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

NTP Technical Report on the Toxicology and Carcinogenesis Studies of Indium Phosphide (CAS No. 22398-80-7) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies)

NTP TR 499

JULY 2001

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF INDIUM PHOSPHIDE

(CAS NO. 22398-80-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

July 2001

NTP TR 499

NIH Publication No. 01-4433

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 Technical Reports printed since 1982 appears on the inside back cover.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF INDIUM PHOSPHIDE

(CAS NO. 22398-80-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

July 2001

NTP TR 499

NIH Publication No. 01-4433

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

J.H. Roycroft, 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.R. Maronpot, D.V.M.
D.P. Orzech, M.S.
G.N. Rao, D.V.M., Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S., Integrated Laboratory Systems, Inc.

Battelle Pacific Northwest Laboratories
Conducted studies and evaluated pathology findings

B.J. Chou, D.V.M., Ph.D., Principal Investigator
J.A. Dill, Ph.D.
S.L. Grumbein, D.V.M., Ph.D.
K.M. Lee, Ph.D.
P.W. Mellick, D.V.M., Ph.D.
R.A. Miller, D.V.M., Ph.D.
H.A. Ragan, D.V.M.
Y.F. Su, Ph.D.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
A. Brix, D.V.M., 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 (2 September 1999)

J.C. Seely, D.V.M., Chairperson
PATHCO, Inc.
A. Brix, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
S. Ching, D.V.M., Ph.D.
SVC Associates, Inc.
J. Everitt, D.V.M.
Chemical Industry Institute of Toxicology
S.L. Grumbein, D.V.M., Ph.D.
Battelle Pacific Northwest Laboratories
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
A. Hubbs, D.V.M., Ph.D., Observer
National Institute for Occupational Safety and Health
E.E. McConnell, D.V.M., M.S.
ToxPath, Inc.
A. Nyska, D.V.M.
National Toxicology Program

Evaluated slides and prepared pathology report on mice (19 October 1999)

J.C. Seely, D.V.M., Chairperson
PATHCO, Inc.
A. Brix, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
S. Ching, D.V.M., Ph.D.
Integrated Laboratory Systems, Inc.
J. Everitt, D.V.M.
Chemical Industry Institute of Toxicology
J.R. Hailey, D.V.M.
National Toxicology Program
A. Hubbs, D.V.M., Ph.D.
National Institute for Occupational Safety and Health
E.E. McConnell, D.V.M., M.S.
ToxPath, Inc.
G. Marit, D.V.M., Observer
Battelle Columbus Laboratories
R.A. Miller, D.V.M., Ph.D.
Battelle Pacific Northwest Laboratories
A. Nyska, D.V.M.
National Toxicology Program

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.
L.M. Leach, B.A.
D.C. Serbus, Ph.D.
P.A. Yount, B.S.

CONTENTS

ABSTRACT

InP

INDIUM PHOSPHIDE

CAS No. 22398-80-7

Chemical Formula: InP Molecular Weight: 145.80

Indium phosphide is used to make semiconductors, injection lasers, solar cells, photodiodes, and light-emitting diodes. Indium phosphide was nominated for study because of its widespread use in the microelectronics industry, the potential for worker exposure, and the absence of chronic toxicity data. Male and female F344/N rats and B6C3F$_1$ mice were exposed to indium phosphide (greater than 99% pure) by inhalation for 14 weeks or 2 years. The frequency of micronuclei was determined in the peripheral blood of mice exposed to indium phosphide for 14 weeks.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to particulate aerosols of indium phosphide with a mass median aerodynamic diameter of approximately 1.2 μm at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 by inhalation, 6 hours per day, 5 days per week (weeks 1 through 4 and weeks 10 through 14) or 7 days per week (weeks 5 through 9) to accommodate a concurrent teratology study. One male in the 100 mg/m^3 group died before the end of the study. Body weight gains of all males and females exposed to 100 mg/m^3 were less than those of the chamber controls.

As a result of indium phosphide exposure, the lungs of all exposed rats had a gray to black discoloration and were significantly enlarged, weighing 2.7- to 4.4-fold more than those of the chamber controls. Indium phosphide particles were observed throughout the respiratory tract and in the lung-associated lymph nodes. A spectrum of inflammatory and proliferative lesions generally occurred in the lungs of all exposed groups of rats and consisted of alveolar proteinosis, chronic inflammation, interstitial fibrosis, and alveolar epithelial hyperplasia. Pulmonary inflammation was attended by increased leukocyte and neutrophil counts in the blood. The alveolar proteinosis was the principal apparent reason for the increase in lung weights. Indium phosphide caused inflammation at the base of the epiglottis of the larynx and hyperplasia of the bronchial and mediastinal lymph nodes. Exposure to indium phosphide affected the circulating erythroid mass. It induced a microcytic erythrocytosis consistent with bone marrow hyperplasia and hematopoietic cell proliferation of the spleen. Hepatocellular necrosis was suggested by increased serum activities of alanine aminotransferase and sorbitol dehydrogenase in all exposed groups of males and in 10 mg/m^3 or greater females and was confirmed microscopically in 100 mg/m^3 males and females.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice were exposed to particulate aerosols of indium phosphide with a mass

median aerodynamic diameter of approximately 1.2 µm at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 by inhalation, 6 hours per day, 5 days per week (weeks 1 through 4 and weeks 10 through 14) or 7 days per week (weeks 5 through 9). Although the effects of indium phosphide exposure were similar in rats and mice, mice were more severely affected in that all males and females in the 100 mg/m^3 groups either died or were removed moribund during the study. One male and three females in the 30 mg/m^3 group were also removed before the end of the study. In general, body weight gains were significantly less in males and females exposed to 3 mg/m^3 or greater compared to those of the chamber controls. Mice exposed to 30 or 100 mg/m^3 were lethargic and experienced rapid, shallow breathing.

As in rats, lungs were discolored and enlarged 2.6- to 4.1-fold greater than those of chamber controls due to the exposure-induced alveolar proteinosis. Indium phosphide particles were observed in the nose, trachea, larynx, and lymph nodes of some exposed males and females. Alveolar proteinosis, chronic active inflammation, interstitial fibrosis, and alveolar epithelial hyperplasia were observed; these effects were more severe than in rats. Hyperplasia in the bronchial lymph nodes and squamous metaplasia, necrosis, and suppurative inflammation of the larynx were observed in some exposed males and females. Exposure to indium phosphide induced a microcytic erythrocytosis which was consistent with the observed hematopoietic cell proliferation of the spleen.

2-YEAR STUDY IN RATS

Groups of 60 male and 60 female rats were exposed to particulate aerosols of indium phosphide at concentrations of 0, 0.03, 0.1, or 0.3 mg/m^3, 6 hours per day, 5 days per week, for 22 weeks (0.1 and 0.3 mg/m^3 groups) or 105 weeks (0 and 0.03 mg/m^3 groups). Animals in the 0.1 and 0.3 mg/m^3 group were maintained on filtered air from exposure termination at week 22 until the end of the studies. Ten males and 10 females per group were evaluated at 3 months.

3-Month Interim Evaluation

Exposure to indium phosphide for 3 months caused a microcytic erythrocytosis and also caused enlarged lungs and lesions in the respiratory tract and lung-associated lymph nodes. Although qualitatively similar to those observed in the 14-week studies, these effects were considerably less severe. However, the lesions in the lungs of rats exposed to 0.1 or 0.3 mg/m^3 were considered sufficiently severe that exposure was discontinued in these groups, and the groups were allowed to continue unexposed for the remainder of the study.

Survival, Body Weights, and Clinical Findings

Exposure to indium phosphide had no effect on survival or body weight gain. During the last 6 months of the study, rats in the 0.03 and 0.3 mg/m^3 groups became lethargic and males breathed abnormally.

Pathology Findings

At 2 years, exposure to indium phosphide caused increased incidences of alveolar/bronchiolar adenomas and carcinomas in rats. Squamous cell carcinoma of the lung occurred in four male rats exposed to 0.3 mg/m^3. As observed in the 14-week study and at the 3-month interim evaluation, a spectrum of inflammatory and proliferative lesions of the lung were observed in all exposed groups of males and females; however, the extent and severity of the lesions were generally greater and included atypical hyperplasia, chronic inflammation, alveolar epithelial hyperplasia and metaplasia, alveolar proteinosis, and interstitial fibrosis.

Exposure to indium phosphide also caused increased incidences of benign and malignant pheochromocytomas of the adrenal gland in males and females. Marginal increases in the incidences of mononuclear cell leukemia in males and females, fibroma of the skin in males, and carcinoma of the mammary gland in females may have been related to exposure to indium phosphide.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female mice were exposed to particulate aerosols of indium phosphide at concentrations of 0, 0.03, 0.1, or 0.3 mg/m^3, 6 hours per day, 5 days per week, for 21 weeks (0.1 and 0.3 mg/m^3 groups) or 105 weeks (0 and 0.03 mg/m^3 groups). Animals in the 0.1 and 0.3 mg/m^3 groups were maintained on filtered air from exposure termination at week 21 until the end of the studies. Ten males and 10 females per group were evaluated at 3 months.

3-Month Interim Evaluation

Exposure to indium phosphide for 3 months affected the circulating erythroid mass and caused enlarged lungs and lesions in the respiratory tract and lung-associated lymph nodes. These effects, although qualitatively similar to those observed in the 14-week studies, were considerably less severe. However, the lesions in the lungs of mice exposed to 0.1 mg/m^3 and greater were considered sufficiently severe that exposure was discontinued in these groups and the groups were allowed to continue unexposed for the remainder of the study.

Survival and Body Weights

In general, exposure to indium phosphide for 2 years reduced survival and body weight gain in exposed males and females.

Pathology Findings

At 2 years, exposure to indium phosphide caused increased incidences of alveolar/bronchiolar carcinomas in males and alveolar/bronchiolar adenomas and carcinomas in females. In addition to the alveolar proteinosis and chronic active inflammation seen at earlier time points, serosa fibrosis and pleural mesothelial hyperplasia were also present.

The incidences of hepatocellular neoplasms were also significantly increased in exposed males and females. Exposed groups of males and females had increased incidences of eosinophilic foci of the liver at 2 years. Marginal increases in the incidences of neoplasms of the small intestines in male mice may have been related to exposure to indium phosphide. Exposure to indium phosphide also caused inflammation of the arteries of the heart, primarily the coronary arteries and the proximal aorta, and to a lesser extent the lung-associated lymph nodes in males and in females.

TISSUE BURDEN ANALYSES

Deposition and clearance studies of indium following long term exposure of rats and mice to indium phosphide by inhalation were performed. Although there were quantitative differences in lung burden and kinetic parameters for rats and mice, qualitatively they were similar. Deposition of indium in the lungs appeared to follow a zero-order (constant rate) process. Retained lung burdens throughout the studies were proportional to exposure concentration and duration. No differences in elimination rates of indium from the lungs were observed as a function of exposure concentration in either rats or mice. These studies indicated that elimination of indium was quite slow. Mice exhibited clearance half-times of 144 and 163 days for the 0.1 and 0.3 mg/m^3 groups, respectively, as compared to 262 and 291 days for rats exposed to the same concentrations.

The lung deposition and clearance model was used to estimate the total amount of indium deposited in the lungs of rats and mice after exposure to 0.03 mg/m^3 for 2 years or to 0.1 or 0.3 mg/m^3 for 21 or 22 weeks, the lung burdens at the end of the 2-year study, and the area under lung burden curves (AUC). For both species, estimates at the end of 2 years indicated that the lung burdens in the continuously exposed 0.03 mg/m^3 groups were greater than those in the 0.1 or 0.3 mg/m^3 groups. The lung burdens were lowest in the 0.1 mg/m^3 groups. Because of the slow clearance of indium, the lung burdens in the 0.1 and 0.3 mg/m^3 groups were approximately 25% of the maximum levels in rats and 8% in mice approximately 83 weeks after exposure was stopped. The AUCs and the total amount of indium deposited per lung at the time exposure was stopped indicate that the 0.3 mg/m^3 groups were exposed to a greater amount of indium phosphide than were the 0.03 or 0.1 mg/m^3 groups, with the 0.1 mg/m^3 group receiving the lowest exposure. In rats and mice, the second-year AUC for the 0.03 mg/m^3 group was equivalent to that of the 0.3 mg/m^3 group. Regardless of how the total dose of indium to the lung was estimated, total exposure to indium in the 0.1 mg/m^3 groups was less than that in the other two groups implying that in these studies, 0.1 mg/m^3 may be considered the low dose.

GENETIC TOXICOLOGY

No significant increases in the frequencies of micronucleated normochromatic erythrocytes were noted in peripheral blood samples of male or female mice exposed to indium phosphide for 14 weeks. Although there was a significant increase in micronucleated polychromatic erythrocytes in 30 mg/m^3 male mice, there was no increase in female mice, and the percentage of polychromatic erythrocytes was not altered in males or females.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of indium phosphide in male and female F344/N rats based on increased incidences of benign and malignant neoplasms of the lung. Increased incidences of pheochromocytoma of the adrenal medulla in males and females were also considered to be exposure related. Marginal increases in incidences of mononuclear cell leukemia in males and females, fibroma of the skin in males, and carcinoma of the mammary gland in females may have been related to exposure to indium phosphide. There was *clear evidence of carcinogenic activity* of indium phosphide in male B6C3F_1 mice based on increased incidences of malignant neoplasms of the lung and benign and malignant neoplasms of the liver. Marginal increases in incidences of adenoma and carcinoma of the small intestine may have been related to exposure to indium phosphide. There was *clear evidence of carcinogenic activity* of indium phosphide in female B6C3F_1 mice based on increased incidences of benign and malignant neoplasms of the lung. Increased incidences of liver neoplasms in females were also considered to be exposure related.

Exposure to indium phosphide by inhalation resulted in nonneoplastic lesions in the lung of male and female rats and mice, the adrenal medulla of female rats, and the liver and heart of male and female mice.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A Summary of the Technical Reports Review Subcommittee comments and the public discussion on the Technical Report appears on page 15.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Indium Phosphide

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 0.03 mg/m^3 (for 2 years), 0.1 or 0.3 mg/m^3 (exposure stopped at 22 weeks)	Chamber control, 0.03 mg/m^3 (for 2 years), 0.1 or 0.3 mg/m^3 (exposure stopped at 22 weeks)	Chamber control, 0.03 mg/m^3 (for 2 years), 0.1 or 0.3 mg/m^3 (exposure stopped at 21 weeks)	Chamber control, 0.03 mg/m^3 (for 2 years), 0.1 or 0.3 mg/m^3 (exposure stopped at 21 weeks)
Body weights	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	0.03 and 0.3 mg/m^3 groups lower than chamber control group	Exposed groups lower than chamber control group
Survival rates	27/50, 29/50, 29/50, 26/50	34/50, 31/50, 36/50, 34/50	37/50, 24/50, 29/50, 27/50	42/50, 13/50, 33/50, 21/50
Nonneoplastic effects	Lung: atypical hyperplasia (0/50, 16/50, 23/50, 39/50); chronic active inflammation (5/50, 50/50, 50/50, 50/50); alveolar epithelium, metaplasia (0/50, 45/50, 45/50, 48/50); alveolus, proteinosis (0/50, 50/50, 48/50, 47/50); interstitium, fibrosis (0/50, 49/50, 50/50, 50/50); alveolar epithelium, hyperplasia (11/50, 20/50, 21/50, 31/50)	Lung: atypical hyperplasia (0/50, 8/50, 8/50, 39/50); chronic active inflammation (10/50, 49/50, 50/50, 49/50); alveolar epithelium, metaplasia (0/50, 46/50, 47/50, 48/50); alveolus, proteinosis (0/50, 49/50, 47/50, 50/50); interstitium, fibrosis (0/50, 48/50, 50/50, 49/50); alveolar epithelium, hyperplasia (8/50, 15/50, 22/50, 16/50); squamous cyst (0/50, 1/50, 1/50, 10/50) Adrenal Medulla: hyperplasia (6/50, 13/48, 9/50, 15/49)	Lung: chronic active inflammation (2/50, 50/50, 45/50, 46/50); alveolus, proteinosis (0/50, 14/50, 0/50, 10/50); serosa, fibrosis (0/50, 50/50, 49/50, 50/50) Pleura: mesothelium, hyperplasia (0/50, 19/50, 4/50, 6/50) Liver: eosinophilic focus (10/50, 16/50, 19/50, 18/50) Heart: artery, inflammation (3/50, 18/50, 14/50, 10/50)	Lung: chronic active inflammation (2/50, 49/50, 45/50, 50/50); alveolus, proteinosis (0/50, 31/50, 0/50, 8/50); serosa, fibrosis (0/50, 50/50, 47/50, 49/50) Pleura: mesothelium, hyperplasia (0/50, 16/50, 3/50, 13/50) Liver: eosinophilic focus (6/50, 9/50, 4/50, 12/50) Heart: artery, inflammation (1/50, 16/50, 11/50, 13/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Indium Phosphide

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects	Lung: alveolar/ bronchiolar adenoma (6/50, 13/50, 27/50, 30/50); alveolar/ bronchiolar carcinoma (1/50, 10/50, 8/50, 16/50); alveolar/ bronchiolar adenoma or carcinoma (7/50, 22/50, 30/50, 35/50); squamous cell carcinoma (0/50, 0/50, 0/50, 4/50) Adrenal Medulla: benign pheochromocytoma (10/50, 22/50, 16/49, 23/50); benign or malignant pheochromocytoma (10/50, 26/50, 18/49, 24/50)	Lung: alveolar/ bronchiolar adenoma (0/50, 7/50, 5/50, 19/50); alveolar/ bronchiolar carcinoma (1/50, 3/50, 1/50, 11/50); alveolar/ bronchiolar adenoma or carcinoma (1/50, 10/50, 6/50, 26/50) Adrenal Medulla: benign pheochromocytoma (2/50, 6/48, 2/50, 9/49)	Lung: alveolar/ bronchiolar carcinoma (6/50, 15/50, 22/50, 13/50) Liver: hepatocellular adenoma (17/50, 24/50, 23/50, 32/50); hepatocellular carcinoma (11/50, 22/50, 23/50, 16/50); hepatocellular adenoma or carcinoma (26/50, 40/50, 37/50, 39/50)	Lung: alveolar/ bronchiolar adenoma (3/50, 6/50, 10/50, 7/50); alveolar/ bronchiolar carcinoma (1/50, 6/50, 5/50, 7/50); alveolar/bronchiolar adenoma or carcinoma (4/50, 11/50, 15/50, 14/50) Liver: hepatocellular adenoma (12/50, 14/50, 18/50, 14/50); hepatocellular carcinoma (6/50, 17/50, 8/50, 10/50); hepatocellular adenoma or carcinoma (18/50, 28/50, 24/50, 23/50)
Uncertain findings	Skin: fibroma (1/50, 4/50, 7/50, 3/50) Mononuclear Cell Leukemia: (16/50, 23/50, 29/50, 25/50)	Mammary Gland: carcinoma (0/50, 8/50, 3/50, 2/50) Mononuclear Cell Leukemia: (14/50, 21/50, 14/50, 24/50)	Small Intestine: carcinoma (0/50, 1/50, 5/50, 3/50); adenoma or carcinoma (1/50, 2/50, 6/50, 3/50)	
Level of evidence of carcinogenic activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology				
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:			Negative	Negative

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 indium phosphide 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., Principal Reviewer
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, D.V.M., 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.
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 indium phosphide received public review by the National Toxicology Program's Board of Scientific Counselor's Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.H. Roycroft, NIEHS, introduced the toxicology and carcinogenesis studies of indium phosphide by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. Additionally, tissue burden (lung deposition and clearance) studies were conducted in rats and mice from the 14-week and 2-year studies. The proposed conclusions for the 2-year studies were *clear evidence of carcinogenic activity* in male and female F344/N rats and B6C3F$_1$ mice.

Dr. Medinsky, a principal reviewer, agreed with the proposed conclusions. She stated that the report was well written and was based on a well-designed study. Dr. Medinsky added that the discussion section of the report excelled in relating the results of these studies to what is known regarding the mechanisms of action of other lung carcinogens. She further stated that the deposition and clearance studies of indium phosphide in the lung and the toxicokinetic model developed from those studies proved to be extremely valuable for relating neoplasm incidences to the actual exposure of indium phosphide in the lungs.

Dr. Cullen, the second principal reviewer, agreed with the proposed conclusions. However, he thought that *some evidence of carcinogenic activity* might be more appropriate for the findings on liver neoplasms in male and female mice in view of limited exposure-related responses and the fact that neoplasm incidences were similar to historical control rates (for mice fed other diets). Dr. J.K. Haseman, NIEHS, said the liver neoplasms in mice could be dealt with in a manner analogous to pheochromocytomas in rats, i.e., "The increased incidences of liver neoplasms in males and females were also considered to be exposure related." Dr. Cullen suggested that since the mechanism of injury for indium phosphide is not known, greater discussion of the significance of grouping the animals on the basis of the exposure concentration or the total lung burden and the effects of the duration of exposure might be useful. Dr. Roycroft responded that he would try to clarify references to continuous versus stop exposures in the Results and Discussion and Conclusions section. Dr. Haseman explained that in terms of the statistical analyses, no attempt was made to rank the continuous exposures versus the stop exposures, and that the exposure-response trends reported were based strictly on the chamber control and two stop-exposure groups.

Dr. Bus, the third principal reviewer, agreed with the proposed conclusions. He commented that the analyses of tissue concentrations of indium phosphide were a valuable component of the study, with the information providing a more accurate assessment of internal dosimetry as well as confirming that the exposures, despite causing pulmonary neoplasms, probably did not result in pulmonary particle overload.

Dr. Cullen commented that he had trouble trying to compare the discontinuous and continuous exposed animals as to whether there was a clear exposure-related effect. Dr. Roycroft noted that although the external exposure of the two higher exposed groups was only 21 or 22 weeks, the tissue clearance of indium phosphide was extremely slow such that at the end of two years about 25% of the deposited material remained in the lung. Dr. Bailer said that he would like to have an idea of the precision associated with area under the curve (AUC) estimates, such as standard errors. Dr. Medinsky speculated that during the 2-year exposure period, the earlier exposures might be more important and thought the important dosimetric might be some weighted AUC giving more weight to the earlier exposures. Dr. Cullen stated that he still had trouble including liver neoplasms in mice under *clear evidence* in that they were treatment-related but not exposure-related effects. Dr. Bus suggested using the wording mentioned by Dr. Haseman.

Dr. Medinsky moved that under the conditions of this study the Technical Report on indium phosphide be

accepted with revisions discussed and the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity*, except that in mice, the citation for liver neoplasms would be included in a separate sentence to read: "The increased incidences of benign and malignant neoplasms of the liver in males and females were also considered to be exposure related." Dr. Cullen seconded the motion. Dr. Haseman pointed out that the trend test for hepatocellular adenomas in males was quite significant and the incidences of hepatocellular carcinomas in males were increased. Dr. J.R. Hailey, NIEHS, affirmed that there was a much stronger response in males. Dr. Medinsky asked that her motion be amended to retain the citation for liver neoplasms in male mice under *clear evidence*, while leaving the citation for liver neoplasms in female mice in the separate sentence. Dr. Cullen agreed to this change. The revised motion was accepted unanimously with six yes votes.

INTRODUCTION

InP

INDIUM PHOSPHIDE

CAS No. 22398-80-7

Chemical Formula: InP Molecular Weight: 145.80

CHEMICAL AND PHYSICAL PROPERTIES

Indium phosphide is a dark gray powder or brittle metallic solid. It has a melting point of 1,070° C and a specific gravity of 1.79 and oxidizes in air at temperatures above 700° C (Smith *et al.,* 1978; *Merck Index,* 1996; *Hawley's*, 1997). Indium phosphide is not soluble in saline or synthetic lung fluid (Gamble's solution) and is only slightly soluble in mineral acids (Dittmar *et al*., 1992; Kabe *et al*., 1996; *Hawley's*, 1997). However, indium phosphide was shown to be soluble in synthetic gastric fluid when heated to 37° C (Kabe *et al*., 1996). The NTP (Battelle, 1995a) determined that indium phosphide was not soluble in deionized water, 1 M ammonium hydroxide, or 1 M nitric acid; however, it completely dissolved in hydrochloric acid or warm aqua regia. Mosovsky *et al*. (1992) reported that small amounts of phosphine gas can be liberated from crystalline indium phosphide when ground (205 ppb) or immersed in water (51 ppb) or hydrochloric acid (150 ppb) but not in phosphoric or hydrofluoric acid. Phosphine gas (176 ppb) has also been detected within inches of a blade during cutting of crystalline indium phosphide (Mosovsky *et al*., 1992). Prior to conducting particulate inhalation toxicity studies, the NTP determined the "dust explosion and fire" characteristics of milled indium phosphide (0.4 μm count median diameter) (Battelle, 1995a). The explosion severity was determined to be 3.85 (greater than 2 is considered a severe explosion hazard), and the minimum spark ignition energy was 0.10 joules, which indicates that indium phosphide is extremely sensitive to ignition by electrostatic discharge.

PRODUCTION, USE, AND HUMAN EXPOSURE

Indium is present in the earth's crust (50 to 200 ppb) and is recovered primarily as a byproduct of zinc smelting; it is also present in a number of ores including iron, tin, lead, and copper (*Patty's*, 1994; Blazka, 1998; *Kirk-Othmer*, 1999). Indium phosphide is prepared by combining indium and phosphorus at high pressure and temperature (400 to 1,100° C). Depending upon the desired product, a number of starting materials are included utilizing various processes. Starting materials include a phosphorous source such as white or red phosphorus, phosphine, tertiary or isobutyl phosphine, and an indium source such as indium metal, indium iodide, or trimethylindium (Smith *et al*., 1978; Adamski and Ahern, 1985; Lee and Moskowitz, 1990; Hoffman *et al*., 1994; *Merck Index*, 1996). Production data for indium phosphide are not currently available; however, it is estimated that 150 tons of indium were produced in 1995 (Blazka, 1998), an increase from the 50 tons per year for 1982 to 1992 (Fowler, 1988; Scansetti, 1992). Indium phosphide is used extensively in the microelectronics industry because of its

photovoltaic properties. Compared to other semiconductor materials, indium phosphide, like gallium arsenide, is faster, requires less power, can handle more output power, and has good thermal characteristics. It is used to make semiconductors, injection lasers, solar cells, photodiodes, and light-emitting diodes (Blazka, 1998).

Exposure to indium phosphide occurs predominantly in the microelectronics industry where workers are involved in the production of indium phosphide crystals, ingots, and wafers; grinding and sawing operations; device fabrication; and sandblasting and clean-up activities (*Patty's*, 1994). The National Institute for Occupational Safety and Health estimated that in 1981, there were approximately 180,000 workers in the microelectronics industry, with over 500 plants manufacturing semiconductors (NIOSH, 1985). Currently, no occupational exposure limits have been established for indium phosphide specifically; however, the time-weighted average threshold limit value for indium and indium compounds set forth by the American Conference of Governmental Industrial Hygienists is 0.1 mg/m^3 (ACGIH, 2000), which is consistent with the NIOSH-recommended exposure limits of 0.1 mg/m^3 (NIOSH, 1997). There are no reports in the literature of the detection of indium phosphide in ambient air, drinking water, or wastewater, nor are there assessments of exposure to indium phosphide in the workplace. However, plant and animal tissue used for food have detectable indium concentrations of up to 10 µg/kg for beef and pork and up to 15 mg/kg for algae, fish, and shellfish from contaminated water near smelters. The average daily human consumption of indium is estimated to be 8 to 10 µg/day (Fowler, 1986; Scansetti, 1992; Blazka, 1998). Indium has been detected in seawater (20 µg/L), air (43 ng/m^3), and rainwater (0.59 µg/L) (Carson *et al*., 1986; Fowler, 1986).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

There is little information in the literature on the absorption, distribution, and excretion of indium phosphide. Kabe *et al*. (1996) investigated the absorption of indium phosphide particles (2.4 µm in diameter) following administration by oral gavage or intraperitoneal injection of single doses of 0, 1,000, 3,000, or 5,000 mg/kg indium phosphide to male ICR mice, which were observed for up to 14 days. Absorption from the gastrointestinal tract was minimal in that less than 0.125 µg indium/mL of serum was detected at all doses. Following intraperitoneal injection, there was a dose-related increase in indium concentration in serum (0.13, 0.6, and 1.75 µg/mL). After a dose of 5,000 mg/kg, indium was detected primarily in the liver and lungs (approximately 150 µg/g tissue), with some being detected in the kidneys and testes (less than 20 µg/g tissue).

Zheng *et al*. (1994) compared the distribution of indium phosphide particles (1.73 µm diameter) in male F344 rats following either a single oral dose, 14 days of oral dosing, or a single intratracheal instillation of 10 mg/kg indium phosphide. Indium phosphide was poorly absorbed from the gastrointestinal tract in both oral studies, with most of the indium being excreted in the feces. Less than 0.23% of the administered dose was excreted in the urine over a 10-day recovery period. Absorbed indium was evenly distributed among the major organs, although less than 0.67% of the dose was retained in tissues or urine following 24 hours in both oral studies, indicating that indium was not accumulating in the bodies of rats following multiple dosing. The urinary elimination half-time was determined to be about 32 hours. Following intratracheal administration of indium phosphide, the majority of tissue indium was in the lungs, with less than 0.36% of the dose being evenly distributed to the other major organs.

Over 73% of the administered dose was found in the gastrointestinal tract, while only 0.02% of the dose was found in urine. By either route, indium phosphide was not well absorbed, which is consistent with its poor solubility in biological fluids (Dittmar *et al*., 1992; Kabe *et al*., 1996).

As part of an NTP inhalation developmental toxicity study with indium phosphide, female Sprague-Dawley rats were exposed to 0, 1, 10, or 100 mg/m^3 indium phosphide particles with a mass median aerodynamic diameter of 1.3 µm from gestation days 4 to 19. Dams were sacrificed on gestation days 7, 14, and 19, and maternal lung and blood as well as fetal (uterus plus contents on day 7) indium concentrations were determined (Battelle, 1995b). In general, lung burdens increased with increasing duration of exposure

and were proportional to exposure concentration. Although maternal blood indium concentrations increased with exposure concentration throughout the study (although not proportionally), indium concentrations in maternal blood remained fairly constant for the later portion of the exposure from days 14 to 19. Fetal indium concentrations were, in general, similar to maternal blood concentrations throughout the study, except for that of the 100 mg/m^3 group on day 19, which was higher.

There are marked differences in the absorption and distribution of indium and indium compounds depending on the route of administration and the chemical form of the compound. Like indium phosphide, gastrointestinal absorption of indium and indium compounds such as In_2O_3, $InCl_3$, $In_2(SO_4)_3$, and $In(C_6H_5O_7)$ is poor with less than 0.5% of the dose being taken up by rats or 2.0% by humans (Smith *et al*., 1978; Fowler, 1986; *Patty's*, 1994; Blazka, 1998). Intratracheal or inhalation exposure of rats to either In_2O_3, $In(OH)_3$, or $In(C_6H_5O_7)$ also results in poor absorption with most of the indium remaining in the lungs or tracheobronchial lymph nodes, often retained with half-times approaching 2 months (Smith *et al*., 1978; Fowler, 1986; Blazka, 1998). Intraperitoneal injection of $InCl_3$ to rats results in higher liver indium concentrations than when given intravenously. Excretion following intraperitoneal injection is primarily in feces, whereas following intravenous administration, excretion is primarily in the urine. In general, subcutaneously administered indium compounds are absorbed faster than those given intramuscularly. Accumulation of indium in tissues is less following intravenous injection than when given via other routes, because indium is cleared from the blood within a few hours. Following intravenous administration, ionic indium is transported in the blood bound to plasma proteins such as transferrin and albumin, accumulated in lysozymes of the proximal tubules of the kidney as nonsoluble phosphate salts, and subsequently excreted via urine (Castronovo and Wagner, 1973; Galle, 1983). Colloidal hydrated indium compounds, following parenteral administration, are cleared from the blood by phagocytotic cells of the reticuloendothelial system (liver, spleen, etc.) and subsequently eliminated in the feces (Smith *et al*., 1978; Carson *et al*., 1986; Fowler, 1986, 1988; *Patty's*, 1994; Blazka, 1998).

Humans

No studies on the absorption, distribution, metabolism, or excretion of indium phosphide in humans were found in the available literature. Absorption and distribution of other indium compounds in humans are similar to that observed in rodents (Smith *et al*., 1978; Fowler, 1986; Blazka, 1998). Indium compounds are not absorbed to any appreciable quantity from the gastrointestinal tract (less than 2%). When administered intratracheally, accumulation is in the major airways with little absorption. Radioisotopes of indium (^{111}In and ^{113}In) administered as specific compounds or as complexes with transferrin, albumin, gelatin, and others have been used in medicine to scan the major organs, identify neoplasms, and label lymphocytes to assess cell kinetics and lymphoproliferative and chronic inflammatory disorders. Although intravenous administration is the primary route, radioisotopes of indium may be given orally (gastrointestinal tract scanning) or intrathecally (Smith *et al*., 1978; Fowler, 1986; Ellis *et al*., 1996; Blazka, 1998).

TOXICITY

Experimental Animals

There is little information in the literature on the toxicity of indium phosphide in animals. Indium phosphide, when compared to the acute toxicity of indium and indium compounds summarized in Table 1, is less toxic. Kabe *et al*. (1996) showed that single intraperitoneal or gavage doses of 1,000, 3,000, or 5,000 mg/kg indium phosphide failed to kill male ICR mice. The mice were observed for 14 days. There was no toxicity caused by indium phosphide in mice dosed by gavage, primarily due to limited absorption of the indium phosphide particles. Although there was no effect on weight gain in mice dosed intraperitoneally, there were dose-related increases in lung and spleen weights and in the pathologic response of several organs. Black granules presumed to be indium phosphide were observed in the spleen, liver, lungs, and lymph nodes. Eosinophilic exudate accompanied by mononuclear cells was seen in the alveoli of the lungs, and there was extramedullary hematopoiesis in the liver. There was notable proliferation of granulocytes in the red pulp and decreased cellularity in the white pulp in the spleen.

TABLE 1
Toxicity Values for Indium Compounds[a]

Compound	Species	mg Dose/kg Body Weight		Route	Parameter
		Compound	Indium		
In_2O_3	Mouse	479	396	Intraperitoneal	LD_{50}
	Mouse	5,005	4,136	Intraperitoneal	LD_{100}
	Rat	1,156	955	Intraperitoneal	LD_{100}
In_2O_3 (hydrated)	Mouse	0.4	0.3	Intravenous	LD_{50}
$In(OH)_3$	Mouse	0.9	0.6	Intravenous	LD_{50}
	Mouse	1.6	1.1	Intravenous	LD_{100}
$InCl_3$	Dog	1.0	0.5	Intravenous	LD_{100}
	Mouse	24.3	12.6	Intravenous	LD_{50}
	Mouse	5	2.6	Intraperitoneal	LD_{50}
	Rat	4,200	2,180	Oral	LD_{50}
	Rat	7.9	4.1	Intravenous	LD_{50}
	Rat	3.5	1.8	Intraperitoneal	LD_{50}
	Rat	6.4	3.3	Intraperitoneal	LD_{100}
	Rabbit	2,138	1,110	Oral	LD_{50}
	Rabbit	0.6	0.3	Intravenous	LD_{100}
	Rabbit	8.9	4.6	Intraperitoneal	LD_{100}
$In(NO_3)_3$	Mouse	3,350	1,279	Oral	LD_{50}
	Mouse	7.5	2.9	Intraperitoneal	LD_{50}
	Mouse	100	38.2	Intraperitoneal	LD_{100}
	Rat	5.5	2.1	Intraperitoneal	LD_{50}
$In_2(SO_4)_3$	Rat	22.5	10	Subcutaneous	LD_{50}
	Rat	28.3	12.5	Subcutaneous	LD_{100}
	Rat	5.6	2.5	Intravenous	LD_{50}
	Rat	28.5	12.6	Intravenous	LD_{50}
	Rat	40.5	18	Intraperitoneal	LD_{100}
	Rabbit	2.5	1.1	Subcutaneous	LD_{100}
	Rabbit	9.7	4.3	Intraperitoneal	LD_{100}
$In(C_6H_5O_7)_3$	Mouse	600	101	Subcutaneous	LD_{50}
InSb	Mouse	4,770	1,800	Intraperitoneal	LD_{50}
	Mouse	5,974	2,900	Intraperitoneal	LD_{100}

[a] Blazka, 1998

Uemura *et al*. (1997) administered indium phosphide intratracheally at doses of 0, 1, 10, or 100 mg/kg (0.8 μm diameter particles) to male F344 rats that were observed for 7 days. There was a dose-dependent increase in the number of neutrophils in broncho-alveolar lavage fluid (BALF); however, there was no increase in the number of macrophages, many of which were found to be disrupted. Those that appeared normal contained indium phosphide particles. Also, there were dose-related increases in BALF LDH and total protein, phospholipid, and cholesterol concentrations. Histopathology of the lungs was consistent with the BALF assessment and included a dose-related increase in the infiltration of macrophages and neutrophils accompanied by broken macrophages, exfoliated alveolar cells, and eosinophilic exudate. There was a thickening of the interstitial walls and epithelium of the bronchioles. Indium phosphide particles were observed in the interstitium as well as in the lumen. There were no histopathologic findings in the liver or spleen. In other experiments from the same laboratory, Oda (1997) intratracheally instilled male

F344 rats with indium phosphide particles (1 µm in diameter) at doses of 0, 1.2, 6.0, or 62.0 µg/kg and observed the rats for 8 days. As observed previously, there was an increase in BALF neutrophil and lymphocyte counts as well as LDH, total protein, phospholipid, and cholesterol concentrations, but only in the 62.0 µg/kg group. BALF superoxide dismutase activity, although increased in all dosed groups, did not increase in a dose-related manner. BALF α-antitrypsin was unaffected by indium phosphide administration, as were hematologic indices. The toxicity of indium and indium compounds has been described by a number of investigators and reviewed by Smith *et al*. (1978), Carson *et al*. (1986), Fowler (1986), *Patty's* (1994), and Blazka (1998). Although indium is considered a nonessential element, it is one of the more toxic metals. Gross signs of indium toxicity in rodents include reduced food and water consumption with accompanying weight loss, pulmonary edema, necrotizing pneumonia, widespread hemorrhaging, inflammatory and degenerative changes in the liver and kidneys (and to a lesser extent the heart, spleen, and adrenal gland), hindlimb paralysis in some species, and death (McCord *et al*., 1942; Castronovo and Wagner, 1973). Some indium salts cause calcification at the site of injection.

The toxicity of indium compounds is dependent upon the form (solubility) of the compound administered, the dose, and the route of administration. Colloidal hydrated indium, such as hydrated In_2O_3, is 40 times more toxic to HRA/IRC mice than ionic indium compounds, such as $InCl_3$, when administered intravenously (Castronovo and Wagner, 1973). Colloidal hydrated indium is cleared from the blood by phagocytic cells of the liver, spleen, and reticuloendothelial system; therefore, these cells are the primary targets of damage. Ionic indium compounds, such as $InCl_3$, are bound to plasma proteins such as transferrin, and to a lesser extent albumin. Although they may cause focal liver necrosis at high doses, they primarily affect the proximal tubules of the kidney. Indium compounds target the endoplasmic reticulum of the liver and kidney, affecting both heme- and nonheme-dependent bio-chemical functions (Conner *et al*., 1993, 1995; Fowler, 1995).

Discussion of the toxicity of indium compounds administered via the respiratory tract is relevant to the evaluation and interpretation of the current indium phosphide studies. Most of the early studies have been reviewed and summarized by Smith *et al*. (1978). Albino rats intratracheally instilled with In_2O_3 and observed for 8 months, displayed increased mortality and had reduced body weight gain. Besides the presence of particles in the lung and lymph nodes, there were lymphoid hyperplasia, proliferation of alveolar membranes, and interstitial fibrosis. A granular dystrophy of the liver and kidney was noted. Intratracheal instillation of 25 mg InSb in guinea pigs resulted in interstitial pneumonia. Particle accumulation was noted in the lungs and spleen. There were granular vacuolization and hyaline droplets in the kidney, fibrosis and necrosis in the spleen, and parenchymal necrosis in the liver. Male and female Wistar rats exposed by inhalation to 64 mg In_2O_3/m^3 4 hours per day for 90 days and observed for 12 weeks after exposure had a marked reduction in rate of weight gain. Lungs were three to five times heavier in exposed animals than in controls, and tracheobronchial lymph nodes were enlarged. The lungs showed evidence of widespread alveolar edema that microscopically appeared granulated and contained few alveolar phagocytes, polymorphonuclear lymphocytes (PMNs), or nuclear debris. The lesion was further characterized by alteration of the alveolar walls by spindle-shaped and other types of cells. There was little change in this lesion during exposure or after the 12-week recovery period. No fibrosis was detected.

Blazka *et al*. (1994a) intratracheally instilled female F344 rats with a single dose of 1.3 mg $InCl_3$/kg and observed them for 56 days. Over the course of the recovery period, lung weights increased to 2.5 times greater than those of the controls, with the maximum increase occurring by day 28. This was also consistent with an increase in lung hydroxyproline and BALF cell number, which was 32 times that of the controls. Initially this increase was due to the influx of PMNs; however, by day 14, there was a significant increase in alveolar macrophages that continued to the end of the study. BALF fibronectin and TNF-α concentrations rose sharply in the first 2 days. After day 2 for fibronectin and day 14 for TNF-α, concentrations of both steadily decreased over the remainder of the recovery period. Histopathology of the lung was consistent with BALF measurements throughout the study in that in the first few days, there were considerable numbers of inflammatory cells, primarily PMNs, within the alveolar spaces and septa and within the bronchial/bronchiolar lumen. Proteinaceous exudate was mixed

with the inflammatory cells. There was focal necrosis as well as regeneration of alveolar and bronchiolar epithelium. Throughout the recovery period, the inflammatory cell population changed, with large foamy macrophages being the predominant inflammatory cell type. Alveolar septal walls thickened, and areas of fibrosis became more prominent. In another study, Blazka *et al*. (1994b) exposed female F344 rats to 0, 0.2, 2.0, or 20 mg $InCl_3/m^3$ with a single 1-hour nose-only exposure and observed the rats for 42 days. By day 7, lung weights were significantly increased in a concentration-related manner; lung hydroxyproline was unaffected. BALF cell counts, fibronectin, and TNF-α concentrations followed a trend similar to that observed in the intratracheal study in that most of the effects were observed early.

Humans

No studies on the toxicity of indium phosphide in humans were found in the literature.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

As part of the overall toxicity assessment of inhalation exposure to indium phosphide, the NTP conducted whole-body inhalation developmental toxicity studies with 0, 1, 10, or 100 mg/m^3 indium phosphide with Sprague-Dawley rats and Swiss (CD-1®) mice (Battelle, 1995b, 1997). Rats were exposed on gestation days 4 through 19, while mice were exposed on gestation days 4 through 17. The pregnancy rates of rats and mice exposed to 100 mg/m^3 were slightly less than those of the controls. Indium phosphide caused no maternal toxicity in rats other than a concentration-related increase in lung weights. There was no fetal toxicity, malformation, or effects of exposure on any developmental toxicity parameters. In contrast to the results with rats, exposure of mice to 100 mg/m^3 indium phosphide resulted in early deaths, reduced body weight gain (although not statistically significant), listless appearance, and labored breathing. Lung weights were significantly increased in all exposed mice. There was no significant fetal toxicity, malformation, or effects on any developmental toxicity parameter that could be attributed to exposure. Kidney hemorrhage was noted in fetuses in two litters in the 100 mg/m^3 group.

Ferm and Carpenter (1970) intravenously injected pregnant hamsters with 0.5, 1, 2, 5, 10, or 20 mg $In(NO_3)_3$/kg on day 8 of gestation, and embryos were removed 4 to 6 days later. All dams that received 2 mg/kg or greater died. Malformations of the digits including fusion, stunting, and, in a few instances, polydactyly, were observed in the 0.5 and 1.0 mg/kg groups.

In reproductive and developmental toxicity studies, Chapin *et al*. (1995) dosed male and female Swiss (CD-1®) mice with 0, 50, 150, or 250 mg $InCl_3$/kg by oral gavage; males were dosed for 17 days, and females were dosed during gestation days 8 to 14 for the reproductive study and during days 6 to 15 of gestation for the teratology study. Doses of 150 mg/kg or greater caused reduced weight gain in male and female mice in the reproductive study. There were no treatment-related effects on male tissues, male reproductive parameters, or female fertility endpoints. In the developmental toxicity study, there was no maternal toxicity other than reduced liver weights in 250 mg/kg females. There were dose-related increases in the numbers of both early and late resorption and significantly fewer live fetuses per litter and more dead fetuses per litter, primarily in the 250 mg/kg group. There was no increase in the incidences of fetal abnormalities as a result of $InCl_3$ treatment. In order to determine whether $InCl_3$ is embryotoxic, gestation day 9 embryos were removed and cultured for 24 to 48 hours with $InCl_3$ concentrations from 5 to 3,000 µM. Fetal toxicity was observed at concentrations as low as 10 µM $InCl_3$ and included alteration in yolk sac vasculature development, incomplete closure of the cranial neural tube, lack of prosencephalic development and expansion, and retardation of the growth and development of the pharyngeal arches and otic pit. Embryotoxic effects due to $InCl_3$ have also been observed in rat embryos (Nakajima *et al*., 1999).

Nakajima *et al*. (1998) treated Wistar rats on day 9 of gestation with $InCl_3$ with either single intravenous doses of 0, 0.1, 0.2, or 0.4 mg indium/kg or single oral doses of 0, 75, 150, or 300 mg indium/kg and observed the rats until gestation day 20. In the intravenous studies, fetal weight was decreased and fetal mortality and malformations were significantly increased at 0.4 mg/kg. Malformations of the tail and digits were

observed. Oral administration had no detrimental effects on the fetuses, nor did it significantly increase fetal abnormalities, although some tail malformations were observed in the 300 mg/kg group.

In summary, indium phosphide administered by inhalation has not been shown to be teratogenic; however, $In(NO_3)_3$ and $InCl_3$, have been shown to cause malformations of the digits in hamsters and rats when administered intravenously (Ferm and Carpenter, 1970; Nakajima *et al*., 1998).

Humans

No studies on developmental or reproductive toxicity of indium phosphide in humans were found in the literature.

CARCINOGENICITY

Experimental Animals

No adequate carcinogenicity studies of indium phosphide in experimental animals were found in the literature. Tanaka *et al*. (1996) intratracheally instilled male Syrian golden hamsters once a week for 15 weeks with indium phosphide or indium arsenide at a weekly dose of 0.5 mg phosphorus or arsenic. Particle mean count diameter was approximately 4 μm for indium arsenide and 3 μm for indium phosphide. Hamsters were observed during their total life span (approximately 105 weeks). Although there was no treatment-related mortality with either material, the hamsters administered indium arsenide gained less weight than did controls or indium phosphide-dosed animals. Similar treatment-related effects were observed in the lungs of treated with indium phosphide or indium arsenide. Particles of each compound were observed in the region of the alveolar septum and space as well as in the lymph nodes. There was a marked alveolar proteinosis expanding the alveoli. Alveolar epithelium was flattened or partially missing; particles were observed within or surrounding these lesions. Macrophages and lymphocytes infiltrated the alveolar space. Surrounding these lesions were areas of alveolar or bronchiolar hyperplasia with or without squamous metaplasia. There were no treatment-related increases in neoplasias of the lungs or other organs when compared to controls for either indium phosphide or indium arsenide.

Humans

No epidemiology studies of indium phosphide in humans were found in the literature.

GENETIC TOXICITY

No genetic toxicity studies for indium phosphide were found in the literature.

STUDY RATIONALE

Indium phosphide was nominated by the National Institute of Environmental Health Sciences for study because of the potential for increased use in the microelectronics industry, the potential for worker exposure, and the absence of chronic toxicity and carcinogenicity data. Inhalation was chosen as the route of exposure because human exposure to indium phosphide occurs primarily by this route.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF INDIUM PHOSPHIDE

Indium phosphide was obtained in three lots from Johnson Matthey, Inc. (Ward Hill, MA). The study laboratory combined two lots into a single lot (lot BNW-12957-21) for use in the 14-week studies. The third lot (lot BNW-13040-127) was combined with lot BNW-12957-21 to make lot BNW-12957-28 which was used in the 2-year studies. Identity, purity, and stability analyses were conducted by the study laboratory. Reports on analyses performed in support of the indium phosphide studies are on file at the National Institute of Environmental Health Sciences.

For lot BNW-12957-21, results of glow-discharge mass spectrometric analyses provided by the manufacturer indicated that impurities totaled less than 120 ppm for the 72 elements assayed; the principal impurities were aluminum (37 ppm), silicon (29 ppm), chlorine (7 ppm), calcium (16 ppm), and arsenic (12 ppm). For lot BNW-13040-127, results of glow-discharge mass spectrometric analyses provided by the manufacturer indicated that impurities totaled less than 2 ppm for the 72 elements assayed. Following micronization, the bulk material was designated lot BNW-12957-28 in three batches over the course of the 14-week and 2-year studies.

Lot BNW-12957-28, a polycrystalline solid, was identified as indium phosphide by X-ray diffraction analyses, which indicated the presence of indium phosphide at greater than 99% purity (Figure J1). Elemental indium was detected at a concentration of approximately 1% or less. The purity of lot BNW-12957-28 was determined by inductively coupled plasma/atomic emission spectroscopy (ICP/AES). The results of ICP/AES analyses were in agreement with the theoretical values. For the two batches of lot BNW-12957-28 prepared for use in the 14-week studies, results of ICP/AES analyses indicated purities of 97.6% ± 0.6% and 99.0% ± 0.4% for indium and 96.8% ± 0.4% and 97.7% ± 1.7% for phosphorus relative to the theoretical values. Arsenic, selenium, antimony, and iron were present in each batch at concentrations greater than 0.01%; other elements were present at concentrations of less than 0.01% or were not detected. The total weight of trace impurities in each batch was less than 0.2%. For the batch of lot BNW-12957-28 prepared for use in the 2-year studies, the results indicated a purity of 97.1% ± 0.3% for indium and a 96.9% ± 0.7% for phosphorus relative to the theoretical values. Arsenic, iron, antimony, and selenium were detected at concentrations of 0.01% to 0.02%. Concentrations of other elements were less than 0.01% or were below the limit of detection. The total weight of trace impurities was less than 0.12%.

Accelerated stability studies were performed on lot L08C07 (not used in the current studies), which was obtained from Johnson Matthey, Inc. Indium phosphide was found to be stable for at least 2 weeks at temperatures up to 60° C when stored under a headspace of nitrogen or air. The bulk chemical was stored in amber glass bottles with Teflon®-lined caps under a nitrogen headspace at room temperature. Stability was monitored throughout the studies with ICP/AES. No degradation of the bulk chemical was detected.

Thermal studies were conducted to assess the stability of micronized indium phosphide in air and in nitrogen at higher temperatures such as those generated by the milling process. Using differential scanning calorimetry, thermal behavior was monitored between 30° and 500° C with temperatures increasing at a rate of 5° C per minute; isothermal analyses were performed in air by heating indium phosphide to 250° C at 320° C per minute and holding at 250° C for 4 hours. A small endothermic reaction (0.1 J/g) occurred in air and nitrogen at around 156.6° C, suggesting some decomposition of indium phosphide into its elements. An exothermic reaction (9 J/g) in air only was observed at around 380° C and may have been associated with the presence of an unidentified impurity. Using scanning thermogravity, thermal behavior was monitored as with differential scanning calorimetry; isothermal analyses were performed in air by heating indium phosphide to

250° C at 160° C per minute and holding at 250° C for 2 hours. No mass change was observed for the endothermic reaction observed in the calorimetric analysis. The exothermic reaction that occurred at approximately 380° C showed a weight gain of approximately 0.5% at termination (500° C). No significant reaction was observed for isothermal analysis at 250° C.

Additional stability studies were performed by Dust Tech, Inc. (Augusta, NJ), using a Hartmann Dust Explosion Apparatus (U.S. Bureau of Mines, Bruceton Station, PA) and a Godbert-Greenwald furnace (U.S. Bureau of Mines) (Battelle, 1995a). Resistivity was measured with a cell, designed for particulate materials, equipped with a high-voltage power supply and an electrometer. The current passing through the standard sample geometry, measured as a function of applied voltage, was used to calculate volume resistivity. Results of analyses indicated that indium phosphide dust is capable of causing a severe explosion. Under conditions in which electrostatic charges are generated, such as milling and pneumatic conveying, indium phosphide is sensitive to ignition by electrostatic discharge and can generate pressure at a rate of up to 10,200 psi per second.

AEROSOL GENERATION AND EXPOSURE SYSTEM

For the 14-week studies, the indium phosphide aerosol generation and delivery system had four basic components: a flexible brush dust feed mechanism developed at the study laboratory, a Trost Model GEM-T air-impact mill (Garlock, Inc., Newton, PA), an aerosol charge neutralizer, and a stainless-steel aerosol distribution system (Figure J2). The generation and distribution system was electrically grounded and bonded and was monitored continuously for proper grounding; the system was designed to shut down automatically if a ground fault was detected. The flexible-brush dust feed mechanism (Figure J3) employed a hopper into which the dry powder was poured. The hopper was reloaded with additional indium phosphide at regular intervals throughout each day's exposure period. Indium phosphide was stored in a nitrogen-purged desiccator to achieve more uniform flow in the generator.

The aerosol generation and delivery system for the 2-year studies is shown in Figure J4. The aerosol generator consisted of a drum, body, and cap (Figure J5). The drum rotated at 60° increments, with set time intervals between drum rotations. Rotation of the drum was controlled by a compressed-air-driven valve driver (VICI Valco Instrument Co., Houston, TX). As the drum rotated, indium phosphide filled six metering ports in a disk at the bottom of the drum and was held in each port by a stainless-steel screen. The metering ports sequentially aligned with a nitrogen inlet in the body and dispersed indium phosphide when a nitrogen solenoid valve was opened. Output of the generator was regulated by adjusting the rotation cadence.

In all studies, the aerosol leaving the generator passed through a corona discharge air-ionizing neutralizer (Conveyostat Static Neutralizing System, Simco, Inc., Hatfield, PA) into the distribution line. At each chamber location, a pneumatic injector developed by the study laboratory drew aerosol from the distribution line into the chamber inlet, where the aerosol was further diluted with HEPA-filtered air to the appropriate concentration. The flow rate through the distribution line was controlled by vacuum pumps (Air-Vac Engineering Company, Inc., Milford, CT); pressure was monitored by photohelic differential pressure gauges (Dwyer Instruments, Inc., Michigan City, IN).

The study laboratory designed the stainless-steel inhalation exposure chambers (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform aerosol concentrations could be maintained throughout the chambers when catch pans were in place. The total active mixing volume of each chamber was 1.7 m^3.

AEROSOL CONCENTRATION MONITORING

Summaries of chamber aerosol concentrations of indium phosphide are given in Tables J1 and J2. Chamber aerosol concentrations were monitored with real-time aerosol monitors (RAMs) (Model Ram-1; MIE, Inc., Bedford, MA) that used a pulsed-light-emitting diode in combination with a silicon detector to sense light scattered over a forward angular range of 45° to 95° by particles traversing the sensing volume. The instrument responds to particles 0.1 to 20 μm in diameter; the geometric diameter of indium phosphide aerosol approached the minimum of this range. The sampling system consisted of a valve which

multiplexed each RAM to two or three exposure chambers and either the control chamber, the room, or a HEPA filter. The monitors were connected to the chambers with sample lines designed to minimize aerosol particle loss through settling or impaction.

CHAMBER ATMOSPHERE CHARACTERIZATION

The particle size distribution in each chamber was determined during the prestudy testing, during the first week of the studies, and monthly thereafter using a Mercer-style seven-stage impactor (In-Tox Products, Albuquerque, NM). The stages (glass coverslips lightly sprayed with silicone) were analyzed by ICP/AES (14-week studies) or inductively coupled plasma/mass spectroscopy (ICP/MS) (2-year studies). The relative mass collected on each stage was analyzed by probit analysis. The mass median aerodynamic particle diameter and the geometric standard deviation of each set of samples were estimated (Tables J3, J4, and J5).

Buildup and decay rates for chamber aerosol 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 aerosol generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after aerosol generation was terminated (T_{10}) was approximately 12.5 minutes. A T_{90} value of 12 minutes was selected for all studies.

Uniformity of aerosol concentration in the 14-week studies was evaluated during prestudy testing without animals present and once during the studies with animals present in exposure chambers. During the 2-year studies, uniformity was evaluated every 2 to 4 months. Chamber concentration uniformity was acceptable throughout the studies. The persistence of indium phosphide aerosol in the exposure chambers was monitored overnight after aerosol delivery ceased. The average indium phosphide concentration decayed to 1% of target concentration within approximately 20 (14-week studies) or 21 minutes (2-year studies).

The stability of indium phosphide in the exposure system was analyzed with XRD and ICP/AES. Results were generally consistent with those expected for indium phosphide.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to indium phosphide and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 12 to 14 days and were approximately 6 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were exposed to particulate aerosols of indium phosphide at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3, 6 hours plus T_{90} (12 minutes) per day, 5 days per week (weeks 1 through 4 and weeks 10 through 14) or 7 days per week (weeks 5 through 9) during the concurrent teratology study. Clinical pathology study groups of 10 male and 10 female rats were exposed to the same concentrations for 14 weeks for clinical pathology analyses and postexposure tissue burden analyses. Groups of 15 male rats designated for tissue burden analyses and five male rats designated for postexposure tissue burden analyses were exposed to the same concentrations for 14 weeks. Beginning the final week of the studies, additional groups of 15 previously unexposed male rats were exposed to the same concentrations for 5 days for a postexposure lung burden study. These animals were age matched to the core study animals. Feed was available *ad libitum* except during exposure and urine collection periods; water was available *ad libitum* except during urine collection periods. Rats and mice were housed individually. The animals were weighed and clinical findings for mice were recorded initially, weekly, and at the end of the studies; clinical findings for rats were recorded at the end of week 1, weekly, and at the end of the study. Details of the study design and animal maintenance are summarized in Table 2.

Blood was collected for hematology and clinical chemistry determinations from clinical pathology study rats on days 3 and 23 and from core study rats and mice (hematology only) at study termination. At all time points, the animals were anesthetized with a 70% CO_2/air mixture and blood was collected from the retroorbital sinus. Clinical pathology study female rats were discarded following the day 23 blood collection.

Blood for hematology determinations was placed in tubes containing potassium EDTA as the anticoagulant. Erythrocyte, leukocyte and platelet counts, hemoglobin concentration, automated hematocrit, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were determined using a Roche Cobas Helios analyzer (Roche Diagnostics, Branchburg, NJ). Manual hematocrit determinations were performed using a Damon/IEC MB microcentrifuge and a Damon IEC capillary reader (International Equipment Company, Needham Heights, MA). Leukocyte differential and nucleated erythrocyte counts were determined by light microscopic examination of blood films stained with Wright-Giemsa in a Wescor 7100 aerospray stainer (Wescor, Inc., Logan, VT). Reticulocytes were stained with new methylene blue and enumerated using the Miller disc method (Brecher and Schneiderman, 1950). Blood for serum chemistry analyses was placed in tubes without anticoagulant, allowed to clot at room temperature, centrifuged, and the sera were separated. Serum chemistry parameters were determined using Roche Cobas Fara methodologies (Roche Diagnostics). Hematology and serum chemistry parameters evaluated are listed in Table 2.

Urine was collected from core study male rats on day 31. Rats were placed in metabolism cages for 16 hours. After 4 hours, collection vials were replaced and urine was examined by dipstick and microscopic analyses. Urine chemistry parameters were evaluated using Roche Cobas Fara methodologies (Roche Diagnostics); variables are listed in Table 2.

Rats designated for tissue burden study were evaluated to determine the extent of distribution of indium in blood, lungs, serum, and testes at five time points during the exposure period. Two or three males per group were evaluated on day 4, 24, 45, 73, or 96. Rats designated for the postexposure tissue burden study (which included 10 male rats from the clinical pathology study group) were examined at four time points after exposure termination to evaluate the elimination of indium from blood, lungs, serum, and testes. Three male rats per group were evaluated 14, 28, 56, or 112 days after exposure termination, except all surviving male rats exposed to 100 mg/m^3 were evaluated on postexposure day 14. Rats designated for the postexposure lung burden study in age-matched animals were exposed to indium phosphide for 5 consecutive days beginning the final week of the 14-week study. Lungs from three males per exposure group were evaluated on exposure day 5 and 14, 28, 56, or 112 days after exposure termination. Animals at each time point were anaesthetized with sodium pentobarbital. Blood was drawn by cardiac puncture and divided into a tube containing EDTA as an anticoagulant and a serum collection tube without anticoagulant. The testes and lungs were removed and weighed. Indium in lung digests was analyzed using ICP/AES (Minitorch Model 3410, Applied Research Laboratories, Inc., Valencia, CA). Indium in blood, serum, and testes digests was measured by ICP/MS (PlasmaQuad, VG Elemental, Winsford, Cheshire, UK) and an autosampler (Gilson Model 222, Gilson Medical Electronics, Middleton, MI). Equations for calculation of lung deposition and clearance parameters are included in Appendix H.

At the end of the 14-week studies, samples were collected for sperm motility and vaginal cytology evaluations on rats and mice exposed to 0, 3, 10, and 30 mg/m^3. The parameters evaluated are listed in Table 2. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were

counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

Necropsies were performed on all surviving core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination 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. A complete histopathologic examination was performed on 0 and 100 mg/m^3 rats and mice, on 30 mg/m^3 mice, and on target organs from all core study rats and mice. Table 2 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats and mice were exposed to particulate aerosols of indium phosphide at concentrations of 0, 0.03, 0.1, or 0.3 mg/m^3, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 22 weeks (rats) and 21 weeks (mice) (0.1 and 0.3 mg/m^3 groups) or 105 weeks (0 and 0.03 mg/m^3 groups). Animals in the 0.1 and 0.3 mg/m^3 groups were maintained on filtered air from exposure termination until the end of the studies. Male and female rats and mice (10 per group) were randomly selected and evaluated at 3 months. Additional groups of 20 male rats and 20 male mice were designated for tissue burden analyses.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 13 (mice) or 15 (rats) days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats and mice were housed individually. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Cages and racks were rotated weekly. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix K.

Tissue Burden Studies

Lungs and sera were collected from five rats and five mice in the 0 and 0.03 mg/m^3 tissue burden study groups at 3, 5 (0.03 mg/m^3 group only), 9, or 12 months for lung burden and serum indium concentration analyses. Additionally, a complete necropsy and complete histopathologic examination was performed on animals in the 0.03 mg/m^3 group at 5 months and the left lungs from animals in the 0 and 0.03 mg/m^3 groups were collected for histopathologic examination at 12 months. Lungs and sera were collected from five rats and five mice in the 0.1 and 0.3 mg/m^3 groups at 3 months for lung burden and serum indium concentration evaluation. Three or four sentinel rats and mice per gender from each group were sacrificed at 5 months for necropsy, complete histopathologic examination, and lung burden and serum indium concentration evaluations. A complete necropsy, left lung histopathologic examination, and lung burden and serum concentration evaluation were performed on two to three rats and one to three mice from the 0.1 and 0.3 mg/m^3 groups 2, 4, 6, 8, or 12 months after exposure termination. In addition, two or three rats and mice from the 0 mg/m^3 group were examined for the same parameters at 2 or 12 months after exposure. Methodologies for determination of lung burden and serum indium concentration were the same as those described for the 14-week studies, except indium in lung digests was analyzed using inductively coupled plasma/mass spectroscopy (PlasmaQuad, VG Elemental, Winsford, Cheshire, UK). Equations for calculation of lung deposition and clearance parameters are included in Appendix H.

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed at the beginning of the studies. Clinical findings and body weights for rats were recorded every 4 weeks from week 4 through 92, except between weeks 44 and 52, and approximately every 2 weeks thereafter. Clinical findings and body weights for mice were recorded every 4 weeks from week 5 through 93 and approximately every 2 weeks thereafter. At the 3-month interim evaluation, blood was collected for hematology and clinical chemistry analyses. Methodologies used were the same as those described for the 14-week studies. The parameters measured are listed in Table 2.

Complete necropsies and microscopic examinations were performed on 0 and 0.3 mg/m^3 core study rats and mice at 3 months and all core study rats and mice at the end of the studies. Target organs were examined in 0.03 and 0.1 mg/m^3 core study rats and mice at 3 months. At 3 months, the heart, right kidney, liver, lung, right testis, and thymus of rats and mice were weighed. 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 studies, a quality assessment pathologist evaluated slides from all tumors (except for testis interstitial cell adenoma) and all potential target organs, which included the larynx, lung, lymph nodes (mediastinal)and bronchial), nose, and trachea of rats and mice; the mammary gland in rats; and the liver in mice. Additionally, the oral cavity in rats was evaluated for hyperplasia and neoplasms; in mice, the spleen was evaluated for hematopoietic cell proliferation and the bone marrow was evaluated for hyperplasia.

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. 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 Inhalation Studies of Indium Phosphide

14-Week Studies	2-Year Studies
Study Laboratory Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Strain and Species F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice
Animal Source Taconic Farms (Germantown, NY)	Taconic Farms (Germantown, NY)
Time Held Before Studies Rats: 12 days (males) or 13 days (females) Mice: 13 days (males) or 14 days (females)	Rats: 15 days Mice: 13 days
Average Age When Studies Began 6 weeks	6 weeks
Date of First Exposure 3 (males) or 4 (females) April 1995	18 (rats) or 25 (mice) January 1996
Duration of Exposure 6 hours plus T_{90} (12 minutes) per day, 5 days per week (weeks 1-4 and 10-14) or 7 days per week (weeks 5-9)	6 hours plus T_{90} (12 minutes) per day, 5 days per week for 22 weeks (rats) and 21 weeks (mice) (0.1 and 0.3 mg/m^3 groups) or 105 weeks (0 and 0.03 mg/m^3 groups)
Date of Last Exposure Rats: 4 (males) or 5 (females) July 1995 Mice: 6 (males) or 7 (females) July 1995	Rats: 14 June 1996 (0.1 and 0.3 mg/m^3 groups) or 16 January 1998 (0 and 0.03 mg/m^3 groups) Mice: 14 June 1996 (0.1 and 0.3 mg/m^3 groups) or 23 January 1998 (0 and 0.03 mg/m^3 groups)
Necropsy Dates Rats: 5 (males) or 6 (females) July 1995 Mice: 7 (males) or 8 (females) July 1995	Rats: 3-Month interim evaluation: 17 (males) or 18 (females) April 1996 Terminal sacrifice: 19-23 January 1998 Mice: 3-Month interim evaluation: 25 (males) or 26 (females) April 1996 Terminal sacrifice: 26-30 January 1998
Average Age at Necropsy 20 weeks	3-Month interim evaluation: 19 weeks Terminal sacrifice: 111 weeks
Size of Study Groups Core studies: 10 males and 10 females Clinical pathology study: 10 male and 10 female rats Tissue burden study: 15 male rats Postexposure tissue burden study: 15 male rats (includes 10 males from the clinical pathology study) Postexposure lung burden study in age-matched animals: 15 male rats	Core studies: 60 males and 60 females Tissue burden studies: 20 males

TABLE 2
Experimental Design and Materials and Methods in the Inhalation Studies of Indium Phosphide

14-Week Studies	2-Year Studies
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 14-week studies
Animals per Cage 1	1
Method of Animal Identification Tail tattoo	Tail tattoo
Diet NTP-2000 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* except during exposure and urine collection periods , changed daily on exposure days (rats) or weekly (mice)	NTP-2000 pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed weekly, irradiated from May 1996 to study termination
Water Softened tap water (Richland municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum* except during urine collection periods, changed weekly	Same as 14-week studies, except water softening terminated January 1997
Cages Stainless steel wire bottom (Hazleton System, Inc., Aberdeen, MD) changed weekly	Same as 14-week studies
Chamber Air Supply Filters Single HEPA (Northland Filter System International, Inc., Mechanicville, NY); Charcoal (RSE, Inc., New Baltimore, MI); Purafil (Environmental Systems, Lynnwood, WA)	Same as 14-week studies
Chambers Stainless steel (Lab Products, Inc., Harford System Division, Aberdeen, MD), changed weekly	Same as 14-week studies
Chamber Environment Temperature: 75° ± 3° F Relative humidity: 55% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 75° ± 3° F Relative humidity: 55% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour
Exposure Concentrations 0, 1, 3, 10, 30, or 100 mg/m^3	0, 0.03, 0.1, or 0.3 mg/m^3
Type and Frequency of Observation Observed twice daily; rats and mice were weighed and clinical findings for mice were recorded initially, weekly, and at the end of the studies; clinical findings for rats were recorded at the end of week 1, weekly, and at the end of the study.	Observed twice daily; body weights for rats were recorded initially and clinical findings and body weights were then recorded every 4 weeks from week 4 through 92, except between weeks 44 and 52, and every 2 weeks thereafter; body weights for mice were recorded initially and clinical findings and body weights were then recorded every 4 weeks from week 5 through 93 and approximately every 2 weeks thereafter.

TABLE 2
Experimental Design and Materials and Methods in the Inhalation Studies of Indium Phosphide

14-Week Studies	2-Year Studies
Method of Sacrifice CO_2 asphyxiation	CO_2 asphyxiation
Necropsy Necropsy was performed on all core study animals. Organs weighed were the heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all core study animals. Organs weighed at 3 months were the heart, right kidney, liver, lung, right testis, and thymus.
Clinical Pathology Blood was collected from the retroorbital sinus of clinical pathology study rats on days 3 and 23 and core study rats surviving to the end of the study for hematology and clinical chemistry analyses. Blood was collected from all mice surviving to the end of the study for hematology analyses. Core study male rats were placed in metabolism cages for urine collection on day 31. ***Hematology:*** hematocrit; packed cell volume; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte counts and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, globulin, albumin/globulin ratio, alanine aminotransferase, creatine kinase, alkaline phosphatase, sorbitol dehydrogenase, bile acids ***Urinalysis:*** creatinine, glucose, protein, alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase, γ-glutamyl-transferase, *N*-acetyl-β-D-glucosaminidase, volume, specific gravity, pH	Blood was collected from the retroorbital sinus of animals designated for the 3-month interim evaluation for hematology and clinical chemistry analyses. ***Hematology:*** manual hematocrit; automated hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte counts and differentials ***Clinical chemistry:*** total iron binding capacity, unbound iron binding capacity, iron
Histopathology Complete histopathology was performed on core study 0 and 100 mg/m^3 rats and on 0, 30, and 100 mg/m^3 mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mediastinal, mesenteric, bronchial), mammary gland with adjacent skin, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin (rats only), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the adrenal gland, bone with marrow, heart, kidney, larynx, lung, lymph nodes (mediastinal, mesenteric, and bronchial), nose, ovary, prostate gland, spleen, testis with epididymis and seminal vesicle, thymus, trachea, and uterus from rats in all remaining exposure groups and the mandibular lymph node from core study rats in the 30 mg/m^3 group were examined. The adrenal gland, bone marrow, heart, larynx, lung, lymph nodes (mediastinal and bronchial), mammary gland (females only), nose, ovary, salivary gland, spleen, thymus, trachea, and uterus from mice in all remaining exposure groups were examined.	Complete histopathology was performed on 0 and 0.3 mg/m^3 core study rats and mice at 3 months and all core study rats and mice at the end of the studies. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mediastinal, mesenteric, bronchial), mammary gland (except male mice), 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. The larynx, lung, lymph nodes (mediastinal and bronchial), mammary gland, nose, and trachea of core study rats in the remaining exposure groups were examined at 3 months. The liver (females only), lymph nodes (mediastinal and bronchial), and spleen from core study mice in the remaining exposure groups were examined.

TABLE 2
Experimental Design and Materials and Methods in the Inhalation Studies of Indium Phosphide

14-Week Studies	2-Year Studies
Sperm Motility and Vaginal Cytology At the end of the studies, sperm samples were collected from male rats and mice in the 0, 3, 10, and 30 mg/m^3 groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for 12 consecutive days prior to the end of the studies from females exposed to 0, 3, 10, or 30 mg/m^3 for vaginal cytology evaluations. The percentage of time spent in the various estrous cycle stages and estrous cycle length were evaluated.	None
Tissue Burden Studies Lung, testis, blood, and serum from male rats in tissue burden study groups were evaluated at five time points. Tissues from up to three rats per group were collected on day 4, 24, 45, 73, or 96. ***Postexposure Lung Burden Study:*** Lung, testes, blood, and serum from male rats designated for postexposure tissue burden study and male rats from clinical pathology study groups were evaluated at four time points. Tissues from three to five rats per group were collected on postexposure day 14, 28, 56, or 112. ***Postexposure Lung Burden Study in Age-Matched Animals:*** Male rats, approximately 20 weeks old and designated for lung burden study in aged animals, were exposed to indium phosphide for five consecutive days, and lungs were evaluated at five time points after exposure termination. Lungs from three rats per exposure group were collected on day 5 and 14, 28, 56, or 112 days after exposure termination.	Lung and serum from two to five male rats and mice in tissue burden study groups were evaluated at 3, 5, 9, or 12 months or 2, 4, 6, 8, or 12 months after exposure termination. A complete necropsy, histopathologic examination of the lung, or lung burden and serum indium concentration evaluation were performed. Three or four male and female sentinel rats and mice from each group were sacrificed at 5 months for complete necropsy, histopathologic examination of the lung, and lung burden and serum indium concentration evaluation.

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were 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, B5, C1, C5, D1, and D5 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, B3, C3, and D3) 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, B3, C3, and D3 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. The trend was based only on those groups with equivalent exposure duration (i.e., the two higher exposure-concentrations, stop-exposure groups) and controls. 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). For neoplasms and nonneoplastic lesions detected at the interim evaluation, the Fisher exact test (Gart *et al.*, 1979), a procedure based on the overall proportion of affected animals, was used.

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. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, urinalysis, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). 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' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn'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). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

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 indium phosphide 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 four studies (indium phosphide, sodium nitrite, *p,p′*-dichlorophenyl sulfone, and naphthalene) reported at the May 18, 2000, peer review and in two others (methacrylonitrile and *p*-nitrotoluene) reported at the May 3, 2001 peer review. 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′*-dichlorophenyl 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) may be used to augment the smaller NTP-2000 database.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were 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 indium phosphide was assessed in a mouse peripheral blood micronucleus assay. The protocol for this study and the results are given in Appendix E.

Clearly positive responses in long-term peripheral blood micronucleus tests are associated with high predictivity for rodent carcinogenicity (Witt *et al.*, 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

RATS

14-WEEK STUDY

One male in the 100 mg/m^3 group died before the end of the study (Table 3). Final mean body weights and body weight gains of all exposed groups of males and of females in the 100 mg/m^3 group were significantly less than those of the chamber controls. Shallow, rapid, abnormal breathing was observed in males and females exposed to 30 or 100 mg/m^3. Animals in the 100 mg/m^3 groups exhibited lethargy, thinness, and ruffled fur.

In all exposed groups of male and female rats on day 23 and at week 14, there was evidence of an exposure concentration-related erythrocytosis, demonstrated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts (Tables 4 and F1). At week 14, the erythrocytosis was accompanied by increased reticulocyte and nucleated erythrocyte cell counts in the 100 mg/m^3 groups, which is consistent with increased erythropoietic activity. At week 14, the erythrocyte indices (mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration) demonstrated exposure concentration-related decreases

TABLE 3
Survival and Body Weights of Rats in the 14-Week Inhalation Study of Indium Phosphide

Concentration (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	128 ± 1	365 ± 6	238 ± 5	
1	10/10	124 ± 3	341 ± 7**	217 ± 6**	93
3	10/10	125 ± 3	320 ± 5**	195 ± 3**	88
10	10/10	121 ± 3	330 ± 4**	209 ± 3**	90
30	10/10	124 ± 2	324 ± 9**	200 ± 8**	89
100	9/10[c]	126 ± 2	176 ± 5**	50 ± 5**	48
Female					
0	10/10	106 ± 1	203 ± 3	97 ± 2	
1	10/10	107 ± 2	203 ± 3	96 ± 3	100
3	10/10	105 ± 1	195 ± 4	89 ± 4	96
10	10/10	109 ± 2	204 ± 3	95 ± 3	101
30	10/10	105 ± 2	194 ± 5	89 ± 4	95
100	10/10	106 ± 2	121 ± 3**	15 ± 3**	60

** Significantly different (P≤0.01) from the chamber control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 13

TABLE 4
Selected Hematology Data for Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male						
n						
Day	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Hematology						
Manual hematocrit (%)						
Day 3	47.2 ± 0.4	47.5 ± 0.4	47.4 ± 0.4	47.0 ± 0.4	47.5 ± 0.4	47.0 ± 0.4
Day 23	51.7 ± 0.3	53.2 ± 0.4	53.1 ± 0.6*	52.7 ± 0.3	53.5 ± 0.3**	53.0 ± 0.3
Week 14	47.0 ± 0.3	49.6 ± 0.2**	51.4 ± 0.4**	50.4 ± 0.3**	50.5 ± 0.5**	55.3 ± 1.6**
Automated hematocrit (%)						
Day 3	44.6 ± 0.3	45.1 ± 0.5	44.8 ± 0.4	44.4 ± 0.4	45.5 ± 0.5	45.0 ± 0.4
Day 23	49.5 ± 0.2	52.0 ± 0.4**	51.3 ± 0.5*	51.1 ± 0.2*	52.5 ± 0.4**	51.1 ± 0.2*
Week 14	45.4 ± 0.4	48.1 ± 0.3**	49.5 ± 0.4**	49.3 ± 0.5**	49.7 ± 0.7**	54.0 ± 1.7**
Hemoglobin (g/dL)						
Day 3	14.9 ± 0.1	15.3 ± 0.1	15.1 ± 0.2	14.9 ± 0.1	15.2 ± 0.1	15.0 ± 0.1
Day 23	16.7 ± 0.1	17.5 ± 0.1**	17.4 ± 0.1**	17.3 ± 0.1*	17.7 ± 0.2**	17.2 ± 0.1
Week 14	15.2 ± 0.2	16.3 ± 0.1**	17.0 ± 0.2**	16.6 ± 0.2**	16.5 ± 0.2**	16.6 ± 0.4**
Erythrocytes (10^6/µL)						
Day 3	7.06 ± 0.08	7.17 ± 0.10	7.17 ± 0.11	7.11 ± 0.08	7.25 ± 0.09	7.24 ± 0.10
Day 23	7.97 ± 0.05	8.41 ± 0.07**	8.27 ± 0.10**	8.25 ± 0.04**	8.48 ± 0.07**	8.29 ± 0.05**
Week 14	8.34 ± 0.09	8.83 ± 0.06**	9.25 ± 0.07**	9.37 ± 0.10**	9.75 ± 0.15**	10.52 ± 0.13**
Reticulocytes (10^6/µL)						
Day 3	0.35 ± 0.04	0.25 ± 0.02	0.26 ± 0.04	0.17 ± 0.02**	0.21 ± 0.02**	0.17 ± 0.03**
Day 23	0.13 ± 0.02	0.12 ± 0.02	0.12 ± 0.02	0.14 ± 0.02	0.13 ± 0.02	0.11 ± 0.01
Week 14	0.10 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.12 ± 0.02	0.44 ± 0.05**
Mean cell volume (fL)						
Day 3	63.1 ± 0.4	62.9 ± 0.3	62.6 ± 0.3	62.4 ± 0.4	62.8 ± 0.4	62.1 ± 0.3
Day 23	62.1 ± 0.3	61.9 ± 0.3	62.3 ± 0.3	62.0 ± 0.2	62.0 ± 0.3	61.7 ± 0.3
Week 14	54.3 ± 0.3	54.5 ± 0.2	53.6 ± 0.2	52.5 ± 0.2**	50.9 ± 0.2**	51.2 ± 1.0**
Mean cell hemoglobin (pg)						
Day 3	21.1 ± 0.1	21.3 ± 0.1	21.0 ± 0.2	21.0 ± 0.1	20.9 ± 0.2	20.8 ± 0.2
Day 23	21.0 ± 0.1	20.8 ± 0.1	21.0 ± 0.1	20.9 ± 0.1	20.8 ± 0.1	20.8 ± 0.2
Week 14	18.3 ± 0.1	18.5 ± 0.1	18.3 ± 0.1	17.7 ± 0.1**	16.9 ± 0.1**	15.8 ± 0.2**
Mean cell hemoglobin concentration (g/dL)						
Day 3	33.4 ± 0.2	33.9 ± 0.1	33.6 ± 0.2	33.6 ± 0.2	33.3 ± 0.2	33.4 ± 0.3
Day 23	33.8 ± 0.1	33.6 ± 0.2	33.9 ± 0.1	33.7 ± 0.1	33.6 ± 0.1	33.7 ± 0.1
Week 14	33.6 ± 0.2	34.0 ± 0.2	34.2 ± 0.2	33.6 ± 0.1	33.1 ± 0.2	30.8 ± 0.3**

TABLE 4
Selected Hematology Data for Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Female						
n	10	10	10	10	10	10
Hematology						
Manual hematocrit (%)						
Day 3	50.5 ± 0.6	48.9 ± 0.5	48.7 ± 0.6	48.6 ± 0.5	49.2 ± 0.7	49.3 ± 0.5
Day 23	50.6 ± 0.7	52.0 ± 0.2*	51.6 ± 0.3	51.9 ± 0.4	52.6 ± 0.4**	53.2 ± 0.3**
Week 14	46.0 ± 0.4	48.5 ± 0.4**	49.4 ± 0.5**	50.6 ± 0.5**	50.4 ± 0.4**	48.4 ± 1.4**
Automated hematocrit (%)						
Day 3	48.7 ± 0.7	46.7 ± 0.4	46.5 ± 0.7	46.2 ± 0.5*	47.3 ± 0.6	47.4 ± 0.5
Day 23	50.4 ± 0.5	52.1 ± 0.4**	52.0 ± 0.4*	51.8 ± 0.4*	52.8 ± 0.4**	53.2 ± 0.3**
Week 14	45.0 ± 0.3	47.3 ± 0.5**	48.0 ± 0.3**	49.7 ± 0.3**	49.3 ± 0.3**	48.4 ± 1.3**
Hemoglobin (g/dL)						
Day 3	16.2 ± 0.2	15.9 ± 0.1	15.7 ± 0.2	15.6 ± 0.2	16.0 ± 0.2	16.1 ± 0.2
Day 23	17.1 ± 0.2	17.7 ± 0.1*	17.8 ± 0.2*	17.7 ± 0.1*	18.0 ± 0.1**	18.1 ± 0.1**
Week 14	15.6 ± 0.1	16.5 ± 0.1	16.6 ± 0.2*	17.2 ± 0.1**	16.9 ± 0.1**	15.3 ± 0.3
Erythrocytes (10^6/µL)						
Day 3	7.84 ± 0.13	7.56 ± 0.08	7.65 ± 0.13	7.45 ± 0.13	7.69 ± 0.09	7.79 ± 0.10
Day 23	8.14 ± 0.09	8.34 ± 0.06	8.33 ± 0.06	8.33 ± 0.10	8.56 ± 0.09**	8.53 ± 0.08**
Week 14	7.77 ± 0.07	8.08 ± 0.08*	8.27 ± 0.06**	8.69 ± 0.06**	8.71 ± 0.07**	10.26 ± 0.19**
Reticulocytes (10^6/µL)						
Day 3	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.11 ± 0.01	0.09 ± 0.01
Day 23	0.07 ± 0.01	0.09 ± 0.02	0.11 ± 0.02	0.08 ± 0.01	0.06 ± 0.00	0.07 ± 0.01
Week 14	0.08 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.08 ± 0.01	0.10 ± 0.01	0.36 ± 0.09**
Mean cell volume (fL)						
Day 3	62.1 ± 0.3	61.6 ± 0.2	60.9 ± 0.3*	61.9 ± 0.5	61.5 ± 0.3	60.9 ± 0.3*
Day 23	61.8 ± 0.4	62.5 ± 0.3	62.5 ± 0.3	62.2 ± 0.4	61.8 ± 0.3	62.4 ± 0.3
Week 14	58.1 ± 0.2	58.5 ± 0.2	57.9 ± 0.2	57.1 ± 0.2**	56.6 ± 0.4**	47.2 ± 0.7**
Mean cell hemoglobin (pg)						
Day 3	20.7 ± 0.1	21.0 ± 0.1	20.6 ± 0.1	21.0 ± 0.2	20.8 ± 0.2	20.7 ± 0.1
Day 23	21.1 ± 0.1	21.2 ± 0.1	21.4 ± 0.1	21.3 ± 0.2	21.0 ± 0.1	21.1 ± 0.1
Week 14	20.1 ± 0.1	20.3 ± 0.1	20.1 ± 0.1	19.8 ± 0.1	19.4 ± 0.2**	14.9 ± 0.2**
Mean cell hemoglobin concentration (g/dL)						
Day 3	33.3 ± 0.2	34.0 ± 0.2	33.8 ± 0.2	33.8 ± 0.2	33.7 ± 0.2	34.0 ± 0.2
Day 23	33.9 ± 0.1	33.9 ± 0.1	34.2 ± 0.2	34.2 ± 0.1	34.0 ± 0.2	33.9 ± 0.1
Week 14	34.7 ± 0.2	34.8 ± 0.2	34.6 ± 0.1	34.6 ± 0.2	34.3 ± 0.2	31.7 ± 0.2**

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

in the 10 mg/m^3 or greater female and/or male groups suggesting that for the high-exposure animals, the circulating erythrocytes were smaller and contained less hemoglobin than would be expected.

