (4%)	12 (18%)
Alveolar epithelium, hyperplasia	2 (3%)	7 (10%)	8 (12%)	4 (6%)
Glands, dilatation	2 (3%)			
Glands, inflammation	7 (10%)	14 (20%)	14 (21%)	8 (12%)
Peribronchiolar, cyst, multifocal	1 (1%)			
Nose	(70)	(69)	(67)	(68)
Congestion, multifocal	3 (4%)			
Hemorrhage			1 (1%)	
Inflammation		67 (97%)	66 (99%)	67 (99%)
Olfactory epithelium, metaplasia		66 (96%)	67 (100%)	67 (99%)
Respiratory epithelium, hyperplasia		66 (96%)	67 (100%)	67 (99%)
Trachea	(70)	(9)	(67)	(67)
Glands, dilatation	2 (3%)		1 (1%)	
Glands, infiltration cellular, lymphocyte, focal			1 (1%)	
Glands, inflammation, suppurative, focal			3 (4%)	
Special Senses System				
Ear	(2)		(1)	(1)
Pinna, inflammation, focal	1 (50%)			
Eye	(3)	(4)	(4)	(3)
Degeneration		1 (25%)		
Dysplasia, multifocal			1 (25%)	
Cornea, inflammation, focal				1 (33%)
Iris, hyperplasia, melanocyte, multifocal				1 (33%)
Lens, cataract	1 (33%)			1 (33%)
Harderian gland	(1)	(1)	(1)	(1)
Cyst, multiple		1 (100%)		
Inflammation, chronic		1 (100%)		
Urinary System				
Kidney	(70)	(16)	(67)	(68)
Congestion, multifocal	1 (1%)			
Degeneration		1 (6%)		
Hydronephrosis	1 (1%)	1 (6%)		
Hypoplasia				1 (1%)
Infarct, focal	1 (1%)		1 (1%)	2 (3%)
Infiltration cellular, lymphocyte, focal			3 (4%)	3 (4%)
Infiltration cellular, lymphocyte, multifocal	17 (24%)	2 (13%)	30 (45%)	18 (26%)
Infiltration cellular, polymorphonuclear	1 (1%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Urinary System (continued)				
Kidney (continued)				
Inflammation, acute, multifocal	2 (3%)	1 (6%)		1 (1%)
Nephropathy	6 (9%)	2 (13%)	8 (12%)	6 (9%)
Pelvis, inflammation, acute	3 (4%)			
Renal tubule, dilatation, focal	1 (1%)	1 (6%)	3 (4%)	
Renal tubule, giant cell, focal				1 (1%)
Renal tubule, hyperplasia, focal	1 (1%)		3 (4%)	
Renal tubule, mineralization, focal	4 (6%)	1 (6%)	1 (1%)	3 (4%)
Urethra	(1)			
Distal, dilatation	1 (100%)			
Epithelium, necrosis, multifocal	1 (100%)			
Urinary bladder	(60)	(16)	(66)	(68)
Dilatation	7 (12%)	6 (38%)	3 (5%)	2 (3%)
Hemorrhage	2 (3%)			
Infiltration cellular, lymphocyte, focal				2 (3%)
Infiltration cellular, lymphocyte, multifocal			6 (9%)	7 (10%)
Infiltration cellular, polymorphonuclear	1 (2%)			
Inflammation, acute	3 (5%)			
Inflammation, chronic active	3 (5%)	2 (13%)		1 (1%)
Serosa, inflammation, chronic		1 (6%)		
Transitional epithelium, hyperplasia, multifocal	1 (2%)			

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Animals from the hematology group that were sacrificed or died prior to becoming part of the 2-year studies; these animals were not examined microscopically.

APPENDIX B
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF NAPHTHALENE

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Naphthalene[a]

	0 ppm	10 ppm	30 ppm	30 ppm
Disposition Summary				
Animals initially in study	75	75	75	75
Special study animals[b]	5	7	6	6
Early deaths				
Natural death	8	6	10	7
Moribund	2	2	6	10
Accidental deaths	1	0		
Survivors				
Died last week of study		1	1	
Terminal sacrifice	59	56	51	50
Missing		3	1	2
Animals examined microscopically	69	65	68	67
Alimentary System				
Gallbladder	(65)	(2)	(60)	(64)
Intestine large, cecum	(66)	(1)	(60)	(64)
Intestine large, colon	(67)	(2)	(62)	(66)
Intestine large, rectum	(67)	(3)	(63)	(63)
Intestine small, duodenum	(66)	(4)	(61)	(63)
Adenocarcinoma		1 (25%)		
Intestine small, ileum	(66)	(1)	(61)	(63)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Intestine small, jejunum	(65)	(1)	(61)	(63)
Liver	(68)	(12)	(67)	(67)
Hepatocellular carcinoma			1 (1%)	
Hepatocellular adenoma	2 (3%)	2 (17%)		2 (3%)
Osteosarcoma, metastatic, bone				1 (1%)
Plasma cell tumor malignant			1 (1%)	
Sarcoma, metastatic, uncertain primary site				1 (1%)
Sarcoma stromal, metastatic		1 (8%)		
Mesentery	(6)		(3)	(3)
Fat, sarcoma, metastatic, uncertain primary site				1 (33%)
Pancreas	(69)	(5)	(65)	(67)
Sarcoma, metastatic, uncertain primary site				1 (1%)
Salivary glands	(68)	(5)	(64)	(67)
Fibrosarcoma				1 (1%)
Stomach, forestomach	(67)	(5)	(67)	(67)
Papilloma squamous	2 (3%)			
Squamous cell carcinoma				1 (1%)
Stomach, glandular	(67)	(5)	(65)	(67)
Cardiovascular System				
Heart	(69)	(4)	(68)	(67)
Fibrous histiocytoma				1 (1%)
Osteosarcoma, metastatic, bone			1 (1%)	
Sarcoma, metastatic, uncertain primary site				1 (1%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Endocrine System				
Adrenal gland	(66)	(4)	(67)	(67)
Capsule, adenoma	1 (2%)			
Capsule, sarcoma, metastatic, uncertain primary site				1 (1%)
Adrenal gland, cortex	(66)	(4)	(67)	(67)
Osteosarcoma, metastatic, bone			1 (1%)	
Adrenal gland, medulla	(64)	(4)	(66)	(66)
Osteosarcoma, metastatic, bone			1 (2%)	
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(69)	(4)	(66)	(67)
Sarcoma, metastatic, uncertain primary site				1 (1%)
Pituitary gland	(61)	(4)	(50)	(54)
Pars distalis, adenoma	1 (2%)			
Thyroid gland	(69)	(4)	(67)	(66)
General Body System				
Tissue NOS	(1)	(1)	(2)	
Osteosarcoma, metastatic, bone			1 (50%)	
Genital System				
Clitoral gland				(1)
Squamous cell carcinoma				1 (100%)
Ovary	(69)	(14)	(66)	(65)
Cystadenocarcinoma, papillary	1 (1%)	1 (7%)		
Cystadenoma, papillary	2 (3%)		4 (6%)	
Granulosa cell tumor benign	1 (1%)		1 (2%)	
Granulosa-theca tumor benign				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Sarcoma stromal, metastatic		1 (7%)		
Teratoma benign				1 (2%)
Endothelium, sarcoma stromal, metastatic	1 (1%)			
Oviduct	(2)	(1)	(4)	(4)
Uterus	(69)	(41)	(67)	(66)
Sarcoma stromal	1 (1%)	2 (5%)		
Endometrium, polyp stromal		1 (2%)		1 (2%)
Hematopoietic System				
Bone marrow	(69)	(4)	(68)	(67)
Hemangioma				1 (1%)
Hemangiosarcoma				1 (1%)
Osteosarcoma, metastatic, bone			1 (1%)	
Lymph node	(69)	(9)	(67)	(67)
Iliac, sarcoma stromal, metastatic, uterus	1 (1%)			
Inguinal, osteosarcoma, metastatic, bone				1 (1%)
Renal, sarcoma stromal, metastatic, uterus	1 (1%)			
Lymph node, bronchial	(46)	(1)	(46)	(40)
Sarcoma, metastatic, uncertain primary site				1 (3%)
Lymph node, mandibular	(66)	(6)	(62)	(65)
Fibrosarcoma				1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Hematopoietic System (continued)				
Lymph node, mediastinal	(60)	(6)	(52)	(57)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Lymph node, mesenteric	(67)	(4)	(60)	(62)
Spleen	(67)	(13)	(67)	(67)
Hemangiosarcoma				3 (4%)
Plasma cell tumor malignant			1 (1%)	
Capsule, sarcoma, metastatic, uncertain primary site				1 (1%)
Thymus	(64)	(3)	(60)	(59)
Integumentary System				
Mammary gland	(69)	(5)	(66)	(66)
Adenocarcinoma	2 (3%)	1 (20%)	1 (2%)	2 (3%)
Skin	(69)	(6)	(67)	(67)
Papilloma squamous			1 (1%)	
Subcutaneous tissue, fibroma				1 (1%)
Subcutaneous tissue, fibrosarcoma	1 (1%)	1 (17%)		2 (3%)
Subcutaneous tissue, sarcoma		1 (17%)		1 (1%)
Musculoskeletal System				
Bone	(69)	(4)	(68)	(67)
Femur, osteosarcoma			1 (1%)	
Humerus, osteosarcoma				1 (1%)
Skeletal muscle			(3)	(3)
Back, osteosarcoma, metastatic, bone				1 (33%)
Hindlimb, fibrosarcoma			1 (33%)	
Hindlimb, hemangiosarcoma				1 (33%)
Sternal, osteosarcoma, metastatic, bone			1 (33%)	
Nervous System				
Brain	(69)	(4)	(68)	(67)
Respiratory System				
Larynx	(68)	(4)	(64)	(64)
Lung	(69)	(65)	(68)	(67)
Adenocarcinoma, metastatic, mammary gland			1 (1%)	1 (1%)
Alveolar/bronchiolar adenoma	5 (7%)	1 (2%)	9 (13%)	12 (18%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	4 (6%)	3 (4%)
Alveolar/bronchiolar carcinoma				1 (1%)
Fibrosarcoma, metastatic, skin		1 (2%)		
Osteosarcoma, metastatic, bone			1 (1%)	1 (1%)
Sarcoma, metastatic, skin				1 (1%)
Sarcoma, metastatic, uncertain primary site				1 (1%)
Mediastinum, sarcoma, metastatic, uncertain primary site				1 (1%)
Nose	(69)	(65)	(68)	(67)
Adenoma		2 (3%)		
Trachea	(69)	(4)	(68)	(66)

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Naphthalene
(continued)

	0 ppm	10 ppm	30 ppm	30 ppm
Special Senses System				
Ear		(1)		
Pinna, fibrosarcoma		1 (100%)		
Eye	(2)	(6)	(2)	(4)
Lids, papilloma squamous				1 (25%)
Harderian gland	(1)	(2)	(1)	(1)
Adenocarcinoma		2 (100%)		
Adenoma				1 (100%)
Urinary System				
Kidney	(69)	(7)	(67)	(67)
Plasma cell tumor malignant			1 (1%)	
Urinary bladder	(67)	(1)	(62)	(63)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Systemic Lesions				
Multiple organs[c]	(69)	(65)	(68)	(67)
Lymphoma malignant histiocytic	1 (1%)	2 (3%)	1 (1%)	3 (4%)
Lymphoma malignant lymphocytic	6 (9%)	5 (8%)	2 (3%)	2 (3%)
Lymphoma malignant mixed	1 (1%)	1 (2%)	4 (6%)	2 (3%)
Tumor Summary				
Total animals with primary neoplasms[d]	23	22	28	35
Total primary neoplasms	28	25	33	48
Total animals with benign neoplasms	15	7	19	22
Total benign neoplasms	15	7	19	24
Total animals with malignant neoplasms	12	18	12	19
Total malignant neoplasms	13	18	14	24
Total animals with secondary neoplasms[e]	1	2	3	4
Total secondary neoplasms	3	3	10	19
Total animals with malignant neoplasms uncertain primary site				1

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Animals from the hematology group that were sacrificed or died prior to becoming part of the 2-year studies; these animals were not examined microscopically.
[c] Number of animals with any tissue examined microscopically
[d] Primary tumors: all tumors except metastatic tumors
[e] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm

Number of Days on Study	1 1 1 5 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	4 4 8 6 7 9 4 5 6 7 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3
	0 0 3 1 4 0 4 5 2 8 9 6 6 6 6 6 6 6 6 6 6 6 6 6 6
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
	1 1 2 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	6 6 7 0 9 5 4 2 7 2 2 1 1 1 1 1 2 2 3 3 3 3 3 4 4
	3 5 2 2 2 5 3 1 1 3 4 1 2 3 4 5 2 5 1 2 3 4 5 1 2
Alimentary System	
Esophagus	+ + + + + + + + M + + + + + + + + + + + + + +
Gallbladder	A + + + A A + + A + + + + + + + + + + + + + +
Intestine large	A +
Intestine large, cecum	A + + + A A + + + + + + + + + + + + + + + + +
Intestine large, colon	A + + + + + + + A + + + + + + + + + + + + + +
Intestine large, rectum	A + + + + A + + + + + + + + + + + + + + + + +
Intestine small	A +
Intestine small, duodenum	A + + + A A + + + + + + + + + + + + + + + + +
Intestine small, ileum	A + + + + A + + + + + + + + + + + + + + + + +
Intestine small, jejunum	A + A + A + + + A + + + + + + + + + + + + + +
Liver	A +
Hepatocellular adenoma	X
Mesentery	+ + + + + +
Pancreas	+ +
Salivary glands	+ +
Stomach	+ + + + M A + + + + + + + + + + + + + + + +
Stomach, forestomach	+ + + + M A + + + + + + + + + + + + + + + +
Papilloma squamous	X
Stomach, glandular	+ + + + M A + + + + + + + + + + + + + + + +
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal gland	+ + + + + + + + M + + + + + + + + + + + + + +
Capsule, adenoma	
Adrenal gland, cortex	+ + + + + + + + M + + + + + + + + + + + + + +
Adrenal gland, medulla	+ + + + + + + + M + + + + + + + + + + + + + +
Pheochromocytoma benign	
Islets, pancreatic	+ +
Parathyroid gland	+ +
Pituitary gland	+ + + M M + + M + + M + + M + + + + + + + + +
Pars distalis, adenoma	
Thyroid gland	+ +

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 1 4 4	0 1 4 5	0 1 5 1	0 1 5 2	0 1 5 3	0 1 5 4	0 1 6 1	0 1 6 2	0 1 6 4	0 1 7 2	0 1 7 3	0 1 7 4	0 1 8 1	0 1 8 2	0 1 8 3	0 1 8 4	0 1 8 5	0 1 9 1	0 1 9 3	0 1 9 4	0 1 9 5	0 2 0 1	0 2 0 2	0 2 0 3	0 2 0 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery							+																		+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																								X	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X																						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 2 0 5	0 2 7 1	0 2 7 3	0 2 7 4	0 2 7 5	0 2 8 1	0 2 8 2	0 2 8 3	0 2 8 4	0 2 8 5	0 2 9 1	0 2 9 3	0 2 9 5	0 1 7 5	0 2 9 2	0 2 9 4	0 2 9 5	0 3 0 1	0 3 0 3	0 3 0 4	0 3 0 5	**Total Tissues/ Tumors**
Alimentary System																						
Esophagus	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	66
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Hepatocellular adenoma										X												2
Mesentery																						6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Salivary glands	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Papilloma squamous												X										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Cardiovascular System																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Endocrine System																						
Adrenal gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Capsule, adenoma																						1
Adrenal gland, cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Adrenal gland, medulla	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	64
Pheochromocytoma benign								X														1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	68
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	61
Pars distalis, adenoma																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	1	1	1	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	4	8	6	7	9	4	5	6	7	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	0	3	1	4	0	4	5	2	8	9	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	6	6	7	0	9	5	4	2	7	2	2	1	1	1	1	1	2	2	3	3	3	3	3	4	4
	3	5	2	2	2	5	3	1	1	3	4	1	2	3	4	5	2	5	1	2	3	4	5	1	2
General Body System																									
Tissue NOS								+																	
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma, papillary																									
Cystadenoma, papillary																									
Granulosa cell tumor benign																									
Endothelium, sarcoma stromal, metastatic																	X								
Oviduct	+								+																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal																	X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, sarcoma stromal, metastatic, uterus																	X								
Renal, sarcoma stromal, metastatic, uterus																	X								
Lymph node, bronchial	M	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	M	
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mediastinal	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	
Lymph node, mesenteric	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 1 4 4	0 1 4 5	0 1 5 1	0 1 5 2	0 1 5 3	0 1 5 4	0 1 6 1	0 1 6 2	0 1 6 4	0 1 7 2	0 1 7 3	0 1 7 4	0 1 8 1	0 1 8 2	0 1 8 3	0 1 8 4	0 1 8 5	0 1 9 1	0 1 9 3	0 1 9 4	0 1 9 5	0 2 0 1	0 2 0 2	0 2 0 3	0 2 0 4
General Body System																									
Tissue NOS																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma, papillary																		X							
Cystadenoma, papillary																		X							
Granulosa cell tumor benign				X																					
Endothelium, sarcoma stromal, metastatic																									
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, sarcoma stromal, metastatic, uterus																									
Renal, sarcoma stromal, metastatic, uterus																									
Lymph node, bronchial	+	M	+	+	M	+	+	+	+	M	+	+	M	+	M	M	+	+	M	+	+	+	M	+	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 2 0 5	0 2 7 1	0 2 7 3	0 2 7 4	0 2 7 5	0 2 8 1	0 2 8 2	0 2 8 3	0 2 8 4	0 2 8 5	0 2 9 1	0 2 9 3	0 2 7 5	0 1 9 2	0 2 9 4	0 2 9 5	0 2 3 1	0 3 0 3	0 3 0 4	0 3 0 5	**Total Tissues/ Tumors**
General Body System																					
Tissue NOS																					1
Genital System																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Cystadenocarcinoma, papillary																					1
Cystadenoma, papillary				X																	2
Granulosa cell tumor benign																					1
Endothelium, sarcoma stromal, metastatic																					1
Oviduct																					2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Sarcoma stromal																					1
Hematopoietic System																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Iliac, sarcoma stromal, metastatic, uterus																					1
Renal, sarcoma stromal, metastatic, uterus																					1
Lymph node, bronchial	M	+	M	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	46
Lymph node, mandibular	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	60
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Integumentary System																					
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Adenocarcinoma										X								X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Subcutaneous tissue, fibrosarcoma																					1
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Nervous System																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 0 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 2 0 5	0 2 7 1	0 2 7 3	0 2 7 4	0 2 7 5	0 2 8 1	0 2 8 2	0 2 8 3	0 2 8 4	0 2 8 5	0 2 9 1	0 2 9 3	0 2 9 5	0 1 7 5	0 2 9 2	0 2 9 4	0 2 9 5	0 3 0 1	0 3 0 3	0 3 0 4	0 3 0 5	**Total Tissues/ Tumors**
Respiratory System																						
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Alveolar/bronchiolar adenoma														X					X	X		5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Special Senses System																						
Eye															+							2
Harderian gland																						1
Urinary System																						
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	67
Systemic Lesions																						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Lymphoma malignant histiocytic																						1
Lymphoma malignant lymphocytic																						6
Lymphoma malignant mixed																						1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4
Carcass ID Number	1 0 4 5	1 0 5 1	1 0 5 3	1 0 5 4	1 0 5 5	1 0 6 1	1 0 6 2	1 0 6 3	1 0 6 4	1 0 6 5	1 0 6 6	1 1 3 1	1 1 3 5	1 1 4 1	1 1 4 2	1 1 4 3	1 1 4 5	1 1 5 1	1 1 5 3	1 1 5 4	1 1 5 5	1 1 6 1	1 1 6 3	1 1 6 4	1 1 6 5	1 1 7 1
Alimentary System																									
Esophagus																									
Gallbladder																									
Intestine large																									
Intestine large, cecum																									
Intestine large, colon																									
Intestine large, rectum																									
Intestine small			+								+					+									
Intestine small, duodenum			+								+					+									
Adenocarcinoma																X									
Intestine small, ileum																									
Intestine small, jejunum																									
Liver														+										+	+
Hepatocellular adenoma														X											
Sarcoma stromal, metastatic																									
Pancreas																									
Salivary glands																			+						
Stomach																									
Stomach, forestomach																									
Stomach, glandular																									
Cardiovascular System																									
Heart																									
Endocrine System																									
Adrenal gland																									
Adrenal gland, cortex																									
Adrenal gland, medulla																									
Islets, pancreatic																									
Parathyroid gland																									
Pituitary gland																					+				
Thyroid gland																									
General Body System																									
Tissue NOS																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	
Carcass ID Number	1 2 1 1	1 2 1 2	1 2 1 3	1 2 1 4	1 2 2 1	1 2 5 1	1 2 5 1	1 2 5 2	1 2 8 3	1 3 5 2	1 2 2 4	1 3 2 1	1 3 2 2	1 3 3 1	1 3 3 2	1 3 3 3	1 3 5 1	1 3 6 1	1 3 6 2	**Total Tissues/ Tumors**
Alimentary System																				
Esophagus																				4
Gallbladder																				2
Intestine large																				3
Intestine large, cecum																				1
Intestine large, colon																				2
Intestine large, rectum																				3
Intestine small																				4
Intestine small, duodenum																				4
Adenocarcinoma																				1
Intestine small, ileum																				1
Intestine small, jejunum																				1
Liver	+	+																		12
Hepatocellular adenoma																				2
Sarcoma stromal, metastatic																				1
Pancreas																				5
Salivary glands																				5
Stomach																				5
Stomach, forestomach																				5
Stomach, glandular																				5
Cardiovascular System																				
Heart																				4
Endocrine System																				
Adrenal gland																				4
Adrenal gland, cortex																				4
Adrenal gland, medulla																				4
Islets, pancreatic																				4
Parathyroid gland																				
Pituitary gland																				4
Thyroid gland																				4
General Body System																				
Tissue NOS									+											1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	1 2 7	1 2 7	1 8 3	1 9 7	2 8 7	4 6 3	5 4 8	5 8 6	6 1 9	7 1 6	7 1 8	7 3 7	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4
Carcass ID Number	1 0 1 1	1 0 3 1	1 1 3 3	1 1 6 2	1 1 5 2	1 0 5 2	1 1 4 4	1 0 1 2	1 0 0 1	1 0 3 2	1 0 9 1	1 3 9 1	0 9 8 1	0 9 9 2	0 9 9 3	1 0 1 3	1 0 1 4	1 0 2 1	1 0 2 2	1 0 2 3	1 0 2 4	1 0 2 5	1 0 4 1	1 0 4 2	1 0 4 3	1 0 4 4
Genital System																									
Ovary			+	M	+		M					+				+	+					+			
Cystadenocarcinoma, papillary																									
Sarcoma stromal, metastatic												X													
Oviduct										+															
Uterus			+	M	+		M					+	+			+		+	+		+	+	+		+	+
Sarcoma stromal												X													
Endometrium, polyp stromal																									
Hematopoietic System																									
Bone marrow			+	+	+		+																		
Lymph node			+	+	+		+									+		+							
Lymph node, bronchial			M	M	M		+																		
Lymph node, mandibular			+	+	+		+											+							
Lymph node, mediastinal			+	+	+		+																		
Lymph node, mesenteric			+	M	+		M									+									
Spleen			+	A	+		+		+											+					
Thymus			+	M	+		M																		
Integumentary System																									
Mammary gland			+	+	+		+																		
Adenocarcinoma																									
Skin			+	+	+		+		+		+														
Subcutaneous tissue, fibrosarcoma											X														
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone			+	+	+		+																		
Nervous System																									
Brain			+	+	+		+																		
Respiratory System																									
Larynx			+	+	+		+																		
Lung			+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Fibrosarcoma, metastatic, skin											X														

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4
Carcass ID Number	1 0 4 5	1 0 5 1	1 0 5 3	1 0 5 4	1 0 5 5	1 0 6 1	1 0 6 2	1 0 6 3	1 0 6 4	1 0 6 5	1 1 3 1	1 1 3 5	1 1 4 1	1 1 4 2	1 1 4 3	1 1 4 5	1 1 5 1	1 1 5 3	1 1 5 4	1 1 5 5	1 1 6 1	1 1 6 3	1 1 6 4	1 1 6 5	1 1 6 7	1 1 7 1
Genital System																									
Ovary					+											+			+	+	+			+	
Cystadenocarcinoma, papillary																									
Sarcoma stromal, metastatic																									
Oviduct																									
Uterus	+	+	+	+			+		+	+	+	+				+	+		+	+			+	+	+	+
Sarcoma stromal																									
Endometrium, polyp stromal			X																						
Hematopoietic System																									
Bone marrow																									
Lymph node						+																			
Lymph node, bronchial																									
Lymph node, mandibular																									
Lymph node, mediastinal						+																			
Lymph node, mesenteric																									
Spleen															+									+	
Thymus																									
Integumentary System																									
Mammary gland														+											
Adenocarcinoma														X											
Skin																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone																									
Nervous System																									
Brain																									
Respiratory System																									
Larynx																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar adenoma, multiple																					X				
Fibrosarcoma, metastatic, skin																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	
Carcass ID Number	1 2 1 1	1 2 1 2	1 2 1 3	1 2 1 4	1 2 2 1	1 2 5 1	1 2 5 1	1 2 5 2	1 2 8 3	1 2 5 2	1 3 2 4	1 3 2 1	1 3 3 2	1 3 3 1	1 3 3 2	1 3 3 3	1 3 5 1	1 3 6 1	1 3 6 2	**Total Tissues/ Tumors**
Genital System																			
Ovary		+											+						14
Cystadenocarcinoma, papillary		X																	1
Sarcoma stromal, metastatic																			1
Oviduct																			1
Uterus		+	+	+	+		+		+	+	+		+	+	+			+	41
Sarcoma stromal																		X	2
Endometrium, polyp stromal																			1
Hematopoietic System																			
Bone marrow																			4
Lymph node								+										+	9
Lymph node, bronchial																			1
Lymph node, mandibular																		+	6
Lymph node, mediastinal								+											6
Lymph node, mesenteric																		+	4
Spleen		+	+								+				+	+		+	13
Thymus								+											3
Integumentary System																			
Mammary gland																			5
Adenocarcinoma																			1
Skin																			6
Subcutaneous tissue, fibrosarcoma																			1
Subcutaneous tissue, sarcoma																			1
Musculoskeletal System																			
Bone																			4
Nervous System																			
Brain																			4
Respiratory System																			
Larynx																			4
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Alveolar/bronchiolar adenoma																			1
Alveolar/bronchiolar adenoma, multiple																			1
Fibrosarcoma, metastatic, skin																			1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	1 2 7	1 2 7	1 8 3	1 9 7	2 8 7	4 6 3	5 4 8	5 8 6	6 6 9	7 1 6	7 1 8	7 3 7	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4
Carcass ID Number	1 0 1 1	1 0 3 1	1 1 3 3	1 1 6 2	1 1 5 2	1 0 5 2	1 1 4 4	1 0 4 2	1 0 1 1	0 0 3 2	1 9 9 1	0 3 8 1	1 9 9 1	0 9 9 2	0 9 9 3	1 0 1 3	1 0 2 4	1 0 2 1	1 0 2 2	1 0 2 3	1 0 2 4	1 0 2 5	1 0 4 1	1 0 4 2	1 0 4 3	1 0 4 4
Respiratory System (continued)																										
Nose			+	+	+	+	+		+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+
Adenoma																	X									
Trachea			+	+	+		+																			
Special Senses System																										
Ear																										
Pinna, fibrosarcoma																										
Eye			+															+								
Harderian gland																		+								
Adenocarcinoma																		X								
Urinary System																										
Kidney			+	+	+		+		+	+																
Urinary bladder			M	M	+		M																			
Systemic Lesions																										
Multiple organs			+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																										
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed																										

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4
Carcass ID Number	1 0 4 5	1 0 5 1	1 0 5 3	1 0 5 4	1 0 5 5	1 0 6 1	1 0 6 2	1 0 6 3	1 0 6 4	1 0 6 5	1 0 6 6	1 1 3 1	1 1 3 5	1 1 4 1	1 1 4 2	1 1 4 3	1 1 4 5	1 1 5 1	1 1 5 3	1 1 5 4	1 1 5 5	1 1 6 1	1 1 6 3	1 1 6 4	1 1 6 5	1 1 6 6	1 1 7 1		
Respiratory System (continued)																													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma															X														
Trachea																													
Special Senses System																													
Ear				+																									
Pinna, fibrosarcoma				X																									
Eye							+					+	+																
Harderian gland																													
Adenocarcinoma																													
Urinary System																													
Kidney																												+	
Urinary bladder																													
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																												X	X
Lymphoma malignant lymphocytic			X			X																							
Lymphoma malignant mixed																													

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 10 ppm
(continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	7 4 5	
Carcass ID Number	1 2 1 1	1 2 1 2	1 2 1 3	1 2 1 4	1 2 2 1	1 2 5 1	1 2 5 2	1 2 5 3	1 3 8 2	1 2 5 4	1 3 2 1	1 3 2 2	1 3 3 1	1 3 3 2	1 3 3 3	1 3 5 1	1 3 6 1	1 3 6 2	**Total Tissues/ Tumors**
Respiratory System (continued)																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Adenoma																			2
Trachea																			4
Special Senses System																			
Ear																			1
Pinna, fibrosarcoma																			1
Eye															+				6
Harderian gland															+				2
Adenocarcinoma															X				2
Urinary System																			
Kidney																			7
Urinary bladder																			1
Systemic Lesions																			
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Lymphoma malignant histiocytic																			2
Lymphoma malignant lymphocytic			X					X								X			5
Lymphoma malignant mixed																		X	1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	0 6 7	2 3 4	3 5 1	3 6 6	4 2 7	4 6 6	6 1 4	6 2 6	6 4 8	6 6 3	6 6 7	6 7 8	6 8 8	6 9 6	7 1 1	7 1 3	7 1 4	7 2 2	7 3 6	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9
Carcass ID Number	0 5 0 5	0 4 8 4	0 4 8 5	0 4 7 2	0 5 7 4	0 4 9 5	0 5 9 1	0 4 5 5	0 4 5 1	0 4 1 1	0 5 8 4	0 5 8 1	0 4 4 1	0 4 7 1	0 4 5 4	0 4 5 4	0 4 9 2	0 4 4 5	0 4 5 2	0 4 1 3	0 4 1 4	0 4 1 5	0 4 1 2	0 4 2 1	0 4 2 2	0 4 2 3
Alimentary System																									
Esophagus	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Gallbladder	+		+	+	M	+	+	+	A	M	+	A	+	+	A	+	A	A	+	+	+	+	+	+	+	+
Intestine large	+		+	+	M	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, cecum	+		+	+	M	M	+	A	A	M	+	A	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Intestine large, colon	+		+	A	M	+	+	+	A	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Intestine large, rectum	+		+	+	M	+	+	+	M	A	+	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+
Intestine small	+		+	A	M	+	+	A	A	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Intestine small, duodenum	+		+	M	M	+	+	A	A	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Intestine small, ileum	+		+	A	M	+	+	A	A	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Intestine small, jejunum	+		+	A	M	+	+	A	A	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Liver	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																	X								
Plasma cell tumor malignant												X													
Mesentery																				+					
Pancreas	+		+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Salivary glands	M		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Stomach	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+		+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone					X																				
Endocrine System																									
Adrenal gland	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone					X																				
Adrenal gland, medulla	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone					X																				
Islets, pancreatic	+		+		+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Parathyroid gland	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+		+		M	+	+	M	+	M	+	+	+	+	M	M	+	+	M	+	+	+	M	+	+	+
Thyroid gland	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 2	7 4 2
Carcass ID Number	0 4 2 4	0 4 2 5	0 4 3 1	0 4 3 2	0 4 3 3	0 4 3 4	0 4 3 5	0 4 4 2	0 4 4 3	0 4 4 4	0 4 4 5	0 4 5 3	0 4 6 1	0 4 6 2	0 4 6 3	0 4 6 4	0 4 6 5	0 4 7 1	0 4 7 3	0 4 7 5	0 4 8 1	0 4 8 2	0 4 8 3	0 4 9 1	0 4 9 3	0 4 9 4
Alimentary System																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Plasma cell tumor malignant																									
Mesentery								+																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel														+											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	M	M	+	+	M	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	0 5 0 1	0 5 0 2	0 5 0 3	0 5 0 4	0 5 7 1	0 5 7 3	0 5 7 5	0 5 8 2	0 5 8 3	0 5 8 5	0 5 9 2	0 5 9 3	0 5 9 4	0 5 9 5	0 6 0 1	0 6 0 2	0 6 0 3	0 6 0 4	0 6 0 5		**Total Tissues/ Tumors**
Alimentary System																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		65
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		60
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		64
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		61
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		61
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		61
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		61
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Hepatocellular carcinoma																					1
Plasma cell tumor malignant																					1
Mesentery													+								3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		65
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		64
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		65
Cardiovascular System																					
Blood vessel																					1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		68
Osteosarcoma, metastatic, bone																					1
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Osteosarcoma, metastatic, bone																					1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		66
Osteosarcoma, metastatic, bone																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		66
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		66
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	M	+		50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	0 6 7	2 3 4	3 5 1	3 6 6	4 2 7	4 6 6	6 1 4	6 2 6	6 4 8	6 6 3	6 7 7	6 8 8	6 9 6	7 1 1	7 1 3	7 1 4	7 2 2	7 3 6	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9
Carcass ID Number	0 5 0 5	0 4 8 4	0 4 8 5	0 4 7 2	0 5 7 4	0 4 9 5	0 5 9 1	0 4 5 5	0 4 5 1	0 4 1 1	0 5 8 4	0 5 8 1	0 4 4 1	0 4 7 4	0 4 5 4	0 4 9 2	0 4 4 5	0 4 5 2	0 4 1 3	0 4 1 4	0 4 1 5	0 4 2 2	0 4 2 1	0 4 2 3
General Body System																								
Tissue NOS					+			+																
Osteosarcoma, metastatic, bone					X																			
Genital System																								
Ovary	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Cystadenoma, papillary																								
Granulosa cell tumor benign																								
Osteosarcoma, metastatic, bone					X																			
Oviduct						+		+	+								+							
Uterus	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hematopoietic System																								
Blood													+											
Bone marrow	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone					X																			
Lymph node	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, bronchial	M		M	+	M	+	+	+	+	+	+	M	M	M	+	+	M	M	+	M	+	+	+	+
Lymph node, mandibular	M		+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Lymph node, mediastinal	M		+	M	M	+	+	+	+	M	+	M	+	+	M	M	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+		+	+	+	M	M	M	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+
Spleen	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Plasma cell tumor malignant												X												
Thymus	+		+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+		+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X											
Skin	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																								
Musculoskeletal System																								
Bone	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma					X																			
Skeletal muscle	+				+		+																	
Hindlimb, fibrosarcoma							X																	
Sternal, osteosarcoma, metastatic, bone					X																			

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 2	7 4 2
Carcass ID Number	0 4 2 4	0 4 2 5	0 4 3 1	0 4 3 2	0 4 3 3	0 4 3 4	0 4 3 5	0 4 4 2	0 4 4 3	0 4 4 4	0 4 4 3	0 4 5 1	0 4 6 2	0 4 6 3	0 4 6 4	0 4 6 5	0 4 7 1	0 4 7 3	0 4 7 5	0 4 8 1	0 4 8 2	0 4 8 3	0 4 9 1	0 4 9 3	0 4 9 4
General Body System																									
Tissue NOS																									
Osteosarcoma, metastatic, bone																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary	X	X													X									X	
Granulosa cell tumor benign													X												
Osteosarcoma, metastatic, bone																									
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	M	+	+	+	M	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant																									
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																									
Skeletal muscle																									
Hindlimb, fibrosarcoma																									
Sternal, osteosarcoma, metastatic, bone																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	0 5 0 1	0 5 0 2	0 5 0 3	0 5 0 4	0 5 7 1	0 5 7 3	0 5 7 5	0 5 8 2	0 5 8 3	0 5 8 5	0 5 9 2	0 5 9 3	0 5 9 4	0 5 9 5	0 6 0 1	0 6 0 2	0 6 0 3	0 6 0 4	0 6 0 5	**Total Tissues/ Tumors**
General Body System																				
Tissue NOS																				2
Osteosarcoma, metastatic, bone																				1
Genital System																				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Cystadenoma, papillary																				4
Granulosa cell tumor benign																				1
Osteosarcoma, metastatic, bone																				1
Oviduct																				4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Hematopoietic System																				
Blood																				1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Osteosarcoma, metastatic, bone	/																			1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	+	M	M	M	M	+	M	+	M	46
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	62
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	60
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Plasma cell tumor malignant																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	60
Integumentary System																				
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Adenocarcinoma																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Papilloma squamous																				1
Musculoskeletal System																				
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Femur, osteosarcoma																				1
Skeletal muscle																				3
Hindlimb, fibrosarcoma																				1
Sternal, osteosarcoma, metastatic, bone																				1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	0 6 7	2 3 4	3 5 1	3 6 6	4 2 7	4 6 6	6 1 4	6 2 6	6 4 8	6 6 3	6 7 7	6 8 8	6 9 6	7 1 1	7 1 3	7 1 4	7 2 2	7 3 6	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9
Carcass ID Number	0 5 0 5	0 4 8 4	0 4 8 5	0 4 7 2	0 5 7 4	0 4 9 5	0 5 9 1	0 4 5 5	0 4 5 1	0 4 5 1	0 5 1 4	0 5 8 1	0 4 8 1	0 4 7 4	0 4 5 4	0 4 9 2	0 4 4 2	0 4 5 5	0 4 1 2	0 4 1 3	0 4 1 4	0 4 1 5	0 4 2 2	0 4 2 1	0 4 2 3
Nervous System																									
Brain	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+		+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lung	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland													X												
Alveolar/bronchiolar adenoma												X		X	X							X			X
Alveolar/bronchiolar adenoma, multiple																									
Lymphoma malignant histiocytic, metastatic, liver																				X					
Osteosarcoma, metastatic, bone					X																				
Nose	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Urinary System																									
Kidney	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Plasma cell tumor malignant												X													
Urinary bladder	+		+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																				X					
Lymphoma malignant lymphocytic																	X		X						
Lymphoma malignant mixed										X															

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 2	7 4 2
Carcass ID Number	0 4 2 4	0 4 2 5	0 4 3 1	0 4 3 2	0 4 3 3	0 4 3 4	0 4 3 5	0 4 4 2	0 4 4 3	0 4 4 4	0 4 4 5	0 4 5 3	0 4 6 1	0 4 6 2	0 4 6 3	0 4 6 4	0 4 6 5	0 4 7 1	0 4 7 3	0 4 7 5	0 4 8 1	0 4 8 2	0 4 8 3	0 4 9 1	0 4 9 3	0 4 9 4
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, metastatic, mammary gland																										
Alveolar/bronchiolar adenoma								X		X																
Alveolar/bronchiolar adenoma, multiple						X									X											
Lymphoma malignant histiocytic, metastatic, liver																										
Osteosarcoma, metastatic, bone																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																+										
Harderian gland							+																			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Plasma cell tumor malignant																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant histiocytic																										
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed						X				X																

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	0 5 0 1	0 5 0 2	0 5 0 3	0 5 0 4	0 5 7 1	0 5 7 3	0 5 7 5	0 5 8 2	0 5 8 3	0 5 8 5	0 5 9 2	0 5 9 3	0 5 9 4	0 5 9 5	0 6 0 1	0 6 0 2	0 6 0 3	0 6 0 4	0 6 0 5	0 6 0 6	**Total Tissues/ Tumors**
Nervous System																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Respiratory System																					
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Adenocarcinoma, metastatic, mammary gland																					1
Alveolar/bronchiolar adenoma			X						X												9
Alveolar/bronchiolar adenoma, multiple															X					X	4
Lymphoma malignant histiocytic, metastatic, liver																					1
Osteosarcoma, metastatic, bone																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Special Senses System																					
Eye							+														2
Harderian gland																					1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Plasma cell tumor malignant																					1
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	62
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Lymphoma malignant histiocytic																					1
Lymphoma malignant lymphocytic																					2
Lymphoma malignant mixed		X																			4

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	1 5 6	2 1 5	4 2 3	4 7 1	6 1 1	6 2 3	6 2 5	6 2 7	6 4 8	6 5 8	6 5 9	6 6 0	6 6 8	6 8 9	6 9 6	7 0 2	7 0 8	7 2 1	7 3 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 7 2 4	0 7 7 2	0 7 1 5	0 7 2 1	0 9 0 4	0 7 3 5	0 9 0 5	0 7 7 1	0 8 7 1	0 7 1 4	0 7 8 4	0 7 8 2	0 7 4 3	0 7 9 4	0 8 0 5	0 8 9 4	0 7 1 2	0 7 3 1	0 7 5 3	0 7 1 1	0 7 1 3	0 7 2 2	0 7 2 3	0 7 2 5	0 7 3 2
Alimentary System																									
Esophagus			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder			+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large			+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum			A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon			+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum			A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Intestine small			A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum			A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small, ileum			A	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																			X						
Intestine small, jejunum			A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+
Liver			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X												
Osteosarcoma, metastatic, bone																	X								
Sarcoma, metastatic, uncertain primary site																			X						
Mesentery					+														+						
Fat, sarcoma, metastatic, uncertain primary site																			X						
Pancreas			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																			X						
Salivary glands			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X	
Stomach			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma														X											
Sarcoma, metastatic, uncertain primary site																			X						

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 7 3 3	0 7 3 4	0 7 4 1	0 7 4 2	0 7 4 4	0 7 4 5	0 7 5 1	0 7 5 2	0 7 5 4	0 7 5 5	0 7 6 1	0 7 6 2	0 7 6 3	0 7 6 4	0 7 6 5	0 7 7 3	0 7 7 4	0 7 7 5	0 7 8 1	0 7 8 3	0 7 8 5	0 7 9 1	0 7 9 2	0 7 9 3	0 7 9 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Intestine small, jejunum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Osteosarcoma, metastatic, bone																									
Sarcoma, metastatic, uncertain primary site																									
Mesentery																							+		
Fat, sarcoma, metastatic, uncertain primary site																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																							X		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
Sarcoma, metastatic, uncertain primary site																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	0 8 0 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 7 2	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 2	0 8 8 3	0 8 8 4	0 8 8 5	0 8 9 1	0 8 9 2	0 8 9 3	0 8 9 5	0 9 0 1	0 9 0 2	0 9 0 3		**Total Tissues/ Tumors**
Alimentary System																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		64
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		66
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		64
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		66
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		65
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Sarcoma, metastatic, uncertain primary site																					1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Hepatocellular adenoma					X																2
Osteosarcoma, metastatic, bone																					1
Sarcoma, metastatic, uncertain primary site																					1
Mesentery																					3
Fat, sarcoma, metastatic, uncertain primary site																					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Sarcoma, metastatic, uncertain primary site																					1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Fibrosarcoma																					1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Squamous cell carcinoma																					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Cardiovascular System																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Fibrous histiocytoma																					1
Sarcoma, metastatic, uncertain primary site																					1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	1 5 6	2 1 5	4 2 3	4 7 1	6 1 1	6 2 3	6 2 5	6 2 7	6 4 8	6 5 8	6 5 9	6 6 0	6 6 8	6 8 9	6 9 6	7 0 2	7 0 8	7 2 1	7 3 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 7 2 4	0 7 7 2	0 7 1 5	0 7 2 1	0 9 0 4	0 7 3 5	0 9 0 5	0 7 7 1	0 8 7 1	0 7 1 4	0 7 8 4	0 7 8 2	0 7 4 3	0 7 9 4	0 8 0 5	0 8 9 4	0 7 1 2	0 7 3 1	0 7 5 3	0 7 1 1	0 7 1 3	0 7 2 2	0 7 2 3	0 7 3 5	0 7 3 2
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, sarcoma, metastatic, uncertain primary site																			X						
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																			X						
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	M	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Squamous cell carcinoma																									
Ovary	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																						X			
Teratoma benign														X											
Oviduct	+			+							+							+							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal																									
Hematopoietic System																									
Blood						+				+					+	+									+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma									X																
Hemangiosarcoma																								X	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, osteosarcoma, metastatic, bone																	X	X							
Lymph node, bronchial	M	M	+	M	M	M	+	+	M	+	M	+	+	M	+	M	+	+	+	+	M	M	+	+	
Sarcoma, metastatic, uncertain primary site																			X						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X	
Lymph node, mediastinal	M	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																			X						

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 7 3 3	0 7 3 4	0 7 4 1	0 7 4 2	0 7 4 4	0 7 4 5	0 7 5 1	0 7 5 2	0 7 5 4	0 7 5 5	0 7 6 1	0 7 6 2	0 7 6 3	0 7 6 4	0 7 6 5	0 7 7 3	0 7 7 4	0 7 7 5	0 7 8 1	0 7 8 3	0 7 8 5	0 7 9 1	0 7 9 2	0 7 9 3	0 7 9 5
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, sarcoma, metastatic, uncertain primary site																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland		+																							
Squamous cell carcinoma		X																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																									
Teratoma benign																									
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal																									
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, osteosarcoma, metastatic, bone																									
Lymph node, bronchial	+	M	+	+	M	M	+	M	+	+	M	M	+	M	+	+	+	+	M	M	+	M	M	M	M
Sarcoma, metastatic, uncertain primary site																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+
Sarcoma, metastatic, uncertain primary site																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	0 8 0 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 7 2	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 2	0 8 8 3	0 8 8 4	0 8 8 5	0 8 9 1	0 8 9 2	0 8 9 3	0 8 9 5	0 9 0 1	0 9 0 2	0 9 0 3	**Total Tissues/ Tumors**	
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Capsule, sarcoma, metastatic, uncertain primary site																				1	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	66	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Sarcoma, metastatic, uncertain primary site																				1	
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	64	
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	54	
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	66	
General Body System																					
None																					
Genital System																					
Clitoral gland																				1	
Squamous cell carcinoma																				1	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65	
Granulosa-theca tumor benign																				1	
Teratoma benign																				1	
Oviduct																				4	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66	
Endometrium, polyp stromal					X															1	
Hematopoietic System																					
Blood																				5	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Hemangioma																				1	
Hemangiosarcoma																				1	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67	
Inguinal, osteosarcoma, metastatic, bone																				1	
Lymph node, bronchial	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	40	
Sarcoma, metastatic, uncertain primary site																				1	
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	65	
Fibrosarcoma																				1	
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	57	
Sarcoma, metastatic, uncertain primary site																				1	

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	1 5 6	2 1 5	4 2 3	4 7 1	6 1 1	6 2 3	6 2 5	6 2 7	6 4 8	6 5 8	6 5 9	6 6 0	6 6 8	6 8 9	6 9 6	7 0 2	7 0 8	7 2 1	7 3 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 7 2 4	0 7 7 2	0 7 1 5	0 7 2 1	0 9 0 4	0 7 3 5	0 9 0 5	0 7 7 1	0 8 7 1	0 7 1 4	0 7 8 4	0 7 8 2	0 7 4 3	0 7 9 4	0 8 0 5	0 8 9 4	0 7 1 2	0 7 3 1	0 7 5 3	0 7 1 1	0 7 1 3	0 7 2 2	0 7 2 3	0 7 3 5	0 7 7 2
Hematopoietic System (continued)																									
Lymph node, mesenteric	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma								X						X											
Capsule, sarcoma, metastatic, uncertain primary site																		X							
Thymus	+	+	M	+	M	M	+	+	+	M	M	+	+	M	+	M	+	+	+	+	+	+	+	+	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma									X							X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma				X																				X	
Subcutaneous tissue, sarcoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Humerus, osteosarcoma																	X								
Skeletal muscle									+								+								
Back, osteosarcoma, metastatic, bone																	X								
Hindlimb, hemangiosarcoma									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, metastatic, mammary gland											X														
Alveolar/bronchiolar adenoma			X								X					X								X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic, bone																	X								
Sarcoma, metastatic, skin						X																			
Sarcoma, metastatic, uncertain primary site																		X							
Mediastinum, sarcoma, metastatic, uncertain primary site																		X							

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 7 3 3	0 7 3 4	0 7 4 1	0 7 4 2	0 7 4 4	0 7 4 5	0 7 5 1	0 7 5 2	0 7 5 4	0 7 5 5	0 7 6 1	0 7 6 2	0 7 6 3	0 7 6 4	0 7 6 5	0 7 7 3	0 7 7 4	0 7 7 5	0 7 8 1	0 7 8 3	0 7 8 5	0 7 9 1	0 7 9 2	0 7 9 3	0 7 9 5
Hematopoietic System (continued)																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Capsule, sarcoma, metastatic, uncertain primary site																									
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma																									
Skeletal muscle														+											
Back, osteosarcoma, metastatic, bone																									
Hindlimb, hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma														X											X
Alveolar/bronchiolar adenoma, multiple			X				X		X																
Alveolar/bronchiolar carcinoma										X															
Osteosarcoma, metastatic, bone																									
Sarcoma, metastatic, skin																									
Sarcoma, metastatic, uncertain primary site																									
Mediastinum, sarcoma, metastatic, uncertain primary site																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	0 8 0 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 7 2	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 2	0 8 8 3	0 8 8 4	0 8 8 5	0 8 9 1	0 8 9 2	0 8 9 3	0 8 9 5	0 9 0 1	0 9 0 2	0 9 0 3	**Total Tissues/ Tumors**
Hematopoietic System (continued)																				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Hemangiosarcoma																				3
Capsule, sarcoma, metastatic, uncertain primary site																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Integumentary System																				
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Adenocarcinoma																				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Subcutaneous tissue, fibroma																				1
Subcutaneous tissue, fibrosarcoma																				2
Subcutaneous tissue, sarcoma																				1
Musculoskeletal System																				
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Humerus, osteosarcoma																				1
Skeletal muscle																				3
Back, osteosarcoma, metastatic, bone																				1
Hindlimb, hemangiosarcoma																				1
Nervous System																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Respiratory System																				
Larynx	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	64
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Adenocarcinoma, metastatic, mammary gland																				1
Alveolar/bronchiolar adenoma		X		X		X			X						X				X	12
Alveolar/bronchiolar adenoma, multiple																				3
Alveolar/bronchiolar carcinoma																				1
Osteosarcoma, metastatic, bone																				1
Sarcoma, metastatic, skin																				1
Sarcoma, metastatic, uncertain primary site																				1
Mediastinum, sarcoma, metastatic, uncertain primary site																				1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	1 5 6	2 1 5	4 2 3	4 7 1	6 1 1	6 2 3	6 2 5	6 2 7	6 4 8	6 5 8	6 5 9	6 6 0	6 6 8	6 8 9	6 9 6	7 0 2	7 0 8	7 2 1	7 3 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	0 7 2 4	0 7 7 2	0 7 1 5	0 7 2 1	0 9 0 4	0 7 3 5	0 9 0 5	0 7 7 1	0 8 7 1	0 7 7 4	0 7 1 4	0 7 8 4	0 7 8 2	0 7 4 3	0 7 9 4	0 8 0 5	0 8 9 4	0 7 1 2	0 7 3 1	0 7 5 3	0 7 1 1	0 7 1 3	0 7 2 2	0 7 2 3	0 7 3 2
Respiratory System (continued)																									
Nose			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+												+									
Lids, papilloma squamous																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder			+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Sarcoma, metastatic, uncertain primary site																			X						
Systemic Lesions																									
Multiple organs			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X				X							X											
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed													X												

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	3	4	4	4	4	5	5	5	5	6	6	6	6	6	7	7	7	8	8	8	9	9	9	9
	3	4	1	2	4	5	1	2	4	5	1	2	3	4	5	3	4	5	1	3	5	1	2	3	5
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Lids, papilloma squamous																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed															X										

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Naphthalene: 30 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	0 8 0 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 7 2	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 2	0 8 8 3	0 8 8 4	0 8 8 5	0 8 9 1	0 8 9 2	0 8 9 3	0 8 9 5	0 9 0 1	0 9 0 2	0 9 0 3		**Total Tissues/ Tumors**
Respiratory System (continued)																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Trachea	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		66
Special Senses System																					
Eye				+	+																4
Lids, papilloma squamous				X																	1
Harderian gland			+																		1
Adenoma			X																		1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+		63
Sarcoma, metastatic, uncertain primary site																					1
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		67
Lymphoma malignant histiocytic																					3
Lymphoma malignant lymphocytic																			X		2
Lymphoma malignant mixed																					2

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Naphthalene

	0 ppm	10 ppm	30 ppm
Liver: Hepatocellular Adenoma			
Overall rates[a]	2/68 (3%)	2/12 (17%)[e]	2/134 (1%)
Adjusted rates[b]	3.4%		1.8%
Terminal rates[c]	2/59 (3%)		1/101 (1%)
First incidence (days)	736 (T)		668
Life table tests[d]			P=0.480N
Logistic regression tests[d]			P=0.443N
Fisher exact test[d]			P=0.413N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	2/68 (3%)	2/12 (17%)[e]	3/134 (2%)
Adjusted rates	3.4%		2.8%
Terminal rates	2/59 (3%)		1/101 (1%)
First incidence (days)	736 (T)		668
Life table tests	P=0.424N		P=0.615N
Logistic regression tests	P=0.342N		P=0.577N
Fisher exact test			P=0.547N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	5/69 (7%)	2/65 (3%)	28/135 (21%)
Adjusted rates	8.3%	3.5%	25.6%
Terminal rates	4/59 (7%)	2/57 (4%)	22/102 (22%)
First incidence (days)	729	736 (T)	471
Life table tests	P≤0.001	P=0.236N	P=0.006
Logistic regression tests	P≤0.001	P=0.233N	P=0.010
Cochran-Armitage test[d]	P≤0.001		
Fisher exact test		P=0.246N	P=0.009
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	5/69 (7%)	2/65 (3%)	29/135 (21%)
Adjusted rates	8.3%	3.5%	26.5%
Terminal rates	4/59 (7%)	2/57 (4%)	23/102 (23%)
First incidence (days)	729	736 (T)	471
Life table tests	P≤0.001	P=0.236N	P=0.004
Logistic regression tests	P≤0.001	P=0.233N	P=0.007
Cochran-Armitage test	P≤0.001		
Fisher exact test		P=0.246N	P=0.006
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rates	1/69 (1%)	3/65 (5%)	1/135 (1%)
Adjusted rates	1.7%	5.3%	1.0%
Terminal rates	1/59 (2%)	3/57 (5%)	1/102 (1%)
First incidence (days)	736 (T)	736 (T)	736 (T)
Life table tests	P=0.323N	P=0.294	P=0.634N
Logistic regression tests	P=0.323N	P=0.294	P=0.634N
Cochran-Armitage test	P=0.274N		
Fisher exact test		P=0.287	P=0.563N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm
All Organs: Hemangiosarcoma			
Overall rates	0/69 (0%)	0/65 (0%)	5/135 (4%)
Adjusted rates	0.0%	0.0%	4.4%
Terminal rates	0/59 (0%)	0/57 (0%)	2/102 (2%)
First incidence (days)			648
Life table tests	P=0.030	–[f]	P=0.118
Logistic regression tests	P=0.034	–[f]	P=0.127
Cochran-Armitage test	P=0.034		
Fisher exact test		–[f]	P=0.124
All Organs: Malignant Lymphoma and Histiocytic Sarcoma			
Overall rates	8/69 (12%)	8/65 (12%)	14/135 (10%)
Adjusted rates	12.4%	14.0%	12.2%
Terminal rates	3/59 (5%)	8/57 (14%)	7/102 (7%)
First incidence (days)	574	736 (T)	423
Life table tests	P=0.520N	P=0.568	P=0.557N
Logistic regression tests	P=0.416N	P=0.554	P=0.487N
Cochran-Armitage test	P=0.417N		
Fisher exact test		P=0.554	P=0.481N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)			
Overall rates	8/69 (12%)	8/65 (12%)	14/135 (10%)
Adjusted rates	12.4%	14.0%	12.2%
Terminal rates	3/59 (5%)	8/57 (14%)	7/102 (7%)
First incidence (days)	574	736 (T)	423
Life table tests	P=0.520N	P=0.568	P=0.557N
Logistic regression tests	P=0.416N	P=0.554	P=0.487N
Cochran-Armitage test	P=0.417N		
Fisher exact test		P=0.554	P=0.481N
All Organs: Benign Tumors			
Overall rates	15/69 (22%)	7/65 (11%)	41/135 (30%)
Adjusted rates	24.6%	12.3%	36.6%
Terminal rates	13/59 (22%)	7/57 (12%)	32/102 (31%)
First incidence (days)	662	736 (T)	471
Life table tests	P=0.006	P=0.063N	P=0.064
Logistic regression tests	P=0.015	P=0.066N	P=0.112
Cochran-Armitage test	P=0.018		
Fisher exact test		P=0.069N	P=0.126
All Organs: Malignant Tumors			
Overall rates	12/69 (17%)	18/65 (28%)	32/135 (24%)
Adjusted rates	18.7%	30.5%	25.5%
Terminal rates	7/59 (12%)	16/57 (28%)	11/102 (11%)
First incidence (days)	574	669	423
Life table tests	P=0.201	P=0.135	P=0.158
Logistic regression tests	P=0.303	P=0.108	P=0.197
Cochran-Armitage test	P=0.302		
Fisher exact test		P=0.111	P=0.203

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0 ppm	10 ppm	30 ppm
All Organs: Benign and Malignant Tumors			
Overall rates	23/69 (33%)	22/65 (34%)	64/135 (47%)
Adjusted rates	35.4%	37.3%	49.9%
Terminal rates	17/59 (29%)	20/57 (35%)	38/102 (37%)
First incidence (days)	574	669	423
Life table tests	P=0.006	P=0.557N	P=0.025
Logistic regression tests	P=0.016	P=0.540	P=0.038
Cochran-Armitage test	P=0.018		
Fisher exact test		P=0.548	P=0.037

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; in other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, no statistical analyses are provided.
[f] Not applicable; no tumors in animal group.

