NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 453

# TOXICOLOGY AND CARCINOGENESIS STUDIES OF NICKEL SUBSULFIDE

(CAS NO. 12035-72-2)

# IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

## FOREWORD

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

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

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

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NTP TECHNICAL REPORT

ON THE

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July 1996

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# CONTENTS

# ABSTRACT

# $Ni_3S_2$

## NICKEL SUBSULFIDE

CAS No. 12035-72-2

Chemical Formula: $Ni_3S_2$ Molecular Weight: 240.25

**Synonyms:** Heazlewoodite, nickel subsulphide, nickel sulfide (3:2), $\alpha$-nickel sulfide (3:2) crystalline, nickel sulphide, nickel tritadisulphide, trinickel disulfide

Nickel subsulfide is used in the manufacture of lithium batteries and is a major component in the refining of certain nickel ores. Nickel subsulfide was nominated as part of a class study of nickel compounds, for which there was little information on the toxic and carcinogenic effects of inhalation exposure. Male and female F344/N rats and B6C3F$_1$ mice were exposed to nickel subsulfide (at least 97% pure; the mean value for the mass median aerodynamic diameter at each exposure concentration ranged from 2.0 to 2.2 $\mu$m) by inhalation 6 hours per day, 5 days per week, for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, and mouse peripheral blood samples were analyzed for frequency of micronucleated normochromatic erythrocytes.

### 16-DAY STUDY IN RATS

Groups of five male and five female F344/N rats were exposed to atmospheres containing 0, 0.6, 1.2, 2.5, 5, or 10 mg nickel subsulfide/m$^3$ (equivalent to 0, 0.44, 0.88, 1.83, 3.65, and 7.33 mg nickel/m$^3$) 6 hours per day, 5 days per week for a total of 12 exposure days during a 16-day period. Additional groups of three male and three female rats were exposed to 0, 0.6, 2.5, or 10 mg/m$^3$ for tissue burden studies. One male exposed to 10 mg nickel subsulfide/m$^3$ in the core study died on day 14; all other rats survived until the end of the study. Final mean body weights and mean body weight gains of males exposed to 5 or 10 mg nickel subsulfide/m$^3$ and females exposed to 2.5, 5, or 10 mg/m$^3$ were significantly lower than those of the controls. Clinical findings of toxicity on day 5 of the study included labored respiration in 10 mg/m$^3$ males and 5 and 10 mg/m$^3$ females and dehydration in 5 and 10 mg/m$^3$ females. Absolute and relative lung weights of 2.5, 5, and 10 mg/m$^3$ males and all exposed groups of females were significantly greater than those of the controls, as was the absolute lung weight of 1.2 mg/m$^3$ males. Inflammation of the lung and atrophy of the nasal olfactory epithelium occurred in all exposed groups. The concentrations of nickel in the lungs of exposed groups of rats increased with exposure concentration (males, 7 to 67 $\mu$g nickel/g lung; females, 9 to 77 $\mu$g/g lung).

### 16-DAY STUDY IN MICE

Groups of five male and five female B6C3F$_1$ mice were exposed to atmospheres containing 0, 0.6, 1.2, 2.5, 5, or 10 mg nickel subsulfide/m$^3$ for 6 hours per day, 5 days per week for a total of 12 exposure days during a 16-day period. Additional groups of three male and three female mice were exposed to 0, 0.6, 2.5, or 10 mg/m$^3$ for tissue burden studies. All male and female mice exposed to 10 mg nickel

subsulfide/m$^3$ in the core study died before the end of the study; the death of one female was accidental. One control male, one control female, and one 1.2 mg/m$^3$ male also died before the end of the study. Final mean body weights and mean body weight gains of 5 mg/m$^3$ males were significantly lower than those of the controls. Clinical findings at day 5 included labored respiration in 10 mg/m$^3$ males and females. The absolute lung weight of 5 mg/m$^3$ males, the absolute and relative lung weights of 10 mg/m$^3$ males and 5 mg/m$^3$ females, and the relative lung weight of 10 mg/m$^3$ females were significantly greater than those of the controls. Inflammation of the lung occurred in 2.5, 5, and 10 mg/m$^3$ male and female mice, fibrosis of the lung occurred 5 mg/m$^3$ males and females, and lymphoid hyperplasia of the bronchial lymph nodes and atrophy of the nasal olfactory epithelium occurred in 1.2, 2.5, 5, and 10 mg/m$^3$ males and females. Nickel concentrations in the lung of exposed male and female mice were greater than those of the controls (males, 10 to 20 $\mu$g nickel/g lung; females, 8 to 20 $\mu$g/g lung).