On days 3 and 23, there was evidence of a transient, exposure-related decrease in the leukocyte count (Table F1). By day 23, this effect occurred in all exposed groups of males and in 30 and 100 mg/m^3 females. The decreased leukocyte counts appeared to be related to the decreased lymphocyte counts. This alteration in lymphocyte counts suggests a transient physiological response and would be consistent with a stress-related/corticosteroid-induced lymphopenia. Rats are considered a steroid-sensitive species and corticosteroid-induced lymphopenia may be related to lympholysis in blood and altered distribution (Jain, 1986). In contrast, at week 14, leukocyte counts were increased in 10 mg/m^3 males and 30 and 100 mg/m^3 males and females. The increased leukocyte counts appeared to be related to an alteration in neutrophil numbers. Neutrophil counts demonstrated exposure-related increases in all exposed groups of males and females and may, in part, be attributed to the pulmonary inflammation observed microscopically.

Platelet counts demonstrated decreases in various higher exposure groups (Table F1). Because of the minimal to mild severity and the lack of an exposure-concentration relationship, alterations in platelet counts were not considered clinically or toxicologically relevant.

The serum and urine chemistry data for rats in the 14-week study of indium phosphide are listed in Table F1. On day 23 and at week 14, there was evidence of a hepatocellular effect demonstrated by increases in serum alanine aminotransferase and sorbitol dehydrogenase activities. By week 14, increased alanine aminotransferase and sorbitol dehydrogenase activities occurred in 10 mg/m^3 or greater females and in all groups of exposed males, which is consistent with the hepatocellular necrosis observed microscopically. Also at week 14, decreased total protein, albumin, and creatinine, and increased urea nitrogen concentrations occurred in 100 mg/m^3 males and females, which is consistent with the decreased weight gain in these exposed groups and possibly reflects a compromised nutritional status.

Lung weights of all exposed groups of males and females were significantly greater than those of the chamber controls and generally increased with increasing exposure concentration (Tables 5 and G1). The 2.7- to 4.4-fold increases in the absolute lung weights were attributed primarily to the accumulation of proteinaceous fluid (alveolar proteinosis) within the alveoli.

Relative heart weights were significantly increased in 30 and 100 mg/m^3 males and females, and absolute heart weights were increased in 10 mg/m^3 or greater females. The increased heart weights were likely a combination of disproportionately lower body weights and physiological hypertrophy due to possible compromised pulmonary function (cor pulmonale secondary to hypertension caused by the lung lesions).

Thymus weights were decreased in 100 mg/m^3 males and females compared to those of the chamber controls; these decreases were considered to be related to the debilitated state of the animals. Alterations in other organ weights were attributed primarily to the significant body weight decreases.

Gross exposure-related lesions were observed in the lungs and generally increased in severity with increasing exposure concentration. Lungs of all exposed rats were enlarged and had a gray to black discoloration and a granular to dimpled appearance.

TABLE 5
Lung Weights and Lung-Weight-to-Body-Weight Ratios for Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male						
n	10	10	10	10	10	9
Necropsy body wt	365 ± 6	341 ± 7**	322 ± 5**	331 ± 4**	325 ± 9**	172 ± 6**
Lung						
Absolute	1.969 ± 0.130	5.326 ± 0.145**	6.451 ± 0.169**	6.341 ± 0.113**	7.159 ± 0.190**	5.080 ± 0.162**
Relative	0.540 ± 0.034	1.563 ± 0.023**	2.001 ± 0.045**	1.914 ± 0.023**	2.205 ± 0.041**	2.957 ± 0.039**
Female						
n	10	10	10	10	10	10
Necropsy body wt	206 ± 3	205 ± 3	199 ± 4	206 ± 3	196 ± 5	117 ± 3**
Lung						
Absolute	1.220 ± 0.051	3.441 ± 0.104**	3.876 ± 0.089**	4.621 ± 0.099**	5.303 ± 0.200**	3.899 ± 0.123**
Relative	0.590 ± 0.019	1.678 ± 0.047**	1.953 ± 0.052**	2.246 ± 0.063**	2.709 ± 0.080**	3.334 ± 0.063**

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' or Dunnett's test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

The discoloration, which was attributed to the presence of indium phosphide particles, was diagnosed microscopically as foreign body and characterized by blackish granules less than 1 µm in diameter (Table 6). The granules were located within epithelial and inflammatory cells and free within the lung parenchyma and alveoli (Plate 2). Marked alveolar proteinosis was present in all exposed animals and likely contributed to the increased lung weights. Alveolar proteinosis was a diffuse change characterized by alveoli often partially filled with a pale, eosinophilic, proteinaceous fluid (Plates 1 and 2).

Chronic active inflammation of the lung occurred in all exposed animals (Plates 1 and 2). The inflammation was multifocal to diffuse and was composed of mixed inflammatory cells (lymphocytes, macrophages, and fewer neutrophils) within the alveoli and interstitium. Within areas of inflammation, there was regenerative alveolar epithelial hyperplasia; the severity generally increased with increasing exposure concentration in males. The hyperplasia was multifocal and was composed of well-differentiated cuboidal epithelial cells (type II) (Plate 2). Interstitial fibrosis occurred in almost all males and in all females exposed to 3 mg/m^3 or greater, and the severities generally increased with increasing exposure concentration (Plate 2). This change varied from barely detectable strands of collagen to an increased prominence of fibroblasts and dense bands of collagen thickening the interstitium.

In the nose, larynx, and trachea of exposed males and females, minimal to mild accumulation of foreign bodies (indium phosphide particles) occurred in the mucosal epithelial cells or the underlying substantia propria, either free or within macrophages (Table 6). Additionally, within the base of the epiglottis of male and female rats in the 3, 10, or 30 mg/m^3 groups, there were minimally severe collections of mononuclear cells (inflammation) associated with the particles.

TABLE 6
Incidences of Selected Nonneoplastic Lesions of the Respiratory System and Associated Lymph Nodes in Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male						
Lung[a]	10	10	10	10	10	10
Foreign Body[b]	0	10** (1.0)[c]	10** (1.5)	10** (2.0)	10** (2.0)	10** (3.0)
Alveolus, Proteinosis	0	10** (3.6)	10** (3.9)	10** (3.9)	10** (4.0)	10** (4.0)
Chronic Active Inflammation	0	10** (2.0)	10** (2.6)	10** (3.0)	10** (3.0)	10** (2.9)
Alveolar Epithelium, Hyperplasia	0	10** (2.0)	10** (2.6)	10** (3.0)	10** (3.1)	10** (3.6)
Interstitium, Fibrosis	0	0	10** (1.2)	10** (2.0)	9** (2.0)	10** (3.0)
Nose	10	10	10	10	10	10
Foreign Body	0	1 (1.0)	1 (1.0)	8** (1.0)	8** (1.0)	10** (1.0)
Larynx	10	10	10	10	10	10
Foreign Body	0	10** (1.1)	10** (1.6)	10** (1.7)	10** (2.0)	9** (1.3)
Chronic Inflammation	0	0	5* (1.4)	8** (1.4)	9** (1.3)	0
Trachea	10	10	10	10	10	10
Foreign Body	0	0	1 (1.0)	2 (1.0)	5* (1.0)	8** (1.0)
Lymph Node, Bronchial	9	10	8	10	10	9
Hyperplasia	0	5* (1.2)	4* (2.0)	3 (2.0)	6** (2.0)	3 (2.3)
Pigmentation	0	9** (1.2)	8** (1.4)	10** (1.3)	10** (1.8)	9** (2.9)
Lymph Node, Mediastinal	9	5	8	10	8	10
Hyperplasia	0	3* (2.0)	7** (2.0)	8** (2.0)	6** (2.0)	8** (2.4)
Pigmentation	0	4** (1.0)	8** (1.4)	9** (1.8)	7** (2.0)	9** (3.2)

TABLE 6
Incidences of Selected Nonneoplastic Lesions of the Respiratory System and Associated Lymph Nodes in Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Female						
Lung	10	10	10	10	10	10
Foreign Body	0	9** (1.0)	10** (2.0)	10** (2.1)	10** (2.9)	10** (3.0)
Alveolus, Proteinosis	0	10** (3.8)	10** (4.0)	10** (4.0)	10** (4.0)	10** (4.0)
Chronic Active Inflammation	0	10** (2.0)	10** (2.4)	10** (2.4)	10** (2.3)	10** (3.0)
Alveolar Epithelium, Hyperplasia	0	10** (2.0)	10** (2.4)	10** (2.3)	10** (2.3)	10** (3.3)
Interstitium, Fibrosis	0	0	10** (1.3)	10** (2.0)	10** (1.8)	10** (3.3)
Nose	10	10	10	10	10	10
Foreign Body	0	3 (1.0)	2 (1.0)	7** (1.0)	9** (1.0)	10** (1.0)
Larynx	10	10	10	10	10	10
Foreign Body	0	10** (1.3)	10** (1.5)	10** (1.6)	9** (1.7)	9** (1.0)
Chronic Inflammation	0	2 (1.0)	6** (1.3)	9** (1.2)	9** (1.3)	0
Trachea	10	10	10	10	10	10
Foreign Body	0	0	0	3 (1.0)	7** (1.0)	7** (1.0)
Lymph Node, Bronchial	7	9	10	10	10	9
Hyperplasia	0	7** (2.0)	7** (1.9)	9** (1.6)	10** (2.2)	5* (1.2)
Pigmentation	0	8** (1.1)	10** (1.8)	9** (1.8)	10** (2.1)	9** (2.8)
Lymph Node, Mediastinal	7	9	8	5	9	8
Hyperplasia	0	8** (2.0)	8** (2.0)	4* (2.3)	5* (2.2)	7** (2.4)
Pigmentation	0	8** (1.3)	8** (1.8)	5** (1.8)	7** (1.7)	8** (3.0)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Most of the bronchial and mediastinal lymph nodes examined from exposed males and females were enlarged and contained increased numbers of lymphocytes and larger immature mononuclear cells. Differences in severities of hyperplasia among exposed groups were marginal (Table 6). Hyperplasia is typical in regional lymph nodes draining areas of foreign material deposition and/or inflammation. Pigmentation (indium phosphide particles) also occurred in the lymph node macrophages of most exposed animals; the quantities (indicated by severity) generally increased with increasing exposure concentration.

Incidences of moderately severe hyperplasia of the bone marrow (males: 0/10, 0/10, 0/10, 0/10, 0/10, 10/10; females: 0/10, 0/10, 0/10, 0/10, 3/10, 10/10) and mild hematopoietic cell proliferation of the spleen (males: 0/10, 0/10, 0/10, 0/10, 0/10, 10/10; females: 0/10, 0/10, 0/10, 0/10, 0/10, 9/10) were significantly increased in males and females exposed to 100 mg/m^3, and likely represented an erythropoietic response secondary to tissue hypoxia and/or a response to pulmonary inflammation.

The incidence of renal nephropathy was significantly increased in 100 mg/m^3 females (1/10, 0/10, 0/10, 1/10, 1/10, 10/10). Minimal nephropathy occurred in chamber control and 1, 3, 10, and 30 mg/m^3 rats, but the severity was moderate in 100 mg/m^3 males and mild in 100 mg/m^3 females. Progressive degenerative

nephropathy occurs spontaneously in F344/N rats, is generally more severe in males, and is often exacerbated by chemical exposure. Microscopic evidence of nephropathy may be seen in males in toxicity studies and includes renal tubule degeneration and regeneration, basement membrane thickening, tubular protein casts, glomerular alterations, and inflammatory infiltrates. Chemicals may have very specific effects within the kidney that are masked by the generalized spontaneous nephropathy. In addition to the exacerbation of nephropathy, some unique glomerular changes were observed in rats in this study. Glomerular capillary tufts were often reduced in size and usually contained variable numbers of large cells with oval nuclei and abundant, poorly stained cytoplasm.

The incidences of centrilobular atrophy and centrilobular necrosis of the liver were significantly increased in male and female rats exposed to 100 mg/m^3 (Table 7). The incidence of hemosiderin pigmentation was increased in females exposed to 100 mg/m^3. Hepatocytes affected by centrilobular atrophy appeared to be small and vacuolated compared to unaffected hepatocytes and were arranged in disorganized cords. Scattered individual necrotic hepatocytes occurred within or adjacent to atrophic areas. It could not be determined if the centrilobular atrophy and necrosis were primary toxic affects or were secondary to hypoxia resulting from the severe lung lesions. The incidence of hepatodiaphragmatic nodules was marginally increased in female rats exposed to 100 mg/m^3. This lesion is a developmental anomaly involving both the diaphragm and the liver. It is formed by a thin fibrous central tendon of the diaphragm into which the liver protrudes and attaches. The reason for the increased incidence of this lesion in females in this study was not determined, but the occurrence was not considered biologically significant.

There were increased incidences of hypertrophy of the heart (males: chamber control, 0/10; 1 mg/m^3, 0/10; 3 mg/m^3, 0/10; 10 mg/m^3, 0/10; 30 mg/m^3, 0/10; 100 mg/m^3, 8/10; females: 0/10, 0/10, 0/10, 0/10, 0/10, 10/10) in male and female rats exposed to 100 mg/m^3. Microscopically, hypertrophy was characterized by minimal increases in the size of cardiomyocytes and an apparently increased myofiber branching and separation. This change is consistent with the increased heart weights of 100 mg/m^3 animals. To lesser degree, heart weight increases also occurred in lower exposure groups, but routine light microscopic examination was not sufficient for detection of such subtle changes.

The incidences of a variety of lesions were significantly increased only in 100 mg/m^3 rats and were considered secondary to debilitation. Cytoplasmic vacuolization of the adrenal cortex zona fasciculata occurred in all males and 4 of 10 females. Thymic atrophy occurred in 8 of 10 males and 9 of 10 females and was characterized by decreased organ size due to fewer lymphocytes. Atrophy was observed in the mandibular lymph nodes of 6 of 10 males and 5 of 9 females examined. Ovarian and uterine atrophy occurred in all females. The ovaries were small with small follicles and corpora lutea and condensed stroma. Uterine horn diameters were decreased, and there were shrunken glands and stromal condensation. Large degenerating cells (degeneration) of testicular germinal epithelial origin were present within seminiferous tubules of the testes of 5 of 10 males and within the epididymi of all males. The glandular epithelium was flattened and there was reduced secretory material (atrophy) within the prostate of all males and seminal vesicles of 9 of 10 males.

No significant differences were noted in sperm morphology or vaginal cytology parameters between exposed and chamber control rats that could be attributed to a direct effect of indium phosphide exposure (Table I1 and I2).

Tissue Burden Analyses

Tissue burden analyses were performed on male rats in the 14-week study and age-matched male rats exposed with the 14-week study animals for the last five days of the 14-week study. These studies included analyses of tissues taken from animals at several timepoints during the 14-week exposure period, during the 16 weeks following the end of the 14-week exposure period, and during the 16 weeks following the end of the 5-day exposure period.

Compared to chamber control animals, lung weights of exposed male rats increased throughout the 14-week exposure period and generally continued to increase throughout the 16-week recovery period (Table H1). The exception was animals in the 1 mg/m^3 group, whose lung weights remained relatively unchanged

TABLE 7
Incidences of Nonneoplastic Lesions of the Liver in Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male						
Number Examined Microscopically	10	1	1	1	0	10
Hepatocyte, Centrilobular, Atrophy[a]	0	0	0	0	0	6** (1.3)[b]
Hepatocyte, Centrilobular, Necrosis	0	0	0	0	0	5* (1.0)
Hemosiderin, Pigmentation	0	0	0	0	0	2 (1.0)
Female						
Number Examined Microscopically	10	1	2	1	2	10
Hepatocyte, Centrilobular, Atrophy	0	0	0	0	0	8** (1.8)
Hepatocyte, Centrilobular, Necrosis	0	0	0	0	0	9** (1.3)
Hemosiderin, Pigmentation	0	0	0	0	0	6** (1.3)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

throughout the 16-week recovery period. Although there was an apparent trend of increased lung weights with increasing exposure concentration, lung weights of rats exposed to 3, 10, or 30 mg/m^3 were generally similar throughout the exposure and recovery periods. Although lung weights of rats exposed to 100 mg/m^3 were greater than those of other exposed groups on day 4, they were similar to the lower exposure concentration groups during the study, and in fact they were lower than the other exposed groups towards the end of the 14 weeks of exposure. This was likely due to the overt toxicity of this exposure concentration which resulted in considerable body weight loss and subsequent mortality in most of the animals in this group in the 2 weeks following the end of the 14-week exposure period.

Lung weights of age-matched male rats exposed for 5 days increased with increasing exposure concentration and continued to increase far more than did chamber control animal lung weights throughout the 16-week recovery period (Table H2). At the end of the recovery period, lung weights were significantly increased; however, the lung weights of the age-matched rats were considerably less than those of rats exposed continuously for 14 weeks.

Lung burdens of indium increased with increasing exposure concentration and each increased throughout the 14 weeks of exposure, indicating that steady-state lung burdens for indium were not achieved (Figure 1, Table H1). Lung burdens during the 14 weeks of exposure and during the subsequent 16-week recovery period were normalized to exposure concentration to assess their proportionality to exposure concentration. These data indicated that throughout the 14-week exposure period and the subsequent recovery period, lung burdens were disproportionately low for the 30 and 100 mg/m^3 groups when compared to the 10 mg/m^3 or lower groups (Figure 2 and Table H1). Calculated lung clearance half-times during the 14-week exposure period were not substantially different between exposed groups (Table H3). Although lung deposition rates increased with increasing exposure concentration, lung deposition rates normalized to exposure concentrations decreased with increasing exposure concentration. Thus at the higher exposure concentration, the amount of indium deposited per unit exposure concentration was less than at lower concentrations. One possible explanation for the altered deposition rates could be that particle sizes were different across exposure groups with the high concentration group having the larger particles.

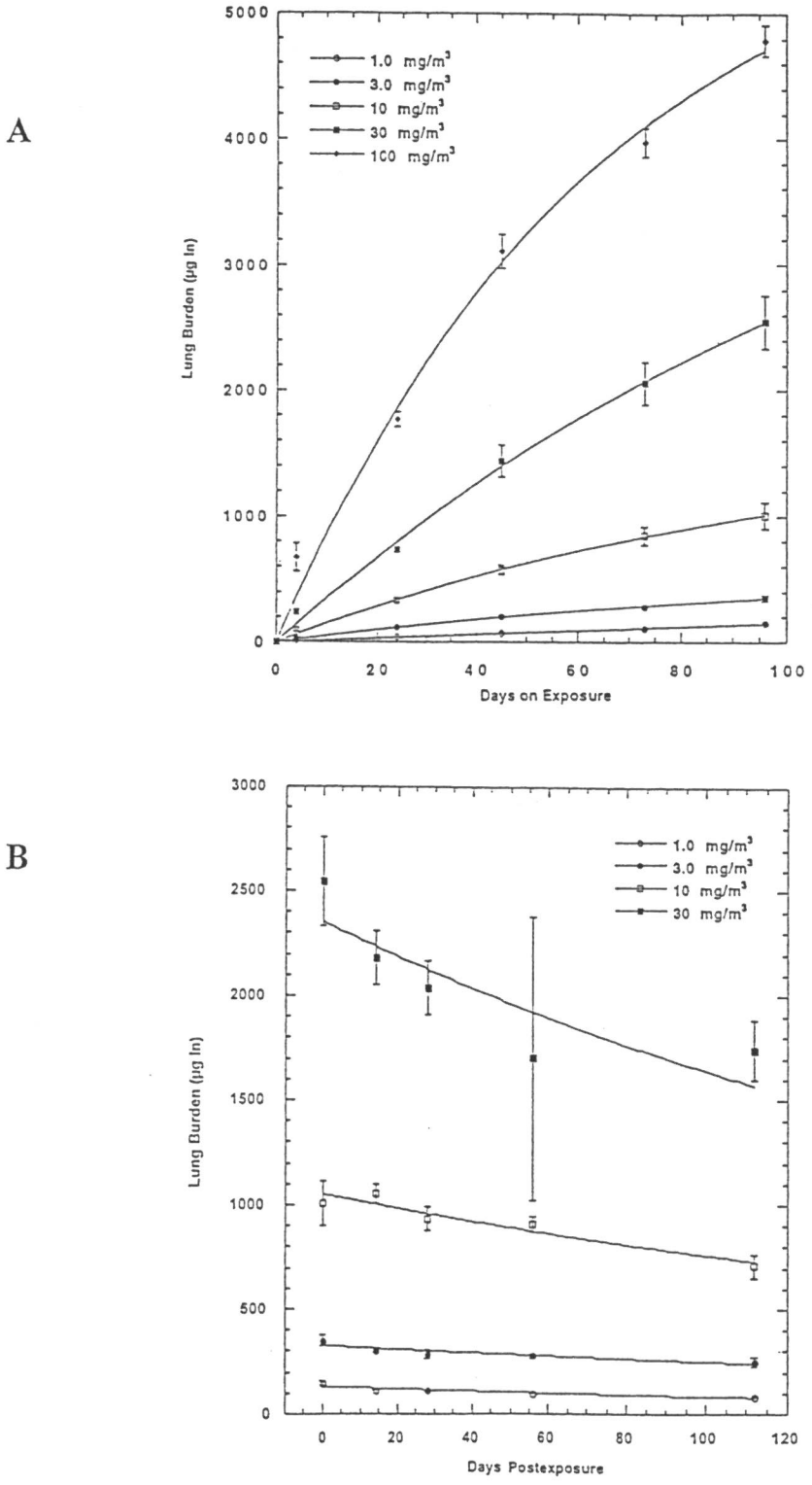


Figure 1
Lung Burden of Indium in Rats During 14 Weeks Exposure (A) or During the 16 Weeks Following Exposure (B) to Indium Phosphide.
Data are presented as mean ± standard deviation. Curves represent the fit of the lung deposition and clearance model to the data.

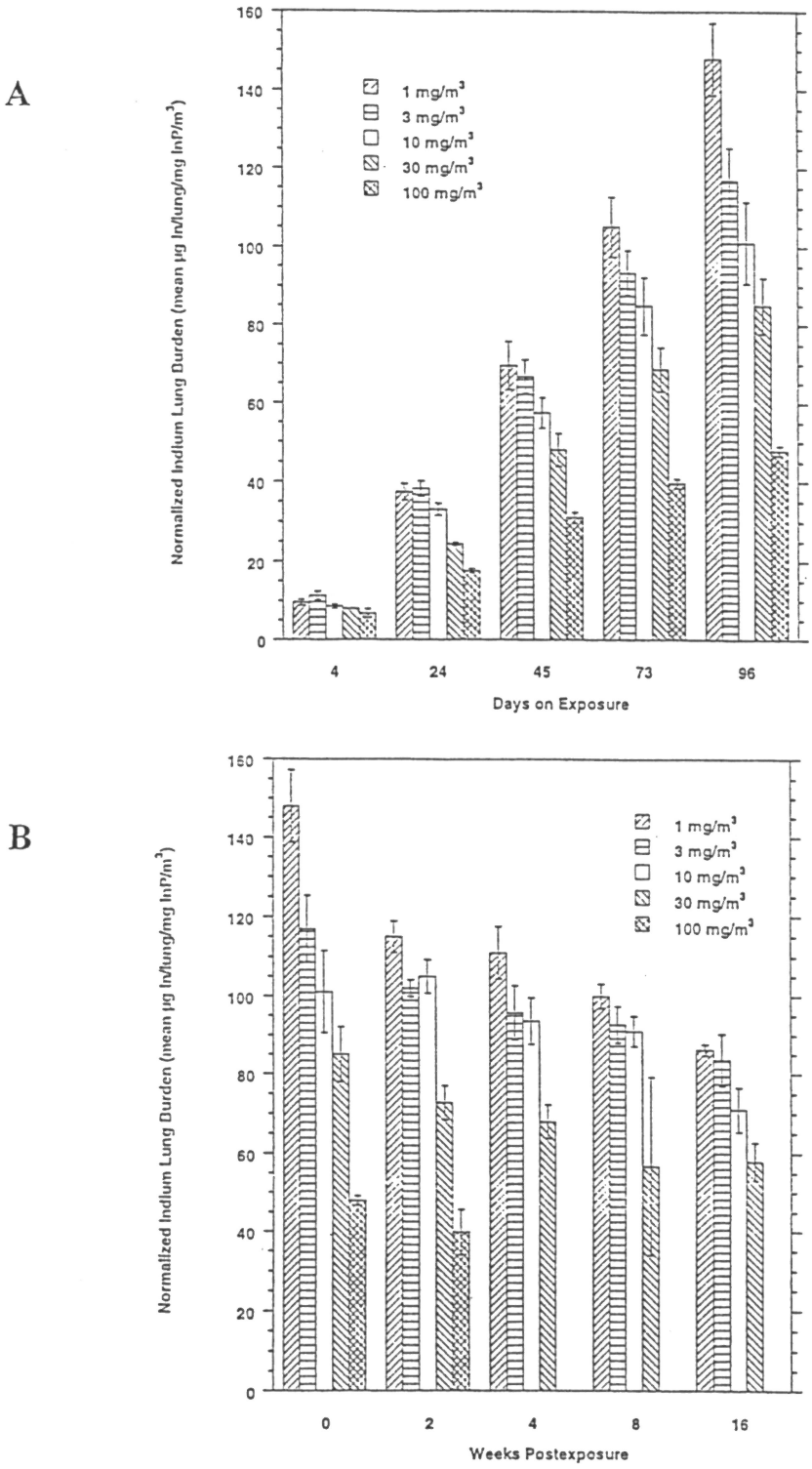


Figure 2
Normalized Lung Burden of Indium in Rats During 14 Weeks of Exposure (A) or During the 16 Weeks Following Exposure (B) to Indium Phosphide. Data are presented as mean ± standard deviation.

However, this was not the case since particle sizes were quite similar throughout all exposure groups (Table J3). A more plausible explanation is that the nonlinearity is due to an alteration in pulmonary function (possibly reduced minute ventilation) caused by inflammatory and proliferative lesions in the lung. Lung burdens also decreased for postexposure animals with time. The calculated lung clearance rate constants or half-times determined during the 16-week recovery period were not different for the 1, 3, 10, or 30 mg/m^3 groups (Table H4).

Overall mean clearance half-time was longer when calculated from the postexposure data (202 ± 44 days) than when calculated from the 14-week exposure data (78 ± 24 days). Possible reasons for these differences could be the fact that the model assumes continuous exposure and continuous clearance with a constant deposition rate. Exposures were not continuous and as the data indicate, the deposition rate was not constant across all exposed groups. In addition, clearance rates estimated from a pure clearance process, as calculated from the postexposure data, are much less subject to the uncertainties associated with variable deposition rates inherent in the data collected during the exposure period.

The normalized lung burdens of age-matched rats in the 5-day study indicated that the lung burdens were directly proportional to exposure concentration except for the 30 and 100 mg/m^3 groups at the initial time point and for the 100 mg/m^3 group at 16 weeks post-exposure (Figure 3 and Table H2). This behavior was similar to that observed following the 14-week study except the subproportionality of lung burdens was more evident at 30 and 100 mg/m^3 throughout the 14-week postexposure period. Normalized deposition rates (data not shown) calculated for the 5-day exposure were not different between exposure groups nor were they different from those calculated from lung burdens determined at 4 days of exposure during the 14-week study. Therefore, lung deposition did not vary as a consequence of age. However, the normalized deposition rates from the 5-day exposure were approximately two fold higher than those calculated from the 14-week study data, suggesting that prolonged exposure to indium phosphide may have caused decreases in deposition rates. The overall mean lung clearance half-times after the 5-day exposure averaged 146 ± 68 days, midway between the clearance half-times measured during the 14-week exposure and 16-week post-exposure periods, and were not different from either (Table H5).

Indium was detected in blood and serum at concentrations several orders of magnitude less than that observed in lung tissue (Tables H1, H6, and H7). Although blood and serum indium concentrations increased with increasing exposure concentration throughout the 14 weeks of exposure, they appeared to be near steady-state throughout the 16-week recovery period. This is most likely due to the continued clearance of indium phosphide from the lungs (Figure 1B and Table H1). Indium was detected in the testis at much higher concentrations than in blood or serum, although still several orders of magnitude less than that in the lung (Table H8). Similarly, testicular indium concentration increased with increasing exposure concentration and throughout the exposure period. Unlike blood and serum indium concentrations, testicular indium continued to increase in all groups following exposure, indicating that indium was accumulating in the testis over time.

Exposure Concentration Selection Rationale: Based on the increased lung weights and the increased incidences and severities of lung lesions in all exposed groups of rats, exposures to concentrations of 1 mg/m^3 and greater were considered too high for use in a 2-year study. To aid in selection of the 2-year exposure concentrations, the lung deposition and clearance model using estimated deposition and clearance rates for the 1 mg/m^3 group from the 5-day study was used to estimate steady-state lung burdens for 0.01, 0.1, and 0.5 mg/m^3, which are 8, 80, and 399 µg indium, respectively. The 399 µg indium, although less than the estimated steady-state lung burden of 617 µg for rats exposed to 3 mg/m^3 in the 14-week study, was considered to be too high, especially because steady-state lung burdens for 1 mg/m^3 could not be calculated from the 14-week data. Therefore, 0.3 mg/m^3 was selected as the highest exposure concentration. For the middle concentration, 0.1 mg/m^3 was selected because the estimated steady-state lung burden for 0.1 mg/m^3 was considerably less than that observed in the 14-week study. The lowest exposure concentration of 0.03 mg/m^3 was set near the lowest concentration that the chamber particle monitor could measure continuously with accuracy.

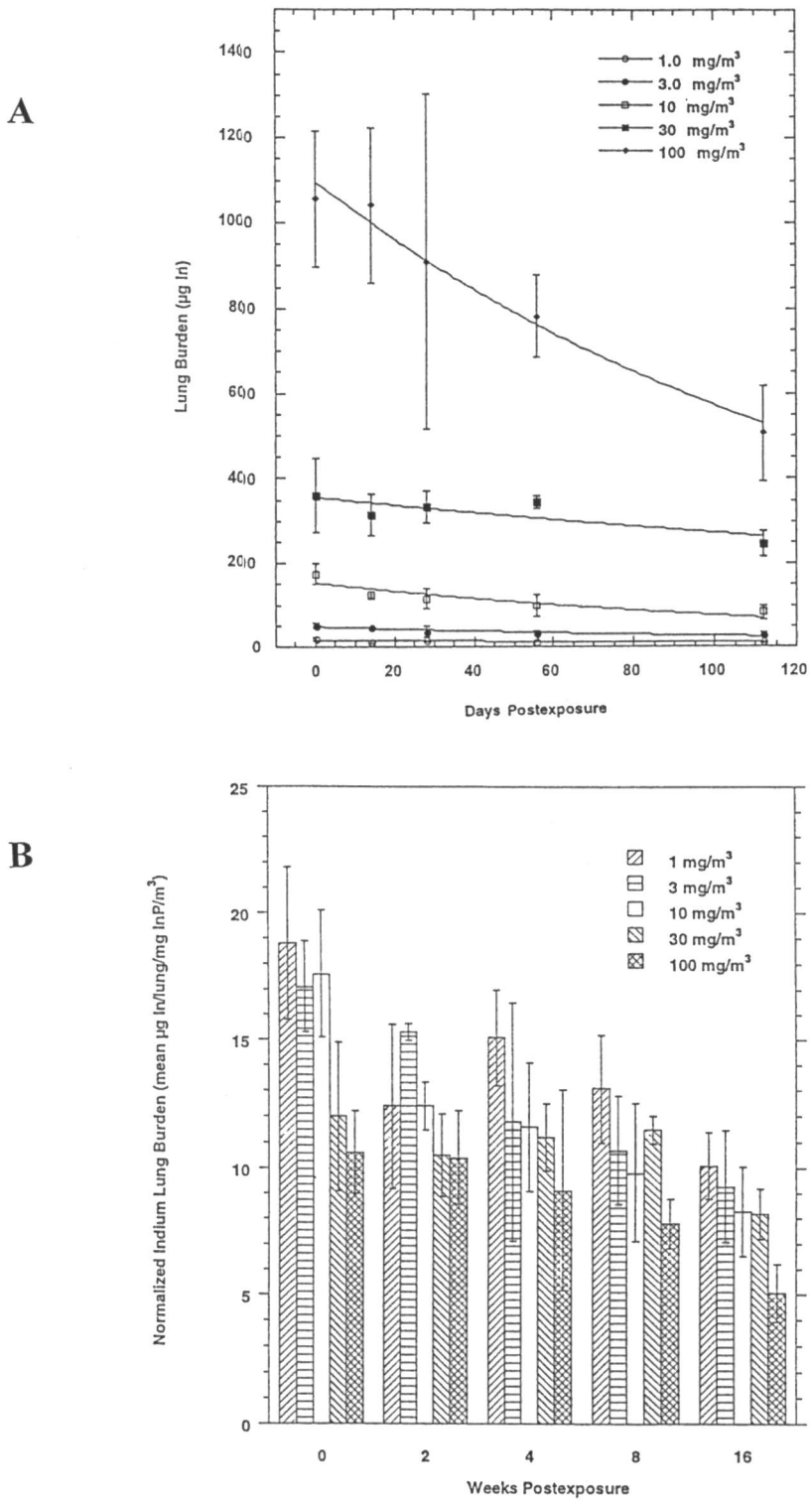


Figure 3

Lung Burden (µg In) (A) and Normalized Lung Burden (µg In/Lung per mg InP/m^3) (B) of Indium in Age-Matched Male Rats Following 5 days of Exposure to Indium Phosphide.

Data are presented as mean ± standard deviation. Curves represent the fit of the lung deposition and clearance model to the data.

3-MONTH INTERIM EVALUATION IN THE 2-YEAR STUDY

Similar to the 14-week study, at the 3-month interim evaluation, all groups of exposed male and female rats demonstrated an exposure concentration-related increased erythron evidenced by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts (Table F2). Unlike the 14-week study, the erythron alterations were not associated with changes in reticulocyte counts or the erythrocyte indices probably because lower exposure concentrations were used in the 2-year study. There was a slight increase in serum iron concentrations in 0.1 and 0.3 mg/m^3 males; there were no changes in iron-binding capacity. No alterations in iron concentration occurred in exposed females.

At 3 months, lung weights of males exposed to 0.1 or 0.3 mg/m^3 and of all groups of exposed females were significantly greater (1.2- to 2.1-fold) than those of the chamber controls (Tables 8 and G2). Significantly increased incidences of chronic inflammation, foreign body (indium phosphide particles), and alveolar proteinosis occurred in most exposed males and females at 3 months (Tables 8, A5, and B5). The severities of these lesions generally increased with increasing exposure concentration. These lesions were qualitatively similar to those observed in the 14-week study, but were generally less severe because of the lower exposure concentrations, although different criteria for severity grades were used between the two studies. Alveolar proteinosis was diffuse in all exposed groups in the 14-week study and in the 0.3 mg/m^3 groups at 3 months but it was scattered and usually in areas of inflammation in the 0.03 and 0.1 mg/m^3 animals at 3 months. Similarly, in lower exposure groups, the chronic inflammation tended to involve less pulmonary tissue and was frequently localized to the subpleural regions of the lung. Though present, indium phosphide particles were difficult to find in rats exposed to 0.03 mg/m^3. At 3 months, there were increased incidences and severities of hyperplasia of the alveolar epithelium in all groups of exposed males and in 0.03 and 0.3 mg/m^3 females. This was similar to the hyperplasia observed in the 14-week study and was considered a reparative response.

Because of the small size of the lymph nodes, sampling was somewhat inconsistent. However, the amounts of foreign body in the bronchial and mediastinal lymph nodes of exposed males and females generally increased with increasing exposure concentration (Tables 8, A5, and B5). At 3 months, the incidences of bronchial lymph node hyperplasia were significantly increased in 0.3 mg/m^3 males and in 0.1 mg/m^3 females, and the incidences of mediastinal lymph node hyperplasia were significantly increased in 0.1 males and 0.3 mg/m^3 males and females.

Stop-Exposure Rationale: Because all exposure concentrations selected for the 2-year studies were less than those used in the 14-week studies, a 3-month interim evaluation was added to the 2-year studies to determine the suitability of exposure concentrations for continuous 2-year exposure. When compared to chamber controls, exposure of rats to 0.1 or 0.3 mg/m^3 caused a 1.6- to 2.1-fold increase in lung weights accompanied by a spectrum of proliferative and inflammatory lesions in the lungs. However, lung weights of rats exposed to 0.03 mg/m^3 were marginally increased (22%) and the lung lesions were considered minimal. Because of the magnitude of the lung weight increases and the severity of the lung lesions in rats exposed to 0.1 or 0.3 mg/m^3, it was determined that these effects were sufficiently extensive to stop exposure of these groups. Exposure was stopped immediately following pathology assessment (at 22 weeks) and these rats were allowed to continue unexposed in chambers for the remainder of the study.

TABLE 8
Lung Weights and Incidences of Nonneoplastic Lesions of the Lung and Associated Lymph Nodes in Rats at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
Male				
Necropsy body wt[a]	326 ± 8	332 ± 5	328 ± 7	323 ± 6
Lung Weight[a]				
Absolute	1.825 ± 0.203	2.227 ± 0.058	2.835 ± 0.191▲▲	3.843 ± 0.098▲▲
Relative	0.558 ± 0.061	0.670 ± 0.014	0.863 ± 0.054▲▲	1.190 ± 0.019▲▲
Lung[b]	10	10	10	10
Chronic Active Inflammation[c]	1 (1.0)[d]	10** (1.2)	10** (2.5)	10** (4.0)
Foreign Body	0	10** (1.0)	10** (2.0)	10** (3.0)
Alveolus, Proteinosis	0	10** (1.0)	10** (2.7)	10** (4.0)
Alveolar Epithelium, Hyperplasia	0	7** (1.0)	10** (1.6)	10** (2.2)
Lymph Node, Bronchial	10	6	10	9
Foreign Body	0	4** (1.0)	2 (1.0)	7** (2.0)
Hyperplasia	0	1 (1.0)	2 (1.0)	5* (1.8)
Lymph Node, Mediastinal	10	5	9	9
Foreign Body	0	3* (1.0)	7** (1.7)	7** (2.0)
Hyperplasia	0	1 (1.0)	6** (1.2)	7** (2.0)
Female				
Necropsy body wt[a]	189 ± 4	184 ± 5	191 ± 3	179 ± 5
Lung Weight[a]				
Absolute	1.107 ± 0.036	1.352 ± 0.037▲▲	1.703 ± 0.052▲▲	2.334 ± 0.089▲▲
Relative	0.588 ± 0.021	0.735 ± 0.013▲▲	0.896 ± 0.030▲▲	1.308 ± 0.036 ▲▲
Lung	10	10	10	10
Chronic Active Inflammation	2 (1.0)	10** (1.0)	10** (1.6)	10** (3.4)
Foreign Body	0	8** (1.0)	10** (1.6)	10** (2.7)
Alveolus, Proteinosis	0	9** (1.0)	10** (2.7)	10** (4.0)
Alveolar Epithelium, Hyperplasia	0	5* (1.0)	1 (1.0)	7** (1.6)
Lymph Node, Bronchial	4	8	8	6
Foreign Body	0	5 (1.0)	7* (1.6)	4 (1.5)
Hyperplasia	0	1 (1.0)	6* (1.3)	3 (2.0)
Lymph Node, Mediastinal	7	9	8	9
Foreign Body	0	6* (1.3)	6** (1.7)	5* (1.8)
Hyperplasia	0	4 (1.0)	3 (1.0)	5* (1.8)

▲▲ Significantly different (P≤0.01) from the chamber control group by Williams' or Dunnett's test
* Significantly different (P≤0.05) from the chamber control group by the Fisher exact test
** P≤0.01
[a] n=10; lung weights (absolute weights) and body weights are given in grams; lung-weight-to-body-weight ratios (relative weights) are given as g lung weight/g body weight as a percentage (mean ± standard error).
[b] Number of animals with tissue examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 9 and in the Kaplan-Meier survival curves (Figure 4). Survival rates of males and females were similar to those of the chamber controls.

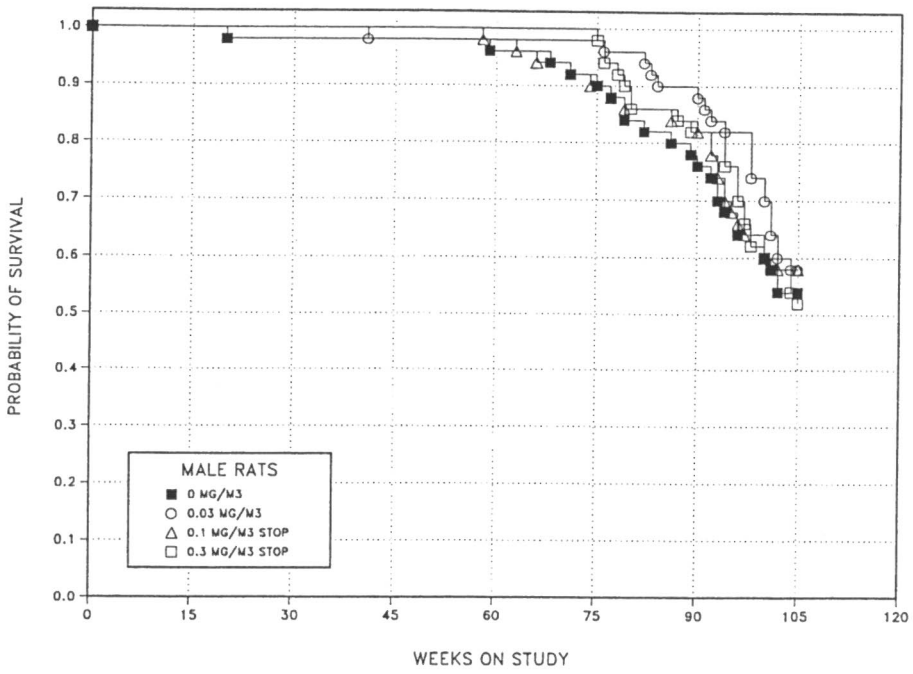
Body Weights and Clinical Findings

Mean body weights of exposed males and females were similar to those of the chamber controls throughout the study (Tables 10 and 11 and Figure 5). Clinical findings were generally observed after 18 months and included lethargy in 0.03 mg/m^3 males and females and 0.3 mg/m^3 males and abnormal breathing in all exposed groups of males.

TABLE 9
Survival of Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male				
Animals initially in study	60	60	60	60
3-Month interim evaluation[a]	10	10	10	10
Moribund	20	18	16	15
Natural eaths	3	3	5	9
Animals surviving to study termination	27	29	29	26
Percent probability of survival at end of study[b]	54	58	58	52
Mean survival (days)[c]	667	695	678	688
Survival analysis[d]	P=1.000	P=0.570N	P=0.803N	P=1.000N
Female				
Animals initially in study	60	60	60	60
3-Month interim evaluation[a]	10	10	10	10
Accidental death[a]	0	1	0	0
Moribund	13	14	14	12
Natural eaths	3	4	0	4
Animals surviving to study termination	34	31[e]	36	34
Percent probability of survival at end of study	68	63	72	68
Mean survival (days)	682	671	697	686
Survival analysis	P=0.998	P=0.850	P=0.726N	P=1.000

[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, the 0.03 mg/m^3 group is excluded from the trend test and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A lower mortality in an exposure group is indicated by **N**.
[e] Includes one animal that died during the last week of the study



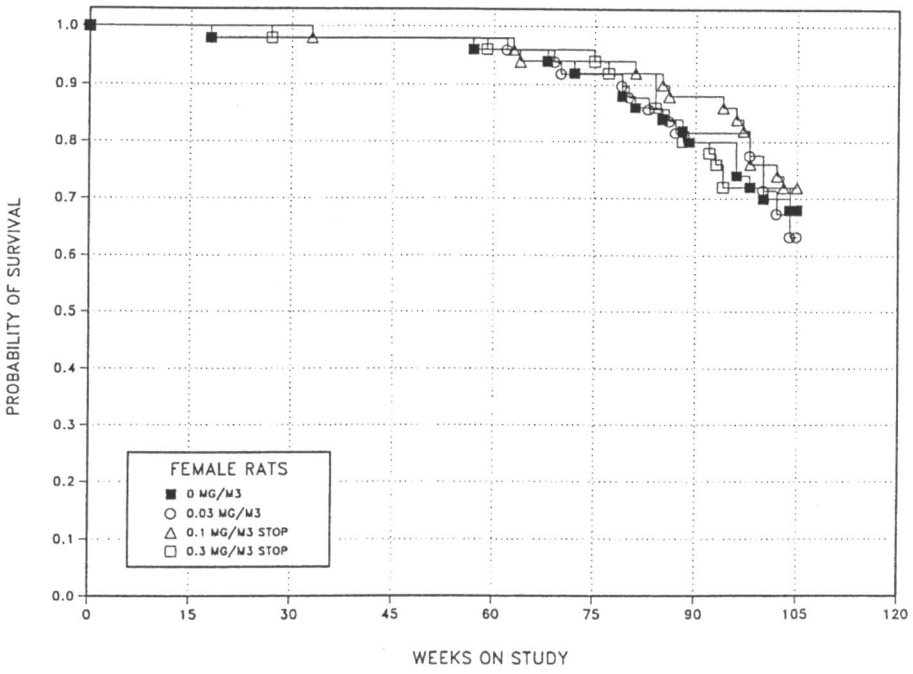


Figure 4
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Indium Phosphide by Inhalation for 2 Years.

TABLE 10
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Indium Phosphide

Weeks on Study	Chamber Control		0.03 mg/m^3			0.1 mg/m^3 (Stop-Exposure)			0.3 mg/m^3 (Stop-Exposure)		
	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	115	60	115	100	60	114	99	60	114	99	60
4	209	60	209	100	60	209	100	60	209	100	60
8	272	60	270	99	60	271	100	60	267	98	60
12	312	60	312	100	60	314	100	60	308	99	60
16[a]	354	50	349	99	50	353	100	50	346	98	50
21	377	49	376	100	50	379	100	50	370	98	50
24	398	49	396	100	50	400	101	50	389	98	50
28	415	49	412	99	50	418	101	50	405	98	50
32	429	49	429	100	50	431	101	50	420	98	50
36	442	49	442	100	50	444	101	50	434	98	50
40	449	49	446	99	50	452	101	50	441	98	50
44	457	49	459	100	49	465	102	50	454	99	50
52	473	49	470	99	49	476	101	50	467	99	50
56	475	49	475	100	49	482	102	50	469	99	50
60	480	48	480	100	49	488	102	49	478	99	50
64	478	48	479	100	49	484	101	48	477	100	50
68	485	48	487	100	49	494	102	47	483	100	50
72	484	46	486	101	49	494	102	46	481	100	50
76	491	45	492	100	48	498	102	45	485	99	47
80	499	42	495	99	48	505	101	43	486	97	45
84	496	41	505	102	45	502	101	43	488	98	43
88	499	40	498	100	45	496	99	42	489	98	42
92	499	37	500	100	42	484	97	41	487	98	41
94	501	34	498	99	42	500	100	36	486	97	40
96	492	34	496	101	41	508	103	33	486	99	37
98	498	32	492	99	38	508	102	32	490	98	32
100	494	31	491	99	36	505	102	31	492	100	30
102	487	28	491	101	32	503	103	29	486	100	29
104	478	27	485	102	29	493	103	29	471	99	29
Mean for weeks											
1-13	227		227	100		227	100		225	99	
14-52	422		420	100		424	100		414	98	
53-104	490		491	100		497	101		483	99	

[a] Interim evaluation occurred during week 14.

TABLE 11
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Indium Phosphide

Weeks on Study	Chamber Control		0.03 mg/m^3			0.1 mg/m^3 (Stop-Exposure)			0.3 mg/m^3 (Stop-Exposure)		
	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	96	60	95	99	60	95	99	60	95	99	60
4	143	60	143	100	59	142	99	60	142	99	60
8	168	60	168	100	59	166	99	60	165	98	60
12	184	60	182	99	59	182	99	60	179	97	60
16[a]	198	50	197	100	49	197	100	50	198	100	50
21	208	49	208	100	48	207	99	50	207	100	50
24	216	49	216	100	48	214	99	50	215	100	50
28	224	49	221	99	48	221	99	50	221	99	49
32	230	49	227	98	48	225	98	50	227	99	49
36	239	49	233	98	48	233	98	49	234	98	49
40	244	49	238	97	48	239	98	49	238	98	49
44	252	49	249	99	48	250	99	49	248	98	49
52	271	49	263	97	48	266	98	49	262	97	49
56	278	49	271	98	48	274	99	49	269	97	49
60	288	48	280	97	48	285	99	49	279	97	48
64	288	48	284	99	47	287	100	48	283	98	48
68	297	48	291	98	47	299	100	47	289	97	48
72	303	47	301	99	45	305	101	47	298	98	48
76	312	46	307	98	45	313	100	47	303	97	47
80	316	44	315	100	44	321	102	47	309	98	46
84	323	43	322	100	42	320	99	46	307	95	45
88	327	41	320	98	40	323	99	44	313	96	40
92	330	40	326	99	40	326	99	44	318	96	39
94	329	40	327	100	40	329	100	43	321	98	36
96	333	37	328	98	40	328	98	43	323	97	36
98	333	36	329	99	39	333	100	40	326	98	36
100	335	35	332	99	35	337	101	38	326	98	36
102	337	35	329	98	35	336	100	38	325	96	36
104	336	34	328	98	32	336	100	36	318	95	34
Mean for weeks											
1-13	148		147	99		146	99		145	98	
14-52	231		228	98		228	98		228	98	
53-104	317		312	98		316	100		307	97	

[a] Interim evaluation occurred during week 14.

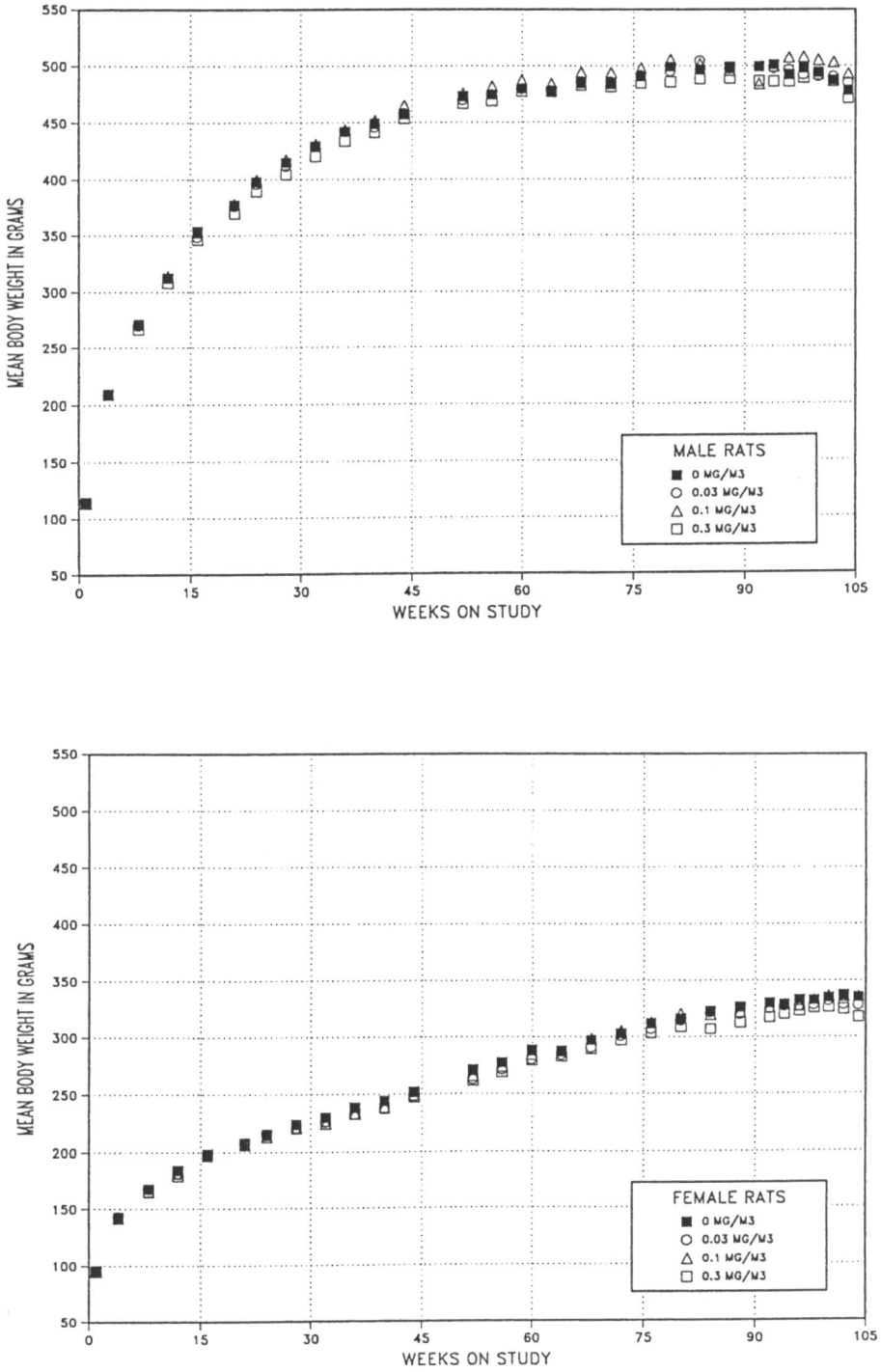


Figure 5
Growth Curves for Male and Female Rats Exposed to Indium Phosphide by Inhalation for 2 Years.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the lung, bronchial and mediastinal lymph nodes, adrenal medulla, mammary gland, skin, and pituitary gland and the incidences of mononuclear cell leukemia. 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.

Lung: At 2 years, the incidences of alveolar/bronchiolar adenoma in male rats exposed to 0.1 or 0.3 mg/m^3 and in all groups of exposed females were significantly greater than those in the chamber controls (Tables 12, A3, and B3). The incidences of alveolar/bronchiolar carcinoma were also significantly increased in all groups of exposed males and in females exposed to 0.3 mg/m^3 at 2 years. The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were increased in all groups of exposed males and in females exposed to 0.03 or 0.3 mg/m^3. The incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) in most exposed groups of males and females exceeded the historical control ranges for 2-year NTP studies in which chamber controls were given NIH-07 feed (inhalation studies) or in which control rats were given NTP-2000 feed (all routes) (Tables 12, A4a, and B4a). At the end of the study, squamous cell carcinoma of the lung occurred in four male rats exposed to 0.3 mg/m^3. Although this was not a significant increase, the incidence exceeded the historical control range for controls given NTP-2000 (all routes) or NIH-07 feed (inhalation studies) and was considered to be exposure related.

Histopathologic analyses were performed on lungs of animals designated for tissue burden studies. Lesions in the lung similar to those seen at the 3-month interim evaluation were observed in tissue burden animals evaluated at 5, 7, 9, 11, 12, 13, and 17 months (data not shown). In general, the lesions progressed in the continuously exposed 0.03 mg/m^3 group, while the severities of lung lesions remained similar in animals exposed to 0.1 or 0.3 mg/m^3 after exposure was discontinued. Additionally, beginning at week 13, lesions similar to those observed at 2 years were observed including one alveolar/bronchiolar adenoma in the 0.3 mg/m^3 group at 17 months. At 2 years, nonneoplastic lesions of the lung included atypical hyperplasia, chronic active inflammation, alveolar epithelial metaplasia, foreign body, alveolar proteinosis, and interstitial fibrosis, and the incidences were significantly increased in all exposed groups (Tables 12, A5, and B5). The incidences and severities of alveolar epithelial hyperplasia were increased in 0.1 and 0.3 mg/m^3 males and females. Alveolar epithelial hyperplasia represented focal lesions located away from the most intense areas of inflammation and was consistent with preneoplastic hyperplasia observed spontaneously. Additionally, two rare spontaneous lesions, squamous metaplasia and squamous cysts, occurred in exposed groups, and the incidence of squamous cysts was significantly increased in 0.3 mg/m^3 females.

A broad spectrum of inflammatory and proliferative (neoplastic and nonneoplastic) lesions occurred within the lungs of exposed rats. Proliferative lesions included alveolar/bronchiolar neoplasms and squamous cell carcinomas as well as alveolar epithelial hyperplasia and atypical hyperplasia. Alveolar epithelial hyperplasia generally represented an increase in the numbers of epithelial cells along alveolar walls with maintenance of normal alveolar architecture. Alveolar/bronchiolar adenomas, typical of those observed spontaneously in F344/N rats, were generally distinct masses that often compressed surrounding tissue. Component epithelial cells were often in acinar and/or irregular papillary structures and occasionally in a solid cellular pattern. These epithelial cells were typically uniform and similar to hyperplastic counterparts. Alveolar/bronchiolar carcinomas had similar cellular patterns but were generally larger and had one or more of the following histologic features: heterogeneous growth pattern, cellular pleomorphism and/or atypia, and local invasion or metastasis (Plates 3 and 4). A number of exposed males and females had multiple alveolar/bronchiolar neoplasms. Microscopically, it was not usually possible to determine if the multiple neoplasms represented intrapulmonary metastases of a malignant neoplasm or were multiple independent neoplasms. Included in the spectrum of lesions was a proliferation of alveolar/bronchiolar epithelium with a very prominent fibrous component; these lesions ranged from a few hundred micrometers to greater than

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung and Associated Lymph Nodes in Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male				
Lung[a]	50	50	50	50
Atypical Hyperplasia[b]	0	16** (3.1)[c]	23** (3.3)	39** (3.8)
Chronic Active Inflammation	5 (1.2)	50** (3.8)	50** (3.4)	50** (4.0)
Alveolar Epithelium, Metaplasia	0	45** (3.1)	45** (2.8)	48** (3.2)
Foreign Body	0	50** (2.2)	50** (1.9)	50** (2.1)
Alveolus, Proteinosis	0	50** (3.7)	48** (2.0)	47** (3.4)
Interstitium, Fibrosis	0	49** (3.7)	50** (3.5)	50** (3.9)
Alveolar Epithelium, Hyperplasia	11 (1.5)	20 (2.4)	21* (2.1)	31** (2.6)
Squamous Metaplasia	0	1 (2.0)	3 (3.0)	4 (2.5)
Squamous Cyst	0	1 (4.0)	3 (3.0)	2 (3.0)
Alveolar/bronchiolar Adenoma, Multiple	1	5	8*	12**
Alveolar/bronchiolar Adenoma (includes multiple)	6	13	27**	30**
Alveolar/bronchiolar Carcinoma, Multiple	0	2	1	5*
Alveolar/bronchiolar Carcinoma (includes multiple)	1	10**	8*	16**
Alveolar/bronchiolar Adenoma or Carcinoma[d]				
Overall rate[e]	7/50 (14%)	22/50 (44%)	30/50 (60%)	35/50 (70%)
Adjusted rate[f]	17.1%	48.7%	69.8%	76.1%
Terminal rate[g]	4/27 (15%)	14/29 (48%)	24/29 (83%)	21/26 (81%)
First incidence (days)	639	635	644	525
Poly-3 test[h]	P<0.001	P<0.001	P<0.001	P<0.001
Squamous Cell Carcinoma[i]				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	9.1%
Terminal rate	0/27 (0%)	0/29 (0%)	0/29 (0%)	0/26 (0%)
First incidence (days)	—[j]	—[k]	—	545
Poly-3 test	P=0.011		—	P=0.071
Lymph Node, Bronchial	26	27	41	44
Foreign Body	0	19** (2.6)	27** (2.7)	36** (2.7)
Lymph Node, Mediastinal	25	19	45	40
Foreign Body	0	8** (2.8)	27** (2.8)	15** (2.9)

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung and Associated Lymph Nodes in Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Female				
Lung	50	50	50	50
Atypical Hyperplasia	0	8** (2.8)	8** (2.9)	39** (3.8)
Chronic Active Inflammation	10 (1.0)	49** (3.0)	50** (2.6)	49** (3.9)
Alveolar Epithelium, Metaplasia	0	46** (3.3)	47** (2.4)	48** (3.8)
Foreign Body	0	49** (2.1)	50** (1.8)	50** (2.0)
Alveolus, Proteinosis	0	49** (3.7)	47** (2.0)	50** (3.8)
Interstitium, Fibrosis	0	48** (2.9)	50** (2.6)	49** (3.9)
Alveolar Epithelium, Hyperplasia	8 (1.5)	15 (2.1)	22** (2.0)	16* (1.8)
Squamous Metaplasia	0	2 (1.5)	1 (2.0)	4 (2.5)
Squamous Cyst	0	1 (4.0)	1 (4.0)	10** (3.6)
Alveolar/bronchiolar Adenoma, Multiple	0	1	1	1
Alveolar/bronchiolar Adenoma (includes multiple)	0	7**	5*	19**
Alveolar/bronchiolar Carcinoma, Multiple	0	1	0	7**
Alveolar/bronchiolar Carcinoma (includes multiple)	1	3	1	11**
Alveolar/bronchiolar Adenoma or Carcinoma[l]				
Overall rate	1/50 (2%)	10/50 (20%)	6/50 (12%)	26/50 (52%)
Adjusted rate	2.3%	23.5%	13.5%	58.8%
Terminal rate	1/34 (3%)	6/31 (19%)	6/36 (17%)	23/34 (68%)
First incidence (days)	735 (T)	694	735 (T)	519
Poly-3 test	P<0.001	P=0.004	P=0.063	P<0.001
Lymph Node, Bronchial	25	30	35	30
Foreign Body	0	23** (2.6)	26** (2.8)	20** (3.0)
Lymph Node, Mediastinal	28	36	39	26
Foreign Body	0	15** (3.1)	18** (2.3)	13** (2.8)

(T) Terminal sacrifice
* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** P≤0.01
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Historical incidence for 2-year studies with control groups given NTP-2000 feed (mean ± standard deviation): 14/299 (4.7% ± 4.8%); range 0%-14%
[e] Number of animals with neoplasm per number of animals with lung examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the chamber control incidence are the P values associated with the trend test (the 0.03 mg/m^3 group was excluded from 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 lower incidence in an exposure group is indicated by **N**.
[i] Historical incidence: 0/299
[j] Not applicable; no neoplasms in animal group
[k] Value of statistic cannot be computed.
[l] Historical incidence: 5/299 (1.7% ± 2.3%); range 0%-6%

one centimeter in diameter. While these lesions are not generally observed spontaneously, they are common in exposed F344/N rats from other particulate inhalation studies conducted by the NTP. Most lesions had a rounded outline and a central fibrous core containing dispersed glandular (alveolar) structures lined by uniformly cuboidal epithelial cells. Aggregates of mostly necrotic inflammatory cells were also present in adjacent alveoli and often within the glandular structures. Peripherally, the fibro-proliferative lesions had one to several layers of epithelium which coursed along and often extended into adjacent alveoli, frequently forming papillary projections (Plates 5 and 6). These epithelial cells were often slightly pleomorphic with occasional mitotic figures. The smallest of these lesions were usually observed adjacent to areas of chronic inflammation. Small lesions with modest amounts of peripheral epithelial proliferation were diagnosed as atypical hyperplasia, while larger lesions with florid epithelial proliferation, marked cellular pleomorphism, and/or local invasion were diagnosed as alveolar/bronchiolar adenoma or carcinoma.

While squamous epithelium is not normally observed within the lung, squamous metaplasia of alveolar/bronchiolar epithelium is a relatively common response to pulmonary injury and occurred in a few rats in each exposed group (Tables 12, A5, and B5). Squamous metaplasia was a minor change consisting of a small cluster of alveoli in which the normal epithelium was replaced by multiple layers of flattened squamous epithelial cells (Plate 7) that occasionally formed keratin. Cystic squamous lesions also occurred and were rimmed by a variably thick (a few to many cell layers) band of viable squamous epithelium with a large central core of keratin (Plates 8 and 9). Squamous cell carcinomas were observed in four males exposed to 0.3 mg/m^3. These neoplasms ranged from fairly well differentiated squamous cell carcinomas (Plate 10) to poorly differentiated and anaplastic ones (Plate 11).

Chronic inflammation, alveolar epithelial metaplasia, foreign body, alveolar proteinosis, and interstitial fibrosis occurred in almost all males and females exposed to indium phosphide (Plates 12 and 13). Grossly, these lesions appeared as multifocal to diffuse areas which were grayish rather than the normal pink color. The lesions tended to be of similar severity in males and females in the 0.03 and 0.3 mg/m^3 groups; the lesions were less severe in the 0.1 mg/m^3 groups. The pulmonary architecture throughout the lungs was distorted by a combination of inflammatory cells, fibrosis, and epithelial metaplasia. Lesions tended to be subpleural or peripheral and/or occurred along larger blood vessels and airways. The chronic inflammation was characterized by accumulations of alveolar macrophages with foamy cytoplasm, occasional multinucleated giant cells and cholesterol clefts, cell debris, and few neutrophils. In these areas, the alveolar interstitium and frequently the overlying pleura were variably thickened by dense fibrous connective tissue (fibrosis) which often effaced alveoli (Plate 13). Although a diffuse change, aggregates of homogeneous to granular eosinophilic material within alveolar lumens (alveolar proteinosis) (Plate 13) were most pronounced within the areas of chronic inflammation. Metaplasia of the alveolar epithelium in alveoli within and at the periphery of foci of inflammation was characterized by replacement of normal type I epithelial cells with plump cuboidal or ciliated columnar epithelial cells with goblet cells and mucin production evident in many instances (Plate 13). Foreign body (indium phosphide particles) was present free within alveoli and within phagocytic inflammatory cells. Foreign body was characterized by scattered blackish specks less than 1 µm in diameter that, while visible, were not overwhelming.

Bronchial and Mediastinal Lymph Nodes: At 2 years, foreign body was observed in 38% to 82% of rats from which the bronchial and mediastinal lymph nodes were sampled (Tables 12, A5, and B5). Foreign body was interpreted as particles of indium phosphide. The blackish particles were less than 1 µm in diameter and were present primarily within phagocytic cells (macrophages) scattered throughout the lymph nodes. At 2 years, the incidences of bronchial lymph node hyperplasia were significantly increased in all exposed groups.

Adrenal Medulla: At 2 years, there were increased incidences of benign pheochromocytoma and benign or malignant pheochromocytoma (combined) in males exposed to 0.03 mg/m^3 and in males and females exposed to 0.3 mg/m^3 (Tables 13, A3, and B3). There were increased incidences of bilateral pheochromocytomas in all exposed groups of males, while only two were observed in 0.3 mg/m^3 females and none were observed in the chamber control group. Although not significantly increased, the incidences of malignant

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male				
Number Examined Microscopically	50	50	49	50
Hyperplasia[a]	26 (2.2)[b]	26 (2.4)	24 (2.4)	32 (2.3)
Benign Pheochromocytoma, Bilateral	0	6*	4	5*
Benign Pheochromocytoma (includes bilateral)				
Overall rate[c]	10/50 (20%)	22/50 (44%)	16/49 (33%)	23/50 (46%)
Adjusted rate[d]	23.8%	48.8%	38.0%	51.1%
Terminal rate[e]	6/27 (22%)	17/29 (59%)	11/28 (39%)	15/26 (58%)
First incidence (days)	537	635	537	525
Poly-3 test[f]	P=0.006	P=0.011	P=0.117	P=0.006
Complex Pheochromocytoma	0	1	0	0
Malignant Pheochromocytoma[g]	0	3	3	1
Benign, Complex or Malignant Pheochromocytoma[h]				
Overall rate	10/50 (20%)	26/50 (52%)	18/49 (37%)	24/50 (48%)
Adjusted rate	23.8%	57.1%	42.6%	53.1%
Terminal rate	6/27 (22%)	19/29 (66%)	12/28 (43%)	15/26 (58%)
First incidence (days)	537	628	537	525
Poly-3 test	P=0.005	P<0.001	P=0.051	P=0.003
Female				
Number Examined Microscopically	50	48	50	49
Hyperplasia	6 (1.8)	13* (2.2)	9 (2.3)	15* (2.1)
Benign Pheochromocytoma, Bilateral	0	0	0	2
Benign Pheochromocytoma (includes bilateral)[i]				
Overall rate	2/50 (4%)	6/48 (13%)	2/50 (4%)	9/49 (18%)
Adjusted rate	4.6%	14.5%	4.5%	20.6%
Terminal rate	1/34 (3%)	4/31 (13%)	2/36 (6%)	6/34 (18%)
First incidence (days)	615	686	735 (T)	588
Poly-3 test	P=0.005	P=0.119	P=0.682N	P=0.026

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Female (continued)				
Number Examined Microscopically	50	48	50	49
Malignant Pheochromocytoma	0	0	0	1
Benign or Malignant Pheochromocytoma[i]				
Overall rate	2/50 (4%)	6/48 (13%)	2/50 (4%)	9/49 (18%)
Adjusted rate	4.6%	14.5%	4.5%	20.6%
Terminal rate	1/34 (3%)	4/31 (13%)	2/36 (6%)	6/34 (18%)
First incidence (days)	615	686	735 (T)	588
Poly-3 test	P=0.005	P=0.119	P=0.682N	P=0.026

(T) Terminal sacrifice
* Significantly different (P≤0.05) 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] Number of animals with neoplasm per number of animals with adrenal gland examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the chamber control incidence are the P values associated with the trend test (the 0.03 mg/m^3 group was excluded from 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 lower incidence in an exposure group is indicated by **N**.
[g] Historical incidence for 2-year studies with control groups given NTP-2000 feed (mean ± standard deviation): 5/299 (1.7% ± 1.5%); range 0%-4%
[h] Historical incidence: 35/299 (11.7% ± 5.0%); range 6%-20%
[i] Historical incidence: 14/297 (4.7% ± 2.1%); range 2%-8%

pheochromocytomas in males exposed to 0.03 or 0.1 mg/m^3 exceeded the historical control range for 2-year studies using NTP-2000 feed (all routes) and were at the upper end of the historical control range for 2-year inhalation studies in which chamber controls were given NIH-07 feed (Table A4b). The incidence of benign or malignant pheochromocytoma (combined) in 0.03 mg/m^3 males and the incidences of benign pheochromocytoma and benign or malignant pheochromocytoma (combined) in 0.3 mg/m^3 females exceeded the historical control ranges for 2-year studies in both NTP-2000 and NIH-07 historical control databases (Tables A4b and B4b). The incidences of hyperplasia were significantly increased in females exposed to 0.03 or 0.3 mg/m^3 but were not significantly increased in exposed males. The increased incidences of neoplasms and nonneoplastic lesions in the adrenal medulla were considered to be exposure related.

Focal hyperplasia and pheochromocytoma were considered to constitute a morphologic continuum in the adrenal medulla. Focal hyperplasia consisted of irregular, small foci of small to normal-sized medullary cells arranged in packets or solid clusters slightly larger than normal; there was little compression of surrounding parenchyma. Benign pheochromocytomas were well-delineated masses often with altered architecture and variable compression of surrounding parenchyma. Neoplastic cells were arranged in variably sized aggregates, clusters, and/or trabecular cords. Larger neoplasms usually exhibited greater cellular pleomorphism and atypia than smaller neoplasms. Malignant pheochromocytomas were identified when there was invasion of or beyond the adrenal capsule or when distant metastases were observed.

Mammary Gland: There was a significantly increased incidence of mammary gland carcinoma (Tables 14 and B3) in females exposed to 0.03 mg/m^3 at 2 years. This incidence exceeded the historical control range for studies in which rats were given NTP-2000 feed but was at the upper end of the range of historical control incidences for inhalation studies in which chamber controls were given NIH-07 feed (Table B4c). The incidence in the concurrent chamber control group is low, as no other study in either NTP historical control database has a control group incidence of zero for mammary gland carcinoma. Although an exposure concentration-related response was not expected, there was no increase in the incidence of mammary gland carcinoma in females exposed to 0.1 or 0.3 mg/m^3. The incidences of fibroadenoma of the mammary gland were not increased in any exposed group (Table B3). However, in NTP studies using F344/N rats, there is not a strong correlation between carcinoma and fibroadenoma, as fibroadenomas are generally considered endstage neoplasms and carcinomas seldom arise from fibroadenomas. Also, while treatment-related increases in the incidences of both neoplasms have occurred in NTP studies, an increase in one or the other is more common (Boorman *et al.*, 1990). While a rare neoplasm in male F344/N rats, a single carcinoma occurred in each of the 0.1 and 0.3 mg/m^3 groups of males (Table A1). Because the incidence of carcinoma in 0.03 mg/m^3 females was outside the NTP historical control range for 2-year studies in which female rats were given NTP-2000 feed, and this group was the only group receiving continued exposure, this increase was considered an uncertain finding.

Spontaneous mammary gland carcinomas in F344/N rats seldom metastasize and many do not exhibit much invasion or destruction of surrounding tissues. The carcinomas in this study were typical of those observed spontaneously and consisted of epithelia in papillary, ductular and/or alveolar arrangements. There was often a variable growth pattern with cellular atypia and cellular and nuclear pleomorphism.

TABLE 14
Incidences of Neoplasms of the Mammary Gland in Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male				
Number Examined Microscopically	24	33	31	24
Carcinoma[a]	0	0	1	1
Female				
Carcinoma[b]				
Overall rate[c]	0/50 (0%)	8/50 (16%)	3/50 (6%)	2/50 (4%)
Adjusted rate[d]	0.0%	18.9%	6.7%	4.7%
Terminal rate[e]	0/34 (0%)	6/31 (19%)	1/36 (3%)	2/34 (6%)
First incidence (days)	—[f]	683	714	735 (T)
Poly-3 test[g]	P=0.316	P=0.003	P=0.127	P=0.238

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Historical incidence for 2-year studies with control groups given NTP-2000 feed (mean ± standard deviation): 9/299 (3.0% ± 2.5%); range 0%-6%
[c] Number of animals with neoplasm per number of animals with mammary gland examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Not applicable; no neoplasms in animal group
[g] Beneath the chamber control incidence are the P values associated with the trend test (the 0.03 mg/m^3 group was excluded from 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.

Skin: The incidences of fibroma (1/50, 4/50, 7/50, 3/50; Table A3) and fibroma or fibrosarcoma (combined) (2/50, 4/50, 8/50, 4/50) were marginally increased in male rats exposed to 0.1 mg/m^3 at 2 years. The incidences in this group were outside the NTP historical control ranges for 2-year studies using NTP-2000 feed [fibroma: 12/299 (4.0% ± 3.7%); range 0%-10%; fibroma or fibrosarcoma (combined): 16/299 (5.4% ± 4.6%); range 2%-14%)] (Table A4c) and were outside NTP historical control ranges for 2-year inhalation studies using NIH-07 feed. Increases were not observed in the 0.03 or 0.3 mg/m^3 groups, which were the groups in which most exposure-related effects were observed. It is uncertain if this marginal increase in the incidence of skin neoplasms was exposure related.

Mononuclear Cell Leukemia: The incidences of mononuclear cell leukemia (males: chamber control, 16/50; 0.03 mg/m^3, 23/50; 0.1 mg/m^3, 29/50; 0.3 mg/m^3, 25/50; females: 14/50, 21/50, 14/50, 24/50; Tables A3 and B3) were significantly increased in 0.1 mg/m^3 males and 0.3 mg/m^3 females at 2 years. The incidence (58%) of mononuclear cell leukemia in 0.1 mg/m^3 males was slightly higher than the range of chamber control incidences of all leukemias in the NTP-2000 feed historical control database [130/299 (43.5% ± 9.6%); range 32%-54%] (Table A4d). The incidence of mononuclear cell leukemia in 0.3 mg/m^3 females (48%) was slightly increased and the incidence also exceeded the historical control range for 2-year studies using NTP-2000 feed [87/299 (29.1% ± 8.5%); range 16%-42%] (Table B4d); the incidence in this group also slightly exceeded the range for the larger historical control database in which chamber controls were given NIH-07 feed [373/1,052 (35.4% ± 6.0%), range 24%-47%]. In addition, the incidence in 0.03 mg/m^3 females was at the upper end of the historical control range for 2-year studies using NTP-2000 feed. Although the number of studies is limited, the incidence of mononuclear cell leukemia in the current set of NTP-2000 studies is lower than in the larger set of NIH-07 studies. The incidence in the concurrent chamber control group of males was low and this in part accounted for the significance of the increase observed in 0.1 mg/m^3 males. Because increased incidences occurred in both males and females, the increased incidences may have been exposure related. Mononuclear cell leukemia is a very common spontaneous neoplasm in F344/N rats, particularly in males. It is thought to arise within the spleen, but rapidly becomes a systemic disease and is often identified within multiple tissues.

Pituitary Gland: At the end of the study, the incidence of pars distalis hyperplasia (5/49, 13/50, 12/50, 15/50; Table A5) was significantly increased in males exposed to 0.3 mg/m^3. Hyperplasia and benign and malignant neoplasms of the pars distalis are thought to represent a morphologic and biologic continuum. The increased incidence of hyperplasia was not supported by an increased incidence of pituitary gland neoplasms in this group; in fact, the incidence of pars distalis adenoma in males exposed to 0.3 mg/m^3 was decreased (36/49, 33/50, 31/50, 30/50; Table A3). Therefore, the increased incidence of hyperplasia was not considered to be related to exposure to indium phosphide.

Tissue Burden Analyses

Tissue burden analyses were performed on male rats during exposure and postexposure periods and on female rats following 22 weeks of exposure (Table H9).

Lung weights of exposed male rats were significantly increased relative to chamber control lung weights and increased with increasing exposure concentration and duration of exposure (Table H10). Following cessation of exposure, lung weights in the 0.1 and 0.3 mg/m^3 groups remained significantly greater than those of the chamber controls, thus showing very little recovery. Lung burdens, like lung weights, increased with time and exposure concentration in all exposed groups (Figure 6). Lung burden data for the 0.03 mg/m^3 group appeared to increase linearly over time, indicating an extremely low clearance rate. Lung burdens were slightly reduced by 2 months after exposure and continued to decline until 12 months after exposure when they had decreased to 35% (0.1 mg/m^3) and 50% (0.3 mg/m^3) of the values observed at the termination of exposure. Thus, lung burdens decreased to a greater extent during the clearance phase of the study than did lung weights, which remained elevated due to the pathologic changes present in the lung. Lung deposition rates increased proportionately to increasing exposure concentration in male rats (Table H11). In

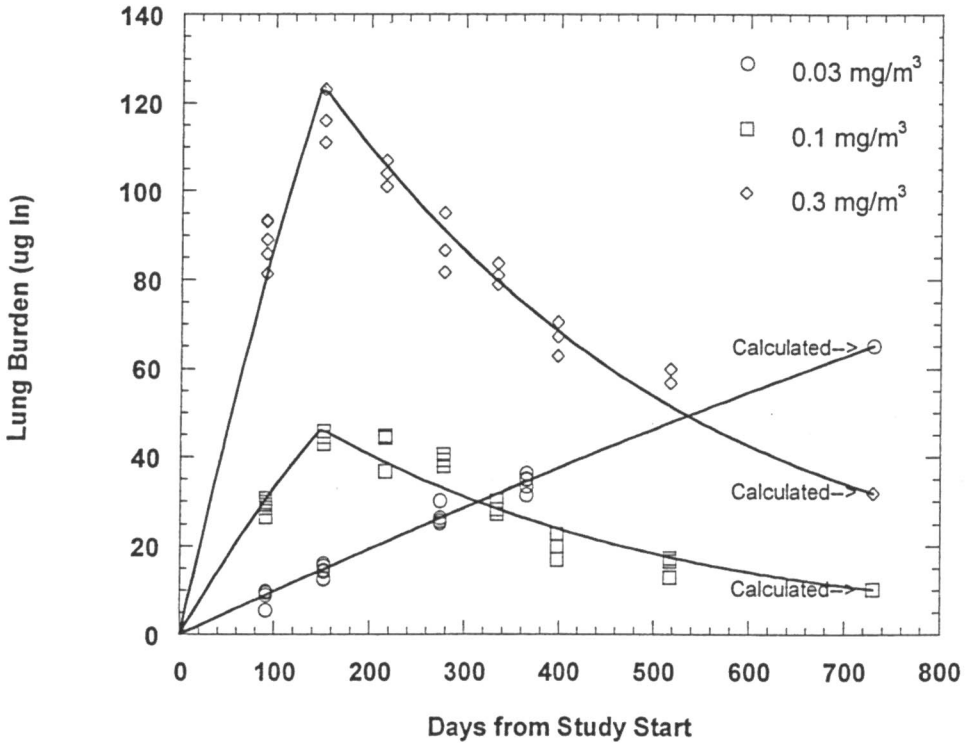


Figure 6
Lung Burden of Indium (µg In) in Male Rats in the 2-Year Inhalation Study of Indium Phosphide.
Data are presented as mean ± standard deviation. Curves represent the fit of the lung deposition and clearance model to the data and the estimated lung burden at 2 years.

general, lung burdens, when normalized to exposure concentrations, remained constant across exposure concentrations indicating linear toxicokinetics (Table H10). The only exception was at the 5-month time point when the normalized lung burden for the 0.3 mg/m^3 groups was slightly lower than that of the two lower exposure groups. This difference was small and was not supported by differences in calculated lung deposition fraction and clearance rates (Table H11). There were no differences in the calculated lung deposition fraction, clearance rate constant, or clearance half-times for the 0.1 and 0.3 mg/m^3 groups. Clearance half-times for indium in the lung were 262 and 291 days for the 0.1 and 0.3 mg/m^3 groups respectively. Because there was an extremely low clearance rate in rats exposed to 0.03 mg/m^3, calculation of the clearance rate constant and clearance half-time was relatively imprecise.