TABLE B4a
Historical Incidence of Lung Alveolar/bronchiolar Tumors in Female B6C3F$_1$ Mice in Inhalation Studies[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	27/466 (5.8%)	13/466 (2.8%)	39/466 (8.4%)
Standard deviation	3.2	2.7	3.5
Range	0%–10%	0%–6%	0%–12%

[a] Data as of 15 September 1990

TABLE B4b
Historical Incidence of Hemangiomas and Hemangiosarcomas in Female B6C3F$_1$ Mice in Inhalation Studies[a]

	Incidence in Controls		
	Hemangiomas	Hemangiosarcomas	Hemangiomas or Hemangiosarcomas
Overall Historical Incidence			
Total	5/467 (1.1%)	12/467 (2.6%)	17/467 (3.6%)
Standard deviation	1.8	2.2	3.4
Range	0%-4%	0%-6%	0%-8%

[a] Data as of 15 September 1990

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Naphthalene[a]

	0ppm	10 ppm	30 ppm	30 ppm
Disposition Summary				
Animals initially in study	75	75	75	75
Special study animals[b]	5	7	6	6
Early deaths				
Natural death	8	6	10	7
Moribund	2	2	6	10
Accidental deaths	1	0		
Survivors				
Died last week of study		1	1	
Terminal sacrifice	59	56	51	50
Missing		3	1	2
Animals examined microscopically	69	65	68	67
Alimentary System				
Gallbladder	(65)	(2)	(60)	(64)
Dilatation				1 (2%)
Infiltration cellular, lymphocyte, focal			2 (3%)	
Infiltration cellular, lymphocyte, multifocal			1 (2%)	1 (2%)
Serosa, inflammation, chronic, multifocal	1 (2%)			
Intestine large, cecum	(66)	(1)	(60)	(64)
Hyperplasia, lymphoid, focal			1 (2%)	1 (2%)
Serosa, inflammation, chronic, multifocal	1 (2%)			
Intestine large, colon	(67)	(2)	(62)	(66)
Parasite metazoan			4 (6%)	3 (5%)
Intestine small, duodenum	(66)	(4)	(61)	(63)
Hyperplasia, lymphoid, focal		1 (25%)	1 (2%)	
Intestine small, ileum	(66)	(1)	(61)	(63)
Amyloid deposition, multifocal				1 (2%)
Serosa, inflammation, chronic, multifocal	1 (2%)			
Intestine small, jejunum	(65)	(1)	(61)	(63)
Serosa, inflammation, chronic, multifocal	1 (2%)			
Liver	(68)	(12)	(67)	(67)
Angiectasis, focal			1 (1%)	1 (1%)
Basophilic focus	1 (1%)			
Clear cell focus			1 (1%)	
Cyst	1 (1%)			
Focal cellular change, focal			1 (1%)	
Hematopoietic cell proliferation, focal			2 (3%)	
Hematopoietic cell proliferation, multifocal	5 (7%)		7 (10%)	5 (7%)
Infiltration cellular, lymphocyte, focal	1 (1%)		5 (7%)	7 (10%)
Infiltration cellular, lymphocyte, multifocal	16 (24%)	1 (8%)	16 (24%)	17 (25%)
Inflammation, chronic, multifocal	2 (3%)			
Mineralization, focal			1 (1%)	1 (1%)
Necrosis, focal			1 (1%)	2 (3%)
Necrosis, multifocal		1 (8%)	2 (3%)	1 (1%)
Pigmentation, focal	1 (1%)			1 (1%)
Bile duct, cytoplasmic alteration, multifocal			1 (1%)	
Hepatocyte, atrophy, diffuse				1 (1%)
Mesentery	(6)		(3)	(3)
Infiltration cellular, lymphocyte, multifocal	1 (17%)			1 (33%)
Infiltration cellular, mixed cell, multifocal			1 (33%)	
Inflammation, chronic, multifocal	1 (17%)			
Inflammation, granulomatous, focal	1 (17%)			
Fat, necrosis	2 (33%)		1 (33%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0ppm	10 ppm	30 ppm	30 ppm
Alimentary System (continued)				
Pancreas	(69)	(5)	(65)	(67)
Atrophy, diffuse	2 (3%)			
Atrophy, focal				1 (1%)
Atrophy, multifocal	1 (1%)		1 (2%)	1 (1%)
Infiltration cellular, lymphocyte, focal	3 (4%)		3 (5%)	1 (1%)
Infiltration cellular, lymphocyte, multifocal	18 (26%)		17 (26%)	17 (25%)
Inflammation, multifocal	3 (4%)		1 (2%)	1 (1%)
Vacuolization cytoplasmic, multifocal			1 (2%)	
Acinus, hyperplasia, focal				1 (1%)
Duct, dilatation	1 (1%)		2 (3%)	1 (1%)
Salivary glands	(68)	(5)	(64)	(67)
Infiltration cellular, lymphocyte, focal	3 (4%)	1 (20%)	3 (5%)	10 (15%)
Infiltration cellular, lymphocyte, multifocal	40 (59%)		34 (53%)	30 (45%)
Stomach, forestomach	(67)	(5)	(67)	(67)
Hyperkeratosis, focal				1 (1%)
Hyperplasia, focal			1 (1%)	1 (1%)
Stomach, glandular	(67)	(5)	(65)	(67)
Hemorrhage, focal				1 (1%)
Infiltration cellular, lymphocyte, multifocal	1 (1%)			
Mucosa, cyst				1 (1%)
Cardiovascular System				
Blood vessel			(1)	
Adventitia, inflammation, multifocal			1 (100%)	
Media, hypertrophy, multifocal			1 (100%)	
Heart	(69)	(4)	(68)	(67)
Infiltration cellular, lymphocyte, focal	1 (1%)			
Mineralization, multifocal		1 (25%)		
Myocardium, inflammation, chronic, focal			1 (1%)	
Myocardium, inflammation, suppurative, focal			1 (1%)	
Valve, pigmentation, focal	3 (4%)		6 (9%)	6 (9%)
Valve, pigmentation, multifocal	7 (10%)		7 (10%)	7 (10%)
Endocrine System				
Adrenal gland	(66)	(4)	(67)	(67)
Capsule, hyperplasia, multifocal	66 (100%)	2 (50%)	67 (100%)	66 (99%)
Capsule, inflammation, chronic, multifocal	1 (2%)			
Adrenal gland, cortex	(66)	(4)	(67)	(67)
Accessory adrenal cortical nodule	1 (2%)			
Congestion, multifocal	1 (2%)		3 (4%)	
Cyst	1 (2%)			
Degeneration, focal	1 (2%)		1 (1%)	
Focal cellular change	2 (3%)			1 (1%)
Hypertrophy, focal			1 (1%)	
Pigmentation, focal	2 (3%)			
Adrenal gland, medulla	(64)	(4)	(66)	(66)
Congestion, multifocal			1 (2%)	
Degeneration				1 (2%)
Hyperplasia	1 (2%)			1 (2%)
Islets, pancreatic	(69)	(4)	(66)	(67)
Hyperplasia, focal	1 (1%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0ppm	10 ppm	30 ppm	30 ppm
Endocrine System (continued)				
Parathyroid gland	(68)		(66)	(64)
Cyst, focal	1 (1%)			1 (2%)
Degeneration, focal				1 (2%)
Infiltration cellular, lymphocyte, focal				1 (2%)
Infiltration cellular, lymphocyte, multifocal				1 (2%)
Bilateral, hyperplasia				1 (2%)
Pituitary gland	(61)	(4)	(50)	(54)
Cyst, multifocal				1 (2%)
Pars distalis, angiectasis	1 (2%)		2 (4%)	
Pars distalis, hyperplasia	4 (7%)	1 (25%)		1 (2%)
Thyroid gland	(69)	(4)	(67)	(66)
Infiltration cellular, lymphocyte, focal			1 (1%)	2 (3%)
Inflammation, acute, focal	1 (1%)		2 (3%)	2 (3%)
Follicle, dilatation, focal	2 (3%)		2 (3%)	5 (8%)
Follicular cell, hyperplasia, focal	3 (4%)		2 (3%)	4 (6%)
Follicular cell, hyperplasia, multifocal	1 (1%)		1 (1%)	1 (2%)
Follicular cell, hypertrophy, multifocal	1 (1%)			1 (2%)
General Body System				
None				
Genital System				
Ovary	(69)	(14)	(66)	(65)
Cyst	11 (16%)	9 (64%)	16 (24%)	11 (17%)
Cyst, multifocal	1 (1%)	1 (7%)	1 (2%)	2 (3%)
Giant cell, multiple				1 (2%)
Hematocyst, focal		2 (14%)	2 (3%)	2 (3%)
Infiltration cellular, histiocyte				1 (2%)
Inflammation, suppurative, multifocal			1 (2%)	
Metaplasia, osseous, focal			1 (2%)	
Mineralization, multifocal				1 (2%)
Pigmentation	1 (1%)			
Follicle, hemorrhage, focal	3 (4%)			1 (2%)
Interstitium, hyperplasia	1 (1%)			
Oviduct	(2)	(1)	(4)	(4)
Mucosa, hyperplasia, cystic		1 (100%)		
Mucosa, vacuolization cytoplasmic, multifocal	1 (50%)			
Uterus	(69)	(41)	(67)	(66)
Angiectasis, multifocal	1 (1%)	1 (2%)	1 (1%)	
Dilatation		2 (5%)	7 (10%)	6 (9%)
Inflammation, suppurative			1 (1%)	1 (2%)
Endometrium, hyperplasia, cystic	61 (88%)	36 (88%)	49 (73%)	56 (85%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0ppm	10 ppm	30 ppm	30 ppm
Hematopoietic System				
Blood			(1)	(5)
Leukocytosis			1 (100%)	3 (60%)
Bone marrow	(69)	(4)	(68)	(67)
Angiectasis	1 (1%)		1 (1%)	
Atrophy			4 (6%)	
Congestion			1 (1%)	
Fibrous osteodystrophy, focal				1 (1%)
Fibrous osteodystrophy, multifocal	1 (1%)			
Hyperplasia	2 (3%)		1 (1%)	1 (1%)
Hyperplasia, lymphoid	4 (6%)			
Hyperplasia, neutrophil				1 (1%)
Myelofibrosis	2 (3%)		3 (4%)	
Pigmentation, focal			1 (1%)	
Pigmentation, multifocal			1 (1%)	
Lymph node	(69)	(9)	(67)	(67)
Hyperplasia				1 (1%)
Lymph node, bronchial	(46)	(1)	(46)	(40)
Congestion			1 (2%)	
Hyperplasia, lymphoid			1 (2%)	2 (5%)
Pigmentation	1 (2%)			
Lymph node, mandibular	(66)	(6)	(62)	(65)
Edema	1 (2%)			
Erythrophagocytosis			1 (2%)	
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (3%)	1 (17%)		4 (6%)
Infiltration cellular, histiocyte				1 (2%)
Pigmentation	15 (23%)		12 (19%)	13 (20%)
Lymph node, mediastinal	(60)	(6)	(52)	(57)
Angiectasis	1 (2%)			
Erythrophagocytosis			1 (2%)	
Hyperplasia, lymphoid	1 (2%)		1 (2%)	2 (4%)
Infiltration cellular, histiocyte		1 (17%)		
Pigmentation	8 (13%)		3 (6%)	1 (2%)
Lymph node, mesenteric	(67)	(4)	(60)	(62)
Erythrophagocytosis	2 (3%)		1 (2%)	1 (2%)
Giant cell, multifocal	17 (25%)		16 (27%)	8 (13%)
Hemorrhage	4 (6%)		2 (3%)	2 (3%)
Hyperplasia, lymphoid	1 (1%)		1 (2%)	1 (2%)
Hyperplasia, plasma cell, multifocal	1 (1%)			
Infiltration cellular, polymorphonuclear	1 (1%)			
Spleen	(67)	(13)	(67)	(67)
Angiectasis, multifocal			1 (1%)	
Congestion			1 (1%)	
Hematopoietic cell proliferation	4 (6%)	3 (23%)	7 (10%)	10 (15%)
Hyperplasia, lymphoid	9 (13%)	3 (23%)	6 (9%)	12 (18%)
Hyperplasia, neutrophil				1 (1%)
Hyperplasia, plasma cell	1 (1%)			1 (1%)
Infiltration cellular, histiocyte		1 (8%)		
Capsule, inflammation, chronic, multifocal	1 (1%)			
Thymus	(64)	(3)	(60)	(59)
Angiectasis	1 (2%)			
Cyst, multiple	1 (2%)			
Depletion lymphoid			1 (2%)	
Hyperplasia, lymphoid	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0ppm	10 ppm	30 ppm	30 ppm
Integumentary System				
Mammary gland	(69)	(5)	(66)	(66)
Hyperplasia, focal	2 (3%)			
Infiltration cellular, lymphocyte, focal			1 (2%)	1 (2%)
Infiltration cellular, lymphocyte, multifocal	1 (1%)		1 (2%)	2 (3%)
Duct, galactocele, multifocal			1 (2%)	
Skin	(69)	(6)	(67)	(67)
Acanthosis, multifocal				1 (1%)
Inflammation, focal				1 (1%)
Subcutaneous tissue, infiltration cellular, lymphocyte, multifocal	1 (1%)			
Subcutaneous tissue, infiltration cellular, polymorphonuclear, multifocal				1 (1%)
Musculoskeletal System				
Bone	(69)	(4)	(68)	(67)
Fibrous osteodystrophy, focal	3 (4%)		4 (6%)	6 (9%)
Fibrous osteodystrophy, multifocal	7 (10%)		12 (18%)	11 (16%)
Hyperplasia, multifocal			1 (1%)	
Metaplasia, cartilagenous, focal			1 (1%)	
Skeletal muscle			(3)	(3)
Head, hemorrhage, multifocal			1 (33%)	
Hindlimb, infiltration cellular, lymphocyte, focal				1 (33%)
Nervous System				
Brain	(69)	(4)	(68)	(67)
Fibrosis, multifocal			1 (1%)	
Hemorrhage, multifocal			1 (1%)	2 (3%)
Metaplasia, osseous, focal	1 (1%)			
Mineralization, focal	3 (4%)	1 (25%)	11 (16%)	3 (4%)
Mineralization, multifocal	34 (49%)		8 (12%)	21 (31%)
Cerebrum, necrosis, focal			1 (1%)	
Respiratory System				
Lung	(69)	(65)	(68)	(67)
Congestion	2 (3%)	1 (2%)	1 (1%)	
Hemorrhage	1 (1%)	1 (2%)	1 (1%)	
Infiltration cellular, lymphocyte	11 (16%)	21 (32%)	20 (29%)	26 (39%)
Infiltration cellular, histiocyte	1 (1%)	5 (8%)	2 (3%)	2 (3%)
Inflammation	3 (4%)	13 (20%)	34 (50%)	18 (27%)
Inflammation, granulomatous		38 (58%)	14 (21%)	28 (42%)
Metaplasia, osseous, focal			1 (1%)	
Alveolar epithelium, hyperplasia	3 (4%)	6 (9%)	5 (7%)	7 (10%)
Glands, inflammation	1 (1%)	3 (5%)	7 (10%)	8 (12%)
Nose	(69)	(65)	(68)	(67)
Hemorrhage	1 (1%)		2 (3%)	1 (1%)
Infiltration cellular, lymphocyte, multifocal	1 (1%)			
Inflammation	1 (1%)	65 (100%)	68 (100%)	67 (100%)
Olfactory epithelium, metaplasia		65 (100%)	68 (100%)	67 (100%)
Respiratory epithelium, hyperplasia		65 (100%)	68 (100%)	67 (100%)
Trachea	(69)	(4)	(68)	(66)
Glands, dilatation, multifocal				1 (2%)
Glands, inflammation, suppurative, multifocal	1 (1%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Naphthalene (continued)

	0ppm	10 ppm	30 ppm	30 ppm
Special Senses System				
Eye	(2)	(6)	(2)	(4)
Degeneration		3 (50%)	1 (50%)	
Inflammation				1 (25%)
Mineralization			1 (50%)	
Pigmentation	1 (50%)			1 (25%)
Bilateral, lens, cataract	1 (50%)			
Cornea, degeneration	1 (50%)			
Lens, cataract		2 (33%)	1 (50%)	2 (50%)
Optic nerve, degeneration	1 (50%)			
Retina, atrophy	1 (50%)			1 (25%)
Harderian gland	(1)	(2)	(1)	(1)
Infiltration cellular, lymphocyte, multifocal	1 (100%)			
Urinary System				
Kidney	(69)	(7)	(67)	(67)
Congestion, multifocal	1 (1%)			
Fibrosis, focal			1 (1%)	
Hemorrhage, multifocal			1 (1%)	
Infarct, focal	1 (1%)		1 (1%)	
Infiltration cellular, lymphocyte, focal	2 (3%)		7 (10%)	1 (1%)
Infiltration cellular, lymphocyte, multifocal	45 (65%)	1 (14%)	40 (60%)	42 (63%)
Inflammation, acute, focal		1 (14%)		
Metaplasia, osseous, focal	1 (1%)			
Nephropathy	3 (4%)	1 (14%)	4 (6%)	4 (6%)
Capsule, inflammation, chronic, multifocal	1 (1%)			
Glomerulus, amyloid deposition, multifocal				1 (1%)
Renal tubule, hyperplasia, focal				1 (1%)
Renal tubule, mineralization, multifocal		1 (14%)		
Urinary bladder	(67)	(1)	(62)	(63)
Dilatation			1 (2%)	1 (2%)
Infiltration cellular, lymphocyte, focal	4 (6%)		6 (10%)	5 (8%)
Infiltration cellular, lymphocyte, multifocal	47 (70%)		42 (68%)	37 (59%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Animals from the hematology group that were sacrificed or died prior to becoming part of the 2-year studies; these animals were not examined microscopically.

APPENDIX C
GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported in Haworth *et al.* (1983) and Mortelmans *et al.* (1986). Naphthalene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of naphthalene. High dose was limited by toxicity. All assays were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987) and presented briefly below. Naphthalene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs) both in the presence and in the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of test chemical; the high dose was limited by toxicity.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing the test chemical was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 to 3 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no test chemical and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining was the same as for cells treated without S9.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 to 10 hours; Colcemid was added and incubation continued for 2 to 3 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8 to 10 hours in fresh medium, with Colcemid present for the final 2 to 3 hours. Cells were harvested in the same manner as for the treatment without S9.

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

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. For the SCE test, usually 25 or 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 200 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P \leq 0.05$) difference for one dose point was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

RESULTS

Naphthalene (0.3-100.0 μg/plate) was negative for the induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 when tested in a preincubation protocol in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Mortelmans *et al.*, 1986) (Table C1). In cytogenetic tests with Chinese hamster ovary cells, naphthalene induced both sister chromatid exchanges and chromosomal aberrations. Sister chromatid exchanges were induced, generally within a dose range of 27 to 90 μg/mL naphthalene, both in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table C2). The positive responses in the chromosomal aberration test were obtained only in the presence of S9, over a dose range of 30 to 67.5 μg/mL naphthalene (Table C3); a delayed harvest protocol was employed to offset naphthalene-induced cell cycle delay and allow accumulation of sufficient metaphases for scoring.

TABLE C1
Mutagenicity of Naphthalene in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	143 ± 4.5	141 ± 4.2	143 ± 11.9	128 ± 6.2	144 ± 2.4	137 ± 8.2
	0.3		121 ± 3.5				
	1	146 ± 5.8	124 ± 3.6	143 ± 13.2	115 ± 7.9	130 ± 2.7	143 ± 16.0
	3.3	124 ± 12.0	117 ± 8.5	155 ± 4.9	135 ± 2.4	133 ± 13.2	133 ± 5.9
	10	145 ± 5.8	113 ± 6.2	140 ± 3.5	118 ± 9.8	135 ± 8.7	121 ± 6.6
	33	141 ± 9.4[c]	113 ± 5.1	147 ± 5.7	133 ± 6.8	142 ± 6.6	121 ± 7.3
	100	Toxic		141 ± 2.0[c]	145 ± 9.0[c]	104 ± 0.6[c]	127 ± 5.4[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,636 ± 45.5	801 ± 28.7	2,534 ± 77.9	754 ± 19.2	1,074 ± 13.2	792 ± 26.4
TA1535	0	22 ± 1.5	19 ± 2.6	11 ± 2.3	8 ± 0.6	9 ± 0.6	12 ± 2.4
	0.3		24 ± 3.1				
	1	21 ± 3.0	26 ± 2.7	10 ± 3.3	11 ± 2.9	13 ± 1.2	16 ± 1.5
	3.3	22 ± 5.2	23 ± 2.3	10 ± 0.9	11 ± 3.8	9 ± 0.7	10 ± 1.7
	10	30 ± 2.6	20 ± 1.2	12 ± 0.6	11 ± 0.3	8 ± 0.7	10 ± 2.6
	33	20 ± 1.2[c]	15 ± 2.3	13 ± 1.0	11 ± 1.7	11 ± 1.5	13 ± 1.2
	100	15 ± 3.5[c]		6 ± 1.9[c]	10 ± 3.2[c]	13 ± 3.4[c]	11 ± 2.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,258 ± 18.8	687 ± 6.4	126 ± 1.7	75 ± 8.9	63 ± 8.0	48 ± 1.9
TA1537	0	8 ± 1.8	8 ± 1.9	10 ± 1.2	6 ± 2.4	11 ± 3.8	10 ± 2.3
	0.3		7 ± 1.2				
	1	8 ± 0.6	5 ± 0.6	11 ± 1.2	8 ± 0.3	10 ± 0.9	8 ± 0.7
	3.3	7 ± 1.5	9 ± 0.6	9 ± 3.2	7 ± 0.9	9 ± 0.9	9 ± 0.9
	10	8 ± 0.7	9 ± 1.5	12 ± 2.0	10 ± 1.5	8 ± 1.7	5 ± 2.2
	33	6 ± 2.0[c]	4 ± 0.9	12 ± 1.5	10 ± 1.5	10 ± 1.9	7 ± 1.5
	100	Toxic		10 ± 1.0[c]	5 ± 0.6[c]	5 ± 1.9[c]	4 ± 0.6[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,010 ± 39.4	185 ± 12.0	205 ± 22.1	77 ± 5.3	87 ± 5.2	86 ± 2.9
TA98	0	14 ± 3.8	17 ± 1.0	35 ± 4.8	20 ± 3.1	29 ± 4.1	23 ± 0.3
	0.3		12 ± 2.2				
	1	15 ± 2.2	17 ± 1.5	30 ± 2.6	29 ± 2.1	27 ± 1.8	23 ± 2.2
	3.3	22 ± 2.3	12 ± 2.6	42 ± 5.5	21 ± 1.9	32 ± 1.7	24 ± 0.7
	10	16 ± 3.3	12 ± 2.6	32 ± 4.2	26 ± 1.2	25 ± 2.6	21 ± 0.9
	33	19 ± 2.5[c]	12 ± 3.2	32 ± 3.1	21 ± 1.2	29 ± 1.9	24 ± 2.8
	100	14 ± 0.3[c]		34 ± 1.5[c]	23 ± 2.4	22 ± 1.2[c]	24 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,772 ± 9.6	1,072 ± 40.3	2,064 ± 71.4	183 ± 10.1	982 ± 43.1	176 ± 16.6

[a] Study performed at EG&G Mason Research Institute. The detailed protocol and these data are presented in Mortelmans *et al.* (1986). Cells and study compound or solvent (acetone) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by toxicity; 0 μg/plate dose is the solvent control.

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

[c] Slight toxicity

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

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Naphthalene[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
-S9								
Trial 1								
Summary: Weak Positive								
Dimethylsulfoxide		50	1,046	388	0.37	7.8	25.8	
Mitomycin-C	0.0010	50	1,049	597	0.56	11.9	25.8	53.43
	0.0100	5	105	217	2.06	43.4	25.8	457.16
Naphthalene	9	50	1,048	406	0.38	8.1	25.8	4.44
	27	50	1,041	442	0.42	8.8	25.8	14.47
	90	50	1,042	578	0.558	11.6	30.9[c]	49.54*
								P≤0.001[d]
Trial 2								
Summary: Positive								
Dimethylsulfoxide		25	525	178	0.33	7.1	25.8	
Mitomycin-C	0.0010	25	525	376	0.71	15.0	25.8	111.24
	0.0100	5	105	263	2.50	52.6	25.8	638.78
Naphthalene	27	25	525	222	0.42	8.9	25.8	24.72*
	45	25	525	268	0.51	10.7	25.8	50.56*
	90	25	525	268	0.51	10.7	25.8	50.56*
								P≤0.001
+S9								
Trial 1								
Summary: Questionable								
Dimethylsulfoxide		50	1,050	423	0.40	8.5	25.8	
Cyclophosphamide	0.4	50	1,050	792	0.75	15.8	25.8	87.24
	2	5	105	197	1.87	39.4	25.8	365.73
Naphthalene	2.7	50	1,050	411	0.39	8.2	25.8	-2.84
	9	50	1,050	493	0.46	9.9	25.8	16.55
	27	50	1,045	505	0.48	10.1	30.9[c]	19.96
								P≤0.001

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Naphthalene (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)
+S9								
Trial 2								
Summary: Positive								
Dimethylsulfoxide		25	525	189	0.36	7.6	25.8	
Cyclophosphamide	0.4	25	525	334	0.63	13.4	25.8	76.72
	2	5	105	174	1.65	34.8	25.8	360.32
Naphthalene	9	25	525	199	0.37	8.0	25.8	5.29
	15	25	525	239	0.45	9.6	25.8	26.45*
	27	25	525	266	0.50	10.6	25.8	40.74*
								P≤0.001

* Positive (≥20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1985, 1987).
[b] Percent increase in SCEs/chromosome of culture exposed to study chemical relative to those of culture exposed to solvent.
[c] Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Naphthalene[a]

-S9[b]					+S9[c]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 – Harvest time: 20.5 hours[d] Summary: Negative					**Trial 1** – Harvest time: 20.5 hours[d] Summary: Positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	1	0.01	0.5		200	3	0.02	1.5
Mitomycin-C					Cyclophosphamide				
0.05	200	31	0.16	11.0	6.25	200	31	0.16	13.5
0.08	25	25	1.00	48.0	12.50	25	17	0.68	44.0
Naphthalene					Naphthalene				
37.5	200	2	0.01	1.0	30	200	29	0.15	11.0*
75	200	3	0.02	1.5	45	100	27	0.27	20.0*
					67.5	100	50	0.50	32.0*
				P=0.157[e]					P≤0.001
Trial 2 – Harvest time: 10.1 hours Summary: Negative					**Trial 2** – Harvest time: 20.2 hours[d] Summary: Positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	1	0.01	0.5		200	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.25	200	19	0.10	8.5	6.25	200	23	0.12	11.5
0.75	25	6	0.24	24.0	12.50	25	19	0.76	52.0
Naphthalene					Naphthalene				
15	200	2	0.01	0.5	45	200	29	0.15	8.5*
37.5	200	0	0.00	0.0	56.25	200	39	0.20	13.5*
					67.5	200	37	0.19	16.0*
				P=0.807					P≤0.001

* Positive (P≤0.05)

[a] Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethylsulfoxide) as described in [b] and [c]. Cells were arrested in first metaphase by addition of Colcemid and harvested by mitotic shake off, fixed, and stained in 6% Giemsa.

[b] In the absence of S9, cells were incubated with naphthalene or solvent for 8 to 10 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 to 3 hours followed by harvest.

[c] In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8 to 10 hours. Colcemid was added for the last 2 to 3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[d] Delayed harvest

[e] Significance of the percentage of cells with aberrations tested by the linear regression trend test vs. log of the dose

APPENDIX D
HEMATOLOGY RESULTS

TABLE D1
Hematology Data at the 14-Day Interim Evaluation in the 2-Year Inhalation Studies of Naphthalene

Analysis	0 ppm	10 ppm	30 ppm
Male			
n	5	4	10
Hematocrit (%)	38.2 ± 0.4	40.1 ± 0.9	39.8 ± 0.6
Hemoglobin (g/dL)	16.8 ± 0.3	17.2 ± 0.2	17.1 ± 0.2
Erythrocytes ($10^6/\mu L$)	7.04 ± 0.15	7.48 ± 0.12	7.49 ± 0.09
Mean cell volume (μ^3)	55.0 ± 0.8	54.5 ± 1.2	53.7 ± 0.3
Reticulocytes ($10^6/\mu L$)	0.17 ± 0.02	0.18 ± 0.02	0.20 ± 0.02
Leukocytes ($10^3/\mu L$)	6.69 ± 0.73	10.65 ± 1.43	5.35 ± 0.28
Female			
n	4	5	10
Hematocrit (%)	39.2 ± 0.4	38.2 ± 0.4	37.6 ± 0.4*
Hemoglobin (g/dL)	17.2 ± 0.2	16.6 ± 0.3	17.6 ± 0.1
Erythrocytes ($10^6/\mu L$)	7.35 ± 0.08	7.22 ± 0.06	7.21 ± 0.05
Mean cell volume (μ^3)	54.0 ± 0.4	53.4 ± 0.2	52.6 ± 0.3*
Reticulocytes ($10^6/\mu L$)	0.20 ± 0.01	0.16 ± 0.01	0.17 ± 0.02
Leukocytes ($10^3/\mu L$)	2.79 ± 0.25	5.18 ± 0.52*	6.93 ± 0.61**

* Statistically significant ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$

APPENDIX E
CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF NAPHTHALENE

Naphthalene (scintillation grade) was obtained from Fisher Scientific Company (Fair Lawn, NJ) in two lots (lot numbers 775379 and 735773). Identity, purity, and stability analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO). MRI reports on the analyses performed in support of the naphthalene studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a white, crystalline solid, was identified as naphthalene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The spectra were consistent with those expected for the structure and with the literature spectra of naphthalene (Figures E1 and E2) (Sadtler Standard Spectra).

The purity of lot number 775379 was found to be greater than 99% by elemental analysis, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed on silica gel plates with two solvent systems: hexanes (100%), and pentane:carbon tetrachloride (50:50). Visualization was accomplished at 254 nm and with iodine vapor. Gas chromatography was performed with flame ionization detection using two columns, 3% SP2100 on 100/120 Supelcoport and 10% Carbowax 20M-TPA on 80/100 Chromasorb W (AW), with nitrogen as the carrier gas at 70 mL/min.

Results of elemental analysis for carbon and hydrogen showed a slightly low level of carbon and a slightly high level of hydrogen. Karl Fischer water analysis indicated the presence of 0.23% water. No impurities were detected by thin-layer chromatography. Gas chromatography showed one impurity with an area of 0.1% relative to the area of the major peak using the first solvent system. The second solvent system detected two impurities that had a combined area of 0.15% relative to that of the major peak.

Heat stability studies performed with gas chromatography (column, 3% SP2100 on 100/120 Supelcoport, nitrogen carrier at 70 mL/min) found that the bulk chemical was stable for 2 weeks at temperatures up to 60° C.

GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

Vapor Generation System: In each of three Hinners-type inhalation chambers, naphthalene vapor was generated by direct sublimation from a 500 mL flask and was delivered through metering valves using nitrogen (Table E1).

Vapor Concentration Monitoring: Naphthalene chamber concentrations were determined with a Miran Model 80 infrared analyzer at a wavelength of 12.8 μm and computer-adjusted to the desired concentration by a software feedback arrangement. Individual monitors were used for each of the exposure chambers. Calibration was performed daily using 1.0 mL injections of freshly prepared naphthalene standard into a closed loop system. Air from each chamber was sampled every 40 seconds and averaged over 5-minute intervals. A summary of the exposure concentrations for the 2-year studies is presented in Table E1 and weekly mean exposure concentrations are presented in Figures E3, E4, and E5.

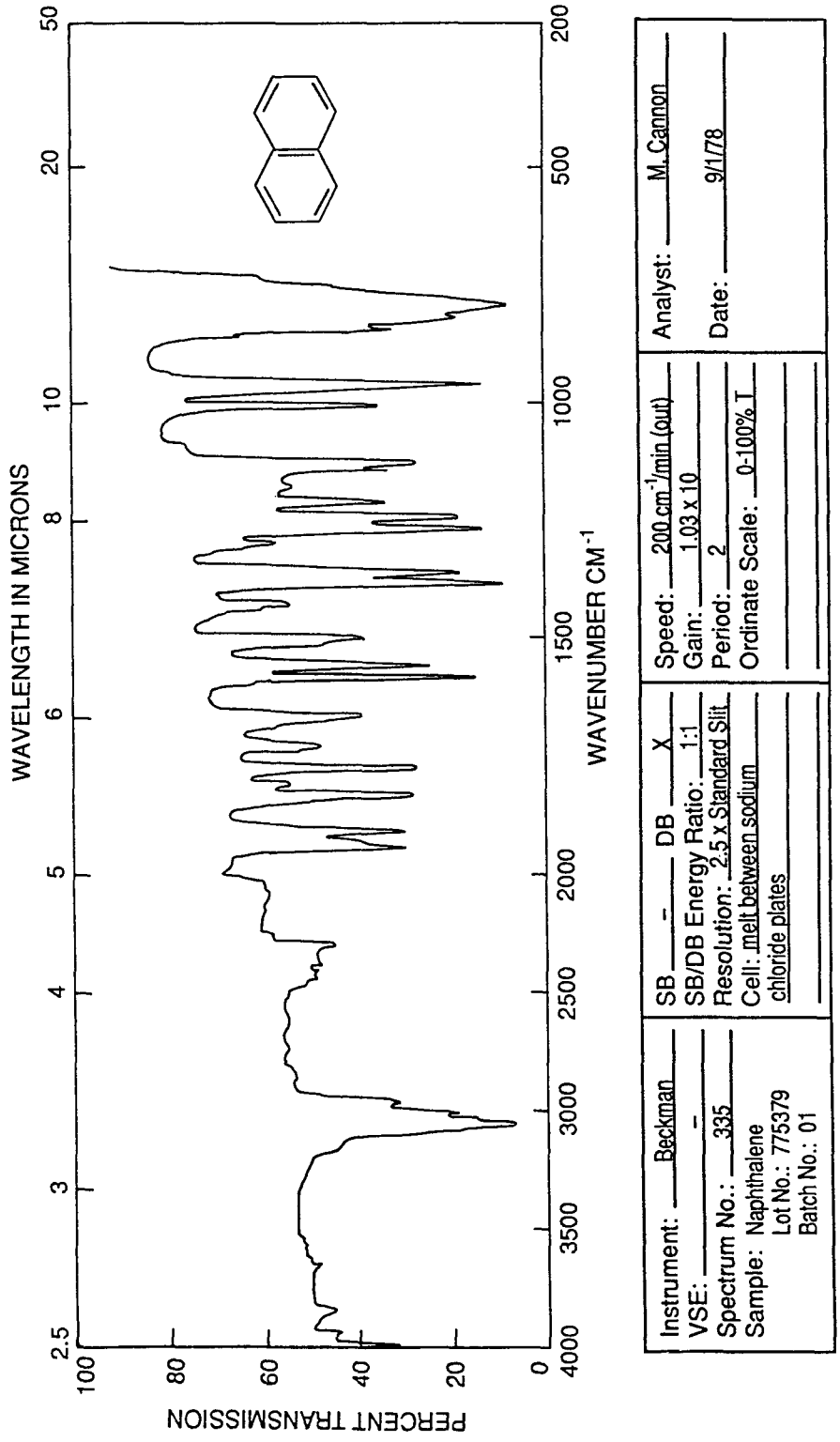


FIGURE E1
Infrared Absorption Spectrum of Naphthalene

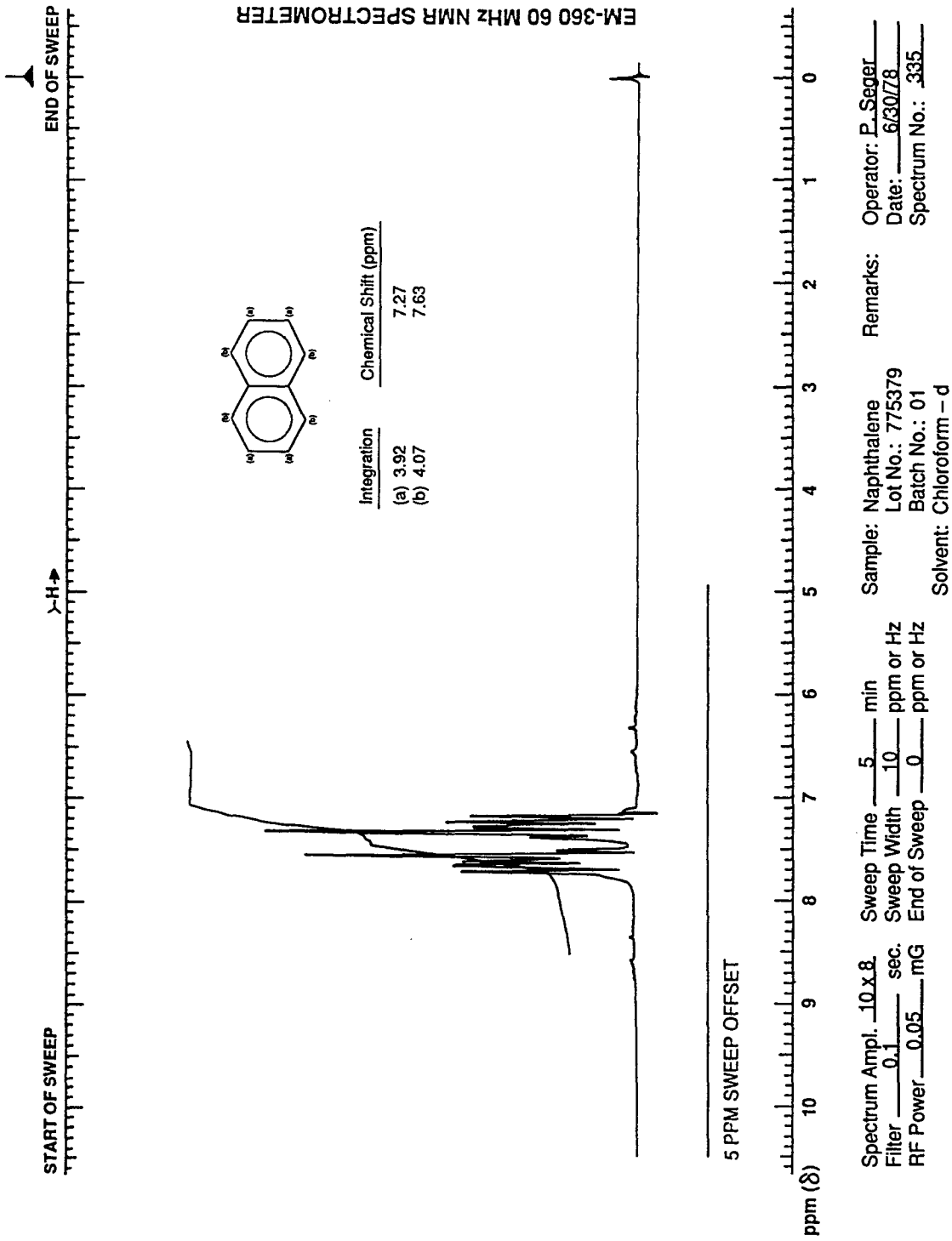


FIGURE E2
Nuclear Magnetic Resonance Spectrum of Naphthalene

TABLE E1
Analysis of Weekly Chamber Concentrations for Mice in the 2-Year Inhalation Studies of Naphthalene

Range	Number of Weeks Exposures Within Specified Concentration		
	10 ppm	30 ppm (Chamber #3)	30 ppm (Chamber #4)
>110%	2	0	0
90%-110%	95	100	99
<90%	7	4	5
Highest reading	11.2	31.0	30.6
Lowest reading	5.5[a]	25.2	24.4[b]

[a] Second lowest: 8.5 ppm
[b] Second lowest: 26.3 ppm

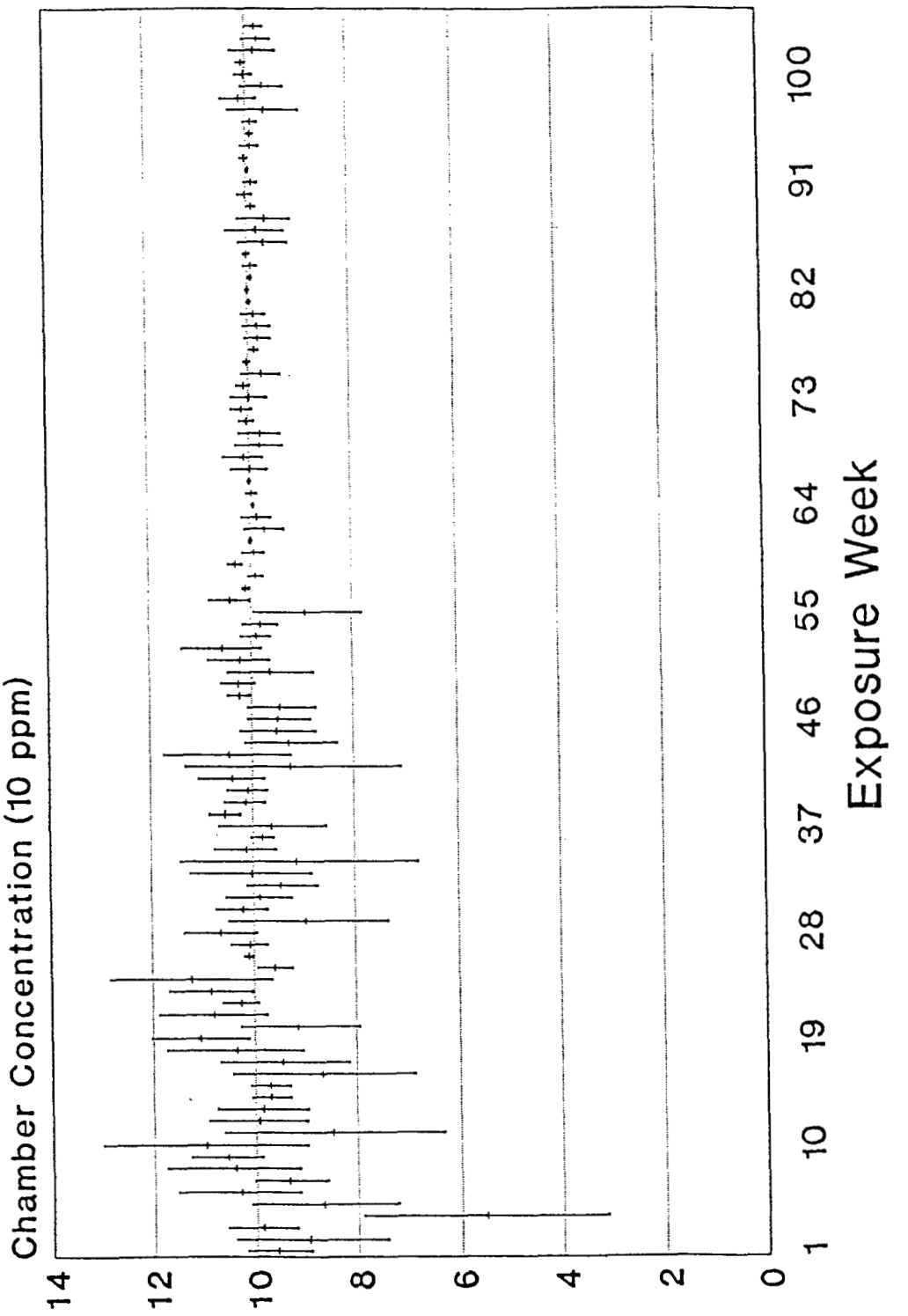


FIGURE E3
Weekly Mean Concentration and Standard Deviation in the 10 ppm Naphthalene Mice Exposure Chamber for the 2-Year Studies

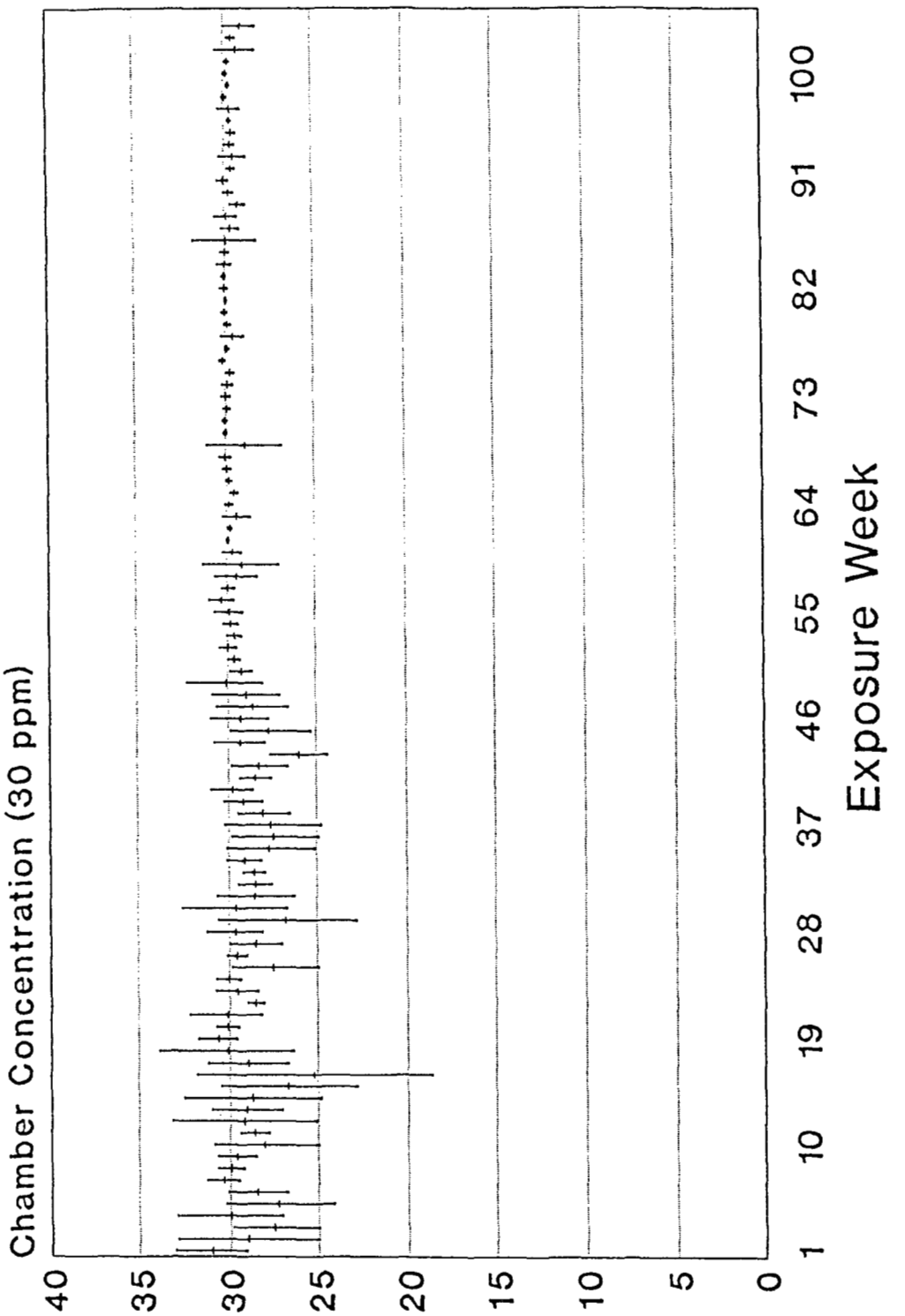


FIGURE E4
Weekly Mean Concentration and Standard Deviation in the 30 ppm Naphthalene Mice Exposure Chamber (Study Chamber 3) for the 2-Year Studies

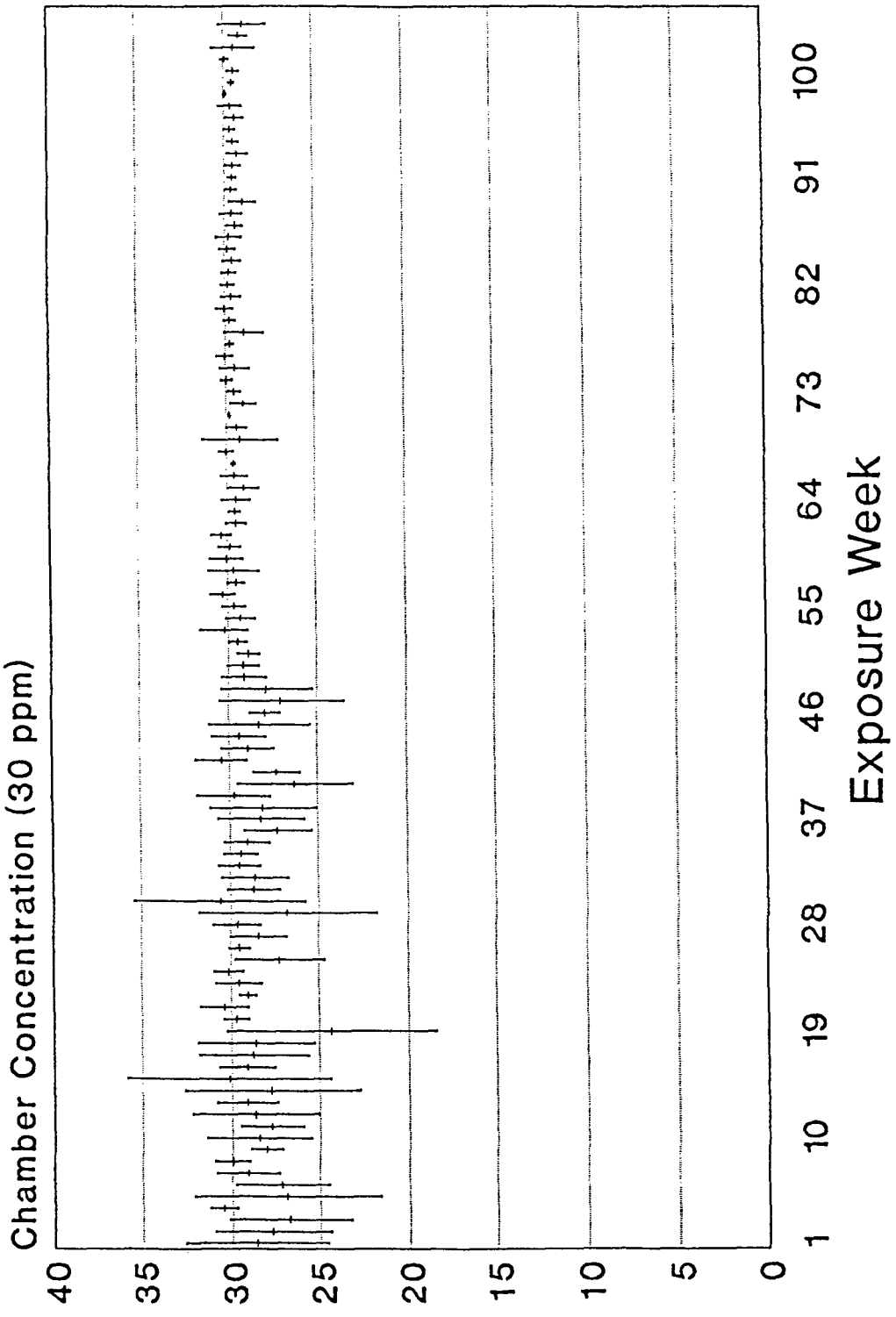


FIGURE E5
Weekly Mean Concentration and Standard Deviation in the 30 ppm Naphthalene Mice Exposure Chamber (Study Chamber 4) for the 2-Year Studies

APPENDIX F
INGREDIENTS AND VITAMINS AND MINERALS IN NIH-31 RAT AND MOUSE RATION

TABLE F1
Ingredients of NIH-31 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	21.0
Ground whole wheat	35.5
Soybean meal (49% protein)	5.00
Fish meal (60% protein)	9.00
Wheat middlings	10.00
Alfalfa meal (dehydrated, 17% protein)	2.0
Corn gluten meal (60% protein)	2.0
Soy oil	1.5
Dried brewer's yeast	1.00
Dicalcium phosphate	1.5
Ground limestone	0.5
Salt	0.5
Premixes (vitamin and mineral)	0.5

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

TABLE F2
Vitamins and Minerals in NIH-31 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	20,000,000 IU	Stabilized vitamin A palmitate or acetate
D_3	3,800,000 IU	D-activated animal sterol
K_3	2.0 g	Menadione
d-α-Tocopheryl acetate	15,000 IU	
Choline	700 g	Choline chloride
Folic acid	1.0 g	
Niacin	20.0 g	
d-Pantothenic acid	25.0 g	*d*-Calcium pantothenate
Riboflavin	5.0 g	
Thiamine	65.0 g	Thiamine mononitrate
B_{12}	14,000 μg	
Pyridoxine	2.0 g	Pyridoxine hydrochloride
Biotin	120.0 mg	*d*-Biotin
Minerals		
Iron	60.0 g	Iron sulfate
Manganese	100.0 g	Manganous oxide
Zinc	10.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.5 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate
Magnesium	400 g	

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

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF MARCH 1992

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

☆ U.S. GOVERNMENT PRINTING OFFICE: 1992 312-103/60009

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF MARCH 1992

TR No.	CHEMICAL
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
399	Titanocene Dichloride
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
415	Polysorbate 80

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 Public Health Service, National Toxicology Program, Central Data Management, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD A0-01
Research Triangle Park, NC 27709

Official Business
Penalty for Private Use - $300

NIH Publication No. 92-3141
April 1992

Appendix B: NTP (2000). Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in F344/N Rats (Inhalation Studies). TR 500. PP B-1 – B-177.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF NAPHTHALENE

(CAS NO. 91-20-3)

IN F344/N RATS

(INHALATION STUDIES)

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

December 2000

NTP TR 500

NIH Publication No. 01-4434

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all the NTP reports printed since 1982 appears on the inside back cover.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF NAPHTHALENE

(CAS NO. 91-20-3)

IN F344/N RATS

(INHALATION STUDIES)

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

December 2000

NTP TR 500

NIH Publication No. 01-4434

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

CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

K.M. Abdo, Ph.D., Study Scientist
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
R.E. Chapin, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
R.A. Herbert, D.V.M., Ph.D.
R.R. Maronpot, D.V.M.
R.L. Melnick, Ph.D.
D.P. Orzech, M.S.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
B.A.T. Willems, Ph.D.
K.L. Witt, M.S., Integrated Laboratory Systems, Inc.