## 13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were exposed to atmospheres containing 0, 0.15, 0.3, 0.6, 1.2, or 2.5 mg nickel subsulfide/m$^3$ (equivalent to 0, 0.11, 0.22, 0.44, 0.88, and 1.83 mg nickel/m$^3$) 6 hours per day, 5 days per week for 13 weeks. Additional groups of 18 male and 18 female rats were exposed to 0, 0.15, 0.6, or 2.5 mg/m$^3$ for tissue burden studies. All core study rats survived until the end of the study. Final mean body weights and mean body weight gains of 2.5 mg/m$^3$ males were significantly lower than those of the controls; final mean body weights of all other exposure groups were similar to those of the controls. Chemical-related clinical findings included labored respiration in 2.5 mg/m$^3$ males and females during weeks 2 through 7. In general, neutrophil and erythrocyte counts, hematocrit values, and hemoglobin concentrations were minimally increased in exposed rats. Absolute and relative lung weights of all exposed groups were significantly greater than those of the controls.

Increases in the number of alveolar macrophages, interstitial infiltrates, or incidences of chronic inflammation of the lung occurred in all groups exposed to nickel subsulfide concentrations of 0.3 mg/m$^3$ or greater; the severity of these lesions generally increased with increasing exposure concentration. Increases in the number of alveolar macrophages were observed in 0.15 mg/m$^3$ males and females. Lymphoid hyperplasia of the bronchial and mediastinal lymph nodes was observed in rats exposed to 0.3 mg/m$^3$ or greater. Most 0.6, 1.2, and 2.5 mg/m$^3$ males and females had atrophy of the nasal olfactory epithelium, and the severity generally increased with increasing exposure concentration.

Nickel concentrations in the lung increased with exposure concentration and were greater than those in the controls in rats exposed for 13 weeks (males, 5 to 18 $\mu$g nickel/g lung; females, 5 to 17 $\mu$g/g lung).

## 13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to atmospheres containing 0, 0.15, 0.3, 0.6, 1.2, or 2.5 mg nickel subsulfide/m$^3$ for 6 hours per day, 5 days per week for 13 weeks. Additional groups of six male and six female mice were exposed to 0, 0.15, 0.6, or 2.5 mg/m$^3$ for tissue burden studies. Final mean body weights of all exposure groups were similar to those of the controls. No chemical-related clinical findings were observed. Lymphocyte counts in 1.2 and 2.5 mg/m$^3$ males were minimally greater than that of the controls. Hemoglobin concentrations and erythrocyte counts in 0.3, 0.6, 1.2, and 2.5 mg/m$^3$ females were minimally greater than those of the controls. Absolute and relative lung weights of 1.2 and 2.5 mg/m$^3$ males and females were significantly greater than those of the controls. An increase in alveolar macrophages was present in mice from the 0.3 mg/m$^3$ and higher exposure groups. Chronic inflammation and fibrosis were observed in the lung of 1.2 and 2.5 mg/m$^3$ males and females. Interstitial infiltrates of lymphocytes were observed in mice exposed to 0.6, 1.2, or 2.5 mg/m$^3$. Lymphoid hyperplasia of the bronchial lymph nodes was observed in groups exposed to 1.2 or 2.5 mg/m$^3$.

Atrophy of the nasal olfactory epithelium occurred in 0.6, 1.2, and 2.5 mg/m$^3$ males and females, and incidences and severity generally increased with increasing exposure concentration.

At 13 weeks, nickel concentrations in the lungs of exposed mice were greater than those of the controls (males, 3 to 17 $\mu$g nickel/g lung; females, 6 to 23 $\mu$g/g lung), and these concentrations increased with increasing exposure concentration.