There were no significant differences between male and female rats in exposure-related lung weight increases, lung indium concentrations, or serum indium concentrations (Tables H10 and H12). In addition, when the differences in lung weights and the percent weight increases were considered, there were no significant differences in lung burden or normalized lung burden between males and females.

The lung deposition and clearance model was used to estimate the total amount of indium deposited in the lung after exposure to 0.03 mg/m^3 for 2 years or to 0.1 or 0.3 mg/m^3 for 22 weeks, the lung burdens at the end of the 2-year study, and the area under the lung burden curves (AUC) shown in Figure 6 for each of these exposure conditions (Table 15). Terminal lung burdens for the 0.03, 0.1, and 0.3 mg/m^3 groups were 65.1, 10.2, and 31.9 µg of indium, respectively, indicating that this estimation predicted more indium in the lungs of rats at 2 years following continuous exposure to 0.03 mg/m^3 indium phosphide than in the lungs of rats exposed to 0.1 or 0.3 mg/m^3 indium phosphide for 22 weeks and then held unexposed until the end of the 2-year study. The estimated total amount of indium deposited in the lung at the time that exposure to indium phosphide was stopped (2 years for the 0.03 mg/m^3 and 22 weeks for the 0.1 and 0.3 mg/m^3 groups) was greater in the 0.3 mg/m^3 group than in the 0.03 or 0.1 mg/m^3 groups; 150, 72, or 57 µg of indium per lung, respectively. Similarly, the AUCs calculated for each exposure concentration over the course of the entire study demonstrated that the 0.3 mg/m^3 group received greater exposure than did the 0.03 or 0.1 mg/m^3 groups. Due to the different exposure durations (2 years or 22 weeks) and the slow clearance of deposited indium, the contribution of the first year on study for 0.03, 0.1 and 0.3 mg/m^3 were 26%, 65%, and 63% of the total estimated AUC values. The second-year AUC for the 0.03 mg/m^3 group was equivalent to that of the 0.3 mg/m^3 group. The difference between the total deposited dose and the lung burden at 2 years reflects the amount of indium cleared from the lungs during the 2-year study. Regardless of how the total "dose" of indium to the lung was estimated, the 0.1 mg/m^3 group received less total exposure than the continuously exposed 0.03 mg/m^3 group or the 0.3 mg/m^3 group exposed for 22 weeks, implying that the 0.1 mg/m^3 group may be considered the "low dose" in this study.

Indium was detectable in serum above the experimental limit of quantitation primarily after 22 weeks of exposure (Table H12). The concentrations of indium in serum were quite low relative to those measured in the lung. Serum indium concentrations increased in proportion to concentration and duration of exposure. Although there was some decline in serum concentrations after termination of exposure for the 0.1 and 0.3 mg/m^3 groups, there was no consistent evidence of elimination of indium from serum, which is consistent with the continuing slow elimination of indium from the lungs.

TABLE 15
Lung Deposition and Clearance Model-Based Estimates of Exposure to Indium for Rats in the 2-Year Inhalation Studies of Indium Phosphide

	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
Lung Burden at 2 Years (µg In/lung)	65.1	10.2	31.9
Lung Deposited Dose (total µg In deposited/lung)[a]	72	57	150
First-Year AUC (µg In/lung • days on study)[b]	6,368	11,502	31,239
Second-Year AUC (µg In/lung • days on study)[c]	18,244	6,275	18,532
Total AUC (µg In/lung • days on study)[d]	24,612	17,777	49,771

[a] Total amount of indium deposited in the lung (2 years exposure for the 0.03 mg/m^3 group and 22 weeks for the 0.1 and 0.3 mg/m^3 groups).
[b] Area under the lung burden curve for the first year
[c] Area under the lung burden curve for the second year
[d] Area under the lung burden curve for 2 years

MICE

14-WEEK STUDY

One 100 mg/m^3 male died during week 8 of the study; all remaining males and all females in the 100 mg/m^3 groups were removed moribund during weeks 7 through 11 (Table 16).

One male exposed to 30 mg/m^3 was killed moribund during week 13. Four females exposed to 30 mg/m^3 died before the end of the study; one death was accidental. Final mean body weights and mean body weight gains were significantly decreased in males exposed to 3 mg/m^3 or greater and in females exposed to 10 or 30 mg/m^3; males in the 30 mg/m^3 group lost weight during the study (Table 16). Beginning in week 7, rapid, shallow breathing was observed in males and females exposed to 10 mg/m^3 or greater. Most exposed animals had ruffled fur, and mice exposed to 30 or 100 mg/m^3 were lethargic and thin.

Hematological changes occurred in mice that were similar to those that occurred in rats (Tables 17 and F3). There was an exposure-related increase in the erythron, evidenced by increases in hematocrit values, hemoglobin concentrations, and erythrocyte counts. Erythron changes occurred in all exposed groups of males and in 10 and 30 mg/m^3 females. Also similar to the rat study, the increase in the erythron was accompanied by increased reticulocyte counts and decreased mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration values.

TABLE 16
Survival and Body Weights of Mice in the 14-Week Inhalation Study of Indium Phosphide

Concentration (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	25.8 ± 0.2	37.2 ± 0.6	11.5 ± 0.6	
1	10/10	25.6 ± 0.2	36.6 ± 0.6	11.1 ± 0.7	98
3	10/10	25.7 ± 0.3	35.2 ± 0.7*	9.5 ± 0.5*	95
10	10/10	25.7 ± 0.2	33.0 ± 0.4**	7.4 ± 0.4**	89
30	9/10[c]	25.6 ± 0.3	24.5 ± 0.8**	–1.1 ± 0.7**	66
100	0/10[d]	25.9 ± 0.3	—	—	—
Female					
0	10/10	20.8 ± 0.2	31.3 ± 0.7	10.4 ± 0.8	
1	10/10	20.6 ± 0.2	32.2 ± 0.5	11.6 ± 0.6	103
3	10/10	20.4 ± 0.3	30.6 ± 0.8	10.2 ± 0.8	98
10	10/10	20.5 ± 0.2	27.9 ± 0.3**	7.4 ± 0.3**	89
30	6/10[e]	20.6 ± 0.3	22.2 ± 0.4**	1.7 ± 0.5**	71
100	0/10[f]	20.7 ± 0.3	—	—	—

* Significantly different (P≤0.05) from the chamber control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 13; weight of animal that died during week 13 was included in calculations of final mean body weight.
[d] Weeks of death: 7, 7, 8, 8, 8, 8, 9, 9, 9, 11
[e] Weeks of death: 4, 11, 12, 14; weight of animal that accidentally died during week 14 was included in calculations of final mean body weight.
[f] Week of deaths: 9

Neutrophil counts were increased in 1 mg/m^3 males and in all exposed groups of females. The increased neutrophil counts are consistent with the pulmonary inflammation observed microscopically.

Lung weights of all exposed groups of males and females were significantly greater than those of the chamber controls and generally increased with increasing exposure concentration (Tables 18 and G3). The 2.6- to 4.1-fold increases were primarily related to the accumulation of proteinaceous fluid (alveolar proteinosis). Although some contribution by other factors could not be entirely eliminated, other organ weight changes were considered secondary to the significant body weight decreases and/or debilitated condition of the animals.

TABLE 17
Selected Hematology Data for Mice in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3
Male					
n	10	9	10	9	9
Manual hematocrit (%)	49.3 ± 0.3	49.7 ± 0.5	51.1 ± 0.4**	52.8 ± 0.7**	60.8 ± 0.9**
Automated hematocrit (%)	49.2 ± 0.3	49.1 ± 0.8	50.8 ± 0.5*	52.3 ± 0.7**	61.0 ± 1.0**
Hemoglobin (g/dL)	15.8 ± 0.1	15.5 ± 0.2	16.0 ± 0.1	16.6 ± 0.2**	18.9 ± 0.3**
Erythrocytes (10^6/μL)	9.49 ± 0.12	9.97 ± 0.14*	10.34 ± 0.09**	11.12 ± 0.13**	13.88 ± 0.21**
Reticulocytes (10^6/μL)	0.02 ± 0.00	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.00	0.04 ± 0.01
Mean cell volume (fL)	51.8 ± 0.5	49.3 ± 0.2**	49.2 ± 0.3**	47.0 ± 0.2**	43.9 ± 0.3**
Mean cell hemoglobin (pg)	16.6 ± 0.2	15.6 ± 0.1**	15.5 ± 0.1**	14.9 ± 0.1**	13.6 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.0 ± 0.1	31.6 ± 0.2	31.5 ± 0.2*	31.8 ± 0.1	31.1 ± 0.2**
Female					
n	10	10	10	10	6
Manual hematocrit (%)	50.0 ± 0.5	48.8 ± 0.4	49.4 ± 0.5	52.0 ± 0.6	60.2 ± 1.2**
Automated hematocrit (%)	49.3 ± 0.7	47.3 ± 0.4	48.9 ± 0.4	51.0 ± 0.6	60.1 ± 1.4**
Hemoglobin (g/dL)	15.8 ± 0.2	15.2 ± 0.1	15.5 ± 0.1	16.4 ± 0.2	18.6 ± 0.4**
Erythrocytes (10^6/μL)	9.64 ± 0.14	9.58 ± 0.11	10.01 ± 0.11	10.72 ± 0.11**	13.40 ± 0.36**
Reticulocytes (10^6/μL)	0.02 ± 0.00	0.02 ± 0.01	0.02 ± 0.00	0.03 ± 0.01	0.05 ± 0.01*
Mean cell volume (fL)	51.2 ± 0.1	49.2 ± 0.3**	48.8 ± 0.2**	47.6 ± 0.3**	45.0 ± 0.3**
Mean cell hemoglobin (pg)	16.4 ± 0.1	15.9 ± 0.2**	15.5 ± 0.1**	15.3 ± 0.1**	13.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.1 ± 0.2	32.1 ± 0.2	31.7 ± 0.1*	32.2 ± 0.1	30.9 ± 0.0**

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data; no data available for the 100 mg/m^3 group due to 100% mortality.

TABLE 18
Lung Weights and Lung-Weight-to-Body-Weight Ratios for Mice in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3
Male					
n	10	10	10	10	9
Necropsy body wt	37.8 ± 0.6	37.4 ± 0.6	35.6 ± 0.6*	32.8 ± 0.5**	24.3 ± 0.8**
Lung					
Absolute	0.219 ± 0.006	0.564 ± 0.010**	0.613 ± 0.014**	0.869 ± 0.016**	0.887 ± 0.035**
Relative	0.581 ± 0.020	1.511 ± 0.033**	1.725 ± 0.040**	2.656 ± 0.071**	3.653 ± 0.134**
Female					
n	10	10	10	10	6
Necropsy body wt	32.5 ± 0.6	32.5 ± 0.5	31.1 ± 0.9	28.4 ± 0.4**	22.2 ± 0.3**
Lung					
Absolute	0.225 ± 0.008	0.582 ± 0.010**	0.684 ± 0.011**	0.861 ± 0.020**	0.808 ± 0.021**
Relative	0.694 ± 0.026	1.791 ± 0.029**	2.211 ± 0.064**	3.042 ± 0.093**	3.650 ± 0.085**

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Lung weights (absolute weights) and body weights are given in grams; lung-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight as a percentage (mean ± standard error).

The most severe exposure-related lesions occurred in the lungs and consisted of alveolar proteinosis, chronic active inflammation, alveolar epithelial hyperplasia, interstitial fibrosis, and foreign body (indium phosphide particles) (Table 19 and Plates 14 and 15). The inflammation was mild to moderate while the proteinosis was moderate to marked in all exposed groups. Foreign body, hyperplasia, and fibrosis were minimal to mild in 1 mg/m^3 animals and generally increased in severity with increasing exposure concentration; these lesions were marked in 100 mg/m^3 animals. While these lung lesions are common in rats exposed to particulates, they are much less common in mice.

The lesions observed in rats and mice were similar in many respects; however, there were quantitative and qualitative differences. In general, the lesions in mice tended to be somewhat more severe than those in rats at the same exposure concentrations. In mice, the inflammation was more neutrophilic (Plate 16) and necrotizing than in rats. While most of the alveolar epithelial hyperplasia was similar to that observed in the rats, in some areas the epithelium was piled up and cells were somewhat atypical, and there were rare foci of squamous cell differentiation. Pulmonary interstitial fibrosis, which is a common response to injury in the rat but uncommon in the mouse, was marked in mice in the 30 and 100 mg/m^3 groups in this study.

Most bronchial lymph nodes examined were enlarged and contained increased numbers of lymphocytes and larger immature mononuclear cells (hyperplasia) (Table 19). The severity of the hyperplasia was only marginally different between exposed groups. Hyperplasia is typical of reactive lymph nodes draining areas of foreign material deposition and/or inflammation. Pigmentation (indium phosphide) also occurred in most exposed animals and increased in severity with increasing exposure concentration. Pigmentation consisted of blackish particles less than 1 µm in diameter, primarily within phagocytic cells in the nodes.

The incidences of foreign body (indium phosphide particles) were increased in the nose of 100 mg/m^3 mice. (Table 19). Indium phosphide particles were present within scattered eosinophilic granular material within the nasal cavity. Similar material was observed within the lumens of the trachea and larynx. Effects on the larynx were primarily observed in mice exposed to 10, 30, or 100 mg/m^3 (Table 19). The predominant change was squamous epithelial cell hyperplasia which occurred along the medial aspects of the arytenoid cartilages of the two most anterior laryngeal sections and occasionally at foci two-thirds of the way down on the lateral walls of the most posterior laryngeal section. This change was characterized by focal piling up of squamous epithelial cells and was commonly accompanied by focal necrosis and/or suppurative inflammation. Male and female mice exposed to 10 mg/m^3 or greater had minimal to mild squamous metaplasia at the base of the epiglottis where the epithelium overlies small serous glands. There were also lipoprotein and indium phosphide particles (foreign body) in the laryngeal lumens of exposed mice.

There were increased incidences of hematopoietic cell proliferation in the spleens of exposed males (chamber control, 0/10; 1 mg/m^3, 5/10; 3 mg/m^3, 3/10; 10 mg/m^3, 3/9; 30 mg/m^3, 6/9; 100 mg/m^3, 9/10) and to a lesser extent in exposed females (1/10, 3/10, 3/10, 0/10, 6/9, 5/10). This subtle red pulp lesion was characterized by multifocal to diffuse increases of primarily erythroid precursors, as well as some megakaryocytes.

Degeneration of the adrenal cortex occurred in female mice exposed to 30 or 100 mg/m^3 (0/10, 0/10, 0/10, 0/10, 8/10, 10/10) and was characterized by narrowing of the X-zone of the cortex due to cell loss and stromal collapse. Degeneration of the submandibular salivary gland occurred only in females (0/10, 0/10, 0/10, 0/10, 3/10, 9/10). This minimal to mild change was characterized by acinar cells with increased amounts of pale basophilic cytoplasm and occasional vacuolation and shrunken duct cells with scant, pale, eosinophilic cytoplasm and occasional vacuolation. Thymic atrophy occurred in 30 and 100 mg/m^3 males and females and was characterized by thinning and hypocellularity of the cortex (males: 0/10, 0/9, 0/10, 0/10, 1/7, 7/7; females: 0/10, 0/10, 0/10, 0/10, 3/9, 9/9), and atrophy of the uterus (0/10, 0/10, 0/10, 0/10, 4/10, 8/10) , ovary (0/9, 0/10, 0/10, 0/10, 9/10, 9/10), and mammary gland fat pad (0/10, 0/10, 0/10, 0/10, 3/10, 10/10) occurred in females exposed to 30 or 100 mg/m^3. Uterine atrophy consisted of a decreased uterine horn diameter, stromal condensation, and shrunken glands. Atrophic ovaries contained follicles but either entirely lacked corpora lutea or had only very few, poorly developed corpora lutea. Mammary fat pad atrophy was characterized by pronounced shrinkage and lipid

TABLE 19
Incidences of Selected Nonneoplastic Lesions of the Respiratory System and the Bronchial Lymph Node in Mice in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male						
Lung[a]	10	10	10	10	10	10
Alveolus, Proteinosis[b]	0	10** (3.6)[c]	10** (4.0)	10** (4.0)	10** (4.0)	10** (4.0)
Chronic Active Inflammation	0	10** (2.7)	10** (2.6)	10** (2.5)	9** (3.0)	10** (3.0)
Alveolar Epithelium, Hyperplasia	0	10** (1.3)	10** (1.4)	10** (3.1)	10** (3.9)	10** (3.6)
Interstitium, Fibrosis	0	10** (1.0)	10** (1.6)	10** (3.1)	10** (3.9)	10** (3.7)
Foreign Body	0	10** (2.4)	10** (3.0)	10** (3.4)	10** (4.0)	10** (4.0)
Lymph Node, Bronchial	8	10	10	10	10	7
Hyperplasia	0	10** (2.6)	10** (2.1)	10** (2.2)	8** (2.1)	7** (1.9)
Pigmentation	0	10** (1.0)	10** (1.1)	10** (1.3)	10** (1.8)	7** (2.4)
Nose	10	10	10	10	10	10
Foreign Body	0	0	0	2 (1.0)	1 (1.0)	9** (2.2)
Trachea	10	10	10	10	10	10
Foreign Body	0	0	2 (1.0)	3 (1.0)	3 (1.0)	3 (2.0)
Larynx	10	10	10	10	10	10
Squamous Epithelium, Hyperplasia	0	0	0	3 (1.3)	9** (2.1)	8** (2.4)
Epiglottis, Squamous Metaplasia	1 (1.0)	0	0	9** (1.0)	8** (1.0)	9** (1.7)
Foreign Body	0	2 (1.0)	2 (1.0)	6** (1.2)	6** (1.2)	4* (1.8)
Female						
Lung	10	10	10	10	10	10
Alveolus, Proteinosis	0	10** (3.4)	10** (3.5)	10** (3.8)	10** (3.7)	10** (4.0)
Chronic Active Inflammation	0	10** (2.5)	10** (2.2)	10** (3.0)	9** (2.7)	10** (3.0)
Alveolar Epithelium, Hyperplasia	0	10** (1.3)	10** (1.6)	10** (1.8)	10** (3.1)	10** (4.0)
Interstitium, Fibrosis	0	10** (1.0)	10** (1.4)	10** (2.7)	9** (4.0)	10** (4.0)
Foreign Body	0	10** (2.2)	10** (3.0)	10** (3.0)	10** (3.9)	10** (4.0)
Lymph Node, Bronchial	9	10	10	10	8	10
Hyperplasia	0	10** (2.3)	10** (2.3)	10** (2.0)	6** (2.3)	8** (2.3)
Pigmentation	0	10** (1.0)	10** (1.1)	10** (1.2)	8** (2.0)	9** (2.3)
Nose	10	10	10	10	10	10
Foreign Body	0	0	0	2 (1.0)	3 (1.3)	10** (1.5)
Trachea	10	10	9	10	10	10
Foreign Body	0	0	1 (1.0)	6** (1.0)	1 (1.0)	5* (1.2)
Larynx	10	10	10	10	10	10
Squamous Epithelium, Hyperplasia	0	0	1 (1.0)	4* (1.3)	7** (2.3)	10** (2.4)
Epiglottis, Squamous Metaplasia	0	0	0	4* (1.3)	5* (1.2)	5* (1.6)
Foreign Body	0	0	1 (1.0)	5* (1.2)	4* (1.5)	6** (1.2)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

depletion of adipocytes with stromal collapse. These lesions occurred almost exclusively in animals that died before the end of the study and were considered secondary effects.

No significant differences were noted in sperm morphology or vaginal cytology parameters between exposed and chamber control mice that could be attributed to a direct effect of indium phosphide exposure (Tables I3 and I4).

Exposure Concentration Selection Rationale: Based on the increased lung weights and the increased incidences and severities of lung lesions in all groups of exposed males and females, concentrations of 1 mg/m^3 and greater were considered so high as to preclude their use in a 2-year study. Because no mouse lung burden data were available to aid in exposure concentration selection for mice, exposure concentrations selected were the same as for rats. Therefore, indium phosphide exposure concentrations selected for the 2-year inhalation study in mice were 0.03, 0.1, and 0.3 mg/m^3.

3-MONTH INTERIM EVALUATION IN THE 2-YEAR STUDY

At 3 months, 0.3 mg/m^3 males and females and 0.1 mg/m^3 females demonstrated an increased erythron as evidenced by increased hematocrit values, hemoglobin concentrations, or erythrocyte counts (Table F4). Decreases in mean cell volume and mean cell hemoglobin and an increase in platelet counts accompanied the increased erythron. There was evidence of an exposure-related increase in leukocyte and neutrophil counts in all exposed groups of female mice, which is consistent with the pulmonary inflammation observed microscopically. There was an increase in unbound iron-binding capacity (in 0.3 mg/m^3 males and in all exposed groups of females) and total iron-binding capacity (0.1 and 0.3 mg/m^3 females); there was no change in serum iron concentration.

Lung weights of all exposed groups of males and females were significantly greater (1.4- to 2.4-fold) than those of the chamber controls at 3 months (Tables 20 and G4). At 3 months, the most prominent lesions induced by exposure to indium phosphide occurred in the lungs and consisted of chronic active inflammation, foreign body (indium phosphide particles), and alveolar proteinosis (Tables 20, C5, and D5). The severity of these lesions tended to be similar between animals exposed to 0.03 and 0.1 mg/m^3 and increased in animals exposed to 0.3 mg/m^3 indium phosphide. Though less severe, these changes were qualitatively similar to those observed at higher concentrations in the 14-week study. The regenerative hyperplasia diagnosed in the 14-week study was present in these 3-month interim evaluation animals, but was not diagnosed separately.

Bronchial lymph nodes were markedly enlarged at 3 months. Hyperplasia at 3 months was similar to that which occurred in the 14-week study (Tables 19, 20, C5, and D5). Hyperplasia of the mediastinal lymph nodes was more subtle. Minimal foreign body (indium phosphide particles) was observed in the bronchial lymph nodes as well.

At 3 months, hematopoietic cell proliferation was observed in the liver of six exposed female mice but not in any chamber controls (Tables 20 and D5). As in the 14-week study, the incidences of hematopoietic cell proliferation in the spleen were increased in exposed mice at 3 months (males: chamber control, 0/10; 0.03 mg/m^3, 4/10; 0.01 mg/m^3, 5/10; 0.1 mg/m^3, 9/10; females: 4/10, 9/10, 10/10, 10/10).

Stop-Exposure Rationale: Because all exposure concentrations selected for the 2-year studies were below those used in the 14-week studies, a 3-month interim evaluation was added to the 2-year studies to determine the suitability of exposure concentrations for continuous 2-year exposure. When compared to the chamber controls, exposure of mice to 0.1 or 0.3 mg/m^3 caused a 1.7- to 2.2-fold increase in lung weights accompanied by a spectrum of proliferative and inflammatory lesions in the lungs. However, lung weights of mice exposed to 0.03 mg/m^3 were increased (40%), although to a lesser extent than those in groups at the higher exposure concentrations, and the lung lesions were considered minimal to mild. Because of the magnitude of the lung weight increases and the severity of the lung lesions in mice exposed to 0.1 or 0.3 mg/m^3, it was determined that these effects were sufficiently extensive to stop exposure of these groups of mice. Exposure was stopped immediately following pathology assessment (at 21 weeks) and these mice were allowed to continue unexposed in chambers until the end of the study.

TABLE 20
Lung Weights and Incidences of Selected Nonneoplastic Lesions in Mice at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
Male				
Necropsy body wt[a]	35.4 ± 0.8	35.9 ± 1.1	33.3 ± 0.6	33.8 ± 0.7
Lung Weight[a]				
Absolute	0.213 ± 0.003	0.300 ± 0.007▲▲	0.366 ± 0.019▲▲	0.451 ± 0.008▲▲
Relative	0.603 ± 0.008	0.849 ± 0.046▲▲	1.103 ± 0.062▲▲	1.340 ± 0.035▲▲
Lung[b]	10	10	10	10
Chronic Active Inflammation[c]	0	6** (2.0)[d]	10** (1.9)	10** (2.8)
Foreign Body	0	10** (1.0)	10** (1.1)	10** (2.0)
Alveolus, Proteinosis	0	10** (1.7)	10** (1.4)	10** (2.8)
Lymph Node, Bronchial	9	10	10	10
Hyperplasia	0	8** (3.1)	10** (3.5)	10** (4.0)
Foreign Body	0	8** (1.0)	9** (1.0)	10** (1.0)
Lymph Node, Mediastinal	6	6	9	6
Hyperplasia	0	3 (1.3)	4 (1.3)	6** (1.0)
Female				
Necropsy body wt[a]	30.5 ± 0.8	30.5 ± 1.3	28.8 ± 0.6	28.3 ± 0.6
Lung Weight[a]				
Absolute	0.216 ± 0.005	0.299 ± 0.008▲▲	0.378 ± 0.020▲▲	0.478 ± 0.018▲▲
Relative	0.713 ± 0.025	0.993 ± 0.040▲▲	1.313 ± 0.064▲▲	1.690 ± 0.059▲▲
Lung	10	10	10	10
Chronic Active Inflammation	0	9** (2.0)	9** (2.4)	9** (3.1)
Foreign Body	0	10** (1.0)	10** (1.1)	10** (2.0)
Alveolus, Proteinosis	0	10** (1.7)	10** (2.0)	10** (3.1)
Lymph Node, Bronchial	9	8	10	10
Hyperplasia	1 (2.0)	5* (2.8)	10** (3.5)	10** (4.0)
Foreign Body	0	4* (1.0)	9** (1.0)	10** (1.0)
Lymph Node, Mediastinal	4	5	6	6
Hyperplasia	0	0	4 (1.0)	3 (1.7)
Liver	10	10	10	10
Hematopoietic Cell Proliferation	0	1 (1.0)	2 (1.0)	3 (1.0)

▲▲ Significantly different (P≤0.01) from the chamber control group by Williams' or Dunnett's test
* Significantly different (P≤0.05) from the chamber control group by the Fisher exact test
** P≤0.01
[a] n=10; lung weights (absolute weights) and body weights are given in grams; lung-weight-to-body-weight ratios (relative weights) are given as g lung weight/g body weight as a percentage (mean ± standard error).
[b] Number of animals with tissue examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 21 and in the Kaplan-Meier survival curves (Figure 7). Survival rates of all exposed groups were lower than those of the chamber controls. Among the exposed groups, the survival rates of the 0.1 mg/m^3 groups were highest, followed by the 0.3 and 0.03 mg/m^3 groups, respectively; this suggests that discontinuation of exposure to the 0.1 and 0.3 mg/m^3 groups at 21 weeks improved the survival rates of those groups.

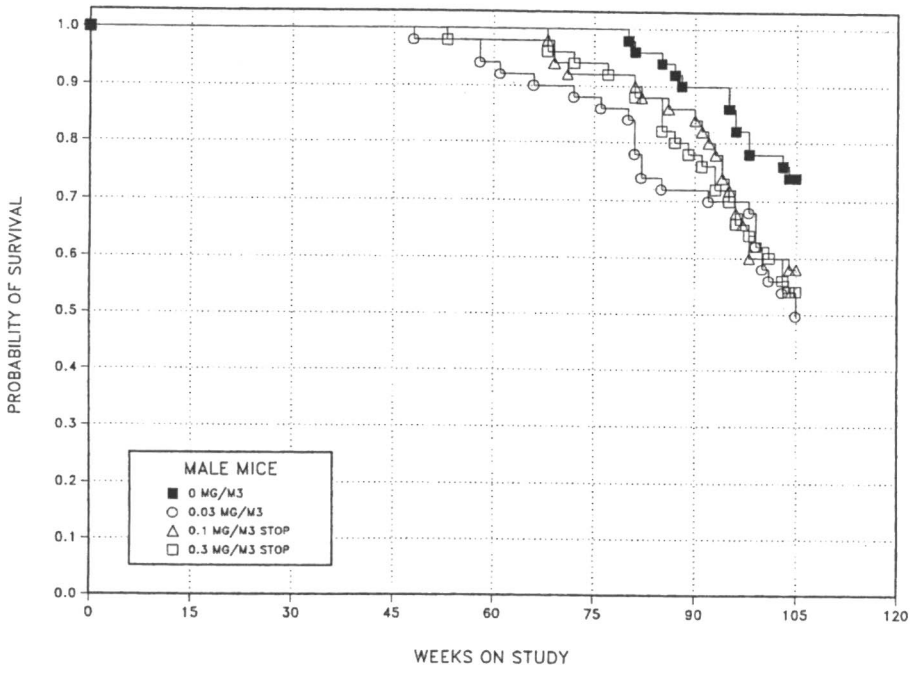
Body Weights and Clinical Findings

Mean body weights of 0.03 and 0.3 mg/m^3 males and all groups of exposed females were less than those of the chamber controls throughout most of the study; these decreases were slightly more severe in females. Mean body weights of the 0.03 and 0.3 mg/m^3 groups were generally similar (Figure 8; Tables 22 and 23).

TABLE 21
Survival of Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male				
Animals initially in study	60	60	60	60
3-Month interim evaluation[a]	10	10	10	10
Accidental death[a]	0	1	0	0
Moribund	5	14	12	12
Natural deaths	8	11	9	11
Animals surviving to study termination	37	24	29	27
Percent probability of survival at end of study[b]	74	50	58	54
Mean survival (days)[c]	711	660	685	679
Survival analysis[d]	P=0.064	P=0.016	P=0.106	P=0.046
Female				
Animals initially in study	60	60	60	60
3-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	1	0	0	1
Moribund	4	31	15	18
Natural deaths	3	6	2	10
Animals surviving to study termination	42	13	33	21
Percent probability of survival at end of study	86	26	66	43
Mean survival (days)	713	655	712	654
Survival analysis	P<0.001	P<0.001	P=0.044	P<0.001

[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, the 0.03 mg/m^3 group was excluded from the trend test and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns.



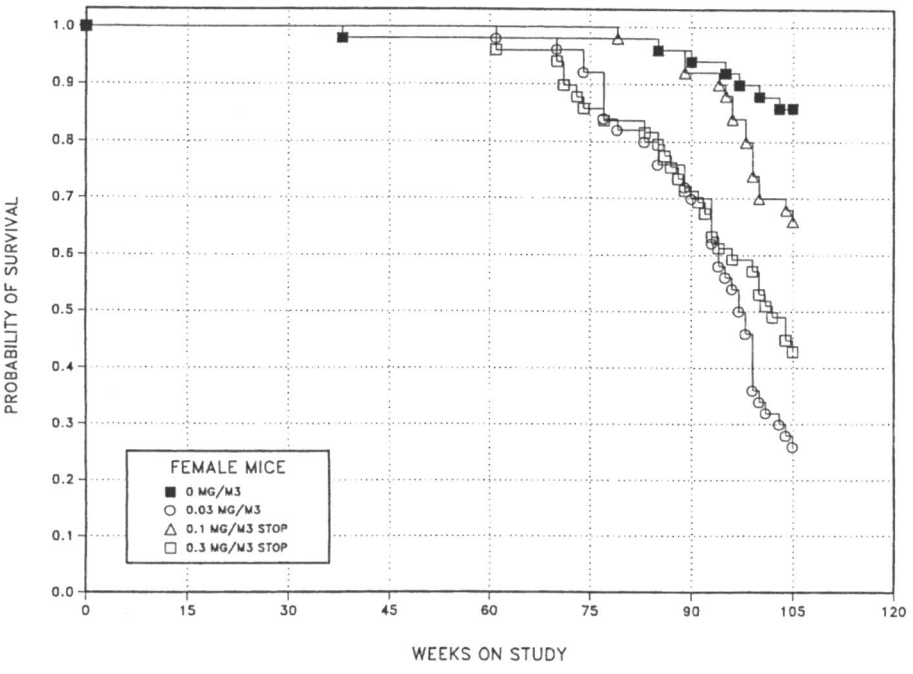


Figure 7
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Indium Phosphide by Inhalation for 2 Years.

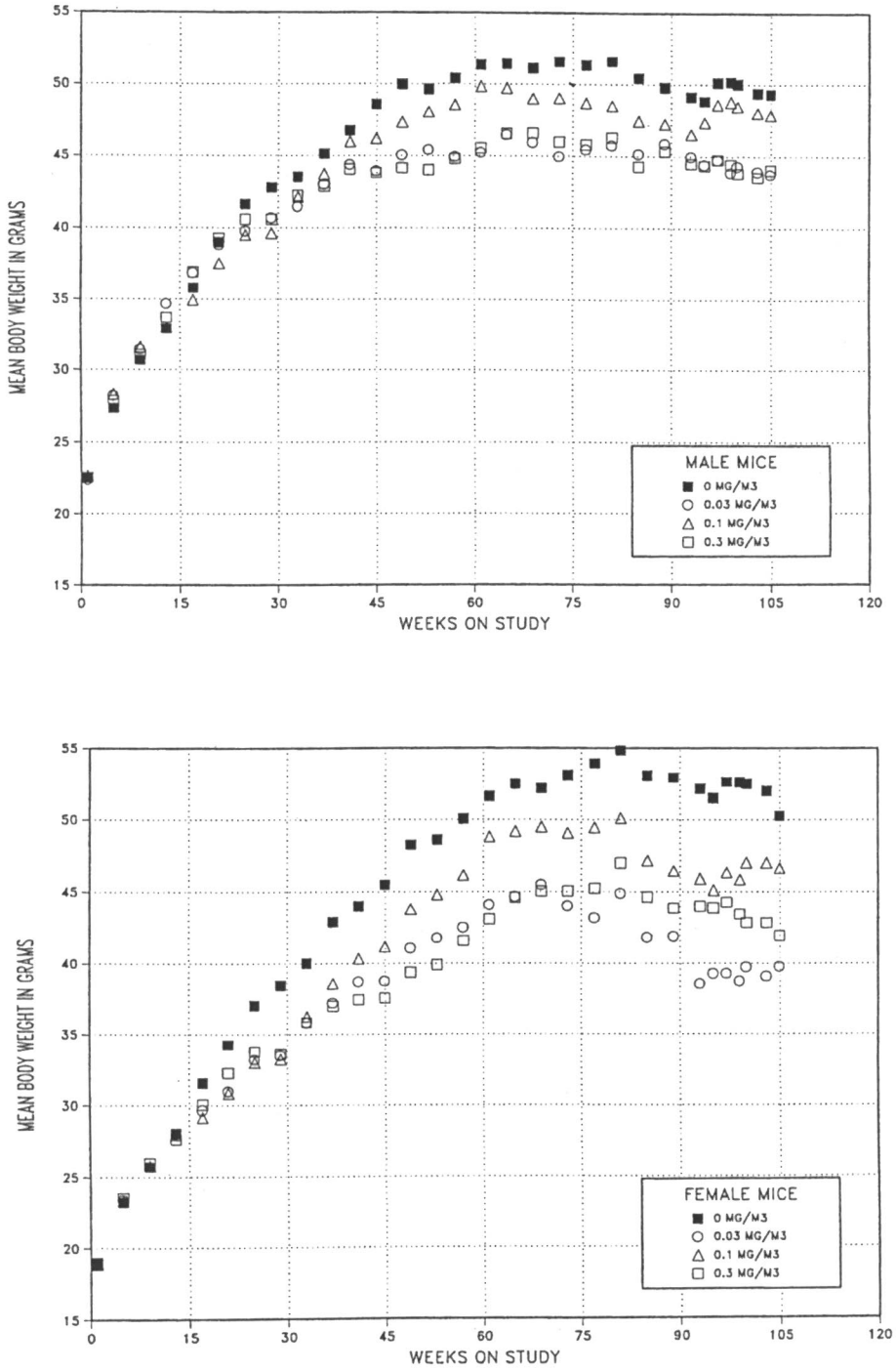


Figure 8
Growth Curves for Male and Female Mice Exposed to Indium Phosphide by Inhalation for 2 Years.

TABLE 22
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Indium Phosphide

Weeks on Study	Chamber Control		0.03 mg/m^3			0.1 mg/m^3 (Stop-Exposure)			0.3 mg/m^3 (Stop-Exposure)		
	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	22.5	60	22.3	99	60	22.6	100	60	22.5	100	60
5	27.3	60	28.2	103	60	28.3	104	60	27.9	102	60
9	30.7	60	31.5	103	60	31.6	103	60	31.1	101	60
13	32.9	60	34.7	106	60	33.0	100	60	33.7	102	60
17[a]	35.8	50	36.9	103	50	34.9	98	50	36.9	103	50
21	39.0	50	38.8	100	50	37.5	96	50	39.3	101	50
25	41.6	50	39.8	96	50	39.5	95	50	40.6	98	50
29	42.8	50	40.7	95	50	39.6	93	50	40.6	95	50
33	43.5	50	41.5	95	50	42.1	97	50	42.2	97	50
37	45.1	50	43.0	95	50	43.7	97	50	42.9	95	50
41	46.8	50	44.4	95	50	46.0	98	50	44.0	94	50
45	48.6	50	43.9	90	50	46.2	95	50	43.8	90	50
49	50.0	50	45.0	90	49	47.3	95	50	44.1	88	50
53	49.6	50	45.4	92	49	48.1	97	50	44.0	89	50
57	50.4	50	45.0	89	49	48.6	96	50	44.8	89	49
61	51.3	50	45.2	88	47	49.8	97	50	45.5	89	49
65	51.4	50	46.5	91	46	49.7	97	50	46.6	91	49
69	51.1	50	45.9	90	45	49.0	96	49	46.6	91	48
73	51.5	50	45.0	87	44	49.0	95	46	46.0	89	47
77	51.3	50	45.5	89	43	48.7	95	46	45.8	89	47
81	51.6	48	45.7	89	42	48.5	94	46	46.3	90	46
85	50.4	48	45.2	90	37	47.5	94	44	44.3	88	44
89	49.8	45	45.9	92	36	47.3	95	43	45.3	91	40
93	49.2	45	45.0	92	35	46.5	95	40	44.5	90	37
95	48.8	45	44.4	91	35	47.4	97	37	44.3	91	36
97	50.1	41	44.7	89	35	48.6	97	34	44.8	89	33
99	50.2	39	43.9	88	34	48.8	97	30	44.4	88	31
100	50.0	39	44.3	89	31	48.5	97	30	43.8	88	31
103	49.4	39	43.9	89	26	48.0	97	30	43.5	88	29
105	49.3	37	43.7	89	26	47.9	97	29	44.0	89	27
Mean for weeks											
1-13	28.4		29.2	103		28.9	102		28.8	101	
14-52	43.7		41.6	95		41.9	96		41.6	95	
53-105	50.3		45.0	89		48.3	96		45.0	89	

[a] Interim evaluation occurred during week 14.

TABLE 23
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Indium Phosphide

Weeks on Study	Chamber Control		0.03 mg/m^3			0.1 mg/m^3 (Stop-Exposure)			0.3 mg/m^3 (Stop-Exposure)		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.0	60	19.0	100	60	19.0	100	60	18.9	100	60
5	23.2	60	23.4	101	60	23.4	101	60	23.5	101	**59**
9	25.7	60	25.7	100	60	25.8	100	60	26.0	101	60
13	28.1	60	28.0	100	60	28.0	100	60	27.7	99	60
17[a]	31.6	50	29.7	94	50	29.2	92	50	30.1	95	50
21	34.3	50	31.0	90	50	30.9	90	50	32.3	94	50
25	37.1	50	33.2	90	50	33.0	89	50	33.8	91	50
29	38.5	50	33.5	87	50	33.2	86	50	33.6	87	49
33	40.0	50	35.8	90	50	36.3	91	50	35.9	90	49
37	42.9	50	37.2	87	50	38.6	90	50	37.0	86	49
41	44.0	49	38.7	88	50	40.3	92	50	37.4	85	49
45	45.5	49	38.8	85	50	41.2	91	50	37.6	83	49
49	48.3	49	41.0	85	50	43.8	91	50	39.4	82	49
53	48.6	49	41.8	86	50	44.8	92	50	39.9	82	49
57	50.0	49	42.5	85	50	46.2	92	50	41.6	83	49
61	51.6	49	44.1	86	50	48.8	95	50	43.1	84	49
65	52.5	49	44.7	85	49	49.2	94	50	44.6	85	47
69	52.2	49	45.5	87	49	49.5	95	50	45.1	86	47
73	53.0	49	44.0	83	48	49.1	93	50	45.0	85	44
77	53.9	48	43.2	80	46	49.5	92	50	45.2	84	42
81	54.8	48	44.9	82	41	50.1	91	49	47.0	86	41
85	53.0	48	41.8	79	40	47.2	89	49	44.6	84	40
89	52.9	47	41.9	79	38	46.5	88	48	43.9	83	36
93	52.1	46	38.6	74	35	45.9	88	46	44.0	85	33
95	51.5	46	39.3	76	29	45.1	88	45	43.9	85	30
97	52.6	45	39.3	75	27	46.3	88	42	44.3	84	29
99	52.6	44	38.8	74	23	45.9	87	40	43.5	83	29
100	52.4	43	39.7	76	18	47.0	90	35	42.9	82	26
103	52.0	42	39.1	75	16	47.0	90	35	42.9	83	24
105	50.3	42	39.8	79	14	46.6	93	34	41.9	83	22
Mean for weeks											
1-13	24.0		24.0	100		24.1	100		24.0	100	
14-52	40.2		35.4	88		36.3	90		35.2	88	
53-104	52.1		41.7	80		47.3	91		43.7	84	

[a] Interim evaluation occurred during week 14.

Clinical findings observed during the study included abnormal breathing, thinness, and ruffled fur. These findings were most common in the 0.03 mg/m^3 groups, followed by the 0.3 and 0.1 mg/m^3 groups. Thinness and ruffled fur were noted as early as 5 months, and abnormal breathing was first observed at 14 months.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the lung, bronchial and mediastinal lymph nodes, liver, small intestine, hematopoietic system, and cardiovascular system. 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 C for male mice and Appendix D for female mice.

Lung: At 2 years, there were significant increases in the incidences of alveolar/bronchiolar carcinoma in all groups of exposed males and in females exposed to 0.03 or 0.3 mg/m^3 (Tables 24, C3, and D3). The incidence of alveolar/bronchiolar adenoma was increased in 0.1 mg/m^3 females, and the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were increased in all exposed groups of females. The incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) in most groups of exposed males and females exceeded historical control ranges for 2-year NTP studies in which chamber controls were given NIH-07 feed (inhalation studies) and control mice were given NTP-2000 (all routes) (Tables 24, C4a, and D4a). The exceptions include the 0.03 mg/m^3 and 0.1 mg/m^3 females which did not exceed the historical ranges for 2-year NTP inhalation studies in which female controls were given NIH-07 feed.

Alveolar/bronchiolar adenomas and many of the alveolar/bronchiolar carcinomas resembled those observed spontaneously. Morphologically, they were composed of epithelium arranged in papillary fronds and/or solid sheets. These neoplasms effaced/replaced normal alveolar architecture and often compressed surrounding lung parenchyma. Carcinomas were distinguished from adenomas by local invasion, metastasis and/or greater anaplasia and/or pleomorphism of component cells. Some of the carcinomas differed somewhat from spontaneous carcinomas. They were very anaplastic with papillary and sclerosing patterns; several appeared to have spread outside the lungs into the mediastinum and distant metastases. A few appeared to have extensive intrapulmonary spread which in several instances was diagnosed as carcinoma, multiple (Plates 17, 18, and 19). Alveolar epithelial hyperplasia in the lung is generally considered to be a precursor to neoplasia in the mouse but was not significantly increased in male or female mice.

Histopathologic analyses were performed on lungs of animals designated for tissue burden studies. At 145 days, the lung lesions were similar albeit somewhat more severe than at the 3-month interim evaluation. At 2 months after discontinuation of exposure to the 0.1 and 0.3 mg/m^3 groups, chronic inflammation, alveolar epithelial hyperplasia and alveolar proteinosis were less severe than at 145 days. Pleural thickening and rounding up of mesothelial cells appeared similar. At 4 and 6 months after cessation of exposure, proteinosis and hyperplasia appeared less severe, but the chronic inflammation appeared similar to that observed at 145 days. The only mice evaluated at 12 months on test were still being exposed to 0.03 mg/m^3. The lesions were clearly more severe than those observed in mice exposed to 0.03 mg/m^3 at 145 days on test and were similar to those observed in the 0.3 mg/m^3 group at 145 days. At 2 years, there were increased incidences of chronic active inflammation, alveolar proteinosis and foreign body (indium phosphide particles) in the lungs of exposed mice. Chronic active inflammation of the lung consisted of collections of varying numbers of macrophages, neutrophils, and lymphocytes both in the alveolar spaces and in the interstitium of alveolar septa and visceral pleura. Prominent mononuclear inflammatory cell cuffs were often present in the perivascular and peribronchiolar areas. Occasionally there were focal, generally peripheral, areas of neutrophil accumulation that were sometimes intense. When this occurred, the chronic active inflammation was generally moderate to marked. This inflammation was more severe in mice exposed to 0.03 mg/m^3 and was least severe in the 0.1mg/m^3 group. A prominent feature of the inflammatory process was the presence of pleural fibrosis (diagnosed

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung and Associated Lymph Nodes in Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male				
Lung[a]	50	50	50	50
Alveolar Epithelium, Hyperplasia[b]	2 (1.5)[c]	5 (2.4)	3 (2.7)	7 (2.1)
Chronic Active Inflammation	2 (1.0)	50** (2.9)	45** (1.6)	46** (2.1)
Alveolus, Proteinosis	0	14** (1.0)	0	10** (1.0)
Foreign Body	0	49** (1.0)	42**	49**
Serosa, Fibrosis	0	50** (3.5)	49** (2.0)	50** (2.4)
Alveolar/bronchiolar Adenoma, Multiple	1	2	0	3
Alveolar/bronchiolar Adenoma, (includes multiple)	13	9	7	13
Alveolar/bronchiolar Carcinoma, Multiple	1	8*	3	4
Alveolar/bronchiolar Carcinoma (includes multiple)[d]				
Overall rate[e]	6/50 (12%)	15/50 (30%)	22/50 (44%)	13/50 (26%)
Adjusted rate[f]	12.9%	36.5%	48.6%	29.7%
Terminal rate[g]	4/37 (11%)	9/24 (38%)	14/29 (48%)	6/27 (22%)
First incidence (days)	664	457	478	589
Poly-3 test[h]	P=0.134	P=0.008	P<0.001	P=0.042
Alveolar/bronchiolar Adenoma or Carcinoma (includes multiple)[i]				
Overall rate	18/50 (36%)	23/50 (46%)	24/50 (48%)	21/50 (42%)
Adjusted rate	38.6%	54.5%	52.6%	47.1%
Terminal rate	15/37 (41%)	13/24 (54%)	15/29 (52%)	12/27 (44%)
First incidence (days)	664	457	478	562
Poly-3 test	P=0.312	P=0.094	P=0.122	P=0.270
Pleura	0	19** (2.1)	4 (2.0)	6* (1.5)
Mesothelium, Hyperplasia				
Lymph Node, Bronchial	35	48	45	48
Hyperplasia	2 (2.5)	36** (2.3)	22** (2.0)	22** (2.0)
Foreign Body	0	43** (1.0)	40** (1.0)	40** (1.0)
Lymph Node, Mediastinal	40	49	45	48
Hyperplasia	0	34** (2.5)	17** (2.1)	27** (2.2)
Foreign Body	0	24** (1.0)	14** (1.0)	25** (1.0)

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung and Associated Lymph Nodes in Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Female				
Lung	50	50	50	50
Alveolar Epithelium, Hyperplasia	0	1 (2.0)	1 (3.0)	2 (2.0)
Chronic Active Inflammation	2 (2.5)	49** (2.9)	45** (1.7)	50** (2.1)
Alveolus, Proteinosis	0	31** (1.1)	0	8** (1.4)
Foreign Body	0	49** (1.0)	35**	49**
Serosa, Fibrosis	0	50** (3.8)	47** (1.8)	49** (2.5)
Alveolar/bronchiolar Adenoma, Multiple	0	0	1	2
Alveolar/bronchiolar Adenoma (includes multiple)[j]	3	6	10*	7
Alveolar/bronchiolar Carcinoma, Multiple	0	1	0	0
Alveolar/bronchiolar Carcinoma (includes multiple)[k]				
Overall rate	1/50 (2%)	6/50 (12%)	5/50 (10%)	7/50 (14%)
Adjusted rate	2.1%	15.8%	10.8%	17.6%
Terminal rate	1/42 (2%)	2/13 (15%)	3/33 (9%)	1/21 (5%)
First incidence (days)	735 (T)	580	664	600
Poly-3 test	P=0.017	P=0.029	P=0.099	P=0.016
Alveolar/bronchiolar Adenoma or Carcinoma[l] (includes multiple)				
Overall rate	4/50 (8%)	11/50 (22%)	15/50 (30%)	14/50 (28%)
Adjusted rate	8.5%	28.8%	31.9%	34.4%
Terminal rate	3/42 (7%)	6/13 (46%)	9/33 (27%)	5/21 (24%)
First incidence (days)	699	580	658	600
Poly-3 test	P=0.006	P=0.014	P=0.004	P=0.002
Pleura	0	16** (1.8)	3 (1.7)	13** (1.9)
Mesothelium, Hyperplasia				
Lymph Node, Bronchial	36	50	48	50
Hyperplasia	5 (1.8)	42** (2.8)	31** (2.2)	28** (2.2)
Foreign Body	0	44** (1.0)	33** (1.0)	40** (1.0)
Lymph Node, Mediastinal	42	48	46	49
Hyperplasia	2 (2.0)	40** (3.0)	11** (2.2)	29** (2.6)
Foreign Body	0	20** (1.0)	7** (1.0)	16** (1.0)

(T) Terminal sacrifice
* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Historical incidence for 2-year control groups given NTP-2000 feed (mean ± standard deviation): 23/249 (9.2% ± 3.9%); range 4%-14%
[e] Number of animals with neoplasm per number of animals with lung examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the chamber control incidence are the P values associated with the trend test (the 0.03 mg/m^3 group was excluded from 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.
[i] Historical incidence: 58/249 (23.3% ± 9.4%); range 12%-36%
[j] Historical incidence: 15/250 (6.0% ± 5.1%); range 0%-12%
[k] Historical incidence: 3/250 (1.2% ± 1.1%); range 0%-2%
[l] Historical incidence: 17/250 (6.8% ± 5.6%); range 0%-12%

as lung, serosa, fibrosis) (Plate 20) which in many instances appeared to involve both visceral and parietal pleura with adhesions. The fibrosis was usually focal, but was sometimes expansive and somewhat diffuse. Usually, these fibrotic areas were associated with areas of inflammation. Pulmonary interstitial fibrosis was uncommon.

Alveolar proteinosis was observed only in mice exposed to 0.03 and 0.3 mg/m^3 and was characterized by the presence of amorphous, granular to homogeneous eosinophilic material (surfactant) in alveoli. When present, it was minimal and was seen in scattered alveoli. Foreign body (indium phosphide) was minimal in all groups and was not always present in animals exposed to 0.1 mg/m^3.

As in the 14-week study and interim sacrifice animals, regenerative alveolar epithelial hyperplasia occurred within areas of chronic active inflammation but was not diagnosed separately.

The incidences of pleural mesothelial hyperplasia of the lung were increased in males and females exposed to 0.03 and 0.3 mg/m^3. Generally associated with the chronic inflammation and fibrosis, the pleural mesothelium from many animals was hypertrophic and/or hyperplastic. Normally, the visceral mesothelium is a single layer of flattened epithelium. Affected mesothelium ranged from a single layer of plump (hypertrophic) cells to several layers of rounded cells (hyperplasia) (Plate 21). In the more severe cases, proliferations formed papillary fronds that projected into the pleural cavity (Plate 21).

Bronchial and Mediastinal Lymph Nodes: At 2 years, the incidences of hyperplasia and the appearance of foreign bodies in the bronchial and mediastinal lymph nodes were increased in all groups of exposed mice; however, the incidences and severities of hyperplasia were greater in the 0.03 mg/m^3 males and females that were continuously exposed for 2 years (Tables 24, C5, and D5). Hyperplasia was characterized by an increase in the size of the lymph nodes, accompanied by an increase in germinal centers and increased cellularity of the medullary and cortical regions by lymphocytes and histiocytes. Foreign bodies represented indium phosphide particles that were primarily located within phagocytic cells within the nodes.

Liver: At 2 years, there were increased incidences of hepatocellular adenoma in the 0.03 and 0.3 mg/m^3 male mice and increased incidences of hepatocellular carcinoma in 0.1 mg/m^3 males and 0.03 mg/m^3 males and females (Tables 25, C3, and D3). The incidences of hepatocellular adenoma or carcinoma (combined) were increased in all groups of exposed males and in the 0.03 mg/m^3 females. The incidences of adenoma, carcinoma, and adenoma or carcinoma (combined) in exposed males and females exceeded the ranges in NTP-2000 studies and the incidence of adenoma in the 0.3 mg/m^3 males exceeded the historical control range in the larger NIH-07 database. The incidence of hepato-cellular adenoma or carcinoma (combined) in the 0.03 mg/m^3 female mice exceeded the historical control range in the NIH-07 database (Tables 25, C4b, and D4b). In some instances, multiplicity was increased in exposed groups. The incidences of eosinophilic foci were increased in all groups of exposed males and in 0.3 mg/m^3 females. Foci of hepatocellular alteration, hepatocellular adenoma, and hepatocellular carcinoma are thought to represent a spectrum that constitutes the progression of proliferative liver lesions. The increased incidences of liver lesions observed in this study are considered related to exposure to indium phosphide.

The adenomas were well-demarcated nodular proliferations which often occupied several lobules and caused compression of the surrounding parenchyma. There was loss of normal lobular architecture and hepatic cords abruptly intersected with those of the surrounding tissue. Although the cellular morphology within neoplasms varied, generally, the neoplastic cells were large, variably vacuolated and contained abundant eosin-ophilic cytoplasm and large round nuclei. Hepatocellular carcinomas were generally larger with more anaplastic cells often arranged in thick trabeculae with some metastasizing to distant sites. The eosinophilic foci were variably sized with the largest occupying several hepatic lobules with limited compression of the adjacent parenchyma. They were composed of large cells as described for the adenomas.

Small Intestine: The incidence of carcinoma of the small intestine in 0.1 mg/m^3 males was slightly increased (chamber control, 0/50; 0.03 mg/m^3, 1/50; 0.1 mg/m^3, 5/50; 0.3 mg/m^3, 3/50) and was equal to the highest incidence in the NTP-2000 historical control

TABLE 25
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus[a]	10	16*	19*	18*
Hepatocellular Adenoma, Multiple	8	13	10	14
Hepatocellular Adenoma (includes multiple)[b]				
Overall rate[c]	17/50 (34%)	24/50 (48%)	23/50 (46%)	32/50 (64%)
Adjusted rate[d]	36.5%	58.9%	51.8%	70.5%
Terminal rate[e]	15/37 (41%)	15/24 (63%)	18/29 (62%)	21/27 (78%)
First incidence (days)	664	562	481	370
Poly-3 test[f]	P<0.001	P=0.026	P=0.099	P<0.001
Hepatocellular Carcinoma, Multiple	1	7*	10**	5
Hepatocellular Carcinoma (includes multiple)[g]				
Overall rate	11/50 (22%)	22/50 (44%)	23/50 (46%)	16/50 (32%)
Adjusted rate	23.2%	46.4%	47.3%	36.1%
Terminal rate	5/37 (14%)	6/24 (25%)	6/29 (21%)	7/27 (26%)
First incidence (days)	607	331	478	562
Poly-3 test	P=0.215	P=0.014	P=0.010	P=0.130
Hepatoblastoma	0	1	0	0
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma (includes multiple)[h]				
Overall rate	26/50 (52%)	40/50 (80%)	37/50 (74%)	39/50 (78%)
Adjusted rate	54.6%	83.2%	76.1%	82.7%
Terminal rate	19/37 (51%)	19/24 (79%)	20/29 (69%)	22/27 (82%)
First incidence (days)	607	331	478	370
Poly-3 test	P=0.003	P<0.001	P=0.019	P=0.002

TABLE 25
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Female				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus	6	9	4	12*
Hepatocellular Adenoma, Multiple	0	8*	6*	4
Hepatocellular Adenoma (includes multiple)[i]				
Overall rate	12/50 (24%)	14/50 (28%)	18/50 (36%)	14/50 (28%)
Adjusted rate	25.6%	36.2%	37.7%	34.7%
Terminal rate	12/42 (29%)	5/13 (39%)	10/33 (30%)	6/21 (29%)
First incidence (days)	735 (T)	589	617	496
Poly-3 test	P=0.265	P=0.205	P=0.148	P=0.245
Hepatocellular Carcinoma, Multiple	2	4	1	2
Hepatocellular Carcinoma (includes multiple)[j]				
Overall rate	6/50 (12%)	17/50 (34%)	8/50 (16%)	10/50 (20%)
Adjusted rate	12.7%	41.7%	17.4%	24.7%
Terminal rate	4/42 (10%)	5/13 (39%)	7/33 (21%)	2/21 (10%)
First incidence (days)	626	489	691	594
Poly-3 test	P=0.102	P<0.001	P=0.365	P=0.120
Hepatoblastoma	0	0	0	1
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma (includes multiple)[k]				
Overall rate	18/50 (36%)	28/50 (56%)	24/50 (48%)	23/50 (46%)
Adjusted rate	38.1%	66.7%	50.1%	54.2%
Terminal rate	16/42 (38%)	10/13 (77%)	15/33 (46%)	8/21 (38%)
First incidence (days)	626	489	617	496
Poly-3 test	P=0.096	P=0.004	P=0.163	P=0.090

(T) Terminal sacrifice
* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion
[b] Historical incidence for 2-year studies with control groups given NTP-2000 feed (mean ± standard deviation): 73/249 (29.3% ± 10.3%); range 12%-38%
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the chamber control incidence are the P values associated with the trend test (the 0.03 mg/m^3 group was excluded from 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.
[g] Historical incidence: 50/249 (20.1% ± 4.2%); range 16%-27%
[h] Historical incidence: 111/249 (44.6% ± 9.5%); range 30%-52%
[i] Historical incidence: 40/249 (16.1% ± 6.1%); range 8%-24%
[j] Historical incidence: 16/249 (6.4% ± 3.3%); range 4%-12%
[k] Historical incidence: 52/249 (20.9% ± 9.1%); range 12%-36%

database [6/249 (2.4% ± 4.3%); range 0%-10%] (Tables C3 and C4c); the incidence exceeded the range observed in the larger NIH-07 database for inhalation studies [6/1,074 (0.6% ± 1.1%); range 0%-4%]. The incidence of adenoma or carcinoma (combined) (1/50, 2/50, 6/50, 3/50) in this group also was within the range for the NTP-2000 historical control database but exceeded the range in the NIH-07 database. As indicated by the NIH-07 historical control database (inhalation studies only), small intestinal epithelial neoplasms are quite uncommon in male mice [8/1,074 (0.8% ± 1.3%); range 0%-4%], however, as evidenced by the NTP-2000 database, recent studies appear to have a higher spontaneous incidence [11/249 (4.4% ± 5.9%); range 0%-14%] with as many as seven occurring in control males from one study. Chemical-induced carcinogenicity in the intestine is relatively uncommon, having been seen in only 14 NTP studies. It is even more rare in mice, having unequivocally occurred in only one study. Although the increased incidence in the 0.1 mg/m^3 males was within the historical control range for the NTP-2000 studies, it fell well outside the range for the larger NIH-07 database and was considered an uncertain finding.

Hematopoietic System: There was a slight positive trend in the incidences of malignant lymphoma in female mice (chamber control, 8/50; 0.03 mg/m^3, 4/50; 0.1 mg/m^3, 10/50; 0.3 mg/m^3, 13/50; Table D3) and the incidences in the 0.1 and 0.3 mg/m^3 groups exceeded the historical control range for NTP-2000 studies [33/250 (13.2% ± 4.6%); range 6%-18%]. However, the incidences in the exposed groups were not significantly increased. Additionally, the incidences in the 0.1 and 0.3 mg/m^3 groups were within the historical range for NIH-07 inhalation studies [162/1,077 (15.1% ± 7.5%); range 6%-32%]. At this time, the mean incidence of malignant lymphomas appears to be similar between the two historical control databases. The incidences for chamber control males and females for the NIH-07 database are 47/1,074 (4.4%) and 162/1,077 (15.1%), respectively. The incidences for control males and females for the NTP-2000 database are 10/249 (4.0%) and 33/250 (13.2%), respectively. The slight positive trend was not considered related to exposure to indium phosphide.

At 2 years, the incidences of hematopoietic cell proliferation in the spleen (males: 14/50, 34/50, 23/48, 29/48; females: 16/50, 36/49, 26/50, 21/49; Table C5 and D5) were increased in all exposed groups of males and in females exposed to 0.03 and 0.1 mg/m^3. As noted in the control animals, minimal hematopoietic cell proliferation is common in the spleen of mice and in this study appeared to be composed equally of erythroid and granulocytic cells.

Cardiovascular System: There were increased incidences of inflammation of the arteries of the heart (males: 3/50, 18/50, 14/50, 10/50; females: 1/50, 16/50, 11/50, 13/50; Tables C5 and D5), primarily the coronary arteries and the proximal aorta at the base of the heart. The arteritis was generally characterized by intimal and medial hypertrophy/hyperplasia and an intense inflammatory reaction containing predominately neutrophils and mononuclear inflammatory cells (Plates 22 and 23). Pyknotic and karyorrhectic cellular debris were also common. Lesser incidences of qualitatively similar vasculitis occurred in other organs including the kidney, mesentery, lung, and mediastinal and bronchial lymph nodes.

Additionally, chronic inflammatory lesions were observed in the pericardium (males: 0/50, 6/50, 0/50, 5/50; females: 0/50, 9/50, 0/50, 4/50) and epicardium (males: 0/50, 2/50, 1/50, 0/50; females: 1/50, 5/50, 0/50, 7/50) of the heart of several animals exposed to 0.03 and 0.3 mg/m^3. These microscopic areas of inflammation correlate to the adhesions noted grossly.

Tissue Burden Analyses

Tissue burden analyses were performed on male mice during exposure and post exposure periods and on female mice following 21 weeks of exposure (Table H13).

Lung weights of exposed male mice were significantly increased relative to chamber control lung weights and increased with increasing exposure concentration and duration of exposure (Table H14). Following cessation of exposure, lung weights in the 0.1 and 0.3 mg/m^3 groups remained significantly elevated, showing very little recovery. Lung burdens, like lung weights, increased with time and with increasing exposure concentration in all groups (Figure 9). For the 0.1 and 0.3 mg/m^3 groups, lung burdens were reduced by 2 months after exposure and continued to decline until 12 months after exposure when they had decreased to 16% and 28% of the values observed at the end of exposure, respectively. Thus lung burdens

decreased to a greater extent during the clearance phase of the study than did lung weights, which remained elevated due to the pathological changes present in the lung. Lung burdens, when normalized to exposure concentrations, remained constant across exposure concentrations, indicating linear toxicokinetics. Lung deposition rates increased proportionately to exposure concentration in male mice (Table H15). There were no differences in the calculated lung deposition fraction, clearance rate constant, or clearance half-times among exposed groups. Although estimated clearance half-times for indium in the lung were 230, 144, and 163 days respectively for the three exposed groups, there was considerable overlap in their uncertainties. The overall mean clearance half-time for the exposed groups was 179 days.

There were no significant differences between male and female mice in exposure-related lung weight increases, lung indium concentrations, lung burdens, normalized lung burdens, or serum indium concentrations (Tables H14 and H16). The lung deposition and clearance model was utilized to estimate the total amount of indium deposited in the lung after exposure to 0.03 mg/m^3 for 2 years or to 0.1 or 0.3 mg/m^3 for 21 weeks, the lung burdens at the end of the 2-year study, and the area under the lung burden curves (AUC) shown in Figure 9 for each of these exposure conditions (Table 26). Terminal lung burdens for the 0.03, 0.1, and 0.3 mg/m^3 groups were 6.2, 0.5, and 2.3 µg of indium, respectively, indicating that this estimation predicted more indium in the lungs of mice at 2 years following continuous exposure to 0.03 mg/m^3 indium phosphide than in the lungs of mice exposed to 0.1 or 0.3 mg/m^3 indium phosphide for 21 weeks and then held unexposed until the end of the 2-year study. The estimated total amount of indium deposited in the lung at the time that exposure to indium phosphide was stopped (2 years for the 0.03 mg/m^3 group and 21 weeks for the 0.1 and 0.3 mg/m^3 groups) was greater in the 0.3 mg/m^3 group than in the 0.03 or 0.1 mg/m^3 groups: 37, 15, or 11 µg of indium per lung, respectively. Similarly, the AUCs calculated for each exposure concentration over the course of the entire study demonstrated that the 0.3 mg/m^3 group received greater exposure than did the 0.03 or 0.1 mg/m^3 groups. Due to the different exposure durations (2 years or 21 weeks) and the slow clearance of deposited indium, the contribution of the first year on study for 0.03, 0.1, and 0.3 mg/m^3 were 33%, 78%, and 75% of the total estimated AUC values. The second-year AUC for the 0.03 mg/m^3 group was equivalent to that of the 0.3 mg/m^3 group. The difference between the total deposited dose and the lung burden at 2 years reflects the amount of indium cleared from the lungs during the 2-year study. Regardless of how the total "dose" of indium to the lung was estimated, the 0.1 mg/m^3 group received less total exposure than the continuously exposed 0.03 mg/m^3 group or the 0.3 mg/m^3 group exposed for 21 weeks, implying that the 0.1 mg/m^3 group may be considered the "low dose" in this study.

Indium concentrations in serum were detectable above the experimental limits of quantitation, primarily in mice exposed to 0.1 and 0.3 mg/m^3 (Table H16). The concentration of indium in serum were quite low relative to those measured in the lung. Serum indium concentrations increased in proportion to concentration and duration of exposure and slowly decreased after exposure termination, which is consistent with the slow elimination of indium from the lungs.

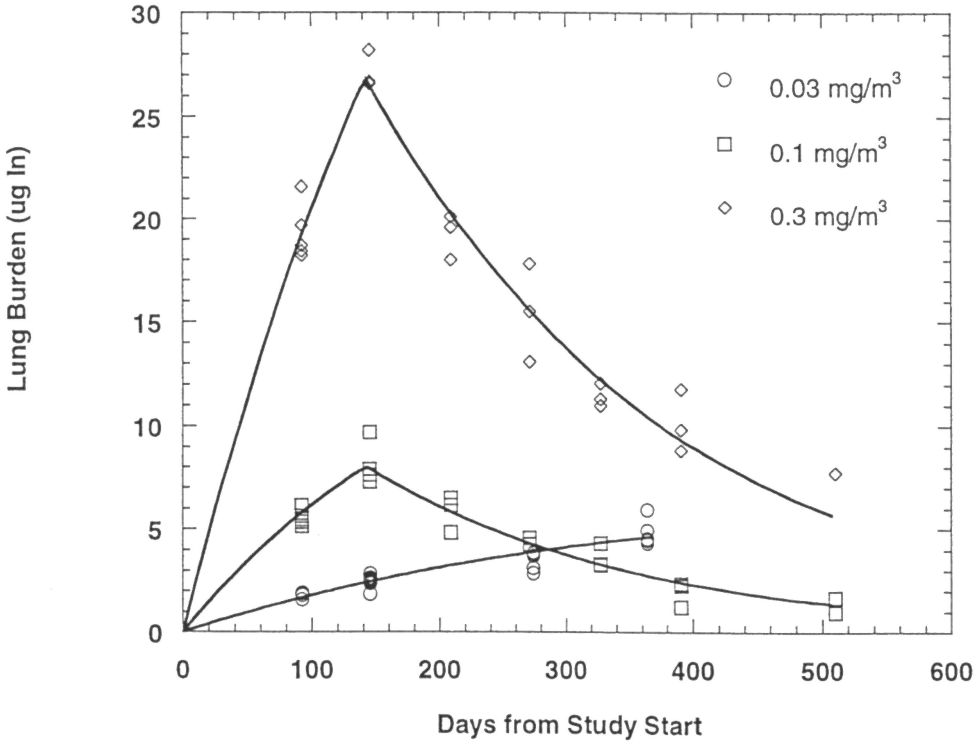


Figure 9
Lung Burden of Indium (µg In) in Male Mice in the 2-Year Inhalation Study of Indium Phosphide.
Data are presented as mean ± standard deviation. Curves represent the fit of the lung deposition and clearance model to the data and the estimated lung burden at 2 years.

TABLE 26
Lung Deposition and Clearance Model-Based Estimates of Exposure to Indium for Mice in the 2-Year Inhalation Studies of Indium Phosphide

	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
Lung Burden at 2 Years (μg In/lung)	6.2	0.5	2.3
Lung Deposited Dose (total μg In deposited/lung)[a]	15	11	37
First-Year AUC (μg In/lung • days on study)[b]	1,001	1,764	6,078
Second-Year AUC (μg In/lung • days on study)[c]	2,032	486	1,986
Total AUC (μg In/lung • days on study)[d]	3,000	2,200	8,000

[a] Total amount of indium deposited in the lung (2 years exposure for the 0.03 mg/m^3 group and 21 weeks for the 0.1 and 0.3 mg/m^3 groups)
[b] Area under the lung burden curve for the first year
[c] Area under the lung burden curve for the second year
[d] Area under the lung burden curve for 2 years

GENETIC TOXICOLOGY

Blood samples from female mice exposed to indium phosphide for 14 weeks by inhalation showed no significant increase in the frequency of micronucleated normochromatic erythrocytes (NCEs) (Table E1). Also in female mice, analysis of micronucleus frequencies in polychromatic erythrocytes (PCEs) in the 30 mg/m^3 group was consistent with the lack of effect seen in the NCE population. In male mice, the trend analysis showed a small but non-significant (P=0.054) concentration-related increase in the frequency of NCEs; a greater effect was observed in PCEs, where a significant increase (P=0.01) in the number of micronuclei was observed in the 30 mg/m^3 group (Table E1). The PCE data for the male mice may indicate a recent induction of genetic damage that is rapidly eliminated or reduced in the mature NCE population, preventing the accumulation of damaged mature erythrocytes with repeated exposure. The fact that similar effects were not seen in female mice is reason to be cautious in interpreting the effects observed in male mice. In neither sex was the percentage of PCEs altered.

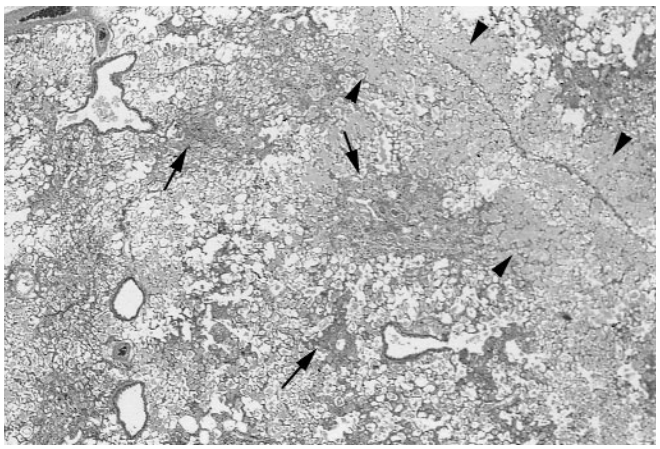


Plate 1

Lung: Low magnification of the lung from a male rat exposed to 100 mg/m^3 indium phosphide in the 90-day inhalation study. Note the diffuse distribution of the inflammation (arrows) and proteinosis (between arrow heads) obscuring the normally clear alveoli. H&E 15X

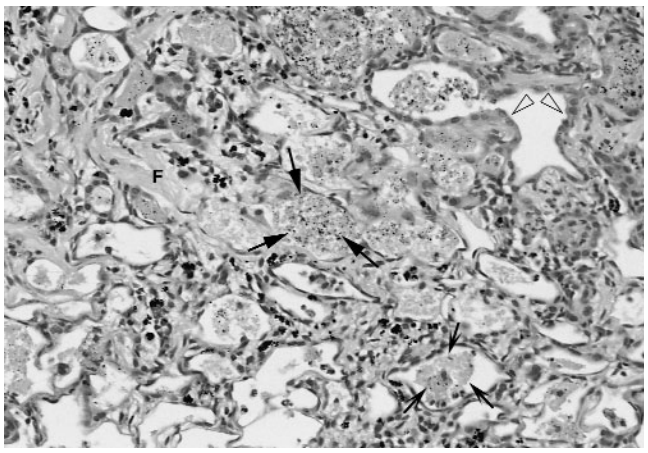


Plate 2

Lung: Higher magnification of an area of inflammation from a male rat exposed to 100 mg/m^3 indium phosphide in the 90-day inhalation study. Note the fibrosis (F) and foamy alveolar macrophages filled with proteinaceous material (small arrows). Indium phosphide particles (black dots; big arrows) are admixed with proteinosis and cellular debris. Normally flattened alveolar epithelium is replaced with cuboidal regenerative epithelium (hyperplasia; open arrow heads). H&E 150X

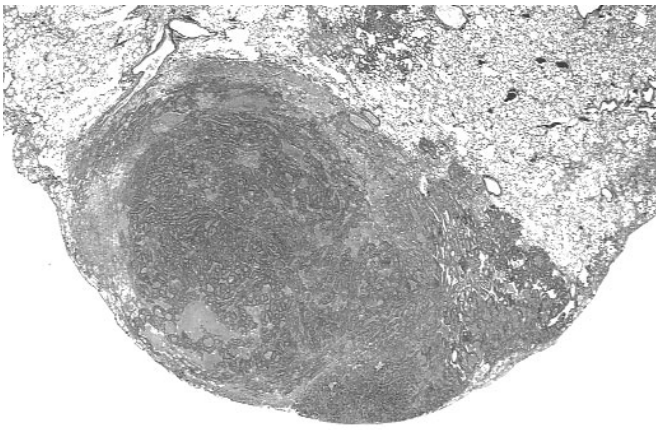


Plate 3

Lung: Alveolar/bronchiolar carcinoma in the lung of a female rat exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 8X

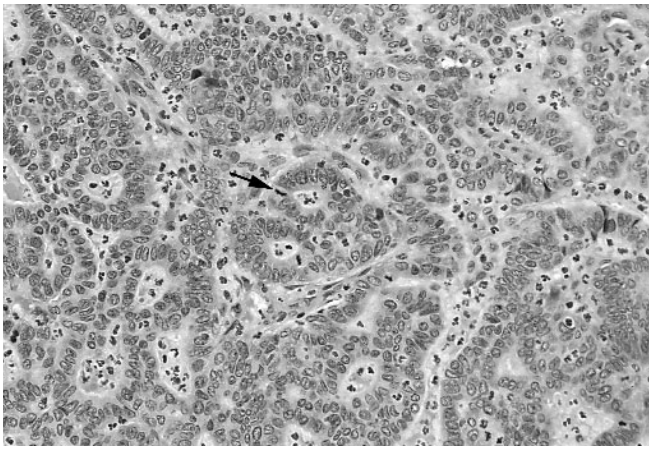


Plate 4

Lung: Higher magnification of plate 3. Component cells are arranged in acini and papillary projections. Note the variation in nuclear size and shape and a mitotic figure (arrow). Female rat exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 150X

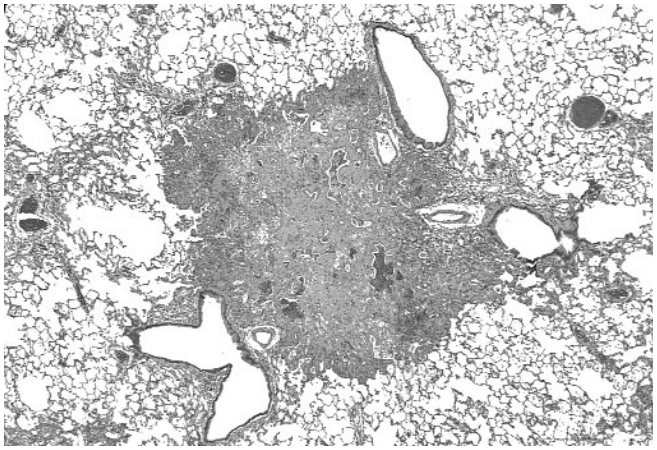


Plate 5
Lung: Atypical hyperplasia in the lung of a male rat exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 18X

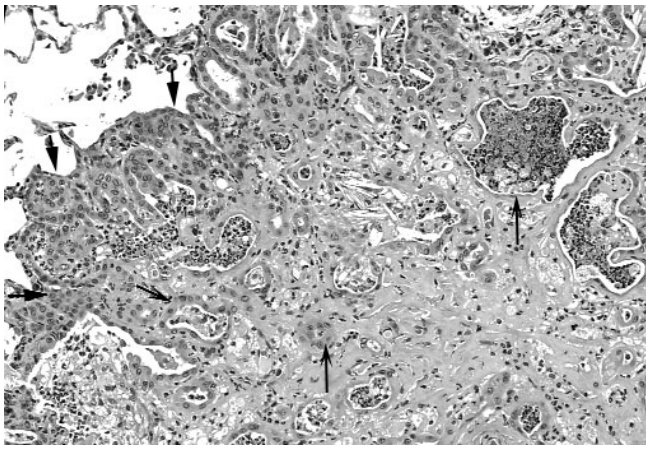


Plate 6
Lung: Higher magnification of plate 5. Note the glandular structures (small arrows) within the fibrous central core. These glands are filled with necrotic cellular debris and are often lined by cuboidal epithelium. Note the proliferative epithelium (big arrows) at the periphery of the lesion. Male rat exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 90X

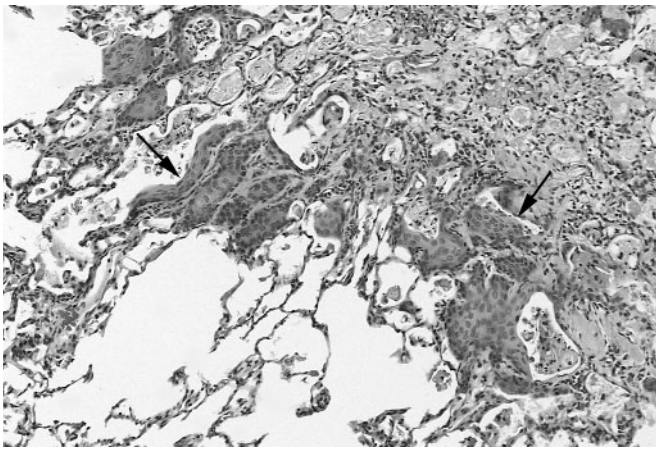


Plate 7
Lung: Squamous metaplasia along the alveolar wall consisting of several layers of squamous epithelium (arrows). Male rat exposed to 0.03 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 75X

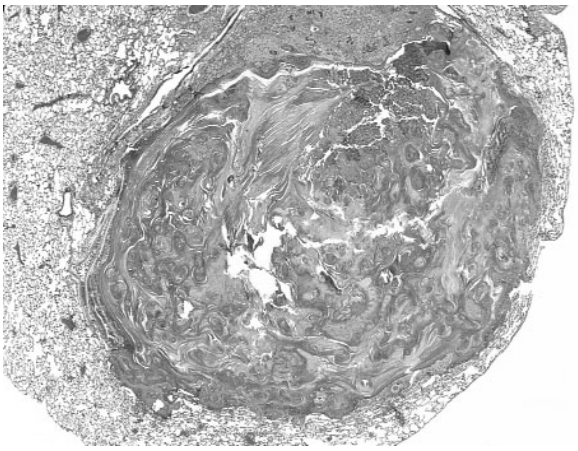


Plate 8
Lung: Low magnification of lung containing a squamous cyst filled with keratinous material. Male rat exposed to 0.03 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 9X

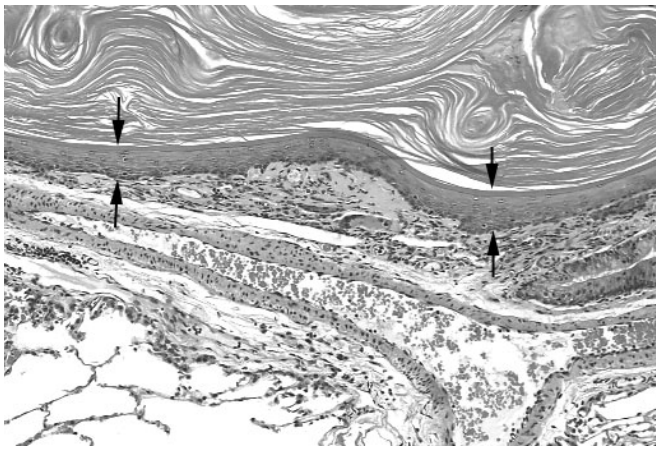


Plate 9
Lung: High magnification of a border of the squamous cyst showing the variably thick wall of squamous epithelium (arrows) and the keratinous contents (top). Male rat exposed to 0.03 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 75X

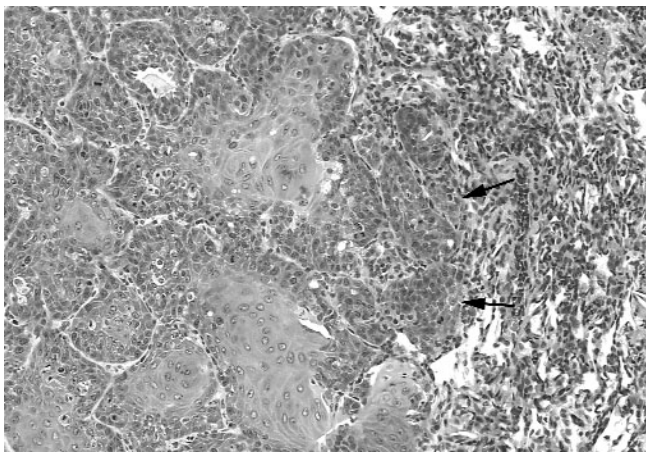


Plate 10
Lung: High magnification of a well differentiated squamous cell carcinoma. Note the border of the neoplasm and invasion (arrows) of squamous epithelium into the adjacent pulmonary parenchyma. Male rat exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 90X

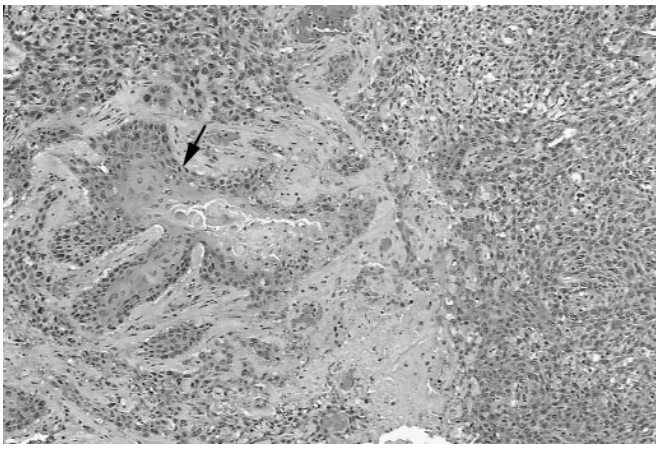


Plate 11
Lung: High magnification of a poorly differentiated squamous cell carcinoma. Note the obvious squamous differentiation to the left (arrow) and a very anaplastic and undifferentitated area to the right. Male rat exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 75X