Battelle Toxicology Northwest
Conducted studies and evaluated pathology findings

B.J. Chou, D.V.M., Ph.D., Principal Investigator
S.L. Grumbein, D.V.M., Ph.D.
R.J. Weigle, Ph.D.
R.B. Westerberg, Ph.D.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
C.C. Shackelford, D.V.M., M.S., Ph.D.

Dynamac Corporation
Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides and prepared pathology report on rats (7 October 1999)

P.K. Hildebrandt, D.V.M., Chairperson
PATHCO, Inc.
S.L. Grumbein, D.V.M., Ph.D.
Battelle Toxicology Northwest
B.F. Hamilton, D.V.M., Ph.D.
Glaxo Wellcome, Inc.
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J. Mahler, D.V.M.
National Toxicology Program
A. Nyska, D.V.M.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.
R.C. Sills, D.V.M., Ph.D.
National Toxicology Program
H. Wall, D.V.M., Ph.D.
Glaxo Wellcome, Inc.

Analytical Sciences, Inc.
Provided statistical analyses

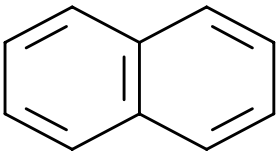
R.W. Morris, M.S., Principal Investigator
L.J. Betz, M.S.
K.P. McGowan, M.B.A.
J.T. Scott, M.S.

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
L.M. Harper, B.S.
D.C. Serbus, Ph.D.
W.D. Sharp, B.A., B.S.
R.A. Willis, B.A., B.S.

CONTENTS

ABSTRACT



NAPHTHALENE

CAS No. 91-20-3

Chemical Formula: $C_{10}H_8$ Molecular Weight: 128.18

Synonyms: Mothballs; moth flakes; naphthalin; naphthaline; naphthene; tar camphor; white tar
Trade names: Albocarbon, Dezodorator, Mighty 150, Mighty RD1

Naphthalene is used as an intermediate in the synthesis of phthalic and anthranilic acids, naphthols, naphthylamines, sulfonic acid, synthetic resins, celluloid, and hydronaphthalenes; it is also used in the preparation of anthraquinone, indigo, salicylic acid, and 1-naphthyl-N-methylcarbamate insecticide. It is an ingredient in some moth repellants and toilet bowl deodorants; it is also used in veterinary medicine in antiseptics for irrigating animal wounds and as an external medication to control lice on livestock and poultry. Naphthalene was selected for study by the National Toxicology Program because previous inhalation studies with naphthalene in mice were positive and existing studies in rats were either considered inadequate or were conducted via routes other than inhalation. Male and female F344/N rats were exposed to naphthalene (greater than 99% pure) by inhalation for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

2-YEAR STUDY

Groups of 49 male and 49 female rats were exposed to naphthalene by inhalation at concentrations of 0, 10, 30, or 60 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 105 weeks. Additional groups of nine male and nine female rats were exposed to 10, 30, or 60 ppm for up to 18 months for evaluation of toxicokinetic parameters.

Survival, Body Weights, and Gross Observations

The survival of all exposed groups of male and female rats was similar to that of the chamber controls. Mean body weights of all exposed groups of males were less than those of the chamber control group throughout most of the study. Masses were observed in the nose of male and female rats. These masses frequently partially occluded the nasal passages or obliterated the normal architecture of the nasal turbinates.

Pathology Findings

The incidences of neuroblastoma of the olfactory epithelium, a rare neoplasm, occurred with positive trends in males and females. Because this neoplasm did not occur in chamber control rats or in male rats exposed to 10 ppm and because this neoplasm has not been seen in the historical chamber control rats in NTP 2-year inhalation studies, the increased incidences of neuroblastoma were considered to be related to naphthalene exposure. In males, the incidences of adenoma of the respiratory epithelium of the nose, another rare neoplasm, occurred with a positive trend and were significantly increased in all exposed groups; none occurred in the chamber controls. In females,

these neoplasms occurred in the 30 and 60 ppm groups but not in the chamber control or 10 ppm groups. Because these neoplasms did not occur in the chamber controls and have not been observed in the historical chamber control rats in NTP 2-year inhalation studies, the incidences of nasal adenoma were considered to be related to naphthalene exposure.

Increased incidences of nonneoplastic lesions of the nose associated with exposure to naphthalene included atypical hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia.

Toxicokinetic Results Model

A physiologically based toxicokinetic model was developed to characterize the disposition of inhaled naphthalene in rats. Because of its low vapor pressure and high blood-to-air partition coefficient, essentially all of the naphthalene that is absorbed into the general circulation is metabolized. At the exposure concentrations used in the 2-year study, approximately 20% to 30% of the inhaled dose was metabolized by male and female rats. Naphthalene that was not absorbed during exposure was assumed to be exhaled. The respective estimated daily doses metabolized by rats exposed to 10, 30, or 60 ppm for 6 hours (i.e., the internalized doses) are 3.6, 10.7, and 20.1 mg naphthalene/kg body weight for males and 3.9, 11.4, and 20.6 mg/kg for females.

GENETIC TOXICOLOGY

Naphthalene was not mutagenic in any of four strains of *Salmonella typhimurium* with or without induced liver S9 enzymes. However, in cytogenetic tests with cultured Chinese hamster ovary cells, naphthalene induced significant increases in sister chromatid exchanges with and without metabolic activation (S9) and in chromosomal aberrations with S9. Naphthalene did not induce chromosomal aberrations in the absence of S9 activation.

CONCLUSIONS

Under the conditions of this 2-year inhalation study, there was *clear evidence of carcinogenic activity** of naphthalene in male and female F344/N rats based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose.

In male and female rats, exposure to naphthalene caused significant increases in the incidences of nonneoplastic lesions of the nose.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 10.

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

	Male F344/N Rats	Female F344/N Rats
Concentrations in air	Chamber control, 10, 30, or 60 ppm	Chamber control, 10, 30, or 60 ppm
Body weights	Exposed groups less than the chamber control group	Exposed groups similar to the chamber control group
Survival rates	24/49, 22/49, 23/48, 21/49	28/49, 21/49, 28/49, 24/49
Nonneoplastic effects	Nose: olfactory epithelium, hyperplasia, atypical (0/49, 48/49, 45/48, 46/48); olfactory epithelium, atrophy (3/49, 49/49, 48/48, 47/48); olfactory epithelium, inflammation, chronic (0/49, 49/49, 48/48, 48/48); olfactory epithelium, degeneration, hyaline (3/49, 46/49, 40/48, 38/48); respiratory epithelium, hyperplasia (3/49, 21/49, 29/48, 29/48); respiratory epithelium, metaplasia, squamous (0/49, 15/49, 23/48, 18/48); respiratory epithelium, degeneration, hyaline (0/49, 20/49, 19/48, 19/48); respiratory epithelium, hyperplasia, goblet cell (0/49, 25/49, 29/48, 26/48); glands, hyperplasia (1/49, 49/49, 48/48, 48/48); glands, metaplasia, squamous (0/49, 3/49, 14/48, 26/48)	Nose: olfactory epithelium, hyperplasia, atypical (0/49, 48/49, 48/49, 43/49); olfactory epithelium, atrophy (0/49, 49/49, 49/49, 47/49); olfactory epithelium, inflammation, chronic (0/49, 47/49, 47/49, 45/49); olfactory epithelium, degeneration, hyaline (13/49, 46/49, 49/49, 45/49); respiratory epithelium, hyperplasia (0/49, 18/49, 22/49, 23/49); respiratory epithelium, metaplasia, squamous (0/49, 21/49, 17/49, 15/49); respiratory epithelium, degeneration, hyaline (8/49, 33/49, 34/49, 28/49); respiratory epithelium, hyperplasia, goblet cell (0/49, 16/49, 29/49, 20/49); glands, hyperplasia (0/49, 48/49, 48/49, 42/49); glands, metaplasia, squamous (0/49, 2/49, 20/49, 20/49)
Neoplastic effects	Nose: respiratory epithelium, adenoma (0/49, 6/49, 8/48, 15/48); olfactory epithelium, neuroblastoma (0/49, 0/49, 4/48, 3/48)	Nose: respiratory epithelium, adenoma (0/49, 0/49, 4/49, 2/49); olfactory epithelium, neuroblastoma (0/49, 2/49, 3/49, 12/49)
Level of evidence of carcinogenic activity	Clear evidence	Clear evidence
Genetic toxicology		
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9	
Sister chromatid exchanges		
Cultured Chinese hamster ovary cells *in vitro*:	Positive with and without S9	
Chromosomal aberrations		
Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9, negative without S9	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on naphthalene on 18 May 2000 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

A. John Bailer, Ph.D., Chairperson
Department of Mathematics and Statistics
Miami University
Oxford, OH

James S. Bus, Ph.D.
Health and Environmental Sciences
Dow Chemical Company
Midland, MI

Linda A. Chatman, D.V.M.
Pfizer, Inc.
Groton, CT

John M. Cullen, Ph.D., V.M.D., Principal Reviewer
Department of Microbiology, Parasitology, and Pathology
College of Veterinary Medicine
North Carolina State University
Raleigh, NC

Harold Davis, Ph.D.*
Director of Toxicology
Amgen, Inc.
Thousand Oaks, CA

Norman R. Drinkwater, Ph.D.
McArdle Laboratory for Cancer Research
University of Wisconsin-Madison
Madison, WI

Susan M. Fischer, Ph.D.*
M.D. Anderson Cancer Center
The University of Texas
Smithville, TX

Stephen S. Hecht, Ph.D., Principal Reviewer
University of Minnesota Cancer Centers
Minneapolis, MN

Michele Medinsky, Ph.D., Principal Reviewer
Durham, NC

Jose Russo, M.D.*
Fox Chase Cancer Center
Philadelphia, PA

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 18 May 2000, the draft Technical Report on the toxicology and carcinogenesis studies of naphthalene received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of naphthalene by discussing the uses of the chemical and rationale for the study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplasms and nonneoplastic lesions in male and female rats. Dr. Abdo reviewed the 1992 NTP report of a 2-year inhalation study in B6C3F_1 mice which found that naphthalene was carcinogenic in female mice resulting in an increased incidence of alveolar/bronchiolar adenomas. He noted that the Centers for Disease Control and Prevention analyzed urine samples from nearly 1,000 adults for the metabolites of naphthalene, 1-naphthol, and 2-naphthol, and found metabolites in over 80% of the samples, suggesting widespread human exposure. The proposed conclusions for the present 2-year study were *clear evidence of carcinogenic activity* in male and female F344/N rats.

Dr. R.L. Melnick, NIEHS, presented information on toxicokinetic modeling efforts aimed at estimating amounts of naphthalene inhaled by rats and mice at exposure concentrations used in the 2-year studies, amounts metabolized during the 6-hour exposure and 18-hour postexposure periods, steady-state concentrations of naphthalene in the lung and liver during exposure, and rates of metabolism in the lung and liver at steady state. Also, after multiple exposures to naphthalene, rats were examined at 2 weeks or 3, 6, 12, or 18 months to compare kinetic parameters over time with the single exposure. Dr. Melnick reported the results: (1) due to its low vapor pressure and high blood-to-air partition coefficient, most of the absorbed naphthalene (internalized dose) is eliminated via metabolism; (2) the steady state naphthalene concentration in the mouse lung at 30 ppm is slightly greater than in the rat lung at 30 ppm but less than in 60 ppm rats; (3) the rate of naphthalene metabolism is higher in mouse lung than rat lung; and (4) data are insufficient to adequately estimate tissue concentrations of naphthalene oxide, the putative carcinogenic intermediate.

Dr. Cullen, a principal reviewer, agreed with the proposed conclusions. He said that because nasal adenomas are uncommon neoplasms, the discussion needs to address the likelihood of nasal adenomas to progress. Further, given the significant background on nasal inflammation and limited evidence of genetic toxicity, the role of inflammation in genesis of these lesions needs to be considered. Dr. R.A. Herbert, NIEHS, said the discussion on nasal adenomas would be expanded. Dr. J.R. Hailey, NIEHS, reported that he and Dr. J.K. Haseman, NIEHS, had looked at the 10 NTP studies showing nasal carcinogenesis and at the two studies showing the most severe degree of inflammation, and noted that these studies also reported the fewest numbers of neoplasms. Dr. Cullen noted that neuroblastomas are uncommon in humans as well as rats, and said that discussion of biological relevance to human health risk is warranted.

Dr. Medinsky, the second principal reviewer, agreed with the proposed conclusions. Her major criticism was that the pharmacokinetic model for naphthalene disposition in rats didn't include a nasal compartment, although the only carcinogenic effect seen was in the nose. She noted data suggesting that the isozyme that metabolizes naphthalene is present in the nose, and that naphthalene's high partition coefficient suggests nasal deposition. Dr. Melnick responded that NTP would like to include a nasal compartment and one way might be to combine the toxicokinetic model with a fluid dynamic model. The difficulty lies in not having data on naphthalene deposition in nasal mucosa to validate model estimates. Information is limited on fluid dynamic flow in the mouse nasal compartment, which would be needed for species comparison.

Dr. Hecht, the third principal reviewer, agreed with the proposed conclusions.

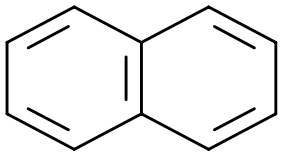
Dr. G. McCarver, Medical College of Wisconsin, asked if there was information on human levels of naphthalene or metabolites and how these would compare with levels in the toxicokinetic studies. Dr. G.W. Lucier, NIEHS, surmised that human levels of naphthalene or metabolites would be two orders of

magnitude lower for average individuals, not necessarily occupationally exposed.

Mr. R. Landis, Landis and Associates, representing the Naphthalene Panel of the Chemical Manufacturers Association, commented that an apparent decrease in thyroid gland neoplasms, the lack of an overall increase in the incidences of neoplasms, and the saturation of lung metabolism with exposure should be addressed in the Results section.

Dr. Cullen moved that the Technical Report on naphthalene be accepted with the revisions discussed and with the conclusions as written. Dr. Drinkwater seconded the motion, which was accepted with six yes votes.

INTRODUCTION



NAPHTHALENE

CAS No. 91-20-3

Chemical Formula: $C_{10}H_8$ Molecular Weight: 128.18

Synonyms: Mothballs; moth flakes; naphthalin; naphthaline; naphthene; tar camphor; white tar
Trade names: Albocarbon, Dezodorator, Mighty 150, Mighty RD1

CHEMICAL AND PHYSICAL PROPERTIES

Naphthalene is a white, crystalline solid with an aromatic odor. It has a boiling point of 218° C at 760 mm Hg, a melting point of 80.2° C, and a specific gravity of 1.162 at 20° C. It sublimes appreciably at temperatures above the freezing point (*Merck Index*, 1989). Naphthalene vapor has a partial pressure of 0.01 mm Hg and a density of 4.42 (*Kirk-Othmer*, 1979, 1981; *Sax's*, 1984). Naphthalene is soluble in alcohol (1 g/13 mL), benzene or toluene (1 g/3.5 mL), olive oil or turpentine (1 g/8 mL), and chloroform or carbon tetrachloride (1 g/2 mL) (*Merck Index*, 1989; Lide, 1992). It has an octanol/water partition coefficient of 3.30 (Hansch *et al.*, 1995).

PRODUCTION, USE, AND HUMAN EXPOSURE

Naphthalene is prepared from coal tar by fractional distillation to produce a crystalline fraction. This fraction is then purified by hot pressing and washing with sulfuric acid, sodium hydroxide, and water, followed by sublimation or a second fractional distillation (*Merck Index*, 1996). United States manufacturers produced 1.09×10^5 metric tons of naphthalene in 1996. United States consumption of naphthalene was 1.08×10^5 metric tons in 1996 and was projected to increase to 1.15×10^5 metric tons in 2001 (*Chemical Economics Handbook*, 2000).

Naphthalene is used as an intermediate in the synthesis of phthalic and anthranilic acids, naphthols, naphthylamines, sulfonic acid, synthetic resins, celluloid, and hydronaphthalenes (*Merck Index*, 1996). It is also used in the preparation of anthraquinone, indigo, salicylic acid, and 1-naphthyl-N-methylcarbamate insecticide (*Kirk-Othmer*, 1978, 1979, 1981). It is an ingredient in some moth repellants and toilet bowl deodorants (Gosselin *et al.*, 1984). Naphthalene is used in antiseptics for irrigating animal wounds and as an external medication to control lice on livestock and poultry (Rossoff, 1974).

Naphthalene is a natural constituent of coal tar and crude oil, which are the major contributors to its presence in the environment. They contain up to 11% and 1.3% of the chemical, respectively (BUA, 1989; *Merck Index*, 1996). Forest fires also contribute to the presence of naphthalene in the environment, as the chemical is a natural combustion product of wood. Naphthalene has been identified in cigarette smoke (USEPA, 1980). Naphthalene may enter the soil and water as a result of spills from factories in which it is used as an intermediate or during the production and transport of products containing naphthalene. The

primary source of human exposure is from the atmosphere, especially in areas of heavy traffic, where fumes from burning gasoline or fuel oil exist, or near petroleum refineries and coal coking operations.

The concentrations of the naphthalene metabolites 1- and 2-naphthol were measured in the urine of human participants in a study conducted by the Centers for Disease Control and Prevention. 1-Naphthol was detected in 86% of 983 urine samples and 2-naphthol in 81% of 977 samples; the average concentrations were 17 µg/L and 7.8 µg/L, respectively. Although 1-naphthol is produced by the cleavage of carbaryl as well as from the oxidation of naphthalene, these results were considered to reflect naphthalene rather than carbaryl exposure due to the similarity of the results between the two metabolites (L. Needham, personal communication).

REGULATORY STATUS

The U.S. Environmental Protection Agency established a reference dose for naphthalene of 0.004 mg/kg per day and a drinking water equivalent concentration of 0.1 mg/L (USEPA, 1990). Several occupational standards were set for naphthalene. The Occupational Safety and Health Administration (OSHA) 8-hour, time-weighted average for exposure to airborne naphthalene is 10 ppm (NIOSH, 1997). Both the National Institute of Occupational Safety and Health (NIOSH, 1997) and the American Conference of Governmental Industrial Hygienists (ACGIH, 1999) recommend threshold limit values of 10 ppm for the 8-hour, time-weighted average and 15 ppm for the 15-minute, short-term exposure limit.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Naphthalene is readily absorbed when inhaled or administered orally or dermally. Naphthalene was not detected in the feces of rats (strain not specified) given 535 or 770 mg in feed or 100 mg by stomach tube, suggesting that naphthalene was readily absorbed (Chang, 1943). Naphthalene was readily absorbed by tissues of laying pullets, swine, and dairy cattle; the respective doses were 0.443, 2.46, or 30.69 mg, administered as a single oral dose, or 0.036, 0.112, or 5.115 mg administered daily for 31 days. The adipose tissue, kidney, liver, and lung of pullets had the highest naphthalene concentrations after a single dose, and the kidney had the highest concentration after 31 days of dosing. In swine, adipose tissue had the highest naphthalene concentration after a single dose, and the lung had the highest concentration after 31 days of dosing. In cattle, the liver had the highest concentrations after both treatments (Eisele, 1985).

Evidence for rapid absorption of naphthalene from the intestines was provided by Bock *et al.* (1979). Thirty minutes after instillation of 100 nmol of ^{14}C-naphthalene into a closed rat intestinal loop, 84% was recovered unmetabolized in the portal blood, and only 1% was found in the luminal contents.

Absorption, metabolism, and excretion of dermally administered naphthalene were demonstrated in Sprague-Dawley rats (Turkall *et al.*, 1994). Each rat received 43 µg ^{14}C-naphthalene through a small opening in a shallow glass cap tightly fixed with Lang's jet acrylic and powder to a shaved area of the skin (13 cm^2) on the right costoabdominal region. The opening was sealed immediately. Forty-eight hours after dosing, 70% of the label was excreted in the urine, 14% in the expired air, and 4% in the feces. Radiolabel (0.01% to 0.02%) was found in the ileum and duodenum; this was considered by the authors to be evidence for biliary excretion of the chemical and its metabolites. Naphthalene metabolites identified in the urine were 2,7- and 1,2-dihydroxynaphthalene, 1,2-naphthoquinone, and 1- and 2-naphthol. Less than 0.5% of the parent compound was excreted in the urine. The plasma half-life was 2.1 hours for the absorption phase and 12 hours for the elimination phase.

As in the case of dermal absorption, naphthalene given intraperitoneally is absorbed, metabolized, and excreted primarily in the urine. Within 48 hours of an intraperitoneal injection of 100 mg/kg ^{14}C-naphthalene in female Sprague-Dawley rats, 23% to 41% of the label was excreted in the urine and 5% to 10% in the bile. Of the label excreted in the urine, 5% to 20% was unconjugated, and 80% to 95% was sulfate, glucuronide, and mercapturic acid conjugates (Chen and Dorough, 1979).

The first step in naphthalene metabolism is the formation of naphthalene 1,2-oxide by oxygen and the

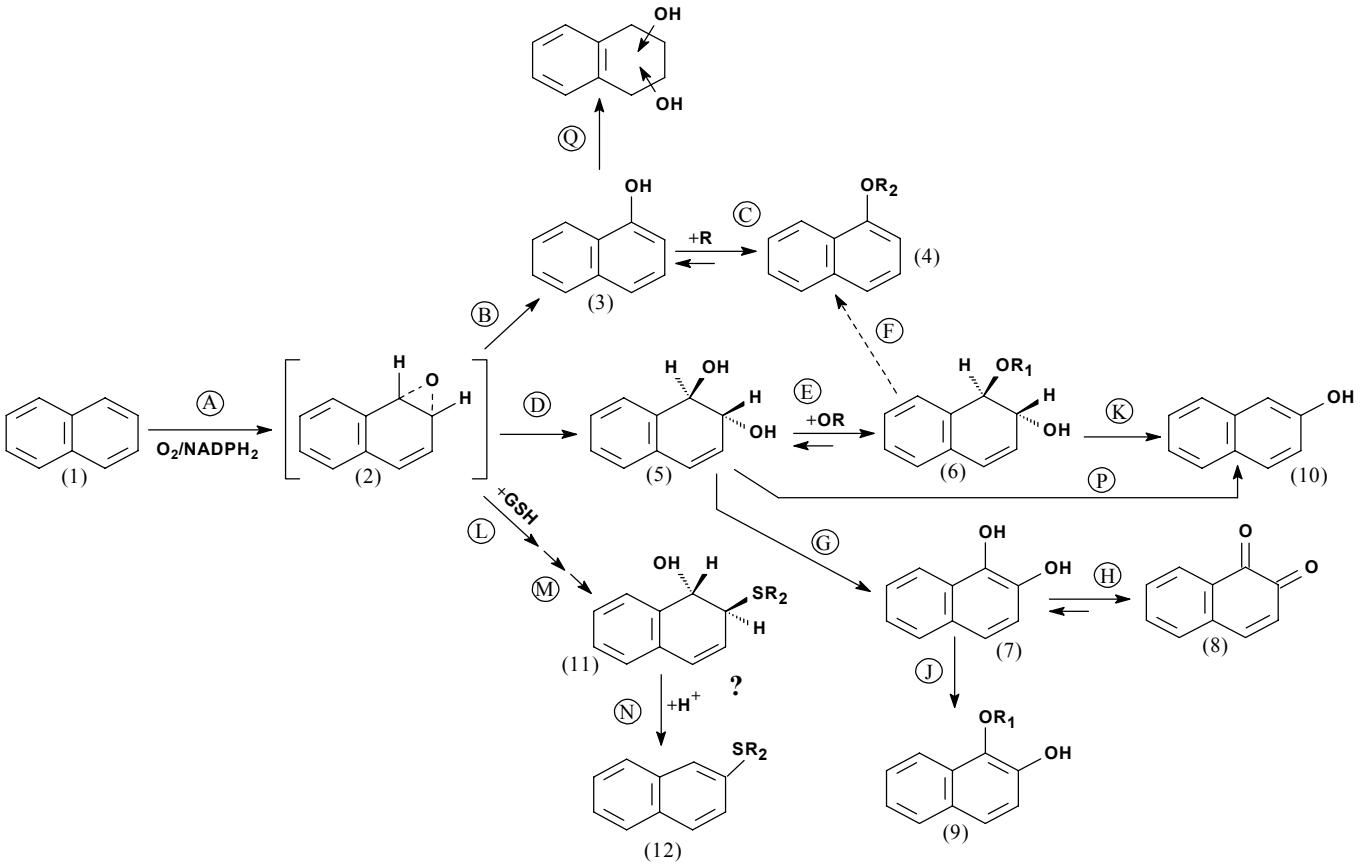
NADPH-dependent microsomal monooxygenase system, followed by the formation of hydroxylated intermediates. These intermediates are then excreted in the urine as glutathione, cysteine, glucuronic acid, and sulfate conjugates (Horning *et al.*, 1980). Approximately 30 naphthalene metabolites were identified in the urine of mammals after oral gavage or intraperitoneal injection (Corner and Young, 1954; Horning *et al.*, 1980). Some of these metabolites are listed in Table 1. The table shows considerable interspecies similarities in the spectra of metabolites formed from naphthalene with some notable exceptions. 1,2-Dihydroxynaphthalene was formed only in guinea pigs, and no glucuronides were detected. Glutathione conjugation of naphthalene metabolites plays an important role in naphthalene's elimination in rodents but not in primates, including humans. Single gavage doses of 30, 75, or 200 mg naphthalene/kg body weight administered to male Wistar rats resulted in a dose-related increase in thioether excretion in the urine. By contrast, this increase was not seen in male or female chimpanzees treated similarly (Summer *et al.*, 1979).

Based on the spectrum of naphthalene metabolites found in mammals, a metabolic pathway for the chemical was suggested by Bock *et al.* (1976) and later modified to the one depicted in Figure 1 (BUA, 1989). An epoxide intermediate (naphthalene 1,2-oxide) was postulated as the initial metabolite, with subsequent conversion to the trans-1,2-diol and other products (Sims and Grover, 1974). Support for this mechanism was first provided by Jerina *et al.* (1970), who demonstrated the formation of 1,2-naphthalene oxide from naphthalene in a microsomal system. Naphthalene was shown to be bioactivated by cytochrome P450 to electrophilic intermediates, which were subsequently metabolized to naphthoquinones and possibly to free radical intermediates (Buckpitt and Warren, 1983; Doherty *et al.*, 1985). Microsomal preparations from liver, lungs, kidneys, and skin were able to transform naphthalene metabolites. Human hepatic microsomal preparations metabolized naphthalene to 1-naphthol and naphthalene 1,2-dihydrodiol (Tingle *et al.*, 1993). Similar preparations from lung tissue metabolized naphthalene to 1,2-naphthalenediol and three different glutathione conjugates (Buckpitt and Richieri, 1984; Buckpitt and Bahnson, 1986), which were later identified as trans-1-(S)-hydroxy-2-(S)-glutathionyl-1,2-dihydronaphthalene; trans-1-(R)-hydroxy-2-(R)-glutathionyl-1,2-dihydronaphthalene, and trans-1-(R)-glutathionyl-2-(R)-hydroxy-1,2-dihydronaphthalene (Buonarati *et al.*, 1990). Pulmonary, hepatic, and renal microsomal preparations from rats, mice, or hamsters converted naphthalene to these conjugates in the presence of glutathione and glutathione transferases (Buckpitt *et al.*, 1987). In a recent *in vitro* study with mouse lung Clara cells treated with naphthalene, Zheng *et al.* (1997) identified 1,2-naphthoquinone to be a major adduct covalently bound to cellular protein.

TABLE 1
Metabolites of Naphthalene Identified in the Urine of Various Species[a]

	Rat	Mouse	Rabbit	Guinea Pig
1-Naphthol	+	+	+	+
1-Naphthyl sulphate	+	+	+	+
1-Naphthyl glucuronide	+	+	+	–
2-Naphthol	+	+	+	+
1,2-Dihydroxynaphthalene	–	–	–	+
1,2-Dihydro-1,2-dihydroxynaphthalene	+	+	+	+
1,2-Dihydro-2-hydroxy-1-naphthyl glucuronide	+	–	+	–
1-Naphthyl mercapturic acid	+	+	+	+

[a] + = metabolite present; – = metabolite not present; from BUA (1989)



(1) Naphthalene
(2) Naphthalene-1,2-oxide
(3) Naphthol
(4) Naphthyl glucuronide or sulphate
(5) Trans-1,2-dihydro-2-hydroxy-naphthalene
(6) Trans-1,2-dihydro-2-hydroxy-naphthyl-1-glucuronide
(7) 1,2-Dihydroxynaphthalene
(8) 1,2-Naphthoquinone
(9) 2-Hydroxynaphthyl-1-sulphate or -glucuronide
(10) 2-Naphthol
(11) N-Acetyl-S-(1,2-dihydro-1-hydroxy-2-naphthyl)-L-cysteine
(12) N-Acetyl-S-(1-naphthyl)-L-cysteine (1-naphthyl mercapturic acid)

GSH = Glutathione
R_1 = Sulphate or glucuronate group
R_2 = N-acetyl-L-cysteine residue

A,Q = O_2- and $NADPH_2$-dependent mono-oxygenase (e.g., cyt-P450-NADP-cytochrome-c-reductase system, microsomal)
B = Spontaneous isomerization
C,E,J = Conjugation reaction with sulphate (sulphotransferase, cystolic) or with glucuronic acid (UDP-glucuronyl-transferase, microsomal)
D = Epoxide hydrolase, synonym: epoxide hydrase (microsomal)
F,N,P = Chemical dehydration
G = Dihydrodiol-dehydrogenase (cystosolic); 3,5-cyclohexadiene-1,2-diol-NADP-oxidoreductase
H = Chemical dehydration
K = Chemical hydrolysis + dehydration
L = Enzymatic reaction with glutathione
M = γ-Glutamyl transferase, peptidase, N-acetylase

FIGURE 1
Essential Metabolic Pathways of Naphthalene and the Resulting Products in Mammals (based on BUA, 1989)

Humans

Absorption of naphthalene is evidenced by the occurrence of toxic symptoms in infants accidentally exposed to vapors from clothes containing naphthalene (Valaes *et al.*, 1963). Transplacental transport of naphthalene and/or its metabolites is evidenced by the occurrence of hemolytic anemia in newborns whose mothers ingested naphthalene during the last 3 months of pregnancy (Zinkham and Childs, 1958; Anziulewicz *et al.*, 1959).

TOXICITY

Experimental Animals

The reported LD_{50} values for rats and mice, respectively, are 1,110 to 9,430 mg/kg and 350 to 710 mg/kg (oral), 2,500 and 969 mg/kg (dermal), and 1,000 and 350 mg/kg (intraperitoneal) (BUA, 1989). These values suggest that mice are more sensitive than rats to the acute effects of naphthalene. The reported LC_{50} value for rats exposed to naphthalene vapors for 8 hours was 500 mg/m^3 (BUA, 1989). The major sites affected by naphthalene toxicity are the hematologic and pulmonary systems and the eye.

Hematologic Effects: Although human subjects accidentally exposed to naphthalene by ingestion developed hemolytic anemia, animals appear to be less sensitive to the hemolytic effects of the chemical. Toxic effects observed in CD-1 mice administered 267 mg/kg naphthalene in corn oil by gavage once a day for 14 days included reduced body weight gain, reduced absolute thymus weight (males), reduced spleen and lung weights (females), elevation of blood bilirubin concentration, and 5% to 10% mortality. There was a slight alteration in hematologic parameters, but there was no hemolytic anemia, cataracts, or lung damage (Shopp *et al.*, 1984).

Dogs that received daily oral doses of naphthalene (263 or 1,525 mg/kg body weight per day for 7 days) mixed in feed developed hemolytic anemia (Zuelzer and Apt, 1949). The cumulative results of the mouse and dog studies suggest that mice are less sensitive than dogs to the hemolytic effects of naphthalene.

Ocular Effects: Lens opacity was reported in black-hooded and brown Norway rats given 700 or 5,000 mg naphthalene/kg per day for 79 to 102 days (Rathbun *et al.*, 1990; Tao *et al.*, 1991). Cataracts involving the whole eye lens occurred in pigmented and albino rabbits within 2 weeks of daily oral administration with 1 g/kg naphthalene, with the greater incidence in the albino strain (Potts, 1996). van Heyningen (1979) reviewed cataract formation in albino rats and albino rabbits resulting from naphthalene administration and concluded that, although the toxic agent in both species is the liver metabolite 1,2-dihydroxynaphthalene, phenol oxidase was the primary metabolic enzyme in rats and catechol oxidase was the primary enzyme in rabbits. This is consistent with the observation that the pigmented strain of rats was more susceptible to cataract formation than the albino strain because phenol oxidase is found only in the pigmented strain. Albino and pigmented rabbits responded similarly to naphthalene for lens opacity (Koch and Doldi, 1975). The strain difference observed in rats also appears to occur in mice. Shichi *et al.* (1980) have reported correlations between the Ah^b allele and cataract formation in nine inbred mouse strains (four responsive at the Ah locus and five nonresponsive), with cataracts developing only in the responsive strains. Animals were exposed concomitantly to daily administration of 60 mg/kg β-naphthoflavones and to 120 mg/kg naphthalene in a 60-day study to determine the induction of total body cytochrome P450 (CYP1A and CYP2A).

A study conducted with biochemical probes on male C57BL/6J mice suggests that naphthalene cataractogenesis requires P450 (CYP1A and CYP2A) bioactivation to a reactive metabolite (possibly a naphthoquinone), a free radical derivative, or a combination of both (Wells *et al.*, 1989). In these studies, a pretreatment of mice with SKF-525A or α-phenyl-N-butylnitrone in addition to treatment with vitamin E or caffeic acid inhibited naphthalene cataractogenicity.

L-Cysteine prodrugs (thiozolidine-4-carboxylic acid; N-acetyl-L-cysteine; N,S-bis-acetyl-L-cysteine; glutathione ethyl ether; 2-mercaptoethanol/L-cysteine) were also effective in preventing naphthalene-induced cataracts in mouse lenses, apparently by maintaining hepatic glutathione concentrations (Rathbun *et al.*, 1996a,b). In a feed study in black-hooded rats, Rathbun *et al.* (1990) found that the glutathione concentration and glutathione peroxidase and glutathione reductase activities were significantly reduced in the eye lens of rats fed diets containing 5,000 mg naphthalene per kg body weight daily for 30 days. No changes were observed in the activity of glutathione

synthetase or γ-glutamylcysteine synthetase. It was concluded that naphthalene-induced cataracts may be due to impairment of the defense system against oxidative damage.

Pulmonary Effects: The respiratory tract has been identified as a site of naphthalene toxicity in rats and mice. A single intraperitoneal injection of 0.05 or 2 mmol/kg induced necrosis of the bronchial/bronchiolar epithelium in C57BL/6J mice (Mahvi *et al.*, 1977). This lesion was reversible, and regeneration occurred after 7 days. Necrosis of the bronchial epithelial (Clara) cells occurred in the lungs of C57BL/6J mice given a single intraperitoneal injection of 125 or 250 mg/kg naphthalene (Tong *et al.*, 1981, 1982).

Rats are more tolerant to naphthalene toxicity than mice. An intraperitoneal injection of 400 or 600 mg/kg in Swiss T.O. mice damaged the Clara cells in the lung and proximal tubule epithelial cells of the kidney. In contrast, an intraperitoneal injection of 1,600 mg/kg in Wistar-derived rats did not produce any damage in the lung or the kidney (O'Brien *et al.*, 1985). The difference in susceptibility was attributed to variation in the metabolism rate of the two species. It was found that the covalent binding and metabolism of naphthalene were 10% greater in microsomes prepared from mouse lung than those prepared from rats. Using microdissected airways, Buckpitt *et al.* (1995) found that the rate of naphthalene metabolism was higher in mouse airways than in the airways of rats or hamsters. Additionally, the metabolism of naphthalene in the distal airways was higher than in the trachea of the mouse, rat, or hamster.

Plopper *et al.* (1992) studied the histopathologic changes of the respiratory tract 24 hours after parenteral administration of a single oral dose of naphthalene in corn oil to Swiss Webster mice (0 to 400 mg/kg), Sprague-Dawley rats (0 to 1,600 mg/kg), and Syrian hamsters (0 to 800 mg/kg). They found that naphthalene injury (swelling, vacuolization, exfoliation, and/or necrosis) to the tracheobronchial epithelium in the mice was specific to Clara cells. It occurred with a dose-related trend in the terminal bronchioles and involved proximal airways. Clara cells in the rat were refractory to injury, and proximal airways were more susceptible than distal airways in the hamster. Naphthalene was cytotoxic to the olfactory epithelium in rats and mice, with the effect seen at a much higher dose in mice (200 mg/kg versus 400 mg/kg). Recent studies with adult and neonatal Swiss Webster mice showed that Clara cells in the neonates are more susceptible to injury by bioactivated naphthalene exposure than those of the adult mice (Fanucchi *et al.*, 1997).

In vivo studies with airway explants from sensitive species (mice) and nonsensitive species (rats and hamsters) showed that the cells from mice contain a unique P450 (CYP2F, a family of microsomal enzymes uniquely expressed in the lung and olfactory mucosal cells; Lakritz *et al.*, 1996; Shultz *et al.*, 1999) enzyme capable of stereospecific metabolism of naphthalene to 1-(R)-2-(S)-naphthalene oxide; 1-(R)-2-(S)-naphthalene epoxide was not detected in rats or hamsters. Cells from rats and hamsters metabolized naphthalene to these two metabolites, with the latter metabolite predominant (Chang *et al.*, 1991). The rate of naphthalene metabolism by microsomal preparations from rat, hamster, or monkey livers was considerably lower (12%, 37%, and 1%, respectively) than that obtained from similar preparations of mouse liver. The mouse lung microsomal preparation favored the formation of the 1-(R)-2-(S)- over the 1-(S)-2-(R)-epoxide. In the nonsensitive species (rats and hamsters), the opposite was true (Buckpitt *et al.*, 1992).

Pulmonary toxicity of a single intraperitoneal injection of naphthalene (1.6 mmol), 2-methylnaphthalene (2.8 mmol), 2-isopropylnaphthalene (17.6 mmol), and 2,6-diisopropylnaphthalene (14.2 mmol) was studied in ddY mice. The first two compounds caused pulmonary toxicity, significant depletion of reduced glutathione, and increased binding to lung tissue relative to isopropylnaphthalenes. These results suggest that lung toxicity of naphthalene and its alkyl substituent is inversely related to the alkyl chain length. Additionally, the results suggest that the toxicity of naphthalene is dependent on its ability to deplete glutathione and to bind to lung tissue (Honda *et al.*, 1990).

Other Effects: Naphthalene administered orally in corn oil (120 mg/kg per day for 120 consecutive days) resulted in oxidative stress (increased lipid peroxidation) and DNA breakage in liver and brain tissue of Sprague-Dawley rats (Bagchi *et al.*, 1998). Vuchetich *et al.* (1996) showed that treatment of female Sprague-Dawley rats with vitamin E succinate 3 days before and 4 days after administration of a single oral

dose of 1,100 mg naphthalene protected these rats from oxidative stress and reduced DNA breakage in hepatic tissue.

A single intraperitoneal injection of naphthalene (1 g/kg) caused ammonia accumulation in the brain of rats. The accumulation of ammonia correlated positively with the lethality of the compound (Bolonova, 1967). Brain ammonia reacts with glutamic acid along with glutamine dehydrogenase as a catalyst to form glutamine (de Bruin, 1976). Naphthalene inhibited aryl hydrocarbon hydroxylase activity in liver homogenates and microsomal preparations obtained from rats given 40 mg/kg intraperitoneal injections for 3 days (Alexandrov and Frayssinet, 1973). A single intraperitoneal dose of 250 mg/kg naphthalene to C57BL/6J mice depressed the enzyme activity of microsomal monooxygenase in the lung by 30% to 70%; enzyme activity was not affected in the liver (Tong *et al.*, 1982).

Humans

Naphthalene inhalation in humans causes headache, confusion, eye irritation, nausea, and profuse perspiration with vomiting, optic neuritis, hematuria, and edema. Naphthalene ingestion has resulted in abdominal pain, nausea, vomiting, diarrhea, darkening of the urine, irritation of the bladder, jaundice, anemia, and hypothermia (Gerarde, 1960). Toxicity and death have been reported in newborn infants exposed to naphthalene vapors from clothes containing it (Valaes *et al.*, 1963).

Cataract formation has been reported in humans exposed to naphthalene. A pharmacist ingesting 5 g naphthalene developed bilateral cataracts as well as optic nerve atrophy and blindness (Lezenius, 1902). Two workers occupationally exposed to powdered naphthalene developed cataracts, retinal hemorrhage, and chorioretinitis (Van der Hoeve, 1906). Cataracts were diagnosed in 8 of 29 chemical plant workers exposed to naphthalene for 5 years (Ghetti and Mariani, 1956).

Naphthalene poisoning has produced hemolytic anemia in children (Zuelzer and Apt, 1949; Dawson *et al.*, 1958; Zinkham and Childs, 1958; Santhanakrishnan *et al.*, 1973) and adults (Taylor and Russell, 1932; Konar *et al.*, 1939). Individuals with decreased glucose-6-phosphate dehydrogenase activity are particularly susceptible to this effect (Haddad and Winchester, 1983; Melzer-Lange and Walsh-Kelly, 1989). This enzyme is essential for the regeneration of erythrocyte NADPH, a cofactor required for the regeneration of reduced glutathione. The latter is used by the antioxidant enzyme erythrocyte glutathione peroxidase (a selenium containing enzyme essential for protecting cell membrane integrity). Notable features of the hemolytic anemia included Heinz-body formation, hemoglobinuria, and decreases in hemoglobin, hematocrit, erythrocyte counts, and stimulation of hematopoiesis. The hemolytic anemia was followed by renal failure (MacGregor, 1954; Gidron and Leurer, 1956). A case of aplastic anemia was reported in a woman exposed to dichlorobenzene and naphthalene vapors, but the association is uncertain due to the lack of other substantiating reports (Harden and Baetjer, 1978).

CARCINOGENICITY

Experimental Animals

In a 2-year inhalation study in B6C3F$_1$ mice, naphthalene was a respiratory toxicant and carcinogen (Abdo *et al.*, 1992; NTP, 1992). In this study, male and female mice were exposed to naphthalene vapors (0, 10, or 30 ppm) 6 hours per day, 5 days per week. Naphthalene was carcinogenic to female mice, resulting in an increased incidence of alveolar/bronchiolar adenoma in the 30 ppm group. Additionally, naphthalene caused exposure-related increases in the incidences of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium of the nose as well as exposure-related increases in the incidences of chronic inflammation of the lung in male and female mice.

Daily 6-hour exposures to atmospheres of 30 ppm naphthalene for 6 months did not elicit a significant increase in the incidence of lung adenoma in A/J mice, but histopathologic evaluation of lungs from the animals revealed an increased incidence of multiple alveolar adenoma relative to the concurrent chamber controls. However, the number of tumors per tumor-bearing lung in the concurrent controls was significantly less than those observed in the unexposed controls for this strain of mice (Adkins *et al.*, 1986). The results of this study suggest that the evidence for carcinogenicity in this strain of mice is equivocal.

Negative results were reported in early naphthalene dermal studies, but experimental details were unavailable (Kennaway, 1930). A rat dermal study with 1,4-naphthoquinone, a naphthalene metabolite, resulted in skin papilloma incidences of 15% to 20%, with some papillomas leading to malignant epitheliomas (Takizawa, 1940). Tumors occurred in 9 of 25 black mice receiving naphthalene in benzene and in 3 of 21 black mice receiving benzene control in a lifetime (5 days/week) dermal study (Knake, 1956). In the exposed mice, four had lymphatic leukemia, three had lung adenomas, one had lymphosarcoma, and one had nonspecified tumor; in the benzene controls, one had lymphosarcoma, one had lung adenoma, and one had nonspecified tumor. Boyland *et al.* (1964) examined the effects of implanting naphthalene in the urinary bladder of mice and found a 4% incidence of carcinoma after 30 weeks, which was similar to the effect of implanting inert substances such as glass.

A group of 40 rats administered seven subcutaneous biweekly doses of 500 mg/kg naphthalene in benzene and then observed for 18 months had a 15% tumor incidence (five animals with lymphosarcoma and one with fibroadenoma), while 5% and 2% tumor incidences occurred in vehicle and unexposed controls (Knake, 1956). No carcinogenic activity or toxic effects were evident, either in rats given a total of 10 g naphthalene orally over a 700-day period or in rats given 820 mg subcutaneously or intraperitoneally over a 40-week period (Schmahl, 1955). No controls were used in this study, but a concurrent study with anthracene administered subcutaneously did detect tumors.

Humans

In East Germany (now part of the Federal Republic of Germany), four cases of laryngeal carcinoma, a case of gastric carcinoma, a case of colon carcinoma, and a case of lupus erythromatosus were reported among 7 of 15 employees involved in the manufacture of naphthalene (Wolf, 1976). Seven tumor-free workers suffered various degrees of rhinopharyngolaryngitis, an inflammation possibly conducive to prodromal carcinogenesis. Laryngeal cancer developed in 4 of 15 naphthalene distillation plant workers (Wolf, 1978). The incidence of laryngeal cancer in these distillation workers was approximately 4,000 times greater than the general incidence of laryngeal cancer in East Germany. Kup (1978) studied 15 patients: 12 with laryngeal carcinomas, two with epipharyngeal cancer, and one with nasal carcinoma. He observed that four of the pharyngeal cancer patients were exposed to naphthalene but suggested that most of the cancer was not work related as most of the workers were smokers as well. No other studies investigating carcinogenesis and exposure to naphthalene in humans were found.

GENETIC TOXICITY

There is little evidence for mutagenic potential of naphthalene in the most widely used genotoxicity assays. Naphthalene was not mutagenic in *Salmonella typhimurium* gene mutation studies, with or without S9 metabolic activation enzymes (Connor *et al.*, 1985; Nohmi *et al.*, 1985; Sakai *et al.*, 1985; Mortelmans *et al.*, 1986; Narbonne *et al.*, 1987; Bos *et al.*, 1988), nor was it active in the SOS chromotest for induction of DNA damage in *Escherichia coli* PQ37 (Mersch-Sundermann *et al.*, 1992). In addition, it failed to induce sister chromatid exchanges in human lymphocytes *in vitro* in the presence of human liver microsomal activation enzymes (Tingle *et al.*, 1993; Wilson *et al.*, 1995). Naphthalene was not mutagenic to metabolically competent human lymphoblastoid MCL-5 cells at either the heterozygous *tk* locus or the hemizygous *hprt* locus (Sasaki *et al.*, 1997). However, a small but significant increase in the number of micronuclei was observed in these cells after exposure to 30 µg/mL naphthalene (Sasaki *et al.*, 1997). These micronuclei were Crest stain negative, indicating that they contained acentromeric fragments rather than whole chromosomes. Naphthalene produced a small dose-related increase in micronucleated erythrocytes of salamanders exposed in water for 12 days during the larval stage to naphthalene concentrations of 0.24 and 0.50 ppm (Djomo *et al.*, 1995).

In a *Drosophila melanogaster* somatic mutation and recombination test, naphthalene, when fed to larvae for 48 hours at concentrations of 1 to 10 mM, induced significant increases in wing spots in a standard cross and in a high bioactivation cross that used strains with increased cytochrome P450 activity (Delgado-Rodriguez *et al.*, 1995). The wing-spot pattern observed following exposure to naphthalene indicated that mutations were induced in both strains of *D. melanogaster*, but the response in the metabolically enhanced strain was stronger; chromosomal recombinations occurred in these flies in addition to mutations.

Two nitro derivatives of naphthalene, 1-nitronaphthalene and 1,5-dinitronaphthalene, also induced somatic mutations in this assay, but the responses were weaker than those observed with naphthalene.

The metabolites of naphthalene, 1,2-dihydro-1,2-dihydroxy naphthalene, 1-naphthol, and 2-naphthol, were nonmutagenic in *S. typhimurium* (Narbonne *et al.*, 1987; Florin *et al.*, 1980; Probst *et al.*, 1981), but 2-naphthol was shown to induce growth inhibition in DNA repair-deficient strains of *E. coli* (Suter and Jaeger, 1982) and *Bacillus subtilis* (Tanooka, 1977; Kawachi *et al.*, 1980; Suter and Jaeger, 1982), presumably through induction of DNA damage. Unscheduled DNA synthesis was not observed in cultured rat hepatocytes treated with 2-naphthol (Probst *et al.*, 1981).

STUDY RATIONALE

NIOSH, OSHA, and USEPA made the original nomination to test naphthalene for carcinogenicity based on the potential for chronic exposure to humans through the use of mothballs in the home and the lack of adequate carcinogenicity studies in the literature to reach a regulatory decision. Potential chronic exposure can occur occupationally and through cigarette smoke (3 µg naphthalene/cigarette; Schmeltz *et al.*, 1978). Based on this nomination and because of the lack of carcinogenic activity of naphthalene in the oral rat study reported by Schmahl (1955), the NTP decided to study the carcinogenic potential of naphthalene in mice only. This study was completed and peer reviewed in 1991 (NTP, 1992). Because of the positive carcinogenic response (an increased incidence of lung adenoma in exposed female mice), members of the peer review panel recommended and the NTP concurred that an inhalation study in rats should be conducted. The recommendation was made because previous studies with naphthalene in rats have been conducted using routes other than inhalation (the major route for human exposure) and because the Schmahl (1955) study would be considered inadequate due to the small number of animals used (28 rats were dosed once daily, six times per week, until each was administered a total of 10 g over a 700-day period, or about 41 mg/kg per day).

A 2-year carcinogenicity study was conducted by exposing groups of 50 male and 50 female F344/N rats to atmospheres containing 0, 10, 30, or 60 ppm naphthalene vapor. The highest exposure concentration selected is the maximum that can be used without condensation of naphthalene in the chambers. The lowest exposure concentration represents the threshold limit value-time-weighted average established by the ACGIH (1999).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF NAPHTHALENE

Naphthalene was obtained from Aldrich Chemical Co. (Milwaukee, WI) in one lot for use in the 2-year study. Identity, purity, and/or stability analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC) and by the study laboratory, Battelle Toxicology Northwest (Richland, WA) (Appendix E). Reports on analyses performed in support of the naphthalene study are on file at the National Institute of Environmental Health Sciences.