## 2-Year Study in Rats

### *Survival, Body Weights, Clinical Findings, and Hematology*

Groups of 63 male and 63 female F344/N rats were exposed to 0, 0.15, or 1 mg nickel subsulfide/m$^3$ (equivalent to 0, 0.11, or 0.73 mg nickel/m$^3$) by inhalation for 6 hours per day, 5 days per week for 104 weeks. Survival of exposed males and female rats was similar to that of the controls. Mean body weights of males and females exposed to 0.15 mg/m$^3$ were similar to those of the controls. Mean body weights of rats exposed to 1 mg/m$^3$ were lower than those of the controls throughout the second year of the study. Chemical-related clinical findings included rapid and shallow breathing following exposure periods. Hematocrit values and hemoglobin concentrations in 1 mg/m$^3$ males and females and the erythrocyte count in 1 mg/m$^3$ males were mildly greater than those in the controls.

### *Pathology Findings*

In general, the absolute and relative lung weights of exposed males and females were significantly greater than those of the controls at 7 and 15 months. There were exposure-related increases in the incidences of alveolar/bronchiolar adenoma in males, alveolar/bronchiolar carcinoma in males and females, and alveolar/bronchiolar adenoma or carcinoma (combined) in males and females at 2 years. Nonneoplastic lung lesions generally observed in exposed males and females included fibrosis; chronic active inflammation; focal alveolar epithelial hyperplasia, macrophage hyperplasia, and proteinosis; bronchial lymphoid hyperplasia; and interstitial inflammation.

At 2 years, there were significant exposure-related increases in the incidences of benign pheochromocytoma, malignant pheochromocytoma, and benign or malignant pheochromocytoma (combined) in males and of benign pheochromocytoma in females. The incidence of adrenal medulla hyperplasia in 1 mg/m$^3$ females was significantly greater than that of the controls.

At 2 years, the incidences of chronic active inflammation of the nose in 1 mg/m$^3$ females and of olfactory epithelial atrophy in 1 mg/m$^3$ males and females were significantly greater than those of the controls.

The incidences of lymphoid hyperplasia of the bronchial lymph node in exposed males at 7 and 15 months and in exposed males and females at 2 years were significantly greater than those of the controls. Incidences of macrophage hyperplasia in the bronchial lymph node of exposed males at 15 months and exposed males and females at 2 years were greater than those of the controls.

### *Tissue Burden Analyses*

Nickel concentrations in the lung of exposed rats were greater than those of the controls at 7 months (males, 6 to 9 $\mu$g nickel/g lung; females, 6 to 9 $\mu$g/g lung) and 15 months (males, 4 to 3 $\mu$g nickel/g lung; females, 4 to 7 $\mu$g/g lung).

## 2-Year Study in Mice

### *Survival, Body Weights, Clinical Findings, and Hematology*

Groups of 80 male and 80 female B6C3F$_1$ mice were exposed to 0, 0.6, or 1.2 mg nickel subsulfide/m$^3$ (equivalent to 0, 0.44, or 0.88 mg nickel/m$^3$) by inhalation for 6 hours per day, 5 days per week for 105 weeks. Survival of exposed male and female mice was similar to that of the controls. Mean body weights of 0.6 and 1.2 mg/m$^3$ males and females were less than those of the controls throughout the second year of the study. Chemical-related clinical findings in male and female mice included labored respiration following exposure periods. The hematocrit value and the segmented neutrophil, monocyte, lymphocyte, and total leukocyte counts in 1.2 mg/m$^3$ females were greater than those in the controls.

### *Pathology Findings*

Absolute and relative lung weights of exposed males and females were generally significantly greater than those of the controls at 7 and 15 months. The incidence of alveolar/bronchiolar carcinoma in 0.6 mg/m$^3$ females and the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 0.6 mg/m$^3$ males and 0.6 and 1.2 mg/m$^3$ females were significantly less than those of the controls. In general, the incidences of chronic active inflammation; bronchialization (alveolar epithelial hyperplasia), macrophage hyperplasia and proteinosis; interstitial infiltration; and fibrosis in exposed groups of males and females were greater than those of the controls at 7 and 15 months and at 2 years.