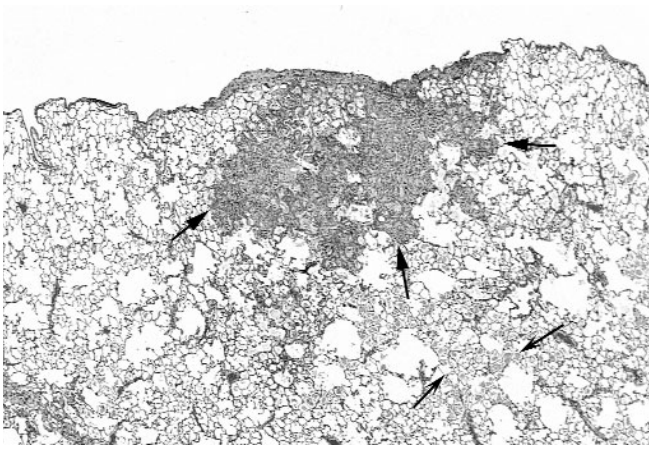


Plate 12
Lung: Low magnification of a lung from a male rat exposed to 0.03 mg/m^3 indium phosphide in the 2-year inhalation study. Note the focal area of inflammation (large arrows) and proteinosis (small arrows) in this section. H&E 15X

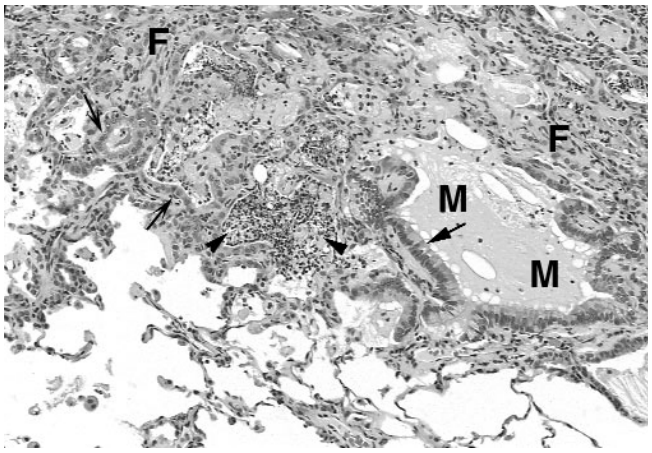


Plate 13
Lung: Higher magnification of an area of inflammation. Note the fibrosis (F), necrotic cellular debris (arrow heads), and regenerative epithelial hyperplasia (small arrows). Respiratory metaplasia (large arrow) with luminal mucinous material (M) is also present. Male rat exposed to 0.03 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 90X

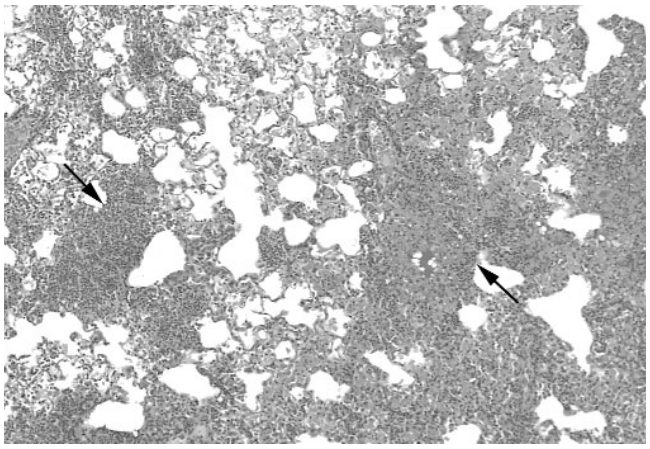


Plate 14
Lung: An area of chronic active inflammation in a male mouse exposed to 100 mg/m^3 indium phosphide in the 13-week toxicology study. Many alveoli are filled with proteinaceous material and inflammatory cells (arrows). Few alveoli are clear and appear normal. H&E 55X

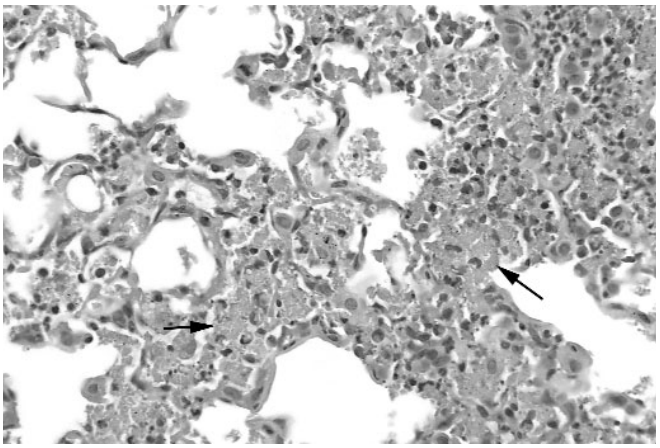


Plate 15
Lung: Higher magnification of plate 14. Most alveoli are filled with proteinaceous material (arrows) and cellular debris. The tiny dark dots were diagnosed as foreign body (indium phosphide). A male mouse exposed to 100 mg/m^3 indium phosphide in the 13-week toxicology study. H&E 230X

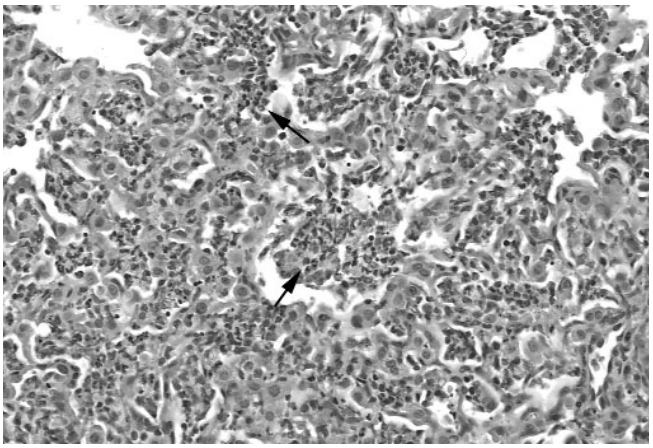


Plate 16
Lung: A high magnification of an area of chronic active inflammation in a male mouse exposed to 100 mg/m^3 indium phosphide in the 13-week toxicology study. In this area, alveoli are filled predominantly with neutrophils (arrows). H&E 185X

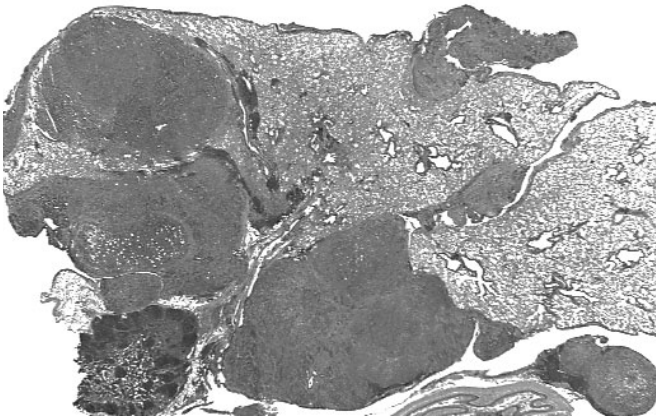


Plate 17
Lung: Alveolar bronchiolar carcinoma in a female mouse exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. Note the multiple nodules of carcinoma. H&E 6X

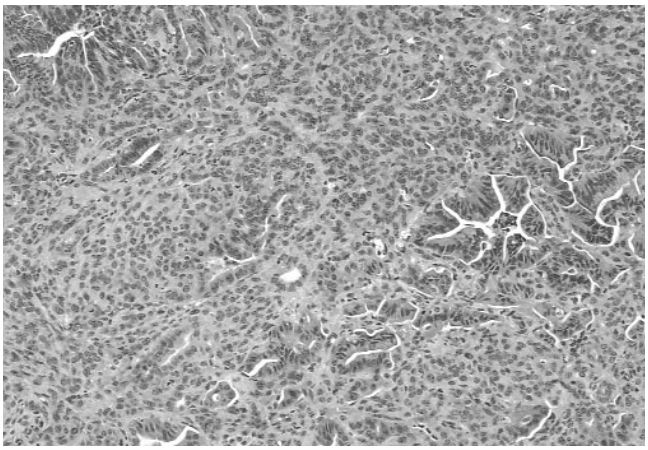


Plate 18
Lung: Higher magnification of plate 17. Note the disorganized and variable growth pattern and pleomorphism of component cells. Female mouse exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 90X

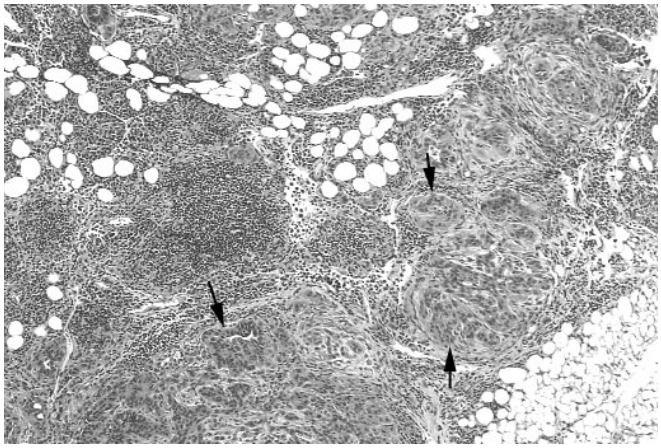


Plate 19
Lung: Metastasis of the carcinoma in plate 17 to the mediastinal lymph node. Much of the lymphoid tissue is effaced by the metastatic alveolar bronchiolar carcinoma (arrows). Female mouse exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 55X

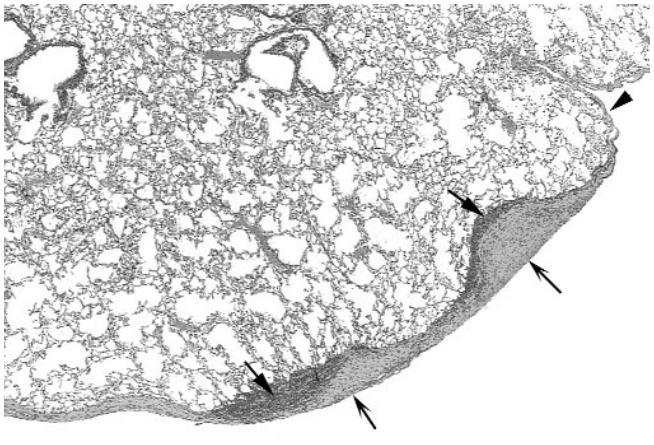


Plate 20
Lung: The pleural surface is thickend (serosal fibrosis) by fibrous connective tissue (small arrows). The darker regions (large arrows) represent infiltration of inflammatory cells. The arrow head points to a rather normal pleural surface. Female mouse exposed to 0.3 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 25X

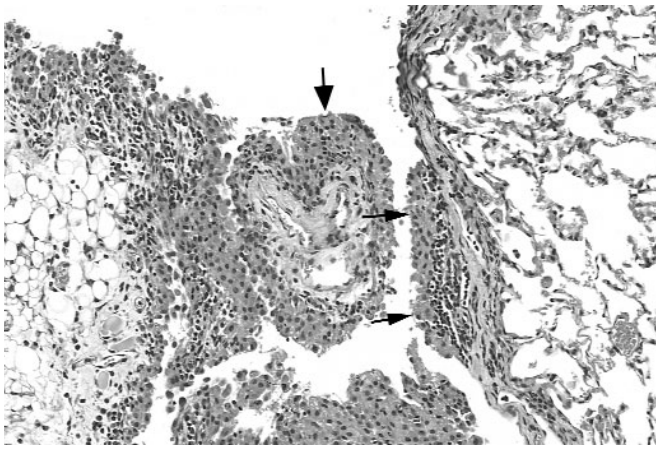


Plate 21
Lung: High magnification of mesothelial hyperplasia. The normally flattened single layer of mesothelial cells are rounded, plump and piled up (small arrows). The pulmonary parenchyma is to the right. In the center (large arrow), there is a papillary frond with a fibrous stalk covered by mesothelial cells. Female mouse exposed to 0.03 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 90X

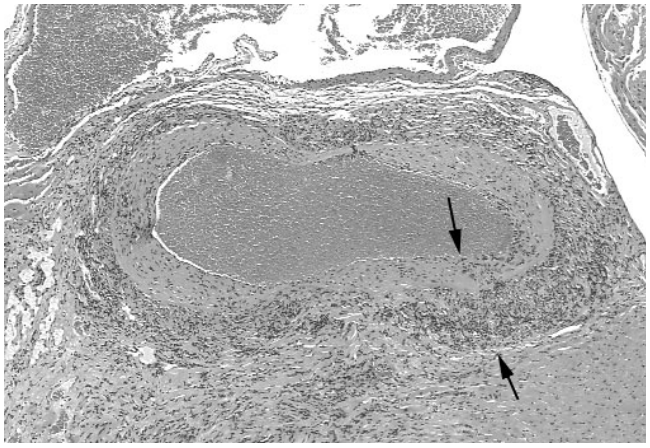


Plate 22
Heart: High magnification of an affected vessel in the heart. Note the increased thickness (arrows) of the vascular wall due to intimal and medial hypertrophy along with infiltrated inflammatory cells. Male mouse exposed to 0.1 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 35X

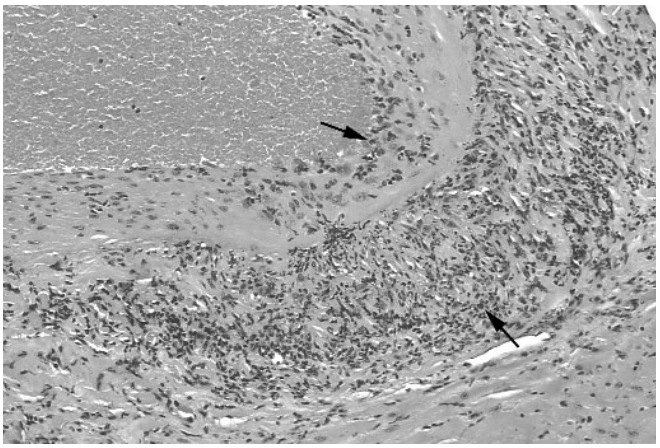


Plate 23
Heart: Higher magnification of the affected vessel (Plate 22). Large numbers of inflammatory cells (arrows) are present. Male mouse exposed to 0.1 mg/m^3 indium phosphide in the 2-year inhalation study. H&E 90X

DISCUSSION AND CONCLUSIONS

The National Institute of Environmental Health Sciences nominated indium phosphide for study because of its widespread use in the microelectronics industry, the potential for worker exposure, and the lack of chronic toxicity data. Particulate indium phosphide was evaluated for toxicity and carcinogenicity in 14-week and 2-year studies in male and female F344/N rats and $B6C3F_1$ mice, utilizing whole body inhalation as the route of exposure.

In the 14-week studies, mice were more severely affected than rats; all mice in the 100 mg/m^3 groups and one male and three females in the 30 mg/m^3 groups either died or were removed moribund, while only one male rat in the 100 mg/m^3 group died early. Mean body weight gains of rats and mice exposed to 100 mg/m^3 and of mice exposed to 10 or 30 mg/m^3 were significantly less than those of the chamber controls.

The respiratory tract was the primary site of toxicity, as indicated by the presence of indium phosphide particles, increased lung weights, and a spectrum of inflammatory and proliferative lesions including alveolar proteinosis, alveolar epithelial hyperplasia, chronic active inflammation, and interstitial fibrosis in the lungs of most exposed rats and mice. Although the lung lesions observed in rats and mice were similar, there were quantitative and qualitative differences. At comparable exposure concentrations, the lesions in mice tended to be more severe in that the inflammation was more neutrophilic and necrotizing. There were areas where the epithelium was piled up and the cells were more atypical. There were also a few foci of squamous cell differentiation. Pulmonary interstitial fibrosis is a common response to particulate exposure in rats; however, it is relatively uncommon in mice. Exposure to indium phosphide caused a reactive hyperplasia in the lymph nodes that drain the respiratory tract in rats and mice and chronic inflammation at the base of the epiglottis in the larynx of rats. The larynx of mice was more severely affected in that on the lateral wall there was squamous cell hyperplasia accompanied by focal necrosis and suppurative inflammation and at the base of the epiglottis there was squamous metaplasia. The respiratory tract lesions caused by exposure to indium phosphide are typical of lesions that would be expected following exposure to relatively insoluble particulates. Some of the lesions observed in the respiratory tract of animals in this study have been seen in rats exposed by nose only or intratracheally instilled with single doses of indium phosphide particles as well as other indium compounds (Smith *et al.,* 1978, Blazka *et al.,* 1994a,b, Uemura *et al.,* 1997). Similar effects were also observed with another semiconductor material, gallium arsenide, following whole body exposure although rats were more severely affected than mice in these studies (NTP, 2000).

Lung burdens for indium increased with increasing exposure concentration and increased throughout the 14-week exposure period indicating steady-state lung burdens were not achieved. In order to assess lung burden proportionality to exposure concentration, lung burdens were normalized to exposure concentration. For linear toxicokinetics, lung burdens normalized to exposure concentration would be expected to remain constant across all exposure concentrations. However, lung burdens normalized to exposure concentrations during the 14-week exposure period were inversely proportional to exposure concentration, indicating nonlinear kinetics. In addition, lung burdens during the 14-week exposure and subsequent 16-week recovery periods were disproportionately low in the 30 and 100 mg/m^3 groups compared to the lower exposure groups.

Calculated lung clearance half-times and clearance rates during the 14-week exposure period were not substantially different between exposed groups. Although lung deposition rates increased with increasing exposure concentration, lung deposition rates decreased when normalized to exposure concentration, indicating that at the higher exposure concentrations the amount of indium being deposited was relatively less than that at lower concentrations. This nonlinearity is probably due to the large amount of lipoprotein and the

inflammatory and proliferative lesions in the alveoli, which could affect pulmonary function. As lung burdens decreased with time for postexposure animals, the calculated lung clearance rate constants or half-times indicate that there were not significant differences in clearance for all exposed groups. However, lung clearance parameters calculated from the postexposure data indicated overall longer clearance half-times (202 ± 44 days) than those calculated from data during the 14-week exposure period (78 ± 24 days). Possible reasons for these differences could be that the model assumes continuous exposure and continuous clearance with a constant deposition rate. Exposure was not continuous, and the data indicate that the deposition rate was not constant across all exposed groups. In addition, clearance rates estimated from a pure clearance process, as calculated from the postexposure data, are much less subject to the uncertainties associated with variable deposition rates inherent in the data collected during the exposure period.

Indium was detected in blood, serum, and testis at concentrations several orders of magnitude less than observed in lung tissue. Blood, serum, and testicular indium concentrations increased with increasing exposure concentration throughout the 14 weeks of exposure. Blood and serum concentrations appeared to be near steady state throughout the postexposure period, most likely due to the continued clearance of indium phosphide from the lungs. However, testicular indium continued to increase in all groups following exposure indicating that indium was accumulating in the testis over time.

The two- to four-fold increases in lung weights and the spectrum and severity of lung lesions in rats and mice exposed to 1 mg/m^3 or greater in the 14-week studies precluded the use of any of the 14-week exposure concentrations in the 2-year studies. Therefore, to aid in selection of the 2-year exposure concentrations, the lung deposition and clearance model, utilizing estimated deposition and clearance rates for the 1 mg/m^3 group from the 5-day study, was used to estimate steady-state lung burdens for 0.01, 0.1, and 0.5 mg/m^3; which are 8, 80, and 399 µg indium, respectively. The burden of 399 µg indium, although less than the estimated steady-state lung burden of 617 µg for rats exposed to 3 mg/m^3 in the 14-week study, was considered to be too high, especially because steady-state lung burdens for 1 mg/m^3 could not be calculated from the 14-week data. Therefore, 0.3 mg/m^3 was selected as the highest exposure concentration. For the middle concentration, 0.1 mg/m^3 was selected because the estimated steady-state lung burden for 0.1 mg/m^3 was considerably less than those observed in the 14-week studies. The lowest exposure concentration of 0.03 mg/m^3 was set near the lowest concentration that the chamber particle monitor could measure continuously with accuracy. Exposure concentrations for mice were the same as those for rats.

Although there were quantitative differences in lung burden and kinetic parameters for rats and mice exposed to indium phosphide in the 2-year studies, qualitatively they were similar. In general, there were no sex-related differences for either species for lung burden and kinetic parameters. Lung weights and lung burdens of rats and mice significantly increased with increasing exposure concentration and duration of exposure. Following cessation of exposure, lung weights remained significantly elevated, showing very little recovery, and were consistent with the progression of lung lesions with time. Lung burdens, on the other hand, declined following cessation of exposure and continued to decline during the 12 months after exposure. They had decreased for the 0.1 and 0.3 mg/m^3 groups to 35% and 50% for rats and 16% and 29% for mice, respectively, of values observed at the end of exposure. Unlike the situation in the 14-week studies, lung burdens normalized to exposure concentrations, in general, remained constant across exposure concentrations, indicating linear toxicokinetics for rats and mice.

Lung deposition rates increased proportionately to exposure concentration for rats and mice. Deposition fractions were relatively consistent across all exposed groups, ranging from 4.3% to 5.1% for mice, and 5.8% to 6.6% for rats. There were no significant differences in the lung clearance rates or half-times for indium with respect to exposure concentration in rats or mice. However, the estimated half-times for clearance of indium from mouse lungs were substantially shorter than those for rats (144 and 163 days for mice, and 262 and 291 days for rats exposed to 0.1 and 0.3 mg/m^3, respectively). These prolonged elimination rates are probably due to an alteration of pulmonary function caused by the inflammatory and proliferative lesions in the lung. Although serum indium concentrations were

increased relative to exposure concentration and duration of exposure for rats and mice, the concentration of indium in serum was quite small relative to that in the lung and was measurable only after 21 or more weeks of exposure. There were no significant differences in serum indium concentrations for rats and mice, and there was no consistent evidence of elimination of indium from serum, which is consistent with the continued slow elimination of indium from the lungs.

In the 2-year studies, survival rates and body weight gains were not affected in rats exposed to indium phosphide; however, survival rates and body weight gains were reduced in all exposed groups of mice except 0.1 mg/m^3 males. Exposure to indium phosphide caused increased incidences of alveolar/bronchiolar adenomas and carcinomas in the lung, occurring with positive trends, in male and female rats. Considering that exposure was stopped at 22 weeks for the 0.1 mg/m^3 groups, the lower incidences of lung neoplasms in these groups may be indicative of lower lung burdens. Although not significantly increased in incidence, rare squamous cell carcinomas of the lung occurred in four male rats exposed to 0.3 mg/m^3 and were considered related to exposure to indium phosphide.

The alveolar/bronchiolar adenomas closely resembled those found spontaneously in aged rats. However, the alveolar/bronchiolar carcinomas and squamous cell carcinomas were larger, more pleomorphic masses that invaded the local architecture of the lung or metastasized to other areas. Pulmonary neoplasms are relatively uncommon in control F344/N rats. The effect of indium phosphide in rats is striking because a positive effect was observed following 2 years of continuous exposure to only 0.03 mg/m^3. This concentration is lower than the 0.1 mg/m^3 concentration recommended for indium and indium compounds by the American Conference of Governmental Industrial Hygienists (ACGIH, 2000) and the recommended exposure limits set forth by the National Institute for Occupational Safety and Health (NIOSH, 1997). More importantly, exposure to 0.1 or 0.3 mg/m^3 for less than 21 weeks also produced significant increases in incidences of pulmonary neoplasms at 2 years. In the 0.3 mg/m^3 groups, 52% of females and 70% of males had pulmonary neoplasms compared to 2% and 14%, respectively, in chamber control rats. Compared to more recent NTP aerosol studies, indium phosphide induced greater incidences of pulmonary neoplasms in rats at lower exposure concentrations than did nickel subsulfide, nickel oxide, cobalt sulfate heptahydrate, or gallium arsenide (NTP, 1996a,b, 1998, 2000). Gallium arsenide is the only one of these aerosols that did not cause increased incidences of neoplasms in male rats.

The spectrum of inflammatory and proliferative lung lesions increased over the course of 2 years. Fibroproliferative lesions of the alveolar/bronchiolar epithelium, although not generally observed spontaneously, are common in NTP F344/N rat aerosol studies. These proliferative lesions appear to be part of a morphologic continuum that may progress to neoplasia. The smallest of these lesions was adjacent to areas of inflammation. Some of these lesions involved several layers of epithelium and often extended into adjacent alveoli, frequently forming papillary projections. The larger, more proliferative and locally invasive lesions were diagnosed as adenoma or carcinoma. Although squamous epithelium is not normally observed in the lung, in a number of rats there were small focal areas where normal epithelium had been replaced by several layers of squamous epithelium. This is a common response to injury by particulates. Chronic inflammation often obscured normal alveolar architecture. As might be expected for particulate exposure, the areas of inflammation were most prominent around alveolar ducts, terminal bronchioles, larger airways, and larger blood vessels. Alveolar septae and pleura overlying areas of inflammation were often thickened by fibrous tissue. Alveolar epithelial metaplasia was observed within and at the edges of chronic inflammation, especially in areas where septae were thickened.

As in the 2-year rat study, exposure of mice to indium phosphide caused significant increases in the incidences of alveolar/bronchiolar carcinomas in males and alveolar/bronchiolar adenomas and carcinomas in females. The individual and combined incidences of each of these neoplasms in male and female mice exceeded the ranges for historical controls in inhalation studies. Many of the alveolar/bronchiolar adenomas and carcinomas resembled those occurring spontaneously in B6C3F$_1$ mice. However, some of the carcinomas were different from those occurring spontaneously in that they were very anaplastic with papillary and sclerosing patterns and often spread outside the lung into the mediastinum and distant

metastases. A few spread extensively throughout the lung and were diagnosed as multiple carcinomas. The neoplastic responses in the lungs of mice are even more significant than those in rats, because mice are generally not responsive to particulate exposure for the development of lung neoplasms even at high exposure concentrations. Contemporary particulate inhalation studies in male and female mice exposed to talc, nickel subsulfide, nickel oxide (males), nickel sulfate hexahydrate, or gallium arsenide at similar or higher concentrations than used in rat studies were negative for carcinogenicity in the mouse lung (NTP, 1993, 1996a,b,c, 2000). Nickel oxide had equivocal evidence of carcinogenicity in female mice. In the current study, it is clear that the neoplastic response in the lungs of rats or mice cannot be attributed to the typical "dust overload" phenomenon observed with many particulate studies at high concentrations and high lung deposition. Assuming that 1 to 5 mg of particulate per gram of lung (Morrow, 1986) are required to impair lung clearance, these deposition levels were not achieved, as the maximum indium phosphide particulate load did not exceed 30 µg/g for rats or 50 µg/g for mice. Moreover, these studies suggest that the nonneoplastic and neoplastic responses in the lungs of rats and mice may be attributable to something other than the presence of particulate indium phosphide. Indium appears to be cytotoxic and in the lung some indium phosphide may be soluble, resulting in localized cytotoxicity. Indium phosphide particles may cause production and release of various chemokines and cytokines that are involved in producing inflammation and proliferative effects in the lung. Cobalt sulfate heptahydrate, when generated as a soluble aqueous aerosol, and in the absence of solid particles, caused increased incidences of pulmonary neoplasms in female mice and female rats at 1.0 mg/m^3 and in male mice and male rats at 3.0 mg/m^3 (NTP, 1998). However, cobalt sulfate heptahydrate did not cause severe inflammatory and noneoplastic proliferative lesions in the lungs of mice as it did in rats.

The spectrum of proliferative and inflammatory lesions in the lungs of mice differed from that in rats. Although alveolar proteinosis occurred in most rats exposed to indium phosphide, when present in mice it was considered minimal and appeared scattered. There were unusual differences in mice compared to rats during gross examination: clear red fluid was frequently found in the thoracic cavity of mice, indicative of an inflammatory response in the pleura. Indium phosphide particles were found in visceral pleural fibrotic lesions by scanning electron microscopy and identified by elemental X-ray analysis (Battelle, 1998). In mice, the lobes of the lung adhered to each other, to the thoracic parietal pleura, to the diaphragm, and on occasion to the pericardium. Chronic inflammation was observed in the epicardium and pericardium of the heart, especially where the pericardium adhered to the heart. Indium phosphide exposure also caused intense inflammation in the coronary arteries and proximal aorta and, to a lesser extent, in the arteries of the kidney, mesentery, lung, and lymph nodes that drain the respiratory tract.

Exposure to indium phosphide caused inflammatory and proliferative lesions of the mesothelium of the visceral and parietal pleura that are uncommon following nonfibrous particulate exposure in mice. Although proliferation of lung mesothelial cells has been observed in mice following inhalation exposure to chrysotile asbestos (Coin *et al.,* 1991) or intratracheal instillation of UICC crocidolite asbestos (Adamson *et al.,* 1993), it was not observed in the contemporary NTP inhalation nonfibrous particulate studies identified previously. Pleural mesothelial hyperplasia was observed in male and female mice exposed to 0.03 and 0.3 mg/m^3. The mesothelium was often hypertrophic or hyperplastic and was generally associated with areas of chronic inflammation and fibrosis. Although visceral meso-thelium is usually single layered, in exposed mice the mesothelium ranged from a single layer of plump hypertrophic cells to several layers of rounded hyperplastic cells. In the more severely affected mice it formed papillary fronds that projected into the pleural cavity. Pleural fibrosis was a prominent component of the chronic inflammation and involved both visceral and parietal pleura with adhesions. Significantly, pulmonary interstitial fibrosis was uncommon in mice exposed to indium phosphide.

Exposure to indium phosphide for 2 years caused increased incidences of benign pheochromocytomas in male and female rats; the effects were observed only in the 0.03 and 0.3 mg/m^3 groups. Increases in incidences of bilateral pheochromocytoma were observed in male rats in those same groups. Increases in incidences of adrenal pheochromocytoma in rats have been observed following inhalation exposure to aerosols in NTP studies of talc, nickel subsulfide, nickel oxide, cobalt sulfate heptahydrate, and gallium arsenide and

now indium phosphide (NTP, 1993, 1996a,b, 1998, 2000). Although there appears to be an association between increased incidence of neoplasms of the adrenal medulla and inhalation exposure of rats to aerosols, especially solid particles, the mechanism of this increase is unknown. Whether this increase is due to the overall stress of inhaling particulates, accumulation of particulate material in the lungs, or absorption of metals contained in each material is unknown. With the exception of cobalt sulfate heptahydrate, which was an aqueous aerosol, the other aerosol inhalation studies performed by the NTP were with relatively insoluble particulates.

Exposure of mice to indium phosphide caused significant increases in the incidences of hepatocellular neoplasms. There were increased incidences of hepatocellular adenomas and carcinomas in male mice exposed to 0.03, 0.1, and 0.3 mg/m^3. The incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) were increased in the 0.03 mg/m^3 group of females. Many mice had multiple hepatocellular adenomas and carcinomas, and incidences of multiple neoplasms were significantly increased in males (carcinoma) and females (adenoma) exposed to 0.03 or 0.1 mg/m^3. The incidences of eosinophilic foci, considered to be part of the spectrum that may progress to proliferative liver lesions, were increased in all groups of exposed males and in females in the 0.3 mg/m^3 group. The increased incidences of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) exceeded the ranges for historical controls from studies using the NTP-2000 diet; however, only the increase in the incidence of hepatocellular adenoma in males in the 0.3 mg/m^3 group and the combined incidence in females in the 0.03 mg/m^3 group exceeded the historical control ranges for studies utilizing the NIH-07 diet. Although the frequency of H-*ras* codon 61 mutations in the indium phosphide-induced hepatocellular neoplasms was similar to that observed in spontaneous hepatocellular neoplasms in chamber controls, somatic mutations of β-catenin were observed in hepatocellular neoplasms from indium phosphide-exposed mice (Table M1). These β-catenin mutations were identified in 40% of the hepatocellular neoplasms from the 0.3 mg/m^3 group and 15% of the hepatocellular neoplasms from the 0.03 mg/m^3 group, compared to the 9% point mutation background incidence in spontaneous hepatocellular neoplasms in B6C3F$_1$ mice (Devereux *et al.*, 1999). Only deletion mutations were detected in 0.03 and 0.3 mg/m^3 groups; these mutations have been found in human hepatocellular neoplasms, suggesting similar pathways of carcinogenesis in both species. The increased incidences of these hepatocellular neoplasms were considered to be exposure related.

As a result of discontinuing exposure of the 0.1 and 0.3 mg/m^3 groups at 21 or 22 weeks, only the 0.03 mg/m^3 groups were exposed continuously for 2 years. Therefore, typical concentration-related responses in neoplasms based solely on external exposure concentration of particulate indium phosphide were not expected. The amount of "indium" retained in the lung and that absorbed systemically must also be considered in the assessment. The lung deposition and clearance model was used to estimate the total amount of indium deposited in the lung of mice and rats after exposure was stopped, the lung burdens at the end of the 2-year study, and the area under the lung burden curves (AUC). For both species, the lung burden estimates at the end of 2 years indicated that the lung burdens in the continuously exposed 0.03 mg/m^3 groups were greater than those of the 0.1 or 0.3 mg/m^3 groups, with the lung burdens of the 0.1 mg/m^3 groups being the lowest. Because of the slow clearance of indium, the lung burdens in the 0.1 and 0.3 mg/m^3 groups were approximately 25% of the maximum levels in rats and 8% in mice 83 to 84 weeks after exposure was stopped. The AUCs and the total amount of indium deposited per lung indicated that the 0.3 mg/m^3 groups were exposed to a greater amount of indium phosphide than were the 0.03 or 0.1 mg/m^3 groups. Once again the 0.1 mg/m^3 group was the lowest. Regardless of how the total "dose" of indium to the lung was estimated, the 0.1 mg/m^3 group received less total exposure than the other two groups, implying that the 0.1 mg/m^3 group may be considered the "low dose" in these studies.

Although the total AUCs indicate that over the course of the 2-year studies the 0.3 mg/m^3 groups received the highest exposures, it is important to examine exposure duration relationships when evaluating tumor response, especially in these studies where exposure was discontinued in two of the three exposure groups after 21 or 22 weeks. For example, the estimated first-year lung burden AUCs indicate that most of the exposures for the 0.1 and 0.3 mg/m^3 groups (63% and 77% for

rats and mice, respectively) actually occurred early in the studies while the greater part of exposures for the 0.03 mg/m^3 groups (67% and 74% for mice and rats, respectively) occurred in the second year of the studies. This is not surprising because exposure to 0.1 or 0.3 mg/m^3 was stopped after 21 or 22 weeks. The higher second-year AUCs for the 0.03 mg/m^3 groups reflect the fact that the rate of deposition was always greater than the rate of clearance. The estimated second-year AUCs for mice and rats exposed to 0.03 and 0.3 mg/m^3 were equivalent, indicating that animals in the 0.03 and 0.3 mg/m^3 groups received the same exposure during the second year of the study. However, the AUCs for the 0.1 mg/m^3 groups were 25% and 33% lower for mice and rats, respectively, than for the other groups. When evaluating tumor response, the relationship between exposure to indium phosphide and total exposure to indium as well as pattern of exposure must be taken into consideration. Although exposures to 0.03 mg/m^3 for 2 years caused increased incidences of lung neoplasms in rats and mice, early exposures for 21 or 22 weeks to higher concentrations of indium phosphide (0.1 or 0.3 mg/m^3) also resulted in increased incidences of lung neoplasms in both species. Although the 0.1 mg/m^3 groups (21- or 22-week exposure durations) had the lowest total exposures, the incidences of lung neoplasms in these groups in some instances were greater than the incidences in the 0.03 mg/m^3 groups (2-year exposure duration). More importantly, these findings indicate that short-term exposure to 0.1 mg/m^3 (the current recom-mended ACGIH and NIOSH TLV/REL) may be an important factor impacting lung cancer risk associated with exposure to indium phosphide.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of indium phosphide in male and female F344/N rats based on increased incidences of benign and malignant neoplasms of the lung. Increased incidences of pheochromocytoma of the adrenal medulla in males and females were also considered to be exposure related. Marginal increases in incidences of mononuclear cell leukemia in males and females, fibroma of the skin in males, and carcinoma of the mammary gland in females may have been related to exposure to indium phosphide. There was *clear evidence of carcinogenic activity* of indium phosphide in male B6C3F$_1$ mice based on increased incidences of malignant neoplasms of the lung and benign and malignant neoplasms of the liver. Marginal increases in incidences of adenoma and carcinoma of the small intestine may have been related to exposure to indium phosphide. There was *clear evidence of carcinogenic activity* of indium phosphide in female B6C3F$_1$ mice based on increased incidences of benign and malignant neoplasms of the lung. Increased incidences of liver neoplasms in females were also considered to be exposure related.

Exposure to indium phosphide by inhalation resulted in nonneoplastic lesions in the lung of male and female rats and mice, the adrenal medulla of female rats, and the liver and heart of male and female mice.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A Summary of the Technical Reports Review Subcommittee comments and the public discussion on the Technical Report appears on page 15.

REFERENCES

Adamski, J.A., and Ahern, B.S. (1985). Rapid synthesis of indium phosphide. *Rev. Sci. Instrum.* **56**, 716-718.

Adamson, I.Y.R., Bakowska, J., and Bowden, D.H. (1993). Mesothelial cell proliferation after instillation of long or short asbestos fibers into mouse lung. *Am. J. Pathol.* **142**, 1209-1216.

American Conference of Governmental Industrial Hygienists (ACGIH) (2000). *2000 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*. Cincinnati.

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.

Battelle Pacific Northwest Laboratories (1995a). Indium phosphide: Subchronic inhalation toxicity study prestart chemistry and exposure report. Contract No. N01-ES-25335; February 1995.

Battelle Pacific Northwest Laboratories (1995b). Inhalation developmental toxicity study of indium phosphide in rats. Contract No. N01-ES-25335; November 1995.

Battelle Pacific Northwest Laboratories (1997). Inhalation developmental toxicity study of indium phosphide (CAS# 22398-80-7; C88124) in mice. Contract No. N01-ES-25335; November 1997.

Battelle Pacific Northwest Laboratories (1998). Two-year chronic inhalation toxicity and carcinogenicity study of indium phosphide (CAS# 22398-80-7; C88124) in mice. Contract No. N01-ES-25335; September 1998.

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.

Blazka, M.E. (1998). Indium. In *Immunotoxicology of Environmental and Occupational Metals* (J.T. Zelikoff and P.T. Thomas, Eds.), pp. 93-109. Taylor and Francis, Philadelphia, PA.

Blazka, M.E., Dixon, D., Haskins, E., and Rosenthal, G.J. (1994a). Pulmonary toxicity to intratracheally administered indium trichloride in Fischer 344 rats. *Fundam. Appl. Toxicol.* **22**, 231-239.

Blazka, M.E., Tepper, J.S., Dixon, D., Winsett, D.W., O'Connor, R.W., and Luster, M.I. (1994b). Pulmonary response of Fischer 344 rats to acute nose-only inhalation of indium trichloride. *Environ. Res*. **67**, 68-83.

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.

Boorman, G.A., Wilson, J.T., van Zwieten, M.J., and Eustis, S.L. (1990). Mammary gland. In *Pathology of the Fischer Rat. Reference and Atlas* (G.A. Boorman, S.L. Eustis, M.R. Elwell, C.A. Montgomery, Jr., and W.F. MacKenzie, Eds.), pp. 295-313. Academic Press, Inc., San Diego.

Brecher, G., and Schneiderman, M. (1950). A time-saving device for the counting of reticulocytes. *Am. J. Clin. Pathol.* **20**, 1079-1083.

Carson, B.L., Ellis, H.V., III, and McCann, J.L., Eds. (1986). Indium. Mammalian Toxicity Summary. In *Toxicology and Biological Monitoring of Metals in Humans*, pp. 115-120. Lewis Publishers, Inc., Chelsea, MI.

Castronovo, F.P., Jr., and Wagner, H.N., Jr. (1973). Comparative toxicity and pharmacodynamics of ionic indium chloride and hydrated indium oxide. *J. Nucl. Med.* **14**, 677-682.

Chapin, R.E., Harris, M.W., Hunter, E.S., III, Davis, B.J., Collins, B.J., and Lockhart, A.C. (1995). The reproductive and developmental toxicity of indium in the Swiss mouse. *Fundam. Appl. Toxicol*. **27**, 140-148.

Code of Federal Regulations (CFR) **21**, Part 58.

Coin, P.G., Moore, L.B., Roggli, V., and Brody, A.R. (1991). Pleural incorporation of ^{3}H-thymidine after inhalation of chrysotile asbestos in the mouse. *Am. Rev. Respir. Dis*. **143**, A603.

Conner, E.A., Yamauchi, H., Fowler, B.A., and Akkerman, M. (1993). Biological indicators for monitoring exposure/toxicity from III-V semiconductors. *J. Expo. Anal. Environ. Epidemiol.* **3**, 431-440.

Conner, E.A., Yamauchi, H., and Fowler, B.A. (1995). Alterations in the heme biosynthetic pathway from the III-V semiconductor metal, indium arsenide (InAs). *Chem. Biol. Interact.* **96**, 273-285.

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

Devereux, T.R., Anna, C.H., Foley, J.F., White, C.M., Sills, R.C., and Barrett, J.C. (1999). Mutation of β-catenin is an early event in chemically induced mouse hepatocellular carcinogenesis. *Oncogene* **18,** 4726-4733.

Dittmar, T.B., Fernando, Q., Leavitt, J.A., and McIntyre, L.C., Jr. (1992). Surface concentrations of indium, phosphorus, and oxygen in indium phosphide single crystals after exposure to Gamble solution. *Anal. Chem.* **64**, 2929-2933.

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.

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

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1096-1121.

Ellis, B.L., Duhme, A.K, Hider, R.C., Hossain, M.B., Rizvi, S., and van der Helm, D. (1996). Synthesis, physicochemical properties, and biological evaluation of hydroxypyranones and hydroxypyridones: Novel bidentate ligands for cell-labeling. *J. Med. Chem*. **39**, 3659-3670.

Ferm, V.H., and Carpenter, S.J. (1970). Teratogenic and embryopathic effects of indium, gallium, and germanium. *Toxicol. Appl. Pharmacol*. **16**, 166-170.

Fowler, B.A. (1986). Indium. In *Handbook on the Toxicology of Metals* (L. Friberg, G.F. Nordberg, and V.B.Vouk, Eds.), pp. 267-275. Elsevier Science Publishers B.V., Amsterdam, The Netherlands.

Fowler, B.A. (1988). Mechanisms of indium, thallium, and arsine gas toxicity: Relationships to biological indicators of cell injury. In *Biological Monitoring of Toxic Metals* (T.W. Clarkson, L. Friberg, G.F. Nordberg, and P.R. Sager), pp. 469-478. Plenum Press, New York.

Fowler, B.A. (1995). Toxic metals in emerging technologies. In *Metal Toxicology* (R.A. Goyer, C.D. Klaassen, and M.P. Waalkes), pp. 187-196. Academic Press, San Diego.

Galle, P. (1983). The role of lysosomes in the renal concentration of mineral elements. *Adv. Nephrol. Necker Hosp.* **12**, 85-99.

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

Hawley's Condensed Chemical Dictionary (1997). 13th ed. (R.J. Lewis, Sr., Ed.), pp. 607-608. Van Nostrand Reinhold, New York.

Hoffman, R.W., Jr., Fatemi, N.S., Wilt, D.M., Jenkins, P.P., Brinker, D.J., and Sheiman, D.A. (1994). High efficiency InP solar cells from low toxicity tertiarybutylphosphine. National Aeronautics and Space Administration (NASA) Technical Memorandum 106598.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Integrated Laboratory Systems (ILS) (1990). Micronucleus Data Management and Statistical Analysis Software, Version 1.4. ILS, P.O. Box 13501, Research Triangle Park, NC 27707.

Jain, N.C. (1986). The lymphocytes and plasma cells. In *Schalm's Veterinary Hematology*, 4th ed. Chapter 30, pp. 790-820. Lea and Febiger, Philadelphia.

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

Kabe, I., Omae, K., Nakashima, H., Nomiyama, T., Uemura, T., Hosoda, K., Ishizuka, C., Yamazaki, K., and Sakurai, H. (1996). *In vitro* solubility and *in vivo* toxicity of indium phosphide. *J. Occup. Health* **38**, 6-12.

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

Kirk-Othmer Concise Encyclopedia of Chemical Technology (1999). 4th ed. (J. Kroschwitz, Ed.), pp. 1113-1114. John Wiley and Sons, New York.

Lee, J.C., and Moskowitz, P.D. (1990). Hazard identification and characterization of organometals in growing III-V semiconductors for the production of photovoltaic cells. *Solar Cells* **28**, 209-222.

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.

McCord, C.P., Meek, S.F., Harrold, G.C., and Heussner, C.E. (1942). The physiologic properties of indium and its compounds. *J. Ind. Hyg. Toxicol.* **24**, 243-254.

MacGregor, J.T., Wehr, C.M., Henika, P.R., and Shelby, M.D. (1990). The *in vivo* erythrocyte micronucleus test: Measurement at steady state increases assay efficiency and permits integration with toxicity studies. *Fundam. Appl. Toxicol.* **14**, 513-522.

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.

The Merck Index (1996). 12th ed. (S. Budavari, Ed.), p. 4994. Merck and Company, Whitehouse Station, NJ.

Morrison, D.F. (1976). *Multivariate Statistical Methods*, 2nd ed., pp. 170-179. McGraw-Hill Book Company, New York.

Morrow, P.E. (1986). The setting of particulate exposure levels for chronic inhalation toxicity studies. *J. Am. Coll. Toxicol.* **6**, 533-544.

Mosovsky, J.A., Rainer, D., Asom, M.T., and Quinn, W.E. (1992). Transient hydride generation during III-V semiconductor processing. *Appl. Occup. Environ. Hyg.* **7**, 375-384.

Nakajima, M., Takahashi, H., Sasaki, M., Kobayashi, Y., Awano, T., Irie, D., Sakemi, K., Ohno, Y., and Usami, M. (1998). Developmental toxicity of indium chloride by intravenous or oral administration in rats. *Teratogenesis Carcinog. Mutagen*. **18**, 231-238.

Nakajima, M., Sasaki, M., Kobayashi, Y., Ohno, Y., and Usami, M. (1999). Developmental toxicity of indium in cultured rat embryos. *Teratogenesis Carcinog. Mutagen*. **19**, 205-209.

National Institute for Occupational Safety and Health (NIOSH) (1985). Hazard Assessment of the Electronic Component Manufacturing Industry. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati.

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 and Prevention, Washington, D.C.

National Toxicology Program (NTP) (1987). Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluations in Toxicity Testing for Rats and Mice, 10/31/82 version (updated December 1987). Research Triangle Park, NC.

National Toxicology Program (1993). Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 421. NIH Publication No. 93-3152. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (1996a). Toxicology and Carcinogenesis Studies of Nickel Subsulfide (CAS No. 12035-72-2) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 453. NIH Publication No. 96-3369. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (1996b). Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313-99-1) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 451. NIH Publication No. 96-3367. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, Research Triangle Park, NC.

National Toxicology Program (1996c). Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate (CAS No. 10101-97-0) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 454. NIH Publication No. 96-3370. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, Research Triangle Park, NC.

National Toxicology Program (1998). 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 (2000). Toxicology and Carcinogenesis Studies of Gallium Arsenide (CAS No. 1303-00-0) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 492. NIH Publication No. 00-3951. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Oda, K. (1997). Toxicity of a low level of indium phosphide (InP) in rats after intratracheal instillation. *Ind. Health* **35**, 61-68.

Patty's Industrial Hygiene and Toxicology (1994). 4th ed. (G.D. Clayton and F.E. Clayton, Eds.), Vol. 2C, pp. 2032-2038. John Wiley and Sons, New York.

Piegorsch, W.W., and Bailer, A.J. (1997). *Statistics for Environmental Biology and Toxicology*, Section 6.3.2., Chapman and Hall, London.

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.

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.

Scansetti, G. (1992). Exposure to metals that have recently come into use. *Sci. Total Environ.* **120**, 85-91.

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

Smith, I.C., Carson, B.L., and Hoffmeister, F., Eds. (1978). Volume 5–Indium. An appraisal of environmental exposure. In *Trace Metals in the Environment*. Ann Arbor Science Publishers, Inc., Ann Arbor, MI.

Tanaka, A., Hisanaga, A., Hirata, M., Omura, M., Makita, Y., Inoue, N., and Ishinishi, N. (1996). Chronic toxicity of indium arsenide and indium phosphide to the lungs of hamsters. *Fukuoka Acta Med*. **87**, 108-115.

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

Tice, R.R., Erexson, G.L., Hilliard, C.J., Huston, J.L., Boehm, R.M., Gulati, D., and Shelby, M.D. (1990). Effect of treatment protocol and sample time on the frequencies of micronucleated polychromatic erythrocytes in mouse bone marrow and peripheral blood. *Mutagenesis* **5**, 313-321.

Uemura, T., Oda, K., Omae, K., Takebayashi, T., Nomiyama, T., Ishizuku, C., Hosoda, K., Sakurai, H., Yamazaki, K., and Kabe, I. (1997). Effects of intratracheally administered indium phosphide on male Fischer 344 rats. *J. Occup. Health* **39**, 205-210.

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.

Witt, K.L., Knapton, A., Wehr, C.M., Hook, G.J., Mirsalis, J., Shelby, M.D., and MacGregor, J.T. (2000). Micronucleated erythrocyte frequency in peripheral blood of B6C3F_1 mice from short-term, prechronic, and chronic studies of the NTP Carcinogenesis Bioassay Program. *Environ. Mol. Mutagen.* **36**, 163-194.

Zheng, W., Winter, S.M., Kattnig, M.J., Carter, D.E., and Sipes, I.G. (1994). Tissue distribution and elimination of indium in male Fischer 344 rats following oral and intratracheal administration of indium phosphide. *J. Toxicol. Environ. Health* **43**, 483-494.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF INDIUM PHOSPHIDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	20	18	16	15
Natural deaths	3	3	5	9
Survivors				
Terminal sacrifice	27	29	29	26
Animals examined microscopically	60	60	60	60
Systems Examined at 3 Months with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)		
Intestine large, colon	(50)	(50)	(47)	(48)
Polyp adenomatous			1 (2%)	
Intestine large, cecum	(48)	(50)	(46)	(46)
Intestine small, duodenum	(49)	(50)	(47)	(48)
Intestine small, jejunum	(48)	(48)	(46)	(43)
Carcinoma		1 (2%)		
Intestine small, ileum	(47)	(49)	(46)	(44)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma		1 (2%)		1 (2%)
Cholangioma		1 (2%)		
Hepatocellular adenoma			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)			
Mesentery	(6)	(6)	(6)	(8)
Squamous cell carcinoma, metastatic, lung				1 (13%)
Oral mucosa	(1)		(3)	(2)
Gingival, squamous cell papilloma			2 (67%)	
Pharyngeal, squamous cell papilloma	1 (100%)		1 (33%)	1 (50%)
Pancreas	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Squamous cell carcinoma, metastatic, lung				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Alimentary System (continued)				
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)	
Stomach, glandular	(50)	(50)	(48)	(49)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)			
Schwannoma benign	1 (2%)			1 (2%)
Squamous cell carcinoma, metastatic, lung				1 (2%)
Pericardium, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma		1 (2%)		
Squamous cell carcinoma, metastatic, lung				1 (2%)
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma malignant		3 (6%)	3 (6%)	1 (2%)
Pheochromocytoma complex		1 (2%)		
Pheochromocytoma benign	10 (20%)	16 (32%)	12 (24%)	18 (36%)
Squamous cell carcinoma, metastatic, lung				1 (2%)
Bilateral, pheochromocytoma benign		6 (12%)	4 (8%)	5 (10%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Carcinoma	2 (4%)		4 (8%)	3 (6%)
Squamous cell carcinoma, metastatic, lung				1 (2%)
Parathyroid gland	(44)	(44)	(45)	(45)
Adenoma	1 (2%)			
Pituitary gland	(49)	(50)	(50)	(50)
Pars distalis, adenoma	36 (73%)	33 (66%)	31 (62%)	30 (60%)
Pars distalis, carcinoma	1 (2%)	1 (2%)		
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(49)	(49)	(48)	(48)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	5 (10%)	7 (14%)	4 (8%)	9 (19%)
C-cell, carcinoma	1 (2%)	4 (8%)	3 (6%)	1 (2%)
Follicular cell, adenoma		1 (2%)		
General Body System				
Peritoneum	(1)	(1)		
Histiocytic sarcoma		1 (100%)		
Tissue NOS				(1)
Chemodectoma malignant				1 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)		
Carcinoma	2 (4%)		1 (2%)	
Prostate	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Adenoma, multiple			1 (2%)	
Seminal vesicle	(50)	(49)	(48)	(49)
Adenoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	27 (54%)	25 (50%)	26 (52%)	17 (34%)
Interstitial cell, adenoma	13 (26%)	10 (20%)	15 (30%)	16 (32%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Lymph node	(2)	(4)		(2)
Renal, squamous cell carcinoma, metastatic, lung				1 (50%)
Lymph node, bronchial	(26)	(27)	(41)	(44)
Histiocytic sarcoma		1 (4%)		
Squamous cell carcinoma, metastatic, lung				1 (2%)
Lymph node, mandibular	(44)	(42)	(47)	(47)
Squamous cell carcinoma, metastatic, lung				1 (2%)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Lymph node, mediastinal	(25)	(19)	(45)	(40)
Squamous cell carcinoma, metastatic, lung				2 (5%)
Spleen	(50)	(50)	(49)	(48)
Thymus	(47)	(47)	(46)	(45)
Integumentary System				
Mammary gland	(24)	(33)	(31)	(24)
Carcinoma			1 (3%)	1 (4%)
Fibroadenoma	2 (8%)	1 (3%)		1 (4%)
Skin	(50)	(50)	(50)	(49)
Histiocytic sarcoma		1 (2%)		
Keratoacanthoma	2 (4%)	3 (6%)	5 (10%)	2 (4%)
Keratoacanthoma, multiple		1 (2%)		
Squamous cell papilloma				1 (2%)
Trichoepithelioma			1 (2%)	
Sebaceous gland, adenoma	1 (2%)	1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)	4 (8%)	7 (14%)	3 (6%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Subcutaneous tissue, liposarcoma			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Osteoma			1 (2%)	
Osteosarcoma	3 (6%)		1 (2%)	1 (2%)
Skeletal muscle			(1)	
Rhabdomyosarcoma			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Glioma benign		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	8 (16%)	19 (38%)	18 (36%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	5 (10%)	8 (16%)	12 (24%)
Alveolar/bronchiolar carcinoma	1 (2%)	8 (16%)	7 (14%)	11 (22%)
Alveolar/bronchiolar carcinoma, multiple		2 (4%)	1 (2%)	5 (10%)
Carcinoma, metastatic, pituitary gland	1 (2%)	1 (2%)		
Carcinoma, metastatic, thyroid gland		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Osteosarcoma, metastatic, bone	2 (4%)			
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)		
Squamous cell carcinoma				4 (8%)
Mediastinum, osteosarcoma, metastatic, bone	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Chondroma	1 (2%)			
Esthesioneuroblastoma			1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)	
Squamous cell carcinoma, metastatic, lung				1 (2%)
Pleura		(2)		(2)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (50%)		1 (50%)
Histiocytic sarcoma		1 (50%)		
Squamous cell carcinoma, metastatic, lung				1 (50%)
Special Senses System				
Zymbal's gland		(1)	(1)	(1)
Adenoma				1 (100%)
Carcinoma		1 (100%)	1 (100%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Liposarcoma			1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Squamous cell carcinoma, metastatic, lung				2 (4%)
Urinary bladder	(50)	(50)	(49)	(50)
Transitional epithelium, papilloma			1 (2%)	1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		3 (6%)		
Leukemia mononuclear	16 (32%)	23 (46%)	29 (58%)	25 (50%)
Mesothelioma malignant	2 (4%)		1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
2-Year study	49	50	50	50
Total primary neoplasms				
2-Year study	142	186	203	197
Total animals with benign neoplasms				
2-Year study	47	48	48	48
Total benign neoplasms				
2-Year study	112	135	145	142
Total animals with malignant neoplasms				
2-Year study	26	37	42	37
Total malignant neoplasms				
2-Year study	30	51	58	55
Total animals with metastatic neoplasms				
2-Year study	3	5	2	4
Total metastatic neoplasms				
2-Year study	7	7	2	17

[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 Indium Phosphide: Chamber Control

Number of Days on Study	1 3 5	4 0 8	4 7 6	4 9 5	5 2 5	5 3 7	5 5 1	5 5 2	5 6 9	6 0 0	6 1 7	6 2 4	6 3 9	6 4 7	6 4 9	6 5 6	6 7 2	6 7 2	6 9 7	7 0 0	7 0 3	7 0 9	7 1 4	7 3 3	7 3 3
Carcass ID Number	0 4 4	0 4 3	0 1 9	0 3 6	0 3 9	0 1 4	0 3 3	0 2 9	0 2 6	0 1 7	0 1 0	0 0 4	0 3 2	0 4 8	0 0 5	0 3 1	0 2 0	0 4 5	0 4 9	0 2 8	0 4 2	0 1 6	0 0 8	0 0 2	0 0 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	I	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X													
Mesentery																							+		+
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth																	+						+		
Cardiovascular System																									
Blood vessel									+																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X													
Schwannoma benign																		X							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign						X		X					X							X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma											X								X						
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X	X			X	X	X	X		X	X	X		X	X	X	X	X		X	X
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X						
C-cell, carcinoma																	X								
General Body System																									
Peritoneum																							+		

+: 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 Indium Phosphide: 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 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	7 5 5	
Carcass ID Number	0 0 7	0 0 9	0 1 2	0 2 5	0 3 4	0 3 8	0 4 0	0 4 6	0 0 1	0 0 6	0 1 1	0 1 3	0 1 5	0 1 8	0 2 1	0 2 2	0 2 4	0 2 7	0 3 0	0 3 7	0 4 1	0 4 7	0 5 0	0 2 3	0 3 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Mesentery										+					+		+			+						6
Oral mucosa																					+					1
Pharyngeal, squamous cell papilloma																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+			+																2
Tooth																										2
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Schwannoma benign																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X	X	X		X				X							X			10
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Carcinoma																										2
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Adenoma																							X			1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X	X	X	X		X	X	X	X	X		X	X		X		X		X	X	X	X	36
Pars distalis, carcinoma																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma			X	X					X								X									5
C-cell, carcinoma																										1
General Body System																										
Peritoneum																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	1 3 5	4 0 8	4 7 6	4 9 5	5 2 5	5 3 7	5 5 1	5 5 2	5 6 9	6 0 0	6 1 7	6 2 4	6 3 9	6 4 7	6 4 9	6 5 6	6 7 2	6 7 2	6 9 7	7 0 0	7 0 3	7 0 9	7 1 4	7 3 3	7 3 3
Carcass ID Number	0 4 4	0 4 3	0 1 9	0 3 6	0 3 9	0 1 4	0 3 3	0 2 9	0 2 6	0 1 7	0 1 0	0 0 4	0 3 2	0 4 8	0 0 5	0 3 1	0 2 0	0 4 5	0 4 9	0 2 8	0 4 2	0 1 6	0 0 8	0 0 2	0 0 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma						X							X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X						X				X	X		X		X	X	X		X	X		
Interstitial cell, adenoma		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
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	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
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Sebaceous gland, adenoma																					X				
Subcutaneous tissue, fibroma																	X								
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																				X					
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma		X										X		X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord							+																		
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X			X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma													X												
Carcinoma, metastatic, pituitary gland																									
Osteosarcoma, metastatic, bone		X										X													
Mediastinum, osteosarcoma, metastatic, bone												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	0 0 0 7	0 0 0 9	0 0 1 2	0 0 2 5	0 0 3 4	0 0 3 8	0 0 4 0	0 0 4 6	0 0 0 1	0 0 0 6	0 0 1 1	0 0 1 3	0 0 1 5	0 0 1 8	0 0 2 1	0 0 2 2	0 0 2 4	0 0 2 7	0 0 3 0	0 0 3 7	0 0 4 1	0 0 4 7	0 0 5 0	0 0 3 3	0 0 3 5	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Carcinoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X		X			X		X	X	X	X	X	X	X	X		X	X	X				27
Interstitial cell, adenoma							X	X															X	X	X	13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+																		2
Lymph node, bronchial	M	M	+	M	M	+	+	M	+	+	+	+	M	M	M	+	M	M	M	+	+	+	M	M	+	26
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	+	+	+	+	M	+	M	+	+	+	+	M	M	M	+	M	M	M	M	M	M	M	M	M	25
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	47
Integumentary System																										
Mammary gland	M	+	+	+	M	M	M	+	M	M	+	+	+	M	M	+	+	M	+	+	+	M	+	+	M	24
Fibroadenoma								X									X									2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma										2					X										X	
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																							X			1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, lipoma		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										3
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X							X		X				5
Alveolar/bronchiolar adenoma, multiple				X																						1
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, pituitary gland																			X							1
Osteosarcoma, metastatic, bone																										2
Mediastinum, osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondroma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	1 3 5	4 0 8	4 7 6	4 9 5	5 2 5	5 3 7	5 5 1	5 5 2	5 6 9	6 0 0	6 1 7	6 2 4	6 3 9	6 4 7	6 4 9	6 5 6	6 7 2	6 7 2	6 9 7	7 0 0	7 0 3	7 0 9	7 1 4	7 3 3	7 3 3
Carcass ID Number	0 4 4	0 4 3	0 1 9	0 3 6	0 3 9	0 1 4	0 3 3	0 2 9	0 2 6	0 1 7	0 1 0	0 0 4	0 3 2	0 4 8	0 0 5	0 3 1	0 2 0	0 4 5	0 4 9	0 2 8	0 4 2	0 1 6	0 0 8	0 0 2	0 0 3
Special Senses System																									
Ear																									
Eye																					+				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X				X								X	X					X	X	
Mesothelioma malignant																							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	0 0 0 7	0 0 0 9	0 0 1 2	0 0 2 5	0 0 3 4	0 0 3 8	0 0 4 0	0 0 4 6	0 0 0 1	0 0 0 6	0 0 1 1	0 0 1 3	0 0 1 5	0 0 1 8	0 0 2 1	0 0 2 2	0 0 2 4	0 0 2 7	0 0 3 0	0 0 3 7	0 0 4 1	0 0 4 7	0 0 5 0	0 0 2 3	0 0 3 5	Total Tissues/ Tumors
Special Senses System																												
Ear																								+			1	
Eye																											1	
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Osteosarcoma, metastatic, bone																											1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear							X	X								X		X		X	X	X		X	X		16	
Mesothelioma malignant																					X						2	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	285	256	269	276	286	268	235	243	258	283	284	285	286	295	300	301	302	307	314	323	333	333	333	333
Carcass ID Number	23801	25002	23404	24101	24303	20405	22505	23106	20806	22707	21202	21306	23303	23707	22404	23202	23209	23505	20916	21016	20201	20004	20104	21104
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+
Carcinoma																								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																								
Cholangioma												X												
Histiocytic sarcoma										X														
Mesentery								+										+	+				+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung														X										
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Carcinoma																		X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant						X																		
Pheochromocytoma complex																X								
Pheochromocytoma benign								X					X		X				X			X		X
Bilateral, pheochromocytoma benign							X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X								
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X		X	X		X	X	X	X	X			X			X	X		X	X	X
Pars distalis, carcinoma																					X			
Pars intermedia, adenoma																	X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																								
C-cell, adenoma							X		X													X		
C-cell, carcinoma																	X							X
Follicular cell, adenoma																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 1 5	2 1 7	2 1 9	2 2 0	2 2 1	2 2 2	2 2 8	2 3 9	2 4 0	2 4 2	2 0 7	2 1 0	2 1 8	2 2 3	2 3 0	2 4 4	2 4 5	2 4 6	2 4 7	2 4 8	2 0 3	2 0 8	2 1 1	2 2 6	2 4 9	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																									1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma												X													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																			X						1
Cholangioma																									1
Histiocytic sarcoma																									1
Mesentery															+		+							6	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Carcinoma																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant							X																X		3
Pheochromocytoma complex																									1
Pheochromocytoma benign	X	X			X									X	X	X				X	X			X	X	16
Bilateral, pheochromocytoma benign			X			X		X	X								X									6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																							2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X				X	X			X		X	X	X	X	X	X	X			X	X	X	X	33
Pars distalis, carcinoma																									1
Pars intermedia, adenoma																									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Bilateral, C-cell, adenoma																		X							1
C-cell, adenoma			X					X															X		X	7
C-cell, carcinoma									4						X										X	
Follicular cell, adenoma										X																1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	2 8 5	5 2 6	5 6 9	5 7 6	5 8 6	6 2 8	6 3 5	6 4 3	6 5 8	6 8 3	6 8 4	6 8 5	6 8 6	6 9 5	7 0 0	7 0 1	7 0 2	7 0 7	7 1 4	7 1 4	7 2 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 3 8	2 5 0	2 3 4	2 4 1	2 4 3	2 0 5	2 2 5	2 3 1	2 0 6	2 2 7	2 1 2	2 3 6	2 3 3	2 3 7	2 2 4	2 3 2	2 2 9	2 3 5	2 0 9	2 1 6	2 0 2	2 0 1	2 0 4	2 1 3	2 1 4
General Body System																									
Peritoneum										+															
Histiocytic sarcoma										X															
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Adenoma																									
Histiocytic sarcoma										X															
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X		X	X						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	M	+	M	+
Histiocytic sarcoma										X															
Lymph node, mandibular	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	+	+	+	+	M	M	M	+	M	M	+	M	M	+	+	+	M	M	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	M	+	M	+	+	M	M	M	+	M	+	+	+	+	+	+	M	+	M	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Keratoacanthoma																									
Keratoacanthoma, multiple				X																					
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma													X						X						
Subcutaneous tissue, fibrosarcoma													X						X						
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																			X						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma benign																		X							
Histiocytic sarcoma									X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 1 5	2 1 7	2 1 9	2 2 0	2 2 1	2 2 2	2 2 8	2 3 9	2 4 0	2 4 2	2 0 7	2 1 0	2 1 8	2 2 3	2 3 0	2 4 4	2 4 5	2 4 6	2 4 7	2 4 8	2 0 3	2 0 8	2 1 1	2 2 6	2 4 9	Total Tissues/ Tumors
General Body System																										
Peritoneum																										1
Histiocytic sarcoma																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													1
Histiocytic sarcoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X	X	X			X		X	X	X	X	X			X	X	X	X				X	25
Interstitial cell, adenoma							X			X							X					X	X	X		10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node									+	+																4
Lymph node, bronchial	M	M	M	+	+	+	M	+	+	+	+	M	M	M	+	+	+	M	M	+	M	M	+	M	M	27
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	M	M	M	M	M	M	+	+	+	M	M	M	M	M	+	+	M	M	+	M	M	+	M	M	19
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	M	M	M	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	M	+	+	+	+	33
Fibroadenoma													X													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Keratoacanthoma											X		X	X												3
Keratoacanthoma, multiple																										1
Sebaceous gland, adenoma			X																							1
Subcutaneous tissue, fibroma					X																		X			4
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, lipoma																			X							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma benign																										1
Histiocytic sarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	285	256	369	576	866	268	355	433	588	833	842	856	866	955	000	011	022	027	144	144	233	333	333	333	333
Carcass ID Number	23838	25030	23404	24041	24043	20405	22525	23031	20106	22707	21212	23636	23633	23737	22424	23232	22929	23535	20916	21616	20202	20001	20404	21013	21114
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									X
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X	X				X		X						
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma							X							X					X		X		X		
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, pituitary gland																					X				
Carcinoma, metastatic, thyroid gland																									X
Histiocytic sarcoma										X															
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura										+				+											
Alveolar/bronchiolar carcinoma, metastatic, lung														X											
Histiocytic sarcoma										X															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																+									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X								X	X															
Leukemia mononuclear					X	X	X	X	X		X	X			X					X		X		X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 1 5	2 1 7	2 1 9	2 2 0	2 2 1	2 2 2	2 2 8	2 3 9	2 4 0	2 4 2	2 0 7	2 1 0	2 1 8	2 2 3	2 3 0	2 4 4	2 4 5	2 4 6	2 4 7	2 4 8	2 0 3	2 0 8	2 1 1	2 2 6	2 4 9	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X	X						X													X					8
Alveolar/bronchiolar adenoma, multiple				X										X					X			X				5
Alveolar/bronchiolar carcinoma																		X						X	X	8
Alveolar/bronchiolar carcinoma, multiple											X				X											2
Carcinoma, metastatic, pituitary gland																										1
Carcinoma, metastatic, thyroid gland																										1
Histiocytic sarcoma																										1
Pheochromocytoma malignant, metastatic, adrenal medulla							X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland									+																	1
Carcinoma									X																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Leukemia mononuclear			X	X					X	X	X		X		X			X	X			X		X	X	23

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	4 0 3	4 3 5	4 6 0	4 9 3	5 1 3	5 3 7	5 5 2	6 0 2	6 3 0	6 4 4	6 4 4	6 4 9	6 5 1	6 5 6	6 5 8	6 6 5	6 6 7	6 7 9	6 9 8	7 0 0	7 1 0	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 3 6	4 4 7	4 3 1	4 0 2	4 2 7	4 2 9	4 0 4	4 4 1	4 3 3	4 2 2	4 4 9	4 5 0	4 4 8	4 2 5	4 1 0	4 2 1	4 0 1	4 1 9	4 2 4	4 1 4	4 1 7	4 0 1	4 0 5	4 0 8	4 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X					
Mesentery															+	+							+		
Oral mucosa																			+						
Gingival, squamous cell papilloma																									
Pharyngeal, squamous cell papilloma																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pericardium, alveolar/bronchiolar carcinoma, metastatic, lung																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																			X						
Pheochromocytoma benign						X			X	X	X													X	X
Bilateral, pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma												X		X											
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X	X			X		X			X	X		X	X	X	X		X		X	X	
Thyroid gland	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																							X		
C-cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 1 5	4 2 0	4 2 3	4 2 6	4 3 8	4 4 6	4 0 6	4 0 7	4 0 9	4 1 1	4 1 2	4 1 8	4 2 8	4 3 2	4 3 4	4 3 5	4 3 7	4 3 9	4 4 2	4 4 3	4 4 5	4 1 6	4 3 0	4 4 0	4 4 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous	X																									1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery	+			+				+																		6
Oral mucosa						+			+																	3
Gingival, squamous cell papilloma						X			X																	2
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																								X		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth				+							+												+			3
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pericardium, alveolar/bronchiolar carcinoma, metastatic, lung																									X	1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	49
Pheochromocytoma malignant													X					X								3
Pheochromocytoma benign			X					X	X					X				X							X	12
Bilateral, pheochromocytoma benign											X					X	X									4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																				X			2
Carcinoma	X									X																4
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X		X	X	X	X		X	X	X			X	X				X	X	X		31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma	X		X													X										4
C-cell, carcinoma								X				X		X												3
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	4 0 3	4 3 5	4 6 0	4 9 3	5 1 3	5 3 7	5 5 2	6 0 2	6 3 0	6 4 4	6 4 4	6 4 9	6 5 1	6 5 6	6 6 8	6 6 5	6 6 7	6 7 9	6 9 8	7 0 0	7 1 0	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 3 6	4 4 7	4 3 1	4 0 2	4 2 7	4 2 9	4 0 4	4 4 1	4 3 3	4 4 2	4 4 9	4 5 0	4 4 8	4 2 5	4 1 0	4 2 1	4 0 3	4 1 9	4 2 4	4 1 4	4 1 7	4 0 1	4 0 5	4 0 8	4 1 3
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Adenoma, multiple																							X		
Seminal vesicle	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X	X	X		X	X					X		X			X
Interstitial cell, adenoma							X	X					X				X	X			X		X	X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	M	+	M	M	+	+	+	+	+	M	+	M	+	+	M	M	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	I	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	M	M	M	+	M	+	M	M	+	M	+	+	+	+	M	M	M	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma																X									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																			X						
Subcutaneous tissue, liposarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																	X								
Osteosarcoma		X																							
Skeletal muscle																			+						
Rhabdomyosarcoma																			X						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord												+													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 1 5	4 2 0	4 2 3	4 2 6	4 3 8	4 4 6	4 0 6	4 0 7	4 0 9	4 1 1	4 1 2	4 1 8	4 2 8	4 3 2	4 3 4	4 3 5	4 3 7	4 3 9	4 4 2	4 4 3	4 4 5	4 1 6	4 3 0	4 4 0	4 4 4	Total Tissues/ Tumors
Genital System																										
Coagulating gland																									+	1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																X										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adenoma, multiple																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X		X	X	X	X		X			X		X	X	X		X	X	26
Interstitial cell, adenoma	X								X					X		X	X		X				X			15
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	41
Lymph node, mandibular	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	M	M	+	+	+	+	+	+	+	M	M	+	+	M	+	M	M	+	+	+	+	+	I	31
Carcinoma																	X									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma	X			X		X											X							X		5
Trichoepithelioma									X																	1
Subcutaneous tissue, fibroma					X	X											X				X	X	X			7
Subcutaneous tissue, fibrosarcoma																								X		1
Subcutaneous tissue, lipoma														X												2
Subcutaneous tissue, liposarcoma									X																	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma																										1
Osteosarcoma																										1
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	4 0 3	4 3 5	4 6 0	4 9 3	5 1 3	5 3 7	5 5 2	6 0 2	6 3 0	6 4 4	6 4 4	6 4 9	6 5 1	6 5 6	6 5 8	6 6 5	6 6 7	6 7 9	6 9 8	7 0 0	7 1 0	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 3 6	4 4 7	4 3 1	4 0 2	4 2 7	4 2 9	4 0 4	4 4 1	4 3 3	4 2 2	4 4 9	4 5 0	4 4 8	4 2 5	4 1 0	4 2 1	4 0 3	4 1 9	4 2 4	4 1 4	4 1 7	4 0 1	4 0 5	4 0 8	4 1 3
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X	X	X		X		X				X			X	X
Alveolar/bronchiolar adenoma, multiple																						X	X		
Alveolar/bronchiolar carcinoma																					X				
Alveolar/bronchiolar carcinoma, multiple																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esthesioneuroblastoma			X																						
Osteosarcoma, metastatic, bone		X																							
Trachea	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																						+			
Carcinoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma										X															
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X				X	X	X	X	X	X	X		X	X	X		X	X	X	X			X		
Mesothelioma malignant														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 1 5	4 2 0	4 2 3	4 2 6	4 3 8	4 4 6	4 0 6	4 0 7	4 0 9	4 1 1	4 1 2	4 1 8	4 2 8	4 3 2	4 3 4	4 3 5	4 3 7	4 3 9	4 4 2	4 4 3	4 4 5	4 1 6	4 3 0	4 4 0	4 4 4	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X						X		X		X		X	X	X		X		X			X		X	19
Alveolar/bronchiolar adenoma, multiple	X				X	X							X						X			X				8
Alveolar/bronchiolar carcinoma	X		X					X	X		X														X	7
Alveolar/bronchiolar carcinoma, multiple													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esthesioneuroblastoma																										1
Osteosarcoma, metastatic, bone																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																	+									1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X				X					X	X		X	X	X		X		X			29
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	525	533	532	545	547	560	600	603	621	656	658	658	711	722	722	726	766	784	866	895	706	728	748	802	733
Carcass ID Number	629	643	620	616	604	608	625	645	649	628	633	650	630	631	637	601	619	606	639	612	641	626	646	617	603
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	A	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	+
Intestine small, ileum	+	+	+	+	A	+	A	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Mesentery						+	+												+	+			+	+	
Squamous cell carcinoma, metastatic, lung							X																		
Oral mucosa															+										
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung							X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth												+													
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung											X														
Schwannoma benign																									
Squamous cell carcinoma, metastatic, lung							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung																		X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X							
Pheochromocytoma benign	X		X						X				X						X						
Squamous cell carcinoma, metastatic, lung																		X							
Bilateral, pheochromocytoma benign										X		X										X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma																		X			X				
Squamous cell carcinoma, metastatic, lung																		X							
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
C-cell, adenoma	X											X				X									
C-cell, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	6 0 5	6 1 0	6 1 1	6 1 3	6 1 4	6 1 5	6 1 8	6 2 3	6 2 4	6 3 2	6 3 6	6 4 4	6 0 2	6 0 9	6 2 7	6 3 5	6 3 8	6 4 0	6 4 2	6 4 7	6 4 8	6 0 7	6 2 1	6 2 2	6 3 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma			X																							1
Mesentery						+														+						8
Squamous cell carcinoma, metastatic, lung																										1
Oral mucosa										+																2
Pharyngeal, squamous cell papilloma										X																1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, lung																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Schwannoma benign		X																								1
Squamous cell carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, lung																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X			X	X			X	X		X	X	X				X	X		X	X		X			18
Squamous cell carcinoma, metastatic, lung																										1
Bilateral, pheochromocytoma benign						X													X							5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X								X									3
Carcinoma														X												3
Squamous cell carcinoma, metastatic, lung																										1
Parathyroid gland	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X		X	X					X	X	X	X	X	X	X		X	X			X		X	30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma			X			X						X				X		X		X						9
C-cell, carcinoma				X																						1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	5 2 5	5 3 0	5 3 2	5 4 5	5 4 7	5 6 0	6 0 0	6 0 3	6 2 1	6 5 6	6 5 8	6 5 8	6 7 1	6 7 2	6 7 2	6 7 6	6 7 6	6 8 4	6 8 6	6 9 5	7 0 6	7 2 8	7 2 8	7 3 0	7 3 3
Carcass ID Number	6 2 9	6 4 3	6 2 0	6 1 6	6 0 4	6 0 8	6 2 5	6 4 5	6 4 9	6 2 8	6 3 3	6 5 0	6 3 0	6 3 1	6 3 7	6 0 1	6 1 9	6 0 6	6 3 9	6 1 2	6 4 1	6 2 6	6 4 6	6 1 7	6 0 3
General Body System																									
Tissue NOS																								+	
Chemodectoma malignant																								X	
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																						+			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X						X					X				X		X	X
Interstitial cell, adenoma			X												X				X	X	X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+																		
Renal, squamous cell carcinoma, metastatic, lung							X																		
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+	+	M	+	M	+	+	+
Squamous cell carcinoma, metastatic, lung																		X							
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung							X																		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	M	+	M	+	+	M	M	+
Squamous cell carcinoma, metastatic, lung				X			X																		
Spleen	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	M	M	M	M	M	+	+	+	+	M	M	M	+	+	M	+	M	+	M	+	M	M
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma						X																			
Subcutaneous tissue, fibroma														X									X		
Subcutaneous tissue, fibrosarcoma													X												
Subcutaneous tissue, lipoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	6 0 5	6 1 0	6 1 1	6 1 3	6 1 4	6 1 5	6 1 8	6 2 3	6 2 4	6 3 2	6 3 6	6 4 4	6 0 2	6 0 9	6 2 7	6 3 5	6 3 8	6 4 0	6 4 2	6 4 7	6 4 8	6 0 7	6 2 1	6 2 2	6 3 4	Total Tissues/ Tumors
General Body System																									
Tissue NOS																									1
Chemodectoma malignant																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																									1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X											X		2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma				X		X	X			X		X	X	X		X				X	X			X	17
Interstitial cell, adenoma	X				X			X	X		X						X	X	X			X	X	X		16
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																									2
Renal, squamous cell carcinoma, metastatic, lung																									1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Squamous cell carcinoma, metastatic, lung																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, lung																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Squamous cell carcinoma, metastatic, lung																									2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																									
Mammary Gland	M	+	M	+	+	M	M	M	+	+	+	M	M	+	+	+	M	M	M	+	+	M	+	+	M	24
Carcinoma					X																				1
Fibroadenoma																							X		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratocanthoma		X														X									2
Squamous cell papilloma																									1
Subcutaneous tissue, fibroma											X														3
Subcutaneous tissue, fibrosarcma																									1
Subcutaneous tissue, lipoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	52 5	53 0	53 2	54 5	54 7	56 0	56 0	60 3	62 1	65 6	65 8	65 8	67 1	67 2	67 2	67 6	67 6	68 4	68 6	69 5	70 6	72 8	72 8	73 0	73 3
Carcass ID Number	62 9	64 3	62 0	61 6	60 4	60 8	62 5	64 5	64 9	62 8	63 3	65 0	63 0	63 1	63 7	60 1	61 9	60 6	63 9	61 2	64 1	62 6	64 6	61 7	60 3
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X	X												X		X	X			X				X	
Alveolar/bronchiolar adenoma, multiple															X						X	X			X
Alveolar/bronchiolar carcinoma									X			X	X							X	X	X			
Alveolar/bronchiolar carcinoma, multiple											X														
Squamous cell carcinoma				X			X							X				X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung							X																		
Pleura							+				+														
Alveolar/bronchiolar carcinoma, metastatic, lung											X														
Squamous cell carcinoma, metastatic, lung							X																		
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																			+						
Zymbal's gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung				X														X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																	X								
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X		X		X		X			X		X		X	X	X	X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	6 0 5	6 1 0	6 1 1	6 1 3	6 1 4	6 1 5	6 1 8	6 2 3	6 2 4	6 3 2	6 3 6	6 4 4	6 0 2	6 0 9	6 2 7	6 3 5	6 3 8	6 4 0	6 4 2	6 4 7	6 4 8	6 0 7	6 2 1	6 2 2	6 3 4	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X			X	X		X			X	X	X		X	X			X	X		18
Alveolar/bronchiolar adenoma, multiple	X	X		X	X								X					X				X			X	12
Alveolar/bronchiolar carcinoma					X	X										X	X	X								11
Alveolar/bronchiolar carcinoma, multiple							X		X											X					X	5
Squamous cell carcinoma																										4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, lung																										1
Pleura																										2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Squamous cell carcinoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Zymbal's gland																						+				1
Adenoma																						X				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, lung																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X	X	X						X			X	X	X	X	X		X	X	X		X	25

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a] 10/50 (20%)	22/50 (44%)	16/49 (33%)	23/50 (46%)	
Adjusted rate[b]	23.8%	48.8%	38.0%	51.1%
Terminal rate[c]	6/27 (22%)	17/29 (59%)	11/28 (39%)	15/26 (58%)
First incidence (days)	537	635	537	525
Poly-3 test[d]	P=0.006	P=0.011	P=0.117	P=0.006
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	0/50 (0%)	3/50 (6%)	3/49 (6%)	1/50 (2%)
Adjusted rate	0.0%	6.8%	7.4%	2.3%
Terminal rate	0/27 (0%)	2/29 (7%)	2/28 (7%)	0/26 (0%)
First incidence (days)	—[e]	628	698	684
Poly-3 test	P=0.586	P=0.136	P=0.119	P=0.511
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	10/50 (20%)	26/50 (52%)	18/49 (37%)	24/50 (48%)
Adjusted rate	23.8%	57.1%	42.6%	53.1%
Terminal rate	6/27 (22%)	19/29 (66%)	12/28 (43%)	15/26 (58%)
First incidence (days)	537	628	537	525
Poly-3 test	P=0.005	P<0.001	P=0.051	P=0.003
Bone: Osteosarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adjusted rate	7.2%	0.0%	2.4%	2.3%
Terminal rate	0/27 (0%)	0/29 (0%)	0/29 (0%)	0/26 (0%)
First incidence (days)	408	—	435	671
Poly-3 test	P=0.268N	P=0.110N	P=0.302N	P=0.298N
Bone: Osteoma or Osteosarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rate	7.2%	0.0%	4.7%	2.3%
Terminal rate	0/27 (0%)	0/29 (0%)	0/29 (0%)	0/26 (0%)
First incidence (days)	408	—	435	671
Poly-3 test	P=0.248N	P=0.110N	P=0.494N	P=0.298N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	13/50 (26%)	27/50 (54%)	30/50 (60%)
Adjusted rate	14.8%	29.1%	62.9%	67.0%
Terminal rate	4/27 (15%)	8/29 (28%)	21/29 (72%)	20/26 (77%)
First incidence (days)	697	685	644	525
Poly-3 test	P<0.001	P=0.090	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	10/50 (20%)	8/50 (16%)	16/50 (32%)
Adjusted rate	2.5%	22.4%	19.3%	36.5%
Terminal rate	0/27 (0%)	6/29 (21%)	7/29 (24%)	9/26 (35%)
First incidence (days)	639	635	710	621
Poly-3 test	P<0.001	P=0.006	P=0.016	P<0.001