The chemical, a white crystalline solid, was identified as naphthalene by infrared and proton nuclear magnetic resonance spectroscopy and by gas chromatography/mass spectroscopy. The purity was determined by elemental analyses, gas chromatography/mass spectroscopy, and gas chromatography with flame ionization detection (FID). Elemental analyses for carbon and hydrogen were in agreement with theoretical values for naphthalene; 0.12% sulfur was also detected. Gas chromatography/mass spectroscopy indicated no impurities. Gas chromatography/FID indicated one major peak and one impurity with an area of approximately 0.6%; the impurity was tentatively identified as thionaphthene. The overall purity was determined to be greater than 99%.

Stability of the bulk chemical was monitored by the study laboratory using gas chromatography with FID. To ensure stability, the bulk chemical was stored under a nitrogen headspace at room temperature in metal drums lined with plastic. No degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

The generator consisted of a 2-L glass reaction flask surrounded by a heated mantle. Heated nitrogen metered into the flask carried the vaporized naphthalene out of the generator. The mantle and nitrogen temperatures were adjusted to maintain the temperature of the vapor above the bulk naphthalene between 66° and 71° C while the bulk chemical was monitored to ensure that its temperature was maintained below the melting point.

A heated Teflon® line transported the vapor to the exposure room. The vapor was diluted with heated, HEPA- and charcoal-filtered air before entering a distribution manifold. Flow into the chamber was controlled by a chamber exposure valve. When the valve was in the exposure position, an AirVac pump (Air-Vac Engineering Co., Inc., Milford, CT) withdrew the appropriate amount of naphthalene vapor from the distribution manifold. The naphthalene vapor was injected into the chamber as it was mixed and diluted with conditioned chamber air to obtain the target concentration.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. Before the study began, a small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that naphthalene vapor, and not aerosol, was produced. A Type CN small particle detector was also used to determine the

maximum attainable concentration without aerosolization. Naphthalene aerosol was detected at a vapor concentration of approximately 85 ppm; therefore, a maximum concentration of 60 ppm was selected. During the 2-year study, no particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

The naphthalene concentrations in the exposure chambers were monitored by an online gas chromatograph; the average chamber concentrations were maintained within 1% of the target concentrations. Samples were drawn from each exposure chamber approximately every 24 minutes using a 12-port stream select valve. The online gas chromatograph was checked throughout the day for instrument drift against an online standard of naphthalene. The online gas chromatograph was calibrated monthly by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes and analyzed by an offline gas chromatograph. The offline gas chromatograph was calibrated with gravimetrically prepared standards of naphthalene containing 1-phenylhexane as an internal standard in toluene.

CHAMBER ATMOSPHERE CHARACTERIZATION

Buildup and decay rates for chamber vapor concentrations were determined with and without animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. Based on experimental data, a T_{90} value of 12 minutes was selected for the study.

Evaluations of chamber uniformity and persistence and monitoring for naphthalene degradation impurities were conducted periodically throughout the study by gas chromatography. Chamber uniformity was maintained; no degradation was detected.

2-YEAR STUDIES

Study Design

The exposure concentrations for the naphthalene study were selected based on the results of a 2-year study in mice in which animals were exposed to 0, 10, or 30 ppm (NTP, 1992). Additionally, the highest exposure concentration (60 ppm) was selected to allow for variations in the maximum achievable concentration without aerosolization, determined by the study laboratory to be approximately 80 ppm, due to changes in temperature or operating conditions within the exposure system. The lowest concentration of 10 ppm is the threshold limit value for naphthalene (ACGIH, 1999).

Groups of 49 male and 49 female rats were exposed to naphthalene at concentrations of 0, 10, 30, or 60 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 105 weeks. Additional groups of male and female rats were exposed similarly to 10, 30, or 60 ppm for up to 18 months for evaluation of toxicokinetic parameters; no additional evaluations of these animals were performed.

Source and Specification of Animals

Male and female F344/N rats were obtained from Taconic Laboratory Animals and Services (Germantown, NY). The animals were quarantined for 14 days before the beginning of the study. Five male and five female rats were randomly selected for parasite evaluation and gross observation of disease. The animals were approximately 6 weeks old at the beginning of the study. The health of the animals was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix G).

Animal Maintenance

The animals were housed individually. Feed was available *ad libitum*, except during the exposure period; water was available *ad libitum*. Cages and chambers were changed weekly. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix F.

Clinical Examinations

All animals were observed twice daily. Body weights were recorded on study day 1, every 4 weeks beginning at week 4, and every 2 weeks beginning at week 92. Clinical findings were recorded every 4 weeks beginning at week 4 and every 2 weeks beginning at week 92.

Toxicokinetics

Groups of nine male and nine female rats were exposed to 10, 30, or 60 ppm naphthalene 6 hours per day plus T_{90} for 5 days per week, excluding holidays and weekends, for up to 18 months. Blood samples were drawn from the retroorbital sinus at 2 weeks and 3, 6, 12, and 18 months. The samples were collected from three males and three females per group at six time points after exposure. Samples were collected twice (2 hours apart) from each rat via alternating sinuses. The samples of whole blood were immediately frozen in plastic screw-cap vials and shipped on dry ice to CEDRA Corporation (Austin, TX) for analyses of naphthalene concentrations. The samples were analyzed with a validated high-performance liquid chromatography method with ultraviolet light detection.

Pathology

Complete necropsies and microscopic examinations were performed on all core study animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the nose and lung of male and female rats. In addition, the liver and preputial gland of male rats and the kidney, pancreas, and uterus of female rats were evaluated for specific lesions.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of exposure groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Inhalation Study of Naphthalene

Study Laboratory
Battelle Toxicology Northwest (Richland, WA)

Strain and Species
F344/N rats

Animal Source
Taconic Laboratory Animals and Services (Germantown, NY)

Time Held Before Studies
14 days

Average Age When Studies Began
6 weeks

Date of First Exposure
28 March 1996

Duration of Exposure
6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks

Date of Last Exposure
27 March 1998

Necropsy Dates
30 March-2 April 1998

Average Age at Necropsy
110-111 (males) or 111 (females) weeks

Size of Study Groups
Core study: 49 males and 49 females
Toxicokinetic study: 9 males and 9 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
1

Method of Animal Identification
Tail tattoo

Diet
NTP-2000 irradiated pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* except during exposure periods, changed weekly

Water
Softened tap water (Richland municipal supply) via automatic watering system (Edstrom Industries, Waterford WI), available *ad libitum*

Cages
Stainless steel, wire-bottom (Hazelton Systems, Inc., Aberdeen, MD), changed weekly

Chamber Air Supply Filters
Single HEPA (Northland Filter Systems International, Mechanicville, NY) charcoal (RSE, Inc., New Baltimore,MI); Purafil (Environmental Systems, Lynnwood, WA)

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Inhalation Study of Naphthalene

Chambers
Stainless steel (Harford System, Division of Lab Products, Inc., Aberdeen, MD), changed weekly

Chamber Environment
Temperature: 75° ± 3° F
Relative humidity: 55% ± 15%
Room fluorescent light: 12 hours/day
Chamber air changes: 15 ± 2/hour

Exposure Concentrations
0, 10, 30, and 60 ppm

Type and Frequency of Observation
Observed twice daily; animals were weighed at the beginning of the studies, every 4 weeks beginning at week 4, and every 2 weeks beginning at week 92. Clinical findings were recorded every 4 weeks beginning at week 4 and every 2 weeks beginning at week 92.

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
Necropsy was performed on all core study animals.

Histopathology
Complete histopathology was performed on all core study animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eyes, heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung with mainstem bronchi, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland (females), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle) thymus, thyroid gland, trachea, urinary bladder, and uterus.

Toxicokinetic Study
Blood was collected from the retroorbital sinus of toxicokinetic study rats at 2 weeks and at 3, 6, 12, and 18 months. Blood was collected 0, 30, 60, 120, 300, and 480 minutes after exposure from rats in the 10 ppm group; 0, 30, 90, 300, 480, and 720 minutes after exposure from rats in the 30 ppm group; and 0, 30, 90, 360, 720, and 960 minutes after exposure from rats in the 60 ppm group. Up to three males and three females were evaluated at each time point.

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. A missexed animal was censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, and B5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3 and B3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3 and B3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts

for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions are represented as 1-P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. Until recently, the NTP historical control database consisted of animals fed NIH-07 diet. In 1995, the NTP changed the diet fed to animals used in toxicity and carcinogenesis studies conducted by the NTP. This new diet (NTP-2000) contains less protein and more fiber and fat than the NIH-07 diet previously used (Rao, 1996, 1997). This dietary change was instituted primarily to increase longevity and decrease the incidence and/or severity of some spontaneous neoplastic and nonneoplastic lesions in the rats and mice used in NTP studies. This study of naphthalene is one of the first in which the animals on study were fed the NTP-2000 diet. Because the incidence of some neoplastic and nonneoplastic lesions are affected by the dietary change, use of the existing historical control database (NIH-07) diet is not appropriate for all neoplasm types.

Currently, the number of studies in which the NTP-2000 diet was used is limited. This diet was used in the four studies (indium phosphide, sodium nitrite, *p*-*p*′-dichlorodiphenyl sulfone, and naphthalene) reported at the May 18, 2000, peer review and in two others (methacrylonitrile and *p*-nitrotoluene) not yet reported. Therefore, a database of incidences of neoplastic lesions was created for this group of six studies. Four routes of administration were used in these six studies: *p*-nitrotoluene and *p*-*p*′-dichlorodiphenyl sulfone were administered by dosed feed; sodium nitrite was administered in the drinking water; methacrylonitrile was administered by gavage using deionized water; and naphthalene and indium phosphide were administered via whole body inhalation. Based on the extensive NTP historical database using the NIH-07 diet, incidences of the vast majority of spontaneous neoplasms are not significantly different between control groups irrespective of the route of administration. There is no reason to expect this to be different with the NTP-2000 diet. Clearly, control animals from dosed feed and dosed water studies are treated no differently and no differences in incidence of neoplasms are expected. There are some exceptions, and if comparisons are necessary for these neoplasm types, only studies with similar routes of administration will be used.

The set of six studies using the NTP-2000 diet will be the primary historical control group used for comparison. However, where appropriate, the larger historical database (NIH-07 diet) may be used to augment the smaller NTP-2000 database.

QUALITY ASSURANCE METHODS

The 2-year study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year study were submitted to the NTP Archives, this study was audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of naphthalene was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix C.

The genetic toxicity studies of naphthalene are part of a larger effort by the NTP to develop a comprehensive database that would permit a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). These short-term genetic toxicity tests were originally developed to clarify mechanisms of chemical-induced DNA damage growing out of the earlier electrophilicity/mutagenicity relationship proposed by Miller and Miller (1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). Therefore, the information obtained from these tests applies only to mutagenic carcinogens.

For mutagenic carcinogens, the combination of DNA reactivity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in multiple species and genders of rodents and at multiple tissue sites (Ashby and Tennant, 1991). Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) and that there is no complementarity among the *in vitro* genetic toxicity tests (Tennant *et al*., 1987; Zeiger *et al*., 1990). That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. Although other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity compared with the *Salmonella* test, these other tests can provide useful information on the types of DNA and chromosomal effects induced by the chemical under investigation.

RESULTS

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 3 and in the Kaplan-Meier survival curves (Figure 2). Survival of all exposed groups of male and female rats was similar to that of the chamber controls.

Body Weights and Clinical Findings

Mean body weights of male and female rats are given in Figure 3 and Tables 4 and 5. Mean body weights of all exposed groups of male rats were less than those of the chamber control group throughout most of the study. Mean body weights of exposed groups of females were generally similar to those of the chamber controls. There were no clinical findings related to naphthalene exposure.

TABLE 3
Survival of Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Male				
Animals initially in study	49	49	49	49
Missexed[a]	0	0	1	0
Moribund	21	22	19	25
Natural deaths	4	5	6	3
Animals surviving to study termination	24	22	23	21
Percent probability of survival at end of study[b]	49	45	48	43
Mean survival (days)[c]	681	669	674	649
Survival analysis[d]	P=0.433	P=0.702	P=0.880	P=0.414
Female				
Animals initially in study	49	49	49	49
Moribund	18	22	16	21
Natural deaths	3	6	5	4
Animals surviving to study termination	28	21	28	24
Percent probability of survival at end of study	57	43	57	49
Mean survival (days)	700	669	681	656
Survival analysis	P=0.572	P=0.127	P=0.892	P=0.277

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns.

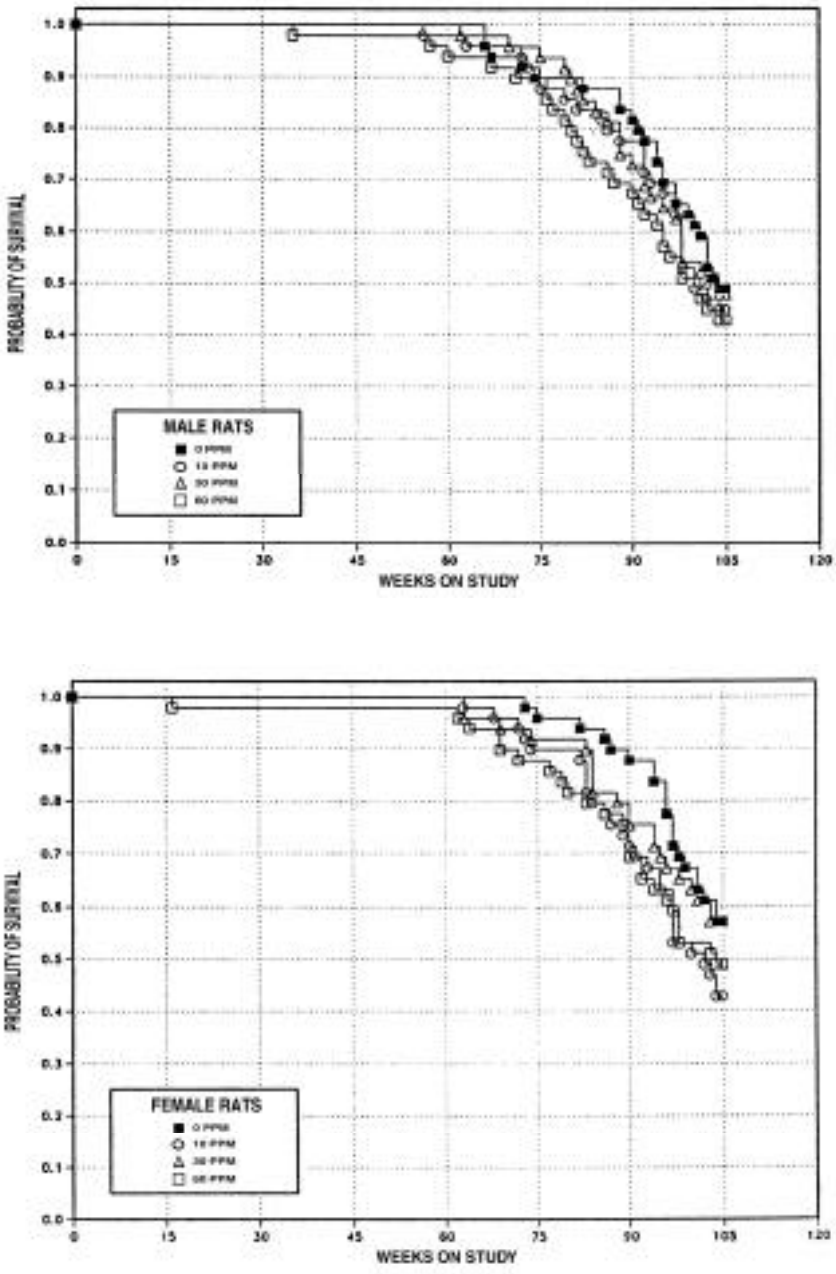


Figure 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Naphthalene by Inhalation for 2 Years

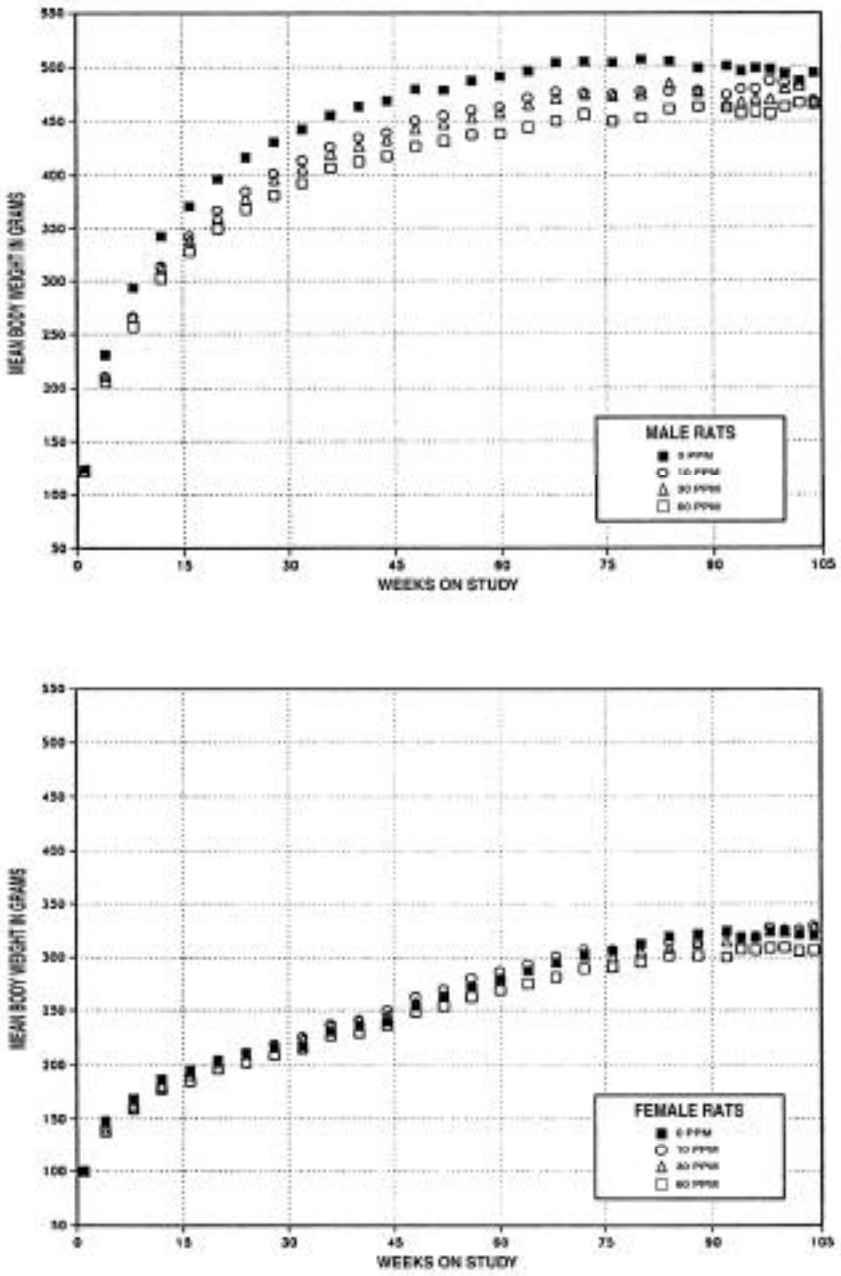


Figure 2
Growth Curves for Male and Female Rats Exposed to Naphthalene by Inhalation for 2 Years

TABLE 4
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Naphthalene

Weeks on Study	Chamber Control		10 ppm			30 ppm			60 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	125	49	122	98	49	123	98	48	122	98	49
4	231	49	211	91	49	211	91	48	206	89	49
8	293	49	267	91	49	267	91	48	257	88	49
12	343	49	314	92	49	312	91	48	302	88	49
16	371	49	343	92	49	339	91	48	328	88	49
20	396	49	367	93	49	361	91	48	350	88	49
24	416	49	385	92	49	378	91	48	368	88	49
28	431	49	401	93	49	396	92	48	381	89	49
32	443	49	414	93	49	406	92	48	393	89	49
36	455	49	426	94	49	420	92	48	407	89	48
40	464	49	435	94	49	427	92	48	412	89	48
44	469	49	439	94	49	433	92	48	418	89	48
48	480	49	451	94	49	443	93	48	427	89	48
52	479	49	455	95	49	448	94	48	432	90	48
56	488	49	461	94	48	453	93	48	438	90	48
60	492	49	463	94	48	458	93	48	438	89	47
64	496	49	471	95	47	465	94	47	444	90	46
68	505	46	477	95	47	472	93	47	450	89	45
72	506	45	477	94	46	475	94	46	457	90	44
76	505	44	475	94	43	474	94	45	450	89	42
80	507	44	478	94	42	475	94	44	453	89	40
84	505	43	478	95	41	485	96	40	462	91	36
88	499	43	479	96	39	477	96	37	463	93	34
92	501	38	475	95	38	467	93	35	462	92	31
94	496	38	480	97	34	468	94	32	457	92	31
96	499	34	480	96	33	471	94	31	459	92	28
98	498	32	488	98	26	470	94	28	457	92	27
100	494	30	485	98	25	480	97	26	463	94	25
102	488	27	483	99	24	483	99	24	467	96	22
104	495	24	469	95	22	468	95	24	466	94	21
Mean for weeks											
1-13	248		229	92		228	92		222	90	
14-52	440		412	94		405	92		392	89	
53-104	498		476	96		471	95		455	91	

TABLE 5
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Naphthalene

Weeks on Study	Chamber Control		10 ppm			30 ppm			60 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	100	49	101	101	49	100	100	49	100	100	49
4	148	49	141	95	49	139	93	49	138	93	49
8	169	49	162	96	49	160	95	49	159	94	49
12	187	49	180	96	49	180	96	49	177	95	49
16	195	49	191	98	49	190	98	49	185	95	49
20	204	49	203	99	49	202	99	49	196	96	48
24	211	49	211	100	49	210	99	49	202	96	48
28	216	49	219	102	49	218	101	49	210	97	48
32	217	49	226	104	49	224	103	49	215	99	48
36	231	49	237	103	49	237	102	49	227	98	48
40	236	49	242	103	49	241	102	49	230	98	48
44	240	49	250	104	49	246	103	49	237	99	48
48	254	49	262	103	49	257	101	49	249	98	48
52	262	49	270	103	49	264	101	49	254	97	48
56	272	49	280	103	49	273	101	49	263	97	48
60	279	49	287	103	49	281	101	49	269	97	48
64	287	49	294	102	48	288	100	47	276	96	46
68	295	49	301	102	47	296	100	47	282	96	46
72	303	49	307	101	47	302	100	46	289	96	44
76	306	47	307	100	44	301	98	45	291	95	43
80	313	47	310	99	44	306	98	45	296	95	40
84	320	46	314	98	40	309	97	43	302	94	39
88	322	44	314	98	37	314	98	40	302	94	38
92	325	43	322	99	34	315	97	37	300	92	33
94	319	43	318	100	33	317	99	35	308	97	31
96	319	41	318	100	31	320	100	34	307	96	30
98	325	34	329	101	26	324	100	33	309	95	27
100	325	33	327	101	26	324	100	32	309	95	26
102	321	31	326	102	25	324	101	30	306	95	26
104	320	29	330	103	21	329	103	28	307	96	24
Mean for weeks											
1-13	151		146	97		145	96		144	95	
14-52	227		231	102		229	101		221	97	
53-104	309		312	101		308	100		295	95	

Gross Observations

Malignant nasal neoplasms were observed in several male and female rats. These masses frequently partially occluded the nasal passages or obliterated the normal architecture of the nasal turbinates and, in some affected animals, invaded the brain.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the nose and lung. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Nose: Increased incidences of a variety of neoplasms and nonneoplastic lesions occurred in the nose of exposed male and female rats. These lesions were observed in all three levels of the nasal cavity that are routinely examined in NTP toxicity and carcinogenicity studies: level I, excised immediately posterior to the upper incisor teeth; level II, excised through the level of the incisive papilla anterior to the first palatial ridge; and level III, excised through the middle of the second molar teeth. Levels I and II contain the naso- and maxilloturbinates that along with the nasal passages (meatuses) and septum are lined by ciliated respiratory-type epithelium. Level III encompasses the olfactory region of the nose with ethmoid turbinates and meatuses lined entirely by specialized olfactory neuroepithelium. Neuroblastomas of the olfactory epithelium occurred in males exposed to 30 or 60 ppm and in all exposed groups of females (Tables 6, A3, and B3). The incidences of neuroblastoma occurred with positive trends in males and females, and the incidence in females exposed to 60 ppm was significantly greater than that in the chamber controls. Neuroblastomas have not been observed in male or female chamber control rats in the database for animals fed NIH-07 feed in 2-year inhalation studies or in the more recent, smaller database for control rats fed NTP-2000 feed (Tables 6, A4, and B4).

Neuroblastomas were variably sized, unilateral or bilateral invasive masses that arose in Level III of the nasal cavity and extended into Levels II and I. Larger masses occluded the nasal passages and often obliterated the nasal architecture invading nerves, nasal bones, and the cribriform plate (Plate 1). Other masses extended along the mucosa and replaced the epithelium of the turbinates and nasal septum (Plate 2). The morphology of the neuroblastomas varied. Component neoplastic cells were round, polygonal, or spindle-shaped and arranged in variably sized, irregular islands, cords, and rosettes separated by fibrovascular stroma (Plate 3). In other masses, component cells were arranged in a glandular pattern. Some cells had scant eosinophilic to amphophilic cytoplasm with pale oval to polygonal vesicular nuclei and prominent central nucleoli; others had abundant cytoplasm and elongate, intensely basophilic nuclei. Small nests of neoplastic cells were present in the lamina propria of the turbinates and nasal septum, and in olfactory nerve bundles. A few neoplasms had focal irregular areas of squamous metaplasia, sometimes extensive with formation of keratin pearls. Variably sized focal areas of coagulative necrosis were also observed in most neuroblastomas. Mitotic figures were abundant. Neoplasms that invaded the cribriform plate extended into the olfactory lobes of the brain (Plate 4). One male each in the 30 and 60 ppm groups had metastases in the lungs (Table A1).

The incidences of adenoma of the respiratory epithelium occurred with a positive trend in male rats and were significantly increased in all exposed groups; the incidences in female rats exposed to 30 or 60 ppm were also increased, but not significantly (Tables 6, A3, and B3). Nasal adenomas have not been observed in male or female chamber control rats in the database for animals fed NIH-07 feed in 2-year inhalation studies or in the more recent, smaller database for control rats fed NTP-2000 feed (Tables 6, A4, and B4). Adenomas arose from the respiratory and transitional epithelia of Levels I and II of the nasal cavity along the medial or lateral aspects or tips of the nasoturbinates or the lateral wall. They were irregular exophytic, polypoid, pedunculated or broad-based sessile masses that varied in size and sometimes partially occluded the nasal passages (Plates 5 and 6). Component neoplastic cells were well-differentiated, simple to cuboidal to columnar and arranged primarily as variably sized glands surrounded by scant fibrovascular stroma with few focal solid areas of cells (Plate 7). In some masses, the epithelium appeared to be pseudostratified. The glands were

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Nose in Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Male				
Number Examined Microscopically	49	49	48	48
Olfactory Epithelium, Hyperplasia, Atypical[a]	0	48** (2.1)[b]	45** (2.5)	46** (3.0)
Olfactory Epithelium, Atrophy	3 (1.3)	49** (2.1)	48** (2.8)	47** (3.5)
Olfactory Epithelium, Inflammation, Chronic	0	49** (2.0)	48** (2.2)	48** (3.0)
Olfactory Epithelium, Degeneration, Hyaline	3 (1.3)	46** (1.7)	40** (1.7)	38** (1.5)
Respiratory Epithelium, Hyperplasia	3 (1.0)	21** (2.2)	29** (2.0)	29** (2.2)
Respiratory Epithelium, Metaplasia, Squamous	0	15** (2.1)	23** (2.0)	18** (1.8)
Respiratory Epithelium, Degeneration, Hyaline	0	20** (1.2)	19** (1.4)	19** (1.2)
Goblet Cell, Respiratory Epithelium, Hyperplasia	0	25** (1.3)	29** (1.2)	26** (1.2)
Glands, Hyperplasia	1 (1.0)	49** (2.2)	48** (2.9)	48** (3.5)
Glands, Metaplasia, Squamous	0	3 (3.0)	14** (2.1)	26** (2.5)
Respiratory Epithelium, Adenoma[c]				
Overall rate[d]	0/49 (0%)	6/49 (12%)	8/48 (17%)	15/48 (31%)
Adjusted rate[e]	0.0%	15.3%	20.6%	38.1%
Terminal rate[f]	0/24 (0%)	5/22 (23%)	7/23 (30%)	7/21 (33%)
First incidence (days)	—[h]	684	685	552
Poly-3 test[g]	P<0.001	P=0.013	P=0.003	P<0.001
Olfactory Epithelium, Neuroblastoma[c]				
Overall rate	0/49 (0%)	0/49 (0%)	4/48 (8%)	3/48 (6%)
Adjusted rate	0.0%	0.0%	10.1%	7.7%
Terminal rate	0/24 (0%)	0/22 (0%)	2/23 (9%)	0/21 (0%)
First incidence (days)	—	—[i]	433	399
Poly-3 test	P=0.027	—	P=0.056	P=0.109
Female				
Number Examined Microscopically	49	49	49	49
Olfactory Epithelium, Hyperplasia, Atypical	0	48** (2.0)	48** (2.4)	43** (2.9)
Olfactory Epithelium, Atrophy	0	49** (1.9)	49** (2.7)	47** (3.2)
Olfactory Epithelium, Inflammation, Chronic	0	47** (1.9)	47** (2.6)	45** (3.4)
Olfactory Epithelium, Degeneration, Hyaline	13 (1.1)	46** (1.8)	49** (2.1)	45** (2.1)
Respiratory Epithelium, Hyperplasia	0	18** (1.6)	22** (1.9)	23** (1.7)
Respiratory Epithelium, Metaplasia, Squamous	0	21** (1.6)	17** (1.5)	15** (1.8)
Respiratory Epithelium, Degeneration, Hyaline	8 (1.0)	33** (1.2)	34** (1.4)	28** (1.2)
Goblet Cell, Respiratory Epithelium, Hyperplasia	0	16** (1.0)	29** (1.2)	20** (1.0)
Glands, Hyperplasia	0	48** (1.9)	48** (3.1)	42** (3.3)
Glands, Metaplasia, Squamous	0	2 (2.0)	20** (2.5)	20** (2.8)

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Nose in Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Female (continued)				
Respiratory Epithelium, Adenoma[c]				
Overall rate	0/49 (0%)	0/49 (0%)	4/49 (8%)	2/49 (4%)
Adjusted rate	0.0%	0.0%	9.8%	5.2%
Terminal rate	0/28 (0%)	0/21 (0%)	3/28 (11%)	1/24 (4%)
First incidence (days)	—	—	721	555
Poly-3 test	P=0.066	—	P=0.053	P=0.212
Olfactory Epithelium, Neuroblastoma[c]				
Overall rate	0/49 (0%)	2/49 (4%)	3/49 (6%)	12/49 (24%)
Adjusted rate	0.0%	5.1%	7.2%	28.2%
Terminal rate	0/28 (0%)	0/21 (0%)	1/28 (4%)	3/24 (13%)
First incidence (days)	—	679	480	429
Poly-3 test	P<0.001	P=0.214	P=0.112	P<0.001

** Significantly different ($P \leq 0.01$) from the chamber control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with control groups given NTP-2000 feed: 0/299
[d] Number of animals with neoplasm per number of animals with organ examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Not applicable; no neoplasms in animal group
[i] Value of statistic cannot be computed.

were often variably distended by luminal accumulations of proteinaceous secretory material and cellular debris. A few adenomas were composed of less well differentiated cells that were squamoid in morphology; these cell were large, round to polygonal, with scant to moderate amounts of eosinophilic cytoplasm and large round to oval nuclei that contained one or two prominent nucleoli.

In addition to the nasal neoplasms, the incidences of a variety of nonneoplastic lesions in exposed males and females were significantly greater than those in the chamber controls (Tables 6, A5, and B5). These lesions included atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia. In general, the severities of olfactory epithelial and glandular lesions increased with increasing exposure concentration.

Atypical hyperplasia of the olfactory epithelium occurred primarily along the nasal septum of the ethmoid region. Atypical hyperplasia consisted of disorganization of olfactory epithelium with proliferation of nests of sensory cells within or beneath the epithelium and multifocal nodular proliferations of basal cells, which extended into the submucosa (Plate 8). Atrophy of olfactory epithelium was characterized by a decrease in the height of the epithelium lining the dorsal meatuses of Level II and the ethmoid turbinates of Level III due to variable loss of epithelial cells (Plate 9). Mild atrophy consisted of only loss of

sustentacular cells. Moderate atrophy consisted of loss of mostly sustentacular cells; however, there was also loss of olfactory neurons. In the most severe cases, there was complete loss of sustentacular cells and neurons, leaving only basal epithelial cells. Frequently, ciliated columnar cells replaced normal olfactory epithelium. Although included in the spectrum of changes diagnosed as olfactory epithelial atrophy, the latter alteration is often classified as respiratory epithelial metaplasia. Chronic inflammation of the olfactory region consisted of infiltrates of primarily mononuclear inflammatory cells within the lamina propria invariably accompanied by fibrosis (Plate 10). In affected sites, there was often synechia between adjacent turbinates.

Respiratory epithelial hyperplasia involved the lateral wall and medial surface of the naso- and maxilloturbinates, and was mostly focal to segmental but sometimes involved most of the turbinate extending onto the lateral wall in Levels I and II of the nasal cavity. The affected epithelia appeared thickened by increased numbers of disorganized, often pseudostratified, epithelial cells (Plate 11); component epithelial cells were non-ciliated flattened, or ciliated cuboidal to columnar ciliated. Frequently, the hyperplastic ciliated epithelium was folded in rugose fashion sometimes extending into the submucosa forming pseudoglands, or was continuous with the epithelium of submucosal glands. Respiratory epithelial squamous metaplasia involved the lateral surfaces of the nasoturbinates and the lateral wall in Level I of the nasal cavity. Metaplasia consisted of replacement of the normally ciliated respiratory epithelium by one to six layers of polygonal cells with flattening of the more superficial cells (Plate 12). Keratinization was seldom noted.

Glandular hyperplasia primarily affected the Bowman's glands of the nasal septum, in the dorsal meatus, and ethmoid turbinates in Level III of the nasal cavity. Hyperplasia consisted of proliferation of glands that were frequently enlarged or distended with cell debris and proteinaceous material (Plate 13). Frequently, affected glands were lined by hyperplastic ciliated epithelium that was continuous with that of the mucosa. The hyperplastic cells were often distended by intracytoplasmic protein or protein globules. Squamous metaplasia of glands often accompanied hyperplasia. It was characterized by replacement of the normal epithelial lining by several layers of nonkeratinized squamous cells that often obliterated the glandular lumen. Goblet cell hyperplasia was generally of minimal severity and primarily involved the respiratory epithelium of the nasal septum in Level I of the nasal cavity. Goblet cells were increased in number, were swollen with mucus, and often formed in small gland-like clusters within the mucosal epithelium (Plate 14). Hyaline degeneration was a focal or multifocal, minimal to mild change that affected both the respiratory and olfactory epithelia. Affected epithelial cells were swollen by intracytoplasmic homogenous, brightly eosinophilic globules (Plate 15). These globules are commonly observed in aging animals, and the severity may increase with age. In chronic inhalation studies, the incidence and severity of this change are often exacerbated in an exposure-dependent manner. Goblet cell hyperplasia and hyaline degeneration are considered nonspecific protective or adaptive responses to chronic inhalation of irritants.

Lung: The incidences of alveolar epithelial hyperplasia in all exposed groups of female rats were greater than that in the chamber controls (chamber control, 4/49; 10 ppm, 11/49; 30 ppm, 11/49; 60 ppm, 9/49; Table B5); the increased incidences in the 10 and 30 ppm groups were significant. However, in male rats, the incidences of hyperplasia were significantly decreased in the 10 and 30 ppm groups (23/49, 12/49, 9/48, 16/49; Table A5). The incidences of minimal chronic inflammation of the lungs were significantly increased in male rats exposed to 10 or 60 ppm (2/49, 13/49, 6/48, 15/49; Table A5). The incidences of lung neoplasms were not affected in exposed males (2/49, 3/49, 1/48, 0/49; Table A3) or females (1/49, 0/49, 0/49, 0/49; Table B1). Chronic inflammation consisted of small focal interstitial and intra-alveolar collections of varying numbers of macrophages, neutrophils, and lymphocytes along with minimal interstitial fibrosis. Mixed with the inflammatory cells were multinucleated giant cells, cell debris, and cholesterol clefts. This change occurred subpleurally and/or at the tips of lung lobes. Such minimal inflammatory foci are often found in chamber control rats, as they were in this study. Although the incidences of chronic inflammation were increased in groups exposed to naphthalene, it was not clear whether this change was exposure related.

Thyroid Gland: The incidences of C-cell adenoma or carcinoma (combined) decreased with increasing exposure concentration in female rats (7/47, 6/46, 4/48, 1/48; Table B3). A similar, but not statistically

significant, decrease was seen in males (chamber control, 10/46; 10 ppm, 8/47; 30 ppm, 5/45; 60 ppm, 5/47; Table A3). These slight differences were not considered biologically significant.

Toxicokinetic Results and Model

A physiologically based pharmacokinetic model representing the uptake, distribution, and metabolism of naphthalene in rats and mice was developed to describe the processes involved in naphthalene toxicokinetics (Appendix D). The model (Figure D1), which is diffusion limited (Kohn, 1997), contains compartments for arterial and venous blood, alveolar space, and tissue and capillary spaces for the lung, liver, kidney, fat and other organs. The compartment for other organs represents both slowly and rapidly perfused tissues (e.g., skin, muscle, bone, heart, and brain). Inhalation of naphthalene from the exposure chamber atmosphere takes place through the alveolar space into the lung. Uptake is modeled as being dependent on the ventilation rate of the animal, permeability of the tissue, and blood flow through the lung. The primary sites for naphthalene metabolism were assumed to be the lung and the liver. One metabolic pathway was modeled in the lung, while in the liver, two pathways were taken into account, one represented by Michaelis-Menten kinetics and the other by Hill kinetics. All the physiological parameters (ventilation rate, cardiac output, tissue volumes, capillary volumes, and blood flow rates to the tissues) used in this model were based on values obtained from the literature and scaled to the body weights of core study rats. Partition coefficients for the different tissues were calculated from the log of the octanol:water partition coefficient. Metabolic rates and permeability constants were estimated by optimizing the model to the available naphthalene blood time-course data. Goodness of fit was evaluated using a maximum-likelihood ratio test.

According to the model, naphthalene is rapidly taken up into the blood as a result of a high blood:air partition coefficient. Metabolism capacity in the lungs seems to be the same between male and female rats and between male and female mice, and the saturation level is equal for male and female rats. However, saturation of metabolism occurs at lower naphthalene blood concentrations in the female mouse than in the male mouse. The liver metabolic pathway represented by the Michaelis-Menten equation shows equal metabolic capacity and saturation level in male and female rats. However, both the metabolic capacity and saturation level are lower in female mice than in male mice. The second liver metabolic pathway, characterized by a Hill equation with a Hill exponent of 2, again shows equal metabolic capacity and saturation level for male and female rats. In mice, the Hill interpretation found that the metabolic capacity is the same for males and females, but the saturation level is lower for females.

Based on the available blood time-course data for naphthalene alone, no conclusions could be reached on which metabolites may be responsible for naphthalene toxicity.

GENETIC TOXICOLOGY

Naphthalene (0.3 to 100 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without induced rat or hamster liver S9 activation enzymes (Table C1; Mortelmans *et al.*, 1986). In contrast to these negative results for gene mutation induction in bacteria, naphthalene was positive for induction of chromosomal effects in mammalian cells *in vitro*. In cultured Chinese hamster ovary cells, naphthalene induced dose-related increases in sister chromatid exchanges, with and without rat liver S9 activation enzymes (Table C2). In addition, chromosomal aberrations were induced by naphthalene in cultured Chinese hamster ovary cells (Table C3). A strong dose-related increase in the percentage of aberrant cells was observed over a concentration range of 30 to 67.5 µg/mL naphthalene in the presence of S9, but no significant increases in chromosomal aberrations were seen without S9.

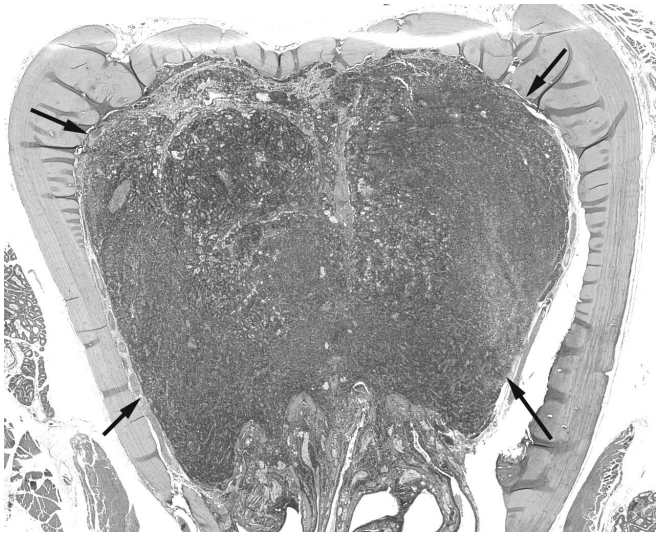


Plate 1

Neuroblastoma (arrows), Level III nasal cavity from a female rat exposed to 30 ppm Naphthalene by inhalation for 2 years. The neoplasm bilaterally obliterates the nasal architecture. H&E; 10X.

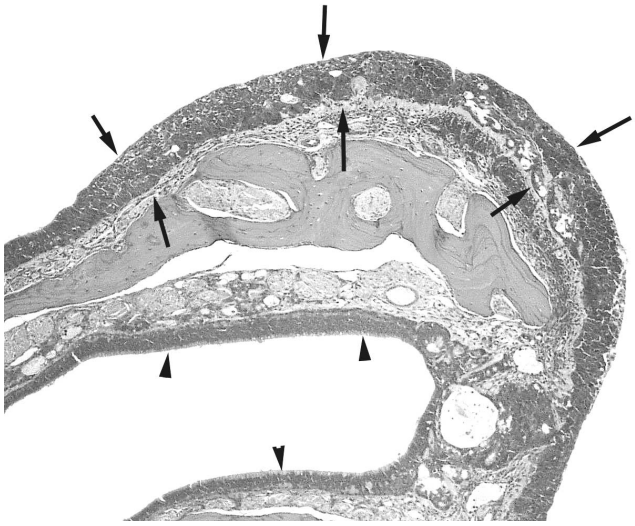


Plate 2

Neuroblastoma, Level III nasal cavity from a female rat exposed to 60 ppm naphthalene by inhalation for 2 years. The neoplasm extends along and thickens mucosa of the ethmoid turbinate (arrows). Note normal olfactory epithelium (arrowheads) lining theopposite side of the turbinate. H&E; 10X.

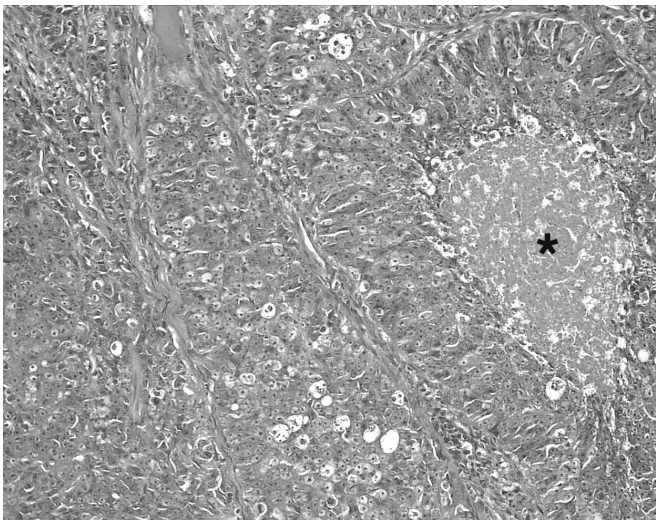


Plate 3

Higher magnification of Plate 1. The neoplastic cells are arranged in irregular lobules of variable size. Mitotic cells are abundant. Note focal area of necrosis (asterisk) within a lobule. H&E; 40X.

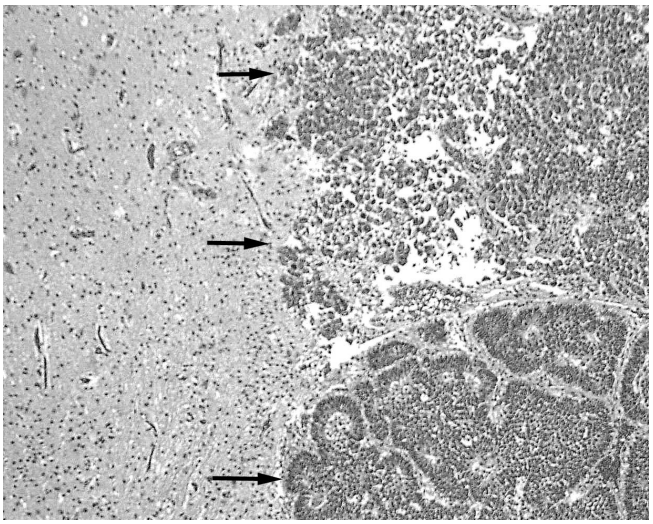


Plate 4

Neuroblastoma (arrows) invading the olfactory lobe of the brain from a female rats exposed to 60 ppm Naphthalene for 2 years. Neuropil of the olfactory lobe is at right. H&E; 10X.

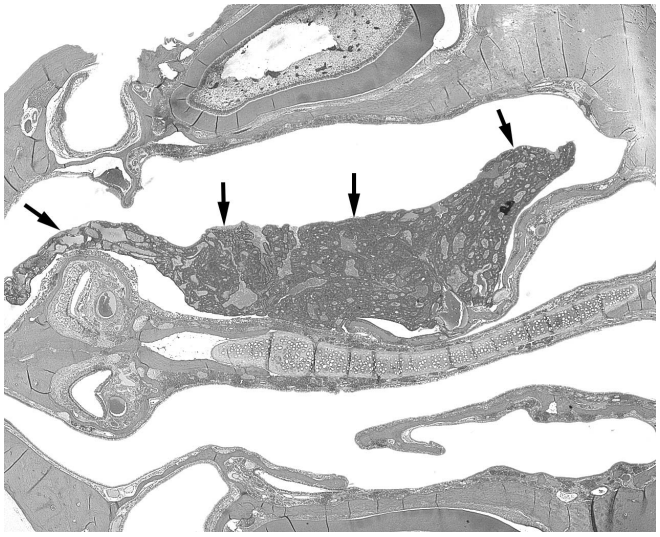


Plate 5
Large respiratory epithelial adenoma (arrows) within the nasal passages, Level I nasal cavity from a male rat exposed to 10 ppm Naphthalene by inhalation for 2 years. H&E; 10X.

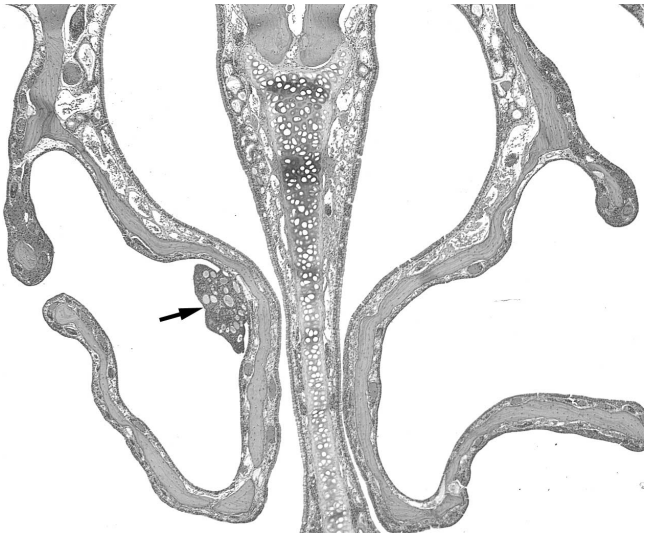


Plate 6
Small respiratory epithelial adenoma (arrow) within the nasal passages, Level I nasal cavity from a male rat exposed to 10 ppm Naphthalene by inhalation for 2 years. H&E; 20X.

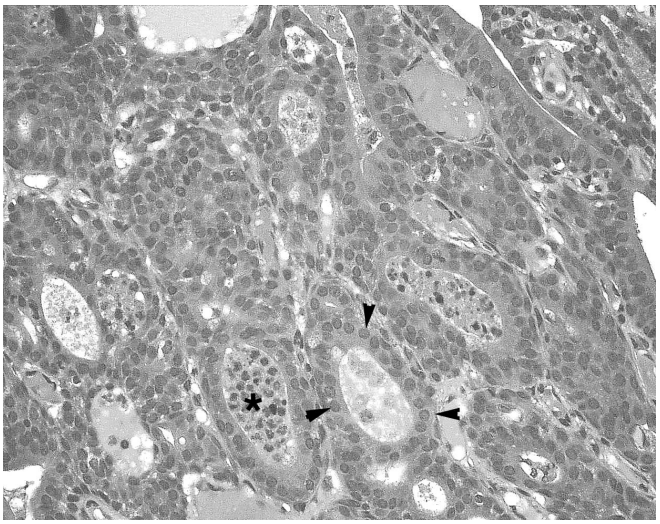


Plate 7
Higher magnification of Plate 5. Component cells are arranged in glands lined by cuboidal epithelial cells (arrowheads). Note cellular debris (asterisk) in the lumen of one gland. H&E; 40X

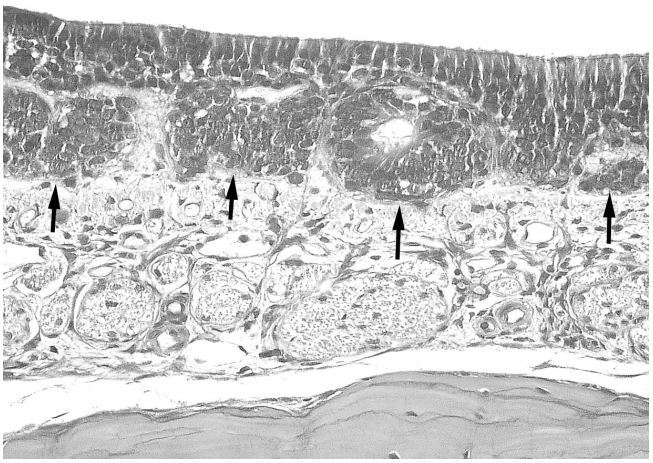


Plate 8
Atypical (basal cell) hyperplasia (arrows) of the olfcatory epithelium, Level III nasal cavity from a female rat exposed to 60 ppm Naphthalene by inhalation for 2 years. The hyperplastic basal cell form small nodules that extend into the submucosa. H&E; 40X.

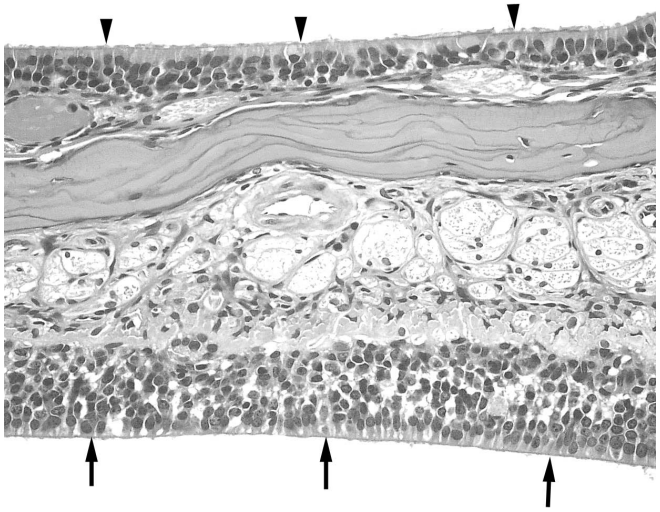


Plate 9

Atrophy (arrowheads) of the olfactory epithelium lining an ethmiod turbinate, Level III nasal cavity from a female rat exposed to 30 ppm Naphthalene for 2 years. The height of the epithelium is reduced due to loss of epithelial cells. Note normal olfactory epithelium (arrows) on the opposite side of the turbinate. H&E; 40X.

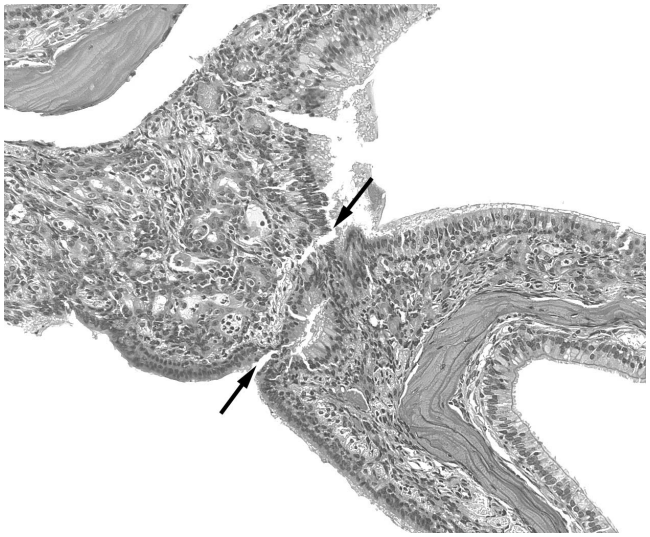


Plate 10

Chronic inflammation in the olfactory epithelium with synechia (arrows) of adjacent ethmoid turbinates, Level III nasal cavity from a female rat exposed to 60 ppm Naphthalene for 2 years. H&E; 20X.