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	7/50 (14%)	22/50 (44%)	30/50 (60%)	35/50 (70%)
Adjusted rate	17.1%	48.7%	69.8%	76.1%
Terminal rate	4/27 (15%)	14/29 (48%)	24/29 (83%)	21/26 (81%)
First incidence (days)	639	635	644	525
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Lung: Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	9.1%
Terminal rate	0/27 (0%)	0/29 (0%)	0/29 (0%)	0/26 (0%)
First incidence (days)	—	—[f]	—	545
Poly-3 test	P=0.011	—	—	P=0.071
Oral Mucosa (Pharynx, Gingiva): Squamous Papilloma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.5%	0.0%	7.2%	2.4%
Terminal rate	1/27 (4%)	0/29 (0%)	2/29 (7%)	1/26 (4%)
First incidence (days)	733 (T)	—	698	733 (T)
Poly-3 test	P=0.526N	P=0.483N	P=0.315	P=0.750N
Pancreatic Islets: Adenoma				
Overall rate	1/50 (2%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.5%	4.5%	4.8%	7.0%
Terminal rate	1/27 (4%)	1/29 (3%)	2/29 (7%)	2/26 (8%)
First incidence (days)	733 (T)	701	733 (T)	658
Poly-3 test	P=0.273	P=0.531	P=0.509	P=0.325
Pancreatic Islets: Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted rate	4.9%	0.0%	9.5%	7.0%
Terminal rate	0/27 (0%)	0/29 (0%)	2/29 (7%)	1/26 (4%)
First incidence (days)	617	—	649	684
Poly-3 test	P=0.526	P=0.221N	P=0.349	P=0.519
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	6/50 (12%)	6/50 (12%)
Adjusted rate	7.3%	4.5%	14.3%	14.0%
Terminal rate	1/27 (4%)	1/29 (3%)	4/29 (14%)	3/26 (12%)
First incidence (days)	617	701	649	658
Poly-3 test	P=0.285	P=0.465N	P=0.253	P=0.265
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	36/49 (73%)	33/50 (66%)	31/50 (62%)	30/50 (60%)
Adjusted rate	79.6%	69.2%	67.6%	64.0%
Terminal rate	21/27 (78%)	20/29 (69%)	19/29 (66%)	16/26 (62%)
First incidence (days)	495	526	435	525
Poly-3 test	P=0.078N	P=0.175N	P=0.135N	P=0.067N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	37/49 (76%)	34/50 (68%)	31/50 (62%)	30/50 (60%)
Adjusted rate	81.8%	71.2%	67.6%	64.0%
Terminal rate	22/27 (82%)	20/29 (69%)	19/29 (66%)	16/26 (62%)
First incidence (days)	495	526	435	525
Poly-3 test	P=0.049N	P=0.161N	P=0.083N	P=0.038N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.3%	4.5%	2.4%	0.0%
Terminal rate	1/27 (4%)	2/29 (7%)	1/29 (3%)	0/26 (0%)
First incidence (days)	537	733 (T)	733 (T)	—
Poly-3 test	P=0.084N	P=0.471N	P=0.304N	P=0.113N
Skin: Keratoacanthoma				
Overall rate	2/50 (4%)	4/50 (8%)	5/50 (10%)	2/50 (4%)
Adjusted rate	5.0%	9.0%	12.1%	4.7%
Terminal rate	2/27 (7%)	3/29 (10%)	5/29 (17%)	2/26 (8%)
First incidence (days)	733 (T)	576	733 (T)	733 (T)
Poly-3 test	P=0.470N	P=0.383	P=0.225	P=0.677N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	2/50 (4%)	4/50 (8%)	5/50 (10%)	3/50 (6%)
Adjusted rate	5.0%	9.0%	12.1%	7.0%
Terminal rate	2/27 (7%)	3/29 (10%)	5/29 (17%)	2/26 (8%)
First incidence (days)	733 (T)	576	733 (T)	560
Poly-3 test	P=0.578	P=0.383	P=0.225	P=0.528
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Trichoepithelioma				
Overall rate	2/50 (4%)	4/50 (8%)	6/50 (12%)	3/50 (6%)
Adjusted rate	5.0%	9.0%	14.5%	7.0%
Terminal rate	2/27 (7%)	3/29 (10%)	6/29 (21%)	2/26 (8%)
First incidence (days)	733 (T)	576	733 (T)	560
Poly-3 test	P=0.591N	P=0.383	P=0.139	P=0.528
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	4/50 (8%)	7/50 (14%)	3/50 (6%)
Adjusted rate	2.5%	9.0%	16.8%	7.0%
Terminal rate	0/27 (0%)	2/29 (7%)	6/29 (21%)	1/26 (4%)
First incidence (days)	672	686	665	672
Poly-3 test	P=0.508	P=0.206	P=0.032	P=0.323
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	8/50 (16%)	4/50 (8%)
Adjusted rate	4.9%	9.0%	19.2%	9.3%
Terminal rate	1/27 (4%)	2/29 (7%)	7/29 (24%)	1/26 (4%)
First incidence (days)	672	686	665	671
Poly-3 test	P=0.519	P=0.378	P=0.047	P=0.362

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Testes: Adenoma				
Overall rate	40/50 (80%)	35/50 (70%)	41/50 (82%)	33/50 (66%)
Adjusted rate	86.1%	76.4%	91.3%	73.9%
Terminal rate	24/27 (89%)	26/29 (90%)	29/29 (100%)	23/26 (89%)
First incidence (days)	408	586	552	532
Poly-3 test	P=0.029N	P=0.157N	P=0.301	P=0.092N
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/49 (10%)	8/49 (16%)	4/48 (8%)	9/48 (19%)
Adjusted rate	12.6%	18.3%	9.9%	21.5%
Terminal rate	4/27 (15%)	6/28 (21%)	4/29 (14%)	6/26 (23%)
First incidence (days)	697	635	733 (T)	525
Poly-3 test	P=0.126	P=0.336	P=0.489N	P=0.218
Thyroid Gland (C-cell): Carcinoma				
Overall rate	1/49 (2%)	4/49 (8%)	3/48 (6%)	1/48 (2%)
Adjusted rate	2.5%	9.3%	7.4%	2.5%
Terminal rate	0/27 (0%)	3/28 (11%)	3/29 (10%)	1/26 (4%)
First incidence (days)	672	702	733 (T)	733 (T)
Poly-3 test	P=0.536N	P=0.202	P=0.310	P=0.756N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/49 (12%)	11/49 (22%)	7/48 (15%)	10/48 (21%)
Adjusted rate	15.0%	25.1%	17.3%	23.9%
Terminal rate	4/27 (15%)	8/28 (29%)	7/29 (24%)	7/26 (27%)
First incidence (days)	672	635	733 (T)	525
Poly-3 test	P=0.188	P=0.188	P=0.509	P=0.230
All Organs: Histiocytic Sarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	6.6%	0.0%	0.0%
Terminal rate	0/27 (0%)	0/29 (0%)	0/29 (0%)	0/26 (0%)
First incidence (days)	—	285	—	—
Poly-3 test	—	P=0.141	—	—
All Organs: Mononuclear Cell Leukemia				
Overall rate	16/50 (32%)	23/50 (46%)	29/50 (58%)	25/50 (50%)
Adjusted rate	37.0%	49.6%	61.6%	55.8%
Terminal rate	9/27 (33%)	14/29 (48%)	14/29 (48%)	14/26 (54%)
First incidence (days)	135	586	403	532
Poly-3 test	P=0.104	P=0.157	P=0.013	P=0.053
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	48/50 (96%)	48/50 (96%)	48/50 (96%)
Adjusted rate	97.0%	97.9%	99.1%	98.0%
Terminal rate	26/27 (96%)	29/29 (100%)	29/29 (100%)	26/26 (100%)
First incidence (days)	408	526	435	525
Poly-3 test	P=0.632	P=0.654	P=0.494	P=0.657

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	37/50 (74%)	42/50 (84%)	37/50 (74%)
Adjusted rate	56.0%	76.6%	85.6%	78.5%
Terminal rate	11/27 (41%)	19/29 (66%)	23/29 (79%)	19/26 (73%)
First incidence (days)	135	285	403	532
Poly-3 test	P=0.030	P=0.024	P<0.001	P=0.014
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	99.1%	100.0%	100.0%	100.0%
Terminal rate	27/27 (100%)	29/29 (100%)	29/29 (100%)	26/26 (100%)
First incidence (days)	135	285	403	525
Poly-3 test	P=0.795	P=0.910	P=0.910	P=0.910

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, 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 (the 0.03 mg/m^3 group was excluded from 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 A4a
Historical Incidence of Lung Neoplasms in Control Male F344/N Rats

Study	Incidence in Controls			
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma	Squamous Cell Carcinoma
Historical Incidence in Controls Given NTP-2000 Feed[a]				
p,p′-Dichlorodiphenyl sulfone (feed)	2/50	0/50	2/50	0/50
Indium phosphide (inhalation)	6/50	1/50	7/50	0/50
Methacrylonitrile (gavage)	0/50	0/50	0/50	0/50
Naphthalene (inhalation)	2/49	0/49	2/49	0/49
p-Nitrotoluene (feed)	1/50	0/50	1/50	0/50
Sodium nitrite (drinking water)	2/50	0/50	2/50	0/50
Overall Historical Incidence in Controls Given NTP-2000 Feed				
Total (%)	13/299 (4.4%)	1/299 (0.3%)	14/299 (4.7%)	0/299
Mean ± standard deviation	4.4% ± 4.1%	0.3% ± 0.8%	4.7% ± 4.8%	
Range	0%-12%	0%-2%	0%-14%	
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]				
Acetonitrile	1/48	1/48	2/48	0/48
2-Butoxyethanol	1/50	0/50	1/50	0/50
Chloroprene	2/50	0/50	2/50	0/50
Cobalt sulfate heptahydrate	1/50	0/50	1/50	0/50
Furfuryl alcohol	0/50	0/50	0/50	0/50
Gallium arsenide	1/50	2/50	3/50	1/50
Glutaraldehyde	0/50	0/50	0/50	0/50
Hexachlorocyclopentadiene	5/50	0/50	5/50	0/50
Isobutene	2/50	0/50	2/50	0/50
Isobutyraldehyde	1/50	0/50	1/50	0/50
Isoprene	0/49	1/49	1/49	0/49
Molybdenum trioxide	0/50	0/50	0/50	0/50
Nitromethane	1/50	0/50	1/50	0/50
Ozone	1/50	1/50	2/50	1/50
Tetrafluoroethylene	0/50	0/50	0/50	0/50
Tetrahydrofuran	0/50	0/50	0/50	0/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed				
Total (%)	18/1,054 (1.7%)	8/1,054 (0.8%)	26/1,054 (2.5%)	4/1,054 (0.4%)
Mean ± standard deviation	1.7% ± 2.4%	0.8% ± 1.2%	2.5% ± 2.6%	0.4% ± 0.8%
Range	0%-10%	0%-4%	0%-10%	0%-2%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE A4b
Historical Incidence of Adrenal Medulla Pheochromocytoma in Control Male F344/N Rats

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence in Controls Given NTP-2000 Feed[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	4/50	2/50	6/50
Indium phosphide (inhalation)	10/50	0/50	10/50
Methacrylonitrile (gavage)	3/50	1/50	4/50
Naphthalene (inhalation)	4/49	1/49	5/49
p-Nitrotoluene (feed)	3/50	0/50	3/50
Sodium nitrite (drinking water)	6/50	1/50	7/50
Overall Historical Incidence in Controls Given NTP-2000 Feed			
Total (%)	30/299 (10.0%)	5/299 (1.7%)	35/299 (11.7%)
Mean ± standard deviation	10.0% ± 5.4%	1.7% ± 1.5%	11.7% ± 5.0%
Range	6%-20%	0%-4%	6%-20%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]			
Acetonitrile	4/48	0/48	4/48
2-Butoxyethanol	15/50	0/50	15/50
Chloroprene	19/50	1/50	19/50
Cobalt sulfate heptahydrate	14/50	0/50	14/50
Furfuryl alcohol	19/50	1/50	19/50
Gallium arsenide	16/50	2/50	16/50
Glutaraldehyde	4/50	1/50	5/50
Hexachlorocyclopentadiene	15/50	2/50	16/50
Isobutene	23/50	0/50	23/50
Isobutyraldehyde	11/49	3/49	14/49
Isoprene	18/50	3/50	20/50
Molybdenum trioxide	15/50	2/50	15/50
Nitromethane	16/50	1/50	17/50
Ozone	17/50	1/50	17/50
Tetrafluoroethylene	19/50	2/50	20/50
Tetrahydrofuran	18/48	0/48	18/48
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed			
Total (%)	320/1,051 (30.5%)	20/1,051 (1.9%)	332/1,051 (31.6%)
Mean ± standard deviation	30.5% ± 10.4%	1.9% ± 2.1%	31.4% ± 10.0%
Range	8%-50%	0%-6%	8%-50%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE A4c
Historical Incidence of Skin Neoplasms in Control Male F344/N Rats

Study	Incidence in Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence in Controls Given NTP-2000 Feed[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	2/50	0/50	2/50
Indium phosphide (inhalation)	1/50	1/50	2/50
Methacrylonitrile (gavage)	3/50	0/50	3/50
Naphthalene (inhalation)	5/49	2/49	7/49
p-Nitrotoluene (feed)	1/50	0/50	1/50
Sodium nitrite (drinking water)	0/50	1/50	1/50
Overall Historical Incidence in Controls Given NTP-2000 Feed			
Total (%)	12/299 (4.0%)	4/299 (1.3%)	16/299 (5.4%)
Mean ± standard deviation	4.0% ± 3.7%	1.4% ± 1.7%	5.4% ± 4.6%
Range	0%-10%	0%-4%	2%-14%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]			
Acetonitrile	3/48	0/48	3/48
2-Butoxyethanol	2/50	1/50	3/50
Chloroprene	0/50	1/50	1/50
Cobalt sulfate heptahydrate	0/50	0/50	0/50
Furfuryl alcohol	4/50	0/50	4/50
Gallium arsenide	3/50	0/50	3/50
Glutaraldehyde	4/50	0/50	4/50
Hexachlorocyclopentadiene	2/50	1/50	3/50
Isobutene	1/50	0/50	1/50
Isobutyraldehyde	3/50	0/49	3/50
Isoprene	0/50	0/50	0/50
Molybdenum trioxide	3/50	0/50	3/50
Nitromethane	3/50	3/50	6/50
Ozone	1/50	0/50	1/50
Tetrafluoroethylene	3/50	0/50	3/50
Tetrahydrofuran	2/50	0/50	2/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed			
Total (%)	41/1,055 (3.9%)	7/1,055 (0.7%)	48/1,055 (4.5%)
Mean ± standard deviation	3.9% ± 2.8%	0.7% ± 1.5%	4.5% ± 3.3%
Range	0%-8%	0%-2%	0% ± 12%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE A4d
Historical Incidence of Mononuclear Cell Leukemia in Control Male F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Feed[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	27/50
Indium phosphide (inhalation)	16/50
Methacrylonitrile (gavage)	20/50
Naphthalene (inhalation)	26/49
p-Nitrotoluene (feed)	24/50
Sodium nitrite (drinking water)	17/50
Overall Historical Incidence in Controls Given NTP-2000 Feed	
Total (%)	130/299 (43.5%)
Mean ± standard deviation	43.5% ± 9.6%
Range	32%-54%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Batelle Pacific Northwest Laboratories[b]	
Acetonitrile	29/48
2-Butoxyethanol	29/50
Chloroprene	33/50
Cobalt sulfate heptahydrate	30/50
Furfuryl alcohol	29/50
Gallium arsenide	19/50
Glutaraldehyde	21/50
Hexachlorocyclopentadiene	29/50
Isobutene	21/50
Isobutyraldehyde	33/50
Isoprene	24/50
Molybdenum trioxide	35/50
Nitromethane	35/50
Ozone	27/50
Tetrafluoroethylene	34/50
Tetrahydrofuran	30/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed	
Total (%)	602/1,055 (57.1%)
Mean ± standard deviation	57.1% ± 8.9%
Range	38%-70%

[a] Data as of 15 March 2000; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia
[b] Data as of 21 December 1999; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	20	18	16	15
Natural deaths	3	3	5	9
Survivors				
Terminal sacrifice	27	29	29	26
Animals examined microscopically	60	60	60	60
3-Month Interim Evaluation				
Alimentary System				
Mesentery			(1)	
Fat, necrosis			1 (100%)	
Stomach, glandular	(10)			(10)
Mineralization	4 (40%)			4 (40%)
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy	4 (40%)			2 (20%)
Endocrine System				
Thyroid gland	(10)			(10)
C-cell, hyperplasia				1 (10%)
Genital System				
Testes	(10)		(1)	(10)
Atrophy			1 (100%)	
Hematopoietic System				
Lymph node, bronchial	(10)	(6)	(10)	(9)
Foreign body		4 (67%)	2 (20%)	7 (78%)
Hyperplasia		1 (17%)	2 (20%)	5 (56%)
Lymph node, mediastinal	(10)	(5)	(9)	(9)
Foreign body		3 (60%)	7 (78%)	7 (78%)
Hyperplasia		1 (20%)	6 (67%)	7 (78%)

[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 Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
3-Month Interim Evaluation (continued)				
Respiratory System				
Larynx	(10)	(10)	(10)	(10)
Inflammation, acute		2 (20%)		
Lung	(10)	(10)	(10)	(10)
Foreign body		10 (100%)	10 (100%)	10 (100%)
Inflammation, chronic active	1 (10%)	10 (100%)	10 (100%)	10 (100%)
Alveolar epithelium, hyperplasia		7 (70%)	10 (100%)	10 (100%)
Alveolus, proteinosis		10 (100%)	10 (100%)	10 (100%)
Nose	(10)	(10)	(10)	(10)
Olfactory epithelium, atrophy				1 (10%)
Urinary System				
Kidney	(10)			(10)
Nephropathy	3 (30%)			3 (30%)
Systems Examined with No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, cecum	(48)	(50)	(46)	(46)
Ulcer				1 (2%)
Intestine small, duodenum	(49)	(50)	(47)	(48)
Necrosis				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)		2 (4%)
Basophilic focus	29 (58%)	29 (58%)	31 (62%)	34 (68%)
Clear cell focus	18 (36%)	16 (32%)	22 (44%)	16 (32%)
Degeneration, cystic	3 (6%)	9 (18%)	5 (10%)	5 (10%)
Eosinophilic focus	3 (6%)	3 (6%)	4 (8%)	3 (6%)
Fatty change	5 (10%)	5 (10%)	7 (14%)	3 (6%)
Hepatodiaphragmatic nodule	3 (6%)	4 (8%)	2 (4%)	9 (18%)
Inflammation, chronic active		1 (2%)		
Inflammation, granulomatous	1 (2%)			1 (2%)
Mixed cell focus	1 (2%)			2 (4%)
Necrosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Regeneration			3 (6%)	
Vacuolization cytoplasmic, focal			1 (2%)	
Bile duct, hyperplasia	39 (78%)	42 (84%)	40 (80%)	36 (72%)
Centrilobular, necrosis	5 (10%)	4 (8%)	6 (12%)	10 (20%)
Serosa, fibrosis			1 (2%)	
Serosa, hemorrhage			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(6)	(6)	(6)	(8)
Artery, inflammation, chronic active				1 (13%)
Artery, mineralization				1 (13%)
Fat, metaplasia, osseous			1 (17%)	
Fat, necrosis	6 (100%)	6 (100%)	6 (100%)	6 (75%)
Oral mucosa	(1)		(3)	(2)
Gingival, abscess				1 (50%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy	14 (28%)	16 (32%)	17 (34%)	19 (38%)
Basophilic focus	3 (6%)	3 (6%)	3 (6%)	
Hyperplasia	2 (4%)	2 (4%)	4 (8%)	2 (4%)
Thrombosis	1 (2%)			
Duct, hyperplasia			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	3 (6%)		2 (4%)
Basophilic focus	2 (4%)			1 (2%)
Necrosis	1 (2%)			
Duct, metaplasia, squamous	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Diverticulum	2 (4%)			
Hyperplasia, basal cell				1 (2%)
Hyperplasia, squamous	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Inflammation, acute	1 (2%)		3 (6%)	
Necrosis			1 (2%)	
Ulcer	1 (2%)		4 (8%)	1 (2%)
Stomach, glandular	(50)	(50)	(48)	(49)
Mineralization	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Necrosis	2 (4%)		2 (4%)	
Tongue	(2)			
Hyperplasia, squamous	2 (100%)			
Tooth	(2)		(3)	(1)
Developmental malformation			1 (33%)	
Inflammation, chronic active	2 (100%)		2 (67%)	1 (100%)
Cardiovascular System				
Blood vessel	(1)			
Necrosis, fibrinoid	1 (100%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	44 (88%)	43 (86%)	43 (86%)	46 (92%)
Necrosis				1 (2%)
Artery, mineralization			1 (2%)	1 (2%)
Atrium, thrombosis	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Epicardium, fibrosis			1 (2%)	
Mesothelium, hyperplasia				1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Atrophy		2 (4%)		1 (2%)
Degeneration, cystic	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	32 (64%)	27 (54%)	33 (66%)	33 (66%)
Hypertrophy	7 (14%)	5 (10%)	3 (6%)	9 (18%)
Necrosis	2 (4%)	2 (4%)	2 (4%)	4 (8%)
Vacuolization cytoplasmic		1 (2%)	1 (2%)	
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	26 (52%)	26 (52%)	24 (49%)	32 (64%)
Necrosis			1 (2%)	
Thrombosis		1 (2%)		1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	4 (8%)	3 (6%)	3 (6%)	1 (2%)
Parathyroid gland	(44)	(44)	(45)	(45)
Hyperplasia		1 (2%)		
Hypertrophy		1 (2%)		
Pituitary gland	(49)	(50)	(50)	(50)
Cyst				1 (2%)
Pars distalis, angiectasis		2 (4%)		
Pars distalis, hyperplasia	5 (10%)	13 (26%)	12 (24%)	15 (30%)
Pars intermedia, angiectasis	1 (2%)			
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(49)	(49)	(48)	(48)
C-cell, hyperplasia	41 (84%)	31 (63%)	42 (88%)	37 (77%)
Follicular cell, hyperplasia		2 (4%)	2 (4%)	1 (2%)
General Body System				
None				
Genital System				
Penis				(1)
Inflammation, suppurative				1 (100%)
Preputial gland	(50)	(50)	(50)	(50)
Cyst			2 (4%)	1 (2%)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic active	3 (6%)	2 (4%)	2 (4%)	4 (8%)
Prostate	(50)	(50)	(50)	(50)
Hyperplasia	14 (28%)	13 (26%)	13 (26%)	9 (18%)
Inflammation, chronic active	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Inflammation, suppurative	1 (2%)			
Necrosis	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Atrophy	8 (16%)	4 (8%)	5 (10%)	10 (20%)
Necrosis		1 (2%)		
Artery, inflammation, chronic active	2 (4%)	1 (2%)		2 (4%)
Germinal epithelium, degeneration			1 (2%)	
Interstitial cell, hyperplasia	6 (12%)	7 (14%)	6 (12%)	9 (18%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hyperplasia, reticulum cell	1 (2%)			
Necrosis				1 (2%)
Thrombosis		1 (2%)		
Lymph node	(2)	(4)		(2)
Ectasia	1 (50%)			
Lymph node, bronchial	(26)	(27)	(41)	(44)
Foreign body		19 (70%)	27 (66%)	36 (82%)
Hyperplasia				1 (2%)
Lymph node, mandibular	(44)	(42)	(47)	(47)
Infiltration cellular, plasma cell			1 (2%)	1 (2%)
Lymph node, mediastinal	(25)	(19)	(45)	(40)
Foreign body		8 (42%)	27 (60%)	15 (38%)
Hyperplasia				1 (3%)
Spleen	(50)	(50)	(49)	(48)
Angiectasis			1 (2%)	
Fibrosis	8 (16%)	15 (30%)	9 (18%)	11 (23%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		1 (2%)
Hemorrhage	2 (4%)		2 (4%)	1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Thymus	(47)	(47)	(46)	(45)
Cyst				1 (2%)
Integumentary System				
Mammary gland	(24)	(33)	(31)	(24)
Galactocele	7 (29%)	4 (12%)	4 (13%)	5 (21%)
Inflammation, chronic			1 (3%)	
Skin	(50)	(50)	(50)	(49)
Cyst epithelial inclusion		1 (2%)	2 (4%)	
Hyperkeratosis				3 (6%)
Inflammation, acute			1 (2%)	
Inflammation, chronic active	4 (8%)			4 (8%)
Necrosis			1 (2%)	
Epidermis, hyperplasia	1 (2%)			
Prepuce, inflammation, chronic active	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Hemorrhage	1 (2%)			
Inflammation, chronic active			1 (2%)	
Artery, inflammation			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Hyperplasia, squamous		1 (2%)		2 (4%)
Inflammation, acute	2 (4%)	3 (6%)	5 (10%)	3 (6%)
Epiglottis, metaplasia, squamous		2 (4%)	1 (2%)	
Respiratory epithelium, hyperplasia		1 (2%)		
Respiratory epithelium, metaplasia, squamous			1 (2%)	
Lung	(50)	(50)	(50)	(50)
Cyst, squamous		1 (2%)	3 (6%)	2 (4%)
Foreign body		50 (100%)	50 (100%)	50 (100%)
Hemorrhage		1 (2%)		
Hyperplasia, atypical		16 (32%)	23 (46%)	39 (78%)
Inflammation, chronic active	5 (10%)	50 (100%)	50 (100%)	50 (100%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Metaplasia, squamous		1 (2%)	3 (6%)	4 (8%)
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	11 (22%)	20 (40%)	21 (42%)	31 (62%)
Alveolar epithelium, metaplasia		45 (90%)	45 (90%)	48 (96%)
Alveolus, infiltration cellular, histiocyte	8 (16%)			
Alveolus, proteinosis		50 (100%)	48 (96%)	47 (94%)
Artery, mediastinum, mineralization			1 (2%)	
Interstitium, fibrosis		49 (98%)	50 (100%)	50 (100%)
Mediastinum, thrombosis			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	9 (18%)	10 (20%)	8 (16%)	8 (16%)
Thrombosis	4 (8%)	4 (8%)	6 (12%)	8 (16%)
Glands, hyperplasia				1 (2%)
Lateral wall, metaplasia, squamous			1 (2%)	
Olfactory epithelium, atrophy	1 (2%)	2 (4%)	1 (2%)	
Olfactory epithelium, metaplasia	6 (12%)	2 (4%)	2 (4%)	7 (14%)
Respiratory epithelium, hyperplasia	5 (10%)	7 (14%)	4 (8%)	5 (10%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Respiratory epithelium, necrosis				1 (2%)
Trachea	(50)	(50)	(49)	(49)
Inflammation, suppurative	1 (2%)	3 (6%)		1 (2%)
Special Senses System				
Eye	(1)	(1)	(1)	(1)
Cataract	1 (100%)		1 (100%)	1 (100%)
Retina, atrophy	1 (100%)		1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet				1 (2%)
Hydronephrosis			2 (4%)	
Infarct		1 (2%)	2 (4%)	1 (2%)
Mineralization			1 (2%)	
Nephropathy	47 (94%)	46 (92%)	43 (86%)	46 (92%)
Renal tubule, hyperplasia				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Hemorrhage			2 (4%)	
Inflammation, chronic active			1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF INDIUM PHOSPHIDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death		1		
Moribund	13	14	14	12
Natural deaths	3	4		4
Survivors				
Died last week of the study		1		
Terminal sacrifice	34	30	36	34
Animals examined microscopically	60	60	60	60
Systems Examined at 3 Months with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(48)	(48)	(50)	(48)
Polyp adenomatous		1 (2%)		1 (2%)
Intestine large, rectum	(49)	(48)	(50)	(47)
Polyp adenomatous			1 (2%)	
Intestine small, ileum	(47)	(46)	(50)	(48)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma				1 (2%)
Histiocytic sarcoma				1 (2%)
Mesentery	(9)	(15)	(15)	(19)
Oral mucosa		(2)		(2)
Gingival, squamous cell carcinoma				1 (50%)
Pharyngeal, squamous cell carcinoma				1 (50%)
Pharyngeal, squamous cell papilloma		1 (50%)		
Pancreas	(50)	(50)	(50)	(49)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(49)
Stomach, glandular	(49)	(50)	(50)	(48)
Carcinoid tumor benign				1 (2%)
Tongue	(1)	(1)	(1)	(1)
Squamous cell carcinoma			1 (100%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma benign		1 (2%)		2 (4%)
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(49)
Adenoma	1 (2%)	1 (2%)		
Carcinoma	1 (2%)			
Adrenal medulla	(50)	(48)	(50)	(49)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	2 (4%)	6 (13%)	2 (4%)	7 (14%)
Bilateral, pheochromocytoma benign				2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	1 (2%)			1 (2%)
Pituitary gland	(50)	(50)	(48)	(49)
Pars distalis, adenoma	30 (60%)	27 (54%)	29 (60%)	25 (51%)
Pars distalis, carcinoma			1 (2%)	
Thyroid gland	(47)	(47)	(50)	(47)
Bilateral, C-cell, adenoma			1 (2%)	1 (2%)
C-cell, adenoma	6 (13%)	6 (13%)	5 (10%)	1 (2%)
C-cell, carcinoma	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma	1 (2%)	1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(49)	(47)	(47)	(49)
Adenoma	5 (10%)	4 (9%)	4 (9%)	6 (12%)
Carcinoma		1 (2%)	3 (6%)	
Carcinoma, multiple		1 (2%)		
Bilateral, carcinoma		1 (2%)		
Ovary	(50)	(50)	(50)	(49)
Granulosa cell tumor malignant		1 (2%)	1 (2%)	
Granulosa cell tumor benign	1 (2%)		1 (2%)	
Granulosa-theca tumor malignant	1 (2%)			
Uterus	(50)	(50)	(50)	(49)
Leiomyosarcoma			1 (2%)	
Polyp stromal	10 (20%)	4 (8%)	10 (20%)	8 (16%)
Polyp stromal, multiple				2 (4%)
Sarcoma stromal		1 (2%)		
Schwannoma malignant		1 (2%)		
Vagina	(1)			
Leiomyosarcoma	1 (100%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(48)
Lymph node	(1)	(5)	(1)	(2)
Deep cervical, carcinoma, metastatic, thyroid gland			1 (100%)	
Lymph node, bronchial	(25)	(30)	(35)	(30)
Lymph node, mandibular	(43)	(48)	(42)	(42)
Lymph node, mesenteric	(50)	(47)	(50)	(47)
Hemangiosarcoma	1 (2%)			
Lymph node, mediastinal	(28)	(36)	(39)	(26)
Spleen	(50)	(50)	(50)	(47)
Thymus	(45)	(47)	(50)	(45)
Thymoma benign		1 (2%)	1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		8 (16%)	3 (6%)	1 (2%)
Carcinoma, multiple				1 (2%)
Fibroadenoma	16 (32%)	14 (28%)	16 (32%)	11 (22%)
Fibroadenoma, multiple	4 (8%)	5 (10%)	2 (4%)	1 (2%)
Skin	(50)	(49)	(50)	(49)
Basal cell adenoma			1 (2%)	
Keratoacanthoma			2 (4%)	
Squamous cell carcinoma	1 (2%)			
Sebaceous gland, carcinoma	1 (2%)			
Subcutaneous tissue, fibroma	3 (6%)		1 (2%)	
Subcutaneous tissue, sarcoma				1 (2%)
Musculoskeletal System				
Skeletal muscle			(1)	
Rhabdomyosarcoma			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland			1 (2%)	
Oligodendroglioma malignant	1 (2%)			
Respiratory System				
Larynx	(50)	(49)	(50)	(49)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		6 (12%)	4 (8%)	18 (36%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	1 (2%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		7 (14%)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Carcinoma, metastatic, uncertain primary site	1 (2%)			
Trachea	(50)	(49)	(50)	(49)
Carcinoma, metastatic, thyroid gland			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Special Senses System				
Zymbal's gland	(1)			
Carcinoma	1 (100%)			
Urinary System				
Kidney	(50)	(49)	(50)	(48)
Lipoma	1 (2%)			
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(49)	(49)	(50)	(49)
Transitional epithelium, papilloma			1 (2%)	1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	14 (28%)	21 (42%)	14 (28%)	24 (48%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
2-Year study	49	47	48	46
Total primary neoplasms				
2-Year study	107	120	111	133
Total animals with benign neoplasms				
2-Year study	44	39	44	40
Total benign neoplasms				
2-Year study	80	78	83	90
Total animals with malignant neoplasms				
2-Year study	24	30	24	32
Total malignant neoplasms				
2-Year study	27	42	28	43
Total animals with metastatic neoplasms				
2-Year study	1		2	
Total metastatic neoplasms				
2-Year study	1		5	
Total animals with malignant neoplasms of uncertain primary site				
2-Year study	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 Indium Phosphide: Chamber Control

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 0 9	1 1 1	1 1 3	1 1 6	1 1 8	1 3 9	1 4 0	1 4 1	1 4 2	1 4 3	1 4 5	1 5 0	1 0 1	1 0 3	1 0 4	1 0 8	1 1 5	1 2 0	1 2 3	1 2 9	1 3 2	1 3 3	1 4 4	1 4 6	1 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+			+																9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue											+															1
Tooth																										2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma							X																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X																			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							1
Parathyroid gland	M	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X			X	X	X		X	X	X			X	X	X	X	X			X		X	30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, adenoma	X			X												X		X						X		6
C-cell, carcinoma				X															X							3
Follicular cell, carcinoma						X																				1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X				X							X				5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																						X				1
Granulosa-theca tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X				X			X							X		X		X					10
Vagina																										1
Leiomyosarcoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	1 2 4	3 9 7	4 7 6	5 0 4	5 5 0	5 5 1	5 6 6	5 9 0	6 1 5	6 2 1	6 6 7	6 6 7	6 6 9	6 8 4	6 9 7	7 2 6	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6
Carcass ID Number	1 1 0	1 1 4	1 3 1	1 2 5	1 1 7	1 3 0	1 2 4	1 3 6	1 0 6	1 3 8	1 1 2	1 2 6	1 2 2	1 0 5	1 4 9	1 2 8	1 0 2	1 1 9	1 2 1	1 2 7	1 3 4	1 3 5	1 3 7	1 4 8	1 0 7
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, bronchial	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	M	+	M	M	M	+	M	+	+	+	M	M	M	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma								X			X									X					
Fibroadenoma, multiple																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Sebaceous gland, carcinoma			X																						
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant												X													
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, uncertain primary site																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland										+															
Carcinoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X			X							X			X		X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 0 9	1 1 1	1 1 3	1 1 6	1 1 8	1 3 9	1 4 0	1 4 1	1 4 2	1 4 3	1 4 5	1 5 0	1 0 1	1 0 3	1 0 4	1 0 8	1 1 5	1 2 0	1 2 3	1 2 9	1 3 2	1 3 3	1 4 4	1 4 6	1 4 7	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																+												1
Lymph node, bronchial	M	M	+	+	M	+	+	M	M	M	+	+	+	M	M	M	+	+	M	+	M	+	+	+	+	+	+	25
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X										1
Lymph node, mediastinal	M	M	+	+	+	M	M	+	M	M	+	+	M	M	M	M	+	+	+	+	+	M	+	M	+			28
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M			45
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Fibroadenoma	X	X			X	X	X	X					X		X	X	X				X		X		X			16
Fibroadenoma, multiple									X										X					X				4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Squamous cell carcinoma																												1
Sebaceous gland, carcinoma																												1
Subcutaneous tissue, fibroma																						X		X	X			3
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Oligodendroglioma malignant																												1
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Alveolar/bronchiolar carcinoma																	X											1
Carcinoma, metastatic, uncertain primary site																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Special Senses System																												
Eye				+																								1
Zymbal's gland																												1
Carcinoma																												1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Lipoma																X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Leukemia mononuclear			X		X				X			X		X		X		X	X									14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	0262	1200	4288	4481	4884	5511	5603	5800	5907	6067	6283	6861	6943	6955	6955	7114	7144	7255	7288	7355	7355	7355	7355	7355	7355
Carcass ID Number	34202	34029	34029	34088	34021	34113	34103	34130	34043	34006	34022	34101	34137	34232	34040	34274	34394	34848	34001	34107	34212	34515	34717	34525	34626
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																X									
Intestine large, rectum	+	+	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+						+								+	+		+		+	+
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X			X									X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X	X	X	X				X	X				X	X		X		
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+
C-cell, adenoma												X				X				X					
C-cell, carcinoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																								X	
Carcinoma			X																						
Carcinoma, multiple							X																		
Bilateral, carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																			X			X			
Sarcoma stromal														X											
Schwannoma malignant													X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	33338	33847	34704	30405	01919	32023	32328	33131	33636	34545	34649	34909	01114	11416	11818	12434	33435	33541	44430	44450	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+	+				+		+				+				+			+						+	15
Oral mucosa			+			+																					2
Pharyngeal, squamous cell papilloma						X																					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+																				1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign					X																						1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X														1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign														X		X					X						6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X	X	X		X	X	X	X		X	X		X	X		X	X		X	X	X			27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, adenoma		X													X									X			6
C-cell, carcinoma												2					X									X	
Follicular cell, carcinoma																							X				1
General Body System																											
None																											
Genital System																											
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Adenoma							X	X										X									4
Carcinoma																											1
Carcinoma, multiple																											1
Bilateral, carcinoma				X																							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																									X		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X							X																	4
Sarcoma stromal																											1
Schwannoma malignant																											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	0262	1200	4288	4814	4855	5511	5600	5803	5907	6073	6683	6866	6945	6955	7145	7144	7255	7288	7335	7355	7355	7355	7355	7355
Carcass ID Number	3402	3602	3629	3708	3721	3713	3703	3730	3743	3706	3722	3710	3737	3732	3740	3727	3739	3748	3801	3807	3812	3815	3817	3825	3826
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+							+						+									
Lymph node, bronchial	+	M	+	M	M	M	+	+	+	+	M	+	+	M	M	+	+	+	M	M	M	+	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	A	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	M	M	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X					X									
Fibroadenoma								X		X								X						X	X
Fibroadenoma, multiple																			X	X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X			X						X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma															X				X						
Alveolar/bronchiolar carcinoma, multiple																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
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 Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	735	735	735	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	33 3	33 8	34 7	04 4	05 5	19 6	20 7	23 8	28 9	31 0	36 1	45 2	46 3	49 4	09 5	11 6	14 7	16 8	18 9	24 10	34 11	35 12	41 13	44 14	50 15	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+																		+	5
Lymph node, bronchial	M	+	+	M	M	M	+	+	+	+	+	+	+	+	M	M	M	M	M	+	+	+	+	+	+	30
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	M	M	M	+	+	+	+	+	+	+	36
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma benign												X														1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X			X	X			X									X			X						8
Fibroadenoma		X	X			X								X		X		X	X			X	X			14
Fibroadenoma, multiple								X			X				X											5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X							X	X										6
Alveolar/bronchiolar adenoma, multiple													X													1
Alveolar/bronchiolar carcinoma																										2
Alveolar/bronchiolar carcinoma, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, carcinoma																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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 Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	2 2 5	4 3 6	4 4 8	5 6 6	5 9 5	6 0 0	6 5 6	6 7 2	6 7 9	6 8 4	6 8 6	6 8 6	7 1 4	7 1 6	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
Carcass ID Number	5 4 3	5 1 5	5 0 5	5 4 5	5 3 2	5 1 0	5 1 2	5 1 9	5 2 3	5 2 5	5 2 4	5 3 1	5 0 9	5 1 1	5 0 6	5 1 3	5 2 7	5 3 0	5 3 9	5 4 0	5 4 7	5 4 9	5 5 0	5 0 1	5 0 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal argec olon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal arger ectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestinal argec ecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestines malld uodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestines malli leum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+			+	+			+			+		+					+						+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary g lands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, f orestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																							X		
C-cell, adenoma								X			X	X									X				
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant	X																								
Granulosa cell tumor benign										X															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																	X								
Polyp stromal																		X			X	X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 0 3	5 0 8	5 1 7	5 1 8	5 2 1	5 2 2	5 2 8	5 3 3	5 3 4	5 3 8	5 4 6	5 0 4	5 0 7	5 1 4	5 1 6	5 2 0	5 2 6	5 2 9	5 3 5	5 3 6	5 3 7	5 4 1	5 4 2	5 4 4	5 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous										X																1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+				+				+				+		+		+		+		15
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																				+						1
Squamous cell carcinoma																				X						1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X					X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	48
Pars distalis, adenoma	X		X	X	X	X		X	X	X		X	X	X	X					X	X	X		X		29
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma				X																						5
C-cell, carcinoma						X											X									2
Follicular cell, adenoma							X																			1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma					X				X			X														4
Carcinoma				X				X										X								3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																										1
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal			X			X		X			X							X					X			10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	2 2 5	4 3 6	4 4 8	5 6 6	5 9 5	6 0 0	6 5 6	6 7 2	6 7 9	6 8 4	6 8 6	6 8 6	7 1 4	7 1 6	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
Carcass ID Number	5 4 3	5 1 5	5 0 5	5 4 5	5 3 2	5 1 0	5 1 2	5 1 9	5 2 3	5 2 5	5 3 4	5 3 1	5 0 9	5 1 1	5 0 6	5 1 3	5 2 7	5 3 0	5 3 9	5 4 0	5 4 7	5 4 9	5 5 0	5 0 1	5 0 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, bronchial	+	M	M	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	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X	X											
Fibroadenoma				X	X			X	X	X	X				X	X	X			X		X		X	X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								X	
Keratoacanthoma																									
Subcutaneous tissue, fibroma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Rhabdomyosarcoma	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland						X																			
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X				X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 0 3	5 0 8	5 1 7	5 1 8	5 2 1	5 2 2	5 2 8	5 3 3	5 3 4	5 3 8	5 4 6	5 0 4	5 0 7	5 1 4	5 1 6	5 2 0	5 2 6	5 2 9	5 3 5	5 3 6	5 3 7	5 4 1	5 4 2	5 4 4	5 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+																				1
Deep cervical, carcinoma, metastatic, thyroid gland						X																				1
Lymph node, bronchial	M	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	M	+	+	+	M	+	+	+	35
Lymph node, mandibular	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	39
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma benign																				X						1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma														X												3
Fibroadenoma						X		X					X													16
Fibroadenoma, multiple							X		X																	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma	X																								X	2
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland						X																				1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X		X																				4
Alveolar/bronchiolar adenoma, multiple																								X		1
Alveolar/bronchiolar carcinoma							X																			1
Carcinoma, metastatic, thyroid gland						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland						X																				1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	2 2 5	4 3 6	4 4 8	5 6 6	5 9 5	6 0 0	6 5 6	6 7 2	6 7 9	6 8 4	6 8 6	6 8 6	7 1 4	7 1 6	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
Carcass ID Number	5 4 3	5 1 5	5 0 5	5 4 5	5 3 2	5 1 0	5 1 2	5 1 9	5 2 3	5 2 5	5 2 4	5 3 1	5 0 9	5 1 1	5 0 6	5 1 3	5 2 7	5 3 0	5 3 9	5 4 0	5 4 7	5 4 9	5 5 0	5 0 1	5 0 2
Special Senses System																									
Eye				+	+																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma		X																							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X			X		X	X	X	X			X	X			X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 0 3	5 0 8	5 1 7	5 1 8	5 2 1	5 2 2	5 2 8	5 3 3	5 3 4	5 3 8	5 4 6	5 0 4	5 0 7	5 1 4	5 1 6	5 2 0	5 2 6	5 2 9	5 3 5	5 3 6	5 3 7	5 4 1	5 4 2	5 4 4	5 4 8	Total Tissues/ Tumors
Special Senses System																										
Eye			+																							3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X		X					X			X				14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	1 8 6	4 1 1	5 1 9	5 3 5	5 8 5	5 8 8	5 8 8	5 9 3	6 1 0	6 1 3	6 4 3	6 5 1	6 5 6	6 5 6	7 2 6	7 2 7	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	7 1 4	7 3 2	7 1 0	7 2 5	7 2 7	7 1 3	7 4 8	7 0 2	7 3 7	7 0 5	7 1 7	7 5 0	7 1 2	7 2 2	7 1 1	7 3 3	7 0 6	7 1 6	7 1 8	7 2 0	7 2 1	7 2 4	7 3 0	7 4 3	7 4 7
Alimentary System																									
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous											X														
Intestine large, rectum	A	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Histiocytic sarcoma																									
Mesentery		+	+		+			+			+	+							+		+		+		+
Oral mucosa																									+
Gingival, squamous cell carcinoma																									X
Pharyngeal, squamous cell carcinoma																									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor benign																									
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									
Endocrine System																									
Adrenal cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign						X							X			X									
Bilateral, pheochromocytoma benign																						X		X	
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	A	M	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+
Pituitary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X	X		X				X		X	X	X		X	X	X	X
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																									
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X		X			
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X						X											X	X	
Polyp stromal, multiple				X																					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 0 1	7 0 7	7 0 8	7 0 9	7 1 5	7 2 8	7 3 5	7 3 6	7 3 8	7 4 0	7 4 1	7 4 4	7 4 6	7 0 3	7 0 4	7 1 9	7 2 3	7 2 6	7 2 9	7 3 1	7 3 4	7 3 9	7 4 2	7 4 5	7 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X																				1
Histiocytic sarcoma																X										1
Mesentery					+	+						+	+				+	+		+		+		+		19
Oral mucosa																+										2
Gingival, squamous cell carcinoma																										1
Pharyngeal, squamous cell carcinoma																X										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoid tumor benign				X																						1
Tongue			+																							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign		X															X									2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																						X				1
Pheochromocytoma benign									X				X									X	X			7
Bilateral, pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X															1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	I	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X	X			X	X	X	X		X				X		X			X	X		X	X	25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bilateral, C-cell, adenoma		X																								1
C-cell, adenoma			X																							1
C-cell, carcinoma																		X								1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X		X			X								X					6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal			X			X					X			X												8
Polyp stromal, multiple	X																									2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	1 8 6	4 1 1	5 1 9	5 3 5	5 8 5	5 8 8	5 8 8	5 9 3	6 1 0	6 1 3	6 4 3	6 5 1	6 5 6	6 5 6	7 2 6	7 2 7	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	7 1 4	7 3 2	7 1 0	7 2 5	7 2 7	7 1 3	7 4 8	7 0 2	7 3 7	7 0 5	7 1 7	7 5 0	7 1 2	7 2 2	7 1 1	7 3 3	7 0 6	7 1 6	7 1 8	7 2 0	7 2 1	7 2 4	7 3 0	7 4 3	7 4 7
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node					+																	+			
Lymph node, bronchial	+	+	+	M	M	+	+	+	M	M	+	+	M	+	M	+	+	M	+	M	+	+	M	M	I
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	M	+	M	M	M	M	M	+	M	M
Spleen	A	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Thymus	A	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, multiple																									
Fibroadenoma								X													X	X	X		X
Fibroadenoma, multiple																									
Skin	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma															X										
Musculoskeletal System																									
Bone	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X			X						X					X	X	X
Alveolar/bronchiolar adenoma, multiple																						X			
Alveolar/bronchiolar carcinoma			X																						
Alveolar/bronchiolar carcinoma, multiple																			X						
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											+
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma						X																			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear		X	X		X	X		X			X	X	X	X		X		X	X			X	X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 0 1	7 0 7	7 0 8	7 0 9	7 1 5	7 2 8	7 3 5	7 3 6	7 3 8	7 4 0	7 4 1	7 4 4	7 4 6	7 0 3	7 0 4	7 1 9	7 2 3	7 2 6	7 2 9	7 3 1	7 3 4	7 3 9	7 4 2	7 4 5	7 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																										2
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	M	M	+	M	M	M	30
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	+	+	M	+	M	M	M	M	M	M	+	+	+	M	+	M	M	+	M	M	M	26
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X														1
Carcinoma, multiple															X											1
Fibroadenoma	X		X				X					X	X											X		11
Fibroadenoma, multiple														X												1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X				X			X	X	X		X	X				X			X	X		X	X		18
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma					X					X						X										4
Alveolar/bronchiolar carcinoma, multiple		X							X					X				X				X	X			7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																			+							3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																X										1
Leukemia mononuclear			X	X	X			X		X		X			X						X	X				24

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a] 2/50 (4%)	6/48 (13%)	2/50 (4%)	9/49 (18%)	
Adjusted rate[b]	4.6%	14.5%	4.5%	20.6%
Terminal rate[c]	1/34 (3%)	4/31 (13%)	2/36 (6%)	6/34 (18%)
First incidence (days)	615	686	735 (T)	588
Poly-3 test[d]	P=0.005	P=0.119	P=0.682N	P=0.026
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	2/50 (4%)	6/48 (13%)	2/50 (4%)	9/49 (18%)
Adjusted rate	4.6%	14.5%	4.5%	20.6%
Terminal rate	1/34 (3%)	4/31 (13%)	2/36 (6%)	6/34 (18%)
First incidence (days)	615	686	735 (T)	588
Poly-3 test	P=0.005	P=0.119	P=0.682N	P=0.026
Clitoral Gland: Adenoma				
Overall rate	5/49 (10%)	4/47 (9%)	4/47 (9%)	6/49 (12%)
Adjusted rate	12.0%	10.2%	9.5%	14.0%
Terminal rate	5/33 (15%)	4/29 (14%)	4/35 (11%)	6/34 (18%)
First incidence (days)	735 (T)	735 (T)	735 (T)	735 (T)
Poly-3 test	P=0.431	P=0.538N	P=0.492N	P=0.520
Clitoral Gland: Carcinoma				
Overall rate	0/49 (0%)	3/47 (6%)	3/47 (6%)	0/49 (0%)
Adjusted rate	0.0%	7.4%	7.1%	0.0%
Terminal rate	0/33 (0%)	1/29 (3%)	3/35 (9%)	0/34 (0%)
First incidence (days)	—[e]	428	735 (T)	—[f]
Poly-3 test	P=0.482N	P=0.113	P=0.120	—
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	5/49 (10%)	7/47 (15%)	7/47 (15%)	6/49 (12%)
Adjusted rate	12.0%	17.3%	16.6%	14.0%
Terminal rate	5/33 (15%)	5/29 (17%)	7/35 (20%)	6/34 (18%)
First incidence (days)	735 (T)	428	735 (T)	735 (T)
Poly-3 test	P=0.525	P=0.359	P=0.387	P=0.520
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	7/50 (14%)	5/50 (10%)	19/50 (38%)
Adjusted rate	0.0%	16.5%	11.2%	43.6%
Terminal rate	0/34 (0%)	5/31 (16%)	5/36 (14%)	17/34 (50%)
First incidence (days)	—	694	735 (T)	610
Poly-3 test	P<0.001	P=0.007	P=0.034	P<0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	11/50 (22%)
Adjusted rate	2.3%	7.1%	2.2%	25.3%
Terminal rate	1/34 (3%)	1/31 (3%)	1/36 (3%)	10/34 (29%)
First incidence (days)	735 (T)	695	735 (T)	519
Poly-3 test	P<0.001	P=0.302	P=0.751N	P=0.002

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	10/50 (20%)	6/50 (12%)	26/50 (52%)
Adjusted rate	2.3%	23.5%	13.5%	58.8%
Terminal rate	1/34 (3%)	6/31 (19%)	6/36 (17%)	23/34 (68%)
First incidence (days)	735 (T)	694	735 (T)	519
Poly-3 test	P<0.001	P=0.004	P=0.063	P<0.001
Mammary Gland: Fibroadenoma				
Overall rate	20/50 (40%)	19/50 (38%)	18/50 (36%)	12/50 (24%)
Adjusted rate	46.1%	44.0%	38.8%	27.7%
Terminal rate	18/34 (53%)	15/31 (48%)	12/36 (33%)	11/34 (32%)
First incidence (days)	590	580	566	593
Poly-3 test	P=0.051N	P=0.509N	P=0.312N	P=0.056N
Mammary Gland: Carcinoma				
Overall rate	0/50 (0%)	8/50 (16%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	18.9%	6.7%	4.7%
Terminal rate	0/34 (0%)	6/31 (19%)	1/36 (3%)	2/34 (6%)
First incidence (days)	—	683	714	735 (T)
Poly-3 test	P=0.316	P=0.003	P=0.127	P=0.238
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	20/50 (40%)	26/50 (52%)	21/50 (42%)	13/50 (26%)
Adjusted rate	46.1%	59.9%	45.1%	30.0%
Terminal rate	18/34 (53%)	20/31 (65%)	13/36 (36%)	12/34 (35%)
First incidence (days)	590	580	566	593
Poly-3 test	P=0.064N	P=0.136	P=0.547N	P=0.088N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	30/50 (60%)	27/50 (54%)	29/48 (60%)	25/49 (51%)
Adjusted rate	64.2%	60.6%	65.7%	56.8%
Terminal rate	20/34 (59%)	20/31 (65%)	23/34 (68%)	21/34 (62%)
First incidence (days)	397	551	448	610
Poly-3 test	P=0.247N	P=0.444N	P=0.529	P=0.302N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	30/50 (60%)	27/50 (54%)	30/48 (63%)	25/49 (51%)
Adjusted rate	64.2%	60.6%	67.3%	56.8%
Terminal rate	20/34 (59%)	20/31 (65%)	23/34 (68%)	21/34 (62%)
First incidence (days)	397	551	448	610
Poly-3 test	P=0.238N	P=0.444N	P=0.465	P=0.302N
Skin: Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.3%	0.0%	6.7%	0.0%
Terminal rate	0/34 (0%)	0/31 (0%)	3/36 (8%)	0/34 (0%)
First incidence (days)	566	—	735 (T)	—
Poly-3 test	P=0.297N	P=0.505N	P=0.316	P=0.501N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.0%	0.0%	2.2%	0.0%
Terminal rate	3/34 (9%)	0/31 (0%)	0/36 (0%)	0/34 (0%)
First incidence (days)	735 (T)	—	716	—
Poly-3 test	P=0.089N	P=0.120N	P=0.289N	P=0.117N
Skin (Subcutaneous Tissue): Fibroma or Sarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adjusted rate	7.0%	0.0%	2.2%	2.3%
Terminal rate	3/34 (9%)	0/31 (0%)	0/36 (0%)	0/34 (0%)
First incidence (days)	735 (T)	—	716	726
Poly-3 test	P=0.276N	P=0.120N	P=0.289N	P=0.303N
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/47 (13%)	6/47 (13%)	6/50 (12%)	2/47 (4%)
Adjusted rate	14.6%	15.0%	13.3%	4.9%
Terminal rate	6/34 (18%)	4/31 (13%)	3/36 (8%)	2/33 (6%)
First incidence (days)	735 (T)	686	672	735 (T)
Poly-3 test	P=0.103N	P=0.602	P=0.556N	P=0.132N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	3/47 (6%)	2/47 (4%)	2/50 (4%)	1/47 (2%)
Adjusted rate	7.3%	5.0%	4.5%	2.4%
Terminal rate	3/34 (9%)	2/31 (7%)	2/36 (6%)	1/33 (3%)
First incidence (days)	735 (T)	735 (T)	735 (T)	735 (T)
Poly-3 test	P=0.257N	P=0.516N	P=0.465N	P=0.305N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/47 (17%)	8/47 (17%)	8/50 (16%)	3/47 (6%)
Adjusted rate	19.4%	20.0%	17.7%	7.3%
Terminal rate	8/34 (24%)	6/31 (19%)	5/36 (14%)	3/33 (9%)
First incidence (days)	735 (T)	686	672	735 (T)
Poly-3 test	P=0.075N	P=0.585	P=0.530N	P=0.096N
Uterus: Stromal Polyp				
Overall rate	10/50 (20%)	4/50 (8%)	10/50 (20%)	10/50 (20%)
Adjusted rate	23.5%	9.5%	22.5%	22.6%
Terminal rate	10/34 (29%)	3/31 (10%)	10/36 (28%)	7/34 (21%)
First incidence (days)	735 (T)	728	735 (T)	535
Poly-3 test	P=0.536N	P=0.073N	P=0.557N	P=0.563N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	10/50 (20%)	5/50 (10%)	10/50 (20%)	10/50 (20%)
Adjusted rate	23.5%	11.8%	22.5%	22.6%
Terminal rate	10/34 (29%)	3/31 (10%)	10/36 (28%)	7/34 (21%)
First incidence (days)	735 (T)	695	735 (T)	535
Poly-3 test	P=0.536N	P=0.129N	P=0.557N	P=0.563N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
All Organs: Mononuclear Cell Leukemia				
Overall rate	14/50 (28%)	21/50 (42%)	14/50 (28%)	24/50 (48%)
Adjusted rate	31.6%	46.3%	30.7%	51.0%
Terminal rate	10/34 (29%)	11/31 (36%)	9/36 (25%)	14/34 (41%)
First incidence (days)	504	428	595	411
Poly-3 test	P=0.021	P=0.110	P=0.555N	P=0.044
All Organs: Benign Neoplasms				
Overall rate	44/50 (88%)	39/50 (78%)	44/50 (88%)	40/50 (80%)
Adjusted rate	92.4%	86.7%	90.6%	86.5%
Terminal rate	32/34 (94%)	28/31 (90%)	32/36 (89%)	31/34 (91%)
First incidence (days)	397	551	436	535
Poly-3 test	P=0.217N	P=0.275N	P=0.521N	P=0.261N
All Organs: Malignant Neoplasms				
Overall rate	25/50 (50%)	30/50 (60%)	24/50 (48%)	32/50 (64%)
Adjusted rate	54.0%	64.6%	51.1%	68.0%
Terminal rate	17/34 (50%)	16/31 (52%)	17/36 (47%)	21/34 (62%)
First incidence (days)	476	428	225	411
Poly-3 test	P=0.073	P=0.203	P=0.467N	P=0.117
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	47/50 (94%)	48/50 (96%)	46/50 (92%)
Adjusted rate	100.0%	97.9%	96.0%	94.8%
Terminal rate	34/34 (100%)	30/31 (97%)	34/36 (94%)	32/34 (94%)
First incidence (days)	397	428	225	411
Poly-3 test	P=0.156N	P=0.496N	P=0.243N	P=0.150N

(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, lung, 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 (the 0.03 mg/m^3 group was excluded from 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 B4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Female F344/N Rats

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Feed[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	0/50	0/50
Indium phosphide (inhalation)	0/50	1/50	1/50
Methacrylonitrile (gavage)	0/50	0/50	0/50
Naphthalene (inhalation)	1/49	0/49	1/49
p-Nitrotoluene (feed)	0/50	0/50	0/50
Sodium nitrite (drinking water)	3/50	0/50	3/50
Overall Historical Incidence in Controls Given NTP-2000 Feed			
Total (%)	4/299 (1.3%)	1/299 (0.3%)	5/299 (1.7%)
Mean ± standard deviation	1.3% ± 2.4%	0.3% ± 0.8%	1.7% ± 2.3%
Range	0%-6%	0%-2%	0%-6%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]			
Acetonitrile	0/48	0/48	0/48
2-Butoxyethanol	0/50	0/50	0/50
Chloroprene	1/49	0/49	1/49
Cobalt sulfate heptahydrate	0/50	0/50	0/50
Furfuryl alcohol	1/50	0/50	1/50
Gallium arsenide	0/50	0/50	0/50
Glutaraldehyde	0/50	0/50	0/50
Hexachlorocyclopentadiene	1/50	0/50	1/50
Isobutene	2/50	0/50	2/50
Isobutyraldehyde	1/49	1/49	2/49
Isoprene	1/50	0/50	1/50
Molybdenum trioxide	0/50	0/50	0/50
Nitromethane	0/50	1/50	1/50
Ozone	0/50	0/50	0/50
Tetrafluoroethylene	0/50	0/50	0/50
Tetrahydrofuran	1/50	0/50	1/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed			
Total (%)	12/1,050 (1.1%)	2/1,050 (0.2%)	14/1,050 (1.3%)
Mean ± standard deviation	1.1% ± 1.3%	0.2% ± 0.6%	1.3% ± 1.5%
Range	0%-4%	0%-2%	0%-4%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE B4b
Historical Incidence of Adrenal Medulla Pheochromocytoma in Control Female F344/N Rats

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence in Controls Given NTP-2000 Feed[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	2/50	0/50	2/50
Indium phosphide (inhalation)	2/50	0/50	2/50
Methacrylonitrile (gavage)	1/50	0/50	1/50
Naphthalene (inhalation)	3/48	0/48	3/48
p-Nitrotoluene (feed)	2/49	0/49	2/49
Sodium nitrite (drinking water)	4/50	0/50	4/50
Overall Historical Incidence in Controls Given NTP-2000 Feed			
Total (%)	14/297 (4.7%)	0/297	14/297 (4.7%)
Mean ± standard deviation	4.7% ± 2.1%		4.7% ± 2.1%
Range	2%-8%		2%-8%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]			
Acetonitrile	1/48	0/48	1/48
2-Butoxyethanol	3/50	0/50	3/50
Chloroprene	3/49	0/49	3/49
Cobalt sulfate heptahydrate	2/48	0/48	2/48
Furfuryl alcohol	4/50	1/50	5/50
Gallium arsenide	4/50	0/50	4/50
Glutaraldehyde	0/50	0/50	0/50
Hexachlorocyclopentadiene	6/47	0/47	6/47
Isobutene	3/50	0/50	4/50
Isobutyraldehyde	1/49	0/49	1/49
Isoprene	1/50	1/50	2/50
Molybdenum trioxide	5/49	0/49	6/49
Nitromethane	1/49	0/49	2/49
Ozone	6/50	0/50	6/50
Tetrafluoroethylene	4/50	0/50	4/50
Tetrahydrofuran	0/50	2/50	2/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed			
Total (%)	54/1,039 (5.2%)	5/1,039 (0.5%)	64/1,039 (6.2%)
Mean ± standard deviation	5.2% ± 3.8%	0.5% ± 1.1%	6.2% ± 3.5%
Range	0%-13%	0%-4%	0%-13%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE B4c
Historical Incidence of Mammary Gland Carcinoma in Control Female F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Feed[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	1/50
Indium phosphide (inhalation)	0/50
Methacrylonitrile (gavage)	3/50
Naphthalene (inhalation)	3/49
p-Nitrotoluene (feed)	1/50
Sodium nitrite (drinking water)	1/50
Overall Historical Incidence in Controls Given NTP-2000 Feed	
Total (%)	9/299 (3.0%)
Mean ± standard deviation	3.0% ± 2.5%
Range	0%-6%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Batelle Pacific Northwest Laboratories[b]	
Acetonitrile	2/48
2-Butoxyethanol	3/50
Chloroprene	4/49
Cobalt sulfate heptahydrate	3/50
Furfuryl alcohol	9/50
Gallium arsenide	8/50
Glutaraldehyde	5/50
Hexachlorocyclopentadiene	3/50
Isobutene	2/50
Isobutyraldehyde	1/50
Isoprene	4/50
Molybdenum trioxide	1/50
Nitromethane	2/50
Ozone	4/50
Tetrafluoroethylene	3/50
Tetrahydrofuran	5/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed	
Total (%)	71/1,052 (6.8%)
Mean ± standard deviation	6.8% ± 4.2%
Range	2%-18%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE B4d
Historical Incidence of Mononuclear Cell Leukemia in Control Female F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Feed[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	8/50
Indium phosphide (inhalation)	14/50
Methacrylonitrile (gavage)	21/50
Naphthalene (inhalation)	16/49
p-Nitrotoluene (feed)	13/50
Sodium nitrite (drinking water)	15/50
Overall Historical Incidence in Controls Given NTP-2000 Feed	
Total (%)	87/299 (29.1%)
Mean ± standard deviation	29.1% ± 8.5%
Range	16%-42%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Batelle Pacific Northwest Laboratories[b]	
Acetonitrile	18/48
2-Butoxyethanol	18/50
Chloroprene	18/49
Cobalt sulfate heptahydrate	15/50
Furfuryl alcohol	21/50
Gallium arsenide	22/50
Glutaraldehyde	18/50
Hexachlorocyclopentadiene	16/50
Isobutene	18/50
Isobutyraldehyde	12/50
Isoprene	14/50
Molybdenum trioxide	18/50
Nitromethane	22/50
Ozone	17/50
Tetrafluoroethylene	16/50
Tetrahydrofuran	17/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed	
Total (%)	373/1,052 (35.5%)
Mean ± standard deviation	35.4% ± 6.0%
Range	24%-47%

[a] Data as of 15 March 2000; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia
[b] Data as of 21 December 1999; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death		1		
Moribund	13	14	14	12
Natural deaths	3	4		4
Survivors				
Died last week of the study		1		
Terminal sacrifice	34	30	36	34
Animals examined microscopically	60	60	60	60
3-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(3)	(2)	(10)
Hematopoietic cell proliferation				2 (20%)
Hepatodiaphragmatic nodule		1 (33%)	1 (50%)	1 (10%)
Inflammation, granulomatous	2 (20%)			3 (30%)
Mesentery	(1)			
Fat, inflammation, chronic	1 (100%)			
Stomach, glandular	(10)			(10)
Mineralization	2 (20%)			1 (10%)
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy	2 (20%)			
Hematopoietic System				
Lymph node, bronchial	(4)	(8)	(8)	(6)
Foreign body		5 (63%)	7 (88%)	4 (67%)
Hyperplasia		1 (13%)	6 (75%)	3 (50%)
Lymph node, mediastinal	(7)	(9)	(8)	(9)
Foreign body		6 (67%)	6 (75%)	5 (56%)
Hyperplasia		4 (44%)	3 (38%)	5 (56%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Foreign body		8 (80%)	10 (100%)	10 (100%)
Inflammation, chronic active	2 (20%)	10 (100%)	10 (100%)	10 (100%)
Alveolar epithelium, hyperplasia		5 (50%)	1 (10%)	7 (70%)
Alveolus, proteinosis		9 (90%)	10 (100%)	10 (100%)
Nose	(10)	(10)	(10)	(10)
Inflammation, suppurative			2 (20%)	
Urinary System				
Kidney	(10)			(10)
Nephropathy	1 (10%)			

[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 Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
3-Month Interim Evaluation (continued)				
Systems Examined with No Lesions Observed				
Endocrine System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, cecum	(47)	(49)	(50)	(46)
Hemorrhage		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)	1 (2%)	1 (2%)
Basophilic focus	46 (92%)	39 (78%)	47 (94%)	44 (88%)
Clear cell focus	17 (34%)	8 (16%)	17 (34%)	9 (18%)
Eosinophilic focus	2 (4%)	5 (10%)	3 (6%)	5 (10%)
Fatty change	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Hepatodiaphragmatic nodule	7 (14%)	4 (8%)	2 (4%)	11 (22%)
Inflammation, chronic active			1 (2%)	
Inflammation, granulomatous	1 (2%)	2 (4%)		1 (2%)
Mixed cell focus	6 (12%)		4 (8%)	4 (8%)
Necrosis		3 (6%)		3 (6%)
Regeneration	1 (2%)	2 (4%)		4 (8%)
Tension lipidosis				1 (2%)
Thrombosis				1 (2%)
Vacuolization cytoplasmic, focal	4 (8%)	1 (2%)		1 (2%)
Bile duct, hyperplasia	4 (8%)	8 (16%)	4 (8%)	10 (20%)
Centrilobular, necrosis	3 (6%)	7 (14%)	3 (6%)	9 (18%)
Periportal, infiltration cellular, mononuclear cell			1 (2%)	
Serosa, hemorrhage			1 (2%)	
Mesentery	(9)	(15)	(15)	(19)
Fat, necrosis	9 (100%)	15 (100%)	15 (100%)	18 (95%)
Oral mucosa		(2)		(2)
Pharyngeal, hyperplasia		1 (50%)		
Pancreas	(50)	(50)	(50)	(49)
Atrophy	5 (10%)	12 (24%)	6 (12%)	8 (16%)
Basophilic focus	1 (2%)		3 (6%)	1 (2%)
Metaplasia, hepatocyte				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	3 (6%)		1 (2%)	2 (4%)
Basophilic focus	3 (6%)			2 (4%)
Stomach, forestomach	(50)	(50)	(50)	(49)
Hyperplasia, squamous	2 (4%)	1 (2%)		2 (4%)
Inflammation, acute		1 (2%)		
Necrosis			1 (2%)	
Ulcer	1 (2%)	2 (4%)		1 (2%)
Stomach, glandular	(49)	(50)	(50)	(48)
Necrosis	1 (2%)	5 (10%)	1 (2%)	2 (4%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Alimentary System (continued)				
Tongue	(1)	(1)	(1)	(1)
Hyperplasia, squamous	1 (100%)	1 (100%)		1 (100%)
Tooth	(2)			
Inflammation, chronic active	2 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	37 (74%)	29 (58%)	41 (82%)	30 (60%)
Atrium, thrombosis		1 (2%)		1 (2%)
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(49)
Atrophy				2 (4%)
Degeneration, cystic	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Hyperplasia	21 (43%)	23 (47%)	27 (54%)	25 (51%)
Hypertrophy	11 (22%)	13 (27%)	3 (6%)	6 (12%)
Necrosis		4 (8%)		3 (6%)
Thrombosis		1 (2%)		
Vacuolization cytoplasmic	1 (2%)		1 (2%)	4 (8%)
Adrenal medulla	(50)	(48)	(50)	(49)
Hyperplasia	6 (12%)	13 (27%)	9 (18%)	15 (31%)
Necrosis				1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia		1 (2%)	1 (2%)	
Pituitary gland	(50)	(50)	(48)	(49)
Cyst	1 (2%)			2 (4%)
Hemorrhage, chronic				1 (2%)
Pars distalis, angiectasis	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Pars distalis, hyperplasia	15 (30%)	15 (30%)	13 (27%)	17 (35%)
Thyroid gland	(47)	(47)	(50)	(47)
C-cell, hyperplasia	41 (87%)	42 (89%)	42 (84%)	39 (83%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(49)	(47)	(47)	(49)
Cyst		1 (2%)		
Hyperplasia	5 (10%)	1 (2%)	2 (4%)	4 (8%)
Ovary	(50)	(50)	(50)	(49)
Cyst	9 (18%)	6 (12%)	7 (14%)	3 (6%)
Inflammation, granulomatous	2 (4%)			
Interstitial cell, hyperplasia	1 (2%)			
Uterus	(50)	(50)	(50)	(49)
Cyst			1 (2%)	1 (2%)
Inflammation, acute			1 (2%)	1 (2%)
Thrombosis				1 (2%)
Ulcer			1 (2%)	
Cervix, hypertrophy	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(48)
Atrophy			1 (2%)	
Inflammation, granulomatous	1 (2%)			1 (2%)
Myelofibrosis	1 (2%)			1 (2%)
Lymph node, bronchial	(25)	(30)	(35)	(30)
Foreign body		23 (77%)	26 (74%)	20 (67%)
Lymph node, mandibular	(43)	(48)	(42)	(42)
Infiltration cellular, plasma cell			1 (2%)	
Lymph node, mediastinal	(28)	(36)	(39)	(26)
Foreign body		15 (42%)	18 (46%)	13 (50%)
Spleen	(50)	(50)	(50)	(47)
Fibrosis		1 (2%)	1 (2%)	4 (9%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	6 (12%)	2 (4%)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)	
Necrosis		1 (2%)		
Thymus	(45)	(47)	(50)	(45)
Atrophy		1 (2%)		
Epithelial cell, hyperplasia		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	2 (4%)	4 (8%)	1 (2%)	5 (10%)
Hyperplasia				1 (2%)
Skin	(50)	(49)	(50)	(49)
Foreign body				1 (2%)
Hyperkeratosis		2 (4%)		
Inflammation, acute		1 (2%)		1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(49)
Osteopetrosis	6 (12%)	7 (14%)	6 (12%)	7 (14%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Necrosis				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Respiratory System				
Larynx	(50)	(49)	(50)	(49)
Inflammation, acute		1 (2%)		1 (2%)
Epiglottis, metaplasia, squamous	3 (6%)	2 (4%)	1 (2%)	
Respiratory epithelium, metaplasia, squamous	4 (8%)	5 (10%)	4 (8%)	6 (12%)
Lung	(50)	(50)	(50)	(50)
Cyst, squamous		1 (2%)	1 (2%)	10 (20%)
Foreign body		49 (98%)	50 (100%)	50 (100%)
Hyperplasia, atypical		8 (16%)	8 (16%)	39 (78%)
Inflammation, chronic active	10 (20%)	49 (98%)	50 (100%)	49 (98%)
Metaplasia, squamous		2 (4%)	1 (2%)	4 (8%)
Thrombosis	2 (4%)			
Alveolar epithelium, hyperplasia	8 (16%)	15 (30%)	22 (44%)	16 (32%)
Alveolar epithelium, metaplasia		46 (92%)	47 (94%)	48 (96%)
Alveolus, infiltration cellular, histiocyte	16 (32%)	1 (2%)		
Alveolus, proteinosis		49 (98%)	47 (94%)	50 (100%)
Bronchiole, inflammation, suppurative	1 (2%)			
Interstitium, fibrosis		48 (96%)	50 (100%)	49 (98%)
Mediastinum, inflammation, chronic		1 (2%)		
Nose	(50)	(50)	(50)	(49)
Inflammation, suppurative	6 (12%)	8 (16%)	3 (6%)	9 (18%)
Thrombosis	2 (4%)	3 (6%)	1 (2%)	6 (12%)
Glands, hyperplasia				1 (2%)
Lateral wall, metaplasia, squamous		2 (4%)		
Olfactory epithelium, metaplasia	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Respiratory epithelium, hyperplasia	2 (4%)	4 (8%)	1 (2%)	7 (14%)
Respiratory epithelium, metaplasia, squamous		3 (6%)		2 (4%)
Special Senses System				
Eye	(1)		(3)	(3)
Cataract	1 (100%)		3 (100%)	3 (100%)
Retina, atrophy	1 (100%)		3 (100%)	3 (100%)
Urinary System				
Kidney	(50)	(49)	(50)	(48)
Accumulation, hyaline droplet		1 (2%)		
Infarct				1 (2%)
Nephropathy	41 (82%)	38 (78%)	42 (84%)	38 (79%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF INDIUM PHOSPHIDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death		1		
Moribund	5	14	12	12
Natural deaths	8	11	9	11
Survivors				
Terminal sacrifice	37	24	29	27
Animals examined microscopically	60	60	60	60
Systems Examined at 3 Months with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine small, duodenum	(43)	(43)	(42)	(44)
Adenoma		1 (2%)	1 (2%)	
Intestine small, jejunum	(47)	(44)	(46)	(44)
Adenoma	1 (2%)			
Carcinoma		1 (2%)	3 (7%)	2 (5%)
Peyer's patch, histiocytic sarcoma		1 (2%)		
Intestine small, ileum	(45)	(47)	(43)	(45)
Carcinoma			2 (5%)	1 (2%)
Peyer's patch, histiocytic sarcoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, intestine small, jejunum				1 (2%)
Hemangiosarcoma	2 (4%)	1 (2%)		2 (4%)
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	10 (20%)	15 (30%)	13 (26%)	11 (22%)
Hepatocellular carcinoma, multiple	1 (2%)	7 (14%)	10 (20%)	5 (10%)
Hepatocellular adenoma	9 (18%)	11 (22%)	13 (26%)	18 (36%)
Hepatocellular adenoma, multiple	8 (16%)	13 (26%)	10 (20%)	14 (28%)
Hepatocholangiocarcinoma				1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Mesentery	(4)	(5)	(5)	(8)
Fat, carcinoma, metastatic, intestine small, jejunum				1 (13%)
Fat, hepatocholangiocarcinoma, metastatic, liver				1 (13%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(50)	(49)	(47)
Carcinoma, metastatic, intestine small, jejunum				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(48)	(50)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma	1 (2%)		2 (4%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(48)	(50)
Adenoma	2 (4%)			
Histiocytic sarcoma		1 (2%)		
Capsule, adenoma			1 (2%)	
Adrenal medulla	(50)	(50)	(48)	(49)
Pheochromocytoma benign		1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(47)
Adenoma	2 (4%)			
Adenoma, multiple	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Pituitary gland	(48)	(47)	(45)	(50)
Pars intermedia, adenoma			2 (4%)	1 (2%)
Thyroid gland	(47)	(48)	(47)	(50)
Follicular cell, carcinoma	1 (2%)			
General Body System				
Peritoneum				(1)
Hepatocholangiocarcinoma, metastatic, liver				1 (100%)
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(49)
Prostate	(50)	(49)	(48)	(48)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	2 (4%)	1 (2%)	1 (2%)	
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)		
Lymph node	(1)	(1)	(1)	(2)
Pancreatic, histiocytic sarcoma		1 (100%)		
Lymph node, bronchial	(35)	(48)	(45)	(48)
Histiocytic sarcoma		1 (2%)		
Lymph node, mandibular	(28)	(32)	(33)	(36)
Histiocytic sarcoma		1 (3%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(47)	(49)	(45)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)		
Lymph node, mediastinal	(40)	(49)	(45)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (3%)		2 (4%)	1 (2%)
Carcinoma, metastatic, intestine small, jejunum				1 (2%)
Hemangiosarcoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		2 (4%)		
Sarcoma, metastatic, skeletal muscle			1 (2%)	
Spleen	(50)	(50)	(48)	(48)
Hemangiosarcoma	2 (4%)		1 (2%)	
Histiocytic sarcoma		1 (2%)		
Thymus	(35)	(39)	(41)	(35)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (3%)		1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (3%)
Histiocytic sarcoma		1 (3%)		
Sarcoma, metastatic, skeletal muscle			1 (2%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Musculoskeletal System				
Bone	(49)	(49)	(50)	(50)
Oligodendroglioma malignant, metastatic, brain	1 (2%)			
Osteosarcoma				1 (2%)
Skeletal muscle			(1)	(2)
Hepatocholangiocarcinoma, metastatic, liver				1 (50%)
Sarcoma			1 (100%)	1 (50%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Oligodendroglioma malignant	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	12 (24%)	7 (14%)	7 (14%)	10 (20%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	2 (4%)		3 (6%)
Alveolar/bronchiolar carcinoma	5 (10%)	7 (14%)	19 (38%)	9 (18%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)	8 (16%)	3 (6%)	4 (8%)
Hepatoblastoma, metastatic, liver		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	1 (2%)	6 (12%)	4 (8%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Sarcoma, metastatic, skeletal muscle			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		2 (4%)	1 (2%)
Mediastinum, carcinoma, metastatic, harderian gland		1 (2%)		
Mediastinum, hemangioma			1 (2%)	
Mediastinum, hemangiosarcoma		1 (2%)		
Mediastinum, sarcoma, metastatic, skeletal muscle			1 (2%)	
Nose	(49)	(50)	(49)	(50)
Carcinoma, metastatic, harderian gland		1 (2%)		
Special Senses System				
Harderian gland	(1)	(1)	(3)	(2)
Adenoma	1 (100%)		2 (67%)	1 (50%)
Adenoma, multiple				1 (50%)
Carcinoma		1 (100%)	1 (33%)	
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)		
Urinary bladder	(50)	(50)	(48)	(47)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)		1 (2%)
Lymphoma malignant	1 (2%)	1 (2%)	3 (6%)	2 (4%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
2-Year study	41	45	46	45
Total primary neoplasms				
2-Year study	66	83	98	90
Total animals with benign neoplasms				
2-Year study	29	27	31	35
Total benign neoplasms				
2-Year study	40	36	42	49
Total animals with malignant neoplasms				
2-Year study	21	35	40	30
Total malignant neoplasms				
2-Year study	26	47	56	41
Total animals with metastatic neoplasms				
2-Year study	6	3	10	7
Total metastatic neoplasms				
2-Year study	8	4	16	20

[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 C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	559	561	590	607	615	662	664	669	671	686	688	711	726	733	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	01959	05600	02909	04707	04404	03730	02242	04363	00909	00131	03737	01155	01262	00223	00033	00055	00066	00838	02727	03322	03335	03355	03366	03388	04140
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	M	A	M	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	M	A	A	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, ileum	+	A	+	+	+	+	A	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Hepatocellular carcinoma				X		X			X	X		X	X								X				
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																				X		X			
Hepatocellular adenoma, multiple							X			X						X									
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel						+																			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X				X			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																							
Adenoma, multiple					X																				
Parathyroid gland	M	+	M	M	M	+	M	+	+	M	M	M	M	+	+	+	M	+	+	+	M	+	M	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									X
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	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	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	
Carcass ID Number	0 4 1	0 4 4	0 4 8	0 0 7	0 1 0	0 1 1	0 1 3	0 1 4	0 1 7	0 1 8	0 2 0	0 2 1	0 2 3	0 2 4	0 3 1	0 3 9	0 4 2	0 4 9	0 1 6	0 2 5	0 2 6	0 2 8	0 3 4	0 4 5	0 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																							X			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					2
Hepatocellular carcinoma				X										X									X			10
Hepatocellular carcinoma, multiple																			X							1
Hepatocellular adenoma	X					X			X	X	X	X												X		9
Hepatocellular adenoma, multiple		X	X												X						X		X			8
Mesentery							+	+		+															+	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Squamous cell carcinoma														X												1
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		2
Adenoma, multiple																										1
Parathyroid gland	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	33
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																					X	2			X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	559	561	590	607	615	662	664	669	671	686	688	711	726	733	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	01939	05500	02909	04707	04404	03030	02202	04303	00909	00301	03707	01505	01202	00202	00303	00005	00006	00008	02707	03232	03303	03305	03306	03308	04040
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Lymph node											+														
Lymph node, bronchial	+	+	M	M	M	M	+	M	M	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+
Lymph node, mandibular	M	M	+	+	+	M	M	M	M	+	+	+	+	M	M	+	+	+	+	M	M	M	M	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Lymph node, mediastinal	+	+	+	+	+	M	+	+	M	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Thymus	+	+	+	+	M	+	+	+	I	M	M	M	M	M	+	+	+	M	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant, metastatic, brain		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant		X																							
Spinal cord					+																				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X			X		X	X		X				
Alveolar/bronchiolar adenoma, multiple																				X					
Alveolar/bronchiolar carcinoma							X				X								X						
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver									X			X	X												
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	I	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																					+				
Adenoma																					X				
Zymbal's gland																				+					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																							+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	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	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	
Carcass ID Number	0 4 1	0 4 4	0 4 8	0 0 7	0 1 0	0 1 1	0 1 3	0 1 4	0 1 7	0 1 8	0 2 0	0 2 1	0 2 3	0 2 4	0 3 1	0 3 9	0 4 2	0 4 9	0 1 6	0 2 5	0 2 6	0 2 8	0 3 4	0 4 5	0 4 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Hemangiosarcoma																										1
Lymph node																										1
Lymph node, bronchial	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	35
Lymph node, mandibular	+	M	+	+	+	+	M	+	M	+	M	+	+	M	M	+	M	M	+	+	+	+	+	+	M	28
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mediastinal	+	+	M	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	40
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							2
Thymus	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	M	M	M	+	+	+	+	+	M	+	35
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Oligodendroglioma malignant, metastatic, brain																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma malignant																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X		X		X	X						X	X						X				12
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma													X							X						5
Alveolar/bronchiolar carcinoma, multiple			X																							1
Hepatocellular carcinoma, metastatic, liver																										3
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Harderian gland																										1
Adenoma																										1
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	5 5 9	5 6 1	5 9 0	6 0 7	6 1 5	6 6 2	6 6 4	6 6 9	6 7 1	6 8 6	6 8 6	6 8 6	7 1 6	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
Carcass ID Number	0 1 9	0 5 0	0 2 9	0 4 7	0 0 4	0 3 0	0 2 2	0 4 3	0 0 9	0 0 1	0 3 7	0 1 5	0 1 2	0 0 2	0 0 3	0 0 5	0 0 6	0 0 8	0 2 7	0 3 2	0 3 3	0 3 5	0 3 6	0 3 8	0 4 0
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant											X															