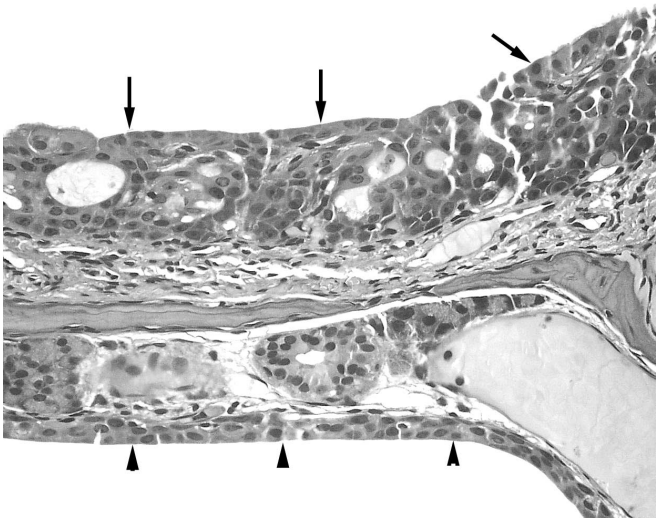


Plate 11

Maxilloturbinate with respiratory epithelial hyperplasia (arrows), Level II nasal cavity from a male rat exposed to 30 ppm Naphthalenee for 2 years. The affected epithelium is thickened by several disorganized layers of hyperplastic epithelial cells. Note normal respiratory epithelium (arrowheads) on the opposite side of the turbinate. H&E; 40X.

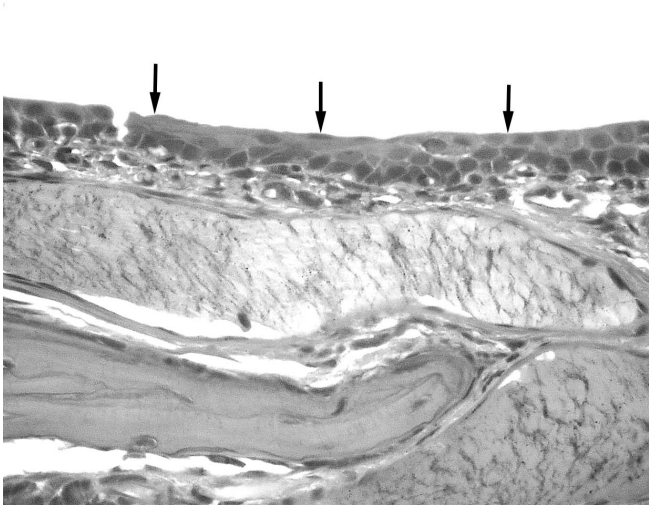


Plate 12

Suamous metaplasia (arrows) of the respiratory epithelium, Level II nasal cavity from a female rats exposed to 30 ppm Naphthalene. H&E; 40X

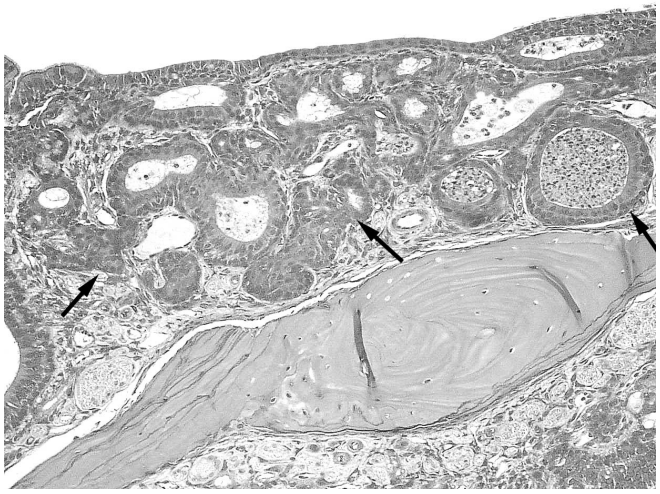


Plate 13

Focal Bowman's gland hyperplasia and squamous metaplasia (arrows), Level III nasal cavity from a female rat exposed to 30 ppm Naphthalene for 2 years. The majority of the glands are lined by non-keratinized squamous epithelium. Many glands are dilated and contain cellular debris and proteinaceous secretion. H&E; 20X

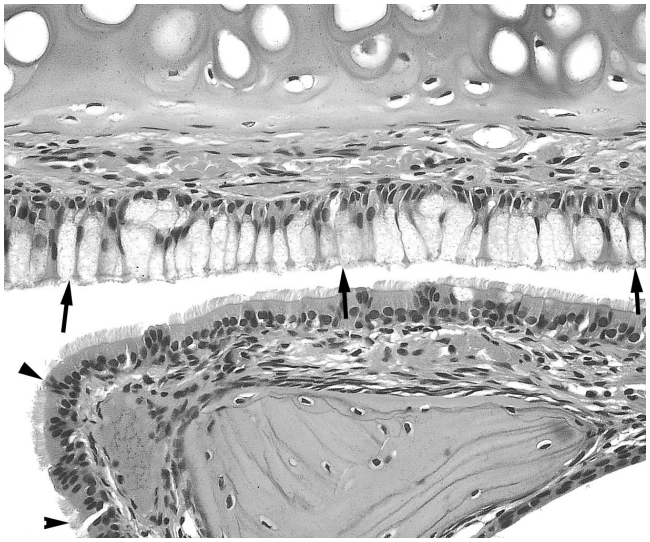


Plate 14

Goblet cell hyperplasia in the respiratory epithelium lining the nasal septum, Level II nasal cavity from a male rat exposed to 10 ppm Naphthalene for 2 years. The epithelium is lined by increased numbers of goblet cells that are swollen with mucus. Note normal respiratory epithelium (arrowheads) lining the maxilloturbinate. H&E; 40 x.

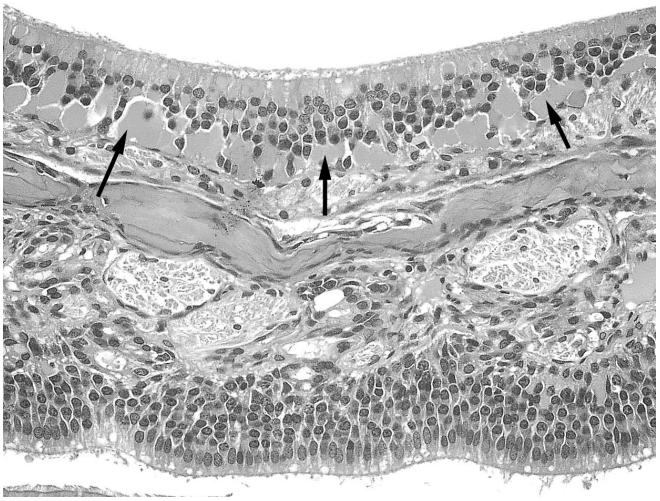


Plate 15

Ethmoid turbinate with hyaline degeneration in the olfactory epithelium, Level III nasal cavity from a male rat exposed to 10 ppm Naphthalene for 2 years. Epithelial cells are distended by hyaline droplets. H&E; 40X.

DISCUSSION AND CONCLUSIONS

Naphthalene, a white crystalline powder, is widely used as moth repellent and chemical intermediate in the synthesis of phthalic acid, naphthylamines, and synthetic resins. The National Institute of Occupational Safety and Health, the Occupational Safety and Health Administration, and the United States Environmental Protection Agency made the original nomination to test naphthalene for carcinogenicity. The nomination was based on the potential for chronic human exposure occupationally or through the use of mothballs in the home and the lack of adequate carcinogenicity studies to determine whether the use of naphthalene should be regulated. Because of the reported lack of carcinogenic activity of naphthalene in an oral rat study by Schmahl (1955), the NTP decided to initially study the carcinogenic potential of naphthalene only in mice. This study was completed and peer reviewed in 1991 (NTP, 1992). Because of the positive carcinogenic response (increased incidences of lung neoplasms in exposed female mice), the peer review panel recommended and the NTP concurred that an inhalation study be conducted in rats. The recommendation was made because previous studies with naphthalene in rats have been conducted via routes other than inhalation (the major route for human exposure) and because the Schmahl (1955) study was considered inadequate due to the small number of animals used (28 rats were dosed once daily, six times per week, until each was administered a total of 10 g over a 700-day period, or about 41 mg/kg per day).

No subchronic study was conducted because rats are considered to be less sensitive to naphthalene toxicity than mice, and mice in the NTP study were exposed to 10 or 30 ppm. The highest exposure concentration used in the current rat study (60 ppm) is the maximum that can be generated without naphthalene condensation. The lowest exposure concentration used equals the threshold limit value for the 8-hour, time-weighted average established by the American Conference of Governmental Industrial Hygienists (ACGIH, 1999). Based on the toxicokinetic model outlined in Appendix D, the daily doses delivered to male and female rats exposed to 0, 10, 30, or 60 ppm in the current study were estimated to be 0, 3.6 to 3.9, 10.7 to 11.4, and 20.1 to 20.6 mg/kg.

Although naphthalene is a known ocular irritant and a cataractogen (Rathbun *et al.,* 1990; Tao *et al.,* 1991), gross or microscopic evaluation of the eye did not reveal any exposure-related ocular abnormalities in rats in the current study. The absence of a cataractogenic effect in rats in the present study, as compared to rats in the studies conducted by Rathbun *et al.* (1990) and Tao *et al.* (1991), may be explained by the differences in exposure concentrations, route of exposure (oral versus inhalation), and/or the strain of rat used.

The nose was the site of toxicity and carcinogenicity in male and female rats. Neuroblastomas of the olfactory epithelium and adenomas of the respiratory epithelium occurred in exposed male and female rats. Because neither neuroblastomas nor adenomas occurred in the nose of concurrent chamber controls, nor have they been observed in the NTP historical control databases, these neoplasms were considered to be related to naphthalene exposure.

Along with the respiratory and olfactory neoplasms observed in the present study, the incidences of several accompanying nonneoplastic lesions were significantly increased in all exposed groups. These lesions included epithelial and goblet cell hyperplasia, squamous metaplasia, and hyaline degeneration of the respiratory epithelium; atrophy, atypical (basal cell) hyperplasia, inflammation, and hyaline degeneration of the olfactory epithelium; and hyperplasia and squamous metaplasia of the Bowman's glands in the olfactory region of the nose. With the exception of atypical hyperplasia of the olfactory epithelium, some or all of the nonneoplastic lesions observed in this study are commonly observed in NTP inhalation studies with chemicals of an irritant nature and appear to be adaptive responses. In some of these studies, the incidences of these lesions increased with increasing exposure concentration (NTP, 1997, 1998a,b, 1999). In a review of several previous NTP inhalation studies, no incidences of olfactory epithelial atypical (basal cell)

hyperplasia similar to those observed in this study were found. In the present study, the cells involved in this lesion and focal areas of intraepithelial hyperplasia/dysplasia appeared to be morphologically similar to and form a continuum with the neuroblastomas. In the respiratory epithelium, there was no clear association between the morphologies of the nonneoplastic proliferative changes and the development of respiratory epithelial adenomas.

Neuroblastomas of the nasal olfactory epithelium are rare neoplasms in rodents (Pino *et al.*, 1999) and humans (McElroy *et al.*, 1998). Experimentally, however, they have been induced by oral, inhalation, or peritoneal exposure to several structurally unrelated chemicals (Pino *et al.*, 1999). In some of these studies, the induction of nasal neoplasms occurred in conjunction with olfactory epithelial nonneoplastic lesions (squamous and respiratory metaplasia, basal cell hyperplasia, glandular hyperplasia). However, the association between these lesions and the development of neuroblastomas is not clear because in other studies, similar lesions occurred without the development of neuroblastomas (Miller *et al.*, 1985).

Some compounds that require metabolic activation by the cytochrome P450 enzyme system have been shown to cause olfactory epithelial injury, chronic hyperplastic/regenerative lesions, and olfactory neoplasms following oral or inhalation exposure. The type IV phosphodiesterase inhibitor RP 73401 induced nasal neuroblastomas and a spectrum of nonneoplastic lesions in the olfactory epithelium that appeared to be similar to those observed in this study (Pino *et al.*, 1999). No lesions occurred in the respiratory or transitional epithelia of the nasal cavity. The toxicity of RP 73401 was related to metabolic activation in the sustentacular cells of the olfactory epithelium. These cells have especially high concentrations of many metabolizing enzymes, particularly those of the cytochrome P450 (CYP2F) system, and are important sites of xenobiotic metabolism (Harkema and Morgan, 1996; Thornton-Manning and Dahl, 1997). The secretory cells of the respiratory epithelium also contain xenobiotic-metabolizing enzymes, including cytochrome P450 enzymes (Harkema and Morgan, 1996). The metabolism of naphthalene appears to be dependent on the cytochrome P450 enzyme system. The observed nasal toxicity observed in this study may be related, in part, to the metabolism of naphthalene in the respiratory and olfactory epithelia.

The carcinogenic effect of naphthalene observed in the nose of F344/N rats in the current study contrasts with the lack of carcinogenic effect of naphthalene observed in an earlier study with rats (strain unspecified) (Schmahl, 1955). The lack of concordance in results is likely due to differences in routes of administration (inhalation versus oral), strain of rat used, and, perhaps, the dose to the target tissue. Although some naphthalene would be expected to be eliminated in exhaled breath following oral administration as in the Schmahl (1955) study, the relatively low volatility and the high capacity for metabolism (Appendix D) may have limited the amount of parent compound that came in contact with the nasal tissue of animals in that study.

In a 2-year NTP inhalation study of naphthalene in $B6C3F_1$ mice, naphthalene was carcinogenic in females exposed to 30 ppm, causing an increased incidence of alveolar/bronchiolar adenoma (NTP, 1992). Two female mice exposed to 10 ppm had adenomas of the nasal respiratory epithelium; these adenomas were not considered to be related to exposure because none were found in females exposed to 30 ppm. In rats, increased incidences of chronic inflammation (males) and alveolar epithelial hyperplasia (females) were the only effects observed in the lung that may have been related to exposure. In mice, increased incidences of minimal to mild focal inflammation and metaplasia of the olfactory epithelium and hyperplasia of the respiratory epithelium occurred in the nose; however, neoplasms of olfactory epithelial origin were not observed.

The difference in sites of neoplasms in rats and mice may be related in part to the difference in anatomy of nasal passages in these two species, which may in turn lead to differences in doses delivered at this site. Swenberg *et al.* (1985) showed that the amount of formaldehyde inhaled by rats per unit time is twice that inhaled by mice when the dosage is normalized to the surface area of the nasal passages. Other potential factors that may account for the species differences in sites of neoplasms are rates of production and clearance of the carcinogenic metabolite of naphthalene by the nasal epithelia and lungs. Activation and deactivation of naphthalene as well as the accumulation of the carcinogenic metabolite could be greater in the nasal

epithelia of rats than in mice; conversely, activation and deactivation of naphthalene and accumulation of the carcinogenic metabolite could be greater in the lungs of mice than in rats.

A physiologically based toxicokinetic model was developed to characterize the disposition of inhaled naphthalene in rats and mice (Appendix D). This model was used to estimate the following parameters: a) the amount of naphthalene inhaled by rats and mice (NTP, 1992) at the exposure concentrations used in the 2-year studies of this chemical, b) the amount of the inhaled dose that was metabolized during the 6-hour (rat) or 6-hour (mouse) exposure and during the 18 hours following exposure, c) the steady-state concentrations of naphthalene in the lung and liver of rats and mice during exposure, and d) the rate of naphthalene metabolism in the lung and liver of rats and mice at these steady-state concentrations. Approximately 22% to 31% of inhaled naphthalene is metabolized by rats and 65% to 73% of inhaled naphthalene is metabolized by mice. These values for the percentage of the inhaled parent compound that is metabolized are greater than those reported for volatile chemicals (Richardson *et al.*, 1999) and probably reflect the low vapor pressure of naphthalene and its very high estimated blood-to-air partition coefficient. Thus, once naphthalene is absorbed into the general circulation, very little parent compound is eliminated by exhalation. Because essentially all of the naphthalene that is absorbed is metabolized, the values for total naphthalene metabolized (presented in mg/kg body weight in Tables D5 and D6) represent the internalized dose of naphthalene in rats and mice resulting from the 6-hour exposures. The species difference in the absorption of inhaled naphthalene probably reflects the greater metabolic capacity of mice compared to rats. Increased metabolism will tend to increase the gradient in concentration of naphthalene in the alveolar space compared to the lung blood and thus enhance further absorption of the compound. Total naphthalene metabolized (i.e., the internalized dose) was nearly equivalent for mice exposed to 10 ppm and rats exposed to 60 ppm. This difference is due to the higher ventilation rates and greater metabolism of naphthalene in mice compared to rats.

These data also show that the steady-state concentration of naphthalene in the lung of rats is not very different from that of mice exposed to equivalent concentrations. For example, after 6 hours of exposure to 30 ppm, the concentration of parent compound was 1.8 µg/mL in rats and 2.6 to 2.8 µg/mL in mice. Rats exposed to 60 ppm naphthalene had higher concentrations of naphthalene in the lung (5.3 µg/mL) than did mice exposed to 30 ppm. Rates of metabolism and the cumulative metabolism of naphthalene in the lung were markedly greater in mice than in rats. Rates of naphthalene metabolism did not increase proportionally with increasing exposure concentration, indicating metabolic saturation in this organ. Metabolic saturation was more evident in the rat lung than in the mouse lung. Naphthalene metabolism was also greater in the mouse liver than in the rat liver; however, the species difference in liver metabolism was not as marked as that in the lung. Metabolic saturation was only apparent in the liver of rats exposed to 60 ppm. For both species, 65% to 75% of the metabolic clearance occurred during the 6-hour exposure periods; only in 60 ppm rats was metabolic clearance at about 50% of the total inhaled dose. This is probably due to metabolic saturation resulting in greater storage of parent compound in the fat at this exposure concentration.

The results from the toxicokinetic model of naphthalene indicate that tissue dosimetry of parent compound does not alone explain why this chemical was carcinogenic to the mouse lung but not to the rat lung. For example, female rats exposed to 60 ppm naphthalene had a higher steady-state concentration of naphthalene in the lung than did female mice exposed to 30 ppm. The higher rates of naphthalene metabolism in the mouse lung compared to the rat lung may have been a contributing factor to this species difference in response. However, because the model does not include information on rates of detoxification of potential carcinogenic intermediates of naphthalene metabolism, it is not possible to compare lung concentrations of naphthalene metabolites to the exposure concentrations administered to rats and mice. If detoxification processes are faster in mice than in rats, then rates of metabolic activation alone could not serve as a reliable predictor of lung cancer risk. Naphthalene oxide is the primary metabolite formed by cytochrome P450-mediated oxidation of naphthalene. Mice appear to be more susceptible to lung neoplasm induction by epoxide and epoxide-forming chemicals than are rats (Melnick and Huff, 1993). Most notable in this respect is the finding that inhalation exposure to ethylene oxide induced lung neoplasms in mice (NTP,

1987) but not in rats (Lynch *et al.*, 1984; Snellings *et al.*, 1984). Thus, if naphthalene oxide is the sole agent responsible for lung neoplasm induction in mice exposed to naphthalene, then the species difference in response at this site may be due to a combination of higher rates of naphthalene oxide production in the mouse lung and, possibly, a greater susceptibility of the mouse lung to epoxide-induced carcinogenesis.

The mutagenic activity of naphthalene, as determined from the literature and from the results of NTP studies, is demonstrated primarily in assays that measure induction of chromosomal effects rather than gene mutations. The chemical did not induce mutations in *Salmonella* or cultured human MCL-5 cells, and the positive results in micronucleus assays (Djomo *et al.*, 1995; Sasaki *et al.*, 1997), chromosomal aberration tests (Appendix C), and recombination tests (Delgado-Rodriguez *et al.*, 1995) are consistent with a clastogenic mechanism of action. The results of the *Drosophila melanogaster* wing spot test (Delgado-Rodriguez *et al.*, 1995) and the NTP *in vitro* chromosomal aberrations test indicate that, at least for some endpoints, naphthalene mutagenicity requires or is enhanced by cytochrome P450 enzymes. The relationship between the *in vitro* mutagenicity test results with naphthalene in certain short-term assays and the carcinogenic response that occurred in the current rat study is unclear, however, because the metabolic activation enzymes in the mutagenicity test systems would not be expected to include the CYP2F2 enzyme that is selectively expressed in lung and olfactory mucosal cells (Wang *et al.*, 1998) and that has been demonstrated recently to play a key role in the bioactivation of naphthalene in the nose (Wang *et al.*, 1998; Shultz *et al.*, 1999). Biotransformation of naphthalene to yield reactive intermediates is likely to be accomplished through additional pathways.

CONCLUSIONS

Under the conditions of this 2-year inhalation study, there was *clear evidence of carcinogenic activity** of naphthalene in male and female F344/N rats based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose.

In male and female rats, exposure to naphthalene caused significant increases in the incidences of nonneoplastic lesions of the nose.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 10.

REFERENCES

Abdo, K.M., Eustis, S.L., McDonald, M., Jokinen, M.P., Adkins, B., Jr., and Haseman, J.K. (1992). Naphthalene: A respiratory tract toxicant and carcinogen for mice. *Inhalat. Toxicol.* **4**, 393-409.

Adkins, B., Jr., Van Stee, E.W., Simmons, J.E., and Eustis, S.L. (1986). Oncogenic response of strain A/J mice to inhaled chemicals. *J. Toxicol. Environ. Health* **17**, 311-322.

The Aldrich Library of FT-IR Spectra (1985). 1st ed. (C.J. Pouchert, Ed.), Vol. 1, p. 956A. Aldrich Chemical Company, Inc., St. Louis, MO.

Alexandrov, K., and Frayssinet, C. (1973). Brief communication: In vivo effect of some naphthalene-related compounds on aryl hydrocarbon (benzo[*a*]pyrene) hydroxylase. *J. Natl. Cancer Inst.* **51**, 1067-1069.

American Conference of Governmental Industrial Hygenists (ACGIH) (1999). *1999 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*. Cincinnati, OH.

Anziulewicz, J.A., Dick, H.J., and Chiarulli, E.E. (1959). Transplacental naphthalene poisoning. *Am. J. Obstet. Gynecol.* **78**, 519-521.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.

Bagchi, D., Bagchi, M., Balmoori, J., Vuchetich, P.J., and Stohs, S.J. (1998). Induction of oxidative stress and DNA damage by chronic administration of naphthalene to rats. *Res. Commun. Mol. Pathol. Pharmacol.* **101**, 249-257.

Bailer, A.J., and Portier, C.J. (1988). Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* **44**, 417-431.

Beratergremium für Umweltrelevante Altostoffe (BUA) (1989). Naphthalene (GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance, Eds.). BUA Report 39. VCH Verlagsgese, Weinheim, Germany.

Bieler, G.S., and Williams, R.L. (1993). Ratio of estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics* **49**, 793-801.

Bock, K.W., van Ackeren, G., Lorch, F., and Birke, F.W. (1976). Metabolism of naphthalene to naphthalene dihydrodiol glucuronide in isolated hepatocytes and in liver microsomes. *Biochem. Pharmacol.* **25**, 2351-2356.

Bock, K.W., von Clausbruch, U.C., and Winne, D. (1979). Absorption and metabolism of naphthalene and benzo(a)pyrene in the rat jejunum *in situ*. *Med. Biol.* **57**, 262-264.

Bolonova, L.N. (1967). Effect of naphthalene and its methyl derivatives on the content of ammonia in the brain of rats. *Farmakol. Toksikol.* **30**, 484-486.

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

Bos, R.P., Theuws, J.L.G., Jongeneelen, F.J., and Henderson, P.T. (1988). Mutagenicity of bi-, tri- and tetra-cyclic aromatic hydrocarbons in the "taped-plate assay" and in the conventional Salmonella mutagenicity assay. *Mutat. Res.* **204**, 203-206.

Boyland, E., Busby, E.R., Dukes, C.E., Grover, P.L., and Manson, D. (1964). Further experiments on implantation of materials into the urinary bladder of mice. *Br. J. Cancer* **18**, 575-581.

Buckpitt, A.R., and Bahnson, L.S. (1986). Naphthalene metabolism by human lung microsomal enzymes. *Toxicology* **41**, 333-341.

Buckpitt, A.R., and Richieri, P. (1984). Comparative biochemistry and metabolism: Part 2. Naphthalene lung toxicity. AFAMRL-TR-84-058. Systems Command, Aerospace Medical Division, Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Buckpitt, A.R., and Warren, D.L. (1983). Evidence for hepatic formation, export and covalent binding of reactive naphthalene metabolites in extrahepatic tissues *in vivo*. *J. Pharmacol. Exp. Ther.* **225**, 8-16.

Buckpitt, A.R., Castagnoli, N., Jr., Nelson, S.D., Jones, A.D., and Bahnson, L.S. (1987). Stereoselectivity of naphthalene epoxidation by mouse, rat, and hamster pulmonary, hepatic, and renal microsomal enzymes. *Drug Metab. Dispos.* **15**, 491-498.

Buckpitt, A., Buonarati, M., Avey, L.B., Chang, A.M., Morin, D., and Plopper, C.G. (1992). Relationship of cytochrome P450 activity and Clara cell cytotoxicity. II. Comparison of stereoselectivity of naphthalene epoxidation in lung and nasal mucosa of mouse, hamster, rat and rhesus monkey. *J. Pharmacol Exp. Ther.* **261**, 364-372.

Buckpitt, A., Chang, A.M., Weir, A., Van Winkle, L., Duan, X., Philpot, R., and Plopper, C. (1995). Relationship of cytochrome P450 activity to Clara cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. *Mol. Pharmacol.* **47**, 74-81.

Buonarati, M., Jones, A.D., and Buckpitt, A. (1990). In vivo metabolism of isomeric naphthalene oxide glutathione conjugates. *Drug. Metab. Dispos.* **18**, 183-189.

Chang, A., Plopper, C., Weir, A., Sassme, H., and Buckpitt, A. (1991). Correlation of species selective pulmonary toxicity to naphthalene (NA) with immunohistochemical localization of cytochrome P450MN and the stereoselective epoxidation of NA in airway explant incubations. *Toxicologist* **11**, 59 (Abstr.).

Chang, L.H. (1943). Fecal excretion of polycyclic hydrocarbons following their administration to the rat. *J. Biol. Chem.* **151**, 93-99.

Chemical Economics Handbook [database online] (2000). SRI International, Menlo Park, CA.

Chen, K.C., and Dorough, H.W. (1979). Glutathione and mercapturic acid conjugations in the metabolism of naphthalene and 1-naphthyl N-methylcarbamate (carbaryl). *Drug Chem. Toxicol.* **2**, 331-354.

Code of Federal Regulations (CFR) **21**, Part 58.

Connor, T.H., Theiss, J.C., Hanna, H.A., Monteith, D.K., and Matney, T.S. (1985). Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol. Lett.* **25**, 33-40.

Corner, E.D.S., and Young, L. (1954). The metabolism of naphthalene in animals of different species. *Biochem. J.* **58**, 647-655.

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

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology. Mechanisms and Toxicity of Chemical Carcinogens and Mutagens* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co., Inc., Princeton, NJ.

Dawson, J.P., Thayer, W.W., and Desforges, J.F. (1958). Acute hemolytic anemia in the newborn infant due to naphthalene poisoning: Report of two cases, with investigations into the mechanism of the disease. *Blood* **13**, 1113-1125.

de Bruin, A. (1976). *Biochemical Toxicology of Environmental Agents*, p. 1544. Elsevier/North-Holland Biomedical Press, New York.

Delgado-Rodriguez, A., Ortíz-Marttelo, R., Graf, U., Villalobos-Pietrini, R., and Gómez-Arroyo, S. (1995). Genotoxic activity of environmentally important polycyclic aromatic hydrocarbons and their nitro derivatives in the wing spot test of *Drosophila melanogaster*. *Mutat. Res.* **341**, 235-247.

Dixon, W.J., and Massey, F.J., Jr. (1951). *Introduction to Statistical Analysis*, 1st ed., pp. 145-147. McGraw-Hill Book Company, Inc., New York.

Djomo, J.E., Ferrier, V., Gauthier, L., Zoll-Moreux, C., and Marty, J. (1995). Amphibian micronucleus test *in vivo*: Evaluation of the genotoxicity of some major polycyclic aromatic hydrocarbons found in a crude oil. *Mutagenesis* **10**, 223-226.

Doherty, M.A., Makowski, R., Gibson, G.G., and Cohen, G.M. (1985). Cytochrome P-450 dependent metabolic activation of 1-naphthol to naphthoquinones and covalent binding species. *Biochem. Pharmacol.* **34**, 2261-2267.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1096-1121.

Eisele, G.R. (1985). Naphthalene distribution in tissues of laying pullets, swine, and dairy cattle. *Bull. Environ. Contam. Toxicol.* **34**, 549-556.

Fanucchi, M.V., Buckpitt, A.R., Murphy, M.E., and Plopper, C.G. (1997). Naphthalene cytotoxicity of differentiating Clara cells in neonatal mice. *Toxicol. Appl. Pharmacol.* **144**, 96-104.

Florin, I., Rutberg, L., Curvall, M., and Enzell, C.R. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology* **15**, 219-232.

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

Gerarde, H.W. (1960). *Toxicology and Biochemistry of Aromatic Hydrocarbons*, pp. 225-232. Elsevier, Amsterdam.

Ghetti, G., and Mariani, L. (1956). Eye changes due to naphthalene. *Med. Lav.* **47**, 524.

Gidron, E., and Leurer, J. (1956). Naphthalene poisoning. *Lancet* **1**, 228-230.

Gosselin, R.E., Smith, R.P., and Hodge, H.C. (1984). *Clinical Toxicology of Commercial Products*, 5th ed., p. III-307. Williams and Wilkins, Baltimore.

Haddad, L.M., and Winchester, J.F. (1983). *Clinical Management of Poisoning and Drug Overdose*, p. 888. Saunders, Philadelphia.

Hansch, C., Leo, A., and Hoekman, D. (1995). *QSAR–Hydrophobic, Electronic, and Steric Constants*. American Chemical Society, Washington, DC.

Harden, R.A., and Baetjer, A.M. (1978). Aplastic anemia following exposure to paradichlorobenzene and naphthalene. *J. Occup. Med.* **20**, 820-822.

Harkema, J.R., and Morgan, K.T. (1996). Proliferative and metaplastic lesions in nonolfactory nasal epithelia induced by inhaled chemicals. In *Respiratory System* (T.C. Jones, D.L. Dungrowth, and U. Mohr, Eds.) 2nd ed., pp. 18-28. Springer-Verlag, Berlin.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Honda, T., Kiyozumi, M., and Kojima, S. (1990). Alkylnaphthalene. XI. Pulmonary toxicity of naphthalene, 2-methylnaphthalene, and isopropylnaphthalenes in mice. *Chem. Pharm. Bull. (Tokyo)* **38**, 3130-3135.

Horning, M.G., Stillwell, W.G., Griffin, G.W., and Tsang, W.S. (1980). Expoxide intermediates in the metabolism of naphthalene by the rat. *Drug Metab. Dispos.* **8**, 404-414.

Jerina, D.M., Daly, J.W., Witkop, B., Zaltzman-Nirenberg, P., and Udenfriend, S. (1970). 1,2-Naphthalene oxide as an intermediate in the microsomal hydroxylation of naphthalene. *Biochemistry* **9**, 147-156.

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

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

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M., and Sugiyama, T. (1980). Cooperative programme on short-term assays for carcinogenicity in Japan. *IARC Sci. Publ.* **27**, 323-330.

Kennaway, E.L. (1930). Further experiments on cancer-producing substances. *Biochem. J.* **24**, 497-504.

Kirk-Othmer Encyclopedia of Chemical Technology (1978). 3rd ed. (M. Grayson, Ed.), Vol. 2, p. 704. John Wiley and Sons, New York.

Kirk-Othmer Encyclopedia of Chemical Technology (1979). 3rd ed. (M. Grayson and D. Eckroth, Eds.), Vol. 8, p. 367. John Wiley and Sons, New York.

Kirk-Othmer Encyclopedia of Chemical Technology (1981). 3rd ed. (M. Grayson and D. Eckroth, Eds.), Vol. 13, p. 466, and Vol. 15, p. 460. John Wiley and Sons, New York.

Knake, E. (1956). Über schwache geschwulsterzeugende Wirkung von Naphthalin und Benzol. *Virchows Arch. Pathol. Anat. Physiol.* **329**, 141-176.

Koch, H.R., and Doldi, K. (1975). Naphthalene cataracts in rats of differently pigmented strains. *Exp. Eye Res.* **20**, 180 (Abstr.).

Konar, N.R., Roy, H.K., and De, M.N. (1939). Naphthalene poisoning. *Indian Med. Gaz.* **74**, 723-725.

Kup, W. (1978). Work-related origin of cancer in the nose, mouth, throat, larynx. *Akad. Wiss.* **2**, 20-25.

Lakritz, J., Chang, A., Weir, A., Nishio, S., Hyde, D., Philpot, R., Buckpitt, A., and Plopper, C. (1996). Cellular and metabolic basis of Clara cell tolerance to multiple doses of cytochrome P450-activated cytotoxicants. I: Bronchiolar epithelial reorganization and expression of cytochrome P450 monooxygenases in mice exposed to multiple doses of naphthalene. *J. Pharmacol. Exp. Ther.* **278**, 1408-1418.

Lezenius, A. (1902). Ein Fall von Naphthalincataract am Menschen. *Klin. Monatsbl. Augenheilkd.* **40**, 129-140.

Lide, D.R., Ed. (1992). *CRC Handbook of Chemistry and Physics*, 73rd ed., p. 3–327. CRC Press, Boca Raton, FL.

Lynch, D.W., Lewis, T.R., Moorman, W.J., Burg, J.R., Groth, D.H., Khan, A., Ackerman, L.J., and Cockrell, B.Y. (1984). Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. *Toxicol. Appl. Pharmacol.* **76**, 69-84.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

McElroy, E.A., Jr., Buckner, J.C., and Lewis, J.E. (1998). Chemotherapy for advanced esthesioneuroblastoma: The Mayo Clinic experience. *Neurosurgery* **42**, 1023-1028.

MacGregor, R.R. (1954). Naphthalene poisoning from the ingestion of moth balls. *Can. Med. Assoc. J.* **70**, 313-314.

Mahvi, D., Bank, H., and Harley, R. (1977). Morphology of a naphthalene-induced bronchiolar lesion. *Am. J. Pathol.* **86**, 558-572.

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

Melnick, R.L., and Huff, J.E. (1993). 1,3-Butadiene induces cancer in experimental animals at all concentrations from 6.25 to 8000 parts per million. *IARC Sci. Publ.* **127**, 309-322.

Melzer-Lange, M., and Walsh-Kelly, C. (1989). Naphthalene-induced hemolysis in a black female toddler deficient in glucose-6-phosphate dehydrogenase. *Pediatr. Emerg. Care* **5**, 24-26.

The Merck Index (1989). 11th ed. (S. Budavari, Ed.), p. 1008. Merck and Company, Inc., Rahway, NJ.

The Merck Index (1996). 12th ed. (S. Budavari, Ed.), p. 1094. Merck and Company, Inc., Whitehouse Station, NJ.

Mersch-Sundermann, V., Mochayedi, S., and Kevekordes, S. (1992). Genotoxicity of polycyclic aromatic hydrocarbons in *Escherichia coli* PQ37. *Mutat. Res.* **278**, 1-9.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Miller, R.R., Young, J.T., Kociba, R.J., Keyes, D.G., Bonder, K.M., Calhoun, L.L., and Ayres, J.A. (1985). Chronic toxicity and oncogenicity bioassay of inhaled ethyl acrylate in Fischer 344 rats and B6C3F1 mice. *Drug Chem. Toxicol.* **8**, 1-42.

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

Narbonne, J.F., Cassand, P., Alzieu, P., Grolier, P., Mrlina, G., and Calmon, J.P. (1987). Structure-activity relationships of the *N*-methylcarbamate series in *Salmonella typhimurium*. *Mutat. Res.* **191**, 21-27.

National Institute for Occupational Safety and Health (NIOSH) (1997). *NIOSH Pocket Guide to Chemical Hazards*. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Washington, DC.

National Toxicology Program (NTP) (1987). Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS No. 75-21-8) in B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 326. NIH Publication No. 88-2582. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1992). Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 410. NIH Publication No. 92-3141. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1997). Toxicology and Carcinogenesis Studies of Nitromethane (CAS No. 75-52-5) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 461. NIH Publication No. 97-3377. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1998a). Toxicology and Carcinogenesis Studies of Chloroprene (CAS No. 126-99-8) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 467. NIH Publication No. 98-3957. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1998b). Toxicology and Carcinogenesis Studies of Cobalt Sulfate Heptahydrate (CAS No. 10026-24-1) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 471. NIH Publication No. 98-3961. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1999). Toxicology and Carcinogenesis Studies of Glutaraldehyde (CAS No. 111-30-8) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 490. NIH Publication No. 99-3980. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nohmi, T., Miyata, R., Yoshikawa, K., and Ishidate, M., Jr. (1985). Mutagenicity tests on organic chemical contaminants in city water and related compounds. I. Bacterial mutagenicity tests [in Japanese, English summary]. *Bull. Natl. Inst. Hyg. Sci.* **103**, 60-64.

O'Brien, K.A.F., Smith, L.L., and Cohen, G.M. (1985). Differences in naphthalene-induced toxicity in the mouse and rat. *Chem. Biol. Interact.* **55**, 109-122.

Piegorsch, W.W., and Bailer, A.J. (1997). *Statistics for Environmental Biology and Toxicology*, Section 6.3.2. Chapman and Hall, London.

Pino, M.V., Valerio, M.G., Miller, G.K., Larson, J.L., Rosolia, D.L., Jayyosi, Z., Crouch, C.N., Trojanowski, J.Q., and Geiger, L.E. (1999). Toxicologic and carcinogenic effects of the Type IV phosphodiesterase inhibitor RP 73401 on the nasal olfactory tissue in rats. *Toxicol. Pathol.* **27**, 383-394.

Plopper, C.G., Suverkropp, C., Morin, D., Nishio, S., and Buckpitt, A. (1992). Relationship of cytochrome P-450 activity to Clara cell cytotoxicity. I. Histopathologic comparison of the respiratory tract of mice, rats and hamsters after parenteral administration of naphthalene. *J. Pharmacol. Exp. Ther.* **261**, 353-363.

Portier, C.J., and Bailer, A.J. (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam. Appl. Toxicol.* **12**, 731-737.

Portier, C.J., Hedges, J.C., and Hoel, D.G. (1986). Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. *Cancer Res.* **46**, 4372-4378.

Potts, A.M. (1996). Toxic responses of the eye. In *Casarett and Doull's Toxicology: The Basic Science of Poisons* (C.D. Klaassen, Ed.), 5th ed., pp. 583-616. McGraw-Hill, New York.

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

Rao, G.N. (1996). New diet (NTP-2000) for rats in the National Toxicology Program toxicity and carcinogenicity studies. *Fundam. Appl. Toxicol.* **32**, 102-108.

Rao, G.N. (1997). New nonpurified diet (NTP-2000) for rodents in the National Toxicology Program's toxicology and carcinogenesis studies. *J. Nutr.* **127**, 842S-846S.

Rathbun, W.B., Holleschau, A.M., Murray, D.L., Buchanan, A., Sawaguchi, S., and Tao, R.V. (1990). Glutathione synthesis and glutathione redox pathways in naphthalene cataract of the rat. *Curr. Eye Res.* **9**, 45-53.

Rathbun, W.B., Nagasawa, H.T., and Killen, C.E. (1996a). Prevention of naphthalene-induced cataract and hepatic glutathione loss by the L-cysteine prodrugs, MTCA and PTCA. *Exp. Eye Res.* **62**, 433-441.

Rathbun, W.B., Holleschau, A.M., Cohen, J.F., and Nagasawa, H.T. (1996b). Prevention of acetaminophen- and naphthalene-induced cataract and glutathione loss by CySSME. *Invest. Opthalmol. Vis. Sci.* **37**, 923-929.

Richardson, K.A., Peters, M.M., Wong, B.A., Megens, R.H., van Elburg, P.A., Booth, E.D., Boogaard, P.J., Bond, J.A., Medinsky, M.A., Watson, W.P., and van Sittert, N.J. (1999). Quantitative and qualitative differences in the metabolism of ^{14}C-1,3-butadiene in rats and mice: Relevance to cancer susceptibility. *Toxicol. Sci.* **49**, 186-201.

Rossoff, I.S. (1974). *Handbook of Veterinary Drugs*, p. 377. Springer Publishing, New York.

Sadtler Standard Spectra. IR No. 169K; NMR No. 62M. Sadtler Research Laboratories, Philadelphia.

Sakai, M., Yoshida, D., and Mizusaki, S. (1985). Mutagenicity of polycyclic aromatic hydrocarbons and quinones on *Salmonella typhimurium* TA97. *Mutat. Res.* **156**, 61-67.

Santhanakrishnan, B.R., Ranganathan, G., and Raju, V.B. (1973). Naphthalene induced haemolytic anaemia with haemoglobinuria. *Indian J. Pediatr.* **40**, 195-197.

Sasaki, J.C., Arey, J., Eastmond, D.A., Parks, K.K., and Grosovsky, A.J. (1997). Genotoxicity induced in human lymphoblasts by atmospheric reaction products of naphthalene and phenanthrene. *Mutat. Res.* **393**, 23-35.

Sax, N.I. (1984). *Dangerous Properties of Industrial Materials*, 6th ed., p. 1971. Van Nostrand Reinhold Company, New York.

Schmahl, D. (1955). Prüfung von Naphthalin und Anthracen auf cancerogene Wirkung an Ratten. *Zeit. Krebsforsch.* **60**, 697-710.

Schmeltz, I., Tosk, J., Hilfrich, J., Horita, N., Hoffman, D., and Wynder, E.L. (1978). Bioassays of naphthalene and alkylnaphthalenes for co-carcinogenic activity: Relation to tobacco carcinogenesis. In *Carcinogenesis–A Comprehensive Survey* (P.W. Jones and R.I. Freudenthal, Eds.), Vol. 3, pp. 47-60. Raven, New York.

Shichi, H., Tanaka, M. Jensen, N.M., and Nebert, D.W. (1980). Genetic differences in cataract and other ocular abnormalities induced by paracetamol and naphthalene. *Pharmacology* **20**, 229-241.

Shopp, G.M., White, K.L., Jr., Holsapple, M.P., Barnes, D.W., Duke, S.S., Anderson, A.C., Condie, L.W., Jr., Hayes, J.R., and Borzelleca, J.F. (1984). Naphthalene toxicity in CD-1 mice: General toxicology and immunotoxicology. *Fundam. Appl. Toxicol.* **4**, 406-419.

Shultz, M.A., Choudary, P.V., and Buckpitt, A.R. (1999). Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. *J. Pharmacol. Exp. Ther.* **290**, 281-288.

Sims, P., and Grover, P.L. (1974). Epoxides in polycyclic aromatic hydrocarbon metabolism and carcinogenesis. *Adv. Cancer Res.* **20**, 165-274.

Snellings, W.M., Weil, C.S., and Maronpot, R.R. (1984). A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. *Toxicol. Appl. Pharmacol.* **75**, 105-117.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233-241.

Summer, K.H., Rozman, K., Coulston, F., and Greim, H. (1979). Urinary excretion of mercapturic acids in chimpanzees and rats. *Toxicol. Appl. Pharmacol.* **50**, 207-212.

Suter, W., and Jaeger, I. (1982). Comparative evaluation of different pairs of DNA repair-deficient and DNA repair-proficient bacterial tester strains for rapid detection of chemical mutagens and carcinogens. *Mutat. Res.* **97**, 1-18.

Swenberg, J.A., Heck, Hd'A, Morgan, K.T., and Star, T.B. (1985). A scientific approach to formaldehyde risk assessment. In *Risk Quantitation and Regulatory Policy: 19th Banbury Report* (D.G. Hoel, R.A. Merrill, and F.P. Perera, Eds.), pp. 255-267. Cold Spring Harbor, NY.

Takizawa, N. (1940). Carcinogenic action of quinones. *Proc. Imp. Acad. (Tokyo)* **16**, 309.

Tanooka, H. (1977). Development and applications of *Bacillus subtilis* test systems for mutagens involving DNA-repair deficiency and suppressible auxotrophic mutations. *Mutat. Res.* **42**, 19-31.

Tao, R.V., Holleschau, A.M., and Rathbun, W.B. (1991). Naphthalene-induced cataract in the rat. II. Contrasting effects of two aldose reductase inhibitors on glutathione and glutathione redox enzymes. *Opthalmic Res.* **23**, 272-283.

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

Taylor, C.J.S.O., and Russell, H. (1932). Blackwater fever and naphthalene poisoning. *West Afr. Med. J.* **5**, 48-49.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* **236**, 933-941.

Thornton-Manning, J.R., and Dahl, A.R. (1997). Metabolic capacity of nasal tissue interspecies comparisons of xenobiotic-metabilizing enzymes. *Mutat. Res.* **380**, 43-59.

Tingle, M.D., Pirmohamed, M., Templeton, E., Wilson, A.S., Madden, S., Kitteringham, N.R., and Park, B.K. (1993). An investigation of the formation of cytotoxic, genotoxic, protein-reactive and stable metabolites from naphthalene by human liver microsomes. *Biochem. Pharmacol.* **46**, 1529-1538.

Tong, S.S., Hirokata, Y., Trush, M.A., Mimnaugh, E.G., Ginsburg, E., Lowe, M.C., and Gram., T.E. (1981). Clara cell damage and inhibition of pulmonary mixed-function oxidase activity by naphthalene. *Biochem. Biophys. Res. Commun.* **100**, 944-950.

Tong, S.S., Lowe, M.C., Trush, M.A., Mimnaugh, E.G., Ginsburg, E., Hirokata, Y., and Gram., T.E. (1982). Bronchiolar epithelial damage and impairment of pulmonary microsomal monooxygenase activity in mice by naphthalene. *Exp. Mol. Pathol.* **37**, 358-369.

Turkall, R.M., Skowronski, G.A., Kadry, A.M., and Abdel-Rahman, M.S. (1994). A comparative study of the kinetics and bioavailability of pure and soil-adsorbed naphthalene in dermally exposed male rats. *Arch. Environ. Contam. Toxicol.* **26**, 504-509.

U.S. Environmental Protection Agency (USEPA) (1980). Ambient Water Quality Criteria for Naphthalene. USEPA 440/5-80-059. NTIS PB81-117707. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. Environmental Protection Agency (USEPA) (1990). Drinking Water Health Advisories for 15 Volatile Organic Chemicals. NTIS PB90-259821. Office of Drinking Water, Washington, DC.

Valaes, T., Doxiadis, S.A., and Fessas, P. (1963). Acute hemolysis due to naphthalene inhalation. *J. Pediatr.* **63**, 904-915.

Van der Hoeve, J. (1906). Choreoretinitis beim Menschen durch die Einwirking von Naphthalin. *Arch. Augenheilk.* **56**, 259.

van Heyningen, R. (1979). Naphthalene cataract in rats and rabbits: A resume. *Exp. Eye Res.* **28**, 435-439.

Vuchetich, P.J, Bagchi, D., Bagchi, M., Hassoun, E.A., Tang, L., and Stohs, S.J. (1996). Naphthalene-induced oxidative stress in rats and the protective effects of vitamin E succinate. *Free Radic. Biol. Med.* **21**, 577-590.

Wang, H., Lanza, D.L., and Yost, G.S. (1998). Cloning and expression of CYP2F3, a cytochrome P450 that bioactivates the selective pneumotoxins 3-methylindole and naphthalene. *Arch. Biochem. Biophys.* **349**, 329-340.

Wells, P.G., Wilson, B., and Lubek, B.M. (1989). *In vivo* murine studies on the biochemical mechanism of naphthalene cataractogenesis. *Toxicol. Appl. Pharmacol.* **99**, 466-473.

Wiley Mass Spectral Database. Spectrum No. 6075. Hewlett-Packard, Palo Alto, CA.

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

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

Wilson, A.S., Tingle, M.D., Kelly, M.D., and Park, B.K. (1995). Evaluation of the generation of genotoxic and cytotoxic metabolites of benzo[a]pyrene, aflatoxin B_1, naphthalene and tamoxifen using human liver microsomes and human lymphocytes. *Hum. Exp. Toxicol.* **14**, 507-515.

Wolf, O. (1976). Cancer among chemical workers of a naphthalene cleaning plant. *Dtsch. Gesundheitsw.* **31**, 996-999.

Wolf, O. (1978). Carcinoma of the larynx in naphthalene cleaners. *Z. Gesamte Hyg.* **24**, 737-739.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four in vitro genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

Zheng, J., Cho, M., Jones, A.D., and Hammock, B.D. (1997). Evidence of quinone metabolites of naphthalene covalently bound to sulfur nucleophiles of proteins of murine Clara cells after exposure to naphthalene. *Chem. Res. Toxicol.* **10**, 1008-1014.

Zinkham, W.H., and Childs, B. (1958). A defect of glutathione metabolism in erythrocytes from patients with naphthalene-induced hemolytic anemia. *Pediatrics* **22**, 461-471.

Zuelzer, W.W., and Apt, L. (1949). Acute hemolytic anemia due to naphthalene poisoning. *J. Am. Med. Assoc.* **141**, 185-190.