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	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	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 4 1	0 4 4	0 4 8	0 0 7	0 1 0	0 1 1	0 1 3	0 1 4	0 1 7	0 1 8	0 2 0	0 2 1	0 2 3	0 2 4	0 3 1	0 3 9	0 4 2	0 4 9	0 1 6	0 2 5	0 2 6	0 2 8	0 3 4	0 4 5	0 4 6	Total Tissues/ Tumors	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymphoma malignant																										1	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	3 3 1	4 0 5	4 0 5	4 2 1	4 5 7	5 0 4	5 3 0	5 5 7	5 6 2	5 6 2	5 6 2	5 7 1	5 7 4	5 8 9	6 3 8	6 8 2	6 8 7	6 8 7	6 8 7	7 0 0	7 0 0	7 0 0	7 0 6	7 1 5	7 2 9
Carcass ID Number	2 1 9	2 3 5	2 5 0	2 1 2	2 2 2	2 3 4	2 0 4	2 2 0	2 2 4	2 2 7	2 4 7	2 1 3	2 1 1	2 0 3	2 0 9	2 1 4	2 3 7	2 4 4	2 4 5	2 0 6	2 2 9	2 3 9	2 3 8	2 2 8	2 0 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	M	A	+
Intestine large, colon	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	I	+	+	A	+
Adenoma												X													
Intestine small, jejunum	+	A	A	+	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+
Carcinoma																									
Peyer's patch, histiocytic sarcoma																									X
Intestine small, ileum	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, histiocytic sarcoma																									X
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Hepatoblastoma																									
Hepatocellular carcinoma	X	X	X	X	X	X		X		X			X				X				X	X	X		
Hepatocellular carcinoma, multiple							X				X									X					
Hepatocellular adenoma										X					X		X	X			X				X
Hepatocellular adenoma, multiple																						X		X	
Histiocytic sarcoma																									X
Mesentery								+		+														+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel													+										+		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	+	M	+	+	M	+	+	+	+	M	M	+	M	+	+	M	M	M	M	+	M
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																				X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	730	733	733	733	733	733	733	733	733	734	744	744	744	744	744	744	744	755	755	755	755	755	755	755	755	
Carcass ID Number	21 7	20 7	00 8	16 6	23 3	23 0	33 2	40 0	44 9	10 0	22 1	31 1	33 3	36 6	41 1	42 2	44 8	01 1	02 1	15 5	18 1	25 5	26 6	43 3	46 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma																								X		1
Peyer's patch, histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Peyer's patch, histiocytic sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma					X																					1
Hepatocellular carcinoma										X												X				15
Hepatocellular carcinoma, multiple					X						X				X								X			7
Hepatocellular adenoma	X			X				X					X												X	11
Hepatocellular adenoma, multiple		X	X							X		X		X				X	X	X	X		X	X		13
Histiocytic sarcoma																										1
Mesentery																	+			+			5			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth							+					+														2
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	M	M	M	+	+	+	I	+	+	M	+	+	M	+	+	+	+	+	M	M	+	+	30
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	331	405	405	421	457	504	530	557	622	622	622	711	714	889	638	682	687	687	687	700	700	700	706	715	729
Carcass ID Number	219	235	250	212	222	234	204	220	224	227	247	213	211	203	209	214	237	244	245	206	229	239	238	228	205
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node																									+
Pancreatic, histiocytic sarcoma																									X
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Histiocytic sarcoma																									X
Lymph node, mandibular	+	+	+	M	+	+	+	M	M	M	M	+	+	M	M	M	+	M	M	+	+	+	+	M	+
Histiocytic sarcoma																									X
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																				X					X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	M	+	M	M	+
Histiocytic sarcoma																									X
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X			X										
Alveolar/bronchiolar adenoma, multiple																				X				X	
Alveolar/bronchiolar carcinoma					X								X						X						
Alveolar/bronchiolar carcinoma, multiple																X		X				X			
Hepatoblastoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver							X																		
Histiocytic sarcoma																									X
Mediastinum, carcinoma, metastatic, harderian gland																									
Mediastinum, hemangiosarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																									
Pleura						+	+										+	+	+					+	
Trachea	+	+	+	+	+	+	+	+	I	+	+	+	+	+	A	+	+	I	+	+	I	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Carcinoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	730	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	
Carcass ID Number	21 7	20 7	00 8	21 6	22 3	23 0	23 2	24 0	24 9	21 0	22 1	23 1	23 3	23 6	24 1	24 2	24 8	20 1	20 2	21 5	21 8	22 5	22 6	24 3	24 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																				X						1
Lymph node																										1
Pancreatic, histiocytic sarcoma																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Lymph node, mandibular	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M	+	+	M	+	+	M	32
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	47
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Hemangiosarcoma																				X						1
Histiocytic sarcoma																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	39
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X				X		X	X										X					7
Alveolar/bronchiolar adenoma, multiple																										2
Alveolar/bronchiolar carcinoma							X			X							X					X				7
Alveolar/bronchiolar carcinoma, multiple			X									X		X					X					X		8
Hepatoblastoma, metastatic, liver					X																					1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Mediastinum, carcinoma, metastatic, harderian gland			X																							1
Mediastinum, hemangiosarcoma																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland			X																							1
Pleura	+		+		+	+	+	+	+		+		+		+				+		+		+			19
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Special Senses System																										
Eye			+																							1
Harderian gland			+																							1
Carcinoma			X																							1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	3 3 1	4 0 5	4 0 5	4 2 1	4 5 7	5 0 4	5 3 0	5 5 7	5 6 2	5 6 2	5 6 2	5 7 1	5 7 4	5 8 9	6 3 8	6 8 2	6 8 7	6 8 7	6 8 7	7 0 0	7 0 0	7 0 0	7 0 6	7 1 5	7 2 9
Carcass ID Number	2 1 9	2 3 5	2 5 0	2 1 2	2 2 2	2 3 4	2 0 4	2 2 0	2 2 4	2 2 7	2 4 7	2 1 3	2 1 1	2 0 3	2 0 9	2 1 4	2 3 7	2 4 4	2 4 5	2 0 6	2 2 9	2 3 9	2 3 8	2 2 8	2 0 5
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																				X					X
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	730	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	
Carcass ID Number	21017	20078	20086	21163	22303	23302	23340	24049	24490	21211	22311	23336	24141	24228	24401	20155	20212	21158	21825	22266	24346	24446	Total Tissues/ Tumors	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant								X																		1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	4 7 5	4 7 8	4 8 1	4 9 1	5 6 2	5 7 2	5 9 7	6 2 5	6 3 5	6 4 4	6 5 0	6 5 7	6 5 7	6 6 4	6 6 9	6 7 2	6 7 8	6 8 1	6 8 1	6 8 2	7 2 8	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 3 4	4 0 3	4 4 2	4 4 8	4 2 3	4 2 0	4 0 6	4 5 0	4 3 5	4 0 5	4 1 4	4 1 0	4 3 0	4 2 6	4 4 0	4 4 1	4 1 1	4 2 1	4 2 2	4 1 6	4 0 2	4 0 1	4 0 4	4 1 2	4 1 7
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	M	A	A	A	+	+	+	A	+	+	+	+	A	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	M	+	A	A	A	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+
Adenoma																								
Intestine small, jejunum	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Carcinoma																					X			
Intestine small, ileum	+	+	+	A	+	A	+	+	A	A	+	A	A	+	+	+	+	A	+	+	+	+	+	+
Carcinoma															X					X				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X	X	X		X	X		X	X	X			X		X			X			X	
Hepatocellular carcinoma, multiple		X				X			X					X		X					X			
Hepatocellular adenoma			X	X				X							X							X		
Hepatocellular adenoma, multiple																X							X	X
Mesentery					+	+											+							
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Stomach, glandular	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								
Cardiovascular System																								
Blood vessel										+														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																								
Adrenal medulla	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	+	A	+	+	M	M	+	M	+	M	M	M	M	+	+	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Pars intermedia, adenoma										X														
Thyroid gland	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 1 9	4 3 1	4 3 2	4 3 6	4 3 7	4 3 9	4 4 4	4 4 5	4 0 7	4 0 8	4 0 9	4 1 3	4 2 4	4 2 7	4 2 8	4 3 8	4 4 3	4 4 6	4 4 7	4 4 9	4 1 5	4 1 8	4 2 5	4 2 9	4 3 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenoma																								X		1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma	X																	X								3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Carcinoma																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																				X						13
Hepatocellular carcinoma, multiple	X							X	X						X											10
Hepatocellular adenoma		X	X		X	X	X			X				X						X						13
Hepatocellular adenoma, multiple	X										X				X	X			X			X	X			10
Mesentery															+	+										5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																		X		X					2	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth									+																	1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Capsule, adenoma																		X								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	I	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Pars intermedia, adenoma																					X					2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma		X																								1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	4 7 5	4 7 8	4 8 1	4 9 1	5 6 2	5 7 2	5 9 7	6 2 5	6 3 5	6 4 4	6 5 0	6 5 7	6 5 7	6 6 4	6 6 9	6 7 2	6 7 8	6 8 1	6 8 1	6 8 2	7 2 8	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 3 4	4 0 3	4 4 2	4 4 8	4 2 3	4 2 0	4 0 6	4 5 0	4 3 5	4 0 5	4 1 4	4 1 0	4 3 0	4 2 6	4 4 0	4 4 1	4 1 1	4 2 1	4 2 2	4 1 6	4 0 2	4 0 1	4 0 4	4 1 2	4 1 7
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																			+					
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	I	+	M	+	+	+	+	M	+	+	+	M	+	+	M	+	+	M	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung			X														X								
Sarcoma, metastatic, skeletal muscle		X																							
Spleen	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Thymus	M	+	+	M	+	+	M	+	A	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Sarcoma, metastatic, skeletal muscle		X																							
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, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
Sarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X		X					X						
Alveolar/bronchiolar carcinoma		X	X		X					X				X				X	X				X	X	
Alveolar/bronchiolar carcinoma, multiple																	X								
Hepatocellular carcinoma, metastatic, liver					X				X			X				X				X					
Sarcoma, metastatic, skeletal muscle		X																							
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			X																				X		
Mediastinum, hemangioma																									
Mediastinum, sarcoma, metastatic, skeletal muscle		X																							
Nose	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura														+		+							+		
Trachea	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+					+					
Harderian gland															+										
Adenoma															X										
Carcinoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 1 9	4 3 1	4 3 2	4 3 6	4 3 7	4 3 9	4 4 4	4 4 5	4 4 5	4 0 7	4 0 8	4 0 9	4 1 3	4 2 4	4 2 7	4 2 8	4 3 8	4 4 3	4 4 6	4 4 7	4 4 9	4 1 5	4 1 8	4 2 5	4 2 9	4 3 3	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											1
Lymph node, bronchial	+	+	M	+	M	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mandibular	+	+	M	M	+	M	M	M	+	M	M	+	+	+	+	+	M	+	M	+	+	M	+	+	+		33
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Alveolar/bronchiolar carcinoma, metastatic, lung																											2
Sarcoma, metastatic, skeletal muscle																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																											1
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		41
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Sarcoma, metastatic, skeletal muscle																											1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma						X																					1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											1
Sarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X											X								X	X		7
Alveolar/bronchiolar carcinoma	X	X			X							X					X	X			X			X	X	X	19
Alveolar/bronchiolar carcinoma, multiple																						X				X	
Hepatocellular carcinoma, metastatic, liver										X																	6
Sarcoma, metastatic, skeletal muscle																											1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																											2
Mediastinum, hemangioma				X																							1
Mediastinum, sarcoma, metastatic, skeletal muscle																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura															+												4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																											
Eye							+																				3
Harderian gland							+																+				3
Adenoma																							X				2
Carcinoma							X																				1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	4 7 5	4 7 8	4 8 1	4 9 1	5 6 2	5 7 2	5 9 7	6 2 5	6 3 5	6 4 4	6 5 0	6 5 7	6 5 7	6 6 4	6 6 9	6 7 2	6 7 8	6 8 1	6 8 1	6 8 2	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 3 4	4 0 3	4 4 2	4 4 8	4 2 3	4 2 0	4 0 6	4 5 0	4 3 5	4 0 5	4 1 4	4 1 0	4 3 0	4 2 6	4 4 0	4 4 1	4 1 1	4 2 1	4 2 2	4 1 6	4 0 2	4 0 1	4 0 4	4 1 2	4 1 7
Urinary System																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																	X								
Urinary bladder	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant													X						X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 1 9	4 3 1	4 3 2	4 3 6	4 3 7	4 3 9	4 4 4	4 4 5	4 0 7	4 0 8	4 0 9	4 1 3	4 2 4	4 2 7	4 2 8	4 3 8	4 4 3	4 4 6	4 4 7	4 4 9	4 1 5	4 1 8	4 2 5	4 2 9	4 3 3	Total Tissues/ Tumors	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Alveolar/bronchiolar carcinoma, metastatic, lung																										1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymphoma malignant						X																				3	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	3 7 0	4 7 1	5 0 1	5 3 3	5 6 2	5 6 2	5 8 9	5 8 9	5 9 5	6 0 8	6 1 9	6 3 2	6 4 5	6 4 8	6 6 4	6 6 8	6 7 1	6 8 5	6 8 7	7 0 6	7 1 5	7 1 5	7 2 7	7 3 3	7 3 3
Carcass ID Number	6 2 8	6 4 8	6 2 3	6 4 6	6 0 6	6 2 1	6 1 4	6 1 8	6 1 2	6 2 0	6 0 2	6 1 0	6 2 7	6 3 9	6 4 3	6 4 0	6 0 3	6 3 3	6 1 5	6 1 7	6 1 3	6 4 4	6 1 6	6 0 5	6 0 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	+	+	+	+	+	+	+	+	A	A	A	+	A	+	+	A	+	+	A	+	+	+
Intestine large, colon	A	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+
Carcinoma										X															
Intestine small, ileum	A	A	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, jejunum										X															
Hemangiosarcoma																									
Hepatocellular carcinoma					X	X				X			X			X	X	X							
Hepatocellular carcinoma, multiple												X									X				
Hepatocellular adenoma					X	X		X						X						X	X	X	X	X	
Hepatocellular adenoma, multiple	X						X		X																X
Hepatocholangiocarcinoma			X																						
Histiocytic sarcoma		X																							
Mesentery			+			+				+				+											
Fat, carcinoma, metastatic, intestine small, jejunum										X															
Fat, hepatocholangiocarcinoma, metastatic, liver			X																						
Oral mucosa																									
Pancreas	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, jejunum										X															
Hepatocholangiocarcinoma, metastatic, liver			X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pheochromocytoma benign																									X
Islets, pancreatic	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X																						
Parathyroid gland	M	+	M	+	+	M	+	M	M	+	I	+	+	M	+	+	+	+	M	+	+	M	M	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Peritoneum			+																						
Hepatocholangiocarcinoma, metastatic, liver			X																						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	6 1 1	6 1 9	6 2 2	6 2 4	6 3 0	6 3 2	6 3 5	6 4 0	6 4 2	6 4 5	6 4 7	6 0 1	6 0 7	6 0 8	6 2 5	6 2 6	6 2 9	6 3 1	6 3 4	6 3 8	6 4 1	6 4 9	6 5 0	6 3 6	6 3 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	I	+	+	+	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma														X												2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma										X																1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, intestine small, jejunum																										1
Hemangiosarcoma														2		X								X		
Hepatocellular carcinoma			X					X								X			X							11
Hepatocellular carcinoma, multiple		X										X					X									5
Hepatocellular adenoma		X		X	X			X				X	X					X				X		X		18
Hepatocellular adenoma, multiple	X						X			X	X				X	X	X		X		X				X	14
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma																										1
Mesentery					+		+								+	+										8
Fat, carcinoma, metastatic, intestine small, jejunum																										1
Fat, hepatocholangiocarcinoma, metastatic, liver																										1
Oral mucosa											A															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, intestine small, jejunum																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth						+			+																	2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																										1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars intermedia, adenoma							X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Peritoneum																										1
Hepatocholangiocarcinoma, metastatic, liver																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	3 7 0	4 7 1	5 0 1	5 3 3	5 6 2	5 6 2	5 8 9	5 8 9	5 9 5	6 0 8	6 1 9	6 3 2	6 4 5	6 4 8	6 6 4	6 6 8	6 7 1	6 8 5	6 8 7	7 0 6	7 1 5	7 1 5	7 2 7	7 3 3	7 3 3
Carcass ID Number	6 2 8	6 4 8	6 2 3	6 4 6	6 0 6	6 2 1	6 1 4	6 1 8	6 1 2	6 2 0	6 0 2	6 1 0	6 2 7	6 3 9	6 4 3	6 4 0	6 0 3	6 3 3	6 1 5	6 1 7	6 1 3	6 4 4	6 1 6	6 0 5	6 0 9
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+																	
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+	M	+	M	+	+	M	M	M	M	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	A	+	M	+	+	+	M	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X																						
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Carcinoma, metastatic, intestine small, jejunum										X															
Hepatocholangiocarcinoma, metastatic, liver			X																						
Spleen	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	M	+	+	+	M	+	M	+	+
Hepatocholangiocarcinoma, metastatic, liver			X																						
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, hemangiosarcoma																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma							X																		
Skeletal muscle			+						+																
Hepatocholangiocarcinoma, metastatic, liver			X																						
Sarcoma									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X									X										X
Alveolar/bronchiolar adenoma, multiple																			X				X		
Alveolar/bronchiolar carcinoma							X	X	X					X			X		X						
Alveolar/bronchiolar carcinoma, multiple																X									
Hepatocellular carcinoma, metastatic, liver					X	X															X				
Hepatocholangiocarcinoma, metastatic, liver			X																						
Histiocytic sarcoma		X																							
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																				+					
Trachea	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	6 1 1	6 1 9	6 2 2	6 2 4	6 3 0	6 3 2	6 3 5	6 4 0	6 4 2	6 4 5	6 4 7	6 0 1	6 0 7	6 0 8	6 2 5	6 2 6	6 2 9	6 3 1	6 3 4	6 3 8	6 4 1	6 4 9	6 5 0	6 3 6	6 3 7	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, intestine small, jejunum																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	35
Hepatocholangiocarcinoma, metastatic, liver																										1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X	X	X						X			X			X			X	10
Alveolar/bronchiolar adenoma, multiple															X											3
Alveolar/bronchiolar carcinoma									X						X	X										9
Alveolar/bronchiolar carcinoma, multiple								X			X										X					4
Hepatocellular carcinoma, metastatic, liver			X																							4
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura				+						+			+	+			+									6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	3 7 0	4 7 1	5 0 1	5 3 3	5 6 2	5 6 2	5 8 9	5 8 9	5 9 5	6 0 8	6 1 9	6 3 2	6 4 5	6 4 8	6 6 4	6 6 8	6 7 1	6 8 5	6 8 7	7 0 6	7 1 5	7 1 5	7 2 7	7 3 3	7 3 3
Carcass ID Number	6 2 8	6 4 8	6 2 3	6 4 6	6 0 6	6 2 1	6 1 4	6 1 8	6 1 2	6 2 0	6 0 2	6 1 0	6 2 7	6 3 9	6 4 3	6 0 4	6 0 3	6 3 3	6 1 5	6 1 7	6 1 3	6 4 4	6 1 6	6 0 5	6 0 9
Special Senses System																									
Eye																									
Harderian gland																									+
Adenoma																									X
Adenoma, multiple																									
Zymbal's gland									+																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Urinary bladder	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Lymphoma malignant					X			X																	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	6 1 1	6 1 9	6 2 2	6 2 4	6 3 0	6 3 2	6 3 5	6 4 0	6 4 2	6 4 5	6 4 7	6 0 1	6 0 7	6 0 8	6 2 5	6 2 6	6 2 9	6 3 1	6 3 4	6 3 8	6 4 1	6 4 9	6 5 0	6 3 6	6 3 7	Total Tissues/ Tumors
Special Senses System																										
Eye																						+				1
Harderian gland																						+				2
Adenoma																										1
Adenoma, multiple																						X				1
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																										2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Harderian Gland: Adenoma or Carcinoma				
Overall rate[a]	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate[b]	2.2%	2.6%	7.1%	4.8%
Terminal rate[c]	1/37 (3%)	1/24 (4%)	2/29 (7%)	2/27 (7%)
First incidence (days)	733 (T)	733 (T)	669	733 (T)
Poly-3 test[d]	P=0.442	P=0.723	P=0.275	P=0.462
Small Intestine (Ileum or Jejunum): Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted rate	0.0%	2.6%	11.7%	7.2%
Terminal rate	0/37 (0%)	1/24 (4%)	2/29 (7%)	2/27 (7%)
First incidence (days)	—[e]	733 (T)	669	608
Poly-3 test	P=0.192	P=0.468	P=0.024	P=0.102
Small Intestine (Duodenum, Ileum, or Jejunum): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	2/50 (4%)	6/50 (12%)	3/50 (6%)
Adjusted rate	2.2%	5.0%	14.1%	7.2%
Terminal rate	1/37 (3%)	1/24 (4%)	3/29 (10%)	2/27 (7%)
First incidence (days)	733 (T)	571	669	608
Poly-3 test	P=0.356	P=0.448	P=0.044	P=0.271
Liver: Hepatocellular Adenoma				
Overall rate	17/50 (34%)	24/50 (48%)	23/50 (46%)	32/50 (64%)
Adjusted rate	36.5%	58.9%	51.8%	70.5%
Terminal rate	15/37 (41%)	15/24 (63%)	18/29 (62%)	21/27 (78%)
First incidence (days)	664	562	481	370
Poly-3 test	P<0.001	P=0.026	P=0.099	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	11/50 (22%)	22/50 (44%)	23/50 (46%)	16/50 (32%)
Adjusted rate	23.2%	46.4%	47.3%	36.1%
Terminal rate	5/37 (14%)	6/24 (25%)	6/29 (21%)	7/27 (26%)
First incidence (days)	607	331	478	562
Poly-3 test	P=0.215	P=0.014	P=0.010	P=0.130
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	11/50 (22%)	22/50 (44%)	23/50 (46%)	16/50 (32%)
Adjusted rate	23.2%	46.4%	47.3%	36.1%
Terminal rate	5/37 (14%)	6/24 (25%)	6/29 (21%)	7/27 (26%)
First incidence (days)	607	331	478	562
Poly-3 test	P=0.215	P=0.014	P=0.010	P=0.130
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	26/50 (52%)	40/50 (80%)	37/50 (74%)	39/50 (78%)
Adjusted rate	54.6%	83.2%	76.1%	82.7%
Terminal rate	19/37 (51%)	19/24 (79%)	20/29 (69%)	22/27 (82%)
First incidence (days)	607	331	478	370
Poly-3 test	P=0.003	P<0.001	P=0.019	P=0.002

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	13/50 (26%)	9/50 (18%)	7/50 (14%)	13/50 (26%)
Adjusted rate	28.2%	22.4%	16.3%	30.7%
Terminal rate	12/37 (32%)	5/24 (21%)	4/29 (14%)	10/27 (37%)
First incidence (days)	726	571	657	562
Poly-3 test	P=0.367	P=0.356N	P=0.138N	P=0.490
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	6/50 (12%)	15/50 (30%)	22/50 (44%)	13/50 (26%)
Adjusted rate	12.9%	36.5%	48.6%	29.7%
Terminal rate	4/37 (11%)	9/24 (38%)	14/29 (48%)	6/27 (22%)
First incidence (days)	664	457	478	589
Poly-3 test	P=0.134	P=0.008	P<0.001	P=0.042
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	18/50 (36%)	23/50 (46%)	24/50 (48%)	21/50 (42%)
Adjusted rate	38.6%	54.5%	52.6%	47.1%
Terminal rate	15/37 (41%)	13/24 (54%)	15/29 (52%)	12/27 (44%)
First incidence (days)	664	457	478	562
Poly-3 test	P=0.312	P=0.094	P=0.122	P=0.270
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/49 (0%)	0/47 (0%)
Adjusted rate	6.4%	0.0%	0.0%	0.0%
Terminal rate	1/37 (3%)	0/24 (0%)	0/29 (0%)	0/27 (0%)
First incidence (days)	561	—	—	—
Poly-3 test	P=0.083N	P=0.155N	P=0.142N	P=0.148N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	6.5%	5.0%	2.4%	7.2%
Terminal rate	2/37 (5%)	1/24 (4%)	0/29 (0%)	2/27 (7%)
First incidence (days)	669	530	681	687
Poly-3 test	P=0.505	P=0.569N	P=0.338N	P=0.611
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	6.5%	5.0%	7.1%	7.2%
Terminal rate	2/37 (5%)	1/24 (4%)	2/29 (7%)	2/27 (7%)
First incidence (days)	669	530	681	687
Poly-3 test	P=0.554	P=0.569N	P=0.620	P=0.611
All Organs: Malignant Lymphoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	2.2%	2.6%	7.0%	4.7%
Terminal rate	0/37 (0%)	1/24 (4%)	1/29 (3%)	0/27 (0%)
First incidence (days)	686	733 (T)	657	562
Poly-3 test	P=0.453	P=0.722	P=0.276	P=0.470

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
All Organs: Benign Neoplasms				
Overall rate	29/50 (58%)	27/50 (54%)	31/50 (62%)	35/50 (70%)
Adjusted rate	61.0%	65.2%	68.2%	76.4%
Terminal rate	24/37 (65%)	16/24 (67%)	22/29 (76%)	22/27 (82%)
First incidence (days)	561	562	481	370
Poly-3 test	P=0.065	P=0.423	P=0.300	P=0.074
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	35/50 (70%)	40/50 (80%)	30/50 (60%)
Adjusted rate	43.2%	72.9%	81.2%	63.0%
Terminal rate	11/37 (30%)	15/24 (63%)	20/29 (69%)	14/27 (52%)
First incidence (days)	561	331	478	471
Poly-3 test	P=0.100	P=0.002	P<0.001	P=0.039
All Organs: Benign or Malignant Neoplasms				
Overall rate	41/50 (82%)	45/50 (90%)	46/50 (92%)	45/50 (90%)
Adjusted rate	83.7%	91.9%	93.4%	91.9%
Terminal rate	30/37 (81%)	21/24 (88%)	26/29 (90%)	24/27 (89%)
First incidence (days)	561	331	478	370
Poly-3 test	P=0.181	P=0.169	P=0.112	P=0.170

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pancreatic islets; 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 (the 0.03 mg/m^3 group was excluded from 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

TABLE C4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Male B6C3F$_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Feed[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	6/50	7/50	13/50
Indium phosphide (inhalation)	13/50	6/50	18/50
Methacrylonitrile (gavage)	2/49	4/49	6/49
p-Nitrotoluene (feed)	6/50	2/50	8/50
Sodium nitrite (drinking water)	10/50	4/50	13/50
Overall Historical Incidence in Controls Given NTP-2000 Feed			
Total (%)	37/249 (14.9%)	23/249 (9.2%)	58/249 (23.3%)
Mean ± standard deviation	14.8% ± 8.4%	9.2% ± 3.9%	23.3% ± 9.4%
Range	4%-26%	4%-14%	12%-36%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]			
Acetonitrile	6/50	4/50	10/50
1,3-Butadiene	18/50	5/50	21/50
2-Butoxyethanol	9/50	5/50	14/50
Chloroprene	8/50	6/50	13/50
Cobalt sulfate heptahydrate	9/50	4/50	11/50
Furfuryl alcohol	16/50	4/50	20/50
Gallium arsenide	13/50	3/50	15/50
Glutaraldehyde	8/48	10/48	18/48
Hexachlorocyclopentadiene	11/49	0/49	11/49
Isobutene	12/50	6/50	17/50
Isobutyraldehyde	5/50	7/50	12/50
Molybdenum trioxide	9/50	2/50	11/50
Nitromethane	11/50	2/50	13/50
Ozone	6/50	8/50	14/50
Tetrahydrofuran	18/50	6/50	21/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed			
Total (%)	201/1,071 (18.8%)	97/1,071 (9.1%)	285/1,071 (26.6%)
Mean ± standard deviation	19.0% ± 8.4%	9.0% ± 5.2%	26.8% ± 8.3%
Range	8%-36%	0%-21%	14%-42%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE C4b
Historical Incidence of Liver Neoplasms in Control Male B6C3F$_1$ Mice

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocullular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence in Controls Given NTP-2000 Feed[a]				
p,p′-Dichlorodiphenyl sulfone (feed)	6/50	9/50	0/50	15/50
Indium phosphide (inhalation)	17/50	11/50	0/50	26/50
Methacrylonitrile (gavage)	17/49	13/49	1/49	24/49
p-Nitrotoluene (feed)	14/50	8/50	0/50	20/50
Sodium nitrite (drinking water)	19/50	9/50	5/50	26/50
Overall Historical Incidence in Controls Given NTP-2000 Feed				
Total (%)	73/249 (29.3%)	50/249 (20.1%)	6/249 (2.4%)	111/249 (44.6%)
Mean ± standard deviation	29.3% ± 10.3%	20.1% ± 4.2%	2.4% ± 4.3%	44.6% ± 9.5%
Range	12%-38%	16%-27%	0%-10%	30%-52%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]				
Acetonitrile	13/50	7/50	0/50	19/50
1,3-Butadiene	13/50	11/50	0/50	21/50
2-Butoxyethanol	22/50	10/50	0/50	30/50
Chloroprene	22/50	24/50	0/50	43/50
Cobalt sulfate heptahydrate	22/50	23/50	4/50	40/50
Furfuryl alcohol	13/50	15/50	1/50	28/50
Gallium arsenide	16/50	13/50	0/50	26/50
Glutaraldehyde	19/49	15/49	0/49	32/49
Hexachlorocyclopentadiene	19/50	7/50	0/50	24/50
Isobutene	20/50	13/50	0/50	30/50
Isobutyraldehyde	12/49	17/49	0/49	27/49
Molybdenum trioxide	20/50	12/50	0/50	30/50
Nitromethane	17/50	16/50	0/50	29/50
Ozone	23/50	12/50	0/50	30/50
Tetrahydrofuran	24/50	14/50	0/50	35/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed				
Total (%)	356/1,072 (33.2%)	279/1,072 (26.0%)	6/1,072 (0.6%)	584/1,072 (54.5%)
Mean ± standard deviation	33.4% ± 9.3%	26.3% ± 9.6%	0.6% ± 1.8%	54.9% ± 14.3%
Range	15%-48%	11%-48%	0%-8%	22%-86%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE C4c
Historical Incidence of Small Intestine Neoplasms in Control Male B6C3F$_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Feed[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	0/50	0/50
Indium phosphide (inhalation)	1/50	0/50	1/50
Methacrylonitrile (gavage)	2/49	1/49	3/49
p-Nitrotoluene (feed)	0/50	0/50	0/50
Sodium nitrite (drinking water)	0/50	5/50	5/50
Overall Historical Incidence in Controls Given NTP-2000 Feed			
Total (%)	3/249 (1.2%)	6/249 (2.4%)	9/249 (3.6%)
Mean ± standard deviation	1.2% ± 1.8%	2.4% ± 4.3%	3.6% ± 4.4%
Range	0%-4%	0%-10%	0%-10%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]			
Acetonitrile	0/50	0/50	0/50
1,3-Butadiene	0/50	0/50	0/50
2-Butoxyethanol	1/50	1/50	2/50
Chloroprene	0/50	0/50	0/50
Cobalt sulfate heptahydrate	0/50	0/50	0/50
Furfuryl alcohol	0/50	0/50	0/50
Gallium arsenide	0/50	2/50	2/50
Glutaraldehyde	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	1/50	1/50
Isobutene	0/50	0/50	0/50
Isobutyraldehyde	0/50	0/50	0/50
Molybdenum trioxide	0/50	0/50	0/50
Nitromethane	0/50	0/50	0/50
Ozone	0/50	1/50	1/50
Tetrahydrofuran	0/50	1/50	1/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed			
Total (%)	2/1,074 (0.2%)	6/1,074 (0.6%)	8/1,074 (0.7%)
Mean ± standard deviation	0.2% ± 0.6%	0.6% ± 1.1%	0.8% ± 1.3%
Range	0%-2%	0%-4%	0%-4%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death		1		
Moribund	5	14	12	12
Natural deaths	8	11	9	11
Survivors				
Terminal sacrifice	37	24	29	27
Animals examined microscopically	60	60	60	60
3-Month Interim Evaluation				
Alimentary System				
Liver	(10)		(4)	(10)
Necrosis	1 (10%)			1 (10%)
Oval cell, hyperplasia	1 (10%)			1 (10%)
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy	5 (50%)			8 (80%)
Genital System				
Testes	(10)			(10)
Atrophy	1 (10%)			
Hematopoietic System				
Lymph node, bronchial	(9)	(10)	(10)	(10)
Foreign body		8 (80%)	9 (90%)	10 (100%)
Hyperplasia		8 (80%)	10 (100%)	10 (100%)
Lymph node, mediastinal	(6)	(6)	(9)	(6)
Hyperplasia		3 (50%)	4 (44%)	6 (100%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation		4 (40%)	5 (50%)	9 (90%)
Respiratory System				
Larynx	(10)		(4)	(10)
Inflammation, suppurative			1 (25%)	1 (10%)
Squamous epithelium, hyperplasia	2 (20%)		1 (25%)	1 (10%)
Lung	(10)	(10)	(10)	(10)
Foreign body		10 (100%)	10 (100%)	10 (100%)
Inflammation, chronic active		6 (60%)	10 (100%)	10 (100%)
Alveolus, proteinosis		10 (100%)	10 (100%)	10 (100%)
Urinary System				
Kidney	(10)			(10)
Nephropathy	1 (10%)			1 (10%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
3-Month Interim Evaluation (continued)				
Systems Examined with No Lesions Observed				
Endocrine System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Gallbladder	(43)	(43)	(41)	(38)
Degeneration, hyaline		1 (2%)		2 (5%)
Inflammation, chronic				1 (3%)
Inflammation, suppurative		1 (2%)	1 (2%)	
Epithelium, hyperplasia		1 (2%)		
Intestine large, colon	(49)	(48)	(48)	(46)
Inflammation, chronic			1 (2%)	1 (2%)
Intestine large, cecum	(47)	(47)	(46)	(46)
Inflammation, suppurative			1 (2%)	
Intestine small, jejunum	(47)	(44)	(46)	(44)
Fibrosis				1 (2%)
Inflammation, acute			1 (2%)	
Inflammation, chronic		1 (2%)		
Intestine small, ileum	(45)	(47)	(43)	(45)
Amyloid deposition		1 (2%)		
Artery, inflammation			1 (2%)	
Epithelium, hyperplasia				1 (2%)
Peyer's patch, hyperplasia	5 (11%)			1 (2%)
Liver	(50)	(50)	(50)	(50)
Amyloid deposition		2 (4%)		
Angiectasis	1 (2%)			
Basophilic focus	2 (4%)	1 (2%)	2 (4%)	
Clear cell focus	1 (2%)	1 (2%)		
Clear cell focus, multiple	1 (2%)		2 (4%)	
Eosinophilic focus	9 (18%)	15 (30%)	14 (28%)	10 (20%)
Eosinophilic focus, multiple	1 (2%)	1 (2%)	5 (10%)	8 (16%)
Hematopoietic cell proliferation	1 (2%)			
Inflammation, chronic active			1 (2%)	
Inflammation, focal, granulomatous	1 (2%)		1 (2%)	
Mixed cell focus			1 (2%)	1 (2%)
Necrosis	4 (8%)	4 (8%)	2 (4%)	7 (14%)
Tension lipidosis	2 (4%)	1 (2%)		
Vacuolization cytoplasmic	2 (4%)		1 (2%)	
Mesentery	(4)	(5)	(5)	(8)
Artery, inflammation		4 (80%)	1 (20%)	1 (13%)
Fat, inflammation				1 (13%)
Fat, necrosis	4 (100%)	1 (20%)	4 (80%)	4 (50%)
Pancreas	(50)	(50)	(49)	(47)
Atrophy	3 (6%)		2 (4%)	2 (4%)
Hypertrophy				2 (4%)
Artery, inflammation			1 (2%)	
Duct, cyst	1 (2%)			1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(48)	(50)
Erosion				2 (4%)
Infiltration cellular			1 (2%)	
Infiltration cellular, mast cell		1 (2%)		
Inflammation, chronic			1 (2%)	
Inflammation, suppurative	1 (2%)			
Ulcer	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Artery, inflammation		1 (2%)		
Epithelium, hyperplasia	2 (4%)	6 (12%)	8 (17%)	5 (10%)
Stomach, glandular	(49)	(49)	(48)	(47)
Infiltration cellular			1 (2%)	
Inflammation, suppurative	1 (2%)		2 (4%)	2 (4%)
Necrosis, focal	1 (2%)		1 (2%)	1 (2%)
Epithelium, hyperplasia	1 (2%)		1 (2%)	
Tooth		(2)	(1)	(2)
Inflammation		2 (100%)	1 (100%)	
Malformation				2 (100%)
Cardiovascular System				
Blood vessel	(1)	(2)	(1)	
Inflammation			1 (100%)	
Mineralization	1 (100%)			
Aorta, aneurysm		1 (50%)		
Aorta, hemorrhage		1 (50%)		
Aorta, inflammation		1 (50%)		
Aorta, mineralization		1 (50%)		
Aorta, necrosis		1 (50%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	39 (78%)	41 (82%)	42 (84%)	41 (82%)
Hemorrhage		1 (2%)		
Mineralization			2 (4%)	1 (2%)
Artery, inflammation	3 (6%)	18 (36%)	14 (28%)	10 (20%)
Artery, mineralization	1 (2%)			
Atrium, inflammation, chronic		1 (2%)		1 (2%)
Atrium, metaplasia, osseous				1 (2%)
Atrium, thrombosis		1 (2%)		2 (4%)
Epicardium, inflammation		2 (4%)	1 (2%)	
Pericardium, inflammation		6 (12%)		5 (10%)
Endocrine System				
Adrenal cortex	(50)	(50)	(48)	(50)
Amyloid deposition		2 (4%)		
Angiectasis		1 (2%)		
Degeneration, focal		1 (2%)		
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Hypertrophy	30 (60%)	15 (30%)	23 (48%)	19 (38%)
Necrosis		1 (2%)		
Adrenal medulla	(50)	(50)	(48)	(49)
Hyperplasia	3 (6%)	2 (4%)	1 (2%)	6 (12%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(49)	(47)
Hyperplasia	8 (16%)	1 (2%)	3 (6%)	4 (9%)
Parathyroid gland	(33)	(30)	(34)	(34)
Amyloid deposition		1 (3%)		
Pituitary gland	(48)	(47)	(45)	(50)
Pars distalis, hyperplasia		1 (2%)	1 (2%)	
Pars intermedia, hyperplasia			1 (2%)	1 (2%)
Thyroid gland	(47)	(48)	(47)	(50)
Amyloid deposition		2 (4%)		
Follicle, degeneration, cystic	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	2 (4%)			2 (4%)
Inflammation	1 (2%)		1 (2%)	2 (4%)
Preputial gland	(50)	(50)	(50)	(49)
Ectasia	25 (50%)	21 (42%)	19 (38%)	20 (41%)
Hyperplasia, squamous	1 (2%)			
Inflammation	5 (10%)		3 (6%)	
Prostate	(50)	(49)	(48)	(48)
Inflammation, suppurative				1 (2%)
Seminal vesicle	(49)	(47)	(48)	(47)
Congestion				1 (2%)
Testes	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Atrophy	6 (12%)	1 (2%)	2 (4%)	2 (4%)
Inflammation, granulomatous				1 (2%)
Interstitial cell, hyperplasia			1 (2%)	2 (4%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hyperplasia	5 (10%)	9 (18%)	6 (12%)	4 (8%)
Lymph node, bronchial	(35)	(48)	(45)	(48)
Foreign body		43 (90%)	40 (89%)	40 (83%)
Hyperplasia	2 (6%)	36 (75%)	22 (49%)	22 (46%)
Artery, inflammation				1 (2%)
Lymph node, mandibular	(28)	(32)	(33)	(36)
Hyperplasia	1 (4%)	2 (6%)	1 (3%)	
Lymph node, mesenteric	(48)	(47)	(49)	(45)
Angiectasis	1 (2%)			
Hemorrhage			1 (2%)	
Hyperplasia	11 (23%)	2 (4%)	10 (20%)	10 (22%)
Inflammation, granulomatous	2 (4%)			
Artery, inflammation	1 (2%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mediastinal	(40)	(49)	(45)	(48)
Foreign body		24 (49%)	14 (31%)	25 (52%)
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hyperplasia		34 (69%)	17 (38%)	27 (56%)
Infiltration cellular, histiocyte				1 (2%)
Artery, inflammation		1 (2%)	2 (4%)	1 (2%)
Spleen	(50)	(50)	(48)	(48)
Amyloid deposition		2 (4%)		
Angiectasis	2 (4%)	2 (4%)		
Hematopoietic cell proliferation	14 (28%)	34 (68%)	23 (48%)	29 (60%)
Hyperplasia, lymphoid		3 (6%)	4 (8%)	3 (6%)
Thymus	(35)	(39)	(41)	(35)
Epithelial cell, hyperplasia			1 (2%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	
Inflammation, suppurative		1 (2%)	3 (6%)	
Mineralization			1 (2%)	
Ulcer			1 (2%)	
Prepuce, inflammation, chronic active	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Subcutaneous tissue, edema				1 (2%)
Musculoskeletal System				
Bone	(49)	(49)	(50)	(50)
Fibrous osteodystrophy	2 (4%)		2 (4%)	2 (4%)
Hyperplasia	1 (2%)			
Maxilla, fracture		1 (2%)	1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Degeneration			1 (2%)	
Developmental malformation				1 (2%)
Meninges, infiltration cellular, mononuclear cell			2 (4%)	
Respiratory System				
Larynx	(50)	(49)	(49)	(50)
Inflammation, suppurative	5 (10%)	3 (6%)	1 (2%)	4 (8%)
Epiglottis, metaplasia, squamous	1 (2%)			
Squamous epithelium, hyperplasia	6 (12%)	3 (6%)	4 (8%)	7 (14%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Respiratory System (continued)				
Lung	(50)	(50)	(50)	(50)
Foreign body		49 (98%)	42 (84%)	49 (98%)
Hemorrhage	5 (10%)	1 (2%)	2 (4%)	2 (4%)
Infiltration cellular, mast cell				1 (2%)
Inflammation, chronic active	2 (4%)	50 (100%)	45 (90%)	46 (92%)
Inflammation, suppurative	1 (2%)			
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	2 (4%)	5 (10%)	3 (6%)	7 (14%)
Alveolus, infiltration cellular, histiocyte		1 (2%)		
Alveolus, proteinosis		14 (28%)		10 (20%)
Artery, mediastinum, inflammation		2 (4%)	2 (4%)	
Bronchiole, hyperplasia	1 (2%)			
Interstitium, fibrosis		2 (4%)		
Serosa, cyst			1 (2%)	
Serosa, fibrosis		50 (100%)	49 (98%)	50 (100%)
Serosa, metaplasia, osseous				1 (2%)
Nose	(49)	(50)	(49)	(50)
Foreign body		1 (2%)		
Hemorrhage		1 (2%)		
Inflammation, suppurative	3 (6%)	5 (10%)	4 (8%)	5 (10%)
Olfactory epithelium, atrophy	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Olfactory epithelium, degeneration, hyaline	1 (2%)			
Respiratory epithelium, degeneration, hyaline	5 (10%)	2 (4%)	3 (6%)	4 (8%)
Pleura		(19)	(4)	(6)
Mesothelium, hyperplasia		19 (100%)	4 (100%)	6 (100%)
Trachea	(48)	(46)	(48)	(47)
Inflammation, suppurative		1 (2%)		
Mineralization			1 (2%)	
Special Senses System				
Eye		(1)	(3)	(1)
Degeneration		1 (100%)	2 (67%)	
Cornea, inflammation			1 (33%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Amyloid deposition		2 (4%)		2 (4%)
Cyst	2 (4%)	1 (2%)		
Infiltration cellular, focal, mixed cell		1 (2%)		
Infiltration cellular, mast cell			1 (2%)	
Inflammation, chronic active				2 (4%)
Metaplasia, osseous	5 (10%)		2 (4%)	1 (2%)
Nephropathy	47 (94%)	40 (80%)	41 (84%)	41 (82%)
Artery, inflammation		5 (10%)	6 (12%)	2 (4%)
Capsule, hemorrhage			2 (4%)	
Capsule, inflammation, chronic				1 (2%)
Glomerulus, inflammation, chronic	1 (2%)	1 (2%)		
Renal tubule, hyperplasia	5 (10%)	2 (4%)	3 (6%)	5 (10%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Urinary System (continued)				
Urinary bladder	(50)	(50)	(48)	(47)
Angiectasis		1 (2%)		
Degeneration				1 (2%)
Inflammation				1 (2%)
Necrosis		1 (2%)		
Transitional epithelium, hyperplasia				1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF INDIUM PHOSPHIDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1			1
Moribund	4	31	15	18
Natural deaths	3	6	2	10
Survivors				
Terminal sacrifice	42	13	33	21
Animals examined microscopically	60	60	60	60
Systems Examined at 3 Months with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, cecum	(47)	(47)	(50)	(48)
Leiomyosarcoma	1 (2%)			
Intestine small, jejunum	(46)	(49)	(49)	(44)
Carcinoma	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Hemangiosarcoma		1 (2%)		1 (2%)
Hepatoblastoma				1 (2%)
Hepatocellular carcinoma	4 (8%)	13 (26%)	7 (14%)	8 (16%)
Hepatocellular carcinoma, multiple	2 (4%)	4 (8%)	1 (2%)	2 (4%)
Hepatocellular adenoma	12 (24%)	6 (12%)	12 (24%)	10 (20%)
Hepatocellular adenoma, multiple		8 (16%)	6 (12%)	4 (8%)
Histiocytic sarcoma		1 (2%)	1 (2%)	2 (4%)
Mesentery	(13)	(8)	(8)	(4)
Carcinoma, metastatic, uncertain primary site		1 (13%)		
Sarcoma	1 (8%)			
Pancreas	(50)	(49)	(50)	(50)
Carcinoma, metastatic, uncertain primary site		1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)
Salivary glands	(49)	(50)	(50)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(49)	(50)	(50)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(49)	(49)	(50)	(49)
Histiocytic sarcoma		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (2%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Histiocytic sarcoma				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Capsule, adenoma				1 (2%)
Adrenal medulla	(49)	(49)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Pheochromocytoma benign	2 (4%)		2 (4%)	
Islets, pancreatic	(50)	(49)	(50)	(50)
Adenoma			2 (4%)	
Pituitary gland	(50)	(50)	(48)	(49)
Carcinoma				1 (2%)
Pars distalis, adenoma	10 (20%)	7 (14%)	11 (23%)	7 (14%)
Pars distalis, carcinoma			1 (2%)	
Pars intermedia, adenoma		1 (2%)		1 (2%)
Thyroid gland	(50)	(49)	(50)	(49)
Bilateral, follicular cell, adenoma			1 (2%)	
General Body System				
Peritoneum		(1)		
Carcinoma, metastatic, uncertain primary site		1 (100%)		
Genital System				
Ovary	(47)	(46)	(44)	(47)
Carcinoma, metastatic, uterus			1 (2%)	
Cystadenoma				1 (2%)
Granulosa cell tumor benign			2 (5%)	
Histiocytic sarcoma				1 (2%)
Teratoma malignant				1 (2%)
Uterus	(50)	(49)	(50)	(50)
Carcinoma			1 (2%)	
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Polyp stromal		1 (2%)	1 (2%)	2 (4%)
Polyp stromal, multiple			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymph node	(1)	(5)	(6)	(8)
Renal, histiocytic sarcoma		1 (20%)		1 (13%)
Lymph node, bronchial	(36)	(50)	(48)	(50)
Carcinoma, metastatic, uterus			1 (2%)	
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Lymph node, mandibular	(36)	(36)	(43)	(42)
Histiocytic sarcoma		1 (3%)	1 (2%)	1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Lymph node, mesenteric	(48)	(49)	(50)	(48)
Carcinoma, metastatic, uterus			1 (2%)	
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Lymph node, mediastinal	(42)	(48)	(46)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, uterus			1 (2%)	
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Spleen	(50)	(49)	(50)	(49)
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Thymus	(47)	(46)	(42)	(42)
Histiocytic sarcoma		2 (4%)		2 (5%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, hemangioma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	2 (4%)	2 (4%)		
Subcutaneous tissue, sarcoma			1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Skeletal muscle				(1)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland			1 (2%)	1 (2%)
Histiocytic sarcoma				1 (2%)
Spinal cord	(1)		(1)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	6 (12%)	9 (18%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	5 (10%)	5 (10%)	7 (14%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Carcinoma, metastatic, uterus			1 (2%)	
Hepatocellular carcinoma, metastatic, liver		2 (4%)		
Histiocytic sarcoma		1 (2%)		2 (4%)
Sarcoma, metastatic, skin			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	1 (2%)
Mediastinum, carcinoma, metastatic, uncertain primary site		1 (2%)		
Mediastinum, hemangioma			1 (2%)	
Mediastinum, histiocytic sarcoma		1 (2%)		
Special Senses System				
Harderian gland	(3)		(2)	(2)
Adenoma	2 (67%)		2 (100%)	2 (100%)
Adenoma, multiple	1 (33%)			
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)		1 (2%)
Urinary bladder	(48)	(49)	(49)	(48)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Lymphoma malignant	8 (16%)	4 (8%)	10 (20%)	13 (26%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
2-Year study	35	37	45	40
Total primary neoplasms				
2-Year study	56	65	80	74
Total animals with benign neoplasms				
2-Year study	25	24	36	26
Total benign neoplasms				
2-Year study	31	29	52	35
Total animals with malignant neoplasms				
2-Year study	20	25	25	27
Total malignant neoplasms				
2-Year study	25	36	28	39
Total animals with metastatic neoplasms				
2-Year study	1	2	5	3
Total metastatic neoplasms				
2-Year study	1	6	11	6
Total animals with malignant neoplasms of uncertain primary site				
2-Year study		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 D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	264	517	593	626	664	678	699	715	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736
Carcass ID Number	108	101	125	128	115	146	137	116	114	118	122	130	136	142	143	148	103	105	109	111	112	113	117	121	124
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	A	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, cecum	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									X
Intestine small, duodenum	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Intestine small, ileum	+	A	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X		X															
Hepatocellular carcinoma, multiple				X												X									
Hepatocellular adenoma												X		X	X					X				X	
Mesentery			+						+								+								+
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma						X																			
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach						X																			
Tooth																									+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pheochromocytoma benign							X																		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X								X	X							X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 2 9	1 3 1	1 3 3	1 3 4	1 3 5	1 3 8	1 3 9	1 4 0	1 4 4	1 4 7	1 5 0	1 0 2	1 0 4	1 0 6	1 0 7	1 1 0	1 1 9	1 2 0	1 2 3	1 2 6	1 2 7	1 3 2	1 4 1	1 4 5	1 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyosarcoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X																					X			4
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma				X							X				X		X	X	X			X				12
Mesentery			+		+	+			+				+			+	+		+	+						13
Sarcoma																			X							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign						X																				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	+	M	+	M	+	+	M	M	+	+	+	+	+	+	+	M	M	+	M	+	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X								X	X			X						X			10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Ovary	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

Number of Days on Study	264	517	593	626	664	678	699	715	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736
Carcass ID Number	108	101	125	128	115	146	137	116	114	118	122	130	136	142	143	148	103	105	109	111	112	113	117	121	124
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Lymph node																									
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	M	M	+	+
Lymph node, mandibular	+	+	+	+	+	M	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	M	M	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Histiocytic sarcoma																									
Thymus	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, hemangiosarcoma					X							X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X													X					
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																					+				
Adenoma																					X				
Adenoma, multiple																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant							X											X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: Chamber Control

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 2 9	1 3 1	1 3 3	1 3 4	1 3 5	1 3 8	1 3 9	1 4 0	1 4 4	1 4 7	1 5 0	1 0 2	1 0 4	1 0 6	1 0 7	1 1 0	1 1 9	1 2 0	2 2 3	2 2 6	2 2 7	2 3 2	2 4 1	4 5	4 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node		+																								1
Lymph node, bronchial	+	M	+	+	M	+	M	M	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	36
Lymph node, mandibular	+	+	+	M	+	+	+	M	+	M	+	M	M	+	+	+	+	+	+	M	+	+	M	+	+	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	42
Histiocytic sarcoma							X																			1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma							X																			1
Thymus	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma												X														1
Subcutaneous tissue, hemangiosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																+										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	3
Alveolar/bronchiolar carcinoma		X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																	+			+						3
Adenoma																				X						2
Adenoma, multiple																	X									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																			1
Lymphoma malignant	X	X														X	X	X		X						8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	426	489	514	544	533	533	533	533	548	580	589	589	617	617	630	645	645	645	645	653	657	659	671	674	674
Carcass ID Number	31 5	30 5	32 6	40 6	42 9	43 5	44 0	44 1	44 8	42 5	41 0	43 4	40 8	43 6	45 0	41 8	43 3	43 9	44 9	40 9	43 0	40 3	44 2	41 7	41 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	+	A	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Hepatocellular carcinoma		X												X		X						X		X	X
Hepatocellular carcinoma, multiple						X													X						
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple											X				X										X
Histiocytic sarcoma					X																				
Mesentery				+								+	+											+	
Carcinoma, metastatic, uncertain primary site																								X	
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																								X	
Histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	M	I	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X				X								X									X
Pars intermedia, adenoma																									
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Peritoneum																								+	
Carcinoma, metastatic, uncertain primary site																								X	
Genital System																									
Clitoral gland	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+
Ovary	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Polyp stromal																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	6 8 6	6 8 6	6 8 7	6 8 7	6 8 8	6 8 8	6 8 8	7 0 0	7 0 6	7 1 5	7 2 7	7 3 2	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 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 3 7	3 3 8	3 1 4	3 2 8	3 1 6	3 2 4	3 3 2	3 1 1	3 4 5	3 0 6	3 0 2	3 0 7	3 1 2	3 1 3	3 2 3	3 3 1	3 2 1	3 2 2	3 4 3	3 4 4	3 0 1	3 0 4	3 2 0	3 2 7	3 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma	X	X			X	X							X									X			X	13
Hepatocellular carcinoma, multiple																X		X								4
Hepatocellular adenoma		X				X					X						X		X					X		6
Hepatocellular adenoma, multiple				X						X		X								X			X			8
Histiocytic sarcoma																										1
Mesentery		+							+						+			+								8
Carcinoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uncertain primary site																										1
Histiocytic sarcoma												X														1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma												X														1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	+	+	+	+	M	+	+	+	M	+	+	M	M	+	M	M	M	+	+	M	+	M	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma															X	X	X									7
Pars intermedia, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
Peritoneum																										1
Carcinoma, metastatic, uncertain primary site																										1
Genital System																										
Clitoral gland	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	40
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Polyp stromal																						X				1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	426	489	514	514	533	533	533	533	548	580	589	589	617	617	630	645	645	645	645	653	657	659	671	674	674
Carcass ID Number	315	305	026	046	029	035	040	041	048	025	010	034	008	036	050	018	033	039	049	090	030	003	042	017	019
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node																									
Renal, histiocytic sarcoma																									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymph node, mandibular	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma					X																				
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma					X																				
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma										X															
Alveolar/bronchiolar carcinoma, multiple																							X		
Hepatocellular carcinoma, metastatic, liver																							X	X	
Histiocytic sarcoma																									
Mediastinum, carcinoma, metastatic, uncertain primary site																							X		
Mediastinum, histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura			+	+			+								+	+									
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	6 8 6	6 8 6	6 8 7	6 8 7	6 8 8	6 8 8	6 8 8	7 0 0	7 0 6	7 1 5	7 2 7	7 3 2	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 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 3 7	3 3 8	3 1 4	3 2 8	3 1 6	3 2 4	3 3 2	3 1 1	3 4 5	3 0 6	3 0 2	3 0 7	3 1 2	3 1 3	3 2 3	3 3 1	3 2 1	3 2 2	3 4 3	3 4 4	3 0 1	3 0 4	3 2 0	3 2 7	3 4 7	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X													1
Lymph node												+					+	+					+		5
Renal, histiocytic sarcoma												X													1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X													2
Lymph node, mandibular	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	M	+	M	+	+	M	M	+	+	36
Histiocytic sarcoma												X													1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma												X													2
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Histiocytic sarcoma												X													2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma									X									X							2
Histiocytic sarcoma																									1
Thymus	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma												X													2
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																X									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma		X							X																2
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X		X	X				X					X		6
Alveolar/bronchiolar carcinoma				X							X				X	X									5
Alveolar/bronchiolar carcinoma, multiple																									1
Hepatocellular carcinoma, metastatic, liver																									2
Histiocytic sarcoma												X													1
Mediastinum, carcinoma, metastatic, uncertain primary site																									1
Mediastinum, histiocytic sarcoma												X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura		+	+				+	+	+	+	+					+		+	+						16
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma												X													2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	
	2	8	1	1	3	3	3	3	4	8	8	8	1	1	3	4	4	4	4	5	5	5	7	7	7	
	6	9	4	4	3	3	3	3	8	0	9	9	7	7	0	5	5	5	5	3	7	9	1	4	4	
Carcass ID Number	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	
	1	0	2	4	2	3	4	4	4	2	1	3	0	3	5	1	3	3	4	0	3	0	4	1	1	
	5	5	6	6	9	5	0	1	8	5	0	4	8	6	0	8	3	9	9	9	0	3	2	7	9	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma					X									X												
Lymphoma malignant														X							X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.03 mg/m^3

Number of Days on Study	6 8 6	6 8 6	6 8 7	6 8 7	6 8 8	6 8 8	6 8 8	7 0 0	7 0 6	7 1 5	7 2 7	7 3 2	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 7	7 3 7	7 3 7	7 3 7	7 3 7		
Carcass ID Number	3 3 7	3 3 8	3 1 4	3 2 8	3 1 6	3 2 4	3 3 2	3 1 1	3 4 5	3 0 6	3 0 2	3 0 7	3 1 2	3 1 3	3 2 3	3 3 1	3 2 1	3 2 2	3 4 3	3 4 4	3 0 1	3 0 4	3 2 0	3 2 7	3 4 7	Total Tissues/ Tumors	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma												X														3	
Lymphoma malignant						X																			X	4	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	5 4 7	5 8 9	6 1 7	6 1 7	6 5 8	6 6 4	6 7 2	6 7 2	6 8 1	6 8 5	6 8 7	6 8 7	6 9 1	6 9 9	6 9 9	7 2 8	7 2 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	5 0 3	5 2 3	5 1 7	5 2 8	5 4 0	5 0 4	5 3 2	5 4 8	5 1 0	5 4 7	5 0 1	5 3 8	5 1 2	5 2 9	5 4 6	5 3 7	5 0 2	5 0 9	5 2 2	5 2 6	5 2 7	5 3 1	5 3 4	5 3 9	5 4 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Hepatocellular carcinoma													X											X	
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma							X	X			X	X								X	X				
Hepatocellular adenoma, multiple			X		X	X								X											
Histiocytic sarcoma													X												
Mesentery				+																				+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+												+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X		X								
Parathyroid gland	+	+	M	M	+	+	+	+	M	M	M	M	+	+	M	M	+	M	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X		X								X	X			
Pars distalis, carcinoma																X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma							X																		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	M	+	M	M	M	I	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+	+	+	+	+
Carcinoma, metastatic, uterus									X																
Granulosa cell tumor benign																									
Oviduct																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 0 5	5 0 6	5 0 7	5 1 1	5 1 3	5 2 0	5 2 1	5 2 4	5 3 0	5 3 3	5 3 5	5 4 2	5 4 4	5 4 9	5 5 0	5 0 8	5 1 4	5 1 5	5 1 6	5 1 8	5 1 9	5 2 5	5 3 6	5 4 1	5 4 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hepatocellular carcinoma										X		X		X			X		X							7
Hepatocellular carcinoma, multiple																					X					1
Hepatocellular adenoma	X		X														X	X	X			X				12
Hepatocellular adenoma, multiple											X													X		6
Histiocytic sarcoma																										1
Mesentery		+	+		+	+		+											+							8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X															X							2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	M	M	I	+	M	M	+	+	M	M	M	M	+	+	+	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Pars distalis, adenoma	X			X					X				X	X	X						X					11
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	41
Ovary	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Carcinoma, metastatic, uterus																										1
Granulosa cell tumor benign	X																X									2
Oviduct																								+		1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	5 4 7	5 8 9	6 1 7	6 1 7	6 5 8	6 6 4	6 7 2	6 7 2	6 8 1	6 8 5	6 8 7	6 8 7	6 9 1	6 9 9	6 9 9	7 2 8	7 2 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	5 0 3	5 2 3	5 1 7	5 2 8	5 4 0	5 0 4	5 3 2	5 4 8	5 1 0	5 4 7	5 0 1	5 3 8	5 1 2	5 2 9	5 4 6	5 3 7	5 0 2	5 0 9	5 2 2	5 2 6	5 2 7	5 3 1	5 3 4	5 3 9	5 4 5
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Polyp stromal																									
Polyp stromal, multiple																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+		+										+											
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus									X																
Histiocytic sarcoma													X												
Lymph node, mandibular	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Histiocytic sarcoma													X												
Sarcoma, metastatic, skin												X													
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus									X																
Histiocytic sarcoma													X												
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Carcinoma, metastatic, uterus									X																
Histiocytic sarcoma													X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Histiocytic sarcoma													X												
Thymus	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																X									
Spinal cord														+											
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X						X	X									X				
Alveolar/bronchiolar adenoma, multiple																	X								
Alveolar/bronchiolar carcinoma						X		X																	
Alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Carcinoma, metastatic, uterus									X																
Sarcoma, metastatic, skin												X													
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Mediastinum, hemangioma							X																		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 0 5	5 0 6	5 0 7	5 1 1	5 1 3	5 2 0	5 2 1	5 2 4	5 3 0	5 3 3	5 3 5	5 4 2	5 4 4	5 4 9	5 5 0	5 0 8	5 1 4	5 1 5	5 1 6	5 1 8	5 1 9	5 2 5	5 3 6	5 4 1	5 4 3	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Polyp stromal													X													1
Polyp stromal, multiple																									X	1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+										+										6
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	43
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Carcinoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X			X				X				X					X					9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma											X			X											X	5
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, uterus																										1
Sarcoma, metastatic, skin																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinum, hemangioma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

Number of Days on Study	5 4 7	5 8 9	6 1 7	6 1 7	6 5 8	6 6 4	6 7 2	6 7 2	6 8 1	6 8 5	6 8 7	6 8 7	6 9 1	6 9 9	6 9 9	7 2 8	7 2 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	5 0 3	5 2 3	5 1 7	5 2 8	5 4 0	5 0 4	5 3 2	5 4 8	5 1 0	5 4 7	5 0 1	5 3 8	5 1 2	5 2 9	5 4 6	5 3 7	5 0 2	5 0 9	5 2 2	5 2 6	5 2 7	5 3 1	5 3 4	5 3 9	5 4 5
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura									+																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Lymphoma malignant	X	X		X	X					X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.1 mg/m^3 (Stop-Exposure)

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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 0 5	5 0 6	5 0 7	5 1 1	5 1 3	5 2 0	5 2 1	5 2 4	5 3 0	5 3 3	5 3 5	5 4 2	5 4 4	5 4 9	5 5 0	5 0 8	5 1 4	5 1 5	5 1 6	5 1 8	5 1 9	5 2 5	5 3 6	5 4 1	5 4 3	Total Tissues/ Tumors
Respiratory System (continued)																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura						+										+										3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								1
Harderian gland		+					+																			2
Adenoma		X					X																			2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant									X						X	X				X	X					10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	7 0 9	7 2 6	7 2 7	7 2 9	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	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 5 0	7 4 7	7 2 8	7 0 7	7 0 4	7 0 9	7 1 2	7 2 9	7 3 2	7 4 0	7 0 3	7 1 6	7 2 2	7 2 7	7 3 1	7 3 5	7 3 7	7 3 8	7 0 1	7 0 2	7 0 8	7 1 4	7 1 8	7 2 1	7 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							1
Hepatoblastoma						X																				1
Hepatocellular carcinoma			X			X				X																8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X	X					X						X			X							X			10
Hepatocellular adenoma, multiple											X						X									4
Histiocytic sarcoma																										2
Mesentery																			+			+	4			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	M	+	M	+	+	+	M	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Pars distalis, adenoma		X		X		X			X			X	X													7
Pars intermedia, adenoma																								X		1
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	1 9 7	4 2 1	4 2 1	4 8 7	4 9 3	4 9 6	5 1 0	5 1 2	5 3 3	5 7 8	5 9 4	6 0 0	6 0 8	6 1 5	6 1 9	6 3 3	6 4 2	6 4 5	6 5 0	6 5 8	6 6 9	6 8 7	6 9 5	6 9 5	7 0 5
Carcass ID Number	7 3 6	7 2 6	7 4 9	7 2 5	7 1 5	7 3 4	7 1 0	7 2 3	7 4 1	7 1 9	7 4 4	7 4 0	7 3 0	7 3 9	7 4 6	7 4 3	7 1 7	7 1 1	7 2 0	7 1 3	7 4 5	7 0 5	7 2 4	7 4 2	7 3 3
Genital System																									
Clitoral gland	+	M	M	+	I	+	+	M	+	+	+	+	M	+	+	+	+	+	M	M	M	+	M	+	+
Ovary	+	+	+	+	I	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Histiocytic sarcoma								X																	
Teratoma malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node							+										+	+						+	+
Renal, histiocytic sarcoma																									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung														X											
Histiocytic sarcoma								X																	
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	M	+	M	M
Histiocytic sarcoma								X																	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																	X								
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																						X			
Histiocytic sarcoma										X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	7 0 9	7 2 6	7 2 7	7 2 9	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	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 5 0	7 4 7	7 2 8	7 0 7	7 0 4	7 0 9	7 1 2	7 2 9	7 3 2	7 4 0	7 0 3	7 1 6	7 2 2	7 2 7	7 3 1	7 3 5	7 3 7	7 3 8	7 0 1	7 0 2	7 0 8	7 1 4	7 1 8	7 2 1	7 4 8	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma		X																								1
Histiocytic sarcoma																										1
Teratoma malignant															X											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X																		X			2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node		+								+											+					8
Renal, histiocytic sarcoma		X																								1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								2
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	42
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma		X																								2
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma		X																								2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma		X																								2
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	42
Histiocytic sarcoma		X																								2
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Skeletal muscle			+																							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Histiocytic sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Indium Phosphide: 0.3 mg/m^3 (Stop-Exposure)

Number of Days on Study	7 0 9	7 2 6	7 2 7	7 2 9	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	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 5 0	7 4 7	7 2 8	7 0 7	7 0 4	7 0 9	7 1 2	7 2 9	7 3 2	7 4 0	7 0 3	7 1 6	7 2 2	7 2 7	7 3 1	7 3 5	7 3 7	7 3 8	7 0 1	7 0 2	7 0 8	7 1 4	7 1 8	7 2 1	7 4 8	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X				X													5
Alveolar/bronchiolar adenoma, multiple														X					X							2
Alveolar/bronchiolar carcinoma				X		X																				7
Histiocytic sarcoma																										2
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+			+							+	+	+									+		+		13
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland											+															2
Adenoma											X															2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								3
Lymphoma malignant			X	X			X	X		X				X		X					X				X	13

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adjusted rate[b]	6.4%	0.0%	4.4%	5.2%
Terminal rate[c]	3/42 (7%)	0/13 (0%)	2/33 (6%)	1/21 (5%)
First incidence (days)	735 (T)	—[d]	735 (T)	512
Poly-3 test[e]	P=0.532N	P=0.167N	P=0.510N	P=0.586N
Liver: Hepatocellular Adenoma				
Overall rate	12/50 (24%)	14/50 (28%)	18/50 (36%)	14/50 (28%)
Adjusted rate	25.6%	36.2%	37.7%	34.7%
Terminal rate	12/42 (29%)	5/13 (39%)	10/33 (30%)	6/21 (29%)
First incidence (days)	735 (T)	589	617	496
Poly-3 test	P=0.265	P=0.205	P=0.148	P=0.245
Liver: Hepatocellular Carcinoma				
Overall rate	6/50 (12%)	17/50 (34%)	8/50 (16%)	10/50 (20%)
Adjusted rate	12.7%	41.7%	17.4%	24.7%
Terminal rate	4/42 (10%)	5/13 (39%)	7/33 (21%)	2/21 (10%)
First incidence (days)	626	489	691	594
Poly-3 test	P=0.102	P<0.001	P=0.365	P=0.120
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	6/50 (12%)	17/50 (34%)	8/50 (16%)	10/50 (20%)
Adjusted rate	12.7%	41.7%	17.4%	24.7%
Terminal rate	4/42 (10%)	5/13 (39%)	7/33 (21%)	2/21 (10%)
First incidence (days)	626	489	691	594
Poly-3 test	P=0.102	P<0.001	P=0.365	P=0.120
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	18/50 (36%)	28/50 (56%)	24/50 (48%)	23/50 (46%)
Adjusted rate	38.1%	66.7%	50.1%	54.2%
Terminal rate	16/42 (38%)	10/13 (77%)	15/33 (46%)	8/21 (38%)
First incidence (days)	626	489	617	496
Poly-3 test	P=0.096	P=0.004	P=0.163	P=0.090
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	6/50 (12%)	10/50 (20%)	7/50 (14%)
Adjusted rate	6.4%	16.1%	21.5%	18.0%
Terminal rate	2/42 (5%)	4/13 (31%)	6/33 (18%)	4/21 (19%)
First incidence (days)	699	645	658	608
Poly-3 test	P=0.128	P=0.142	P=0.033	P=0.092
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	6/50 (12%)	5/50 (10%)	7/50 (14%)
Adjusted rate	2.1%	15.8%	10.8%	17.6%
Terminal rate	1/42 (2%)	2/13 (15%)	3/33 (9%)	1/21 (5%)
First incidence (days)	735 (T)	580	664	600
Poly-3 test	P=0.017	P=0.029	P=0.099	P=0.016

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	11/50 (22%)	15/50 (30%)	14/50 (28%)
Adjusted rate	8.5%	28.8%	31.9%	34.4%
Terminal rate	3/42 (7%)	6/13 (46%)	9/33 (27%)	5/21 (24%)
First incidence (days)	699	580	658	600
Poly-3 test	P=0.006	P=0.014	P=0.004	P=0.002
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	10/50 (20%)	7/50 (14%)	11/48 (23%)	7/49 (14%)
Adjusted rate	21.2%	18.1%	24.8%	18.5%
Terminal rate	9/42 (21%)	3/13 (23%)	9/32 (28%)	4/21 (19%)
First incidence (days)	664	514	687	619
Poly-3 test	P=0.429N	P=0.462N	P=0.439	P=0.486N
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma or Carcinoma				
Overall rate	10/50 (20%)	7/50 (14%)	12/48 (25%)	8/49 (16%)
Adjusted rate	21.2%	18.1%	27.0%	21.1%
Terminal rate	9/42 (21%)	3/13 (23%)	9/32 (28%)	4/21 (19%)
First incidence (days)	664	514	687	619
Poly-3 test	P=0.532N	P=0.462N	P=0.344	P=0.598N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.4%	10.7%	2.2%	2.6%
Terminal rate	2/42 (5%)	1/13 (8%)	1/33 (3%)	0/21 (0%)
First incidence (days)	664	674	735 (T)	727
Poly-3 test	P=0.320N	P=0.378	P=0.315N	P=0.386N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.5%	10.7%	4.3%	2.6%
Terminal rate	3/42 (7%)	1/13 (8%)	1/33 (3%)	0/21 (0%)
First incidence (days)	664	674	672	727
Poly-3 test	P=0.202N	P=0.513	P=0.348N	P=0.251N
All Organs: Histiocytic Sarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.1%	7.9%	2.2%	7.7%
Terminal rate	1/42 (2%)	0/13 (0%)	0/33 (0%)	0/21 (0%)
First incidence (days)	735 (T)	533	691	512
Poly-3 test	P=0.154	P=0.235	P=0.757	P=0.245
All Organs: Malignant Lymphoma				
Overall rate	8/50 (16%)	4/50 (8%)	10/50 (20%)	13/50 (26%)
Adjusted rate	17.0%	10.6%	20.9%	33.2%
Terminal rate	7/42 (17%)	1/13 (8%)	5/33 (15%)	7/21 (33%)
First incidence (days)	699	617	547	600
Poly-3 test	P=0.053	P=0.299N	P=0.413	P=0.066

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
All Organs: Benign Neoplasms				
Overall rate	25/50 (50%)	24/50 (48%)	36/50 (72%)	26/50 (52%)
Adjusted rate	52.9%	59.6%	74.9%	61.7%
Terminal rate	23/42 (55%)	12/13 (92%)	25/33 (76%)	13/21 (62%)
First incidence (days)	664	514	617	496
Poly-3 test	P=0.332	P=0.337	P=0.018	P=0.263
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	25/50 (50%)	25/50 (50%)	27/50 (54%)
Adjusted rate	41.7%	58.8%	51.2%	62.6%
Terminal rate	15/42 (36%)	6/13 (46%)	14/33 (42%)	9/21 (43%)
First incidence (days)	626	489	547	512
Poly-3 test	P=0.033	P=0.075	P=0.234	P=0.035
All Organs: Benign or Malignant Neoplasms				
Overall rate	35/50 (70%)	37/50 (74%)	45/50 (90%)	40/50 (80%)
Adjusted rate	73.0%	82.7%	90.0%	89.0%
Terminal rate	30/42 (71%)	13/13 (100%)	28/33 (85%)	18/21 (86%)
First incidence (days)	626	489	547	496
Poly-3 test	P=0.045	P=0.180	P=0.025	P=0.038

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pituitary 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] Not applicable; no neoplasms in animal group
[e] Beneath the chamber control incidence are the P values associated with the trend test (the 0.03 mg/m^3 was excluded from 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**.

TABLE D4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Feed[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	0/50	0/50
Indium phosphide (inhalation)	3/50	1/50	4/50
Methacrylonitrile (gavage)	6/50	1/50	6/50
p-Nitrotoluene (feed)	5/50	1/50	6/50
Sodium nitrite (drinking water)	1/50	0/50	1/50
Overall Historical Incidence in Controls Given NTP-2000 Feed			
Total (%)	15/250 (6.0%)	3/250 (1.2%)	17/250 (6.8%)
Mean ± standard deviation	6.0% ± 5.1%	1.2% ± 1.1%	6.8% ± 5.6%
Range	0%-12%	0%-2%	0%-12%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]			
Acetonitrile	7/49	1/49	8/49
1,3-Butadiene	4/50	0/50	4/50
2-Butoxyethanol	7/50	0/50	7/50
Chloroprene	2/50	2/50	4/50
Cobalt sulfate heptahydrate	3/50	1/50	4/50
Furfuryl alcohol	2/50	4/50	6/50
Gallium arsenide	6/50	1/50	7/50
Glutaraldehyde	2/50	1/50	3/50
Hexachlorocyclopentadiene	4/48	3/48	7/48
Isobutene	2/49	4/49	6/49
Isobutyraldehyde	0/50	3/50	3/50
Molybdenum trioxide	1/50	2/50	3/50
Nitromethane	3/50	0/50	3/50
Ozone	4/50	2/50	6/50
Tetrahydrofuran	1/50	1/50	2/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed			
Total (%)	67/1,075 (6.2%)	43/1,075 (4.0%)	109/1,075 (10.1%)
Mean ± standard deviation	6.3% ± 3.7%	3.9% ± 3.2%	10.1% ± 3.6%
Range	0%-14%	0%-12%	4%-16%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE D4b
Historical Incidence of Liver Neoplasms in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocullular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence in Controls Given NTP-2000 Feed[a]				
p,p′-Dichlorodiphenyl sulfone (feed)	4/50	3/50	0/50	6/50
Indium phosphide (inhalation)	12/50	6/50	0/50	18/50
Methacrylonitrile (gavage)	9/50	2/50	0/50	10/50
p-Nitrotoluene (feed)	6/49	3/49	0/49	8/49
Sodium nitrite (drinking water)	9/50	2/50	0/50	10/50
Overall Historical Incidence in Controls Given NTP-2000 Feed				
Total (%)	40/249 (16.1%)	16/249 (6.4%)	0/249	52/249 (20.9%)
Mean ± standard deviation	16.1% ± 6.1%	6.4% ± 3.3%		20.9% ± 9.1%
Range	8%-24%	4%-12%		12%-36%
Historical Incidence in Chamber Controls Given NIH-07 Feed at Battelle Pacific Northwest Laboratories[b]				
Acetonitrile	4/49	7/49	0/49	9/49
1,3-Butadiene	11/49	4/49	0/49	15/49
2-Butoxyethanol	16/50	10/50	0/50	22/50
Chloroprene	17/50	4/50	0/50	20/50
Cobalt sulfate heptahydrate	8/50	12/50	0/50	18/50
Furfuryl alcohol	7/50	9/50	0/50	14/50
Gallium arsenide	11/50	12/50	0/50	21/50
Glutaraldehyde	11/50	4/50	0/50	14/50
Hexachlorocyclopentadiene	5/49	4/49	0/49	9/49
Isobutene	20/47	5/47	0/47	23/47
Isobutyraldehyde	9/49	6/49	0/49	12/49
Molybdenum trioxide	9/50	19/50	0/50	23/50
Nitromethane	14/50	10/50	0/50	19/50
Ozone	20/50	15/50	0/50	27/50
Tetrahydrofuran	12/50	6/50	0/50	17/50
Overall Historical Incidence in Chamber Controls Given NIH-07 Feed				
Total (%)	224/1,072 (20.9%)	168/1,072 (15.7%)	0/1,072	348/1,072 (32.5%)
Mean ± standard deviation	21.0% ± 9.8%	15.7% ± 8.1%		32.6% ± 10.5%
Range	8%-43%	8%-38%		18%-54%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Disposition Summary				
Animals initially in study	60	60	60	60
3-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1			1
Moribund	4	31	15	18
Natural deaths	3	6	2	10
Survivors				
Terminal sacrifice	42	13	33	21
Animals examined microscopically	60	60	60	60
3-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation		1 (10%)	2 (20%)	3 (30%)
Necrosis		1 (10%)		1 (10%)
Oval cell, hyperplasia			1 (10%)	2 (20%)
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy	5 (50%)			7 (70%)
Hematopoietic System				
Lymph node, bronchial	(9)	(8)	(10)	(10)
Foreign body		4 (50%)	9 (90%)	10 (100%)
Hyperplasia	1 (11%)	5 (63%)	10 (100%)	10 (100%)
Lymph node, mandibular	(7)			(8)
Hyperplasia	1 (14%)			
Lymph node, mediastinal	(4)	(5)	(6)	(6)
Hyperplasia			4 (67%)	3 (50%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	4 (40%)	9 (90%)	10 (100%)	10 (100%)
Respiratory System				
Larynx	(10)			(10)
Inflammation, suppurative	1 (10%)			
Squamous epithelium, hyperplasia	2 (20%)			3 (30%)
Lung	(10)	(10)	(10)	(10)
Foreign body		10 (100%)	10 (100%)	10 (100%)
Inflammation, chronic active		9 (90%)	9 (90%)	9 (90%)
Alveolus, proteinosis		10 (100%)	10 (100%)	10 (100%)
Special Senses System				
Lacrimal gland	(1)			
Inflammation, suppurative	1 (100%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
3-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)			(10)
Nephropathy	1 (10%)			4 (40%)
Systems Examined with No Lesions Observed				
Endocrine System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
2-Year Study				
Alimentary System				
Gallbladder	(46)	(45)	(48)	(43)
Degeneration, hyaline		1 (2%)		
Inflammation, suppurative	2 (4%)	2 (4%)	3 (6%)	
Intestine large, rectum	(47)	(49)	(50)	(49)
Inflammation, suppurative			1 (2%)	
Intestine small, jejunum	(46)	(49)	(49)	(44)
Peyer's patch, hyperplasia	1 (2%)			
Intestine small, ileum	(46)	(48)	(50)	(48)
Epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Peyer's patch, hyperplasia	2 (4%)			1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	2 (4%)
Basophilic focus	2 (4%)	2 (4%)		2 (4%)
Clear cell focus	2 (4%)			2 (4%)
Eosinophilic focus	6 (12%)	5 (10%)	4 (8%)	10 (20%)
Eosinophilic focus, multiple		4 (8%)		2 (4%)
Hematopoietic cell proliferation	3 (6%)	3 (6%)	4 (8%)	3 (6%)
Hyperplasia, lymphoid	1 (2%)			
Inflammation		1 (2%)	1 (2%)	
Karyomegaly	1 (2%)			
Necrosis	4 (8%)	3 (6%)	9 (18%)	3 (6%)
Tension lipidosis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic	1 (2%)		1 (2%)	
Bile duct, cyst	1 (2%)			
Bile duct, degeneration, hyaline				1 (2%)
Mesentery	(13)	(8)	(8)	(4)
Angiectasis	1 (8%)			
Artery, inflammation		4 (50%)	2 (25%)	1 (25%)
Fat, necrosis	10 (77%)	3 (38%)	6 (75%)	3 (75%)
Pancreas	(50)	(49)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	2 (4%)
Salivary glands	(49)	(50)	(50)	(50)
Inflammation			1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(49)	(50)	(50)
Erosion			2 (4%)	
Foreign body				1 (2%)
Inflammation, chronic				1 (2%)
Ulcer		2 (4%)		
Epithelium, hyperplasia	1 (2%)	4 (8%)	4 (8%)	3 (6%)
Stomach, glandular	(49)	(49)	(50)	(49)
Inflammation, suppurative	2 (4%)		1 (2%)	1 (2%)
Necrosis, focal				1 (2%)
Epithelium, hyperplasia			1 (2%)	
Tooth	(1)		(2)	
Inflammation			2 (100%)	
Malformation	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	45 (90%)	39 (78%)	46 (92%)	38 (76%)
Mineralization			2 (4%)	
Necrosis				1 (2%)
Artery, inflammation	1 (2%)	16 (32%)	11 (22%)	13 (26%)
Atrium, thrombosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Epicardium, inflammation	1 (2%)	5 (10%)		7 (14%)
Pericardium, inflammation		9 (18%)		4 (8%)
Valve, inflammation			1 (2%)	
Valve, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Amyloid deposition	2 (4%)	1 (2%)		2 (4%)
Degeneration, cystic	1 (2%)		1 (2%)	
Degeneration, focal				1 (2%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hyperplasia				1 (2%)
Hypertrophy	9 (18%)	7 (14%)	3 (6%)	10 (20%)
Capsule, hyperplasia		1 (2%)		
Adrenal medulla	(49)	(49)	(50)	(49)
Hyperplasia	4 (8%)	5 (10%)	2 (4%)	3 (6%)
Islets, pancreatic	(50)	(49)	(50)	(50)
Hyperplasia	2 (4%)		2 (4%)	1 (2%)
Parathyroid gland	(34)	(31)	(29)	(30)
Hyperplasia	1 (3%)			
Pituitary gland	(50)	(50)	(48)	(49)
Pars distalis, hyperplasia	16 (32%)	15 (30%)	21 (44%)	15 (31%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(49)	(50)	(49)
Inflammation, suppurative		2 (4%)	4 (8%)	1 (2%)
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	1 (2%)		2 (4%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
General Body System				
None				
Genital System				
Ovary	(47)	(46)	(44)	(47)
Angiectasis	2 (4%)	2 (4%)		1 (2%)
Cyst	12 (26%)	9 (20%)	11 (25%)	9 (19%)
Thrombosis		1 (2%)	1 (2%)	2 (4%)
Interstitial cell, hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Uterus	(50)	(49)	(50)	(50)
Angiectasis	1 (2%)	3 (6%)	3 (6%)	5 (10%)
Hydrometra	8 (16%)	8 (16%)	8 (16%)	5 (10%)
Hyperplasia, cystic	38 (76%)	31 (63%)	36 (72%)	32 (64%)
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Mineralization		1 (2%)		
Thrombosis			1 (2%)	2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis	2 (4%)		1 (2%)	
Hyperplasia	6 (12%)	13 (26%)	5 (10%)	7 (14%)
Lymph node	(1)	(5)	(6)	(8)
Iliac, angiectasis		1 (20%)		
Iliac, hematopoietic cell proliferation				1 (13%)
Iliac, hyperplasia		1 (20%)		1 (13%)
Lumbar, angiectasis			1 (17%)	
Lumbar, hemorrhage			1 (17%)	
Lumbar, hyperplasia		1 (20%)		1 (13%)
Lumbar, inflammation, chronic			1 (17%)	
Renal, angiectasis			1 (17%)	
Lymph node, bronchial	(36)	(50)	(48)	(50)
Foreign body		44 (88%)	33 (69%)	40 (80%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	5 (14%)	42 (84%)	31 (65%)	28 (56%)
Artery, inflammation		2 (4%)	1 (2%)	1 (2%)
Lymph node, mandibular	(36)	(36)	(43)	(42)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia				1 (2%)
Lymph node, mesenteric	(48)	(49)	(50)	(48)
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hyperplasia	8 (17%)	6 (12%)	7 (14%)	7 (15%)
Inflammation, chronic active	1 (2%)			
Lymph node, mediastinal	(42)	(48)	(46)	(49)
Foreign body		20 (42%)	7 (15%)	16 (33%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	2 (5%)	40 (83%)	11 (24%)	29 (59%)
Spleen	(50)	(49)	(50)	(49)
Hematopoietic cell proliferation	16 (32%)	36 (73%)	26 (52%)	21 (43%)
Hyperplasia, lymphoid	15 (30%)	3 (6%)	11 (22%)	14 (29%)
Metaplasia, osseous			1 (2%)	
Thymus	(47)	(46)	(42)	(42)
Hyperplasia, lymphoid		3 (7%)	3 (7%)	2 (5%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	4 (8%)	3 (6%)
Metaplasia, squamous		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Hyperplasia				1 (2%)
Inflammation, suppurative		2 (4%)		1 (2%)
Hair follicle, atrophy				1 (2%)
Subcutaneous tissue, angiectasis		1 (2%)		
Subcutaneous tissue, hemorrhage				1 (2%)
Subcutaneous tissue, inflammation, chronic		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, inflammation, chronic active	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Fibrous osteodystrophy	11 (22%)	14 (28%)	14 (28%)	16 (32%)
Inflammation, chronic		1 (2%)		
Maxilla, fracture				1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meninges, infiltration cellular, mononuclear cell	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	1 (2%)	2 (4%)
Squamous epithelium, hyperplasia	9 (18%)	17 (34%)	10 (20%)	15 (30%)
Lung	(50)	(50)	(50)	(50)
Foreign body		49 (98%)	35 (70%)	49 (98%)
Hematopoietic cell proliferation				1 (2%)
Hemorrhage	4 (8%)	3 (6%)	4 (8%)	4 (8%)
Inflammation, chronic active	2 (4%)	49 (98%)	45 (90%)	50 (100%)
Thrombosis			1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia		1 (2%)	1 (2%)	2 (4%)
Alveolus, infiltration cellular, histiocyte		2 (4%)	2 (4%)	3 (6%)
Alveolus, proteinosis		31 (62%)		8 (16%)
Artery, inflammation		1 (2%)	1 (2%)	
Artery, mediastinum, inflammation			1 (2%)	
Bronchiole, bronchus, degeneration, hyaline				2 (4%)
Interstitium, fibrosis		1 (2%)		2 (4%)
Mediastinum, inflammation, chronic active	1 (2%)			
Perivascular, infiltration cellular, mononuclear cell	1 (2%)			
Serosa, fibrosis		50 (100%)	47 (94%)	49 (98%)
Serosa, metaplasia, osseous		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Inflammation, suppurative	7 (14%)	7 (14%)	7 (14%)	2 (4%)
Olfactory epithelium, atrophy	6 (12%)	1 (2%)	3 (6%)	2 (4%)
Olfactory epithelium, degeneration, hyaline	3 (6%)	3 (6%)	10 (20%)	2 (4%)
Respiratory epithelium, degeneration, hyaline	28 (56%)	17 (34%)	27 (54%)	14 (28%)
Respiratory epithelium, hyperplasia			1 (2%)	
Pleura		(16)	(3)	(13)
Mesothelium, hyperplasia		16 (100%)	3 (100%)	13 (100%)
Trachea	(50)	(48)	(50)	(50)
Degeneration, hyaline				1 (2%)
Inflammation, suppurative	1 (2%)			
Special Senses System				
Eye			(1)	
Degeneration			1 (100%)	
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Cyst			1 (2%)	
Inflammation, chronic active	1 (2%)			
Metaplasia, osseous	2 (4%)	3 (6%)	4 (8%)	2 (4%)
Nephropathy	37 (74%)	30 (61%)	43 (86%)	36 (72%)
Artery, inflammation			1 (2%)	3 (6%)
Glomerulus, inflammation, chronic				1 (2%)
Renal tubule, karyomegaly			1 (2%)	
Urinary bladder	(48)	(49)	(49)	(48)
Angiectasis	2 (4%)	1 (2%)	3 (6%)	2 (4%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 14-week study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange (Tice *et al*., 1990) and coded. Slides were scanned to determine the frequency of micronuclei in 1,000 polychromatic erythrocytes (PCEs) and 1,000 normochromatic erythrocytes (NCEs) in up to 10 animals per exposure group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs and PCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single exposed group is less than or equal to 0.025 divided by the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results of the 14-week studies were accepted without repeat tests, because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

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 protocol. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different 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

Blood samples from female mice exposed to indium phosphide for 14 weeks by inhalation showed no significant increase in the frequency of micronucleated NCEs (Table E1). Also in female mice, analysis of micronucleus frequencies in PCEs in the 30 mg/m^3 group was consistent with the lack of effect seen in the NCE population. In male mice, the trend analysis showed a small but nonsignificant (P=0.054) concentration-related increase in the frequency of NCEs; a greater effect was observed in PCEs, where a significant increase (P=0.0108) in the number of micronuclei was observed in the 30 mg/m^3 group (Table E1). The PCE data for the male mice may indicate a recent induction of genetic damage that was rapidly eliminated or reduced in the mature NCE population, preventing the accumulation of damaged mature erythrocytes with repeated exposure. The fact that similar effects were not seen in female mice is reason to be cautious in interpreting the effects observed in male mice. In neither gender was the percentage of PCEs altered.

TABLE E1
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Indium Phosphide by Inhalation for 14 Weeks[a]

Exposure Concentration (mg/m^3)	Number of Mice with Erythrocytes Scored	Micronucleated Cells/1,000 Cells[b]		PCEs (%)
		NCEs[c]	PCEs	
Male				
Chamber Control	10	1.50 ± 0.27	1.70 ± 0.42	2.73
1	9	1.67 ± 0.37	—[d]	2.89
3	10	2.40 ± 0.43	—	2.56
10	9	1.89 ± 0.35	—	2.30
30	9	2.78 ± 0.22	4.11 ± 0.68*	2.46
		P=0.054[e]		
Female				
Chamber Control	10	1.10 ± 0.31	0.90 ± 0.35	2.52
1	10	1.30 ± 0.33	—	2.48
3	10	1.10 ± 0.31	—	2.24
10	10	1.30 ± 0.21	—	2.12
30	6	1.67 ± 0.55	1.33 ± 0.33	2.70
		P=0.177		

* Significantly different (P=0.0108) from the chamber control by pairwise comparison (ILS, 1990)
[a] Study was performed at Integrated Laboratory Systems, Inc. The detailed protocol is presented by MacGregor *et al.* (1990).
[b] NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Differences from the chamber control group were not significant by pairwise comparison, significant at P≤0.006 (ILS, 1990).
[e] Not scored
Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed Cochran-Armitage trend test, significant at P≤0.025 (ILS, 1990)

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male						
Hematology						
n						
Day 3	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Manual hematocrit (%)						
Day 3	47.2 ± 0.4	47.5 ± 0.4	47.4 ± 0.4	47.0 ± 0.4	47.5 ± 0.4	47.0 ± 0.4
Day 23	51.7 ± 0.3	53.2 ± 0.4	53.1 ± 0.6*	52.7 ± 0.3	53.5 ± 0.3**	53.0 ± 0.3
Week 14	47.0 ± 0.3	49.6 ± 0.2**	51.4 ± 0.4**	50.4 ± 0.3**	50.5 ± 0.5**	55.3 ± 1.6**
Automated hematocrit (%)						
Day 3	44.6 ± 0.3	45.1 ± 0.5	44.8 ± 0.4	44.4 ± 0.4	45.5 ± 0.5	45.0 ± 0.4
Day 23	49.5 ± 0.2	52.0 ± 0.4**	51.3 ± 0.5*	51.1 ± 0.2*	52.5 ± 0.4**	51.1 ± 0.2*
Week 14	45.4 ± 0.4	48.1 ± 0.3**	49.5 ± 0.4**	49.3 ± 0.5**	49.7 ± 0.7**	54.0 ± 1.7**
Hemoglobin (g/dL)						
Day 3	14.9 ± 0.1	15.3 ± 0.1	15.1 ± 0.2	14.9 ± 0.1	15.2 ± 0.1	15.0 ± 0.1
Day 23	16.7 ± 0.1	17.5 ± 0.1**	17.4 ± 0.1**	17.3 ± 0.1*	17.7 ± 0.2**	17.2 ± 0.1
Week 14	15.2 ± 0.2	16.3 ± 0.1**	17.0 ± 0.2**	16.6 ± 0.2**	16.5 ± 0.2**	16.6 ± 0.4**
Erythrocytes (10^6/µL)						
Day 3	7.06 ± 0.08	7.17 ± 0.10	7.17 ± 0.11	7.11 ± 0.08	7.25 ± 0.09	7.24 ± 0.10
Day 23	7.97 ± 0.05	8.41 ± 0.07**	8.27 ± 0.10**	8.25 ± 0.04**	8.48 ± 0.07**	8.29 ± 0.05**
Week 14	8.34 ± 0.09	8.83 ± 0.06**	9.25 ± 0.07**	9.37 ± 0.10**	9.75 ± 0.15**	10.52 ± 0.13**
Reticulocytes (10^6/µL)						
Day 3	0.35 ± 0.04	0.25 ± 0.02	0.26 ± 0.04	0.17 ± 0.02**	0.21 ± 0.02**	0.17 ± 0.03**
Day 23	0.13 ± 0.02	0.12 ± 0.02	0.12 ± 0.02	0.14 ± 0.02	0.13 ± 0.02	0.11 ± 0.01
Week 14	0.10 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.12 ± 0.02	0.44 ± 0.05**
Nucleated erythrocytes/100 leukocytes						
Day 3	1.20 ± 0.39	1.50 ± 0.45	0.70 ± 0.34	0.60 ± 0.27	1.70 ± 0.47	0.90 ± 0.41
Day 23	0.20 ± 0.13	0.20 ± 0.13	0.50 ± 0.22	0.20 ± 0.13	0.00 ± 0.00	0.30 ± 0.15
Week 14	0.80 ± 0.20	0.50 ± 0.17	0.40 ± 0.22	0.20 ± 0.20	0.30 ± 0.15	8.44 ± 3.36
Mean cell volume (fL)						
Day 3	63.1 ± 0.4	62.9 ± 0.3	62.6 ± 0.3	62.4 ± 0.4	62.8 ± 0.4	62.1 ± 0.3
Day 23	62.1 ± 0.3	61.9 ± 0.3	62.3 ± 0.3	62.0 ± 0.2	62.0 ± 0.3	61.7 ± 0.3
Week 14	54.3 ± 0.3	54.5 ± 0.2	53.6 ± 0.2	52.5 ± 0.2**	50.9 ± 0.2**	51.2 ± 1.0**
Mean cell hemoglobin (pg)						
Day 3	21.1 ± 0.1	21.3 ± 0.1	21.0 ± 0.2	21.0 ± 0.1	20.9 ± 0.2	20.8 ± 0.2
Day 23	21.0 ± 0.1	20.8 ± 0.1	21.0 ± 0.1	20.9 ± 0.1	20.8 ± 0.1	20.8 ± 0.2
Week 14	18.3 ± 0.1	18.5 ± 0.1	18.3 ± 0.1	17.7 ± 0.1**	16.9 ± 0.1**	15.8 ± 0.2**
Mean cell hemoglobin concentration (g/dL)						
Day 3	33.4 ± 0.2	33.9 ± 0.1	33.6 ± 0.2	33.6 ± 0.2	33.3 ± 0.2	33.4 ± 0.3
Day 23	33.8 ± 0.1	33.6 ± 0.2	33.9 ± 0.1	33.7 ± 0.1	33.6 ± 0.1	33.7 ± 0.1
Week 14	33.6 ± 0.2	34.0 ± 0.2	34.2 ± 0.2	33.6 ± 0.1	33.1 ± 0.2	30.8 ± 0.3**
Platelets (10^3/µL)						
Day 3	1,038.2 ± 16.4	1,008.0 ± 17.3	1,004.3 ± 17.4	1,059.2 ± 16.4	997.4 ± 25.3	1,019.3 ± 16.5
Day 23	755.8 ± 11.0	735.4 ± 12.2	698.5 ± 10.5**	730.4 ± 10.8*	659.2 ± 11.9**	660.2 ± 11.6**
Week 14	614.3 ± 7.4	620.3 ± 10.4	587.2 ± 8.6	571.2 ± 6.3	520.5 ± 11.5**	737.2 ± 34.7
Leukocytes (10^3/µL)						
Day 3	10.55 ± 0.54	11.78 ± 0.46	10.43 ± 0.75	10.22 ± 0.61	9.68 ± 0.47	10.19 ± 0.56
Day 23	12.24 ± 0.27	11.21 ± 0.26*	10.55 ± 0.40**	10.58 ± 0.42**	10.22 ± 0.43**	9.25 ± 0.42**
Week 14	5.87 ± 0.29	6.14 ± 0.32	6.63 ± 0.34	7.61 ± 0.44**	7.95 ± 0.27**	8.23 ± 0.62**

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male (continued)						
Hematology (continued)						
n						
Day 3	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Segmented neutrophils (10^3/µL)						
Day 3	1.02 ± 0.07	2.01 ± 0.23**	1.39 ± 0.08	1.10 ± 0.16	0.10 ± 0.10	1.30 ± 0.11
Day 23	1.27 ± 0.13	1.80 ± 0.19	1.86 ± 0.22	1.69 ± 0.13	1.88 ± 0.14*	1.82 ± 0.14
Week 14	1.22 ± 0.18	1.85 ± 0.13*	2.06 ± 0.13**	2.13 ± 0.14**	2.20 ± 0.13**	3.12 ± 0.31**
Bands (10^3/µL)						
Day 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/µL)						
Day 3	9.41 ± 0.51	9.65 ± 0.36	8.96 ± 0.72	8.96 ± 0.47	8.58 ± 0.42	8.75 ± 0.55
Day 23	10.89 ± 0.24	9.32 ± 0.26**	8.58 ± 0.33**	8.82 ± 0.37**	8.26 ± 0.36**	7.36 ± 0.38**
Week 14	4.45 ± 0.24	4.10 ± 0.24	4.40 ± 0.28	5.35 ± 0.43	5.59 ± 0.28*	4.90 ± 0.40
Monocytes (10^3/µL)						
Day 3	0.04 ± 0.02	0.11 ± 0.05	0.04 ± 0.03	0.13 ± 0.09	0.06 ± 0.03	0.07 ± 0.03
Day 23	0.04 ± 0.03	0.06 ± 0.02	0.05 ± 0.03	0.01 ± 0.01	0.04 ± 0.03	0.02 ± 0.01
Week 14	0.15 ± 0.04	0.12 ± 0.03	0.17 ± 0.04	0.11 ± 0.03	0.16 ± 0.03	0.20 ± 0.05
Basophils (10^3/µL)						
Day 3	0.013 ± 0.013	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)						
Day 3	0.06 ± 0.03	0.01 ± 0.01	0.04 ± 0.03	0.02 ± 0.02	0.04 ± 0.02	0.06 ± 0.02
Day 23	0.05 ± 0.03	0.03 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.05 ± 0.03
Week 14	0.05 ± 0.02	0.03 ± 0.01	0.00 ± 0.00	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Clinical Chemistry						
n						
Day 3	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Urea nitrogen (mg/dL)						
Day 3	14.9 ± 0.7	14.0 ± 0.3	14.2 ± 0.5	13.8 ± 0.6	12.4 ± 0.6*	14.3 ± 0.5
Day 23	14.7 ± 0.3	14.5 ± 0.4	15.1 ± 0.6	14.0 ± 0.5	14.6 ± 0.3	13.0 ± 0.4*
Week 14	18.9 ± 0.3	20.5 ± 1.0	17.9 ± 0.3	20.2 ± 0.3*	20.5 ± 0.6*	36.7 ± 3.9**
Creatinine (mg/dL)						
Day 3	0.65 ± 0.02	0.68 ± 0.03	0.66 ± 0.02	0.60 ± 0.02	0.61 ± 0.01	0.67 ± 0.03
Day 23	0.76 ± 0.02	0.76 ± 0.02	0.76 ± 0.02	0.74 ± 0.02	0.74 ± 0.03	0.72 ± 0.02
Week 14	0.92 ± 0.02	0.96 ± 0.02	0.93 ± 0.02	0.91 ± 0.02	0.87 ± 0.03	0.69 ± 0.03**
Total protein (g/dL)						
Day 3	6.0 ± 0.0	6.0 ± 0.1	6.1 ± 0.1	5.8 ± 0.0	6.1 ± 0.1	6.1 ± 0.1
Day 23	6.6 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	6.6 ± 0.0	6.6 ± 0.1	6.5 ± 0.1
Week 14	7.5 ± 0.1	7.4 ± 0.1	7.4 ± 0.5	7.4 ± 0.1	7.5 ± 0.1	5.7 ± 0.1**

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male (continued)						
Clinical chemistry (continued)						
n						
Day 3	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Albumin (g/dL)						
Day 3	3.7 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.6 ± 0.1	3.9 ± 0.1
Day 23	3.8 ± 0.0	3.7 ± 0.0	3.8 ± 0.1	3.8 ± 0.0	3.8 ± 0.1	3.8 ± 0.0
Week 14	4.4 ± 0.0	4.4 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	2.5 ± 0.1**
Globulin (g/dL)						
Day 3	2.4 ± 0.1	2.5 ± 0.2	2.5 ± 0.1	2.2 ± 0.1	2.5 ± 0.1	2.2 ± 0.1
Day 23	2.8 ± 0.0	2.9 ± 0.1	2.9 ± 0.1	2.8 ± 0.0	2.9 ± 0.1	2.8 ± 0.0
Week 14	3.1 ± 0.1	3.0 ± 0.1	3.0 ± 0.1	3.1 ± 0.1	3.2 ± 0.1	3.1 ± 0.1
A/G ratio						
Day 3	1.6 ± 0.2	1.5 ± 0.2	1.5 ± 0.1	1.8 ± 0.1	1.5 ± 0.1	1.8 ± 0.1
Day 23	1.4 ± 0.0	1.3 ± 0.0	1.3 ± 0.0	1.3 ± 0.0	1.4 ± 0.1	1.4 ± 0.0
Week 14	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.4 ± 0.0	0.8 ± 0.1**
Alanine aminotransferase (IU/L)						
Day 3	36 ± 1	36 ± 1	38 ± 1	35 ± 1	37 ± 1	37 ± 1
Day 23	35 ± 1	40 ± 2	41 ± 3	38 ± 1	40 ± 1*	40 ± 1
Week 14	53 ± 2	67 ± 4**	76 ± 7**	86 ± 7**	105 ± 7**	195 ± 26**
Creatine kinase (IU/L)						
Day 3	293 ± 33	358 ± 55	303 ± 25	282 ± 31	422 ± 98	352 ± 46
Day 23	375 ± 22	236 ± 17**	412 ± 55	284 ± 37*	328 ± 34	271 ± 18*
Week 14	122 ± 15	136 ± 10	149 ± 21	135 ± 13	96 ± 5	125 ± 9
Alkaline phosphatase (IU/L)						
Day 3	660 ± 12	661 ± 16	666 ± 14	642 ± 13	671 ± 14	656 ± 18
Day 23	437 ± 11	473 ± 11	455 ± 9	449 ± 12	464 ± 8	458 ± 8
Week 14	310 ± 6	328 ± 5	292 ± 6	311 ± 7	379 ± 10**	326 ± 15
Sorbitol dehydrogenase (IU/L)						
Day 3	14 ± 0	15 ± 1	14 ± 0	14 ± 0	14 ± 0	14 ± 1
Day 23	14 ± 1	17 ± 1	16 ± 1	18 ± 1	17 ± 1	16 ± 1
Week 14	21 ± 0	27 ± 2**	26 ± 2**	28 ± 2**	33 ± 2**	43 ± 4**
Bile acids (μmol/L)						
Day 3	30.7 ± 1.0	33.9 ± 3.0	33.9 ± 2.6	29.8 ± 1.9	36.7 ± 3.7	34.8 ± 3.2
Day 23	39.9 ± 7.7	32.7 ± 2.4	41.1 ± 6.4	29.5 ± 1.0	33.6 ± 1.7	33.4 ± 3.6
Week 14	23.4 ± 0.9	22.8 ± 0.6	23.4 ± 2.1	22.5 ± 0.7[b]	23.2 ± 0.7	41.3 ± 5.7
Urinalysis						
n	10	10	10	10	10	10
Creatinine (mg/dL)	34.70 ± 8.63	29.60 ± 2.43	28.30 ± 2.18	28.60 ± 1.84	23.40 ± 2.49	24.70 ± 3.36
Glucose (mg/mg creatinine)	0.17 ± 0.02	0.12 ± 0.01	0.11 ± 0.01*	0.14 ± 0.02	0.12 ± 0.01	0.11 ± 0.01*
Protein (mg/mg creatinine)	2.0 ± 0.1	1.9 ± 0.1	1.9 ± 0.0	1.9 ± 0.1	2.0 ± 0.0	1.9 ± 0.1
Alkaline phosphatase (U/mg creatinine)	0.44 ± 0.02	0.49 ± 0.02	0.53 ± 0.02	0.46 ± 0.02	0.53 ± 0.02	0.45 ± 0.02
Aspartate aminotransferase (mU/mg creatinine)	11.9 ± 1.3	15.0 ± 1.6	12.6 ± 1.0	11.9 ± 0.8	11.1 ± 1.3	12.0 ± 1.3

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male (continued)						
Urinalysis (continued)						
n	10	10	10	10	10	10
Lactate dehydrogenase (mU/mg creatinine)	59.5 ± 4.1	53.9 ± 4.1	56.8 ± 2.6	51.8 ± 3.7	57.5 ± 4.8	48.2 ± 5.5
γ-Glutamyltransferase (U/mg creatinine)	2.9 ± 0.1	3.0 ± 0.1	3.1 ± 0.1	3.1 ± 0.1	3.3 ± 0.1	2.9 ± 0.1
N-acetyl-β-D-glucosaminidase (mU/mg creatinine)	16.6 ± 0.6	17.6 ± 0.6	17.8 ± 0.9	16.0 ± 0.5	17.6 ± 0.6	17.4 ± 0.9
Volume (mL/16 hr)	24.2 ± 3.0	23.2 ± 2.1	22.1 ± 1.8	22.1 ± 1.6	26.6 ± 3.0	25.3 ± 2.7
Specific gravity	1.012 ± 0.003	1.010 ± 0.001	1.009 ± 0.001	1.009 ± 0.001	1.008 ± 0.001	1.008 ± 0.001
pH	7.00 ± 0.11	7.15 ± 0.13	7.15 ± 0.11	7.00 ± 0.08	7.22 ± 0.12	7.55 ± 0.14*
Female						
Hematology						
n	10	10	10	10	10	10
Manual hematocrit (%)						
Day 3	50.5 ± 0.6	48.9 ± 0.5	48.7 ± 0.6	48.6 ± 0.5	49.2 ± 0.7	49.3 ± 0.5
Day 23	50.6 ± 0.7	52.0 ± 0.2*	51.6 ± 0.3	51.9 ± 0.4	52.6 ± 0.4**	53.2 ± 0.3**
Week 14	46.0 ± 0.4	48.5 ± 0.4**	49.4 ± 0.5**	50.6 ± 0.5**	50.4 ± 0.4**	48.4 ± 1.4**
Automated hematocrit (%)						
Day 3	48.7 ± 0.7	46.7 ± 0.4	46.5 ± 0.7	46.2 ± 0.5*	47.3 ± 0.6	47.4 ± 0.5
Day 23	50.4 ± 0.5	52.1 ± 0.4**	52.0 ± 0.4*	51.8 ± 0.4*	52.8 ± 0.4**	53.2 ± 0.3**
Week 14	45.0 ± 0.3	47.3 ± 0.5**	48.0 ± 0.3**	49.7 ± 0.3**	49.3 ± 0.3**	48.4 ± 1.3**
Hemoglobin (g/dL)						
Day 3	16.2 ± 0.2	15.9 ± 0.1	15.7 ± 0.2	15.6 ± 0.2	16.0 ± 0.2	16.1 ± 0.2
Day 23	17.1 ± 0.2	17.7 ± 0.1*	17.8 ± 0.2*	17.7 ± 0.1*	18.0 ± 0.1**	18.1 ± 0.1**
Week 14	15.6 ± 0.1	16.5 ± 0.1	16.6 ± 0.2*	17.2 ± 0.1**	16.9 ± 0.1**	15.3 ± 0.3
Erythrocytes (10^6/μL)						
Day 3	7.84 ± 0.13	7.56 ± 0.08	7.65 ± 0.13	7.45 ± 0.13	7.69 ± 0.09	7.79 ± 0.10
Day 23	8.14 ± 0.09	8.34 ± 0.06	8.33 ± 0.06	8.33 ± 0.10	8.56 ± 0.09**	8.53 ± 0.08**
Week 14	7.77 ± 0.07	8.08 ± 0.08*	8.27 ± 0.06**	8.69 ± 0.06**	8.71 ± 0.07**	10.26 ± 0.19**
Reticulocytes (10^6/μL)						
Day 3	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.11 ± 0.01	0.09 ± 0.01
Day 23	0.07 ± 0.01	0.09 ± 0.02	0.11 ± 0.02	0.08 ± 0.01	0.06 ± 0.00	0.07 ± 0.01
Week 14	0.08 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.08 ± 0.01	0.10 ± 0.01	0.36 ± 0.09**
Nucleated erythrocytes/100 leukocytes						
Day 3	0.30 ± 0.15	0.20 ± 0.20	0.40 ± 0.22	0.60 ± 0.34	1.30 ± 0.50	0.30 ± 0.15
Day 23	0.10 ± 0.10	0.10 ± 0.10	0.40 ± 0.22	0.10 ± 0.10	0.20 ± 0.13	0.20 ± 0.13
Week 14	0.50 ± 0.40	0.00 ± 0.00	0.30 ± 0.15	0.10 ± 0.10	0.10 ± 0.10	5.80 ± 2.88*
Mean cell volume (fL)						
Day 3	62.1 ± 0.3	61.6 ± 0.2	60.9 ± 0.3*	61.9 ± 0.5	61.5 ± 0.3	60.9 ± 0.3*
Day 23	61.8 ± 0.4	62.5 ± 0.3	62.5 ± 0.3	62.2 ± 0.4	61.8 ± 0.3	62.4 ± 0.3
Week 14	58.1 ± 0.2	58.5 ± 0.2	57.9 ± 0.2	57.1 ± 0.2**	56.6 ± 0.4**	47.2 ± 0.7**

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Female (continued)						
Hematology (continued)						
n	10	10	10	10	10	10
Mean cell hemoglobin (pg)						
Day 3	20.7 ± 0.1	21.0 ± 0.1	20.6 ± 0.1	21.0 ± 0.2	20.8 ± 0.2	20.7 ± 0.1
Day 23	21.1 ± 0.1	21.2 ± 0.1	21.4 ± 0.1	21.3 ± 0.2	21.0 ± 0.1	21.1 ± 0.1
Week 14	20.1 ± 0.1	20.3 ± 0.1	20.1 ± 0.1	19.8 ± 0.1	19.4 ± 0.2**	14.9 ± 0.2**
Mean cell hemoglobin concentration (g/dL)						
Day 3	33.3 ± 0.2	34.0 ± 0.2	33.8 ± 0.2	33.8 ± 0.2	33.7 ± 0.2	34.0 ± 0.2
Day 23	33.9 ± 0.1	33.9 ± 0.1	34.2 ± 0.2	34.2 ± 0.1	34.0 ± 0.2	33.9 ± 0.1
Week 14	34.7 ± 0.2	34.8 ± 0.2	34.6 ± 0.1	34.6 ± 0.2	34.3 ± 0.2	31.7 ± 0.2**
Platelets (10^3/μL)						
Day 3	1022.2 ± 20.7	1023.6 ± 31.3	1025.6 ± 21.1	1008.1 ± 38.2	1011.0 ± 35.3	998.8 ± 31.8
Day 23	664.4 ± 34.6	698.5 ± 12.9	659.2 ± 20.8	713.7 ± 16.7	641.8 ± 18.4	665.4 ± 16.1
Week 14	566.3 ± 19.3	590.9 ± 11.2	556.4 ± 21.9	555.4 ± 14.3	559.4 ± 35.2	495.3 ± 30.5*
Leukocytes (10^3/μL)						
Day 3	13.08 ± 0.40	12.44 ± 0.45	11.35 ± 0.58*	11.37 ± 0.54*	10.56 ± 0.26**	12.22 ± 0.67*
Day 23	11.25 ± 0.63	10.81 ± 0.49	9.95 ± 0.40	10.69 ± 0.40	9.45 ± 0.39*	9.29 ± 0.36**
Week 14	6.73 ± 0.52	6.01 ± 0.29	6.41 ± 0.23	6.30 ± 0.34	7.88 ± 0.29*	9.45 ± 1.09*
Segmented neutrophils (10^3/μL)						
Day 3	0.92 ± 0.08	1.72 ± 0.15**	1.13 ± 0.17	1.07 ± 0.12	1.33 ± 0.15	1.32 ± 0.16
Day 23	1.03 ± 0.17	1.28 ± 0.13	1.17 ± 0.13	1.39 ± 0.12	1.09 ± 0.09	1.50 ± 0.17
Week 14	1.20 ± 0.17	1.68 ± 0.09*	1.53 ± 0.12	1.84 ± 0.13**	2.26 ± 0.19**	3.84 ± 0.63**
Bands (10^3/μL)						
Day 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)						
Day 3	12.00 ± 0.38	10.63 ± 0.47	10.15 ± 0.62*	10.25 ± 0.48**	9.11 ± 0.20**	10.74 ± 0.71**
Day 23	10.01 ± 0.63	9.13 ± 0.49	8.55 ± 0.40	9.02 ± 0.47	8.18 ± 0.40*	7.43 ± 0.40**
Week 14	5.39 ± 0.46	4.15 ± 0.26	4.71 ± 0.17	4.39 ± 0.24	5.43 ± 0.16	5.52 ± 0.55
Monocytes (10^3/μL)						
Day 3	0.08 ± 0.03	0.02 ± 0.02	0.01 ± 0.01	0.06 ± 0.04	0.05 ± 0.04	0.07 ± 0.04
Day 23	0.15 ± 0.04	0.34 ± 0.08	0.17 ± 0.04	0.24 ± 0.08	0.16 ± 0.04	0.27 ± 0.06
Week 14	0.09 ± 0.03	0.15 ± 0.03	0.12 ± 0.02	0.04 ± 0.02	0.13 ± 0.04	0.08 ± 0.04
Basophils (10^3/μL)						
Day 3	0.028 ± 0.019	0.039 ± 0.020	0.008 ± 0.008	0.000 ± 0.000	0.022 ± 0.022	0.009 ± 0.009
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)						
Day 3	0.07 ± 0.02	0.03 ± 0.02	0.05 ± 0.02	0.00 ± 0.00	0.06 ± 0.03	0.08 ± 0.04
Day 23	0.06 ± 0.03	0.06 ± 0.03	0.06 ± 0.02	0.04 ± 0.02	0.02 ± 0.01	0.09 ± 0.03
Week 14	0.06 ± 0.01	0.03 ± 0.01	0.05 ± 0.02	0.03 ± 0.01	0.05 ± 0.02	0.00 ± 0.00**

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 14-Week Inhalation Study of Indium Phosphide

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Female (continued)						
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 3	16.6 ± 0.5	17.6 ± 0.5	15.0 ± 0.6	15.5 ± 0.6	15.4 ± 0.8	16.2 ± 0.6
Day 23	13.8 ± 0.4	13.3 ± 0.3	13.5 ± 0.4	12.9 ± 0.3	13.4 ± 1.0	13.4 ± 0.5
Week 14	20.7 ± 0.6	20.2 ± 0.5	20.4 ± 0.5	18.7 ± 0.4	19.0 ± 0.8	31.2 ± 2.2*
Creatinine (mg/dL)						
Day 3	0.62 ± 0.01	0.60 ± 0.00	0.61 ± 0.02	0.60 ± 0.00	0.59 ± 0.02[b]	0.62 ± 0.01
Day 23	0.70 ± 0.03	0.72 ± 0.02	0.69 ± 0.01	0.68 ± 0.01	0.62 ± 0.01*	0.68 ± 0.01
Week 14	0.89 ± 0.03	0.92 ± 0.03	0.87 ± 0.03	0.82 ± 0.03	0.82 ± 0.01	0.66 ± 0.02**
Total protein (g/dL)						
Day 3	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.0	6.0 ± 0.1
Day 23	6.2 ± 0.1	6.2 ± 0.0	6.3 ± 0.1	6.3 ± 0.1	6.2 ± 0.1	6.4 ± 0.1*
Week 14	7.5 ± 0.1	7.4 ± 0.1	7.5 ± 0.1	7.3 ± 0.1	7.1 ± 0.1*	6.1 ± 0.1**
Albumin (g/dL)						
Day 3	3.8 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	3.9 ± 0.0	3.8 ± 0.1	3.8 ± 0.1
Day 23	3.7 ± 0.0	3.8 ± 0.0	3.8 ± 0.1	3.9 ± 0.1	3.8 ± 0.0	3.8 ± 0.0
Week 14	4.3 ± 0.1	4.2 ± 0.1	4.4 ± 0.1	4.2 ± 0.1	4.1 ± 0.1	3.1 ± 0.1**
Globulin (g/dL)						
Day 3	2.2 ± 0.1	2.2 ± 0.1	2.3 ± 0.1	2.1 ± 0.0	2.2 ± 0.1	2.2 ± 0.1
Day 23	2.4 ± 0.1	2.5 ± 0.1	2.5 ± 0.0	2.4 ± 0.1	2.4 ± 0.1	2.6 ± 0.1
Week 14	3.2 ± 0.1	3.2 ± 0.1	3.1 ± 0.1	3.1 ± 0.1	3.0 ± 0.1	3.1 ± 0.1
A/G ratio						
Day 3	1.8 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	1.7 ± 0.1	1.8 ± 0.1
Day 23	1.5 ± 0.0	1.6 ± 0.0	1.5 ± 0.0	1.6 ± 0.1	1.6 ± 0.0	1.5 ± 0.1
Week 14	1.4 ± 0.1	1.3 ± 0.0	1.4 ± 0.0	1.4 ± 0.1	1.4 ± 0.0	1.0 ± 0.1**
Alanine aminotransferase (IU/L)						
Day 3	35 ± 1	36 ± 2	35 ± 1	35 ± 1	36 ± 1	33 ± 1
Day 23	28 ± 1	28 ± 2	32 ± 2	28 ± 1	30 ± 1	36 ± 2**
Week 14	49 ± 2[b]	49 ± 3	51 ± 2	64 ± 5*	84 ± 8**	289 ± 68**
Alkaline phosphatase (IU/L)						
Day 3	539 ± 15	536 ± 9	544 ± 9	550 ± 18	539 ± 15	521 ± 19
Day 23	321 ± 12	330 ± 8	330 ± 8	315 ± 5	330 ± 6	360 ± 12*
Week 14	277 ± 7	273 ± 10	284 ± 8	267 ± 12	365 ± 14**	408 ± 21**
Creatine kinase (IU/L)						
Day 3	359 ± 64	343 ± 31	280 ± 45	306 ± 57	225 ± 20**[b]	242 ± 27*
Day 23	318 ± 35	305 ± 20	402 ± 107	305 ± 10	239 ± 27	308 ± 17
Week 14	185 ± 39	204 ± 37	128 ± 27	130 ± 23	106 ± 9	196 ± 20
Sorbitol deyhdrogenase (IU/L)						
Day 3	15 ± 1	14 ± 0	14 ± 0	15 ± 0	14 ± 0	15 ± 0
Day 23	17 ± 1	16 ± 1	17 ± 1	17 ± 1	18 ± 1	18 ± 1
Week 14	19 ± 1[b]	20 ± 1	20 ± 1	22 ± 2	30 ± 3*	43 ± 7**
Bile acids (µmol/L)						
Day 3	21.0 ± 0.9	25.4 ± 2.4	24.5 ± 3.3	24.4 ± 2.2	22.5 ± 1.8[b]	22.7 ± 1.4
Day 23	27.0 ± 3.8	26.2 ± 5.8	28.4 ± 5.4	28.0 ± 5.8	27.0 ± 2.8	29.8 ± 3.9
Week 14	34.4 ± 7.2	23.2 ± 3.1	26.2 ± 5.6	19.9 ± 2.0	19.2 ± 1.0	30.6 ± 3.2

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE F2
Hematology and Clinical Chemistry Data for Rats at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
n	10	10	10	10
Male				
Hematology				
Manual hematocrit (%)	44.4 ± 0.4	46.4 ± 0.4**	47.4 ± 0.4**	48.8 ± 0.3**
Automated hematocrit (%)	44.4 ± 0.3	46.4 ± 0.4**	47.7 ± 0.5**	48.8 ± 0.3**
Hemoglobin (g/dL)	14.3 ± 0.1	15.1 ± 0.1**	15.4 ± 0.1**	15.7 ± 0.1**
Erythrocytes (10^6/µL)	7.98 ± 0.07	8.33 ± 0.08*	8.49 ± 0.08**	8.71 ± 0.06**
Reticulocytes (10^6/µL)	0.14 ± 0.01	0.17 ± 0.01	0.14 ± 0.01	0.15 ± 0.01
Nucleated erythrocytes (10^3/µL)	6.60 ± 0.34	7.10 ± 0.24	7.08 ± 0.23	6.43 ± 0.23
Mean cell volume (fL)	55.7 ± 0.3	55.8 ± 0.2	56.3 ± 0.2	56.2 ± 0.3
Mean cell hemoglobin (pg)	18.0 ± 0.1	18.1 ± 0.1	18.2 ± 0.1	18.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.3 ± 0.2	32.5 ± 0.2	32.3 ± 0.2	32.3 ± 0.2
Platelets (10^3/µL)	534.1 ± 11.3	560.7 ± 9.9	551.3 ± 11.2	549.8 ± 7.9
Leukocytes (10^3/µL)	6.60 ± 0.34	7.10 ± 0.24	7.08 ± 0.23	6.43 ± 0.23
Segmented neutrophils (10^3/µL)	1.03 ± 0.05	1.28 ± 0.08*	1.31 ± 0.07*	1.20 ± 0.06
Lymphocytes (10^3/µL)	5.25 ± 0.32	5.45 ± 0.19	5.40 ± 0.21	4.87 ± 0.21
Monocytes (10^3/µL)	0.22 ± 0.03	0.29 ± 0.03	0.35 ± 0.09	0.25 ± 0.03
Basophils (10^3/µL)	0.068 ± 0.012	0.050 ± 0.006	0.064 ± 0.012	0.078 ± 0.015
Eosinophils (10^3/µL)	0.03 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.03 ± 0.01
Clinical Chemistry				
Total iron binding capacity (µg/dL)	539.2 ± 9.3	555.4 ± 5.8	555.2 ± 6.8	562.2 ± 5.9
Unbound iron binding capacity (µg/dL)	407.0 ± 9.1	409.8 ± 8.6	407.1 ± 7.0	413.2 ± 6.3
Iron (µg/dL)	132.2 ± 2.6	145.6 ± 6.7	148.1 ± 4.0*	149.0 ± 3.9*

TABLE F2
Hematology and Clinical Chemistry Data for Rats at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
n	10	10	10	10
Female				
Hematology				
Manual hematocrit (%)	45.3 ± 0.3	46.3 ± 0.4	47.0 ± 0.4**	48.0 ± 0.4**
Automated hematocrit (%)	44.9 ± 0.4	46.3 ± 0.4*	47.1 ± 0.5**	47.9 ± 0.2**
Hemoglobin (g/dL)	14.9 ± 0.1	15.3 ± 0.1*	15.4 ± 0.1**	15.8 ± 0.1**
Erythrocytes (10^6/µL)	7.71 ± 0.07	7.89 ± 0.06	7.97 ± 0.07*	8.15 ± 0.02**
Reticulocytes (10^6/µL)	0.14 ± 0.01	0.15 ± 0.01	0.14 ± 0.01	0.16 ± 0.01
Nucleated erythrocytes (10^3/µL)	7.09 ± 0.36	6.68 ± 0.43	6.22 ± 0.32	6.34 ± 0.31
Mean cell volume (fL)	58.3 ± 0.2	58.6 ± 0.2	59.2 ± 0.5	58.8 ± 0.1
Mean cell hemoglobin (pg)	19.3 ± 0.1	19.4 ± 0.1	19.4 ± 0.1	19.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.1 ± 0.1	32.9 ± 0.3	32.7 ± 0.2	33.0 ± 0.2
Platelets (10^3/µL)	563.6 ± 6.7	562.7 ± 10.5	538.7 ± 8.1	569.6 ± 11.5
Leukocytes (10^3/µL)	7.09 ± 0.36	6.68 ± 0.43	6.22 ± 0.32	6.34 ± 0.31
Segmented neutrophils (10^3/µL)	1.20 ± 0.10	1.46 ± 0.10	1.40 ± 0.07	1.31 ± 0.10
Lymphocytes (10^3/µL)	5.45 ± 0.23	4.81 ± 0.31	4.43 ± 0.27*	4.66 ± 0.20
Monocytes (10^3/µL)	0.37 ± 0.04	0.34 ± 0.05	0.32 ± 0.04	0.31 ± 0.03
Basophils (10^3/µL)	0.041 ± 0.006	0.039 ± 0.008	0.047 ± 0.004	0.032 ± 0.005
Eosinophils (10^3/µL)	0.03 ± 0.00	0.03 ± 0.00	0.02 ± 0.00	0.03 ± 0.00
Clinical Chemistry				
Total iron binding capacity (µg/dL)	523.2 ± 5.0	512.2 ± 5.7	532.0 ± 9.4	529.7 ± 7.9
Unbound iron binding capacity (µg/dL)	308.5 ± 7.6	308.2 ± 15.0	315.1 ± 15.3	318.5 ± 9.1
Iron (µg/dL)	214.7 ± 7.3	204.0 ± 10.7	216.9 ± 15.6	211.2 ± 11.0

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE F3
Hematology Data for Mice in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3
Male					
n	10	9	10	9	9
Manual hematocrit (%)	49.3 ± 0.3	49.7 ± 0.5	51.1 ± 0.4**	52.8 ± 0.7**	60.8 ± 0.9**
Automated hematocrit (%)	49.2 ± 0.3	49.1 ± 0.8	50.8 ± 0.5*	52.3 ± 0.7**	61.0 ± 1.0**
Hemoglobin (g/dL)	15.8 ± 0.1	15.5 ± 0.2	16.0 ± 0.1	16.6 ± 0.2**	18.9 ± 0.3**
Erythrocytes (10^6/μL)	9.49 ± 0.12	9.97 ± 0.14*	10.34 ± 0.09**	11.12 ± 0.13**	13.88 ± 0.21**
Reticulocytes (10^6/μL)	0.02 ± 0.00	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.00	0.04 ± 0.01
Nucleated erythrocytes/ 100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	51.8 ± 0.5	49.3 ± 0.2**	49.2 ± 0.3**	47.0 ± 0.2**	43.9 ± 0.3**
Mean cell hemoglobin (pg)	16.6 ± 0.2	15.6 ± 0.1**	15.5 ± 0.1**	14.9 ± 0.1**	13.6 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.0 ± 0.1	31.6 ± 0.2	31.5 ± 0.2*	31.8 ± 0.1	31.1 ± 0.2**
Platelets (10^3/μL)	751.0 ± 13.5	974.1 ± 35.1	865.7 ± 23.5	711.1 ± 34.4	656.8 ± 23.7
Leukocytes (10^3/μL)	3.75 ± 0.29	6.53 ± 0.30**	4.83 ± 0.41	4.19 ± 0.31	4.92 ± 0.29
Segmented neutrophils (10^3/μL)	2.79 ± 0.25	5.36 ± 0.28**	3.33 ± 0.38	2.97 ± 0.26	3.09 ± 0.27
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	0.87 ± 0.09	1.04 ± 0.14	1.33 ± 0.05**	1.10 ± 0.06**	1.74 ± 0.22**
Monocytes (10^3/μL)	0.08 ± 0.03	0.12 ± 0.04	0.17 ± 0.04	0.12 ± 0.04	0.10 ± 0.02
Basophils	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Female					
n	10	10	10	10	6
Manual hematocrit (%)	50.0 ± 0.5	48.8 ± 0.4	49.4 ± 0.5	52.0 ± 0.6	60.2 ± 1.2**
Automated hematocrit (%)	49.3 ± 0.7	47.3 ± 0.4	48.9 ± 0.4	51.0 ± 0.6	60.1 ± 1.4**
Hemoglobin (g/dL)	15.8 ± 0.2	15.2 ± 0.1	15.5 ± 0.1	16.4 ± 0.2	18.6 ± 0.4**
Erythrocytes (10^6/μL)	9.64 ± 0.14	9.58 ± 0.11	10.01 ± 0.11	10.72 ± 0.11**	13.40 ± 0.36**
Reticulocytes (10^6/μL)	0.02 ± 0.00	0.02 ± 0.01	0.02 ± 0.00	0.03 ± 0.01	0.05 ± 0.01*
Nucleated erythrocytes/ 100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	51.2 ± 0.1	49.2 ± 0.3**	48.8 ± 0.2**	47.6 ± 0.3**	45.0 ± 0.3**
Mean cell hemoglobin (pg)	16.4 ± 0.1	15.9 ± 0.2**	15.5 ± 0.1**	15.3 ± 0.1**	13.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.1 ± 0.2	32.1 ± 0.2	31.7 ± 0.1*	32.2 ± 0.1	30.9 ± 0.0**
Platelets (10^3/μL)	782.7 ± 29.4	915.7 ± 24.9	833.5 ± 30.1	679.5 ± 14.4*	613.0 ± 12.7**
Leukocytes (10^3/μL)	2.44 ± 0.13	6.62 ± 1.63**	2.78 ± 0.19	2.86 ± 0.32	4.25 ± 0.83*
Segmented neutrophils (10^3/μL)	0.26 ± 0.03	2.68 ± 0.74**	0.90 ± 0.11**	0.74 ± 0.13**	2.08 ± 0.51**
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	2.16 ± 0.12	3.76 ± 0.84	1.83 ± 0.13	2.06 ± 0.19	2.12 ± 0.36
Monocytes (10^3/μL)	0.01 ± 0.01	0.17 ± 0.12	0.04 ± 0.01	0.05 ± 0.02	0.02 ± 0.01
Basophils	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.01 ± 0.00	0.01 ± 0.01	0.01 ± 0.00	0.00 ± 0.00	0.02 ± 0.02

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data; no data were available for the 100 mg/m^3 group due to 100% mortality.

TABLE F4
Hematology and Clinical Chemistry Data for Mice at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
Male				
Hematology				
n	10	10	10	10
Manual hematocrit (%)	47.4 ± 0.4	47.6 ± 0.3	47.0 ± 0.4	46.6 ± 0.3
Automated hematocrit (%)	47.8 ± 0.5	47.6 ± 0.4	47.2 ± 0.5	46.8 ± 0.4
Hemoglobin (g/dL)	15.6 ± 0.1	15.5 ± 0.1	15.2 ± 0.1	15.2 ± 0.1
Erythrocytes (10^6/µL)	9.63 ± 0.10	9.69 ± 0.08	9.83 ± 0.05	9.90 ± 0.07*
Reticulocytes (10^6/µL)	0.23 ± 0.01	0.23 ± 0.01	0.28 ± 0.03	0.31 ± 0.04
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	49.5 ± 0.2	49.1 ± 0.3	48.1 ± 0.5**	47.1 ± 0.3**
Mean cell hemoglobin (pg)	16.2 ± 0.1	16.0 ± 0.1	15.4 ± 0.1**	15.3 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.6 ± 0.2	32.6 ± 0.1	32.1 ± 0.2	32.4 ± 0.1
Platelets (10^3/µL)	766.1 ± 12.6	846.9 ± 30.3	887.5 ± 49.4*	1,019.1 ± 55.3**
Leukocytes (10^3/µL)	4.95 ± 0.36	5.02 ± 0.44	5.24 ± 0.56	6.66 ± 0.62
Segmented neutrophils (10^3/µL)	3.35 ± 0.31	3.34 ± 0.31	3.57 ± 0.63	4.65 ± 0.50
Bands (10^3/µL)	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Lymphocytes (10^3/µL)	1.55 ± 0.13	1.64 ± 0.15	1.58 ± 0.22	1.92 ± 0.21
Monocytes (10^3/µL)	0.04 ± 0.02	0.02 ± 0.01	0.06 ± 0.02	0.04 ± 0.03
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.01**
Clinical Chemistry				
n	10	10	10	9
Total iron binding capacity (µg/dL)	431.4 ± 55.0	417.4 ± 34.6	455.6 ± 44.1	464.0 ± 39.8
Unbound iron binding capacity (µg/dL)	178.4 ± 7.4	217.2 ± 20.2	224.6 ± 34.8	271.3 ± 14.0*
Iron (µg/dL)	253.0 ± 54.2	200.2 ± 30.5	231.0 ± 44.3	192.7 ± 48.7

TABLE F4
Hematology and Clinical Chemistry Data for Mice at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
Female				
Hematology				
n	10	10	10	10
Manual hematocrit (%)	48.8 ± 0.3	48.6 ± 0.4	47.6 ± 0.7	46.1 ± 0.5**
Automated hematocrit (%)	49.4 ± 0.4	48.9 ± 0.5	48.3 ± 0.8	46.0 ± 0.6**
Hemoglobin (g/dL)	16.2 ± 0.1	16.0 ± 0.1	15.6 ± 0.2*	15.0 ± 0.2**
Erythrocytes (10^6/µL)	9.81 ± 0.06	9.85 ± 0.08	10.05 ± 0.16	9.64 ± 0.09
Reticulocytes (10^6/µL)	0.21 ± 0.01	0.25 ± 0.02	0.24 ± 0.03	0.30 ± 0.04
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	50.4 ± 0.2	49.5 ± 0.3*	48.0 ± 0.4**	47.6 ± 0.4**
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.2 ± 0.1*	15.6 ± 0.1**	15.6 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	32.8 ± 0.1	32.6 ± 0.1	32.4 ± 0.2	32.7 ± 0.1
Platelets (10^3/µL)	730.4 ± 12.2	777.8 ± 43.2	903.4 ± 53.2**	945.0 ± 46.8**
Leukocytes (10^3/µL)	2.50 ± 0.14	3.23 ± 0.24*	4.73 ± 0.57**	6.58 ± 1.00**
Segmented neutrophils (10^3/µL)	0.28 ± 0.05	0.63 ± 0.14*	1.97 ± 0.53**	3.00 ± 0.79**
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02	0.01 ± 0.01
Lymphocytes (10^3/µL)	2.20 ± 0.14	2.52 ± 0.14	2.64 ± 0.19	3.38 ± 0.32**
Monocytes (10^3/µL)	0.02 ± 0.01	0.07 ± 0.03	0.11 ± 0.05	0.18 ± 0.06*
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)	0.00 ± 0.00	0.01 ± 0.00	0.01 ± 0.01	0.02 ± 0.01
Clinical Chemistry				
n	10	10	10	10
Total iron binding capacity (µg/dL)	420.4 ± 5.2	436.8 ± 6.6	480.6 ± 13.2**	564.6 ± 44.6**
Unbound iron binding capacity (µg/dL)	210.0 ± 7.6	277.7 ± 19.2**	279.2 ± 25.5*	360.8 ± 30.5**
Iron (µg/dL)	210.4 ± 8.5	159.1 ± 13.2	201.4 ± 24.7	203.8 ± 64.7

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

APPENDIX G
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
Male						
n	10	10	10	10	10	9
Necropsy body wt	365 ± 6	341 ± 7**	322 ± 5**	331 ± 4**	325 ± 9**	172 ± 6**
Heart						
Absolute	1.025 ± 0.017	0.977 ± 0.017	0.960 ± 0.022	0.974 ± 0.015	0.999 ± 0.021	1.003 ± 0.026
Relative	0.281 ± 0.004	0.287 ± 0.004	0.298 ± 0.005	0.294 ± 0.003	0.308 ± 0.006*	0.587 ± 0.018**
R. Kidney						
Absolute	1.147 ± 0.018	1.093 ± 0.025	1.042 ± 0.021*	1.068 ± 0.016*	1.053 ± 0.027**	0.957 ± 0.036**
Relative	0.315 ± 0.006	0.321 ± 0.005	0.323 ± 0.005	0.323 ± 0.004	0.324 ± 0.005	0.561 ± 0.028**
Liver						
Absolute	11.897 ± 0.211	11.135 ± 0.326	10.504 ± 0.364*	11.219 ± 0.297*	10.642 ± 0.298**	6.843 ± 0.258**
Relative	3.267 ± 0.056	3.267 ± 0.056	3.256 ± 0.091	3.390 ± 0.092	3.274 ± 0.042	3.992 ± 0.131**
Lung						
Absolute	1.969 ± 0.130	5.326 ± 0.145**	6.451 ± 0.169**	6.341 ± 0.113**	7.159 ± 0.190**	5.080 ± 0.162**
Relative	0.540 ± 0.034	1.563 ± 0.023**	2.001 ± 0.045**	1.914 ± 0.023**	2.205 ± 0.041**	2.957 ± 0.039**
R. Testis						
Absolute	1.434 ± 0.023	1.441 ± 0.023	1.430 ± 0.031	1.429 ± 0.010	1.436 ± 0.029	0.762 ± 0.070**
Relative	0.394 ± 0.007	0.424 ± 0.004	0.444 ± 0.008*	0.432 ± 0.005*	0.443 ± 0.008*	0.437 ± 0.028*
Thymus						
Absolute	0.319 ± 0.017	0.281 ± 0.017	0.321 ± 0.021	0.330 ± 0.016	0.301 ± 0.017	0.146 ± 0.016**
Relative	0.087 ± 0.004	0.083 ± 0.005	0.100 ± 0.007	0.099 ± 0.005	0.093 ± 0.005	0.084 ± 0.007
Female						
n	10	10	10	10	10	10
Necropsy body wt	206 ± 3	205 ± 3	199 ± 4	206 ± 3	196 ± 5	117 ± 3**
Heart						
Absolute	0.658 ± 0.011	0.655 ± 0.010	0.662 ± 0.010	0.722 ± 0.012**	0.718 ± 0.021**	0.788 ± 0.017**
Relative	0.319 ± 0.003	0.319 ± 0.003	0.334 ± 0.007	0.351 ± 0.007	0.367 ± 0.008**	0.679 ± 0.026**
R. Kidney						
Absolute	0.684 ± 0.014	0.661 ± 0.010	0.672 ± 0.011	0.689 ± 0.009	0.664 ± 0.021	0.617 ± 0.019**
Relative	0.332 ± 0.006	0.323 ± 0.005	0.338 ± 0.006	0.334 ± 0.003	0.339 ± 0.006	0.530 ± 0.018**
Liver						
Absolute	6.341 ± 0.146	6.168 ± 0.126	6.212 ± 0.254	6.642 ± 0.179	6.380 ± 0.231	4.372 ± 0.133**
Relative	3.074 ± 0.059	3.005 ± 0.031	3.113 ± 0.074	3.219 ± 0.062	3.252 ± 0.060	3.742 ± 0.071**
Lung						
Absolute	1.220 ± 0.051	3.441 ± 0.104**	3.876 ± 0.089**	4.621 ± 0.099**	5.303 ± 0.200**	3.899 ± 0.123**
Relative	0.590 ± 0.019	1.678 ± 0.047**	1.953 ± 0.052**	2.246 ± 0.063**	2.709 ± 0.080**	3.334 ± 0.063**
Thymus						
Absolute	0.241 ± 0.012	0.233 ± 0.016	0.248 ± 0.016	0.244 ± 0.015	0.242 ± 0.008	0.097 ± 0.009**
Relative	0.117 ± 0.005	0.113 ± 0.007	0.125 ± 0.007	0.117 ± 0.006	0.124 ± 0.006	0.082 ± 0.007**

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
n	10	10	10	10
Male				
Necropsy body wt	326 ± 8	332 ± 5	328 ± 7	323 ± 6
Heart				
Absolute	1.089 ± 0.181	0.943 ± 0.017	1.074 ± 0.177	0.908 ± 0.018
Relative	0.336 ± 0.057	0.284 ± 0.003	0.327 ± 0.052	0.281 ± 0.003
R. Kidney				
Absolute	1.075 ± 0.178	0.934 ± 0.023	1.088 ± 0.179	0.918 ± 0.026
Relative	0.331 ± 0.056	0.281 ± 0.004	0.331 ± 0.053	0.284 ± 0.005
Liver				
Absolute	10.453 ± 0.381	10.537 ± 0.205	10.359 ± 0.292	10.576 ± 0.349
Relative	3.205 ± 0.066	3.174 ± 0.050	3.154 ± 0.057	3.276 ± 0.083
Lung				
Absolute	1.825 ± 0.203	2.227 ± 0.058	2.835 ± 0.191**	3.843 ± 0.098**
Relative	0.558 ± 0.061	0.670 ± 0.014	0.863 ± 0.054**	1.190 ± 0.019**
R. Testis				
Absolute	1.514 ± 0.182	1.362 ± 0.024	1.550 ± 0.185	1.351 ± 0.019
Relative	0.467 ± 0.058	0.410 ± 0.006	0.472 ± 0.055	0.419 ± 0.006
Thymus				
Absolute	0.489 ± 0.180	0.313 ± 0.013	0.505 ± 0.173	0.328 ± 0.014
Relative	0.152 ± 0.057	0.094 ± 0.003	0.153 ± 0.052	0.101 ± 0.003
Female				
Necropsy body wt	189 ± 4	184 ± 5	191 ± 3	179 ± 5
Heart				
Absolute	0.595 ± 0.010	0.584 ± 0.016	0.595 ± 0.012	0.597 ± 0.021
Relative	0.315 ± 0.005	0.317 ± 0.005	0.312 ± 0.003	0.334 ± 0.006*
R. Kidney				
Absolute	0.568 ± 0.013	0.553 ± 0.014	0.574 ± 0.011	0.546 ± 0.017
Relative	0.301 ± 0.004	0.300 ± 0.003	0.301 ± 0.003	0.306 ± 0.005
Liver				
Absolute	5.525 ± 0.131	5.136 ± 0.162	5.197 ± 0.182	5.004 ± 0.173
Relative	2.926 ± 0.046	2.788 ± 0.046	2.722 ± 0.057**	2.798 ± 0.025
Lung				
Absolute	1.107 ± 0.036	1.352 ± 0.037**	1.703 ± 0.052**	2.334 ± 0.089**
Relative	0.588 ± 0.021	0.735 ± 0.013**	0.896 ± 0.030**	1.308 ± 0.036 **
Thymus				
Absolute	0.235 ± 0.013	0.235 ± 0.011	0.254 ± 0.012	0.259 ± 0.008
Relative	0.125 ± 0.007	0.127 ± 0.004	0.133 ± 0.004	0.145 ± 0.005**

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3
Male					
n	10	10	10	10	9
Necropsy body wt	37.8 ± 0.6	37.4 ± 0.6	35.6 ± 0.6*	32.8 ± 0.5**	24.3 ± 0.8**
Heart					
Absolute	0.164 ± 0.004	0.170 ± 0.006	0.167 ± 0.006	0.168 ± 0.006	0.141 ± 0.005*
Relative	0.435 ± 0.013	0.457 ± 0.022	0.469 ± 0.014	0.513 ± 0.022**	0.582 ± 0.020**
R. Kidney					
Absolute	0.309 ± 0.010	0.300 ± 0.008	0.298 ± 0.007	0.297 ± 0.007	0.237 ± 0.010**
Relative	0.816 ± 0.017	0.803 ± 0.022	0.838 ± 0.017	0.906 ± 0.018**	0.970 ± 0.018**
Liver					
Absolute	1.603 ± 0.046	1.541 ± 0.049	1.480 ± 0.040	1.485 ± 0.064	1.163 ± 0.040**
Relative	4.248 ± 0.141	4.132 ± 0.162	4.166 ± 0.122	4.544 ± 0.231	4.779 ± 0.076*
Lung					
Absolute	0.219 ± 0.006	0.564 ± 0.010**	0.613 ± 0.014**	0.869 ± 0.016**	0.887 ± 0.035**
Relative	0.581 ± 0.020	1.511 ± 0.033**	1.725 ± 0.040**	2.656 ± 0.071**	3.653 ± 0.134**
R. Testis					
Absolute	0.117 ± 0.002	0.120 ± 0.002	0.108 ± 0.003	0.113 ± 0.002	0.103 ± 0.003**
Relative	0.311 ± 0.005	0.322 ± 0.007	0.305 ± 0.012	0.345 ± 0.009*	0.424 ± 0.015**
Thymus					
Absolute	0.039 ± 0.003	0.039 ± 0.003	0.034 ± 0.001	0.038 ± 0.003	0.017 ± 0.002**
Relative	0.104 ± 0.007	0.104 ± 0.008	0.095 ± 0.004	0.115 ± 0.011	0.068 ± 0.007**
Female					
n	10	10	10	10	6
Necropsy body wt	32.5 ± 0.6	32.5 ± 0.5	31.1 ± 0.9	28.4 ± 0.4**	22.2 ± 0.3**
Heart					
Absolute	0.133 ± 0.003	0.143 ± 0.003	0.143 ± 0.003	0.142 ± 0.003	0.137 ± 0.005
Relative	0.410 ± 0.007	0.440 ± 0.007	0.462 ± 0.015**	0.501 ± 0.012**	0.610 ± 0.016**
R. Kidney					
Absolute	0.217 ± 0.007	0.223 ± 0.004	0.212 ± 0.003	0.219 ± 0.006	0.188 ± 0.004**
Relative	0.669 ± 0.023	0.687 ± 0.015	0.686 ± 0.022	0.773 ± 0.023**	0.850 ± 0.012**
Liver					
Absolute	1.574 ± 0.031	1.595 ± 0.023	1.564 ± 0.036	1.499 ± 0.033	1.322 ± 0.028**
Relative	4.850 ± 0.096	4.906 ± 0.052	5.035 ± 0.069	5.281 ± 0.088**	5.971 ± 0.134**
Lung					
Absolute	0.225 ± 0.008	0.582 ± 0.010**	0.684 ± 0.011**	0.861 ± 0.020**	0.808 ± 0.021**
Relative	0.694 ± 0.026	1.791 ± 0.029**	2.211 ± 0.064**	3.042 ± 0.093**	3.650 ± 0.085**
Thymus					
Absolute	0.047 ± 0.004	0.051 ± 0.003	0.048 ± 0.003	0.046 ± 0.003	0.024 ± 0.004**
Relative	0.144 ± 0.012	0.156 ± 0.009	0.155 ± 0.008	0.161 ± 0.009	0.109 ± 0.019

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error). No data were available for the 100 mg/m^3 group due to 100% mortality.

TABLE G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 3-Month Interim Evaluation in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
n	10	10	10	10
Male				
Necropsy body wt	35.4 ± 0.8	35.9 ± 1.1	33.3 ± 0.6	33.8 ± 0.7
Heart				
Absolute	0.148 ± 0.002	0.151 ± 0.004	0.147 ± 0.004	0.147 ± 0.003
Relative	0.420 ± 0.010	0.423 ± 0.011	0.441 ± 0.006	0.436 ± 0.009
R. Kidney				
Absolute	0.300 ± 0.011	0.297 ± 0.009	0.277 ± 0.007	0.280 ± 0.009
Relative	0.848 ± 0.022	0.832 ± 0.025	0.833 ± 0.015	0.830 ± 0.025
Liver				
Absolute	1.438 ± 0.032	1.427 ± 0.041	1.357 ± 0.044	1.340 ± 0.026
Relative	4.073 ± 0.084	3.989 ± 0.070	4.073 ± 0.085	3.974 ± 0.081
Lung				
Absolute	0.213 ± 0.003	0.300 ± 0.007**	0.366 ± 0.019**	0.451 ± 0.008**
Relative	0.603 ± 0.008	0.849 ± 0.046**	1.103 ± 0.062**	1.340 ± 0.035**
R. Testis				
Absolute	0.109 ± 0.005	0.114 ± 0.002	0.109 ± 0.002	0.111 ± 0.002
Relative	0.310 ± 0.013	0.321 ± 0.010	0.329 ± 0.008	0.330 ± 0.006
Thymus				
Absolute	0.035 ± 0.002	0.035 ± 0.002	0.037 ± 0.002	0.039 ± 0.002
Relative	0.100 ± 0.004	0.097 ± 0.005	0.110 ± 0.006	0.115 ± 0.008
Female				
Necropsy body wt	30.5 ± 0.8	30.5 ± 1.3	28.8 ± 0.6	28.3 ± 0.6
Heart				
Absolute	0.128 ± 0.002	0.129 ± 0.003	0.132 ± 0.002	0.129 ± 0.003
Relative	0.423 ± 0.014	0.428 ± 0.016	0.459 ± 0.010	0.457 ± 0.010
R. Kidney				
Absolute	0.195 ± 0.005	0.197 ± 0.004	0.197 ± 0.005	0.189 ± 0.004
Relative	0.642 ± 0.017	0.654 ± 0.024	0.684 ± 0.013	0.669 ± 0.015
Liver				
Absolute	1.250 ± 0.026	1.280 ± 0.034	1.256 ± 0.037	1.292 ± 0.042
Relative	4.119 ± 0.101	4.228 ± 0.092	4.365 ± 0.118	4.569 ± 0.136*
Lung				
Absolute	0.216 ± 0.005	0.299 ± 0.008**	0.378 ± 0.020**	0.478 ± 0.018**
Relative	0.713 ± 0.025	0.993 ± 0.040**	1.313 ± 0.064**	1.690 ± 0.059**
Thymus				
Absolute	0.044 ± 0.002	0.045 ± 0.002	0.042 ± 0.002	0.043 ± 0.003
Relative	0.144 ± 0.006	0.148 ± 0.007	0.146 ± 0.007	0.153 ± 0.010

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

APPENDIX H
TISSUE BURDEN RESULTS

LUNG DEPOSITION AND CLEARANCE EQUATIONS

Lung deposition and clearance parameters were calculated from measured lung concentrations during the prechronic and 2-year studies using a model that assumes a constant deposition rate and a first-order clearance rate. The model used is described by Equation (1).

Equation (1): $A(t)=\alpha/k\ (1-e^{-kt})$

In Equation (1), A(t) is the lung burden (µg indium) at time t (days); α is the amount of indium deposited per day (µg/day); and k is the fraction of indium cleared from the lungs per day (day^{-1}). With this model, steady-state or equilibrium lung burdens (A_e, µg indium) may be calculated according to Equation (2).

Equation (2): $A_e=\alpha/k$

Lung clearance rates from postexposure data were calculated using Equation (3).

Equation (3): $A(t)=A_0(e^{-kt})$

In Equation (3), A(t) is the postexposure lung burden (µg indium) at postexposure time t (days); A_0 is the amount of indium in the lungs at the beginning of the postexposure period (t=0); and k is the fraction of indium cleared from the lungs per day (day^{-1}).

Equation (1) was used to fit lung burden data collected during the 14-week study. Equation (3) was used to fit postexposure lung burden data that were collected following the 14-week exposure period and following the 5-day exposure period. In these prechronic studies, fits of lung burden data to Equations (1) and (3) were performed separately, because there were no lung burden data collected during the 5-day exposure period. This approach allowed direct comparison of the postexposure data following the 14-week exposure period to that following the 5-day exposure period. However, for the chronic study, Equations (1) and (3) were fit simultaneously to all lung burden data collected during exposure and following exposure for the 0.1 and 0.3 mg/m^3 groups. This was done by solving Equation (1) for the lung burden at day 0 (A_0) and substituting this into Equation (3) (for A_0) before fitting the data. Equation (1) was used to fit lung burden data collected from the 0.03 mg/m^3 group during the chronic study, because no postexposure data were collected from this group.

The lung clearance half-time ($t_{1/2}$) can be calculated from Equation (4).

Equation (4): $t_{1/2}=\ln 2/k$

To test for kinetic nonlinearities in deposition, normalized deposition rates were calculated by dividing the deposition rate determined from Equation 1 by the exposure concentration as in Equation (5).

Equation (5): $\alpha^*=\alpha/C$

In Equation (5), α* is the normalized deposition rate (µg indium/day per mg indium phosphide/m^3), α is the deposition rate calculated from Equation (1) in micrograms of indium per day, and C is the exposure concentration in milligrams of indium phosphide per cubic meter.

TABLE H1
Lung Weight and Lung Burden in Male Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
n	3	3	3	3	3	3
Absolute lung wt (g)						
Day 4	0.695 ± 0.088	0.798 ± 0.021	0.889 ± 0.089*	0.819 ± 0.076*	0.848 ± 0.037*	0.936 ± 0.007**
Day 24	0.811 ± 0.017	1.906 ± 0.068**	2.232 ± 0.263**	1.951 ± 0.093**	2.236 ± 0.128**	2.250 ± 0.130**
Day 45	1.098 ± 0.146	3.015 ± 0.190**	3.463 ± 0.612**	3.325 ± 0.488**	3.741 ± 0.130**	4.114 ± 0.317**
Day 73	1.211 ± 0.254	4.145 ± 0.281**	4.609 ± 0.428**	4.568 ± 0.280**	5.625 ± 0.611**	5.337 ± 0.246**
Day 96	1.107 ± 0.059	4.644 ± 0.277**	6.003 ± 0.353**	5.513 ± 0.204**	6.408 ± 0.623**	4.600 ± 0.388**
Postexposure day 14	1.091 ± 0.133	5.568 ± 0.746**	6.728 ± 0.870**	6.972 ± 0.511**	7.637 ± 0.517**	4.625 ± 0.331**[b]
Postexposure day 28[c]	1.170 ± 0.026	5.157 ± 0.253**	6.770 ± 0.997**	7.630 ± 0.776**	7.800 ± 0.317**	
Postexposure day 56[c]	1.266 ± 0.057	5.705 ± 0.305**	9.367 ± 0.184**	8.824 ± 0.488**	7.732 ± 2.014**	
Postexposure day 112[c]	1.329 ± 0.152	5.389 ± 0.108**	11.103 ± 1.361**	11.624 ± 1.102**	10.303 ± 0.375**	
µg In/lung						
Day 4	—[d]	10 ± 1	34 ± 3	85 ± 6[e]	237 ± 1	673 ± 112
Day 24	—	38 ± 2	115 ± 6	331 ± 15	736 ± 14	1,770 ± 60
Day 45	—	70 ± 6	200 ± 13	574 ± 39	1,440 ± 125	3,110 ± 132
Day 73	—	105 ± 8	280 ± 17	849 ± 73	2,060 ± 171	3,970 ± 115
Day 96	—	148 ± 9	351 ± 25	1,010 ± 105	2,550 ± 212	4,790 ± 122
Postexposure day 14	—	115 ± 4	305 ± 6	1,050 ± 43	2,180 ± 128	3,990 ± 576[b]
Postexposure day 28[c]	—	111 ± 7	287 ± 21	936 ± 60	2,040 ± 127	
Postexposure day 56[c]	—	100 ± 3	278 ± 14	910 ± 39	1,700 ± 678	
Postexposure day 112[c]	—	86 ± 1	251 ± 20	710 ± 56	1,740 ± 145	
µg In/g lung						
Day 4	—	12 ± 1	39 ± 3	110 ± 5[e]	284 ± 14	742 ± 125
Day 24	—	20 ± 0.4	53 ± 6	174 ± 7	338 ± 16	806 ± 66
Day 45	—	23 ± 1	61 ± 16	179 ± 30	394 ± 26	770 ± 82
Day 73	—	26 ± 0.2	62 ± 8	190 ± 16	377 ± 57	759 ± 41
Day 96	—	33 ± 3	60 ± 5	191 ± 27	416 ± 62	1,080 ± 110
Postexposure day 14	—	21 ± 3	47 ± 6	156 ± 7	292 ± 19	878 ± 141[b]
Postexposure day 28[c]	—	22 ± 2	44 ± 10	126 ± 17	268 ± 23	
Postexposure day 56[c]	—	18 ± 1	30 ± 1	106 ± 1	219 ± 41	
Postexposure day 112[c]	—	16 ± 0	23 ± 2	63 ± 4	174 ± 10	
µg In/lung per mg InP/m^3						
Day 4	NA	9.5 ± 0.72	11.3 ± 1.1	8.51 ± 0.56[e]	7.90 ± 0.04	6.73 ± 1.12
Day 24	NA	37.5 ± 2.0	38.3 ± 1.9	33.1 ± 1.5	24.5 ± 0.47	17.7 ± 0.60
Day 45	NA	69.6 ± 6.2	66.7 ± 4.5	57.4 ± 3.9	48.0 ± 4.17	31.1 ± 1.32
Day 73	NA	105 ± 7.6	93.5 ± 5.6	84.9 ± 7.3	68.7 ± 5.70	39.7 ± 1.15
Day 96	NA	148 ± 9.2	117 ± 8.5	101 ± 10.5	85.0 ± 7.07	47.9 ± 1.22
Postexposure day 14	NA	115 ± 3.9	102 ± 2.1	105 ± 4.3	72.7 ± 4.27	39.9 ± 5.76[b]
Postexposure day 28[c]	NA	111 ± 6.6	95.7 ± 7.0	93.6 ± 6.0	68.0 ± 4.23	
Postexposure day 56[c]	NA	100 ± 3.1	92.7 ± 4.7	91.0 ± 3.9	56.7 ± 22.6	
Postexposure day 112[c]	NA	86.2 ± 1.4	83.7 ± 6.7	71.0 ± 5.6	58.1 ± 4.82	

(NA) Not applicable
* Significantly different (P≤0.05) from the chamber control group by Williams' or Dunnett's test
** P≤0.01
[a] Data are presented as mean ± standard deviation.
[b] n=5
[c] No data are available for the 100 mg/m^3 group; most of the animals did not survive past 14 days postexposure.
[d] The value was below the experimental limit of quantitation (7.8 µg In/g lung).
[e] n=2

TABLE H2
Lung Weight and Lung Burden in Age-Matched Male Rats after 5 Days of Exposure to Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
n	3	3	3	3	3	3
Absolute lung wt (g)						
Day 5	1.165 ± 0.089	1.571 ± 0.355	1.580 ± 0.211	1.690 ± 0.294*	2.129 ± 0.265**	2.194 ± 0.071**
Postexposure day 14	1.450 ± 0.174	1.753 ± 0.241	2.542 ± 0.094**	3.870 ± 0.142**	3.953 ± 0.053**	4.016 ± 0.508**
Postexposure day 28	1.200 ± 0.060	2.220 ± 0.125**	2.483 ± 0.045**	3.477 ± 0.305**	4.547 ± 0.297**	5.343 ± 0.458**
Postexposure day 56	1.297 ± 0.012	2.713 ± 0.705**	3.049 ± 0.444**	3.925 ± 0.105**	5.010 ± 0.454**	6.607 ± 0.210**
Postexposure day 112	1.293 ± 0.126	2.248 ± 0.234*	3.170 ± 0.434**	4.803 ± 0.186**	7.037 ± 0.677**	8.409 ± 0.757**
µg In/lung						
Day 5	—[b]	19 ± 3	51 ± 5	176 ± 25	361 ± 88	1,060 ± 160
Postexposure day 14	—	12 ± 3	46 ± 1	124 ± 9	314 ± 48	1,040 ± 182
Postexposure day 28	—	15 ± 2	35 ± 14	116 ± 25	335 ± 39	911 ± 393
Postexposure day 56	—	13 ± 2	32 ± 6	98 ± 27	346 ± 16	782 ± 98
Postexposure day 112	—	10 ± 1	28 ± 6	83 ± 18	246 ± 31	507 ± 113
µg In/g lung						
Day 5	—	13 ± 5	34 ± 7	114 ± 39	180 ± 68	500 ± 69
Postexposure day 14	—	7 ± 1[c]	18 ± 1	33 ± 3	80 ± 11	270 ± 73
Postexposure day 28	—	7 ± 1[c]	15 ± 6	34 ± 6	76 ± 9	182 ± 96
Postexposure day 56	—	6 ± 1[c]	11 ± 3	25 ± 7	71 ± 9	121 ± 14
Postexposure day 112	—	5 ± 0[c]	9 ± 1	18 ± 3	36 ± 8	62 ± 13
µg In/lung per mg InP/m^3						
Day 5	NA	18.8 ± 3.0	17.1 ± 1.8	17.6 ± 2.5	12.0 ± 2.9	10.6 ± 1.60
Postexposure day 14	NA	12.4 ± 3.2	15.3 ± 0.33	12.4 ± 0.93	10.5 ± 1.6	10.4 ± 1.82
Postexposure day 28	NA	15.1 ± 1.9	11.8 ± 4.67	11.6 ± 2.5	11.2 ± 1.3	9.11 ± 3.93
Postexposure day 56	NA	13.1 ± 2.1	10.7 ± 2.1	9.82 ± 2.70	11.5 ± 0.53	7.82 ± 0.98
Postexposure day 112	NA	10.1 ± 1.3	9.27 ± 2.2	8.29 ± 1.77	8.20 ± 1.0	5.07 ± 1.13

(NA) Not applicable
* Significantly different (P≤0.05) from the chamber control group by Williams' or Dunnett's test
** P≤0.01
[a] Data are presented as mean ± standard deviation. The age-matched animals were exposed during the last 5 days of the 14-week study.
[b] The value was below the experimental limit of quantitation (7.8 µg In/g lung).
[c] The value was above the limit of detection (3.7 µg In/g lung) but was below the experimental limit of quantitation (7.8 µg In/g lung).

TABLE H3
Lung Deposition and Clearance Parameters with Error Estimates and 95% Confidence Intervals for Male Rats During the 14-Week Inhalation Study of Indium Phosphide

Parameter[a]	Exposure Concentration (mg/m^3)	Mean Value	Asymptotic Standard Error	95% Confidence Interval	
				Lower Limit	Upper Limit
α					
	1	1.48	0.115	1.23	1.73
	3	5.31	0.361	4.52	6.09
	10	15.5	1.34	12.6	18.4
	30	35.9	2.94	29.6	42.3
	100	92.1	5.82	79.5	105
α*					
	1	1.51	0.118	1.26	1.77
	3	1.72	0.117	1.46	1.97
	10	1.56	0.134	1.26	1.85
	30	1.20	0.098	0.986	1.41
	100	0.932	0.059	0.804	1.06
k					
	1	−0.0005	0.0019	−0.0045	0.0035
	3	0.0086	0.0019	0.0044	0.0128
	10	0.0085	0.0025	0.0032	0.0139
	30	0.0067	0.0022	0.0019	0.0116
	100	0.0148	0.0020	0.0104	0.0192
$t_{1/2}$					
	1	—[b]	—	—	—
	3	81	18	42	119
	10	82	24	30	133
	30	104	34	30	177
	100	47	6	33	61
A_e[c]					
	1	—			
	3	617			
	10	1,820			
	30	5,360			
	100	6,220			

[a] α=deposition rate (µg In/day), α*=normalized deposition rate (µg In/day per mg InP/m^3), k=clearance rate constant (day^{-1}), A_e=steady-state lung burden (µg In), $t_{1/2}$=lung clearance half-time (days)
[b] A negative coefficient was derived for the rate constant, and values for derived parameters were thus indeterminate.
[c] Calculated values for steady-state lung burden are not mean values; therefore, there are no asymptotic standard errors or confidence intervals.

TABLE H4
Lung Clearance Parameters with Error Estimates and 95% Confidence Intervals for Male Rats Following the 14-Week Inhalation Study of Indium Phosphide

Parameter[a]	Exposure Concentration (mg/m^3)	Mean Value	Asymptotic Standard Error	95% Confidence Interval	
				Lower Limit	Upper Limit
k					
	1	0.00464	0.00075	0.00302	0.00627
	3	0.00273	0.00055	0.00155	0.00391
	10	0.00323	0.00054	0.00206	0.00440
	30	0.00362	0.00123	0.00095	0.00628
	100	—[b]	—	—	—
A_0					
	1	133.9	4.5	124.3	143.6
	3	328.2	8.9	309.0	347.4
	10	1,050.4	27.4	991.3	1,109.5
	30	2,353.6	136.5	2,058.8	2,648.5
	100	—	—	—	—
$t_{1/2}$					
	1	149.2	24.2	97	201.5
	3	253.9	50.7	144.3	363.5
	10	214.4	35.9	136.9	291.9
	30	191.7	65.3	50.6	332.8
	100	—	—	—	—

[a] k=clearance rate constant (day^{-1}), A_0=initial postexposure lung burden (µg In), $t_{1/2}$=lung clearance half-time (days)
[b] No data available. Most of the animals in the 100 mg/m^3 group did not survive past 14 days postexposure.