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

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

	Chamber Control	10 ppm	30 ppm	60 ppm
Disposition Summary				
Animals initially in study	49	49	49	49
Early deaths				
Moribund	21	22	19	25
Natural deaths	4	5	6	3
Survivors				
Terminal sacrifice	24	22	23	21
Missexed			1	
Animals examined microscopically	49	49	48	49
Alimentary System				
Intestine large, colon	(48)	(49)	(48)	(48)
Polyp adenomatous			1 (2%)	
Intestine large, cecum	(46)	(49)	(47)	(48)
Intestine small, jejunum	(45)	(47)	(43)	(47)
Carcinoma				1 (2%)
Leiomyosarcoma				1 (2%)
Intestine small, ileum	(45)	(47)	(45)	(47)
Liver	(49)	(49)	(48)	(49)
Hepatocellular carcinoma	1 (2%)			1 (2%)
Hepatocellular adenoma	1 (2%)			3 (6%)
Mesentery	(13)	(6)	(9)	(8)
Hemangiosarcoma				1 (13%)
Sarcoma	1 (8%)			
Pancreas	(49)	(49)	(48)	(49)
Adenoma	1 (2%)			2 (4%)
Carcinoma				1 (2%)
Mixed tumor benign			1 (2%)	
Salivary glands	(49)	(49)	(47)	(49)
Stomach, forestomach	(49)	(49)	(48)	(49)
Stomach, glandular	(49)	(49)	(48)	(49)
Tongue		(1)	(1)	
Squamous cell carcinoma		1 (100%)		
Cardiovascular System				
Heart	(49)	(49)	(48)	(49)
Schwannoma benign		1 (2%)	2 (4%)	
Schwannoma malignant, metastatic, skin			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Endocrine System				
Adrenal cortex	(49)	(49)	(48)	(49)
Adenoma	2 (4%)		1 (2%)	2 (4%)
Adrenal medulla	(49)	(49)	(47)	(49)
Pheochromocytoma malignant	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Pheochromocytoma benign	4 (8%)	6 (12%)	6 (13%)	8 (16%)
Bilateral, pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(49)	(49)	(48)	(49)
Adenoma	2 (4%)	5 (10%)	3 (6%)	2 (4%)
Carcinoma	4 (8%)	4 (8%)	4 (8%)	4 (8%)
Pituitary gland	(49)	(49)	(47)	(49)
Pars distalis, adenoma	31 (63%)	31 (63%)	35 (74%)	29 (59%)
Thyroid gland	(46)	(47)	(45)	(47)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	9 (20%)	5 (11%)	4 (9%)	4 (9%)
C-cell, carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma		1 (2%)		
General Body System				
Tissue NOS		(1)		
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (100%)		
Genital System				
Epididymis	(49)	(49)	(48)	(49)
Preputial gland	(48)	(49)	(47)	(49)
Adenoma	3 (6%)		1 (2%)	1 (2%)
Carcinoma	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Prostate	(49)	(49)	(48)	(49)
Seminal vesicle	(47)	(49)	(47)	(47)
Carcinoma			1 (2%)	
Testes	(49)	(49)	(48)	(49)
Bilateral, interstitial cell, adenoma	24 (49%)	22 (45%)	19 (40%)	20 (41%)
Interstitial cell, adenoma	14 (29%)	10 (20%)	17 (35%)	11 (22%)
Hematopoietic System				
Bone marrow	(49)	(49)	(48)	(49)
Lymph node	(3)	(3)	(8)	(4)
Lymph node, bronchial	(29)	(36)	(38)	(35)
Lymph node, mandibular	(40)	(45)	(46)	(44)
Lymph node, mesenteric	(47)	(49)	(48)	(49)
Lymph node, mediastinal	(24)	(28)	(44)	(41)
Spleen	(49)	(49)	(48)	(49)
Hemangiosarcoma		1 (2%)		1 (2%)
Thymus	(47)	(46)	(43)	(46)
Schwannoma malignant, metastatic, skin			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Integumentary System				
Mammary gland	(21)	(20)	(30)	(28)
Carcinoma	1 (5%)	1 (5%)	1 (3%)	
Fibroadenoma				3 (11%)
Skin	(48)	(48)	(48)	(48)
Basal cell adenoma		1 (2%)	2 (4%)	
Keratoacanthoma	4 (8%)	3 (6%)	2 (4%)	2 (4%)
Squamous cell carcinoma		1 (2%)		
Sebaceous gland, adenoma	1 (2%)	1 (2%)		1 (2%)
Sebaceous gland, carcinoma			1 (2%)	
Subcutaneous tissue, fibroma	5 (10%)	2 (4%)	2 (4%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)		2 (4%)
Subcutaneous tissue, fibrosarcoma, multiple		1 (2%)		
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)	3 (6%)	
Subcutaneous tissue, neural crest tumor				1 (2%)
Subcutaneous tissue, sarcoma		1 (2%)	2 (4%)	
Subcutaneous tissue, schwannoma malignant			1 (2%)	
Musculoskeletal System				
Bone	(49)	(49)	(48)	(49)
Osteosarcoma	1 (2%)	1 (2%)		
Nervous System				
Brain	(49)	(49)	(48)	(49)
Neuroblastoma, metastatic, nose				2 (4%)
Spinal cord		(1)		
Respiratory System				
Larynx	(49)	(49)	(48)	(49)
Schwannoma malignant, metastatic, skin			1 (2%)	
Lung	(49)	(49)	(48)	(49)
Alveolar/bronchiolar adenoma	2 (4%)		1 (2%)	
Alveolar/bronchiolar carcinoma		3 (6%)		
Carcinoma, metastatic, preputial gland	1 (2%)			
Carcinoma, metastatic, thyroid gland	1 (2%)			
Carcinoma, metastatic, Zymbal's gland			1 (2%)	1 (2%)
Neuroblastoma, metastatic, nose			1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)	1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)	1 (2%)	1 (2%)	
Schwannoma malignant, metastatic, skin			1 (2%)	
Nose	(49)	(49)	(48)	(48)
Olfactory epithelium, neuroblastoma			4 (8%)	3 (6%)
Respiratory epithelium, adenoma		6 (12%)	8 (17%)	15 (31%)
Special Senses System				
Eye	(48)	(48)	(48)	(48)
Zymbal's gland			(1)	(1)
Carcinoma			1 (100%)	
Bilateral, carcinoma				1 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Urinary System				
Kidney	(49)	(49)	(48)	(49)
Schwannoma malignant, metastatic, skin			1 (2%)	
Renal tubule, carcinoma				1 (2%)
Transitional epithelium, carcinoma	1 (2%)			
Urinary bladder	(48)	(49)	(48)	(49)
Transitional epithelium, papilloma	1 (2%)			2 (4%)
Systemic Lesions				
Multiple organs[b]	(49)	(49)	(48)	(49)
Leukemia mononuclear	26 (53%)	21 (43%)	24 (50%)	17 (35%)
Mesothelioma benign	2 (4%)		1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	48	49	48	49
Total primary neoplasms	149	139	152	148
Total animals with benign neoplasms	46	47	47	47
Total benign neoplasms	107	96	110	108
Total animals with malignant neoplasms	34	32	34	32
Total malignant neoplasms	42	43	42	39
Total animals with metastatic neoplasms	4	3	4	2
Total metastatic neoplasms	4	3	8	2
Total animals with uncertain neoplasms–benign or malignant				1
Total uncertain neoplasms				1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	460	460	469	502	516	572	615	611	624	634	639	657	658	660	660	677	678	692	695	703	708	709	713	721	726
Carcass ID Number	03939	04045	04044	00046	00068	02025	03731	04141	03132	01416	01009	01013	04148	02427	04343	04404	02424	02121	01210	02007	04046	02323	03434	01518
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma									X																
Mesentery				+	+			+				+				+		+							
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+																								
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X									X				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X							
Pheochromocytoma benign											X						X				X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Carcinoma																X			X						
Parathyroid gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X	X	X	X	X	X	X		X	X	X		X	X			X		X
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A
C-cell, adenoma		X									X														
C-cell, carcinoma																									
General Body System																									
None																									

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 2	0 0 3	0 0 5	0 1 1	0 1 2	0 1 4	0 1 5	0 2 2	0 2 6	0 2 8	0 3 3	0 3 5	0 4 2	0 4 7	0 4 9	0 4 4	0 1 7	0 1 9	0 2 9	0 3 0	0 3 6	0 3 7	0 3 8	0 4 4	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma															X										1
Hepatocellular adenoma																									1
Mesentery	+			+		+					+					+					+	+			13
Sarcoma						X																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																X									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																									1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																									1
Pheochromocytoma benign							X																		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X													2
Carcinoma			X																X						4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X			X	X			X		X	X				X	X	X	X	X	X	X	X	31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell, adenoma	X			X			X		X	X	X											X			9
C-cell, carcinoma																								X	1
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	460	460	469	502	516	572	615	615	624	634	639	657	658	660	660	677	678	692	695	703	708	709	713	721	726
Carcass ID Number	03939	04505	04044	00066	00088	02525	03131	04111	03212	01616	01099	01313	04818	02727	04343	04040	02424	02121	01010	02020	00707	04646	02323	03434	01118
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma							X							X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma												X					X				X	X			
Interstitial cell, adenoma		X			X			X	X					X	X			X					X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node														+						+		+			
Lymph node, bronchial	+	+	M	+	+	M	M	+	+	M	M	M	+	+	M	M	+	M	M	M	M	M	M	+	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	M	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Lymph node, mediastinal	+	+	+	M	+	+	M	M	+	M	M	M	+	+	M	M	+	M	M	+	M	+	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	M	+	M	+	+	+	M	+	M	+	M	M	M	M	M	M	M	M	+	M	M	+	M
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																		X			X				
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma		X																							
Subcutaneous tissue, fibrosarcoma																	X								
Subcutaneous tissue, lipoma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																					X				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, preputial gland							X																		
Carcinoma, metastatic, thyroid gland																									
Osteosarcoma, metastatic, bone																					X				
Pheochromocytoma malignant, metastatic, adrenal medulla																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 2	0 0 3	0 0 5	0 1 1	0 1 2	0 1 4	0 1 5	0 2 2	0 2 6	0 2 8	0 3 3	0 3 5	0 4 2	0 4 7	0 4 9	0 1	0 1 7	0 1 9	0 2 9	0 3 0	0 3 6	0 3 7	0 3 8	0 4 4	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48	
Adenoma								X						X							X				3	
Carcinoma															X										3	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X			X	X	X	X	24	
Interstitial cell, adenoma			X									X							X	X					14	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph node																									3	
Lymph node, bronchial	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	29	
Lymph node, mandibular	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	40	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Lymph node, mediastinal	M	M	M	M	M	+	M	M	M	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	24	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	47	
Integumentary System																										
Mammary gland	M	M	+	+	M	+	M	M	M	M	M	I	+	+	+	M	+	+	M	+	+	M	+	+	21	
Carcinoma																								X	1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	48	
Keratoacanthoma				X															X						4	
Sebaceous gland, adenoma																			X						1	
Subcutaneous tissue, fibroma			X										X	X									X		5	
Subcutaneous tissue, fibrosarcoma											X														2	
Subcutaneous tissue, lipoma																									1	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Osteosarcoma																									1	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Alveolar/bronchiolar adenoma	X					X																			2	
Carcinoma, metastatic, preputial gland																									1	
Carcinoma, metastatic, thyroid gland																								X	1	
Osteosarcoma, metastatic, bone																									1	
Pheochromocytoma malignant, metastatic, adrenal medulla																									1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	460	460	469	502	516	572	615	615	624	634	639	657	658	660	660	677	678	692	695	703	708	709	713	721	726
Carcass ID Number	03 9	04 5	04 4	00 6	00 8	02 5	03 1	04 1	03 2	01 6	01 9	01 3	04 8	02 7	04 3	04 0	02 4	02 1	01 0	02 0	00 7	04 6	02 3	03 4	01 8
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X			X	X	X				X	X	X		X	X		X		X	X
Mesothelioma benign																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 2	0 0 3	0 0 5	0 1 1	0 1 2	0 1 4	0 1 5	0 2 2	0 2 6	0 2 8	0 3 3	0 3 5	0 4 2	0 4 7	0 4 9	0 0 1	0 1 7	0 1 9	0 2 9	0 3 0	0 3 6	0 3 7	0 3 8	0 4 4	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, carcinoma																										1
Urinary bladder	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional epithelium, papilloma				X																						1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X	X		X		X	X	X				X	X						X	X		X	X		26
Mesothelioma benign		X						X																		2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	390	435	502	505	520	525	551	567	593	600	615	643	643	643	648	665	677	678	680	681	681	684	684	695	700
Carcass ID Number	221	242	210	239	348	418	105	443	417	428	424	206	416	429	236	222	232	246	266	211	215	202	208	244	231
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																	+		+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue											+														
Squamous cell carcinoma											X														
Tooth						+							+												
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																								X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																									
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X		X	X		X	X		X	X			X		X		X			X	X	X		
Thyroid gland	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma							X				X														
C-cell, carcinoma														X											
Follicular cell, carcinoma																					X				
General Body System																									
Tissue NOS																									
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X			X	X	X			X		X	X				X	
Interstitial cell, adenoma					X			X							X							X			X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	7 1 3	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 3 3	2 0 1	2 0 3	2 0 4	2 0 7	2 0 9	2 1 2	2 1 4	2 1 9	2 2 3	2 2 5	2 3 0	2 3 5	2 3 7	2 3 8	2 4 9	2 1 3	2 2 0	2 2 7	2 3 4	2 4 0	2 4 1	2 4 5	2 4 7	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery						+							+					+						+	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																									1
Squamous cell carcinoma																									1
Tooth																									2
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma benign																				X					1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant			X	X																X					3
Pheochromocytoma benign							X					X				X		X			X		X		6
Bilateral, pheochromocytoma benign																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X									X					X	X							5
Carcinoma											X			X		X			X						4
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X		X		31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bilateral, C-cell, adenoma			X																						1
C-cell, adenoma				X					X										X						5
C-cell, carcinoma							X																		2
Follicular cell, carcinoma																									1
General Body System																									
Tissue NOS			+																						1
Pheochromocytoma malignant, metastatic, adrenal medulla			X																						1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma		X	X				X	X	X		X	X	X		X			X			X	X	X	X	22
Interstitial cell, adenoma	X			X	X														X	X					10

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	3 9 0	4 3 5	5 0 2	5 0 5	5 2 0	5 2 5	5 5 1	5 6 7	5 9 3	6 0 0	6 1 5	6 4 3	6 4 3	6 4 3	6 4 8	6 6 5	6 7 7	6 7 8	6 8 0	6 8 1	6 8 1	6 8 4	6 8 4	6 9 5	7 0 0
Carcass ID Number	2 2 1	2 4 2	2 1 0	2 3 9	2 4 8	2 1 8	2 0 5	2 4 3	2 1 7	2 2 8	2 2 4	2 0 6	2 1 6	2 2 9	2 3 6	2 2 2	2 3 2	2 4 6	2 2 6	2 1 1	2 1 5	2 2 0	2 2 8	2 4 4	2 3 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																			+						+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	+	M	M	+	M
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	M	M	+	+	M	M	M	M	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	M	M	M	M	+	M	M	+	M	M	+	M	+	+	M	+	M	M	M	M	M	+	M
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Basal cell adenoma																					X				
Keratoacanthoma								X																	
Squamous cell carcinoma																			X						
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, fibrosarcoma, multiple																						X			
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																							X		
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma									X																
Osteosarcoma, metastatic, bone																							X		
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	7 1 3	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 3 3	2 0 1	2 0 3	2 0 4	2 0 7	2 0 9	2 1 2	2 1 4	2 1 9	2 2 3	2 2 5	2 3 0	2 3 5	2 3 7	2 3 8	2 4 9	2 1 3	2 2 0	2 2 7	2 3 4	2 4 0	2 4 4	2 4 5	2 4 7	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+																								3
Lymph node, bronchial	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	M	+	36
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	M	M	M	+	+	M	+	+	+	+	+	+	M	+	M	M	M	M	M	M	28
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	46
Integumentary System																									
Mammary gland	M	+	+	+	+	M	I	+	M	M	+	+	+	+	+	+	M	+	M	M	M	M	M	M	20
Carcinoma													X												1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Basal cell adenoma																									1
Keratoacanthoma							X		X																3
Squamous cell carcinoma																									1
Sebaceous gland, adenoma	X																								1
Subcutaneous tissue, fibroma				X				X																	2
Subcutaneous tissue, fibrosarcoma	X																								1
Subcutaneous tissue, fibrosarcoma, multiple																									1
Subcutaneous tissue, lipoma										X															1
Subcutaneous tissue, sarcoma																	X								1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma																									1
Skeletal muscle																		+							1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord																									1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma				X				X																	3
Osteosarcoma, metastatic, bone																									1
Pheochromocytoma malignant, metastatic, adrenal medulla																				X					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory epithelium, adenoma					X		X		X													X		X	6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Eye	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	7 1 3	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 3 3	2 0 1	2 0 3	2 0 4	2 0 7	2 0 9	2 1 2	2 1 4	2 1 9	2 2 3	2 2 5	2 3 0	2 3 5	2 3 7	2 3 8	2 4 9	2 1 3	2 2 0	2 2 7	2 3 4	2 4 0	2 4 1	2 4 5	2 4 7	Total Tissues/ Tumors
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X	X	X	X							X		X								X	X			21

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	728	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	
Carcass ID Number	423	401	002	003	133	200	227	343	366	388	433	444	455	466	499	508	510	514	515	519	521	529	535	539	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous			X																						1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesentery		+										+	+				+							+	9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mixed tumor benign																							X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue										+															1
Tooth										+			+												4
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Schwannoma benign						X									X										2
Schwannoma malignant, metastatic, skin																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma malignant							X																		1
Pheochromocytoma benign			X						X	X										X					6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma											X														3
Carcinoma				X																		X			4
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma	X	X	X	X		X		X		X	X	X	X	X		X	X	X	X	X		X		X	35
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
C-cell, adenoma																									4
C-cell, carcinoma																X									1
Follicular cell, adenoma																									1
General Body System																									
Peritoneum																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	4 3 3	4 8 9	5 2 3	5 4 7	5 6 0	5 6 3	5 7 4	5 8 2	6 0 0	6 1 3	6 1 3	6 1 5	6 3 0	6 4 3	6 4 3	6 5 0	6 6 3	6 7 7	6 8 1	6 8 1	6 8 5	6 8 5	7 0 7	7 1 0
Carcass ID Number	4 3 7	4 1 6	4 2 5	4 1 1	4 0 5	4 3 0	4 4 8	4 2 2	4 2 4	4 0 9	4 4 2	4 3 2	4 1 7	4 2 6	4 4 0	4 2 8	4 1 8	4 4 1	4 0 6	4 4 7	4 0 4	4 3 1	4 3 3	4 0 7
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma							X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X							X		X		X	X		X	
Interstitial cell, adenoma					X					X	X	X	X	X					X			X		X
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+			+					+	+		+	+
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	M	M	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Schwannoma malignant, metastatic, skin										X														
Integumentary System																								
Mammary gland	+	M	M	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	M	M	+	M	+	+
Carcinoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																			X					
Keratoacanthoma																				X				
Sebaceous gland, carcinoma																								
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, lipoma																								X
Subcutaneous tissue, sarcoma																								
Subcutaneous tissue, schwannoma malignant										X														
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin										X														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Carcinoma, metastatic, Zymbal's gland																								
Neuroblastoma, metastatic, nose	X																							
Pheochromocytoma malignant, metastatic, adrenal medulla																								
Schwannoma malignant, metastatic, skin										X														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	728	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	744	744	744	744	744	744	744	744	
Carcass ID Number	42303	40101	40002	40103	41113	42200	42207	43304	43336	43388	44343	44404	44455	44606	44949	40808	41010	41144	41515	41919	42201	42909	43505	43939	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X																								1
Carcinoma																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, interstitial cell, adenoma	X	X	X		X				X	X	X	X	X					X			X		X	X	19
Interstitial cell, adenoma						X	X							X	X	X	X		X			X			17
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																			+	+					8
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	38
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	43
Schwannoma malignant, metastatic, skin																									1
Integumentary System																									
Mammary gland	+	M	M	M	M	+	+	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+	+	M	30
Carcinoma																		X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Basal cell adenoma																			X						2
Keratoacanthoma																X									2
Sebaceous gland, carcinoma																X									1
Subcutaneous tissue, fibroma						X													X						2
Subcutaneous tissue, lipoma														X						X					3
Subcutaneous tissue, sarcoma							X					X													2
Subcutaneous tissue, schwannoma malignant																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Schwannoma malignant, metastatic, skin																									1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma						X																			1
Carcinoma, metastatic, Zymbal's gland								X																	1
Neuroblastoma, metastatic, nose																									1
Pheochromocytoma malignant, metastatic, adrenal medulla							X																		1
Schwannoma malignant, metastatic, skin																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	4 3 3	4 8 9	5 2 3	5 4 7	5 6 0	5 6 3	5 7 4	5 8 2	6 0 0	6 1 3	6 1 3	6 1 5	6 3 0	6 4 3	6 4 3	6 5 0	6 6 3	6 7 7	6 8 1	6 8 1	6 8 5	6 8 5	7 0 7	7 1 0
Carcass ID Number	4 3 7	4 1 6	4 2 5	4 1 1	4 0 5	4 3 0	4 4 8	4 2 2	4 2 4	4 0 9	4 4 2	4 3 2	4 1 7	4 2 6	4 4 0	4 2 8	4 1 8	4 4 1	4 0 6	4 4 7	4 0 4	4 3 1	4 3 3	4 0 7
Respiratory System (continued)																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory epithelium, neuroblastoma	X																	X						
Respiratory epithelium, adenoma																						X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																								
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin										X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X	X	X		X	X	X	X	X		X		X	X	X		X	X
Mesothelioma benign		X																						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 2 3	4 0 1	4 0 2	4 0 3	4 1 3	4 2 0	4 2 7	4 3 4	4 3 6	4 3 8	4 4 3	4 4 4	4 4 5	4 4 6	4 4 9	4 0 8	4 1 0	4 1 4	4 1 5	4 1 9	4 2 1	4 2 9	4 3 5	4 3 9	Total Tissues/ Tumors
Respiratory System (continued)																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Olfactory epithelium, neuroblastoma											X													X		4
Respiratory epithelium, adenoma			X				X				X		X			X	X			X						8
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Zymbal's gland								+																		1
Carcinoma								X																		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Schwannoma malignant, metastatic, skin																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Leukemia mononuclear	X		X	X												X			X	X		X	X			24
Mesothelioma benign																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	7 0 7	7 1 2	7 2 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 3 5	6 0 5	6 1 1	6 0 1	6 0 2	6 1 0	6 1 4	6 1 8	6 2 3	6 2 4	6 2 7	6 3 8	6 3 9	6 4 2	6 4 5	6 4 9	6 0 7	6 1 7	6 2 0	6 2 1	6 2 2	6 3 2	6 3 3	6 3 6	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																									1
Leiomyosarcoma																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																									1
Hepatocellular adenoma					X														X		X				3
Mesentery						+						+		+		+		+						+	8
Hemangiosarcoma												X													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X													X	2
Carcinoma																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																				+					2
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X						2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant												X													1
Pheochromocytoma benign									X			X							X			X			8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X								X													2
Carcinoma	X																		X	X		X			4
Parathyroid gland	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X				X			X	X	X	X			X	X	X	X	X		X			X	29
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, adenoma																							X	X	4
C-cell, carcinoma					X																				1
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	2 4 5	3 9 9	4 1 9	4 6 9	4 9 6	5 2 6	5 2 7	5 3 9	5 5 2	5 6 0	5 6 2	5 7 2	5 7 5	6 0 0	6 0 8	6 2 4	6 3 2	6 3 9	6 5 7	6 5 9	6 6 0	6 7 1	6 8 5	6 8 5	7 0 3
Carcass ID Number	6 1 5	6 3 0	6 2 9	6 1 6	6 2 5	6 3 1	6 4 4	6 3 7	6 4 0	6 0 9	6 2 8	6 4 1	6 4 3	6 4 6	6 4 8	6 1 3	6 0 4	6 4 7	6 3 4	6 0 8	6 0 3	6 1 2	6 0 6	6 1 9	6 2 6
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma					X																				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X					X				X					X			X		X	
Interstitial cell, adenoma		X													X								X		X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+																+		
Lymph node, bronchial	M	M	+	+	M	+	+	+	M	M	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	M	M	+	M	+	+	M	M	M	M	+	+	+	M	+	M	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Keratoacanthoma																				X					X
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma													X	X											
Subcutaneous tissue, neural crest tumor																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neuroblastoma, metastatic, nose		X		X																					
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																								X	
Neuroblastoma, metastatic, nose				X																					
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory epithelium, neuroblastoma		X		X				X																	
Respiratory epithelium, adenoma									X		X		X			X		X					X	X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	7 0 7	7 1 2	7 2 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 3 5	6 0 5	6 1 1	6 0 1	6 0 2	6 1 0	6 1 4	6 1 8	6 2 3	6 2 4	6 2 7	6 3 8	6 3 9	6 4 2	6 4 5	6 4 9	6 0 7	6 1 7	6 2 0	6 2 1	6 2 2	6 3 2	6 3 3	6 3 6	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X					1
Carcinoma																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X			X	X	X		X					X		X		X	X		X	X	X	20
Interstitial cell, adenoma				X	X				X			X	X	X				X							11
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+		+																						4
Lymph node, bronchial	+	+	+	+	+	+	M	+	M	+	+	+	+	M	M	M	M	+	+	+	+	+	+	+	35
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Integumentary System																									
Mammary gland	+	+	+	+	M	M	M	+	M	+	+	M	+	M	+	M	+	M	M	M	+	M	+	+	28
Fibroadenoma								X							X								X		3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Keratoacanthoma																									2
Sebaceous gland, adenoma																X									1
Subcutaneous tissue, fibroma																			X		X				2
Subcutaneous tissue, fibrosarcoma																									2
Subcutaneous tissue, neural crest tumor		X																							1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neuroblastoma, metastatic, nose																									2
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, Zymbal's gland																									1
Neuroblastoma, metastatic, nose																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Olfactory epithelium, neuroblastoma																									3
Respiratory epithelium, adenoma			X					X					X	X		X	X	X	X						15
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	245	399	419	469	496	526	527	539	552	560	562	572	575	600	608	624	632	639	657	659	660	671	685	685	703
Carcass ID Number	615	630	629	616	625	631	644	647	640	609	628	641	643	646	648	613	604	647	634	608	603	612	606	619	626
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																								+	
Bilateral, carcinoma																								X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X								X		X		X			X	X		X
Mesothelioma benign																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	7 0 7	7 1 2	7 2 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 3 5	6 0 5	6 1 1	6 0 1	6 0 2	6 1 0	6 1 4	6 1 8	6 2 3	6 2 4	6 2 7	6 3 8	6 3 9	6 4 2	6 4 5	6 4 9	6 0 7	6 1 7	6 2 0	6 2 1	6 2 2	6 3 2	6 3 3	6 3 6	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	48
Zymbal's gland																									1
Bilateral, carcinoma																									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, carcinoma											X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma													X						X						2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X	X	X				X	X				X	X			X			X				X		17
Mesothelioma benign										X															1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/49 (8%)	7/49 (14%)	6/47 (13%)	8/49 (16%)
Adjusted rate[b]	9.7%	17.9%	15.7%	21.1%
Terminal rate[c]	1/24 (4%)	6/22 (27%)	4/23 (17%)	4/21 (19%)
First incidence (days)	639	695	681	562
Poly-3 test[d]	P=0.151	P=0.226	P=0.320	P=0.133
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/49 (2%)	3/49 (6%)	1/47 (2%)	1/49 (2%)
Adjusted rate	2.4%	7.7%	2.6%	2.7%
Terminal rate	0/24 (0%)	3/22 (14%)	1/23 (4%)	1/21 (5%)
First incidence (days)	692	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.431N	P=0.287	P=0.745	P=0.736
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	5/49 (10%)	10/49 (20%)	7/47 (15%)	8/49 (16%)
Adjusted rate	12.0%	25.6%	18.3%	21.1%
Terminal rate	1/24 (4%)	9/22 (41%)	5/23 (22%)	4/21 (19%)
First incidence (days)	639	695	681	562
Poly-3 test	P=0.331	P=0.098	P=0.321	P=0.215
Liver: Hepatocellular Adenoma				
Overall rate	1/49 (2%)	0/49 (0%)	0/48 (0%)	3/49 (6%)
Adjusted rate	2.4%	0.0%	0.0%	8.2%
Terminal rate	0/24 (0%)	0/22 (0%)	0/23 (0%)	3/21 (14%)
First incidence (days)	624	—[e]	—	733 (T)
Poly-3 test	P=0.070	P=0.511N	P=0.512N	P=0.264
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	2/49 (4%)	0/49 (0%)	0/48 (0%)	4/49 (8%)
Adjusted rate	4.9%	0.0%	0.0%	10.8%
Terminal rate	1/24 (4%)	0/22 (0%)	0/23 (0%)	3/21 (14%)
First incidence (days)	624	—	—	632
Poly-3 test	P=0.080	P=0.249N	P=0.250N	P=0.289
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/49 (0%)	3/49 (6%)	0/48 (0%)	0/49 (0%)
Adjusted rate	0.0%	7.6%	0.0%	0.0%
Terminal rate	0/24 (0%)	2/22 (9%)	0/23 (0%)	0/21 (0%)
First incidence (days)	—	593	—[f]	—
Poly-3 test	P=0.242N	P=0.112	—	—
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/49 (4%)	3/49 (6%)	1/48 (2%)	0/49 (0%)
Adjusted rate	4.9%	7.6%	2.6%	0.0%
Terminal rate	2/24 (8%)	2/22 (9%)	1/23 (4%)	0/21 (0%)
First incidence (days)	733 (T)	593	733 (T)	—
Poly-3 test	P=0.102N	P=0.485	P=0.518N	P=0.261N
Mammary Gland: Fibroadenoma				
Overall rate	0/49 (0%)	0/49 (0%)	0/48 (0%)	3/49 (6%)
Adjusted rate	0.0%	0.0%	0.0%	8.2%
Terminal rate	0/24 (0%)	0/22 (0%)	0/23 (0%)	3/21 (14%)
First incidence (days)	—	—	—	733 (T)
Poly-3 test	P=0.009	—	—	P=0.100

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	1/49 (2%)	1/49 (2%)	1/48 (2%)	3/49 (6%)
Adjusted rate	2.5%	2.6%	2.6%	8.2%
Terminal rate	1/24 (4%)	1/22 (5%)	1/23 (4%)	3/21 (14%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.141	P=0.751	P=0.750	P=0.267
Nose: Adenoma				
Overall rate	0/49 (0%)	6/49 (12%)	8/48 (17%)	15/48 (31%)
Adjusted rate	0.0%	15.3%	20.6%	38.1%
Terminal rate	0/24 (0%)	5/22 (23%)	7/23 (30%)	7/21 (33%)
First incidence (days)	—	684	685	552
Poly-3 test	P<0.001	P=0.013	P=0.003	P<0.001
Nose: Neuroblastoma				
Overall rate	0/49 (0%)	0/49 (0%)	4/48 (8%)	3/48 (6%)
Adjusted rate	0.0%	0.0%	10.1%	7.7%
Terminal rate	0/24 (0%)	0/22 (0%)	2/23 (9%)	0/21 (0%)
First incidence (days)	—	—	433	399
Poly-3 test	P=0.027	—	P=0.056	P=0.109
Pancreas: Adenoma or Carcinoma				
Overall rate	1/49 (2%)	0/49 (0%)	0/48 (0%)	3/49 (6%)
Adjusted rate	2.5%	0.0%	0.0%	8.1%
Terminal rate	1/24 (4%)	0/22 (0%)	0/23 (0%)	2/21 (10%)
First incidence (days)	733 (T)	—	—	660
Poly-3 test	P=0.070	P=0.509N	P=0.510N	P=0.270
Pancreatic Islets: Adenoma				
Overall rate	2/49 (4%)	5/49 (10%)	3/48 (6%)	2/49 (4%)
Adjusted rate	4.9%	12.8%	7.6%	5.5%
Terminal rate	1/24 (4%)	4/22 (18%)	1/23 (4%)	2/21 (10%)
First incidence (days)	624	680	560	733 (T)
Poly-3 test	P=0.432N	P=0.195	P=0.484	P=0.653
Pancreatic Islets: Carcinoma				
Overall rate	4/49 (8%)	4/49 (8%)	4/48 (8%)	4/49 (8%)
Adjusted rate	9.7%	10.3%	10.2%	10.9%
Terminal rate	2/24 (8%)	4/22 (18%)	2/23 (9%)	3/21 (14%)
First incidence (days)	677	733 (T)	650	707
Poly-3 test	P=0.504	P=0.615	P=0.618	P=0.582
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	6/49 (12%)	9/49 (18%)	7/48 (15%)	6/49 (12%)
Adjusted rate	14.5%	23.0%	17.4%	16.3%
Terminal rate	3/24 (13%)	8/22 (36%)	3/23 (13%)	5/21 (24%)
First incidence (days)	624	680	560	707
Poly-3 test	P=0.504N	P=0.242	P=0.475	P=0.535
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	31/49 (63%)	31/49 (63%)	35/47 (74%)	29/49 (59%)
Adjusted rate	68.3%	68.5%	79.0%	67.0%
Terminal rate	15/24 (63%)	17/22 (77%)	17/23 (74%)	12/21 (57%)
First incidence (days)	516	390	489	469
Poly-3 test	P=0.517	P=0.583	P=0.173	P=0.543N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Preputial Gland: Adenoma				
Overall rate	3/48 (6%)	0/49 (0%)	1/47 (2%)	1/49 (2%)
Adjusted rate	7.6%	0.0%	2.6%	2.7%
Terminal rate	3/23 (13%)	0/22 (0%)	0/23 (0%)	1/21 (5%)
First incidence (days)	733 (T)	—	728	733 (T)
Poly-3 test	P=0.350N	P=0.121N	P=0.319N	P=0.334N
Preputial Gland: Carcinoma				
Overall rate	3/48 (6%)	1/49 (2%)	1/47 (2%)	1/49 (2%)
Adjusted rate	7.4%	2.6%	2.6%	2.7%
Terminal rate	1/23 (4%)	0/22 (0%)	0/23 (0%)	0/21 (0%)
First incidence (days)	615	695	574	496
Poly-3 test	P=0.271N	P=0.316N	P=0.321N	P=0.333N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	6/48 (13%)	1/49 (2%)	2/47 (4%)	2/49 (4%)
Adjusted rate	14.9%	2.6%	5.2%	5.4%
Terminal rate	4/23 (17%)	0/22 (0%)	0/23 (0%)	1/21 (5%)
First incidence (days)	615	695	574	496
Poly-3 test	P=0.176N	P=0.059N	P=0.145N	P=0.157N
Skin: Keratoacanthoma				
Overall rate	4/49 (8%)	3/49 (6%)	2/48 (4%)	2/49 (4%)
Adjusted rate	9.8%	7.6%	5.1%	5.4%
Terminal rate	2/24 (8%)	2/22 (9%)	1/23 (4%)	0/21 (0%)
First incidence (days)	692	567	681	659
Poly-3 test	P=0.280N	P=0.520N	P=0.360N	P=0.384N
Skin: Keratoacanthoma or Squamous Cell Carcinoma				
Overall rate	4/49 (8%)	4/49 (8%)	2/48 (4%)	2/49 (4%)
Adjusted rate	9.8%	10.1%	5.1%	5.4%
Terminal rate	2/24 (8%)	2/22 (9%)	1/23 (4%)	0/21 (0%)
First incidence (days)	692	567	681	659
Poly-3 test	P=0.230N	P=0.627	P=0.360N	P=0.384N
Skin: Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	4/49 (8%)	5/49 (10%)	4/48 (8%)	2/49 (4%)
Adjusted rate	9.8%	12.5%	10.2%	5.4%
Terminal rate	2/24 (8%)	2/22 (9%)	2/23 (9%)	0/21 (0%)
First incidence (days)	692	567	681	659
Poly-3 test	P=0.251N	P=0.483	P=0.618	P=0.384N
Skin (Subcutaneous Tissue): Lipoma				
Overall rate	1/49 (2%)	1/49 (2%)	3/48 (6%)	0/49 (0%)
Adjusted rate	2.5%	2.6%	7.7%	0.0%
Terminal rate	0/24 (0%)	1/22 (5%)	2/23 (9%)	0/21 (0%)
First incidence (days)	709	733 (T)	710	—
Poly-3 test	P=0.469N	P=0.751	P=0.286	P=0.521N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	5/49 (10%)	2/49 (4%)	2/48 (4%)	2/49 (4%)
Adjusted rate	12.1%	5.1%	5.2%	5.5%
Terminal rate	4/24 (17%)	2/22 (9%)	2/23 (9%)	2/21 (10%)
First incidence (days)	460	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.232N	P=0.240N	P=0.243N	P=0.268N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	2/49 (4%)	3/49 (6%)	2/48 (4%)	2/49 (4%)
Adjusted rate	4.9%	7.6%	5.2%	5.3%
Terminal rate	1/24 (4%)	1/22 (5%)	2/23 (9%)	0/21 (0%)
First incidence (days)	678	684	733 (T)	575
Poly-3 test	P=0.534N	P=0.481	P=0.674	P=0.664
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	7/49 (14%)	5/49 (10%)	4/48 (8%)	4/49 (8%)
Adjusted rate	16.8%	12.7%	10.3%	10.6%
Terminal rate	5/24 (21%)	3/22 (14%)	4/23 (17%)	2/21 (10%)
First incidence (days)	460	684	733 (T)	575
Poly-3 test	P=0.258N	P=0.421N	P=0.302N	P=0.320N
Testes: Adenoma				
Overall rate	38/49 (78%)	32/49 (65%)	36/48 (75%)	31/49 (63%)
Adjusted rate	85.5%	74.3%	83.5%	75.9%
Terminal rate	24/24 (100%)	17/22 (77%)	20/23 (87%)	18/21 (86%)
First incidence (days)	460	520	560	399
Poly-3 test	P=0.284N	P=0.120N	P=0.516N	P=0.162N
Thyroid Gland (C-cell): Adenoma				
Overall rate	9/46 (20%)	6/47 (13%)	4/45 (9%)	4/47 (9%)
Adjusted rate	22.8%	15.3%	10.6%	11.0%
Terminal rate	7/24 (29%)	4/22 (18%)	0/22 (0%)	2/20 (10%)
First incidence (days)	460	551	615	632
Poly-3 test	P=0.106N	P=0.289N	P=0.129N	P=0.146N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	10/46 (22%)	8/47 (17%)	5/45 (11%)	5/47 (11%)
Adjusted rate	25.3%	20.3%	13.3%	13.8%
Terminal rate	8/24 (33%)	5/22 (23%)	1/22 (5%)	3/20 (15%)
First incidence (days)	460	551	615	632
Poly-3 test	P=0.107N	P=0.394N	P=0.145N	P=0.165N
All Organs: Mononuclear Cell Leukemia				
Overall rate	26/49 (53%)	21/49 (43%)	24/48 (50%)	17/49 (35%)
Adjusted rate	58.0%	48.3%	54.3%	43.5%
Terminal rate	12/24 (50%)	6/22 (27%)	7/23 (30%)	7/21 (33%)
First incidence (days)	469	502	560	527
Poly-3 test	P=0.169N	P=0.240N	P=0.447N	P=0.127N
All Organs: Benign Neoplasms				
Overall rate	46/49 (94%)	47/49 (96%)	47/48 (98%)	47/49 (96%)
Adjusted rate	98.2%	98.6%	99.6%	99.1%
Terminal rate	24/24 (100%)	22/22 (100%)	23/23 (100%)	21/21 (100%)
First incidence (days)	460	390	489	399
Poly-3 test	P=0.482	P=0.886	P=0.758	P=0.821
All Organs: Malignant Neoplasms				
Overall rate	34/49 (69%)	32/49 (65%)	34/48 (71%)	32/49 (65%)
Adjusted rate	74.2%	72.0%	74.1%	70.4%
Terminal rate	16/24 (67%)	13/22 (59%)	13/23 (57%)	11/21 (52%)
First incidence (days)	469	502	433	245
Poly-3 test	P=0.407N	P=0.499N	P=0.590N	P=0.428N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/49 (98%)	49/49 (100%)	48/48 (100%)	49/49 (100%)
Adjusted rate	99.5%	100.0%	100.0%	100.0%
Terminal rate	24/24 (100%)	22/22 (100%)	23/23 (100%)	21/21 (100%)
First incidence (days)	460	390	433	245
Poly-3 test	P=0.941	P=0.999	P=0.999	P=0.999

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, nose, pancreas, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4
Historical Incidence of Nasal Adenoma or Neuroblastoma in Control Male F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Feed[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	0/50
Indium phosphide (inhalation)	0/50
Methacrylonitrile (gavage)	0/50
Naphthalene (inhalation)	0/49
p-Nitrotoluene (feed)	0/50
Sodium nitrite (drinking water)	0/50
Overall Historical Incidence in Controls Given NTP-2000 Feed	
Total	0/299
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]	
Acetonitrile	0/48
2-Butoxyethanol	0/48
Chloroprene	0/50
Cobalt sulfate heptahydrate	0/50
Furfuryl alcohol	0/50
Gallium arsenide	0/50
Glutaraldehyde	0/50
Hexachlorocyclopentadiene	0/48
Isobutene	0/49
Isobutyraldehyde	0/50
Isoprene	0/50
Molybdenum trioxide	0/50
Nitromethane	0/50
Ozone	0/50
Tetrafluoroethylene	0/50
Tetrahydrofuran	0/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed	
Total	0/1,048

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

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

	Chamber Control	10 ppm	30 ppm	60 ppm
Disposition Summary				
Animals initially in study	49	49	49	49
Early deaths				
Moribund	21	22	19	25
Natural deaths	4	5	6	3
Survivors				
Terminal sacrifice	24	22	23	21
Missexed			1	
Animals examined microscopically	49	49	48	49
Alimentary System				
Liver	(49)	(49)	(48)	(49)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Basophilic focus	34 (69%)	31 (63%)	28 (58%)	32 (65%)
Clear cell focus	14 (29%)	14 (29%)	14 (29%)	11 (22%)
Degeneration, cystic	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Eosinophilic focus	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Fatty change	2 (4%)	2 (4%)	4 (8%)	5 (10%)
Hepatodiaphragmatic nodule	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Inflammation, granulomatous		1 (2%)		
Mixed cell focus	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Necrosis			1 (2%)	
Regeneration	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Syncytial alteration				1 (2%)
Tension lipidosis			1 (2%)	
Artery, inflammation	1 (2%)			
Bile duct, hyperplasia	35 (71%)	32 (65%)	28 (58%)	21 (43%)
Centrilobular, necrosis	13 (27%)	11 (22%)	7 (15%)	4 (8%)
Mesentery	(13)	(6)	(9)	(8)
Artery, inflammation, chronic active	3 (23%)			1 (13%)
Artery, mineralization			1 (11%)	
Fat, hemorrhage		1 (17%)		
Fat, inflammation		1 (17%)		
Fat, necrosis	10 (77%)	4 (67%)	8 (89%)	6 (75%)
Pancreas	(49)	(49)	(48)	(49)
Atrophy	19 (39%)	17 (35%)	17 (35%)	14 (29%)
Basophilic focus		1 (2%)	1 (2%)	1 (2%)
Hyperplasia		3 (6%)	2 (4%)	1 (2%)
Artery, inflammation	1 (2%)		1 (2%)	
Duct, cyst				1 (2%)
Salivary glands	(49)	(49)	(47)	(49)
Atrophy		1 (2%)		
Metaplasia, squamous	1 (2%)			
Necrosis	1 (2%)			
Stomach, forestomach	(49)	(49)	(48)	(49)
Diverticulum	1 (2%)			
Hyperplasia, squamous	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Inflammation, acute			1 (2%)	
Necrosis				1 (2%)
Ulcer	1 (2%)	6 (12%)	3 (6%)	2 (4%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(49)	(48)	(49)
Inflammation, acute			1 (2%)	
Mineralization		2 (4%)	1 (2%)	
Necrosis	7 (14%)	2 (4%)	2 (4%)	3 (6%)
Ulcer		1 (2%)		1 (2%)
Artery, inflammation	1 (2%)			
Tongue		(1)	(1)	
Epithelium, hyperplasia			1 (100%)	
Tooth	(1)	(2)	(4)	(2)
Inflammation, chronic active	1 (100%)	1 (50%)	4 (100%)	
Malformation		1 (50%)		2 (100%)
Cardiovascular System				
Heart	(49)	(49)	(48)	(49)
Cardiomyopathy	42 (86%)	44 (90%)	37 (77%)	42 (86%)
Necrosis	1 (2%)			
Atrium, thrombosis	5 (10%)	2 (4%)	3 (6%)	2 (4%)
Valve, thrombosis, chronic		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(49)	(48)	(49)
Angiectasis	1 (2%)	1 (2%)		
Degeneration, cystic		2 (4%)	1 (2%)	1 (2%)
Hyperplasia	30 (61%)	28 (57%)	23 (48%)	36 (73%)
Hypertrophy	7 (14%)	6 (12%)	9 (19%)	4 (8%)
Necrosis		1 (2%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic	1 (2%)	1 (2%)	3 (6%)	
Adrenal medulla	(49)	(49)	(47)	(49)
Hyperplasia	26 (53%)	13 (27%)	23 (49%)	12 (24%)
Necrosis		1 (2%)		
Islets, pancreatic	(49)	(49)	(48)	(49)
Hyperplasia		1 (2%)	2 (4%)	1 (2%)
Pituitary gland	(49)	(49)	(47)	(49)
Angiectasis	1 (2%)			1 (2%)
Cyst		1 (2%)		1 (2%)
Pars distalis, hyperplasia	11 (22%)	12 (24%)	10 (21%)	15 (31%)
Thyroid gland	(46)	(47)	(45)	(47)
C-cell, hyperplasia	32 (70%)	36 (77%)	31 (69%)	33 (70%)
Follicular cell, hyperplasia	2 (4%)		3 (7%)	
General Body System				
Peritoneum			(1)	
Inflammation, suppurative			1 (100%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Genital System				
Epididymis	(49)	(49)	(48)	(49)
Angiectasis		1 (2%)		
Granuloma sperm		1 (2%)		
Preputial gland	(48)	(49)	(47)	(49)
Cyst			1 (2%)	1 (2%)
Hyperplasia, squamous	1 (2%)			
Inflammation, chronic active	2 (4%)		2 (4%)	2 (4%)
Prostate	(49)	(49)	(48)	(49)
Hyperplasia	11 (22%)	8 (16%)	16 (33%)	8 (16%)
Inflammation, chronic active	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Epithelium, hyperplasia	1 (2%)			
Seminal vesicle	(47)	(49)	(47)	(47)
Inflammation, chronic active				1 (2%)
Testes	(49)	(49)	(48)	(49)
Atrophy	2 (4%)	4 (8%)	2 (4%)	4 (8%)
Artery, inflammation, chronic active		2 (4%)		2 (4%)
Interstitial cell, hyperplasia	5 (10%)	9 (18%)	2 (4%)	11 (22%)
Hematopoietic System				
Lymph node	(3)	(3)	(8)	(4)
Iliac, hemorrhage	1 (33%)			
Lymph node, mandibular	(40)	(45)	(46)	(44)
Infiltration cellular, plasma cell	1 (3%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear	1 (3%)			
Spleen	(49)	(49)	(48)	(49)
Fibrosis	7 (14%)	12 (24%)	6 (13%)	6 (12%)
Hematopoietic cell proliferation	4 (8%)	3 (6%)	1 (2%)	4 (8%)
Hemorrhage	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Necrosis	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Thrombosis	1 (2%)			1 (2%)
Integumentary System				
Mammary gland	(21)	(20)	(30)	(28)
Galactocele			1 (3%)	
Skin	(48)	(48)	(48)	(48)
Cyst epithelial inclusion			1 (2%)	
Hyperkeratosis	4 (8%)	2 (4%)		1 (2%)
Hyperplasia, basal cell			1 (2%)	
Hyperplasia, squamous				1 (2%)
Inflammation, acute		1 (2%)		
Inflammation, chronic active	4 (8%)	1 (2%)		
Epithelium, hyperplasia, basal cell	1 (2%)			
Musculoskeletal System				
Bone	(49)	(49)	(48)	(49)
Osteopetrosis			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Nervous System				
Brain	(49)	(49)	(48)	(49)
Degeneration	1 (2%)		1 (2%)	
Necrosis			1 (2%)	
Artery, inflammation	1 (2%)			
Respiratory System				
Larynx	(49)	(49)	(48)	(49)
Metaplasia, squamous		1 (2%)	2 (4%)	
Lung	(49)	(49)	(48)	(49)
Cyst, squamous		1 (2%)		
Foreign body	1 (2%)			1 (2%)
Hemorrhage	1 (2%)			
Inflammation, chronic active	2 (4%)	13 (27%)	6 (13%)	15 (31%)
Inflammation, granulomatous	1 (2%)			1 (2%)
Inflammation, suppurative		1 (2%)		
Metaplasia, osseous	1 (2%)			
Thrombosis	1 (2%)	1 (2%)		
Alveolar epithelium, hyperplasia	23 (47%)	12 (24%)	9 (19%)	16 (33%)
Alveolar epithelium, metaplasia	1 (2%)			
Alveolus, infiltration cellular, histiocyte	12 (24%)	9 (18%)	6 (13%)	15 (31%)
Bronchiole, hyperplasia	1 (2%)	1 (2%)		
Nose	(49)	(49)	(48)	(48)
Foreign body	1 (2%)			
Inflammation, suppurative	12 (24%)	18 (37%)	16 (33%)	9 (19%)
Thrombosis	6 (12%)	7 (14%)	6 (13%)	3 (6%)
Glands, hyperplasia	1 (2%)	49 (100%)	48 (100%)	48 (100%)
Glands, metaplasia, squamous		3 (6%)	14 (29%)	26 (54%)
Goblet cell, respiratory epithelium, hyperplasia		25 (51%)	29 (60%)	26 (54%)
Olfactory epithelium, atrophy	3 (6%)	49 (100%)	48 (100%)	47 (98%)
Olfactory epithelium, degeneration, hyaline	3 (6%)	46 (94%)	40 (83%)	38 (79%)
Olfactory epithelium, hyperplasia, atypical		48 (98%)	45 (94%)	46 (96%)
Olfactory epithelium, inflammation, chronic		49 (100%)	48 (100%)	48 (100%)
Respiratory epithelium, degeneration, hyaline		20 (41%)	19 (40%)	19 (40%)
Respiratory epithelium, hyperplasia	3 (6%)	21 (43%)	29 (60%)	29 (60%)
Respiratory epithelium, metaplasia, squamous		15 (31%)	23 (48%)	18 (38%)
Trachea	(49)	(49)	(48)	(49)
Inflammation, suppurative			1 (2%)	
Special Senses System				
Eye	(48)	(48)	(48)	(48)
Cataract	4 (8%)	2 (4%)	1 (2%)	3 (6%)
Hemorrhage				1 (2%)
Inflammation, suppurative	1 (2%)			
Retina, atrophy	2 (4%)	1 (2%)	1 (2%)	2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Urinary System				
Kidney	(49)	(49)	(48)	(49)
Infarct	3 (6%)		1 (2%)	3 (6%)
Inflammation, suppurative				1 (2%)
Metaplasia, osseous			1 (2%)	
Nephropathy	43 (88%)	44 (90%)	45 (94%)	43 (88%)
Renal tubule, hyperplasia			1 (2%)	1 (2%)
Urinary bladder	(48)	(49)	(48)	(49)
Hemorrhage	1 (2%)			
Transitional epithelium, hyperplasia				1 (2%)

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

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

	Chamber Control	10 ppm	30 ppm	60 ppm
Disposition Summary				
Animals initially in study	49	49	49	49
Early deaths				
Moribund	18	22	16	21
Natural deaths	3	6	5	4
Survivors				
Terminal sacrifice	28	21	28	24
Animals examined microscopically	49	49	49	49
Alimentary System				
Intestine large, colon	(49)	(49)	(49)	(49)
Intestine small, jejunum	(49)	(48)	(48)	(46)
Intestine small, ileum	(49)	(48)	(47)	(46)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Liver	(49)	(49)	(49)	(49)
Hepatocellular carcinoma		1 (2%)	1 (2%)	
Mesentery	(13)	(8)	(7)	(5)
Pancreas	(49)	(49)	(49)	(49)
Salivary glands	(49)	(49)	(49)	(49)
Adenoma				1 (2%)
Stomach, forestomach	(49)	(49)	(49)	(49)
Stomach, glandular	(49)	(48)	(49)	(49)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Tongue	(1)	(1)		(1)
Squamous cell papilloma				1 (100%)
Epithelium, squamous cell papilloma		1 (100%)		
Cardiovascular System				
Heart	(49)	(49)	(49)	(49)
Schwannoma benign			1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(49)
Adenoma	1 (2%)	2 (4%)	1 (2%)	
Adrenal medulla	(48)	(49)	(49)	(49)
Pheochromocytoma benign	2 (4%)		1 (2%)	2 (4%)
Bilateral, pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(49)	(49)	(49)	(49)
Adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Carcinoma	1 (2%)			
Parathyroid gland	(42)	(40)	(41)	(48)
Pituitary gland	(49)	(49)	(49)	(48)
Pars distalis, adenoma	23 (47%)	27 (55%)	24 (49%)	20 (42%)
Pars distalis, carcinoma			1 (2%)	
Thyroid gland	(47)	(46)	(48)	(48)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	4 (9%)	3 (7%)	2 (4%)	1 (2%)
C-cell, carcinoma	3 (6%)	2 (4%)	2 (4%)	
Follicular cell, carcinoma	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
General Body System				
None				
Genital System				
Clitoral gland	(49)	(47)	(49)	(48)
Adenoma	3 (6%)	7 (15%)	4 (8%)	2 (4%)
Carcinoma		1 (2%)	1 (2%)	1 (2%)
Bilateral, adenoma	1 (2%)			
Ovary	(49)	(49)	(49)	(49)
Granulosa cell tumor malignant	2 (4%)	2 (4%)		
Granulosa-theca tumor malignant	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Uterus	(49)	(49)	(49)	(49)
Carcinoma			1 (2%)	
Polyp stromal	14 (29%)	5 (10%)	8 (16%)	7 (14%)
Bilateral, polyp stromal	1 (2%)	2 (4%)	1 (2%)	
Hematopoietic System				
Bone marrow	(49)	(49)	(49)	(49)
Lymph node	(2)	(3)	(2)	(3)
Lymph node, bronchial	(42)	(33)	(34)	(36)
Lymph node, mandibular	(47)	(39)	(46)	(47)
Lymph node, mesenteric	(49)	(49)	(49)	(49)
Lymph node, mediastinal	(40)	(39)	(41)	(31)
Spleen	(49)	(49)	(49)	(49)
Hemangiosarcoma	1 (2%)			
Osteosarcoma, metastatic, bone		1 (2%)		
Thymus	(46)	(45)	(48)	(41)
Integumentary System				
Mammary gland	(49)	(49)	(49)	(49)
Carcinoma	3 (6%)	5 (10%)	3 (6%)	3 (6%)
Fibroadenoma	14 (29%)	16 (33%)	17 (35%)	10 (20%)
Fibroadenoma, multiple	3 (6%)	4 (8%)	1 (2%)	4 (8%)
Skin	(49)	(49)	(49)	(49)
Basal cell adenoma			1 (2%)	
Keratoacanthoma				1 (2%)
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, fibroma			1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma				1 (2%)
Subcutaneous tissue, hemangioma	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(49)	(49)	(49)	(49)
Osteosarcoma		1 (2%)		
Skeletal muscle		(2)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Nervous System				
Brain	(49)	(49)	(49)	(49)
Carcinoma, metastatic, pituitary gland			1 (2%)	
Glioma malignant			1 (2%)	
Neuroblastoma, metastatic, nose		1 (2%)		4 (8%)
Respiratory System				
Larynx	(49)	(49)	(49)	(49)
Lung	(49)	(49)	(49)	(49)
Alveolar/bronchiolar adenoma	1 (2%)			
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)		
Nose	(49)	(49)	(49)	(49)
Olfactory epithelium, neuroblastoma		2 (4%)	3 (6%)	12 (24%)
Respiratory epithelium, adenoma			4 (8%)	2 (4%)
Special Senses System				
Zymbal's gland	(2)	(1)		
Carcinoma	2 (100%)	1 (100%)		
Urinary System				
Kidney	(48)	(49)	(49)	(49)
Renal tubule, carcinoma	1 (2%)			
Urinary bladder	(48)	(49)	(49)	(49)
Transitional epithelium, papilloma	1 (2%)		1 (2%)	
Systemic Lesions				
Multiple organs[b]	(49)	(49)	(49)	(49)
Leukemia mononuclear	16 (33%)	21 (43%)	15 (31%)	15 (31%)
Mesothelioma benign			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	44	48	47	44
Total primary neoplasms	104	106	97	89
Total animals with benign neoplasms	38	41	43	35
Total benign neoplasms	72	69	69	53
Total animals with malignant neoplasms	26	34	26	27
Total malignant neoplasms	32	37	28	36
Total animals with metastatic neoplasms		3	1	
Total metastatic neoplasms		7	1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	509	519	572	602	604	625	657	657	671	711	713	716	717	719	784	890	005	017	113	255	272	343	344	344	344
Carcass ID Number	13202	12707	12209	11414	14242	14249	12424	14545	12222	13030	13037	11313	12020	11411	14040	13303	10303	13434	12121	13636	11012	10401	10002	10404	10006
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+						+	+				+								+	+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue														+											
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X													
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma																						X			
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X				X			X	X	X	X	X			X	X		X			X			
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
C-cell, adenoma				X								X							X				X		
C-cell, carcinoma																X									
Follicular cell, carcinoma																					X				
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant													X												
Granulosa-theca tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X	X					X				X	X	X										X	
Bilateral, polyp stromal																									

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 0 8	1 2 8	1 4 4	1 0 7	1 0 9	1 1 0	1 1 6	1 1 8	1 1 9	1 2 3	1 2 6	1 3 1	1 3 5	1 3 8	1 3 9	1 4 1	1 4 3	1 4 6	1 4 8	1 0 5	1 1 5	1 1 7	1 2 5	1 4 7	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery	+	+											+	+				+	+			+			13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																									1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																							1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign					X																				2
Bilateral, pheochromocytoma benign																					X				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									1
Carcinoma																									1
Parathyroid gland	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X			X			X		X	X					X				X	X	X		23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, adenoma																									4
C-cell, carcinoma			X												X										3
Follicular cell, carcinoma																									1
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X		X																				3
Bilateral, adenoma						X																			1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor malignant		X																							2
Granulosa-theca tumor malignant																				X					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal		X			X					X							X				X		X	X	14
Bilateral, polyp stromal						X																			1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	5 0 9	5 1 9	5 7 2	6 0 2	6 0 4	6 2 5	6 5 7	6 5 7	6 7 1	6 7 1	6 7 1	6 7 6	6 7 7	6 7 9	6 8 4	6 9 0	7 0 5	7 0 7	7 1 3	7 2 5	7 2 7	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 3 2	1 2 7	1 2 9	1 1 4	1 4 2	1 4 9	1 2 4	1 4 5	1 2 2	1 3 0	1 3 7	1 3 3	1 2 0	1 1 1	1 4 0	1 3 3	1 0 3	1 3 4	1 2 1	1 3 6	1 1 2	1 0 1	1 0 2	1 0 4	1 0 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																				+	+				
Lymph node, bronchial	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	M	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Thymus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma						X				X						X	X						X		
Fibroadenoma, multiple																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, hemangioma																				X					
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Zymbal's gland								+							+										
Carcinoma								X							X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X			X	X	X		X	X		X	X	X		X		X	X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: Chamber Control

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 0 8	1 2 8	1 4 4	1 0 7	1 0 9	1 1 0	1 1 6	1 1 8	1 1 9	1 2 3	1 2 6	1 3 1	1 3 5	1 3 8	1 3 9	1 4 1	1 4 3	1 4 6	1 4 8	1 0 5	1 1 5	1 1 7	1 2 5	1 4 7	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																									2
Lymph node, bronchial	M	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	M	+	M	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma		X					X											X							3
Fibroadenoma						X	X	X	X	X			X					X			X			X	14
Fibroadenoma, multiple					X																	X			3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma										X															1
Subcutaneous tissue, hemangioma																									1
Subcutaneous tissue, sarcoma													X												1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma		X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Zymbal's gland																									2
Carcinoma																									2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Renal tubule, carcinoma									X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional epithelium, papilloma																	X								1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X				X																	X			16

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	4 4 0	4 7 1	5 0 3	5 0 9	5 1 8	5 7 4	5 7 7	5 8 1	5 8 1	5 8 7	6 0 2	6 0 9	6 2 2	6 2 5	6 3 5	6 4 7	6 6 3	6 6 5	6 7 7	6 7 7	6 7 7	6 7 9	6 9 9	6 9 9	7 1 3
Carcass ID Number	3 1 4	3 3 4	3 4 6	3 3 0	3 4 1	3 3 7	3 1 2	3 0 2	3 2 7	3 1 5	3 3 2	3 0 9	3 3 8	3 2 9	3 3 5	3 1 6	3 1 3	3 1 0	3 0 4	3 2 6	3 4 8	3 4 0	3 4 7	3 1 1	3 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																				X					
Mesentery										+	+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																				X					
Tongue																							+		
Epithelium, squamous cell papilloma																							X		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X	X	X	X		X	X		X		X					X	X	X	X		
Thyroid gland	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																				X					
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X															X			X		
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Hepatocellular carcinoma, metastatic, liver																				X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																					X				X
Bilateral, polyp stromal															X										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	7 2 1	7 2 3	7 2 6	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 4 4	3 1 9	3 1 7	3 0 3	3 0 6	3 0 7	3 0 8	3 3 6	3 0 5	3 1 8	3 2 0	3 2 1	3 2 2	3 2 3	3 2 4	3 2 5	3 2 8	3 3 1	3 4 2	3 4 5	3 0 1	3 3 9	3 4 3	3 4 9	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																									1
Mesentery				+		+					+			+		+				+					8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver																									1
Tongue																									1
Epithelium, squamous cell papilloma																									1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X					2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X	1
Parathyroid gland	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					X	X		X		X	X		X		X	X		X	X	X	X	X		X	27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Bilateral, C-cell, adenoma																X									1
C-cell, adenoma																		X			X				3
C-cell, carcinoma														X									X		2
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma					X		X					X					X								7
Carcinoma							X																		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor malignant												X											X		2
Hepatocellular carcinoma, metastatic, liver																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal					X						X									X					5
Bilateral, polyp stromal													X												2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	440	447	503	509	518	574	577	581	581	587	602	609	622	625	635	647	663	665	677	677	677	679	699	699	713
Carcass ID Number	31 4	33 4	34 6	33 0	34 1	31 7	31 2	30 2	32 7	31 5	33 2	30 9	33 8	32 9	33 5	31 6	31 3	31 0	33 4	32 6	34 8	34 0	34 7	31 1	33 3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																								+	+
Lymph node, bronchial	+	+	+	M	+	M	M	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone	X																								
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X			X		X													
Fibroadenoma									X					X	X				X	X					
Fibroadenoma, multiple																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma	X																								
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neuroblastoma, metastatic, nose																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Hepatocellular carcinoma, metastatic, liver																				X					
Osteosarcoma, metastatic, bone	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory epithelium, neuroblastoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X			X		X	X					X		X	X	X	X		X			X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 10 ppm

Number of Days on Study	7 2 1	7 2 3	7 2 6	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 4 4	3 1 9	3 1 7	3 0 3	3 0 6	3 0 7	3 0 8	3 3 6	3 0 5	3 1 8	3 2 0	3 2 1	3 2 2	3 2 3	3 2 4	3 2 5	3 2 8	3 3 1	3 4 2	3 4 5	3 0 1	3 3 9	3 4 3	3 4 9	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+																								3
Lymph node, bronchial	+	M	+	M	+	M	+	+	+	M	+	+	+	+	M	+	M	+	M	M	M	+	+	+	33
Lymph node, mandibular	+	+	+	+	+	+	M	M	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	+	39
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	39
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic, bone																									1
Thymus	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma			X															X							5
Fibroadenoma	X	X		X						X						X		X	X	X	X		X	X	16
Fibroadenoma, multiple					X												X					X			4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma																									1
Skeletal muscle	+						+																		2
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neuroblastoma, metastatic, nose		X																							1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, Zymbal's gland															X										1
Hepatocellular carcinoma, metastatic, liver																									1
Osteosarcoma, metastatic, bone																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Olfactory epithelium, neuroblastoma		X																							2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	47
Zymbal's gland															+										1
Carcinoma															X										1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X				X	X				X	X			X		X								X	21

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	5 1 8	5 3 0	5 3 1	5 3 3	5 3 7	5 4 7	5 0 2	5 0 3	5 0 4	5 0 7	5 2 2	5 2 4	5 2 5	5 2 6	5 2 8	5 3 2	5 3 4	5 3 6	5 4 1	5 4 6	5 1 0	5 2 3	5 2 9	5 3 4	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																							X		1
Mesentery																	+		+						7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																									1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma benign			X																						1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X																					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X			X		X					X	X	X	X		X			X			24
Pars distalis, carcinoma																									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma									X			X													2
C-cell, carcinoma											X					X									2
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																		X			X		4
Carcinoma																									1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma					X																				1
Polyp stromal	X			X							X				X		X						X	X	8
Bilateral, polyp stromal																									1
Vagina																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	4 4 0	4 4 0	4 8 0	5 1 2	5 8 1	5 8 6	5 8 7	5 8 7	5 8 8	6 1 5	6 2 4	6 3 0	6 5 3	6 5 3	6 6 0	6 7 1	6 8 5	6 9 9	7 0 7	7 1 5	7 2 1	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	5 1 9	5 2 1	5 4 4	5 0 8	5 4 3	5 4 2	5 1 6	5 1 7	5 3 9	5 2 7	5 1 3	5 4 0	5 0 6	5 4 5	5 4 8	5 1 1	5 1 2	5 2 0	5 3 8	5 1 5	5 3 5	5 0 1	5 0 5	5 0 9	5 1 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node														+				+							
Lymph node, bronchial	M	M	M	+	M	M	+	M	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	M	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X									X								
Fibroadenoma	X						X	X					X	X	X		X	X				X			
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									X
Subcutaneous tissue, fibroma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																					X				
Glioma malignant				X																					
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory epithelium, neuroblastoma			X									X													
Respiratory epithelium, adenoma																					X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																			X						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X				X	X	X		X	X			X		X	
Mesothelioma benign																								X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 30 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	5 1 8	5 3 0	5 3 1	5 3 3	5 3 7	5 4 7	5 0 2	5 0 3	5 0 4	5 0 7	5 2 2	5 2 4	5 2 5	5 2 6	5 2 8	5 3 2	5 3 4	5 3 6	5 4 1	5 4 6	5 1 0	5 2 3	5 2 9	5 4 9	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																									2
Lymph node, bronchial	+	M	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	34
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																					X				3
Fibroadenoma				X		X		X					X			X	X			X			X		17
Fibroadenoma, multiple			X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma																									1
Subcutaneous tissue, fibroma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland																									1
Glioma malignant																									1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Olfactory epithelium, neuroblastoma		X																							3
Respiratory epithelium, adenoma									X		X			X											4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Eye	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																									1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X							X	X			X						X		X				15
Mesothelioma benign																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	7 4 3	7 4 4	7 4 6	7 0 3	7 0 7	7 0 8	7 1 1	7 1 3	7 1 8	7 1 9	7 2 1	7 2 4	7 2 6	7 3 8	7 4 0	7 4 7	7 4 8	7 4 9	7 0 5	7 1 5	7 2 5	7 3 2	7 4 2	7 4 5	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery		+							+														+		5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue													+												1
Squamous cell papilloma													X												1
Tooth																									1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																	X			X					2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma														X											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X					X	X	X	X	X		X				X	X				X	X		20
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma							X																		1
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																									2
Carcinoma							X																		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal	X							X					X					X	X	X					7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	1 1 1	4 2 9	4 4 5	4 7 8	4 8 2	5 0 3	5 3 6	5 4 7	5 5 5	5 7 9	6 0 1	6 1 7	6 2 4	6 2 5	6 2 5	6 4 2	6 4 3	6 5 6	6 6 7	6 7 7	6 8 0	6 8 4	6 8 5	7 2 0	7 2 2
Carcass ID Number	7 2 2	7 1 7	7 3 4	7 2 3	7 3 6	7 3 0	7 3 9	7 0 1	7 2 9	7 0 2	7 3 1	7 1 2	7 0 4	7 1 0	7 3 5	7 4 1	7 3 7	7 3 3	7 1 6	7 2 0	7 2 7	7 1 4	7 0 6	7 2 8	7 0 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node													+												+
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	+	+	+	+	+	+	M	M	M	+	+	+	+	M	+	+	M	M	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X						X													
Fibroadenoma															X							X	X		
Fibroadenoma, multiple																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																					X				
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neuroblastoma, metastatic, nose		X	X																X		X				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory epithelium, neuroblastoma		X	X				X	X	X			X	X						X		X				
Respiratory epithelium, adenoma									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland				+																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X		X	X	X			X	X					X		X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Naphthalene: 60 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	7 4 3	7 4 4	7 4 6	7 0 3	7 0 7	7 0 8	7 1 1	7 1 3	7 1 8	7 1 9	7 2 1	7 2 4	7 2 6	7 3 8	7 4 0	7 4 7	7 4 8	7 4 9	7 0 5	7 1 5	7 2 5	7 3 2	7 4 2	7 4 5	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node							+																		3
Lymph node, bronchial	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	M	M	+	M	+	M	+	+	+	36
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	M	M	M	+	M	M	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	31
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	41
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma										X															3
Fibroadenoma							X	X							X		X		X				X	X	10
Fibroadenoma, multiple																X					X	X			4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																									1
Subcutaneous tissue, fibroma									X																1
Subcutaneous tissue, fibrosarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neuroblastoma, metastatic, nose																									4
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Olfactory epithelium, neuroblastoma				X											X			X							12
Respiratory epithelium, adenoma									X																2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X						X							X				X	X		X				15

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/48 (6%)	0/49 (0%)	1/49 (2%)	2/49 (4%)
Adjusted rate[b]	7.0%	0.0%	2.4%	5.3%
Terminal rate[c]	2/28 (7%)	0/21 (0%)	0/28 (0%)	2/24 (8%)
First incidence (days)	676	—[e]	671	734 (T)
Poly-3 test[d]	P=0.598N	P=0.137N	P=0.319N	P=0.554N
Clitoral Gland: Adenoma				
Overall rate	4/49 (8%)	7/47 (15%)	4/49 (8%)	2/48 (4%)
Adjusted rate	9.3%	18.1%	9.7%	5.2%
Terminal rate	4/28 (14%)	4/21 (19%)	3/28 (11%)	0/24 (0%)
First incidence (days)	734 (T)	518	615	617
Poly-3 test	P=0.168N	P=0.198	P=0.617	P=0.392N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	4/49 (8%)	7/47 (15%)	5/49 (10%)	3/48 (6%)
Adjusted rate	9.3%	18.1%	11.9%	7.8%
Terminal rate	4/28 (14%)	4/21 (19%)	3/28 (11%)	1/24 (4%)
First incidence (days)	734 (T)	518	440	617
Poly-3 test	P=0.316N	P=0.198	P=0.481	P=0.564N
Mammary Gland: Fibroadenoma				
Overall rate	17/49 (35%)	20/49 (41%)	18/49 (37%)	14/49 (29%)
Adjusted rate	38.5%	49.1%	41.2%	36.1%
Terminal rate	12/28 (43%)	12/21 (57%)	10/28 (36%)	10/24 (42%)
First incidence (days)	625	581	440	625
Poly-3 test	P=0.319N	P=0.216	P=0.484	P=0.503N
Mammary Gland: Carcinoma				
Overall rate	3/49 (6%)	5/49 (10%)	3/49 (6%)	3/49 (6%)
Adjusted rate	6.9%	12.4%	7.2%	7.7%
Terminal rate	3/28 (11%)	1/21 (5%)	1/28 (4%)	1/24 (4%)
First incidence (days)	734 (T)	577	587	503
Poly-3 test	P=0.478N	P=0.315	P=0.643	P=0.614
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	18/49 (37%)	24/49 (49%)	19/49 (39%)	17/49 (35%)
Adjusted rate	40.7%	56.9%	43.5%	42.7%
Terminal rate	13/28 (46%)	12/21 (57%)	11/28 (39%)	11/24 (46%)
First incidence (days)	625	577	440	503
Poly-3 test	P=0.379N	P=0.092	P=0.483	P=0.517
Nose: Adenoma				
Overall rate	0/49 (0%)	0/49 (0%)	4/49 (8%)	2/49 (4%)
Adjusted rate	0.0%	0.0%	9.8%	5.2%
Terminal rate	0/28 (0%)	0/21 (0%)	3/28 (11%)	1/24 (4%)
First incidence (days)	—	—[f]	721	555
Poly-3 test	P=0.066	—	P=0.053	P=0.212
Nose: Neuroblastoma				
Overall rate	0/49 (0%)	2/49 (4%)	3/49 (6%)	12/49 (24%)
Adjusted rate	0.0%	5.1%	7.2%	28.2%
Terminal rate	0/28 (0%)	0/21 (0%)	1/28 (4%)	3/24 (13%)
First incidence (days)	—	679	480	429
Poly-3 test	P<0.001	P=0.214	P=0.112	P<0.001

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	23/49 (47%)	27/49 (55%)	24/49 (49%)	20/48 (42%)
Adjusted rate	49.5%	61.2%	54.2%	48.1%
Terminal rate	12/28 (43%)	14/21 (67%)	14/28 (50%)	11/24 (46%)
First incidence (days)	509	509	581	482
Poly-3 test	P=0.335N	P=0.176	P=0.405	P=0.534N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	23/49 (47%)	27/49 (55%)	25/49 (51%)	20/48 (42%)
Adjusted rate	49.5%	61.2%	56.4%	48.1%
Terminal rate	12/28 (43%)	14/21 (67%)	14/28 (50%)	11/24 (46%)
First incidence (days)	509	509	581	482
Poly-3 test	P=0.351N	P=0.176	P=0.325	P=0.534N
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/47 (9%)	4/46 (9%)	2/48 (4%)	1/48 (2%)
Adjusted rate	9.4%	10.8%	5.0%	2.7%
Terminal rate	1/28 (4%)	3/21 (14%)	2/28 (7%)	1/24 (4%)
First incidence (days)	602	677	734 (T)	734 (T)
Poly-3 test	P=0.106N	P=0.569	P=0.366N	P=0.223N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	3/47 (6%)	2/46 (4%)	2/48 (4%)	0/48 (0%)
Adjusted rate	7.2%	5.4%	5.0%	0.0%
Terminal rate	2/28 (7%)	2/21 (10%)	2/28 (7%)	0/24 (0%)
First incidence (days)	690	734 (T)	734 (T)	—
Poly-3 test	P=0.102N	P=0.557N	P=0.523N	P=0.142N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/47 (15%)	6/46 (13%)	4/48 (8%)	1/48 (2%)
Adjusted rate	16.4%	16.1%	10.0%	2.7%
Terminal rate	3/28 (11%)	5/21 (24%)	4/28 (14%)	1/24 (4%)
First incidence (days)	602	677	734 (T)	734 (T)
Poly-3 test	P=0.024N	P=0.606N	P=0.299N	P=0.047N
Uterus: Stromal Polyp				
Overall rate	15/49 (31%)	7/49 (14%)	9/49 (18%)	7/49 (14%)
Adjusted rate	33.1%	17.8%	21.4%	18.3%
Terminal rate	9/28 (32%)	4/21 (19%)	7/28 (25%)	6/24 (25%)
First incidence (days)	519	635	480	667
Poly-3 test	P=0.118N	P=0.085N	P=0.162N	P=0.099N
All Organs: Mononuclear Cell Leukemia				
Overall rate	16/49 (33%)	21/49 (43%)	15/49 (31%)	15/49 (31%)
Adjusted rate	34.6%	48.2%	35.1%	36.4%
Terminal rate	3/28 (11%)	7/21 (33%)	8/28 (29%)	6/24 (25%)
First incidence (days)	572	471	587	478
Poly-3 test	P=0.398N	P=0.134	P=0.569	P=0.519
All Organs: Benign Neoplasms				
Overall rate	38/49 (78%)	41/49 (84%)	43/49 (88%)	35/49 (71%)
Adjusted rate	79.3%	89.1%	90.4%	80.3%
Terminal rate	22/28 (79%)	19/21 (91%)	24/28 (86%)	19/24 (79%)
First incidence (days)	509	509	440	482
Poly-3 test	P=0.507N	P=0.141	P=0.100	P=0.558

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
All Organs: Malignant Neoplasms				
Overall rate	26/49 (53%)	34/49 (69%)	26/49 (53%)	27/49 (55%)
Adjusted rate	56.0%	73.5%	56.5%	58.9%
Terminal rate	12/28 (43%)	12/21 (57%)	12/28 (43%)	9/24 (38%)
First incidence (days)	572	440	440	429
Poly-3 test	P=0.349N	P=0.055	P=0.563	P=0.472
All Organs: Benign or Malignant Neoplasms				
Overall rate	44/49 (90%)	48/49 (98%)	47/49 (96%)	44/49 (90%)
Adjusted rate	90.6%	98.0%	97.5%	91.7%
Terminal rate	24/28 (86%)	20/21 (95%)	27/28 (96%)	20/24 (83%)
First incidence (days)	509	440	440	429
Poly-3 test	P=0.479N	P=0.124	P=0.151	P=0.571

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, nose, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Historical Incidence of Nasal Adenoma or Neuroblastoma in Control Female F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Feed[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	0/50
Indium phosphide (inhalation)	0/50
Methacrylonitrile (gavage)	0/50
Naphthalene (inhalation)	0/49
p-Nitrotoluene (feed)	0/50
Sodium nitrite (drinking water)	0/50
Overall Historical Incidence in Controls Given NTP-2000 Feed	
Total	0/299
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]	
Acetonitrile	0/47
2-Butoxyethanol	0/50
Chloroprene	0/49
Cobalt sulfate heptahydrate	0/50
Furfuryl alcohol	0/49
Gallium arsenide	0/50
Glutaraldehyde	0/50
Hexachlorocyclopentadiene	0/50
Isobutene	0/50
Isobutyraldehyde	0/49
Isoprene	0/50
Molybdenum trioxide	0/48
Nitromethane	0/50
Ozone	0/50
Tetrafluoroethylene	0/50
Tetrahydrofuran	0/49
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed	
Total	0/1,044

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

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

	Chamber Control	10 ppm	30 ppm	60 ppm
Disposition Summary				
Animals initially in study	49	49	49	49
Early deaths				
Moribund	18	22	16	21
Natural deaths	3	6	5	4
Survivors				
Terminal sacrifice	28	21	28	24
Animals examined microscopically	49	49	49	49
Alimentary System				
Intestine large, cecum	(49)	(48)	(48)	(48)
Inflammation, acute				1 (2%)
Liver	(49)	(49)	(49)	(49)
Angiectasis	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Basophilic focus	46 (94%)	44 (90%)	46 (94%)	44 (90%)
Clear cell focus	7 (14%)	16 (33%)	8 (16%)	6 (12%)
Cyst				1 (2%)
Eosinophilic focus	1 (2%)		6 (12%)	2 (4%)
Fatty change	10 (20%)	3 (6%)	2 (4%)	4 (8%)
Hepatodiaphragmatic nodule	4 (8%)	1 (2%)	6 (12%)	5 (10%)
Inflammation, chronic	2 (4%)			
Mixed cell focus	6 (12%)	6 (12%)	7 (14%)	6 (12%)
Necrosis	1 (2%)	1 (2%)	1 (2%)	
Regeneration	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Vacuolization cytoplasmic, focal	1 (2%)	1 (2%)		
Bile duct, hyperplasia	5 (10%)	5 (10%)	5 (10%)	6 (12%)
Centrilobular, necrosis	11 (22%)	11 (22%)	7 (14%)	9 (18%)
Hepatocyte, atrophy			1 (2%)	
Mesentery	(13)	(8)	(7)	(5)
Fat, hemorrhage	1 (8%)			
Fat, inflammation		1 (13%)		
Fat, necrosis	13 (100%)	7 (88%)	6 (86%)	5 (100%)
Pancreas	(49)	(49)	(49)	(49)
Atrophy	18 (37%)	9 (18%)	11 (22%)	10 (20%)
Basophilic focus		1 (2%)	1 (2%)	
Hyperplasia		1 (2%)		
Duct, cyst		1 (2%)		
Salivary glands	(49)	(49)	(49)	(49)
Atrophy	1 (2%)			2 (4%)
Basophilic focus	1 (2%)			
Stomach, forestomach	(49)	(49)	(49)	(49)
Hyperplasia, squamous				1 (2%)
Inflammation, acute	1 (2%)			
Ulcer	3 (6%)	2 (4%)	2 (4%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(48)	(49)	(49)
Hyperplasia			1 (2%)	
Mineralization	2 (4%)	2 (4%)		2 (4%)
Necrosis	3 (6%)	2 (4%)	1 (2%)	
Ulcer	1 (2%)		1 (2%)	
Tongue	(1)	(1)		(1)
Epithelium, hyperplasia	1 (100%)			
Tooth			(1)	(1)
Malformation			1 (100%)	1 (100%)
Cardiovascular System				
Heart	(49)	(49)	(49)	(49)
Cardiomyopathy	32 (65%)	31 (63%)	31 (63%)	34 (69%)
Atrium, thrombosis	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(49)
Atrophy	2 (4%)			
Degeneration, cystic	4 (8%)	4 (8%)	3 (6%)	3 (6%)
Hyperplasia	23 (47%)	12 (24%)	18 (37%)	24 (49%)
Hypertrophy	7 (14%)	4 (8%)	12 (24%)	6 (12%)
Necrosis	4 (8%)	2 (4%)		1 (2%)
Thrombosis	1 (2%)			
Vacuolization cytoplasmic		2 (4%)		1 (2%)
Adrenal medulla	(48)	(49)	(49)	(49)
Hyperplasia	10 (21%)	3 (6%)	9 (18%)	5 (10%)
Necrosis	2 (4%)	1 (2%)		
Thrombosis	1 (2%)			
Islets, pancreatic	(49)	(49)	(49)	(49)
Hyperplasia			1 (2%)	
Parathyroid gland	(42)	(40)	(41)	(48)
Hyperplasia			1 (2%)	
Pituitary gland	(49)	(49)	(49)	(48)
Angiectasis	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Cyst				1 (2%)
Pars distalis, hyperplasia	24 (49%)	13 (27%)	18 (37%)	15 (31%)
Thyroid gland	(47)	(46)	(48)	(48)
C-cell, hyperplasia	39 (83%)	37 (80%)	37 (77%)	42 (88%)
Follicular cell, hyperplasia			1 (2%)	
General Body System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Genital System				
Clitoral gland	(49)	(47)	(49)	(48)
Hyperplasia	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic active	2 (4%)		1 (2%)	1 (2%)
Ovary	(49)	(49)	(49)	(49)
Cyst	7 (14%)	9 (18%)	11 (22%)	8 (16%)
Inflammation, granulomatous	1 (2%)	1 (2%)		2 (4%)
Uterus	(49)	(49)	(49)	(49)
Cyst	1 (2%)			
Vagina			(1)	
Inflammation, suppurative			1 (100%)	
Hematopoietic System				
Bone marrow	(49)	(49)	(49)	(49)
Atrophy				1 (2%)
Hyperplasia, reticulum cell	1 (2%)		1 (2%)	
Myelofibrosis	1 (2%)			
Lymph node, mediastinal	(40)	(39)	(41)	(31)
Congestion			1 (2%)	
Hemorrhage			1 (2%)	
Spleen	(49)	(49)	(49)	(49)
Fibrosis	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Hematopoietic cell proliferation	2 (4%)	4 (8%)	1 (2%)	4 (8%)
Hemorrhage		2 (4%)		1 (2%)
Metaplasia, osseous				1 (2%)
Necrosis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Thymus	(46)	(45)	(48)	(41)
Cyst			1 (2%)	
Integumentary System				
Mammary gland	(49)	(49)	(49)	(49)
Galactocele	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, atypical				1 (2%)
Inflammation, chronic active	2 (4%)			
Skin	(49)	(49)	(49)	(49)
Hyperkeratosis				1 (2%)
Inflammation, acute				2 (4%)
Inflammation, chronic active	1 (2%)			
Epidermis, hyperplasia	1 (2%)			
Subcutaneous tissue, hemorrhage		1 (2%)		
Musculoskeletal System				
Bone	(49)	(49)	(49)	(49)
Osteopetrosis	10 (20%)	4 (8%)	7 (14%)	5 (10%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Naphthalene

	Chamber Control	10 ppm	30 ppm	60 ppm
Nervous System				
Brain	(49)	(49)	(49)	(49)
Angiectasis			1 (2%)	
Degeneration	1 (2%)			
Thrombosis	1 (2%)			
Respiratory System				
Larynx	(49)	(49)	(49)	(49)
Hyperplasia				1 (2%)
Metaplasia, squamous	2 (4%)		4 (8%)	1 (2%)
Lung	(49)	(49)	(49)	(49)
Congestion, chronic			1 (2%)	
Inflammation, chronic active	16 (33%)	15 (31%)	19 (39%)	22 (45%)
Metaplasia, osseous			1 (2%)	
Alveolar epithelium, hyperplasia	4 (8%)	11 (22%)	11 (22%)	9 (18%)
Alveolus, infiltration cellular, histiocyte	19 (39%)	7 (14%)	11 (22%)	14 (29%)
Bronchiole, hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Nose	(49)	(49)	(49)	(49)
Inflammation, suppurative	2 (4%)	5 (10%)	5 (10%)	5 (10%)
Thrombosis	7 (14%)	4 (8%)	3 (6%)	3 (6%)
Glands, hyperplasia		48 (98%)	48 (98%)	42 (86%)
Glands, metaplasia, squamous		2 (4%)	20 (41%)	20 (41%)
Goblet cell, respiratory epithelium, hyperplasia		16 (33%)	29 (59%)	20 (41%)
Olfactory epithelium, atrophy		49 (100%)	49 (100%)	47 (96%)
Olfactory epithelium, degeneration, hyaline	13 (27%)	46 (94%)	49 (100%)	45 (92%)
Olfactory epithelium, hyperplasia, atypical		48 (98%)	48 (98%)	43 (88%)
Olfactory epithelium, inflammation, chronic		47 (96%)	47 (96%)	45 (92%)
Respiratory epithelium, degeneration, hyaline	8 (16%)	33 (67%)	34 (69%)	28 (57%)
Respiratory epithelium, hyperplasia		18 (37%)	22 (45%)	23 (47%)
Respiratory epithelium, metaplasia, squamous		21 (43%)	17 (35%)	15 (31%)
Special Senses System				
Eye	(48)	(47)	(46)	(48)
Cataract	5 (10%)	2 (4%)	6 (13%)	3 (6%)
Cornea, infiltration cellular, polymorphonuclear	2 (4%)			
Retina, atrophy	5 (10%)	2 (4%)	4 (9%)	2 (4%)
Harderian gland				(1)
Inflammation, chronic				1 (100%)
Urinary System				
Kidney	(48)	(49)	(49)	(49)
Cyst		1 (2%)		
Infarct			1 (2%)	1 (2%)
Nephropathy	41 (85%)	38 (78%)	34 (69%)	31 (63%)
Renal tubule, necrosis	1 (2%)	1 (2%)		

APPENDIX C
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Naphthalene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of naphthalene. The high dose was limited by toxicity. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Naphthalene was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of naphthalene. The high dose was limited by toxicity. A single flask per dose was used, and all tests were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 25.8 hours with naphthalene in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 25.8 hours, the medium containing naphthalene was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with naphthalene, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no naphthalene. Incubation proceeded for an additional 25.8 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell at each dose. Due to the high frequencies of SCEs seen, only 25 cells were scored in the repeat trials under each activation condition. Because significant chemical-induced cell cycle delay was anticipated at the highest concentration of naphthalene in the initial trials with and without S9, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a

statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with naphthalene for 8.2 or 18.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with naphthalene and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for approximately 18 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: the incubation period was extended in all but the second trial without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level, except in the first trial with S9, in which only 100 cells were scored at the two highest doses due to high numbers of aberrant cells. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentages of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and differing results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

Naphthalene (0.3 to 100 µg/plate) was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without induced rat or hamster liver S9 activation enzymes (Table C1; Mortelmans *et al.*, 1986). In contrast to these negative results for gene mutation induction in bacteria, naphthalene was positive for induction of chromosomal effects in mammalian cells *in vitro*. In cultured CHO cells, naphthalene induced dose-related increases in SCEs, with and without rat liver S9 activation enzymes (Table C2). In addition, Abs were induced by naphthalene in CHO cells (Table C3). A strong dose-related increase in the percent aberrant cells was observed over a concentration range of 30 to 67.5 µg/mL naphthalene in the presence of S9, but no significant increases in Abs were seen without S9.

TABLE C1
Mutagenicity of Naphthalene in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b]					
		-S9		+10% hamster S9		+10% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0.0	143 ± 4.5	141 ± 4.2	143 ± 11.9	128 ± 6.2	144 ± 2.4	137 ± 8.2
	0.3		121 ± 3.5				
	1.0	146 ± 5.8	124 ± 3.6	143 ± 13.2	115 ± 7.9	130 ± 2.7	143 ± 16.0
	3.3	124 ± 12.0	117 ± 8.5	155 ± 4.9	135 ± 2.4	133 ± 13.2	133 ± 5.9
	10.0	145 ± 5.8	113 ± 6.2	140 ± 3.5	118 ± 9.8	135 ± 8.7	121 ± 6.6
	33.0	141 ± 9.4[c]	113 ± 5.1	147 ± 5.7	133 ± 6.8	142 ± 6.6	121 ± 7.3
	100.0	Toxic		141 ± 2.0[c]	145 ± 9.0[c]	104 ± 0.6[c]	127 ± 5.4[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,636 ± 45.5	801 ± 28.7	2,534 ± 77.9	754 ± 19.2	1,074 ± 13.2	792 ± 26.4
TA1535	0.0	22 ± 1.5	19 ± 2.6	11 ± 2.3	8 ± 0.6	9 ± 0.6	12 ± 2.4
	0.3		24 ± 3.1				
	1.0	21 ± 3.0	26 ± 2.7	10 ± 3.3	11 ± 2.9	13 ± 1.2	16 ± 1.5
	3.3	22 ± 5.2	23 ± 2.3	10 ± 0.9	11 ± 3.8	9 ± 0.7	10 ± 1.7
	10.0	30 ± 2.6	20 ± 1.2	12 ± 0.6	11 ± 0.3	8 ± 0.7	10 ± 2.6
	33.0	20 ± 1.2[c]	15 ± 2.3	13 ± 1.0	11 ± 1.7	11 ± 1.5	13 ± 1.2
	100.0	15 ± 3.5[c]		6 ± 1.9[c]	10 ± 3.2[c]	13 ± 3.4[c]	11 ± 2.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,258 ± 18.8	687 ± 6.4	126 ± 1.7	75 ± 8.9	63 ± 8.0	48 ± 1.9
TA1537	0.0	8 ± 1.8	8 ± 1.9	10 ± 1.2	6 ± 2.4	11 ± 3.8	10 ± 2.3
	0.3		7 ± 1.2				
	1.0	8 ± 0.6	5 ± 0.6	11 ± 1.2	8 ± 0.3	10 ± 0.9	8 ± 0.7
	3.3	7 ± 1.5	9 ± 0.6	9 ± 3.2	7 ± 0.9	9 ± 0.9	9 ± 0.9
	10.0	8 ± 0.7	9 ± 1.5	12 ± 2.0	10 ± 1.5	8 ± 1.7	5 ± 2.2
	33.0	6 ± 2.0[c]	4 ± 0.9	12 ± 1.5	10 ± 1.5	10 ± 1.9	7 ± 1.5
	100.0	Toxic		10 ± 1.0[c]	5 ± 0.6[c]	5 ± 1.9[c]	4 ± 0.6[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,010 ± 39.4	185 ± 12.0	205 ± 22.1	77 ± 5.3	87 ± 5.2	86 ± 2.9
TA98	0.0	14 ± 3.8	17 ± 1.0	35 ± 4.8	20 ± 3.1	29 ± 4.1	23 ± 0.3
	0.3		12 ± 2.2				
	1.0	15 ± 2.2	17 ± 1.5	30 ± 2.6	29 ± 2.1	27 ± 1.8	23 ± 2.2
	3.3	22 ± 2.3	12 ± 2.6	42 ± 5.5	21 ± 1.9	32 ± 1.7	24 ± 0.7
	10.0	16 ± 3.3	12 ± 2.6	32 ± 4.2	26 ± 1.2	25 ± 2.6	21 ± 0.9
	33.0	19 ± 2.5[c]	12 ± 3.2	32 ± 3.1	21 ± 1.2	29 ± 1.9	24 ± 2.8
	100.0	14 ± 0.3[c]		34 ± 1.5[c]	23 ± 2.4	22 ± 1.2[c]	24 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,772 ± 9.6	1,072 ± 40.3	2,064 ± 71.4	183 ± 10.1	982 ± 43.1	176 ± 16.6

[a] Study was performed at EG&G Mason Research. The detailed protocol and these data are presented by Mortelmans *et al.* (1986). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Naphthalene[a]

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Trial 1								
Summary: Weakly positive								
Dimethylsulfoxide[c]		50	1,046	388	0.37	7.8	25.8	
Naphthalene	9	50	1,048	406	0.38	8.1	25.8	4.44
	27	50	1,041	442	0.42	8.8	25.8	14.47
	90	50	1,042	578	0.55	11.6	30.9[d]	49.54*
	270	Toxic						
					P<0.001[e]			
Mitomycin-C[f]	0.001	50	1,049	597	0.56	11.9	25.8	53.43*
	0.010	5	105	217	2.06	43.4	25.8	457.16*
Trial 2								
Summary: Positive								
Dimethylsulfoxide		25	525	178	0.33	7.1	25.8	
Naphthalene	27	25	525	222	0.42	8.9	25.8	24.72*
	45	25	525	268	0.51	10.7	25.8	50.56*
	90	25	525	268	0.51	10.7	25.8	50.56*
					P<0.001			
Mitomycin-C	0.001	25	525	376	0.71	15.0	25.8	111.24*
	0.010	5	105	263	2.50	52.6	25.8	638.78*

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Naphthalene

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9								
Trial 1								
Summary: Equivocal								
Dimethylsulfoxide		50	1,050	423	0.40	8.5	25.8	
Naphthalene	2.7	50	1,050	411	0.39	8.2	25.8	-2.84
	9.0	50	1,050	493	0.46	9.9	25.8	16.55
	27.0	50	1,045	505	0.48	10.1	30.9[f]	19.96
	90.0	Toxic						
					P<0.001			
Cyclophosphamide[f]	0.4	50	1,050	792	0.75	15.8	25.8	87.24*
	2.0	5	105	197	1.87	39.4	25.8	365.73*
Trial 2								
Summary: Positive								
Dimethylsulfoxide		25	525	189	0.36	7.6	25.8	
Naphthalene	9	25	525	199	0.37	8.0	25.8	5.29
	15	25	525	239	0.45	9.6	25.8	26.45*
	27	25	525	266	0.50	10.6	25.8	40.74*
	45	Toxic						
					P<0.001			
Cyclophosphamide	0.4	25	525	334	0.63	13.4	25.8	76.72*
	2.0	5	105	174	1.65	34.8	25.8	360.32*

* Positive response (≥20% increase over solvent control)
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol is presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.
[e] Significance tested by the linear regression trend test versus log of the dose
[f] Positive control

TABLE C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Naphthalene[a]

Compound	Dose (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
-S9					
Trial 1					
Harvest time: 20.5 hours					
Summary: Negative					
Dimethylsulfoxide[b]		200	1	0.01	0.5
Naphthalene	37.5	200	2	0.01	1.0
	75.0	200	3	0.02	1.5
	112.5	Toxic			
					P=0.157[c]
Mitomycin-C[d]	0.05	200	31	0.16	11.0*
	0.08	25	25	1.00	48.0*
Trial 2					
Harvest time: 10.2 hours					
Summary: Negative					
Dimethylsulfoxide		200	1	0.01	0.5
Naphthalene	15.0	200	2	0.01	0.5
	37.5	200	0	0.00	0.0
					P=0.807
Mitomycin-C	0.25	200	19	0.10	8.5*
	0.75	25	6	0.24	24.0*

TABLE C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Naphthalene

Compound	Dose (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
+S9					
Trial 1					
Harvest time: 20.5 hours					
Summary: Positive					
Dimethylsulfoxide		200	3	0.02	1.5
Naphthalene	30.0	200	29	0.15	11.0*
	45.0	100	27	0.27	20.0*
	67.5	100	50	0.50	32.0*
	90.0	Toxic			
					P<0.001
Cyclophosphamide[d]	6.25	200	31	0.16	13.5*
	12.50	25	17	0.68	44.0*
Trial 2					
Harvest time: 20.2 hours					
Summary: Positive					
Dimethylsulfoxide		200	0	0.00	0.0
Naphthalene	45.00	200	29	0.15	8.5*
	56.25	200	39	0.20	13.5*
	67.50	200	37	0.19	16.0*
					P<0.001
Cyclophosphamide	6.25	200	23	0.12	11.5*
	12.50	25	19	0.76	52.0*

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol is presented by Galloway *et al*. (1987).
[b] Solvent control
[c] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose
[d] Positive control

APPENDIX D
TOXICOKINETIC RESULTS AND MODEL

TOXICOKINETIC RESULTS AND MODEL

INTRODUCTION

A physiologically based pharmacokinetic model representing the uptake, distribution, and metabolism of naphthalene in rats and mice was developed to describe the processes involved in naphthalene toxicokinetics. Blood time-course data of the parent compound following inhalation exposure were available to model the distribution of naphthalene throughout the body and to estimate metabolic rates in the lung and liver. No information was available on the rate of production or distribution of the metabolites or on the excretion of the parent compound or its metabolites.

MATERIALS AND METHODS

Whole blood samples from groups of nine male and nine female toxicokinetic study rats from the 2-year study, which were administered 10, 30, or 60 ppm naphthalene by inhalation, were analyzed for naphthalene concentrations at 2 weeks and 3, 6, 12, and 18 months. Additional groups of 12 male and 12 female rats and mice were obtained from the same suppliers used in the 2-year study; rats were evaluated after a single 6-hour inhalation exposure to 10, 30, or 60 ppm naphthalene, and mice were evaluated after a single 6-hour exposure to 10 or 30 ppm. Blood was taken at eight (single-exposure groups) or 10 (toxicokinetic study groups) time points postexposure per collection period; each group of toxicokinetic study rats was evaluated at 6 of the 10 time points. Each animal was bled twice. At each time point, blood was taken from up to three animals per group, and naphthalene concentrations in whole blood were measured. The samples were analyzed by CEDRA Corporation (Austin, TX) using a previously validated high-performance liquid chromatography method with ultraviolet light detection (CEDRA, 1994).

MODEL DEVELOPMENT

The model, which is diffusion limited (Kohn, 1997), contains compartments for arterial and venous blood, alveolar space, and tissue and capillary spaces for the lung, liver, kidney, fat, and other organs (Figure D1). The compartment for other organs represents both slowly and rapidly perfused tissues (e.g., skin, muscle, bone, heart, and brain). Inhalation of naphthalene from chamber air takes place through the alveolar space into the lung. Uptake is modeled as being dependent on the ventilation rate of the animal, permeability of the tissue, and blood flow through the lung. The primary sites for naphthalene metabolism were assumed to be the lung and the liver. In the lung, one metabolic pathway was used, while in the liver, two pathways were taken into account, one represented by Michaelis-Menten kinetics and the other by Hill kinetics. The same K_m was used in the lung and the Michaelis-Menten pathway in the liver, but different values were estimated for V_{max} in all three pathways. The other compartments were included due to their role in distribution kinetics. All the physiological parameters (ventilation rate, cardiac output, tissue volumes, capillary volumes, and blood flow rates to the tissues) used in this model were based on values obtained from the literature and scaled to the body weights of the 2-year core study rats. Partition coefficients for the different tissues were calculated from the log octanol:water partition coefficient (K_{ow}) using methods developed by Fiserova-Bergerova *et al.* (1984), Abraham *et al.* (1985), and Lyman *et al.* (1990) and are the same for male and female rats ($P_{blood:air}$=571, $P_{lung:blood}$=1.81, $P_{liver:blood}$=7.0, $P_{fat:blood}$=160.4, $P_{kidney:blood}$=4 and $P_{other:blood}$=4).

Metabolic rates and permeability constants were estimated by optimizing the model to the available naphthalene blood time-course data. Goodness of fit was evaluated using a maximum-likelihood ratio test (Kotz and Johnson, 1983). The program package MATLAB (The MathWorks, Inc., Natick, MA), including Simulink, was used for simulation and optimization of the model.

The physiologically based pharmacokinetic model consists of the ordinary differential equations presented below. In this model, naphthalene is taken up from the exposure chamber atmosphere via the alveolar space into the lung capillary blood (Equations 0.1 and 0.2). From the lung capillary blood, it can enter the arterial blood (Equation 0.3) and distribute to the other tissues or go into the lung tissue and subsequently undergo metabolism (Equations 0.4 and 0.5). The effluent from all of the tissue capillary spaces except the lung capillary space goes to the venous blood compartment and is then redirected to the lung capillary space (Equation 0.6). The liver is the only tissue other than the lung in which metabolism was assumed to take place (Equations 0.7 and 0.8). All other nonmetabolizing tissues (fat, kidney, and other) are represented by Equations 0.9 and 0.10.

Differential Equations

Chamber:

$$\frac{dAMT_{air}}{dt} = Dose - Dose \bullet Q_{vent} \tag{0.1}$$

Alveolar space:

$$\frac{dAMT_{alv}}{dt} = Dose \bullet Q_{vent} + \frac{AMT_{lungcap}}{V_{lungcap}} \bullet \frac{Q_{vent}}{P_{air}} \bullet Perm - \ldots \\ \frac{AMT_{alv}}{V_{alv}} \bullet Q_{vent} \bullet Perm - \frac{AMT_{alv}}{V_{alv}} \bullet Q_{vent} \tag{0.2}$$

Arterial blood:

$$\frac{dAMT_{art}}{dt} = \frac{AMT_{lungcap}}{V_{lungcap}} \bullet Q_{total} - \frac{AMT_{art}}{V_{art}} \bullet Q_{total} \tag{0.3}$$

Lung:

$$\frac{dAMT_{lungcap}}{dt} = \frac{AMT_{ven}}{V_{ven}} \bullet Q_{total} + \frac{AMT_{alv}}{V_{alv}} \bullet Q_{vent} \bullet Perm + \ldots \\ \frac{AMT_{lung}}{V_{lung}} \bullet \frac{Q_{total}}{P_{lung}} \bullet Perm - \frac{AMT_{lungcap}}{V_{lungcap}} \bullet Q_{total} - \ldots \\ \frac{AMT_{lungcap}}{V_{lungcap}} \bullet Q_{total} \bullet Perm - \frac{AMT_{lungcap}}{V_{lungcap}} \bullet \frac{Q_{vent}}{P_{air}} \bullet Perm \tag{0.4}$$

$$\frac{dAMT_{lung}}{dt} = \frac{AMT_{lungcap}}{V_{lungcap}} \bullet Q_{total} \bullet Perm - \frac{AMT_{lung}}{V_{lung}} \bullet \frac{Q_{total}}{P_{lung}} \bullet Perm - \ldots \\ \frac{V_{\max lung} \bullet V_{lung} \bullet AMT_{lung}}{K_{mlung} \bullet V_{lung} + AMT_{lung}} \tag{0.5}$$

Venous blood:

$$\frac{dAMT_{ven}}{dt} = \sum \frac{AMT_{tissuecap}}{V_{tissuecap}} \bullet Q_{tissue} - \frac{AMT_{ven}}{V_{ven}} \bullet Q_{total} \tag{0.6}$$

Liver:

$$\frac{dAMT_{livercap}}{dt} = \frac{AMT_{art}}{V_{art}} \bullet Q_{liver} + \frac{AMT_{liver}}{V_{liver}} \bullet \frac{Q_{liver}}{P_{liver}} \bullet Perm - \ldots \\ \frac{AMT_{livercap}}{V_{livercap}} \bullet Q_{liver} - \frac{AMT_{livercap}}{V_{livercap}} \bullet Q_{liver} \bullet Perm \tag{0.7}$$

$$\frac{dAMT_{liver}}{dt} = \frac{AMT_{livercap}}{V_{livercap}} \bullet Q_{liver} \bullet Perm - \frac{AMT_{liver}}{V_{liver}} \bullet \frac{Q_{liver}}{P_{liver}} \bullet Perm - \ldots \\ \frac{V_{\max liver1} \bullet V_{liver} \bullet AMT_{liver}}{K_{mliver1} \bullet V_{liver} + AMT_{liver}} - \frac{V_{\max liver2} \bullet V_{liver} \bullet AMT_{liver}^{\,n}}{(K_{mliver2} \bullet V_{liver})^n + AMT_{liver}^{\,n}} \tag{0.8}$$

Fat, kidney, and other nonmetabolizing tissues:

$$\frac{dAMT_{tissuecap}}{dt} = \frac{AMT_{art}}{V_{art}} \bullet Q_{tissue} + \frac{AMT_{tissue}}{V_{tissue}} \bullet \frac{Q_{tissue}}{P_{tissue}} \bullet Perm - \ldots \\ \frac{AMT_{tissuecap}}{V_{tissuecap}} \bullet Q_{tissue} - \frac{AMT_{tissuecap}}{V_{tissuecap}} \bullet Q_{tissue} \bullet Perm \tag{0.9}$$

$$\frac{dAMT_{tissue}}{dt} = \frac{AMT_{tissuecap}}{V_{tissuecap}} \bullet Q_{tissue} \bullet Perm - \frac{AMT_{tissue}}{V_{tissue}} \bullet \frac{Q_{tissue}}{P_{tissue}} \bullet Perm \tag{0.10}$$

Definitions of Abbreviations

V volume of tissue or blood (mL)

Concentrations:
Dose chamber concentration of naphthalene (ppm)
AMT_{air} amount in the air (mg)
AMT_{alv} amount in the alveolar space (mg)
AMT_{art} amount in the arterial blood (mg)
AMT_{ven} amount in the venous blood (mg)
$AMT_{tissuecap}$ amount in the tissue capillary blood (mg)
AMT_{tissue} amount in the tissue (mg)

Flows:
Q_{vent} ventilation rate (mL/min)
Q_{total} total blood flow (mL/min)
Q_{tissue} blood flow to the tissue (mL/min)

Partition coefficients and permeability constant:
Perm capillary permeability constant
P_{tissue} tissue:blood partition coefficient
P_{air} blood:air partition coefficient

Metabolism rates:
$V_{\max}$ maximum velocity of saturable metabolism (nmol/mL per minute)
K_m Michaelis-Menten constant for metabolism (nmol/mL)
n Hill constant

RESULTS

The model is shown in Figure D1. The blood time-course data for rats are given in Tables D1 and D2; the blood time-course data for mice are given in Table D3. A graphic representation of these data and the fits of the model are shown in Figures D2 and D3 for male and female rats and Figure D4 for mice. The physiological parameters for the model are given in Table D4. Estimates of naphthalene concentrations and metabolism in the lung and liver are given in Tables D5 and D6 for rats and mice, respectively.

This model was the best-fitting product after testing several alternative models. Sweeney *et al.* (1996) and Quick and Shuler (1999) developed models for naphthalene and naphthalene oxide metabolism in rats and mice in which they presented two Michaelis-Menten based metabolic pathways in both the lung and the liver. In the model described in this report, the metabolism of naphthalene oxide was not included, as there were no data available on the blood concentrations of the two different naphthalene metabolites, 1-(R)-2-(S)- and 1-(S)-2-(R)-naphthalene oxide. In an initial model, only one metabolic pathway for naphthalene metabolism in both the lung and liver was applied, as the use of two metabolic pathways did not improve the fit. Using this single metabolic pathway model resulted in an underprediction of the blood concentrations for the first 60 to 90 minutes postexposure, and the predicted maximum concentration in the blood at the end of the exposure period was not great enough to match the experimental data. Several attempts were made to eliminate this problem (e.g., modeling competitive inhibition of the P450 enzymes, noncompetitive inhibition, and suicidal inhibition) without any improvement in fit, as indicated by the likelihood test. However, introducing a second metabolic pathway in the liver, in the form of a Hill equation, greatly improved the fit to the data even though there is still an underprediction of the first time point at the highest exposure concentration. Graphic

representations of the fits of the model are shown in Figures D2 and D3 for male and female rat data, respectively, and in Figure D4 for mouse data. The predictions of the model for 2 weeks and 3, 6, 12, and 18 months were the same; therefore, data from these exposure durations were combined and presented as single figures for male and female rats. The single-exposure data for rats and mice are presented separately.

DISCUSSION

After a rapid uptake of naphthalene into the blood ($P_{blood:air}$=571), male and female rats appear to have an equal capacity for metabolism in the lungs, as do male and female mice. However, saturation of the metabolism occurs at lower naphthalene blood concentrations in female mice than in male mice. Similarly, the liver metabolic pathway represented by the Michaelis-Menten equation shows the same metabolic capacity and saturation level in male and female rats. Both the metabolic capacity and saturation level are lower in female mice than in male mice. The second liver metabolic pathway, characterized by a Hill equation with a Hill exponent of 2, shows a similar metabolic capacity and saturation level in male and female rats. In mice, the metabolic capacity is the same for males and females, but the saturation level is lower in females. The permeability of fat is less than that of the other tissues. Permeabilities are approximately similar between male and female rats. The permeability of fat in female mice is lower than that in males. Based on the available blood time-course data for naphthalene alone, no conclusions can be reached on which metabolites may be responsible for naphthalene toxicity.

Even though data are available from a single-dose intravenous injection study (NTP, unpublished), these were not included in the modeling effort in this report. The model outcomes from the inhalation and intravenous injection studies show a discrepancy. To be able to get a reasonable fit for the intravenous injection data, the parameters for the permeability of the fat and other tissues need to be much higher than those observed in the inhalation study. Why this occurred cannot be explained at this time. Nevertheless, as exposure to naphthalene through inhalation was the route of exposure used in the chronic study, and more data are therefore available for the inhalation route, the model developed from these data has been given preference. Secondly, there is also a large spread in the intravenous injection data, possibly attributable to errors in administering the dose into the tail vein of the animals, and these data should be interpreted with caution when used for modeling purposes.

The model developed to characterize the disposition of inhaled naphthalene in rats and mice was used to estimate the following parameters: a) the amounts of naphthalene inhaled by rats and mice (NTP, 1992) at the exposure concentrations used in the 2-year studies of this chemical, b) the amount of the inhaled dose that was metabolized during the 6-hour (rat) or 6-hour (mouse) exposure and during the 18 hours following exposure, c) the steady-state concentrations of naphthalene in the liver and lung of rats and mice during exposure, and d) the rate of naphthalene metabolism in the liver and lung of rats and mice at these steady-state concentrations. Approximately 22% to 31% of inhaled naphthalene is metabolized by rats and 65% to 73% of inhaled naphthalene is metabolized by mice. These values for the percentage of the inhaled parent compound that is metabolized are greater than those reported for volatile chemicals (Richardson *et al.*, 1999) and probably reflect the low vapor pressure of naphthalene and its very high estimated blood-to-air partition coefficient. Thus, once naphthalene is absorbed into the general circulation, very little parent compound is eliminated by exhalation. Because essentially all of the naphthalene that is absorbed is metabolized, the values for total naphthalene metabolized (presented in mg/kg body weight in Tables D5 and D6) represent the internalized dose of naphthalene in rats and mice resulting from 6-hour exposures, respectively. The species difference in the absorption of inhaled naphthalene probably reflects the greater metabolic capacity of mice compared to rats. Increased metabolism will tend to increase the gradient in concentration of naphthalene in the alveolar space compared to the lung blood and thus enhance further absorption of the compound. Total naphthalene metabolized (i.e., the internalized dose) was nearly equivalent for mice exposed to 10 ppm and

rats exposed to 60 ppm. This difference is due to the higher ventilation rates and greater metabolism of naphthalene in mice compared to rats.