TABLE H5
Lung Clearance Parameters with Error Estimates and 95% Confidence Intervals for Age-Matched Male Rats after 5 Days of Exposure to Indium Phosphide

Parameter[a]	Exposure Concentration (mg/m^3)	Mean Value	Asymptotic Standard Error	95% Confidence Interval	
				Lower Limit	Upper Limit
k					
	1	0.00465	0.00159	0.00123	0.00808
	3	0.00611	0.00165	0.00253	0.00968
	10	0.00708	0.00177	0.00327	0.01090
	30	0.00265	0.00114	0.00019	0.00510
	100	0.00648	0.00187	0.00245	0.01052
A_0					
	1	16.59	1.17	14.08	19.11
	3	48.28	3.25	41.25	55.30
	10	154.4	10.5	131.7	177.1
	30	356.1	20.2	312.6	399.7
	100	1,095.0	81.5	918.8	1,271.1
$t_{1/2}$					
	1	148.97	50.76	39.32	258.62
	3	113.53	30.75	47.10	179.95
	10	97.9	24.4	45.2	150.6
	30	262.0	112.6	18.8	505.2
	100	107.0	30.8	40.4	173.5

[a] k=clearance rate constant (day^{-1}), A_0=initial postexposure lung burden (μg In), $t_{1/2}$=lung clearance half-time (days)

TABLE H6
Blood Indium Concentrations in Male Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
n	3	3	3	3	3	3
µg In/g blood						
Day 4	0.004 ± 0.0004	0.003 ± 0.0006[b]	0.003 ± 0.0003[b]	0.004 ± 0.001	0.007 ± 0.002[b]	0.013 ± 0.007
Day 24	0.001 ± 0.0008	0.004 ± 0.0002[b]	0.008 ± 0.0009	0.015 ± 0.0008	0.036 ± 0.001	0.122 ± 0.004
Day 45	—[c]	0.006 ± 0.0003	0.016 ± 0.002	0.04 ± 0.01	0.08 ± 0.01	0.27 ± 0.02
Day 73	0.003 ± 0.001	0.016 ± 0.001	0.038 ± 0.002	0.078 ± 0.007	0.18 ± 0.06	0.41 ± 0.04
Day 96	0.003 ± 0.0005	0.020 ± 0.0007	0.043 ± 0.002	0.081 ± 0.004	0.19 ± 0.02	0.47 ± 0.07
Postexposure day 14[d]	0.0014 ± 0.0002	0.019 ± 0.001	0.042 ± 0.008	0.096 ± 0.008	0.21 ± 0.01	0.34 ± 0.07
Postexposure day 28[d]	—	0.017 ± 0.002	0.041 ± 0.003[b]	0.096 ± 0.004	0.21 ± 0.02[b]	
Postexposure day 56[d]	—	0.017 ± 0.0005	0.039 ± 0.001	0.129 ± 0.006	0.19 ± 0.02	
Postexposure day 112[d]	—	0.015 ± 0.0004	0.035 ± 0.002	0.091 ± 0.016	0.20 ± 0.02	

[a] Data are presented as mean ± standard deviation.
[b] n=2
[c] The value was below the experimental limit of quantitation (0.001 µg In/g blood).
[d] No data were available for the 100 mg/m^3 group; most of the animals did not survive past 14 days postexposure.

TABLE H7
Serum Indium Concentrations in Male Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
n	3	3	3	3	3	3
µg In/g serum						
Day 4	—[b]	—	0.003 ± 0.0002	0.005 ± 0.0003	0.006 ± 0.001[c]	0.021 ± 0.013
Day 24	—	0.006 ± 0.0006[c]	0.013 ± 0.0009	0.022 ± 0.0002	0.056 ± 0.002	0.205 ± 0.009
Day 45	—	0.010 ± 0.001	0.028 ± 0.003	0.070 ± 0.020	0.141 ± 0.021	0.490 ± 0.049
Day 73	—	0.019 ± 0.002	0.051 ± 0.004	0.114 ± 0.012	0.270 ± 0.096	0.641 ± 0.087
Day 96	—	0.025 ± 0.001	0.058 ± 0.009	0.121 ± 0.006	0.315 ± 0.021	0.696 ± 0.199
Postexposure day 14	—	0.023 ± 0.003	0.055 ± 0.012	0.130 ± 0.007	0.30 ± 0.01	0.37 ± 0.17[d]
Postexposure day 28[e]	—	0.024 ± 0.003	0.063 ± 0.005	0.145 ± 0.015	0.33 ± 0.03	
Postexposure day 56[e]	—	0.023 ± 0.0003	0.058 ± 0.006	0.182 ± 0.016	0.25 ± 0.05	
Postexposure day 112[e]	—	0.019 ± 0.0004	0.052 ± 0.004[c]	0.146 ± 0.006[c]	0.30 ± 0.05	

[a] Data are presented as mean ± standard deviation.
[b] The value was below the experimental limit of quantitation (0.003 µg In/g serum).
[c] n=2
[d] n=4
[e] No data were available for the 100 mg/m^3 group; most of the animals did not survive past 14 days postexposure.

TABLE H8
Testis Indium Concentrations in Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	1 mg/m^3	3 mg/m^3	10 mg/m^3	30 mg/m^3	100 mg/m^3
n	3	3	3	3	3	3
µg In/g testis						
Day 4	—[b]	—	0.003 ± 0.0001	0.003 ± 0.0001	0.004 ± 0.0008	0.014 ± 0.011
Day 24	—	0.009 ± 0.0009	0.032 ± 0.020	0.036 ± 0.002	0.101 ± 0.004	0.252 ± 0.012
Day 45	0.003 ± 0.0009	0.021 ± 0.0006	0.054 ± 0.007	0.118 ± 0.024	0.266 ± 0.018	0.700 ± 0.049
Day 73	0.003 ± 0.003	0.059 ± 0.004	0.132 ± 0.009	0.291 ± 0.026	0.657 ± 0.186	1.90 ± 0.10
Day 96	—	0.092 ± 0.002	0.216 ± 0.010	0.373 ± 0.011	0.905 ± 0.081	5.64 ± 1.13
Postexposure day 14	—	0.114 ± 0.006	0.25 ± 0.04	0.56 ± 0.03	1.22 ± 0.08	7.20 ± 2.4[c]
Postexposure day 28[d]	—	0.112 ± 0.007	0.26 ± 0.02	0.51 ± 0.03	1.36 ± 0.15	
Postexposure day 56[d]	—	0.159 ± 0.008	0.38 ± 0.02	1.07 ± 0.14	3.71 ± 2.09	
Postexposure day 112[d]	—	0.196 ± 0.009	0.43 ± 0.02	0.87 ± 0.09	2.15 ± 0.20	

[a] Data are presented as mean ± standard deviation.
[b] The value was below the experimental limit of quantitation (0.003 µg In/g testis).
[c] n=5
[d] No data were available for the 100 mg/m^3 group; most of the animals did not survive past 14 days postexposure.

TABLE H9
Study Design for the Rat Tissue Burden and Clearance Study in the 2-Year Inhalation Study of Indium Phosphide

	Time Point		Number of Animals per Group by Target Exposure Concentration[a]			
	Month	Day	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
(Months or days on test)	3	91	5M	5M	5M	5M
	5	152[b]	4M/4F	9M/4F	4M/4F	3M/3F
	9	274	5M	5M		
	12	365	5M	5M		
(Months or days postexposure)	2	67	3M		3M	3M
	4	129			3M	3M
	6	185			3M	3M
	8	249			3M	3M
	12	368	2M		3M	2M

[a] M=male; F=female
[b] Exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 149.

TABLE H10
Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male[b]				
Absolute lung wt (g)				
Month 3	1.042 ± 0.02	1.474 ± 0.29*	2.198 ± 0.20**	3.360 ± 0.27**
Month 5	1.048 ± 0.06	1.884 ± 0.17**	2.606 ± 0.22**	3.937 ± 0.12**
Month 9	1.179 ± 0.09	2.555 ± 0.11**		
Month 12	1.324 ± 0.05	2.784 ± 0.18**		
Postexposure month 2	1.805 ± 0.60		2.897 ± 0.15*	4.626 ± 0.47**
Postexposure month 4			3.048 ± 0.10	5.847 ± 0.42
Postexposure month 6			2.868 ± 0.10	5.369 ± 0.36
Postexposure month 8			2.471 ± 0.28	4.382 ± 0.24
Postexposure month 12	1.460		2.594 ± 0.18	3.507*
µg In/lung				
Month 3	—[c]	8.70 ± 1.82	28.9 ± 1.61	88.5 ± 5.03
Month 5	—	14.4 ± 1.48	44.0 ± 1.35	117 ± 5.69
Month 9	—	26.6 ± 2.02		
Month 12	—	34.3 ± 1.87		
Postexposure month 2	—		41.9 ± 4.51	104 ± 3.07
Postexposure month 4			39.2 ± 1.33	87.8 ± 6.83
Postexposure month 6			28.5 ± 1.43	81.3 ± 2.31
Postexposure month 8			19.8 ± 2.85	66.9 ± 3.81
Postexposure month 12	—		15.6 ± 2.37	58.4
µg In/g lung				
Month 3	—	5.89 ± 0.40	13.2 ± 0.60	26.4 ± 1.53
Month 5	—	7.65 ± 0.36	16.9 ± 0.87	29.6 ± 1.39
Month 9	—	10.4 ± 0.37		
Month 12	—	12.3 ± 0.43		
Postexposure month 2	—		14.4 ± 0.83	22.6 ± 1.62
Postexposure month 4			12.9 ± 0.07	15.1 ± 1.82
Postexposure month 6			9.94 ± 0.20	15.2 ± 0.85
Postexposure month 8			8.00 ± 0.46	15.3 ± 0.49
Postexposure month 12	—		5.99 ± 0.51	17.0
µg In/lung per mg InP/m^3				
Month 3	NA	290 ± 60.7	289 ± 16.1	295 ± 16.8
Month 5	NA	481 ± 48.9	440 ± 13.5	389 ± 19.0
Month 9	NA	886 ± 67.3		
Month 12	NA	1,143 ± 62.2		
Postexposure month 2	NA		419 ± 45.1	347 ± 10.2
Postexposure month 4	NA		392 ± 13.3	293 ± 22.8
Postexposure month 6	NA		285 ± 14.3	271 ± 7.7
Postexposure month 8	NA		198 ± 28.5	223 ± 12.7
Postexposure month 12	NA		156 ± 23.7	195

TABLE H10
Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Female[b]				
Absolute lung wt (g)				
Month 5	0.763 ± 0.024	1.335 ± 0.092**	1.855 ± 0.195**	2.794 ± 0.684**
µg In/lung				
Month 5	—[c]	9.15 ± 0.84	30.9 ± 1.41	85.2 ± 7.91
µg In/g lung				
Month 5	—	6.85 ± 0.44	16.7 ± 1.30	31.6 ± 7.50
µg In/lung per mg InP/m^3				
Month 5	NA	305 ± 28	309 ± 14	284 ± 26

(NA) Not applicable
* Significantly different (P≤0.05) from the chamber control group by Williams' or Dunnett's test
** P≤0.01
[a] Data are presented as mean ± standard deviation.
[b] See Table H9 for the number of animals used in the study.
[c] The value was below the experimental limit of quantitation (0.15 µg In/g lung).

TABLE H11
Lung Deposition and Clearance Parameters with Error Estimates and 95% Confidence Intervals for Male Rats in the 2-Year Inhalation Study of Indium Phosphide

Parameter[a]	Exposure Concentration (mg/m^3)[b]	Mean Value	Asymptotic Standard Error	95% Confidence Interval	
				Lower Limit	Upper Limit
α					
	0.03	0.099	0.006	0.087	0.111
	0.1	0.377	0.016	0.345	0.409
	0.3	0.989	0.028	0.930	1.048
k					
	0.03	0.00029	0.00038	−0.00049	0.00107
	0.1	0.00265	0.00024	0.00215	0.00315
	0.3	0.00238	0.00016	0.00205	0.00271
A_e					
	0.03	347	437	−560	1,254
	0.1	142	9	124	160
	0.3	415	19	375	455
$t_{1/2}$					
	0.03	2,422	3,181	−4,176	9,020
	0.1	262	24	213	311
	0.3	291	19	250	332

[a] α=deposition rate (μg In/day), k=clearance rate constant (day^{-1}), A_e=steady-state lung burden (μg In), $t_{1/2}$=lung clearance half-time (days)
[b] Exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 142.

TABLE H12
Serum Indium Concentrations in Rats in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male[b]				
ng In/g serum				
Month 3	—[c]	—	—	11 ± 1
Month 5	—	—	4.8 ± 0.3	15.5 ± 0.8
Month 9	—	3.3 ± 0.5		
Month 12	—	3.4 ± 0.2		
Postexposure month 2	—		4.3 ± 0.7	14.3 ± 04
Postexposure month 4			4.7 ± 0.2	12.4 ± 0.9
Postexposure month 6			4.3 ± 0.2	14.6 ± 0.7
Postexposure month 8			3.5 ± 0.6	11.3 ± 0.3
Postexposure month 12	—		3.2 ± 0.4	14
Female[b]				
ng In/g serum				
Month 5	—	—	5.8 ± 0.9	19 ± 4

[a] Data are presented as mean ± standard deviation.
[b] See Table H9 for the number of animals used in the study.
[c] The value was below the experimental limit of quantitation (3 ng In/g serum).

TABLE H13
Study Design for the Mouse Tissue Burden and Clearance Study in the 2-Year Inhalation Study of Indium Phosphide

	Time Point		Number of Animals per Group by Target Exposure Concentration[a]			
	Month	Day	Chamber Control	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
(Months or days on test)	3	92[b]	5M	5M	5M	5M
	5	145	4M/4F	9M/4F	4M/4F	3M/3F
	9	274	5M	5M		
	12	364	5M	5M		
(Months or days postexposure)	2	67	3M		3M	3M
	4	129			3M	3M
	6	185			3M	3M
	8	249			3M	3M
	12	368	2M		2M	1M

[a] M=male; F=female
[b] Exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 142.

TABLE H14
Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male[b]				
Absolute lung wt (g)				
Month 3	0.159 ± 0.004	0.231 ± 0.01**	0.307 ± 0.02**	0.392 ± 0.03**
Month 5	0.196 ± 0.02	0.295 ± 0.04**	0.339 ± 0.04**	0.495 ± 0.02**
Month 9	0.163 ± 0.01	0.361 ± 0.04**		
Month 12	0.188 ± 0.008	0.404 ± 0.06**		
Postexposure month 2	0.173 ± 0.01		0.365 ± 0.04**	0.396 ± 0.05**
Postexposure month 4			0.297 ± 0.04	0.428 ± 0.05
Postexposure month 6			0.325 ± 0.04	0.345 ± 0.03
Postexposure month 8			0.359 ± 0.06	0.407 ± 0.04
Postexposure month 12	0.237		0.318**	0.425
µg In/lung				
Month 3	—[c]	1.81 ± 0.13	5.54 ± 0.37	19.3 ± 1.36
Month 5	—	2.48 ± 0.28	8.13 ± 1.08	27.2 ± 0.86
Month 9	—	3.49 ± 0.46		
Month 12	—	4.87 ± 0.65		
Postexposure month 2	—		5.83 ± 0.88	19.2 ± 1.08
Postexposure month 4			4.37 ± 0.18	15.5 ± 2.34
Postexposure month 6			3.64 ± 0.61	11.5 ± 0.60
Postexposure month 8			1.95 ± 0.62	10.3 ± 1.50
Postexposure month 12	—		1.33	7.75
µg In/g lung				
Month 3	—	7.81 ± 0.22	18.1 ± 1.93	49.4 ± 2.53
Month 5	—	8.52 ± 1.44	24.0 ± 1.77	55.0 ± 3.51
Month 9	—	9.84 ± 2.05		
Month 12	—	12.2 ± 1.81		
Postexposure month 2	—		16.3 ± 4.26	49.3 ± 9.17
Postexposure month 4			14.8 ± 1.35	36.1 ± 2.08
Postexposure month 6			11.1 ± 0.62	33.3 ± 2.54
Postexposure month 8			5.41 ± 1.50	25.4 ± 4.47
Postexposure month 12	—		4.27	18.2
µg In/lung per mg InP/m^3				
Month 3	NA	60.3 ± 4.3	55.4 ± 3.7	64.3 ± 4.5
Month 5	NA	82.7 ± 9.3	81.3 ± 10.8	90.7 ± 2.9
Month 9	NA	116.3 ± 15.3		
Month 12	NA	162.3 ± 21.7		
Postexposure month 2	NA		58.3 ± 8.8	64.0 ± 3.6
Postexposure month 4	NA		43.7 ± 1.8	51.7 ± 7.8
Postexposure month 6	NA		36.4 ± 6.1	38.3 ± 2.0
Postexposure month 8	NA		19.5 ± 6.2	34.0 ± 5.1
Postexposure month 12	NA		13.3	25.8

TABLE H14
Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Indium Phosphide

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Female[b]				
Absolute lung wt (g)				
Month 5	0.166 ± 0.011	0.307 ± 0.049*	0.351 ± 0.022**	0.527 ± 0.055**
µg In/lung				
Month 5	—[c]	2.26 ± 0.67	6.51 ± 0.44	26.1 ± 1.29
µg In/g lung				
Month 5	—	7.28 ± 1.04	18.6 ± 1.51	50.0 ± 6.64
µg In/lung per mg InP/m^3				
Month 5	NA	75.4 ± 22.4	65.1 ± 4.4	87.0 ± 4.2

(NA) Not applicable
* Significantly different (P≤0.05) from the chamber control group by Williams' or Dunnett's test
** P≤0.01
[a] Data are presented as mean ± standard deviation.
[b] See Table H13 for the number of animals used in the study.
[c] The value was below the experimental limit of quantitation (1.5 µg In/g lung).

TABLE H15
Lung Deposition and Clearance Parameters with Error Estimates and 95% Confidence Intervals for Male Mice in the 2-Year Inhalation Study of Indium Phosphide

Parameter[a]	Exposure Concentration (mg/m^3)[b]	Mean Value	Asymptotic Standard Error	95% Confidence Interval	
				Lower Limit	Upper Limit
α					
	0.03	0.0210	0.0021	0.0166	0.0254
	0.1	0.0780	0.0034	0.0708	0.0852
	0.3	0.252	0.0078	0.236	0.268
k					
	0.03	0.00301	0.00082	0.00131	0.00471
	0.1	0.00481	0.00036	0.00407	0.00555
	0.3	0.00425	0.00023	0.00377	0.00473
A_e					
	0.03	6.97	1.24	4.39	9.55
	0.1	16.2	0.756	14.6	17.8
	0.3	59.4	2.02	55.2	63.6
$t_{1/2}$					
	0.03	230	63	100	360
	0.1	144	11	122	166
	0.3	163	9	145	181

[a] α=deposition rate (μg In/day), k=clearance rate constant (day^{-1}), A_e=steady-state lung burden (μg In), $t_{1/2}$=lung clearance half-time (days)
[b] Exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 142.

TABLE H16
Serum Indium Concentrations in Mice in the 2-Year Inhalation Study of Indium Phosphide[a]

	Chamber Control	0.03 mg/m^3	0.1 mg/m^3 (Stop-Exposure)	0.3 mg/m^3 (Stop-Exposure)
Male[b]				
ng In/g serum				
Month 3	—[c]	—	4.4 ± 0.9	12.5 ± 0.4
Month 5	—	3 ± 2	8 ± 2	19 ± 4
Month 9	—	4 ± 2		
Month 12	—	—		
Postexposure month 2	—		4 ± 1	16 ± 3
Postexposure month 4			5 ± 1	11.3 ± 0.4
Postexposure month 6[d]				
Postexposure month 8			—	8.4 ± 0.3
Postexposure month 12	—		4	7.1
Female[b]				
ng In/g serum				
Month 5	—	7 ± 10	6 ± 2	19 ± 6

[a] Data are presented as mean ± standard deviation.
[b] See Table H13 the for number of animals used in the study.
[c] Value was below the experimental limit of quantitation (3 ng In/g serum).
[d] Serum assays not reported for the 0.1 and 0.3 mg/m^3 groups due to instrument problems

APPENDIX I
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE I1
Summary of Reproductive Tissue Evaluations for Male Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	3 mg/m^3	10 mg/m^3	30 mg/m^3
n	10	10	10	10
Weights (g)				
Necropsy body wt	365 ± 6	322 ± 5**	331 ± 4**	325 ± 9**
L. Cauda epididymis	0.2236 ± 0.0049	0.2179 ± 0.0043	0.2196 ± 0.0069	0.2014 ± 0.0051**
L. Epididymis	0.4980 ± 0.0078	0.4966 ± 0.0059	0.4943 ± 0.0096	0.4724 ± 0.0105
L. Testis	1.4165 ± 0.1014	1.5231 ± 0.0122	1.4850 ± 0.0153	1.4839 ± 0.0243
Spermatid measurements				
Spermatid heads (10^7/g testis)	9.86 ± 1.67	8.16 ± 0.22	8.28 ± 0.16	7.96 ± 0.27
Spermatid heads (10^7/testis)	12.47 ± 0.29	12.41 ± 0.27	12.29 ± 0.23	11.78 ± 0.32
Spermatid count (mean/10^{-4} mL suspension)	62.35 ± 1.46	62.05 ± 1.35	61.43 ± 1.16	58.90 ± 1.60
Epididymal spermatozoal measurements				
Motility (%)	89.17 ± 1.79	86.92 ± 3.88	88.73 ± 1.67	85.99 ± 2.15
Concentration (10^6/g cauda epididymal tissue)	631 ± 29	651 ± 30	695 ± 46	695 ± 30

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' test
[a] Data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (left testis weight), Williams' test (left epididymis weight), or Dunn's test (spermatid and epididymal spermatazoal measurements).

TABLE I2
Estrous Cycle Characterization for Female Rats in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	3 mg/m^3	10 mg/m^3	30 mg/m^3
n	10	10	10	10
Necropsy body wt (g)	206 ± 3	199 ± 4	206 ± 3	196 ± 5
Estrous cycle length (days)	4.86 ± 0.14[b]	4.90 ± 0.18	4.85 ± 0.11	4.60 ± 0.16
Estrous stages[c] (% of cycle)				
Diestrus	65.0	58.3	50.8	51.7
Proestrus	10.0	18.3	20.0	24.2
Estrus	15.8	20.0	25.0	16.7
Metestrus	9.2	3.3	4.2	7.5

[a] Necropsy body weights and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length).
[b] Estrous cycle was longer than 12 days or unclear in 3 of 10 animals.
[c] Evidence shows that exposed females differ significantly (Wilk's Criterion, $P \leq 0.05$) from the chamber control females in the relative length of time spent in the estrous stages. Exposed females spent more time in proestrus and less time in diestrus than did the chamber control females.

TABLE I3
Summary of Reproductive Tissue Evaluations for Male Mice in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	3 mg/m^3	10 mg/m^3	30 mg/m^3
n	9	10	8	9
Weights (g)				
Necropsy body wt	37.8 ± 0.6	35.6 ± 0.6*	32.8 ± 0.5**	24.3 ± 0.8**
L. Cauda epididymis	0.0243 ± 0.0014	0.0212 ± 0.0007	0.0222 ± 0.0011	0.0177 ± 0.0012**
L. Epididymis	0.0502 ± 0.0020	0.0460 ± 0.0010	0.0493 ± 0.0027	0.0405 ± 0.0018**
L. Testis	0.1178 ± 0.0018	0.1059 ± 0.0027*	0.1095 ± 0.0014*	0.1068 ± 0.0049*
Spermatid measurements				
Spermatid heads (10^7/g testis)	15.94 ± 0.65	17.03 ± 0.81	16.35 ± 0.66	16.93 ± 0.87
Spermatid heads (10^7/testis)	1.87 ± 0.07	1.79 ± 0.08	1.79 ± 0.08	1.79 ± 0.09
Spermatid count (mean/10^{-4} mL sufspension)	58.56 ± 2.25	56.08 ± 2.53	55.97 ± 2.46	56.08 ± 2.79
Epididymal spermatozoal measurements				
Motility (%)	74.03 ± 3.08	73.89 ± 3.14	75.15 ± 3.70	76.04 ± 2.55
Concentration (10^6/g cauda epididymal tissue)	988 ± 79	840 ± 78	950 ± 57	845 ± 53

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' test
** $P \leq 0.01$
[a] Data are presented as mean ± standard error. Differences from the chamber control group for spermatid and epididymal spermatazoal measurements are not significant by Dunn's test.

TABLE I4
Estrous Cycle Characterization for Female Mice in the 14-Week Inhalation Study of Indium Phosphide[a]

	Chamber Control	3 mg/m^3	10 mg/m^3	30 mg/m^3
n	10	10	10	8
Necropsy body wt (g)	32.5 ± 0.6	31.1 ± 0.9	28.4 ± 0.4**	20.9 ± 0.9**
Estrous cycle length (days)	4.61 ± 0.44[b]	3.95 ± 0.12	4.25 ± 0.13	6.33 ± 1.33[c]
Estrous stages (% of cycle)				
Diestrus	35.0	32.5	30.8	58.9
Proestrus	20.0	23.3	18.3	11.1
Estrus	25.0	24.2	29.2	20.0
Metestrus	20.0	20.0	21.7	10.0

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' test
[a] Necropsy body weights and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.
[c] Estrous cycle was longer than 12 days or unclear in five of eight animals.

APPENDIX J
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF INDIUM PHOSPHIDE

Indium phosphide was obtained in three lots from Johnson Matthey, Inc. (Ward Hill, MA). The study laboratory combined two lots into a single lot (lot BNW-12957-21) for use in the 14-week studies. The third lot (lot BNW 13040-127) was combined with lot BNW-12957-21 to make lot BNW 12957-28 which was used in the 2-year studies. Identity, purity, and stability analyses were conducted by the study laboratory. Reports on analyses performed in support of the indium phosphide studies are on file at the National Institute of Environmental Health Sciences.

Initially, the study laboratory premicronized lot BNW-12957-21 in a Model SR-3 Rotor Beater (Brinkmann Instruments, Westbury, NY) equipped with a 0.5-mm stainless steel sieve and then micronized the bulk chemical in a Sturtevant Micronizer (Sturtevant, Inc., Boston, MA) to a count median diameter of approximately 0.4 μm and a geometric standard deviation of approximately 1.9, as determined by electron microscopy. The rotor beater was enclosed in a nitrogen-filled cabinet, and the micronizer was operated with compressed nitrogen to reduce the possibility of fire or explosion. The micronized indium phosphide was assigned lot number BNW-12957-28; two batches were prepared. For the 2-year studies, lot BNW-13040-127 was micronized as described for lot BNW-12957-21 and combined with micronized lot BNW-12957-21 to form an additional batch of lot BNW-12957-28.

For lot BNW-12957-21, results of glow-discharge mass spectrometric analyses provided by the manufacturer indicated that impurities totaled less than 120 ppm for the 72 elements assayed; the principal impurities were aluminum (37 ppm), silicon (29 ppm), chlorine (7 ppm), calcium (16 ppm), and arsenic (12 ppm). For lot BNW-13040-127, results of glow-discharge mass spectrometric analyses provided by the manufacturer indicated that impurities totaled less than 2 ppm for the 72 elements assayed.

Lot BNW-12957-28, a polycrystalline solid, was identified as indium phosphide by X-ray diffraction (XRD) analyses. A Philips 3000 series X-ray diffractometer (Philips Analytical, Mahwah, NJ) with a fixed copper anode source at 40 kV and 45 mA was used; diffraction patterns were matched to computer library reference patterns (JCPDS/ICDD, reference No. 32-452). XRD analysis indicated the presence of indium phosphide with a purity greater than 99% (Figure J1). Elemental indium was detected at a concentration of approximately 1% or less.

The purity of lot BNW-12957-28 was determined by inductively coupled plasma/atomic emission spectroscopy (ICP/AES). Samples were dissolved in a mixture of nitric and hydrochloric acid (10:3) and analyzed for indium at 303.936 nm and phosphorus at 214.914 nm. Results were normalized against those of indium and phosphorus reference standards obtained from the National Institute of Standards Technology. The results of ICP/AES analyses for indium and phosphorus were in agreement with the theoretical values. For the two batches of lot BNW-12957-28 prepared for use in the 14-week studies, results of ICP/AES analyses indicated purities of 97.6% ± 0.6% and 99.0% ± 0.4% for indium and 96.8% ± 0.4% and 97.7% ± 1.7% for phosphorus relative to the theoretical values. Arsenic, selenium, antimony, and iron were present in each batch at concentrations greater than 0.01%; other elements were present at concentrations of less than 0.01% or were not detected. The total weight of trace impurities in each batch was less than 0.2%.

For the batch of lot BNW-12957-28 prepared for use in the 2-year studies, the results indicated a purity of 97.1% ± 0.3% for indium and a 96.9% ± 0.7% for phosphorus relative to the theoretical values. Arsenic, iron, antimony, and selenium were detected at concentrations of 0.01% to 0.02%. Concentrations of other elements were less than 0.01% or were below the limit of detection. The total weight of trace impurities was less than 0.12%.

Accelerated stability studies were performed on lot L08C07 (not used in the current studies), which was obtained from Johnson Matthey, Inc. The sample was milled with a stainless-steel grinding mill (WIG-L-BUG, Model 3110B, Crescent Dental Manufacturing Co., Elgin, IL) before ICP/AES and XRD were performed. Indium phosphide was found to be stable for at least 2 weeks at temperatures up to 60° C when stored under a headspace of nitrogen or air. The bulk chemical was stored in amber glass bottles with Teflon®-lined caps under a nitrogen headspace at room temperature. Stability was monitored throughout the studies with ICP/AES. No degradation of the bulk chemical was detected.

Thermal studies were conducted to assess the stability of micronized indium phosphide in air and in nitrogen at higher temperatures such as those generated by the milling process. Using differential scanning calorimetry, thermal behavior was monitored between 30° and 500° C with temperatures increasing at a rate of 5° C per minute; isothermal analyses were performed in air by heating indium phosphide to 250° C in 40 seconds and holding at 250° C for 4 hours. The calorimeter was calibrated for temperature using the melting points of indium (156.6° C) and zinc (419.5° C) and for energy using the heat of melting for indium; the energy calibration was verified using the heat of melting for zinc. Duplicate 35- to 40-mg samples were analyzed. A small endothermic reaction (0.1 J/g) occurred in air and nitrogen at around 156.6° C, suggesting some decomposition of indium phosphide into its elements. An exothermic reaction (9 J/g) in air was observed at around 380° C and may have been associated with the presence of an unidentified impurity. Using scanning thermogravity, thermal behavior was monitored as with differential scanning calorimetry; isothermal analyses were performed in air by heating indium phosphide to 250° C at 160° C per minute and holding at 250° C for 2 hours. The thermogravimeter was calibrated for temperature using the curie point transitions of alumel (160° C) and perkalloy (596° C) and for weight using a 100-mg class S standard weight. Duplicate samples of approximately 15 mg were analyzed. No mass change was observed for the endothermic reaction observed in the calorimetric analysis. The exothermic reaction that occurred at approximately 380° C showed a weight gain of approximately 0.5% at termination (500° C). No significant reaction was observed for isothermal analysis at 250° C.

Additional stability studies were performed by Dust Tech, Inc. (Augusta, NJ), using a Hartmann Dust Explosion Apparatus (U.S. Bureau of Mines, Bruceton Station, PA) and a Godbert-Greenwald furnace (U.S. Bureau of Mines) (Battelle, 1995a). Resistivity was measured with a cell designed for particulate materials and equipped with a high-voltage power supply and an electrometer. The current passing through the standard sample geometry, measured as a function of applied voltage, was used to calculate volume resistivity. Results of analyses indicated that indium phosphide dust is capable of causing a severe explosion. Under conditions in which electrostatic charges are generated, such as milling and pneumatic conveying, indium phosphide is sensitive to ignition by electrostatic discharge and can generate pressure at a rate of up to 10,200 psi per second.

AEROSOL GENERATION AND EXPOSURE SYSTEM

For the 14-week studies, the indium phosphide aerosol generation and delivery system had four basic components: a flexible brush dust feed mechanism developed at the study laboratory, a Trost Model GEM-T air-impact mill (Garlock, Inc., Newton, PA), an aerosol charge neutralizer, and a stainless-steel aerosol distribution system (Figure J2). The generation and distribution system was electrically grounded and bonded and was monitored continuously for proper grounding; the system was designed to shut down automatically if a ground fault was detected. The flexible-brush dust feed mechanism (Figure J3) employed a hopper into which the dry powder was poured. This hopper enclosed a random-wound, large bristle brush that continually rotated, stirring the powder and delivering it into a feed tube through a small hole in the bottom of the hopper. The feed tube contained a spiral-wound feed brush that was rotated at a controlled rate by a stepper motor. The dust fell from the end of the feed tube and was aspirated into the impact mill. The hopper was reloaded with additional indium phosphide at regular intervals throughout each day's exposure period. Indium

phosphide was stored in a nitrogen-purged desiccator to achieve more uniform flow in the generator. The air-impact mill used fluid energy from opposing air jets to cause particle-to-particle, head-on impacts to deagglomerate and reduce the size distribution of indium phosphide. The particles were then swept into a classification chamber; smaller particles passed through while larger ones were thrown to the perimeter by centrifugal force. Larger particles were reentrained into the impacting air jets until they were sufficiently reduced in size.

The aerosol generation and delivery system for the 2-year studies is shown in Figure J4. The aerosol generator consisted of a drum, body, and cap (Figure J5). The drum rotated at 60° increments, with set time intervals between drum rotations. Rotation of the drum was controlled by a compressed-air-driven valve driver (VICI Valco Instrument Co., Houston, TX). As the drum rotated, indium phosphide filled six metering ports in a disk at the bottom of the drum and was held in each port by a stainless-steel screen. The metering ports sequentially aligned with a nitrogen inlet in the body and dispersed indium phosphide when a nitrogen solenoid valve was opened. The aerosol passed through a delivery tube penetrating the cap into the distribution system. A spring-loaded Teflon® tip, attached to the bottom of the delivery tube, scraped excess indium phosphide from the metering ports and captured material dispersed by the puff of nitrogen through the metering port. Output of the generator was regulated by adjusting the rotation cadence.

In all studies, to control static charge, the aerosol leaving the generator passed through a corona discharge air-ionizing neutralizer (Conveyostat Static Neutralizing System, Simco, Inc., Hatfield, PA), which generated an ion stream that brought the aerosol near Boltzmann equilibrium. The ozone generated by the system's corona discharge was monitored with a Dasibi Model 1003-PC ozone monitor (Glendale, CA) equipped with an internal ozone standard generator. Aerosol passed through the charge neutralizer into the distribution line. In the 14-week studies, this line was branched to allow predilution of the test article distributed to the 1, 3, and 10 mg/m^3 chambers to achieve the desired concentration range. At each chamber location, a pneumatic injector developed by the study laboratory drew aerosol from the distribution line into the chamber inlet, where the aerosol was further diluted with HEPA-filtered air to the appropriate concentration. The flow rate through the distribution line was controlled by vacuum pumps (Air-Vac Engineering Company, Inc., Milford, CT); pressure was monitored by photohelic differential pressure gauges (Dwyer Instruments, Inc., Michigan City, IN).

The study laboratory designed the stainless-steel inhalation exposure chambers (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform aerosol concentrations could be maintained throughout the chambers when catch pans were in place. The total active mixing volume of each chamber was 1.7 m^3.

AEROSOL CONCENTRATION MONITORING

Summaries of chamber aerosol concentrations of indium phosphide are given in Tables J1 and J2. Chamber aerosol concentrations were monitored with real-time aerosol monitors (RAMs) (Model Ram-1; MIE, Inc., Bedford, MA) that used a pulsed-light-emitting diode in combination with a silicon detector to sense light scattered over a forward angular range of 45° to 95° by particles traversing the sensing volume. The instrument responds to particles 0.1 to 20 μm in diameter; the geometric diameter of indium phosphide aerosol approached the minimum of this range. The sampling system consisted of a valve which multiplexed each RAM to two or three exposure chambers and either the control chamber, the room, or a HEPA filter. The monitors were connected to the chambers with sample lines designed to minimize aerosol particle loss through settling or impaction. Selection of sampling streams and data acquisition from each RAM was remotely controlled by a computer (Gateway 2000, San Diego, CA). Equations for calibration curves were stored in the computers and were used to convert the measured voltages to exposure concentrations.

Each RAM was calibrated by correlating the measured voltage with indium phosphide concentrations determined by analyzing exposure chamber samples collected on fiberglass filters (Teflon®-coated Pallflex, Pallflex Corp., Putnum, CT). Filters for the 14-week studies were dissolved in hydrochloric acid and analyzed for indium phosphide using ICP/AES. Filters for the 2-year studies were dissolved in hydrochloric acid and analyzed for indium phosphide using inductively coupled plasma mass spectroscopy (ICP/MS). RAMs were calibrated approximately every 2 weeks (14-week studies) or as needed according to the results of the calibration verification analyses (2-year studies). During the 14-week studies, calibration was verified by ICP/AES analysis of filter samples collected every other day (control chambers) or daily. During the 2-year studies, calibration was verified by ICP/MS analysis of filter samples collected at least every other exposure day.

CHAMBER ATMOSPHERE CHARACTERIZATION

The particle size distribution in each chamber was determined during the prestudy testing, during the first week of the studies, and monthly thereafter using a Mercer-style seven-stage impactor (In-Tox Products, Albuquerque, NM). The stages (glass coverslips lightly sprayed with silicon) were analyzed by ICP/AES (14-week studies) or ICP/MS (2-year studies). The relative mass collected on each stage was analyzed by probit analysis. The mass median aerodynamic particle diameter and the geometric standard deviation of each set of samples were estimated (Tables J3, J4, and J5).

Buildup and decay rates for chamber aerosol 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 aerosol generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after aerosol generation was terminated (T_{10}) was approximately 12.5 minutes. For rats and mice in the 14-week studies, T_{90} values ranged from 8 to 11 minutes without animals present and from 9 to 11 minutes with animals; T_{10} values ranged from 5 to 9 minutes with and without animals present. In the 2-year rat study, T_{90} values ranged from 6 to 8 minutes without animals present and was 8 to 13 minutes with animals; the T_{10} value was 8 minutes without animals present and ranged from 8 to approximately 12 minutes with animals. In the 2-year mouse studies, the T_{90} value was 7 or 8 minutes without animals present and ranged from 6 to 15 minutes with animals; the T_{10} value was 9 minutes without animals present and ranged from 10 to 12 minutes with animals. A T_{90} value of 12 minutes was selected for all studies.

Uniformity of aerosol concentration in the 14-week studies was evaluated during prestudy testing without animals present and once during the studies with animals present in exposure chambers. During the 2-year studies, uniformity was evaluated every 2 to 4 months. Measurements were taken from 12 different chamber positions (one in front and one in back for each of the six possible animal cage unit positions per chamber). An extension tube fitted to the sampling lines of each RAM allowed sampling from all of the chamber ports. Chamber concentration uniformity was acceptable throughout the studies.

The persistence of indium phosphide aerosol in the exposure chambers was monitored overnight after aerosol delivery ceased. The 100 mg/m^3 exposure chambers were monitored during the 14-week studies; for the 2-year studies, an 0.5 mg/m^3 chamber (without animals) was monitored during prestudy testing and the 0.3 mg/m^3 rat chamber (with animals) was monitored during exposure. The average indium phosphide concentration decayed to 1% of target concentration within approximately 20 (14-week studies) or 21 minutes (2-year studies).

The stability of indium phosphide in the generator reservoir, distribution line, 1 and 100 mg/m^3 exposure chambers (with and without animals present) (14-week studies), and 0.03, 0.1, and 0.3 mg/m^3 chambers (2-year studies) was tested with XRD. Samples were collected from the generator reservoir at the beginning

and end of the generation period. The samples were analyzed, along with samples of the bulk chemical, for crystalline phases by XRD analysis. Samples from the distribution lines and exposure chambers in the 14-week studies were collected on Gelman A/E fiberglass filters (Gelman Sciences, Ann Arbor, MI) mounted on an off-axis, single-crystal, quartz plate; samples from the generator reservoir were packed into an off-axis, single-crystal, quartz cavity. All samples were tested on an XRD system consisting of a diffraction apparatus and a Philips XRG3100 X-ray generator operating a fixed-anode, long-fine-focus copper tube at 40 kV and 45 mA. Samples from the 2-year studies were collected on Gelman A/E fiberglass filters and analyzed with a Philips 3000 series X-ray diffractometer using a fixed copper anode source operated at 45 kV and 40 mA. The XRD patterns for all samples were consistent with that expected for indium phosphide.

Stability analyses were also performed with ICP/AES. Filter samples from the 1, 3, and 100 mg/m^3 exposure chambers (14-week studies), 0.03, 0.1, and 0.3 mg/m^3 chambers (2-year studies), and aerosol distribution lines were collected as described for RAM calibration and analyzed as described for the bulk chemical purity analyses to determine whether inorganic impurities were introduced by the exposure generation system. The filters were analyzed by ICP/AES and compared to samples of indium phosphide collected from the generator reservoir. For the 14-week studies, results for samples from the generator reservoir, distribution line, and exposure chambers were in agreement with the theoretical values for indium and phosphorus. Trace element impurities totaled less than 0.3% for generator reservoir samples and less than 0.2% for distribution line samples; samples from the 1, 3, and 100 mg/m^3 chambers totaled less than 1.6%, 0.6%, and 0.6% impurities, respectively. For the 2-year studies, the percentages of indium and phosphorus in the generator reservoir samples were slightly less than the theoretical values; all samples contained 0.8% impurities or less.

Before and during the 14-week study, the concentration of ozone in the 1 and 100 mg/m^3 chambers and the distribution line were determined using an ozone monitor with an internal ozone standard generator. Ozone concentrations in the distribution line (0.055 ppm) were elevated over ambient concentrations. Concentrations in the exposure chambers were two to three times greater without the generator operating than with the generator operating, indicating that indium phosphide aerosol may react with ozone. Introduction of purified dilution air reduced the ozone concentrations; ozone concentrations in the 0 and 1 mg/m^3 chambers were approximately 0.001 ppm, and the concentration in the 100 mg/m^3 chamber was approximately 0.003 ppm.

Phosphine concentrations were measured prior to the 14-week study using phosphine/arsine detector tubes (Kitagawa, Inc., East Rutherford, NJ). The phosphine concentration in the distribution line was 0.02% relative to the indium phosphide concentration; phosphine concentrations in the 1 and 100 mg/m^3 exposure chambers were less than the limits of detection. In all locations, the phosphine concentration was less than 0.1% of the test chemical concentration. This determination was not made with animals in the chambers because of ammonia interference.

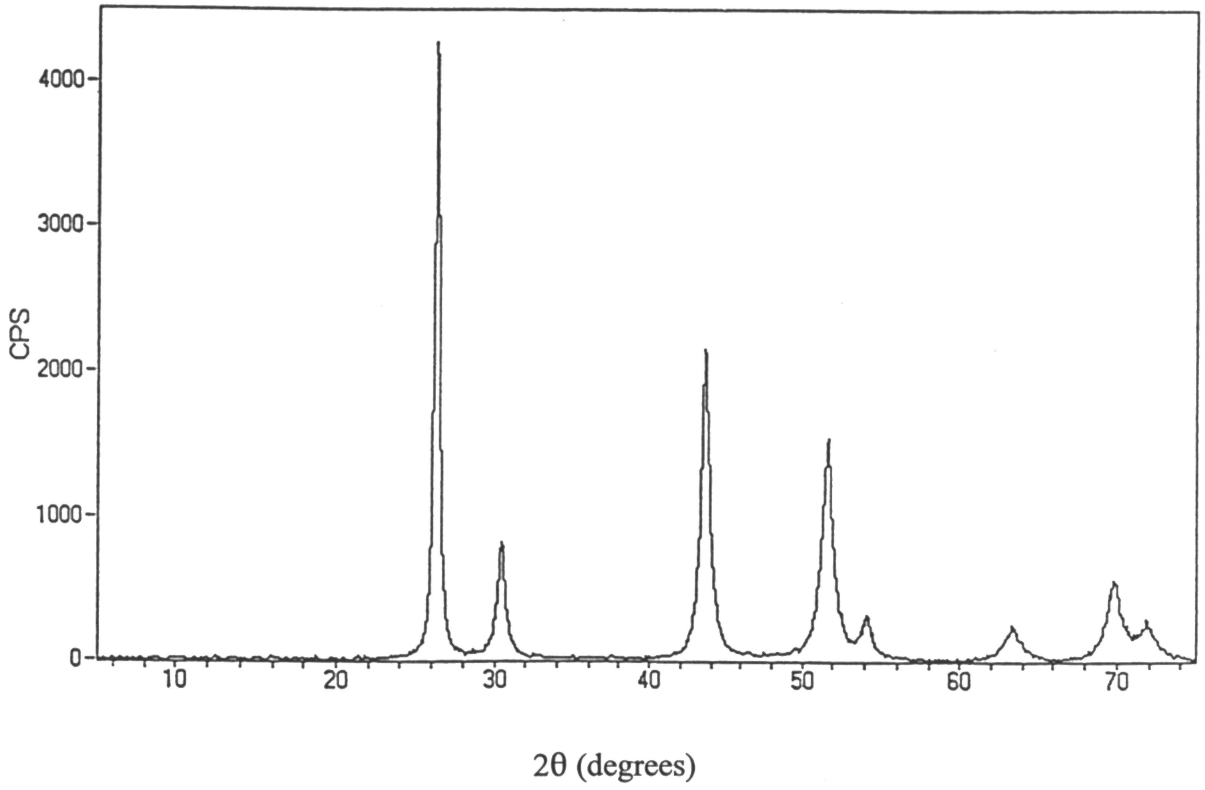


Figure J1
X-ray Diffraction Pattern of Indium Phosphide.

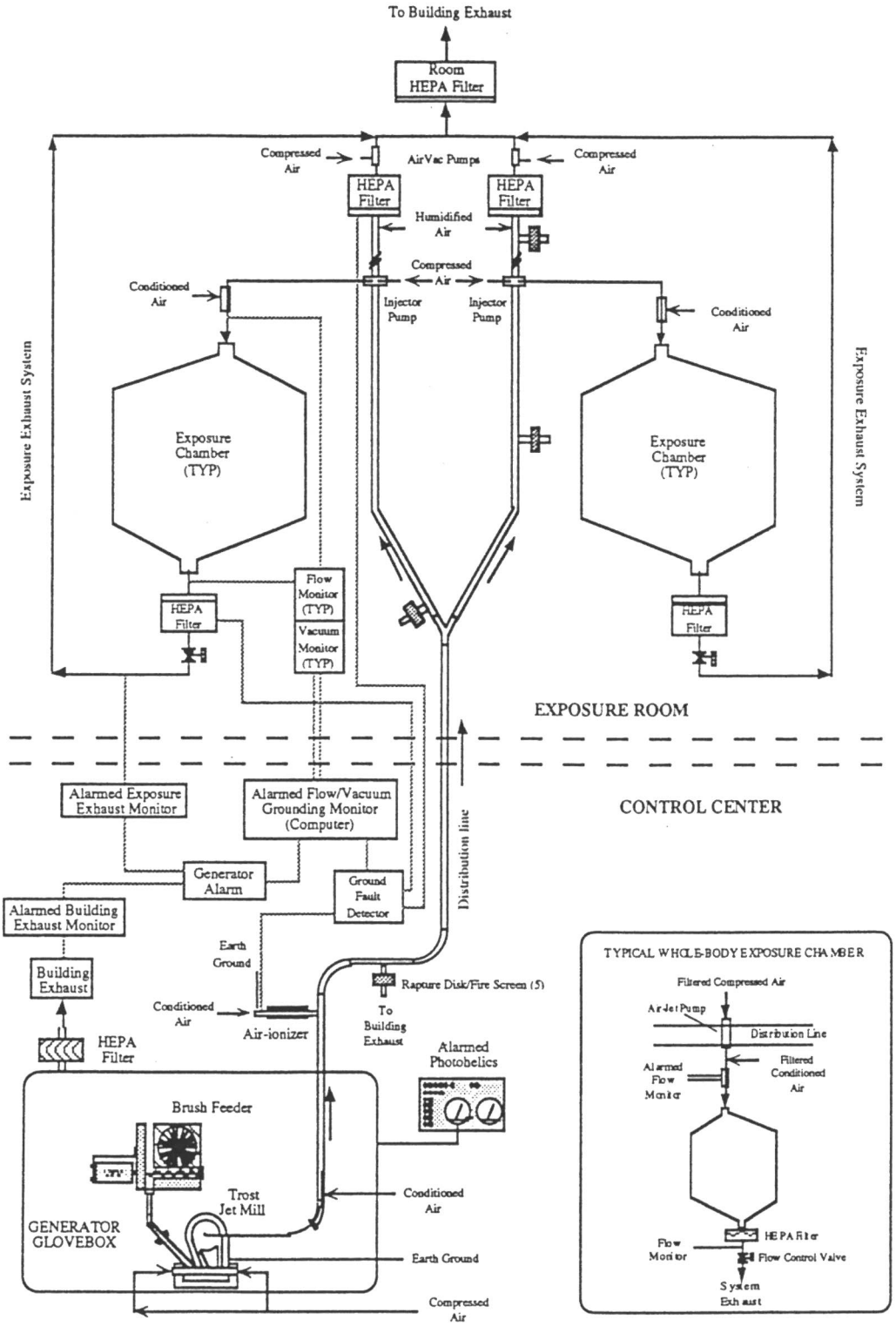


Figure J2
Schematic of the Aerosol Generation and Delivery System in the 14-Week Inhalation Studies of Indium Phosphide.

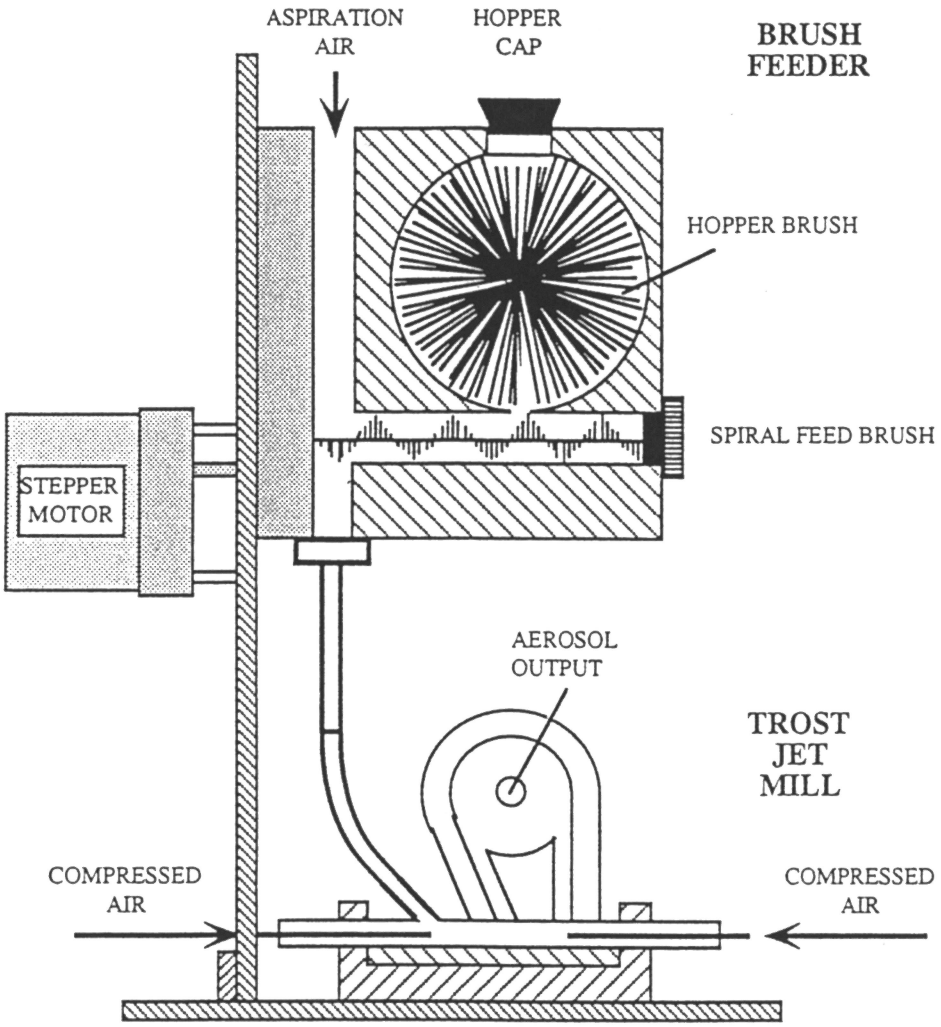


Figure J3
Schematic of the Flexible-Brush Dust Feed Mechanism in the 14-Week Inhalation Studies of Indium Phosphide.

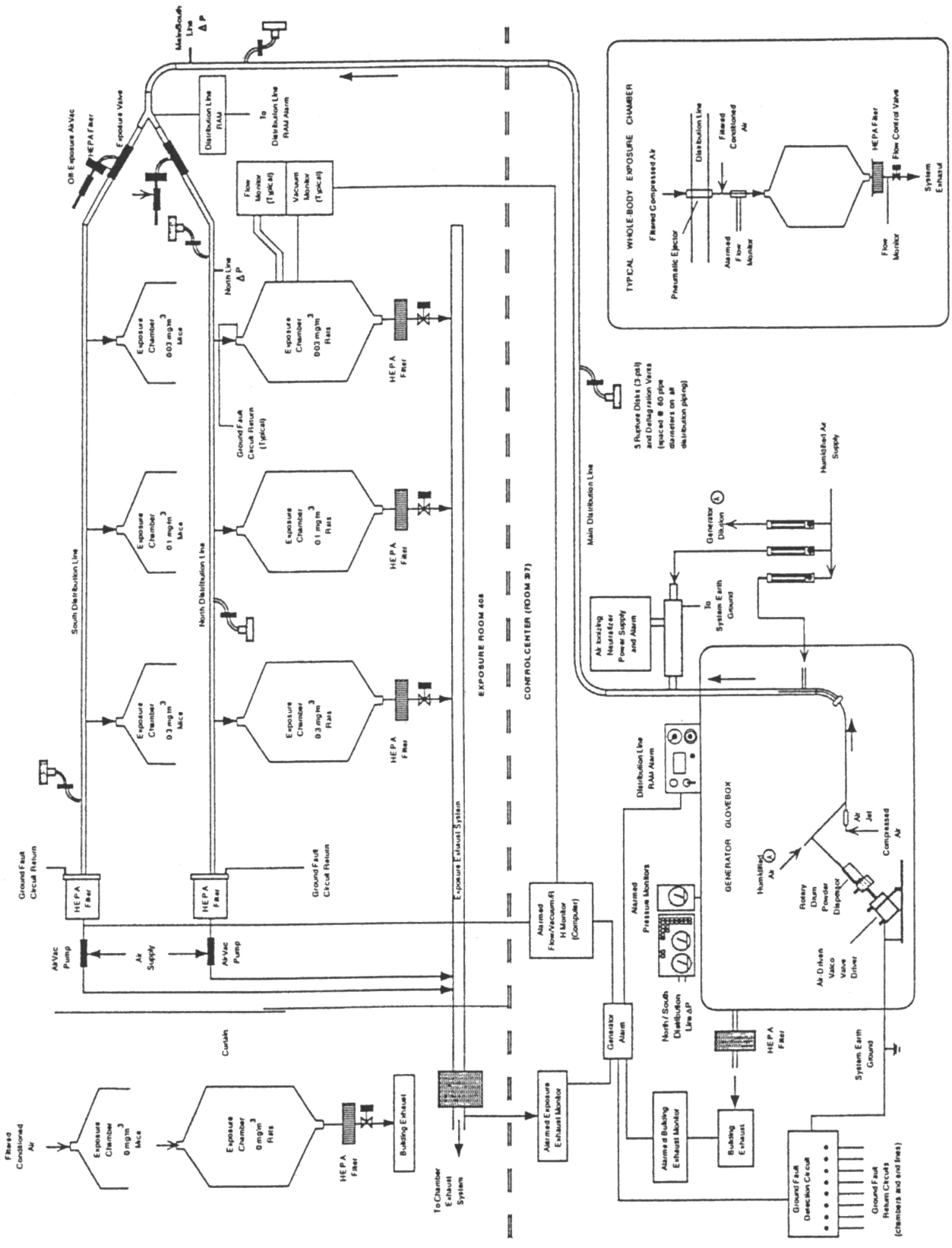


Figure J4
Schematic of the Aerosol Generation and Delivery System in the 2-Year Inhalation Studies of Indium Phosphide.

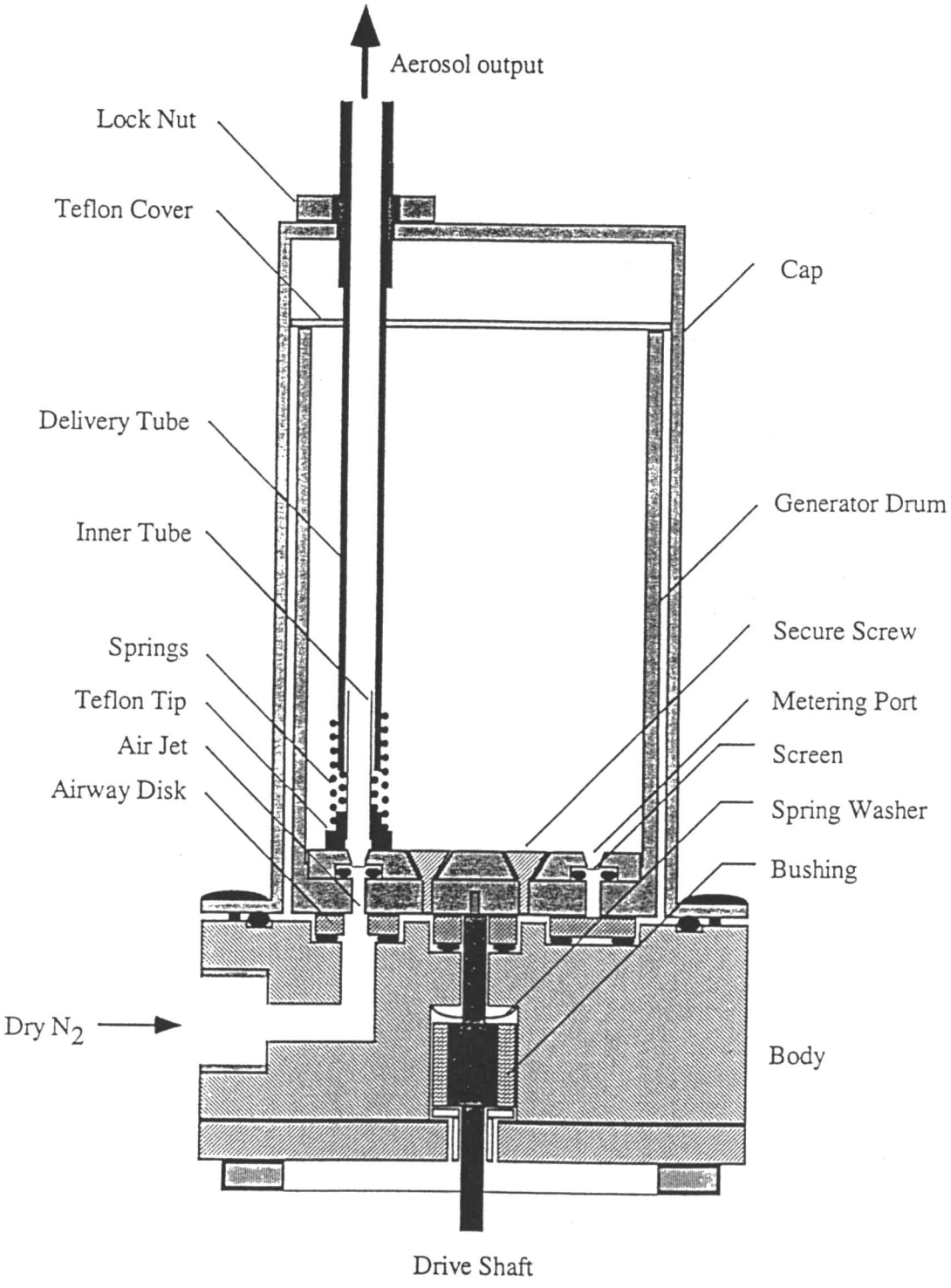


Figure J5
Schematic of the Rotary Drum Generator
in the 2-Year Inhalation Studies of Indium Phosphide.

TABLE J1
Summary of Chamber Concentrations in the 14-Week Inhalation Studies of Indium Phosphide

Target Concentration (mg/m^3)	Total Number of Readings	Average Concentration[a] (mg/m^3)
Rat Chambers		
1	759	0.98 ± 0.12
3	757	3.09 ± 0.39
10	758	9.95 ± 1.08
30	760	30.0 ± 4.5
100	759	98.8 ± 12.0
Mouse Chambers		
1	779	0.98 ± 0.13
3	777	3.09 ± 0.38
10	778	9.96 ± 1.08
30	780	30.0 ± 4.6
100	779	98.9 ± 12.0

[a] Mean ± standard deviation

TABLE J2
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Indium Phosphide

Target Concentration (mg/m^3)	Total Number of Readings	Average Concentration[a] (mg/m^3)
Rat Chambers		
0.03	4,915	0.030 ± 0.003
0.1[b]	1,026	0.100 ± 0.009
0.3	1,026	0.297 ± 0.026
Mouse Chambers		
0.03	4,911	0.030 ± 0.003
0.1	977	0.100 ± 0.008
0.3	977	0.300 ± 0.022

[a] Mean ± standard deviation
[b] Exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 142.

TABLE J3
Summary of Aerosol Size Measurements for the Rat and Mouse Exposure Chambers in the 14-Week Inhalation Studies of Indium Phosphide[a]

	1 mg/m^3		3 mg/m^3		10 mg/m^3		30 mg/m^3		100 mg/m^3	
	MMAD (µm)	GSD	MMAD (µm)	GSD	MMAD (µm)	GSD	MMAD (µm)	GSD	MMAD (µm)	GSD
April 1995	1.3	1.6	1.4	1.7	1.5	1.5	1.5	1.6	1.5	1.6
May 1995	1.4	1.6	1.4	1.6	1.3	1.6	1.4	1.6	1.3	1.6
June 1995	1.2	1.6	1.2	1.7	1.4	1.6	1.3	1.5	1.2	1.6

[a] MMAD=mass median aerodynamic diameter; GSD=geometric standard deviation

TABLE J4
Summary of Aerosol Size Measurements for the Rat Exposure Chambers in the 2-Year Inhalation Studies of Indium Phosphide[a]

	0.03 mg/m^3		0.1 mg/m^3		0.3 mg/m^3	
	MMAD (µm)	GSD	MMAD (µm)	GSD	MMAD (µm)	GSD
January 1996	1.1	1.8	1.2	1.6	1.3	1.7
February 1996	1.2	1.8	1.2	1.8	1.2	1.7
March 1996	1.2	1.7	1.1	1.8	1.2	1.7
April 1996	1.2	1.8	1.1	1.8	1.1	1.8
May 1996	1.2	1.8	1.2	1.8	1.3	1.7
June 1996	1.3	1.6	1.3	1.6	1.2	1.8
July 1996	1.2	1.6				
August 1996	1.2	1.7				
September 1996	1.2	1.6				
October 1996	1.2	1.6				
November 1996	1.1	1.8				
December 1996	1.2	1.8				
January 1997	1.1	1.8				
February 1997	1.1	1.8				
March 1997	1.2	1.7				
April 1997	1.2	2.0				
May 1997	1.2	1.9				
July 1997	1.3	1.8				
July 1997	1.3	1.8				
August 1997	1.1	1.8				
September 1997	1.1	1.8				
October 1997	1.1	1.8				
November 1997	1.1	1.9				
December 1997	1.2	1.8				
January 1998	1.1	1.9				
Mean ± standard deviation	1.2 ± 0.1	1.8 ± 0.1	1.2 ± 0.1	1.7 ± 0.1	1.2 ± 0.1	1.7 ± 0.1

[a] MMAD=mass median aerodynamic diameter; GSD=geometric standard deviation; exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 142.

TABLE J5
Summary of Aerosol Size Measurements for the Mouse Exposure Chambers in the 2-Year Inhalation Studies of Indium Phosphide[a]

	0.03 mg/m^3		0.1 mg/m^3		0.3 mg/m^3	
	MMAD (µm)	GSD	MMAD (µm)	GSD	MMAD (µm)	GSD
February 1996	1.2	1.8	1.2	1.7	1.3	1.8
March 1996	1.2	1.8	1.2	1.7	1.2	1.8
April 1996	1.2	1.8	1.2	1.7	1.3	1.7
May 1996	1.1	1.8	1.2	1.7	1.3	1.7
June 1996	1.2	1.9	1.2	1.8	1.2	1.9
July 1996	1.2	1.8				
August 1996	1.2	1.7				
September 1996	1.2	1.6				
October 1996	1.3	1.6				
November 1996	1.2	1.8				
December 1996	1.2	1.9				
January 1997	1.2	1.8				
February 1997	1.2	1.8				
March 1997	1.3	1.8				
April 1997	1.3	1.8				
May 1997	1.3	1.9				
July 1997	1.3	1.8				
July 1997	1.3	1.8				
August 1997	1.1	1.8				
September 1997	1.2	1.8				
October 1997	1.2	1.9				
November 1997	1.2	1.8				
December 1997	1.2	1.8				
January 1998	1.2	1.9				
Mean ± standard deviation	1.2 ± 0.1	1.8 ± 0.1	1.2 ± 0.0	1.7 ± 0.0	1.3 ± 0.1	1.8 ± 0.1

[a] MMAD=mass median aerodynamic diameter; GSD=geometric standard deviation; exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 142.

APPENDIX K
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE K1
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 K2
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 K3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.5 ± 0.51	12.5 – 14.7	22
Crude fat (% by weight)	8.1 ± 0.32	7.5 – 8.7	22
Crude fiber (% by weight)	9.7 ± 0.48	8.5 – 10.3	22
Ash (% by weight)	5.0 ± 0.15	4.8 – 5.4	22
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)	4,718 ± 1,291	2,780 – 8,140	22
Vitamin D (IU/kg)[a]	1,000		
α-Tocopherol (ppm)	77.2 ± 10.94	62.2 – 87.1	6
Thiamine (ppm)[b]	8.4 ± 1.96	6.0 – 15.0	22
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 (%)	0.963 ± 0.042	0.867 – 1.050	22
Phosphorus (%)	0.568 ± 0.020	0.533 – 0.620	22
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 K4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.25 ± 0.131	0.10 – 0.50	22
Cadmium (ppm)	0.05 ± 0.014	0.040 – 0.10	22
Lead (ppm)	0.11 ± 0.074	0.06 – 0.40	22
Mercury (ppm)	<0.02		22
Selenium (ppm)	0.17 ± 0.037	0.11 – 0.26	22
Aflatoxins (ppb)	<5.00		22
Nitrate nitrogen (ppm)[c]	15.4 ± 5.88	9.0 – 31.9	22
Nitrite nitrogen (ppm)[c]	0.71 ± 0.424	0.30 – 2.00	22
BHA (ppm)[d]	1.0 ± 0.35	0.01 – 2.14	22
BHT (ppm)[d]	1.0 ± 0.35	0.01 – 1.80	22
Aerobic plate count (CFU/g)[e]	205,500 ± 389,559	25,000 – 1,000,000	6
Coliform (MPN/g)[e]	11 ± 10	3 – 30	6
Escherichia coli (MPN/g)[e]	<10		22
Salmonella (MPN/g)[e]	Negative		22
Total nitrosoamines (ppb)[f]	5.7 ± 3.85	2.1 – 20.9	22
N-Nitrosodimethylamine (ppb)[f]	2.6 ± 1.85	1.0 – 6.4	22
N-Nitrosopyrrolidine (ppb)[f]	3.1 ± 2.84	1.0 – 14.5	22
Pesticides (ppm)			
α-BHC	<0.01		22
β-BHC	<0.02		22
γ-BHC	<0.01		22
δ-BHC	<0.01		22
Heptachlor	<0.01		22
Aldrin	<0.01		22
Heptachlor epoxide	<0.01		22
DDE	<0.01		22
DDD	<0.01		22
DDT	<0.01		22
HCB	<0.01		22
Mirex	<0.01		22
Methoxychlor	<0.05		22
Dieldrin	<0.01		22
Endrin	<0.01		22
Telodrin	<0.01		22
Chlordane	<0.05		22
Toxaphene	<0.01		22
Estimated PCBs	<0.20		22
Ronnel	<0.01		22
Ethion	<0.02		22
Trithion	<0.05		22
Diazinon	<0.10		22
Methyl chlorpyrifos	0.063 ± 0.055	0.010 – 0.200	21
Methyl parathion	<0.02		22
Ethyl parathion	<0.02		22
Malathion	0.187 ± 0.201	0.020 – 0.830	22
Endosulfan I	<0.01		22
Endosulfan II	<0.01		22
Endosulfan sulfate	<0.03		22

[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 L
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 and mice during the 14-week and 2-year studies. 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 (Bethesda, 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
RATS	
14-Week Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Immunofluorescence Assay	
M. arthritidis	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	5, 12, and 17 months, study termination
RCV/SDA	5, 12, and 17 months, study termination
Sendai	5, 12, and 17 months, study termination
Immunofluorescence Assay	
M. arthritidis	Study termination
Parvovirus	Study termination

Method and Test	Time of Analysis
RATS (continued)	
2-Year Study (continued)	
Hemagglutination Inhibition	
H-1	5, 12, and 17 months
KRV	5, 12, and 17 months
MICE	
14-Week Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
MCMV (mouse cytomegalovirus)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
2-Year Study	
ELISA	
Ectromelia virus	6, 12, and 17 months, study termination
EDIM	6, 12, and 17 months, study termination
GDVII	6, 12, and 17 months, study termination
LCM	6, 12, and 17 months, study termination
Mouse adenoma virus-FL	6, 12, and 17 months, study termination
MHV	6, 12, and 17 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 17 months, study termination
Reovirus 3	6, 12, and 17 months, study termination
Sendai	6, 12, and 17 months, study termination

Method and Test	Time of Analysis
MICE (continued)	
2-Year Study (continued)	
Immunofluorescence Assay	
EDIM	Study termination
GDVII	Study termination
Mouse ademona virus-FL	12 months and study termination
MCMV	Study termination
M. arthritidis	Study termination
Parvovirus	Study termination
PVM	Study termination
Hemagglutination Inhibition	
K	6, 12, and 17 months
MVM	6, 12, and 17 months
Polyoma virus	6, 12, and 17 months

RESULTS

All results were negative.

APPENDIX M
MUTATIONS OF β-CATENIN AND H-*ras* IN HEPATOCELLULAR ADENOMAS AND CARCINOMAS OF B6C3F$_1$ MICE EXPOSED TO INDIUM PHOSPHIDE FOR 2 YEARS

Robert C. Sills, Thai Vu Ton, Shim-mo Hayashi, Hue-Hua L. Hong, Joseph H. Roycroft, and Theodora R. Devereux

National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

MUTATIONS OF β-CATENIN AND H-*ras* IN HEPATOCELLULAR ADENOMAS AND CARCINOMAS OF B6C3F$_1$ MICE EXPOSED TO INDIUM PHOSPHIDE FOR 2 YEARS

INTRODUCTION

In the 2-year indium phosphide mouse study, there was a significant increase in the incidences of lung and hepatocellular neoplasms. The focus of this study was to evaluate both spontaneous and indium phosphide-induced hepatocellular neoplasms for mutations in cancer genes important in the pathogenesis of human cancer. A representative number of frozen mouse hepatocellular neoplasms from the 2-year study were available for analysis.

In evaluating potential hazards of chemical exposure to humans, it is important to assess how the chemical acts at the molecular level, i.e., through a genotoxic mechanism or via other indirect mechanisms such as promotion of spontaneous DNA damage. In the past, the patterns of mutations in proto-oncogenes such as *ras* and in tumor suppressor genes such as p53 have been found to help in the understanding of tumorigenesis (Harris, 1993; Maronpot *et al.*, 1995). For example, in some neoplasms, the profiles of activating mutations in *ras* genes are specific for particular chemicals and differ from those detected in spontaneous neoplasms (Sills *et al*., 1999). In this study, hepatocellular adenomas and carcinomas from B6C3F$_1$ mice exposed to indium phosphide by inhalation for up to 2 years were examined for genetic alterations in H-*ras* and β-catenin; genes shown to be altered in human hepatocellular and colon cancer (De La Coste *et al.*, 1998; Mirabelli-Primdahl *et al.*, 1999).

MATERIALS AND METHODS

Hepatocellular Neoplasms: Similar numbers of hepatocellular neoplasms (approximately 10) from male and female B6C3F$_1$ mice in each group (0, 0.03, 0.1, and 0.3 mg/m^3) were used.

DNA Isolation: The DNA isolation procedure has been described previously (Marmur, 1961; Devereux *et al*., 1993).

Mutation Detection and Identification: Single-strand conformation polymorphism (SSCP) analysis was carried out on polymerase chain reaction (PCR) products corresponding to exon 2 of H-*ras* and exon 2 of β-catenin (Devereux *et al.*, 1999). For cases that showed PCR products with altered mobility in the SSCP gel electrophoresis analysis, samples were reamplified and cycle-sequenced using a ^{33}P-ddNTP ThermoSequenase™ kit (Amersham Pharmacia Biotech, Piscataway, NJ).

Immunohistochemistry: Hepatocellular neoplasms were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin. Localization of β-catenin expression was investigated using a polyclonal goat anti-β-catenin antibody (Santa Cruz Biotechnology, Santa Cruz, CA). Nonimmune rabbit IgG (Jackson Immunoresearch Labs, West Grove, PA) at equivalent conditions in place of the primary antibody was used as the negative control.

RESULTS

Indium phosphide-induced hepatocellular neoplasms were analyzed for mutations in codon 61 of the H-*ras* proto-oncogene. The *ras* mutation spectra in exposed groups were similar to those in the chamber control groups and consisted primarily of CAA-to-AAA transversions. Compared to the presence of CAA-to-CGA transitions in the 0.3 mg/m^3 groups and chamber control groups, there was a lack of this mutation in the 0.03 and 0.1 mg/m^3 groups.

All of the indium phosphide-induced and spontaneous hepatocellular neoplasms were examined by immunohistochemical methods for accumulation of the β-catenin protein. Minimal to mild membrane staining for the β-catenin protein was observed in all spontaneous and indium phosphide-induced hepatocellular neoplasms. Moderate membrane staining for the β-catenin protein was seen in one hepatocellular carcinoma and a hepatoblastoma with a deletion mutation. One hepatocellular carcinoma with both nuclear and membrane staining for the β-catenin protein had a point mutation. Compared to the histologically normal liver where β-catenin accumulation was also seen staining the membrane of hepatocytes, the accumulation within hepatocellular neoplasms was generally greater.

Based on the detection of the β-catenin protein by immunohistochemistry methods, spontaneous and indium phosphide-induced hepatocellular neoplasms from B6C3F$_1$ mice were examined for molecular alterations in exon 2 of the β-catenin gene, the region that contains potential phosphorylation sites for the glycogen-synthase kinase-3β (GSK-3β) enzyme. In the 10 spontaneous hepatocellular neoplasms, only one (10%) had a β-catenin point mutation at codon 41, consisting of an A-to-G transition. Two of thirteen (15%) from the 0.03 mg/m^3 exposure group, 0 of 10 (0%) from the 0.1 mg/m^3 exposure group, and 4 of 10 neoplasms (40%) from the 0.3 mg/m^3 exposure group had β-catenin mutations. All of the point mutations affected codons 32, 41, or 45, sites that are targeted for phosphorylation by the GSK-3β kinase or that are involved in ubiquitination of the protein and are important in regulation of β-catenin turnover. Three different base substitutions were represented among the three mutant codons.

DISCUSSION

The finding of a predominance of H-*ras* codon 61 AAA mutations in both spontaneous and indium phosphide-induced hepatocellular neoplasms is consistent with other studies where *ras* mutations have been shown to play a role in the pathogenesis of mouse liver tumors (Devereux *et al.*, 1993; Maronpot *et al.*, 1995; Hong *et al*., 1998). Chemical-specific *ras* mutations were not detected in indium phosphide-induced neoplasms, however, there was a lack of CGA mutations at the 0.03 and 0.1 mg/m^3 exposure concentrations.

The β-catenin protein was detected in all spontaneous and indium phosphide-induced hepatocellular neoplasms suggesting that the Wnt-signaling pathway was involved in the carcinogenic process. β-Catenin protein accumulation and upregulation of the Wnt-signaling pathway have been shown following mutations in either the adenomatous polyposis coli (APC) or β-catenin gene (Behrens, 1999). In addition, alterations in the Axin complex may result in enhanced β-catenin expression; β-catenin and APC interact with Axin, and the phosphorylation and stability of β-catenin are regulated by the Axin complex (Kikuchi, 1999). Recently, mutations in Axin have been identified in human hepatocellular carcinomas (Satoh *et al.*, 2000).

Consistent with the immunohistochemical detection of the β-catenin protein, somatic mutations of β-catenin were identified in 15% of hepatocellular neoplasms from the 0.03 mg/m^3 exposure group and in 40% of indium phosphide-induced hepatocellular neoplasms from the 0.3 mg/m^3 exposure group, compared to 10% of spontaneous hepatocellular neoplasms, or 9% (2/22) in other spontaneous hepatocellular neoplasms evaluated (De La Coste *et al*., 1998; Devereux *et al*., 1999). The lack of β-catenin mutations in the 0.1 mg/m^3 group and in other hepatocellular neoplasms which were positive for the β-catenin protein suggests other players in the Wnt-signaling pathway may be involved in the development of hepatocellular neoplasms. Alternatively,

β-catenin mutations outside the exons examined may provide clues for the enhanced accumulation of β-catenin protein. The 0.1 mg/m^3 exposure concentration could also be considered the "low dose" based on lung burden.

It is of interest that deletion mutations were detected only at the 0.03 and 0.3 mg/m^3 exposure concentrations when it was estimated that the lung burden of the continuously-exposed 0.03 mg/m^3 group was equal to or greater than that of the 0.3 mg/m^3 group at the end of the study. These results are of significance since the deletion mutations are suggestive of a chemical effect. Identical mutations have been found in human hepatocellular neoplasms, suggesting similar pathways of carcinogenesis in each species.

REFERENCES

Behrens, J. (1999). Cadherins and catenins: Role in signal transduction and tumor progression. *Cancer Metastasis Rev.* **18,** 15-30.

De La Coste, A., Romagnolo, B., Billuart, P., Renard, C., Buendia, M., Soubrane, O., Fabre, M., Chelly, J., Beldjord, C., Kahn, A., and Perret, C. (1998). Somatic mutations of β-catenin gene are frequent in mouse and human hepatocellular carcinomas. *Proc. Natl. Acad. Sci. USA* **95,** 8847-8851.

Devereux, T.R., Foley, J.F., Maronpot, R.R., Kari, F., and Anderson, M.W. (1993). Ras proto-oncogene activation in liver and lung tumors from B6C3F1 mice exposed chronically to methylene chloride. *Carcinogenesis* **14,** 795-801.

Devereux, T.R., Anna, C.H., Foley, J.F., White, C.M., Sills, R.C., and Barrett, J.C. (1999). Mutation of β-catenin is an early event in chemically induced mouse hepatocellular carcinogenesis. *Oncogene* **18,** 4726-4733.

Harris, C.C. (1993). p53: At the crossroads of molecular carcinogenesis and risk assessment. In *Science*, pp. 1980-1981.

Hong, H.L., Devereux, T.R., Roycroft, J.H., Boorman, G.A., and Sills, R.C. (1998). Frequency of ras mutations in liver neoplasms from B6C3F1 mice exposed to tetrafluoroethylene for two years. *Toxicol. Pathol.* **26,** 646-650.

Kikuchi, A. (1999). Roles of axin in the Wnt signaling pathway. *Cell. Signal.* **11,** 777-788.

Marmur, J. (1961). A procedure for isolation of deoxyribonucleic acid from microorganisms. *J. Mol. Biol.* **3,** 208-218.

Maronpot, R.R., Fox, T., Malarkey, D., and Goldsworthy, T. (1995). Mutations in the ras proto-oncogene: Clues to etiology and molecular pathogenesis of mouse liver tumors. *Toxicology* **101,** 125-156.

Mirabelli-Primdahl, L., Gryfe, R., Kim, H., Millar, A., Luceri, C., Dale, D., Holowaty, E., Bapat, B., Gallinger, S., and Redston, M. (1999). β-catenin mutations are specific for colorectal carcinomas with microsatellite instability but occur in endometrial carcinomas irrespective of mutator pathway. *Cancer Res.* **59,** 3346-3351.

Satoh, S., Daigo, Y., Furukawa, Y., Kato, T., Miwa, N., Nishiwaki, T., Kawasoe, T., Ishiguro, H., Fujita, M., Tokino, T., Sasaki, Y., Imaoka, S., Murata, M., Shimano, T., Yamaoka Y., and Nakamura, Y. (2000). AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1. *Nature Genet.* **24,** 245-250.

Sills, R.C., Boorman, G.A., Neal, G.E., Hong, H.L., and Devereux, T. R. (1999). Mutations in ras genes in experimental tumors of rodents. In *The use of short- and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation* (D.B. McGregor, J.M. Rice, and S. Venitt., Eds.), pp. 55-86. International Agency for Research on Cancer, Lyon, France.

TABLE M1
Mutations of β-Catenin and H-*ras* Genes in Spontaneously Occurring and Indium Phosphide-Induced Hepatocellular Neoplasms from Mice in the 2-Year Inhalation Study of Indium Phosphide[a]

Animal ID Number	Gender	Exposure Concentration (mg/m^3)[d]	Neoplasm	H-*ras* Codon 61			Membrane Staining[b]	β-Catenin
				CGA	CTA	AAA		
312	F	0.03	HC			+	+	
317	F	0.03	HC				++[c]	Codon 32, GAT to GCT
318	F	0.03	HA			+	+	
324	F	0.03	HC			+	+	
331	F	0.03	HC				+	
206-1	M	0.03	HC				++	
206-2	M	0.03	HC				++	
207	M	0.03	HC				++	
221	M	0.03	HC				++	
223-HB	M	0.03	HB				+++	Deletion 5-7
223-HC	M	0.03	HC				+	
226-HC	M	0.03	HC				++	
226-HA	M	0.03	HA				+	
402	M	0.1	HC				+	
407	M	0.1	HC				+	
411	M	0.1	HC				++	
414	M	0.1	HC				++	
416	M	0.1	HC			+	++	
512	F	0.1	HC				+	
514	F	0.1	HC			+	++	
516	F	0.1	HC			+	++	
539	F	0.1	HC				++	
549	F	0.1	HC				+	
709	F	0.3	HA				+	Codon 45, TCC to TTC
711	F	0.3	HC			+	++	Deletion 5-8
712	F	0.3	HA			+	++	
720-1	F	0.3	HC			+	+	
720-2	F	0.3	HC				+	
601	M	0.3	HC	+			++	Deletion 5-12
603	M	0.3	HC			+	+	
613	M	0.3	HC	+			+++	Deletion 23-36
619	M	0.3	HC				+	
620	M	0.3	HC	+			+++	
118	F	0	HA			+	+	
123	F	0	HA	+			+	
131	F	0	HC			+	++	
141	F	0	HC	+			++	
148	F	0	HC			+	++	
12	M	0	HC	+			++	
18	M	0	HA				++	
24	M	0	HC				+	
30	M	0	HC				+	
47	M	0	HC	+			++	Codon 41, ACC to GCC

[a] HA=hepatocellular adenoma, HC=hepatocellular carcinoma, HB=hepatoblastoma
[b] β-Catenin immunohistochemistry membrane staining. + = minimal, ++ = mild, +++ = moderate
[c] Mild nuclear staining was also observed.
[d] Exposures for the 0.1 and 0.3 mg/m^3 groups were discontinued on day 142.

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
P.O. Box 12233, MD K2-05
Durham, NC 27709
Tel: 984-287-3211
ntpwebrequest@niehs.nih.gov

https://ntp.niehs.nih.gov

ISSN 2378-8925