These data also show that the steady-state concentration of naphthalene in the lung of rats is not very different from that of mice exposed to equivalent concentrations. For example, after 6 hours of exposure to 30 ppm, the concentration of parent compound was 1.8 µg/mL in rats and 2.6 to 2.8 µg/mL in mice. Rats exposed to 60 ppm naphthalene had higher concentrations of naphthalene in the lung (5.3 µg/mL) than did mice exposed to 30 ppm. Rates of metabolism and the cumulative metabolism of naphthalene in the lung were markedly greater in mice than in rats. Rates of naphthalene metabolism did not increase proportionally with increasing exposure concentration, indicating metabolic saturation in this organ. Metabolic saturation was more evident in the rat lung than in the mouse lung. Naphthalene metabolism was also greater in the mouse liver than in the rat liver; however, the species difference in liver metabolism was not as marked as that in the lung. Metabolic saturation was only apparent in the liver of rats exposed to 60 ppm. For both species, 65% to 75% of the metabolic clearance occurred during the 6-hour exposure periods; only in the 60 ppm rats was metabolic clearance at about 50% of the total inhaled dose. This is probably due to metabolic saturation resulting in greater storage of parent compound in the fat at this exposure concentration.

REFERENCES

Abraham, M.H., Kamlet, M.J., Taft, R.W., Doherty, R.M., and Weathersby, P.K. (1985). Solubility properties in polymers and biological media. 2. The correlation and prediction of the solubilities of nonelectrolytes in biological tissues and fluids. *J. Med. Chem.* **28**, 865-870.

Altman, P.L., and Dittmer, D.S., Eds. (1971). *Respiration and Circulation*. Federation of American Societies for Experimental Biology, Bethesda, MD.

Brown, R.P., Delp, M.D., Lindstedt, S.L., Rhomberg, L.R., and Beliles, R.P. (1997). Physiological parameter values for physiologically based pharmacokinetic models. *Toxicol. Ind. Health* **13**, 407-484.

CEDRA Corporation (1994). Biological Sample Method Development Report for Naphthalene in Rodent Blood. DCN No. A92-21-04/278.

Davies, B., and Morris, T. (1993). Physiological parameters in laboratory animals and humans. *Pharm. Res.* **10**, 1093-1095.

Fiserova-Bergerova, V., Tichy, M., and Di Carlo, F.J. (1984). Effects of biosolubility on pulmonary uptake and disposition of gases and vapors of lipophilic chemicals. *Drug Metab. Rev.* **15**, 1033-1070.

Kohn, M.C. (1997). The importance of anatomical realism for validation of physiological models of disposition of inhaled toxicants. *Toxicol. Appl. Pharmacol.* **147**, 448-458.

Kotz, S., and Johnson, N.L., Eds. (1983). *Encyclopedia of Statistical Sciences*, Vol. 5. John Wiley and Sons, New York.

Lyman, W.J., *et al.* (1990). *Handbook of Chemical Property Estimation Methods*. American Chemical Society, Washington, DC.

National Toxicology Program (NTP) (1992). Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 410. NIH Publication No. 92-3141. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Quick, D.J., and Shuler, M.L. (1999). Use of in vitro data for construction of a physiologically based pharmacokinetic model for naphthalene in rats and mice to probe species differences. *Biotechnol. Prog.* **15**, 540-555.

Richardson, K.A., Peters, M.M., Wong, B.A., Megens, R.H., van Elburg, P.A., Booth, E.D., Boogaard, P.J., Bond, J.A., Medinsky, M.A., Watson, W.P., and van Sittert, N.J. (1999). Quantitative and qualitative differences in the metabolism of ^{14}C-1,3-butadiene in rats and mice: Relevance to cancer susceptibility. *Toxicol. Sci.* **49**, 186-201.

Schmidt-Nielsen, K. (1979). *Animal Physiology: Adaptation and Environment*, 2nd ed. Cambridge University Press, Cambridge.

Sweeney, L.M., Shuler, M.L., Quick, D.J., and Babish, J.G. (1996). A preliminary physiologically based pharmacokinetic model for naphthalene and naphthalene oxide in mice and rats. *Ann. Biomed. Eng.* **24**, 305-320.

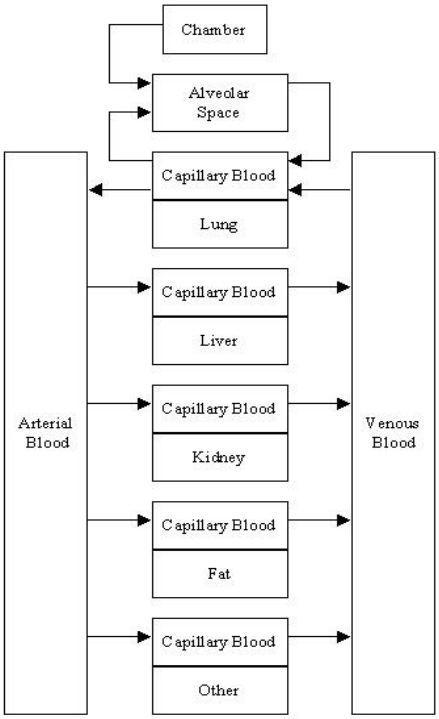


FIGURE D1
Diffusion-Limited Pharmacokinetic Model for Rats Exposed to Naphthalene by Inhalation

TABLE D1
Blood Concentrations of Naphthalene in F344/N Rats after a Single 6-Hour Inhalation Exposure[a]

Time after Exposure (minutes)	10 ppm	30 ppm	60 ppm
n	3	3	3
Male			
0	0.463 ± 0.034	1.387 ± 0.052	5.360 ± 0.666
30	0.308 ± 0.009	0.911 ± 0.051	3.193 ± 0.336
60	0.171 ± 0.008	0.661 ± 0.059	2.227 ± 0.388
90	0.094 ± 0.009	0.476 ± 0.018	1.143 ± 0.256
120	0.100 ± 0.011	0.239 ± 0.028	0.838 ± 0.149
240	0.051 ± 0.002	0.138 ± 0.007	0.380 ± 0.042
360	0.029 ± 0.001	0.071 ± 0.001	0.252 ± 0.009
480	0.014 ± 0.003	0.060 ± 0.003	0.174 ± 0.023
Female			
0	0.442 ± 0.029	1.667 ± 0.157	4.850 ± 0.112
30	0.243 ± 0.007	0.841 ± 0.086	2.483 ± 0.142
60	0.135 ± 0.008	0.632 ± 0.065	1.610 ± 0.286
90	0.087 ± 0.014	0.397 ± 0.046	0.870 ± 0.158
120	0.101 ± 0.014	0.408 ± 0.031	0.868 ± 0.072
240	0.050 ± 0.007	0.182 ± 0.016	0.428 ± 0.078
360	0.034 ± 0.005	0.100 ± 0.019	0.312 ± 0.020
480	0.016 ± 0.006	0.069 ± 0.009	0.192 ± 0.027

[a] Data are given in µg/mL as the mean ± standard error.

TABLE D2
Blood Concentrations of Naphthalene in Rats at 2 Weeks and 3, 6, 12, and 18 Months in the 2-Year Inhalation Study of Naphthalene[a]

Time after Exposure (minutes)	10 ppm	30 ppm	60 ppm
n	3	3	3
Male			
Week 2			
0	0.331 ± 0.032[b]	1.540 ± 0.067	3.730 ± 0.205
30	0.192 ± 0.015	0.765 ± 0.041	1.640 ± 0.050[b]
60	0.118 ± 0.007		
90		0.210 ± 0.020	0.544 ± 0.056
120	0.045[c]		
300	0.015 ± 0.004	0.047 ± 0.004	
360			0.069 ± 0.003
480	0.006 ± 0.000[b]	0.020 ± 0.004	
720		0.007[c]	0.022 ± 0.003
960			0.008 ± 0.002[b]
Month 3			
0	0.424[c]	1.483 ± 0.145	3.707 ± 0.416
30	0.309 ± 0.020	1.130 ± 0.046	2.010 ± 0.100
60	0.164 ± 0.009		
90		0.448 ± 0.013	0.905 ± 0.033
120	0.116[c]		
300	0.029 ± 0.003	0.078 ± 0.013	
360			0.160 ± 0.012
480	0.011 ± 0.003	0.047 ± 0.003	
720		0.025 ± 0.002	0.054 ± 0.005
960			0.034 ± 0.006
Month 6			
0	0.363[c]	1.490 ± 0.160	3.233 ± 0.147
30	0.231 ± 0.011	0.816 ± 0.024	1.980 ± 0.080[b]
60	0.164 ± 0.008		
90		0.481 ± 0.035	1.008 ± 0.031
120	0.117[c]		
300	0.029 ± 0.005	0.094 ± 0.004	
360			0.183 ± 0.028
480	0.011 ± 0.003	0.050 ± 0.004	
720		0.037 ± 0.002	0.075 ± 0.001[b]
960			0.034 ± 0.003
Month 12			
0	0.522[c]	1.523 ± 0.137	3.153 ± 0.173
30	0.363 ± 0.021	1.064 ± 0.071	2.650 ± 0.240[b]
60	0.269 ± 0.016		
90		0.884 ± 0.014	1.473 ± 0.217
120	0.157[c]		
300	0.054 ± 0.002	0.174 ± 0.016	
360			0.350 ± 0.012
480	0.023 ± 0.004	0.084 ± 0.010	
720		0.055 ± 0.006	0.122 ± 0.002[b]
960			0.072 ± 0.017

TABLE D2
Blood Concentrations of Naphthalene in Rats at 2 Weeks and 3, 6, 12, and 18 Months in the 2-Year Inhalation Study of Naphthalene

Time after Exposure (minutes)	10 ppm	30 ppm	60 ppm
n	3	3	3
Male (continued)			
Month 18			
0	0.423 ± 0.030	1.327 ± 0.037	2.893 ± 0.066
30	0.273 ± 0.018	0.987 ± 0.028	1.940 ± 0.071
60	0.268 ± 0.005		
90		0.773 ± 0.029	1.607 ± 0.174
120	0.206 ± 0.015		
300	0.074 ± 0.009	0.262 ± 0.023	
360			0.479 ± 0.083
480	0.044 ± 0.002	0.134 ± 0.012	
720		0.084 ± 0.011	0.125 ± 0.024
960			0.108 ± 0.019
Female			
Week 2			
0	0.241 ± 0.013	1.137 ± 0.022	2.910 ± 0.040[b]
30	0.130 ± 0.024	0.606 ± 0.011	1.193 ± 0.127
60	0.102 ± 0.002		
90		0.200 ± 0.027	0.515 ± 0.010
120	0.043 ± 0.002		
300	0.010 ± 0.001	0.049 ± 0.003	
360			0.087 ± 0.017
480	0.026[c]	0.016 ± 0.002	
720		0.008[c]	0.006 ± 0.001[b]
960			0.011[c]
Month 3			
0	0.323 ± 0.021	1.261 ± 0.135	3.717 ± 0.619
30	0.197 ± 0.018	0.868 ± 0.003	1.413 ± 0.115
60	0.115 ± 0.009		
90		0.335 ± 0.028	0.623 ± 0.018
120	0.081 ± 0.008		
300	0.015 ± 0.001[b]	0.071 ± 0.004	
360			0.176 ± 0.028
480	0.009 ± 0.001[b]	0.045 ± 0.005	
720		0.019 ± 0.003	0.034 ± 0.001
960			0.024 ± 0.002

TABLE D2
Blood Concentrations of Naphthalene in Rats at 2 Weeks and 3, 6, 12, and 18 Months in the 2-Year Inhalation Study of Naphthalene

Time after Exposure (minutes)	10 ppm	30 ppm	60 ppm
n	3	3	3
Female (continued)			
Month 6			
0	0.326 ± 0.040	1.437 ± 0.232	3.243 ± 0.217
30	0.181 ± 0.001[b]	0.559 ± 0.064	1.383 ± 0.020
60	0.114 ± 0.006		
90		0.362 ± 0.016	0.667 ± 0.053
120	0.081 ± 0.005		
300	0.021 ± 0.004[b]	0.079 ± 0.022	
360			0.204 ± 0.013
480	0.012 ± 0.003	0.032 ± 0.006	
720		0.019 ± 0.003	0.037 ± 0.005
960			0.014 ± 0.004
Month 12			
0	0.319 ± 0.059	1.248 ± 0.205[b]	3.010[c]
30	0.162 ± 0.006[b]	0.717 ± 0.002[b]	1.400 ± 0.071
60	0.138 ± 0.008		
90		0.398 ± 0.030	0.767 ± 0.048
120	0.096 ± 0.005		
300	0.031[c]	0.107 ± 0.013	
360			0.279[c]
480	0.019 ± 0.003[b]	0.080 ± 0.007	
720		0.037 ± 0.010	0.076 ± 0.002
960			0.047 ± 0.011
Month 18			
0	0.323 ± 0.016	1.052 ± 0.059	2.463 ± 0.225
30	0.204 ± 0.011	0.560 ± 0.014	1.260 ± 0.036
60	0.168 ± 0.002		
90		0.429 ± 0.016	0.806 ± 0.058
120	0.129 ± 0.002		
300	0.049 ± 0.003	0.177 ± 0.013	
360			0.282 ± 0.031
480	0.031 ± 0.004	0.100 ± 0.012	
720		0.061 ± 0.011	0.111 ± 0.009
960			0.062 ± 0.002

[a] Data are given in µg/mL as the mean ± standard error.
[b] n=2
[c] n=1; no standard error calculated

TABLE D3
Blood Concentrations of Naphthalene in B6C3F$_1$ Mice after a Single 6-Hour Inhalation Exposure[a]

Time after Exposure (minutes)	10 ppm	30 ppm
n	3	3
Male		
0	0.594 ± 0.300	1.953 ± 0.325
30	0.129 ± 0.073	1.355 ± 0.125[b]
60	0.049 ± 0.014	0.447 ± 0.143
90	0.022 ± 0.000	0.214 ± 0.036
120	0.038 ± 0.010	0.219 ± 0.066
240	0.023 ± 0.004	0.199 ± 0.076
360	0.021 ± 0.001	0.084 ± 0.034
480	0.020 ± 0.001	0.028 ± 0.009
Female		
0	0.271 ± 0.057	1.763 ± 0.443
30	0.066 ± 0.028	0.786 ± 0.148
60	0.052 ± 0.013	0.269 ± 0.102
90	0.036 ± 0.003[b]	0.122 ± 0.016
120	0.041 ± 0.011	0.115 ± 0.048
240	0.038 ± 0.008	0.033 ± 0.010
480	0.031[c]	

[a] Data are given in µg/mL as the mean ± standard error.
[b] n=2
[c] n=1; no standard error calculated

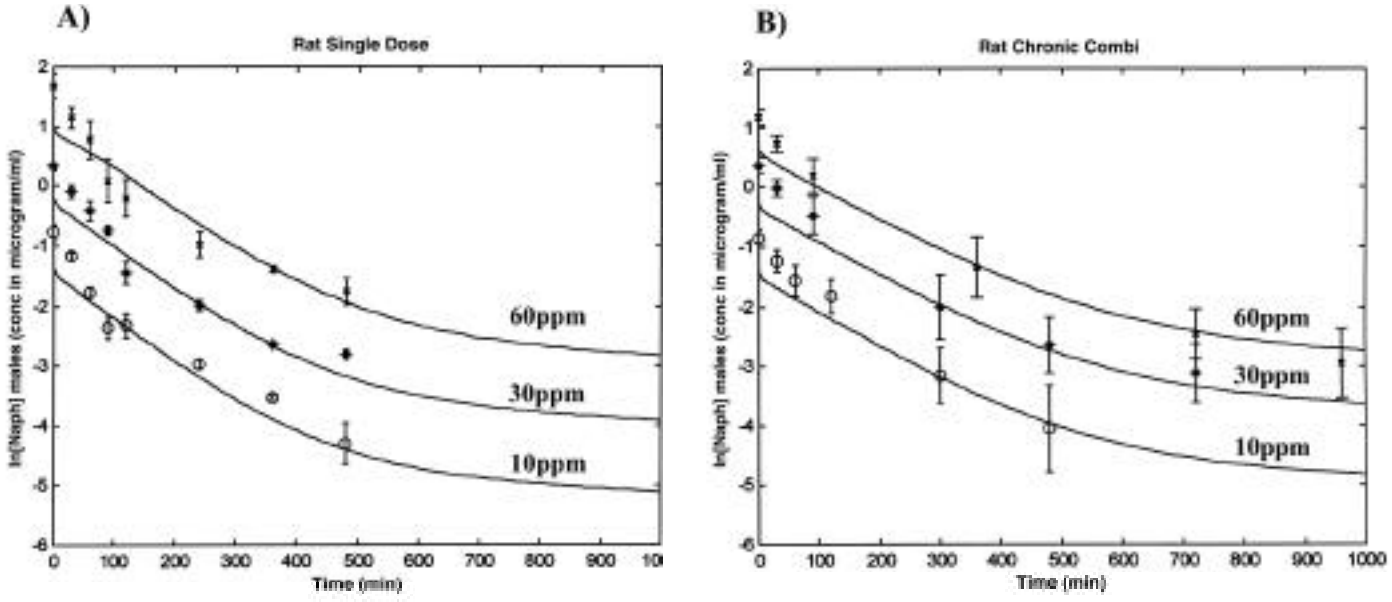


Figure D2
Blood Concentrations of Naphthalene (mean ± standard deviation, in µg/mL) in Male Rats after (A) a Single Exposure or (B) Exposure for 2 Weeks or 3, 6, 12, or 18 Months to Naphthalene by Inhalation

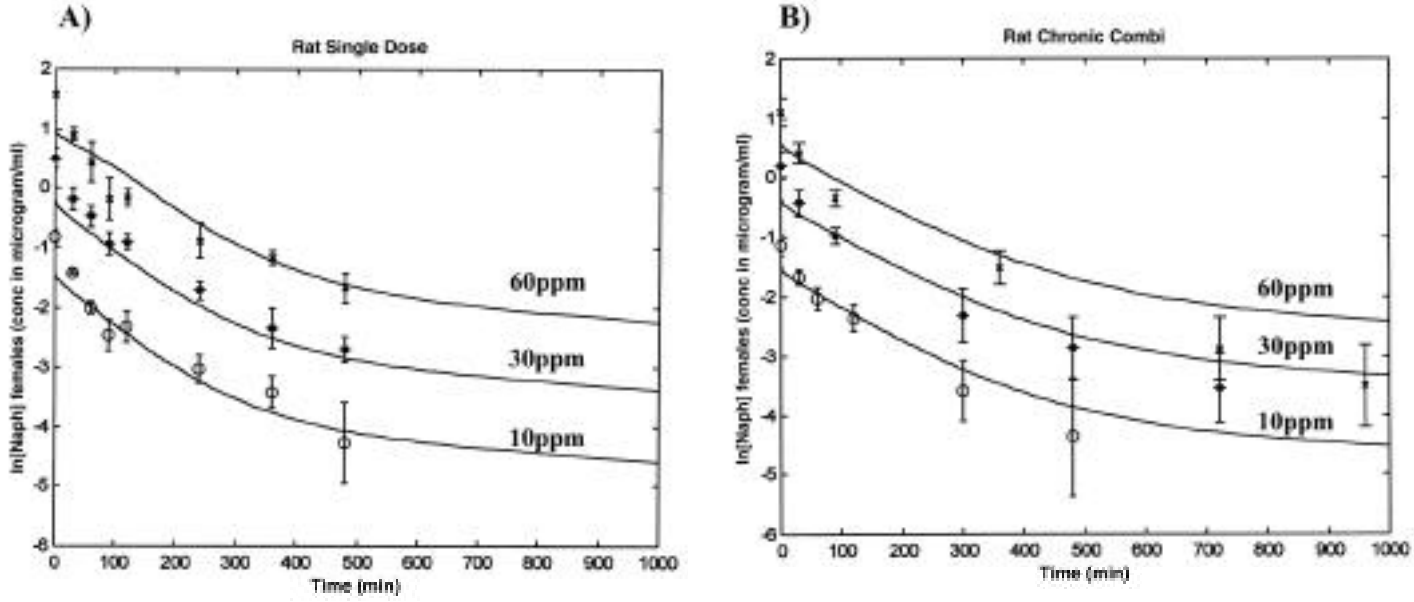


Figure D3
Blood Concentrations of Naphthalene (mean ± standard deviation, in µg/mL) in Female Rats after (A) a Single Exposure or (B) Exposure for 2 Weeks or 3, 6, 12, or 18 Months to Naphthalene by Inhalation

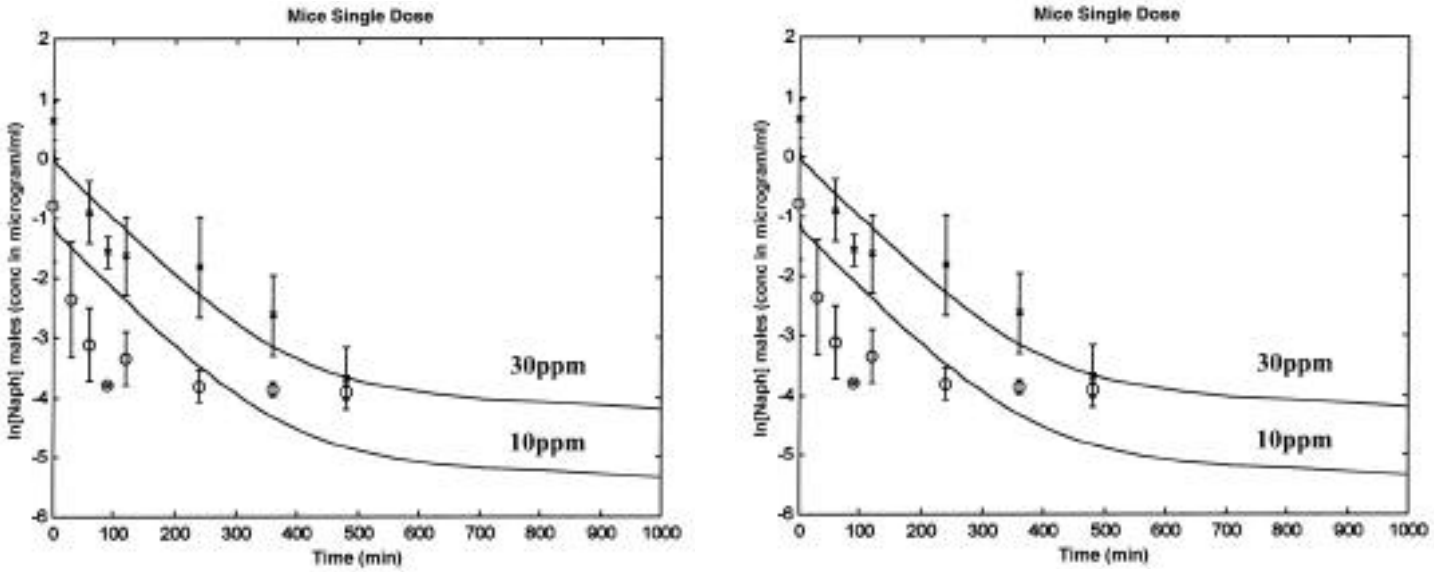


Figure D4
Blood Concentrations of Naphthalene (mean ± standard deviation, in µg/mL)
in Male and Female Mice after a Single Exposure to Naphthalene by Inhalation

TABLE D4
Cardiac Output, Organ Volumes, Organ Blood Perfusion Rates, and Optimized Metabolic Parameters of Rats and Mice for the Physiologically Based Pharmacokinetic Model of Naphthalene[a]

	Rats		Mice	
	Male	Female	Male	Female
Body Weight (kg)	0.125 – 0.504	0.1 – 0.306	30	30
Cardiac Output (L/hr/kg$^{0.7}$)	14.7	14.7	11.9	11.9
Ventilation Rate (L/hr/kg$^{0.7}$)	20	20	24.4	24.4
Tissue Volumes (% of body weight)				
Arterial blood	1.8	1.8	2	2
Venous blood	3.6	3.6	4	4
Alveolar space[b]	0.5	0.5	0.5	0.5
Lung[c]	0.52	0.52	0.6	0.6
Liver[d]	3.7	3.7	5.5	5.5
Fat[d]	7.0	7.0	6	6
Kidney	1.48	1.48	1.7	1.7
Other (residual value)	81.4	81.4	79.7	79.7
Tissue Capillary Volumes (% of tissue volume)[e]				
Lung	18.0	18.0	11	11
Liver	13.8	13.8	11	11
Fat	2.0	2.0	3	3
Kidney	16.0	16.0	10.2	10.2
Other	4.5	4.5	4.2	4.2
Tissue Blood Flow (% of cardiac output)[f]				
Liver	17.4	17.4	16.2	16.2
Fat	7.0	7.0	5	5
Kidney	14.1	14.1	16.3	16.3
Other	61.5	61.5	62.5	62.5
Metabolic Parameters[g]				
$V_{maxliver1}$	6.5	5.8	229.6	124.5
$K_{mliver1}$	1.2	1.2	40.2	6.0
$V_{maxliver2}$	0.96	1.34	201.4	205.7
$K_{mliver2}$	1.55	1.37	99.6	20.7
Hill constant	2	2	2	2
$V_{maxlung}$	0.75	0.75	58.1	44.5
K_{mlung}	1.2	1.2	40.2	6.0
Permeability				
Fat	0.23	0.30	1.2	0.22
Other Tissues	0.54	0.39	2.7	1.9

[a] Body weights are given as ranges from weeks 1 through 76 for the 2-year core study rats. Blood and organ volumes are scaled to the changing body weights.
[b] Davies and Morris (1993)
[c] Schmidt-Nielson (1979)
[d] Average of several literature values
[e] Altman and Dittmer (1971); Brown *et al.* (1997)
[f] Brown *et al.* (1997)
[g] V_{max}=maximum velocity of saturable metabolism (nmol/mL per minute); K_m=Michaelis-Menten constant for metabolism (nmol/mL)

TABLE D5
Model-Based Estimates of Naphthalene Concentration and Metabolism in the Liver and Lung of Rats[a]

	10 ppm	30 ppm	60 ppm
Male			
End of 6-Hour Exposure			
Lung			
Steady-state concentration (µg/mL)	0.5	1.8	5.3
Metabolic rate at steady state (mg/hr/mL)	0.0043	0.0049	0.0056
Cumulative metabolism (mg/kg)	0.16	0.16	0.16
Liver			
Steady-state concentration (µg/mL)	0.06	0.7	12.3
Metabolic rate at steady state (mg/hr/mL)	0.013	0.04	0.05
Cumulative metabolism (mg/kg)	2.4	7.2	10.4
18 Hours Postexposure			
Cumulative metabolism (mg/kg)			
Lung	0.248	0.376	0.52
Liver	3.36	10.3	19.6
Total			
Naphthalene metabolized (mg/kg)	3.6	10.7	20.1
Naphthalene inhaled (mg/kg)	11.7	35.0	70.1
Inhaled dose metabolized (%)	30.8	30.5	28.7
Female			
End of 6-Hour Exposure			
Lung			
Steady-state concentration (µg/mL)	0.54	1.8	5.3
Metabolic rate at steady state (mg/hr/mL)	0.0047	0.0055	0.0055
Cumulative metabolism (mg/kg)	0.13	0.16	0.17
Liver			
Steady-state concentration (µg/mL)	0.07	1.2	13.4
Metabolic rate at steady state (mg/hr/mL)	0.014	0.038	0.047
Cumulative metabolism (mg/kg)	2.5	7.1	9.7
18 Hours Postexposure			
Cumulative metabolism (mg/kg)			
Lung	0.3	0.4	0.6
Liver	3.6	11	20
Total			
Naphthalene metabolized (mg/kg)	3.9	11.4	20.6
Naphthalene inhaled (mg/kg)	15.7	46.9	93.9
Inhaled dose metabolized (%)	24.8	24.3	21.9

[a] For male rats, body weight=125 g, lung tissue volume=0.67 mL, liver tissue volume=4.78 mL. For female rats, body weight=100 g, lung tissue volume=0.53 mL, liver tissue volume=3.78 mL

TABLE D6
Model-Based Estimates of Naphthalene Concentration and Metabolism in the Liver and Lung of Mice[a]

	10 ppm	30 ppm
Male		
End of 6-Hour Exposure		
Lung		
Steady-state concentration (µg/mL)	0.88	2.8
Metabolic rate at steady state (mg/hr/mL)	0.06	0.16
Cumulative metabolism (mg/kg)	2.1	5
Liver		
Steady-state concentration (µg/mL)	0.1	0.34
Metabolic rate at steady state (mg/hr/mL)	0.035	0.11
Cumulative metabolism (mg/kg)	10	31.3
18 Hours Postexposure		
Cumulative metabolism (mg/kg)		
Lung	3	7.7
Liver	14.3	45.3
Total		
Naphthalene metabolized (mg/kg)	17.3	53.0
Naphthalene inhaled (mg/kg)	25.7	76.7
Inhaled dose metabolized (%)	67.3	69.1
Female		
End of 6-Hour Exposure		
Lung		
Steady-state concentration (µg/mL)	0.67	2.6
Metabolic rate at steady state (mg/hr/mL)	0.16	0.27
Cumulative metabolism (mg/kg)	5.4	9.2
Liver		
Steady-state concentration (µg/mL)	0.022	0.092
Metabolic rate at steady state (mg/hr/mL)	0.027	0.10
Cumulative metabolism (mg/kg)	7.9	29.6
18 Hours Postexposure		
Cumulative metabolism (mg/kg)		
Lung	7.08	12.9
Liver	10.4	38.7
Total		
Naphthalene metabolized (mg/kg)	17.5	51.6
Naphthalene inhaled (mg/kg)	25.7	76.7
Inhaled dose metabolized (%)	63.5	62.8

[a] For male mice, body weight=30 g, lung tissue volume=0.18 mL, liver tissue volume=1.65 mL. For female mice, body weight=24 g, lung tissue volume=0.14 mL, liver tissue volume=1.32 mL

APPENDIX E
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF NAPHTHALENE

Naphthalene was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (09820LG) for use during the 2-year study. Identity and purity analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC) and by the study laboratory, Battelle Toxicology Northwest (Richland, WA). Reports on analyses performed in support of the naphthalene study are on file at the National Institute of Environmental Health Sciences.

The chemical, a white crystalline solid, was identified as naphthalene by the analytical chemistry laboratory with infrared and proton nuclear magnetic resonance spectroscopy and by gas chromatography/mass spectrometry by system A (Table E1). The chemical was identified as naphthalene by the study laboratory with infrared spectroscopy. Chemir/Polytech Industries (Maryland Heights, MO) compared samples of lot 09820LG obtained from the analytical chemistry laboratory and the study laboratory using proton and ^{13}C nuclear magnetic resonance spectroscopy; the spectra of the samples from each laboratory were similar. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*; *Wiley Mass Spectral Database*; *Aldrich,* 1985) of naphthalene. The infrared and nuclear magnetic resonance spectra are presented in Figures E1 and E2.

The purity of lot 09820LG was determined by elemental analyses, gas chromatography/mass spectrometry, and gas chromatography with flame ionization detection (FID). Elemental analyses were performed by Chemir/Polytech Laboratories. Purity analysis by gas chromatography/mass spectrometry using system A was performed by the analytical chemistry laboratory. Purity analysis of each of the 15 drums of lot 09820LG was performed by the study laboratory with gas chromatography/FID using systems B and C.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for naphthalene; additionally, 0.12% sulfur was detected. Gas chromatography/mass spectrometry indicated no impurities. Gas chromatography/FID indicated one major peak and one impurity with an area of approximately 0.6% relative to the major peak area; the impurity was tentatively identified as thionaphthene by gas chromatography (system C) and an authentic standard of thionaphthene. The overall purity of lot 09820LG was determined to be greater than 99%. The results of analyses of individual drums of this lot indicated no differences between the drums.

The bulk chemical was stored under a nitrogen headspace at room temperature in 6-gallon, plastic-lined, metal drums. Stability of the bulk chemical was monitored by the study laboratory throughout the study with gas chromatography using systems B and C. No degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

A diagram of the naphthalene generation and delivery system is shown in Figure E3. Naphthalene was heated in a flask surrounded by a heated mantle. Heated nitrogen metered into the flask carried the vaporized naphthalene out of the generator. The flask was replaced every 2 weeks. The mantle and nitrogen temperatures were adjusted to maintain the naphthalene vapor temperature above the bulk naphthalene at 66° to 71° C. A temperature probe was used to monitor the bulk chemical to ensure that its temperature was maintained below the melting point (80° to 82° C).

A heated Teflon® line transported the vapor to the exposure room. The vapor was mixed with heated, HEPA- and charcoal-filtered air before it entered a vapor distribution manifold. From the distribution manifold, an AirVac pump (Air-Vac Engineering Co., Inc., Milford, CT) withdrew the appropriate amount of naphthalene vapor into the heated Teflon® delivery lines to obtain the target concentration. Flow from the manifold into the delivery line was controlled by a chamber exposure valve which diverted vapor to the exhaust until the concentration of naphthalene was stable. When the valve was in the exposure position, the naphthalene vapor was injected into the chamber inlet duct where it was further diluted with conditioned chamber air.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. Before the study began, a small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that naphthalene vapor, and not aerosol, was produced. A Type CN small particle detector was also used to determine the maximum attainable concentration without aerosolization. Naphthalene aerosol was detected at up to 1,950 particles/cm^3 at vapor concentrations of approximately 85 to 115 ppm; therefore, a maximum concentration of 60 ppm was selected. During the study, no particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

A summary of the chamber concentrations for the study is in Table E2. The naphthalene concentrations in the exposure chambers were monitored by an on-line gas chromatograph (system D). Samples were drawn from each exposure chamber approximately every 24 minutes using a 12-port stream select valve (Valco Instruments Company, Houston, TX). The online gas chromatograph was checked throughout the day for instrument drift against an on-line standard of naphthalene in nitrogen supplied by a diffusion tube standard generator (Model 360, Thermo Environmental Instruments, Franklin, MA). The online gas chromatograph was calibrated monthly by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes (ORBO™-101, Supelco, Bellefonte, PA), extracted with toluene containing 1-phenylhexane as an internal standard, and analyzed by an off-line gas chromatograph (system E). The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of naphthalene containing 1-phenylhexane as an internal standard in toluene.

CHAMBER ATMOSPHERE CHARACTERIZATION

Buildup and decay rates for chamber vapor concentrations were determined with and without animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. T_{90} values ranged from 9 to 12 minutes without animals present and from 9 to 14 minutes with animals present; T_{10} values ranged from 12 to 14 minutes without animals present and from 17 to 68 minutes with animals present. A T_{90} value of 12 minutes was selected for the study.

The uniformity of naphthalene vapor concentration in the inhalation exposure chambers without animals was evaluated before the study began; concentration uniformity with animals present in the chambers was measured periodically during the study. The vapor concentration was determined with the on-line gas chromatograph. The automatic 12-port sampling valve was disabled to allow continuous monitoring from a

single line. Samples were collected from several positions in each chamber. Chamber concentration uniformity was maintained throughout the study.

The persistence of naphthalene in the chamber after vapor delivery ended was determined by monitoring the concentration overnight in the 60 ppm chamber, with and without animals present in the chambers. The concentration decreased to less than 1% of the target concentration within 327 minutes with animals present and within 238 minutes without animals present.

The stability of naphthalene in the 10 and 60 ppm exposure chambers, the distribution line, and the generator reservoir flask was monitored by analyzing grab samples with gas chromatography by systems C and E. Samples were collected before the studies began without animals present in the chambers and during the study with animals present. Commercial standards of potential degradation products and impurities were obtained from Aldrich Chemical Company (Milwaukee, WI). Two standard 0.5 and 5 µg/mL naphthalene mixtures were analyzed by system E. 1,2-Naphthoquinone was detected only in the 5 µg/mL standard; all other degradation products and impurities were detected in each standard mixture. Thionaphthene was the only impurity with a peak area greater than 0.1% relative to the major peak area, and no impurities were detected in the exposure chamber samples that were not present in the bulk material. Samples were taken from the generator reservoir at the end of weeks 1 and 2 of exposure and from the bulk chemical, exposure chambers, and distribution line at the beginning and end of an exposure period. A slight brown discoloration was observed at the bottom of the generator flask at the end of week 2; samples of the discolored material were also analyzed. Thionaphthene was the only impurity detected in the sample with a peak area greater than 0.1% relative to the major peak area. Approximately 0.5% to 0.7% thionaphthene was present in the bulk chemical and in the generator flask samples; 0.4% to 0.5% was detected in the distribution line and exposure chambers.

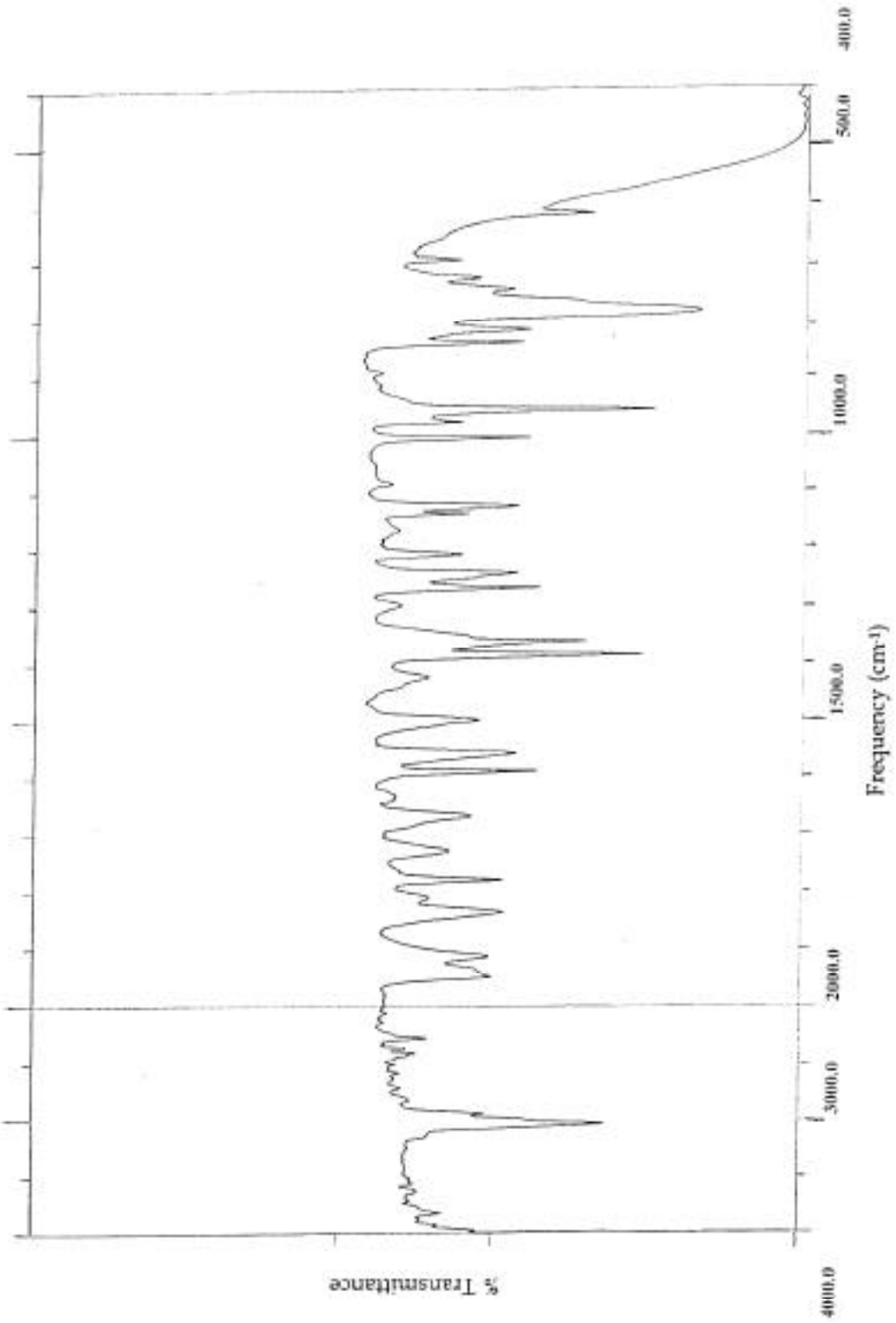


Figure E1
Infrared Absorption Spectrum of Naphthalene

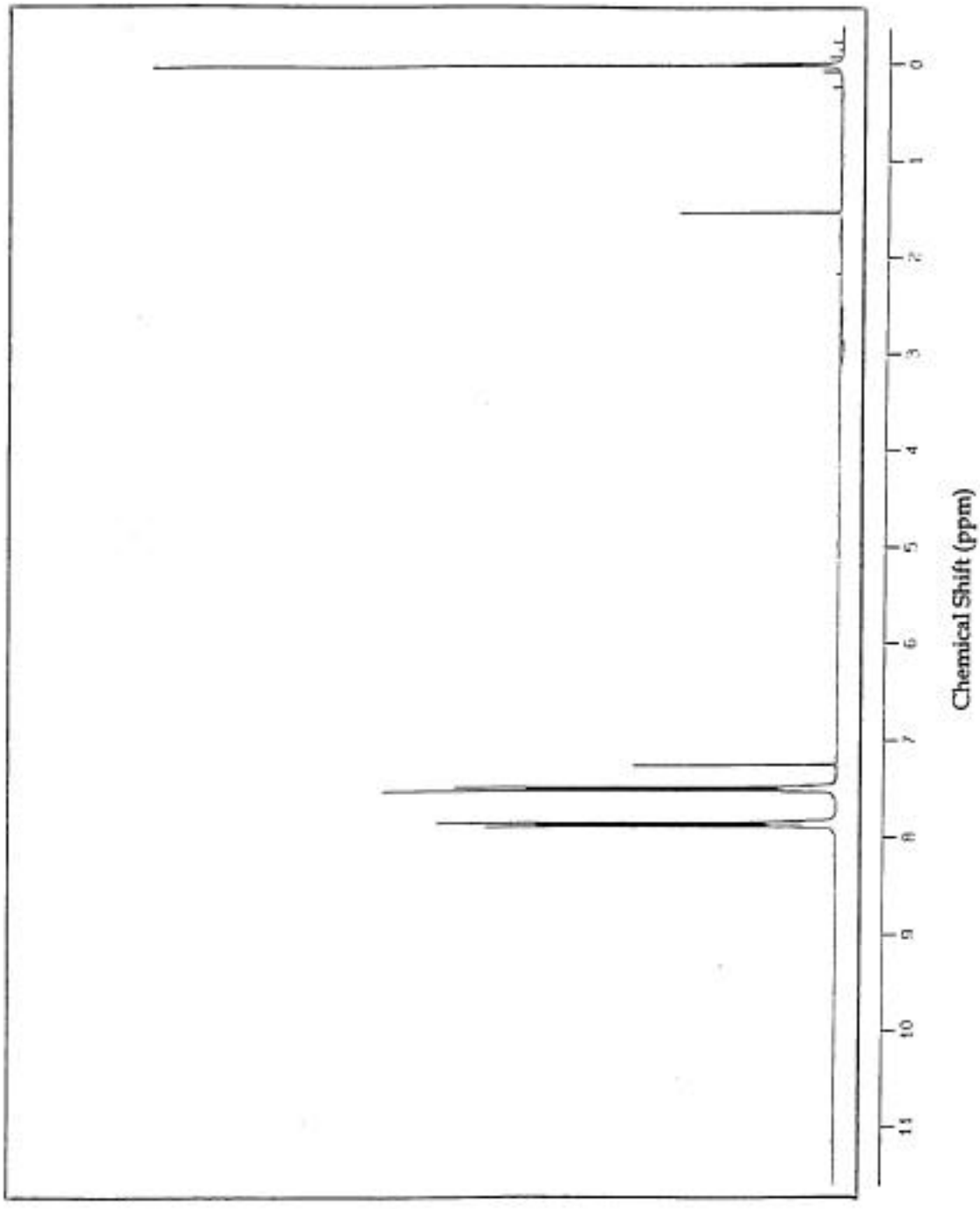


Figure E2
Nuclear Magnetic Resonance Spectrum of Naphthalene

TABLE E1
Gas Chromatography Systems Used in the Inhalation Study of Naphthalene[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Quadrupole mass spectrometer with electron impact ionization (70 eV)	DB-5, 30 m × 0.25 mm, 0.25 µm film (J&W Scientific, Folsom, CA)	Helium at 1.2 mL/minute	50° C for 0.5 minutes, then 15° C/minute to 280° C
System B			
Flame ionization	DB-5, 30 m × 0.25 mm, 1 µm film (J&W Scientific)	Helium at 24 psi head pressure	50° C for 1 minute, then 4° C/minute to 200° C, then 20° C/minute to 300° C
System C			
Flame ionization	DB-5, 30 m × 0.25 mm, 1 µm film (J&W Scientific)	Helium at 24 psi head pressure	50° C for 1 minute, then 4° C/minute to 200° C, then 15° C/minute to 300° C
System D			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5 µm film (J&W Scientific)	Nitrogen at approximately 25 mL/minute	Isothermally at 175° C
System E			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5 µm film (J&W Scientific)	Helium at 6 psi head pressure	60° C for 1 minute, then 16° C/minute to 200° C

[a] All gas chromatographs were model 5890, manufactured by Hewlett-Packard (Palo Alto, CA).

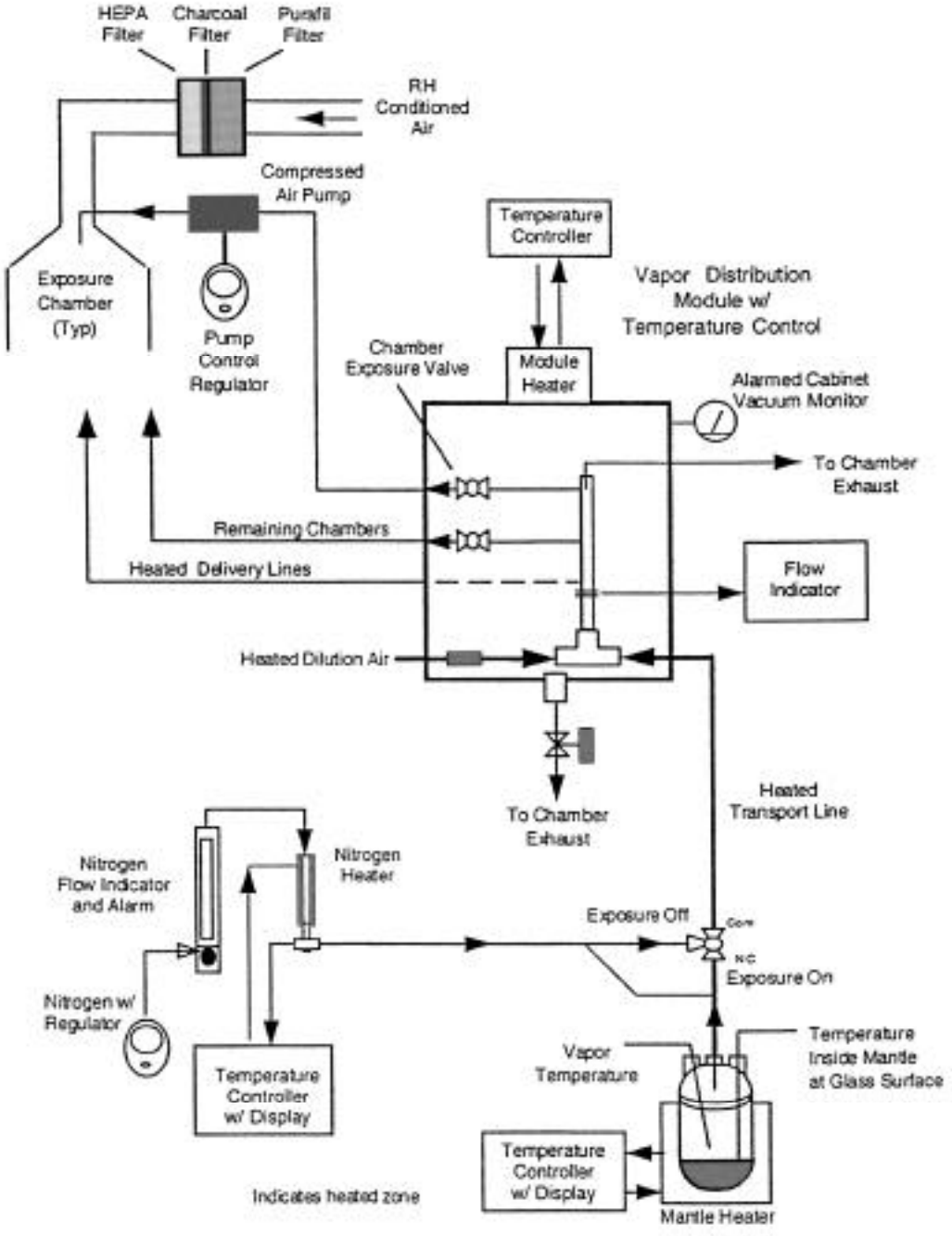


Figure E3
Schematic of the Vapor Generation and Delivery System in the 2-Yearr Inhalation Study of Naphthalene

TABLE E2
Summary of Chamber Concentrations in the 2-Year Inhalation Study of Naphthalene in Rats

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
10	8,549	10.0 ± 0.7
30	8,531	30.2 ± 1.7
60	8,542	60.3 ± 3.9

[a] Mean ± standard deviation

APPENDIX F
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE F1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE F2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

TABLE F3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.5 ± 0.52	12.5 – 14.7	23
Crude fat (% by weight)	8.1 ± 0.31	7.5 – 8.7	23
Crude fiber (% by weight)	9.6 ± 0.51	8.5 – 10.3	23
Ash (% by weight)	5.0 ± 0.16	4.8 – 5.4	23
Amino Acids (% of total diet)			
Arginine	0.732 ± 0.050	0.670 – 0.800	6
Cystine	0.220 ± 0.011	0.210 – 0.240	6
Glycine	0.683 ± 0.048	0.620 – 0.740	6
Histidine	0.333 ± 0.020	0.310 – 0.350	6
Isoleucine	0.522 ± 0.054	0.430 – 0.590	6
Leucine	1.065 ± 0.070	0.960 – 1.130	6
Lysine	0.705 ± 0.066	0.620 – 0.790	6
Methionine	0.402 ± 0.042	0.350 – 0.460	6
Phenylalanine	0.600 ± 0.042	0.540 – 0.640	6
Threonine	0.512 ± 0.056	0.430 – 0.590	6
Tryptophan	0.125 ± 0.015	0.110 – 0.150	6
Tyrosine	0.410 ± 0.037	0.360 – 0.460	6
Valine	0.628 ± 0.052	0.550 – 0.690	6
Essential Fatty Acids (% of total diet)			
Linoleic	3.98 ± 0.325	3.59 – 4.54	6
Linolenic	0.30 ± 0.048	0.21 – 0.35	6
Vitamins			
Vitamin A (IU/kg)	4,598 ± 1,184	2,780 – 8,140	23
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	77.2 ± 10.94	62.2 – 87.1	6
Thiamine (ppm)[b]	8.1 ± 1.30	6.0 – 11.0	23
Riboflavin (ppm)	5.6 ± 1.24	4.20 – 7.70	6
Niacin (ppm)	73.1 ± 4.13	66.4 – 78.8	6
Pantothenic acid (ppm)	24.2 ± 2.92	21.4 – 29.1	6
Pyridoxine (ppm)[b]	9.37 ± 2.50	6.7 – 12.4	6
Folic acid (ppm)	1.70 ± 0.43	1.26 – 2.32	6
Biotin (ppm)	0.349 ± 0.18	0.225 – 0.704	6
Vitamin B_{12} (ppb)	83.4 ± 67.1	30.0 – 174.0	6
Choline (ppm)	3,082 ± 232	2,700 – 3,400	6
Minerals			
Calcium (%)	0.965 ± 0.043	0.867 – 1.050	23
Phosphorus (%)	0.566 ± 0.020	0.533 – 0.620	23
Potassium (%)	0.660 ± 0.026	0.627 – 0.691	6
Chloride (%)	0.356 ± 0.031	0.300 – 0.392	6
Sodium (%)	0.193 ± 0.020	0.160 – 0.212	6
Magnesium (%)	0.197 ± 0.010	0.185 – 0.213	6
Sulfur (%)	0.182 ± 0.023	0.153 – 0.209	6
Iron (ppm)	158 ± 15.2	135 – 173	6
Manganese (ppm)	51.8 ± 4.05	46.2 – 56.0	6
Zinc (ppm)	53.2 ± 5.68	45.0 – 61.1	6
Copper (ppm)	6.49 ± 0.786	5.38 – 7.59	6
Iodine (ppm)	0.487 ± 0.204	0.233 – 0.843	6
Chromium (ppm)	0.763 ± 0.620	0.330 – 2.000	6
Cobalt (ppm)	0.53 ± 0.720	0.20 – 2.0	6

[a] From formulation
[b] As hydrochloride

TABLE F4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.25 ± 0.139	0.10 – 0.50	23
Cadmium (ppm)	0.05 ± 0.014	0.04 – 0.10	23
Lead (ppm)	0.09 ± 0.033	0.06 – 0.20	23
Mercury (ppm)	<.02		23
Selenium (ppm)	0.16 ± 0.034	0.11 – 0.26	23
Aflatoxins (ppb)	<5.00		23
Nitrate nitrogen (ppm)[c]	17.0 ± 7.78	9.0 – 39.6	23
Nitrite nitrogen (ppm)[c]	0.72 ± 0.406	0.40 – 2.00	23
BHA (ppm)[d]	1.1 ± 0.44	0.01 – 2.47	23
BHT (ppm)[d]	1.0 ± 0.31	0.01 – 1.80	23
Aerobic plate count (CFU/g)[e]	231,600 ± 429,635	25,000 – 1,000,000	5
Coliform (MPN/g)[e]	11 ± 11	3 – 30	5
Escherichia coli (MPN/g)	<10		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[f]	5.7 ± 3.79	2.1 – 20.9	23
N-Nitrosodimethylamine (ppb)[f]	2.5 ± 1.79	1.0 – 6.4	23
N-Nitrosopyrrolidine (ppb)[f]	3.3 ± 2.82	1.0 – 14.5	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl chlorpyrifos	0.072 ± 0.061	0.010 – 0.220	22
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.157 ± 0.178	0.020 – 0.830	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] Nonirradiated samples. Microbial counts for irradiated samples were below the detection limit.
[f] All values were corrected for percent recovery.

APPENDIX G
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats during the 2-year study. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc., or MA BioServices, Inc. (Rockville, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

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

RESULTS

All test results were negative.