The incidences of atrophy of the nasal olfactory epithelium and inflammation of the nose in exposed mice were also generally greater than those of the controls. At 2 years, the incidences of degeneration of olfactory epithelium in exposed females were significantly less than that of the controls.

The incidences of lymphoid hyperplasia of the bronchial lymph node in 1.2 mg/m$^3$ males at 15 months, in 0.6 and 1.2 mg/m$^3$ females at 15 months, and in 0.6 and 1.2 mg/m$^3$ males and females at 2 years were significantly greater than those of the controls. The incidences of macrophage hyperplasia in 1.2 mg/m$^3$ males at 7 and 15 months, in 0.6 and 1.2 mg/m$^3$ females at 15 months, and in 0.6 and 1.2 mg/m$^3$ males and females at 2 years were significantly greater than those of the controls.

### *Tissue Burden Analyses*

Nickel concentrations in the lungs of exposed mice were greater than those of the controls at 7 months (males, 10 to 11 $\mu$g nickel/g lung; females, 10 to 14 $\mu$g/g lung) and 15 months (males, 12 to 20 $\mu$g nickel/g lung; females, 15 to 26 $\mu$g/g lung).

## GENETIC TOXICOLOGY

Nickel subsulfide was considered to be equivocal in the *Salmonella* gene mutation assay overall. Sporadic weakly positive and equivocal responses were obtained in strain TA100 with and without S9 metabolic activation enzymes; all other strain/activation combinations gave negative results. No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples from male or female mice exposed to nickel subsulfide by inhalation for 13 weeks.

## CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of nickel subsulfide in male F344/N rats based on increased incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined) and on increased incidences of benign, malignant, and benign or malignant (combined) pheochromocytoma of the adrenal medulla. There was *clear evidence of carcinogenic activity* of nickel subsulfide in female F344/N rats based on increased incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) and an increased incidence of benign pheochromocytoma of the adrenal medulla. There was *no evidence of carcinogenic activity* of nickel subsulfide in male or female B6C3F$_1$ mice exposed to 0.6 or 1.2 mg/m$^3$.

Exposure of male and female rats to nickel subsulfide by inhalation for 2 years resulted in inflammation, hyperplasia, and fibrosis in the lung; inflammation and atrophy of the olfactory epithelium in the nose; and hyperplasia in the adrenal medulla (females). Exposure of male and female mice to nickel subsulfide by inhalation for 2 years resulted in inflammation, bronchialization, hyperplasia, and fibrosis in the lung and inflammation and atrophy of the olfactory epithelium in the nose.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this report appears on page 13.

## Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Nickel Subsulfide

| | Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|---|
| **Exposure concentrations** | 0, 0.15, or 1 mg nickel subsulfide/$m^3$ (0, 0.11, or 0.73 mg nickel/$m^3$) | 0, 0.15, or 1 mg nickel subsulfide/$m^3$ (0, 0.11, or 0.73 mg nickel/$m^3$) | 0, 0.6, or 1.2 mg nickel subsulfide/$m^3$ (0, 0.44, or 0.88 mg nickel/$m^3$) | 0, 0.6, or 1.2 mg nickel subsulfide/$m^3$ (0, 0.44, or 0.88 mg nickel/$m^3$) |
| **Body weights** | 1 mg/$m^3$ group lower than controls | 1 mg/$m^3$ group lower than controls | 0.6 and 1.2 mg/$m^3$ groups lower than controls | 0.6 and 1.2 mg/$m^3$ groups lower than controls |
| **2-Year survival rates** | 13/53, 21/53, 18/53 | 25/53, 25/53, 28/53 | 26/61, 25/60, 26/60 | 36/58, 34/60, 38/60 |
| **Nonneoplastic effects** | Lung: chronic active inflammation (9/53, 53/53, 51/53); focal alveolar epithelial hyperplasia (2/53, 6/53, 11/53); macrophage hyperplasia (9/53, 48/53, 52/53); fibrosis (2/53, 48/53, 40/53) Nose: chronic active inflammation (12/53, 10/53, 18/52); olfactory epithelial atrophy (2/53, 1/53, 9/52) | Lung: chronic active inflammation (7/53, 51/53, 51/53); focal alveolar epithelial hyperplasia (2/53, 10/53, 11/53); macrophage hyperplasia (8/53, 51/53, 52/53); fibrosis (0/53, 50/53, 44/53) Adrenal medulla: hyperplasia (5/53, 11/53, 16/53) Nose: chronic active inflammation (6/53, 9/53, 20/52); olfactory epithelial atrophy (0/53, 0/53, 16/52) | Lung: chronic active inflammation (1/61, 52/59, 53/58); bronchialization (3/61, 53/59, 54/58); macrophage hyperplasia (6/61, 57/59, 58/58); fibrosis (0/61, 3/59, 16/58) Nose: acute inflammation (0/61, 0/59, 3/59); olfactory epithelial atrophy (1/61, 27/59, 55/59) | Lung: chronic active inflammation (1/58, 46/59, 58/60); bronchialization (3/58, 53/59, 58/60); macrophage hyperplasia (5/58, 57/59, 60/60); fibrosis (0/58, 7/59, 17/60) Nose: acute inflammation (0/58, 11/59, 14/60); olfactory epithelial atrophy (1/58, 11/59, 41/60) |
| **Neoplastic effects** | Lung: alveolar/ bronchiolar adenoma (0/53, 3/53, 6/53); alveolar/ bronchiolar carcinoma (0/53, 3/53, 7/53); alveolar/bronchiolar adenoma or carcinoma (0/53, 6/53, 11/53) Adrenal medulla: benign pheochromocytoma (13/53, 30/52, 38/53); malignant pheochromocytoma (0/53, 2/52, 10/53); benign or malignant pheochromocytoma (14/53, 30/52, 42/53) | Lung: alveolar/ bronchiolar carcinoma (0/53, 0/53, 4/53); alveolar/bronchiolar adenoma or carcinoma or squamous cell carcinoma (2/53, 6/53, 9/53); Adrenal medulla: benign pheochromocytoma (2/53, 7/53, 36/53) | None | None |

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Nickel Subsulfide** (continued)

| | Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|---|
| **Level of evidence of carcinogenic activity** | Clear evidence | Clear evidence | No evidence | No evidence |
| **Genetic toxicology** | | | | |
| *Salmonella typhimurium* gene mutations: | | Equivocal with and without S9 in strain TA100, negative with and without S9 in strains TA97, TA98, TA102, and TA1535 | | |
| Micronucleated erythrocytes Mouse peripheral blood *in vivo*: | | Negative in male and female mice | | |

# 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 nickel subsulfide on November 29, 1994, 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 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.

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## SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 29, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of nickel subsulfide received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of nickel subsulfide by describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic lesions in rats and nonneoplastic lesions in rats and mice. The proposed conclusions were *clear evidence of carcinogenic activity* in male and female F344/N rats, and *no evidence of carcinogenic activity* in male or female $B6C3F_1$ mice.

Dr. Reddy, a principal reviewer, agreed with the proposed conclusions. He was unable to attend the meeting but had submitted his review, which Dr. L.G. Hart, NIEHS, read into the record.

Dr. Klaassen, the second principal reviewer, agreed with the proposed conclusions. He commented that the wide range of exposure concentrations in rats was appropriate but needed to be discussed. Dr. Dunnick explained that the highest exposure concentration was selected to repeat that used in a previous study. The lower exposure concentration was selected based on the presence of a similar spectrum and severity of histopathologic lung changes in the 13-week study that were present at the highest exposure concentrations selected for the nickel oxide and nickel sulfate hexahydrate studies. Dr. Goldsworthy suggested a more appropriate way to have set exposure concentrations that might have yielded mechanistic information would have been to choose a high exposure concentration that affects pulmonary clearance compared to a low exposure concentration that does not. Dr. Klaassen said there needed to be more discussion of the observation that nickel subsulfide exposure increases alveolar/bronchiolar adenomas and carcinomas in rats while it decreases these lesions in mice. Dr. J.K. Haseman, NIEHS, commented that there was a consistent trend in the three nickel studies of an association between higher lung weights at the 15-month interim evaluation and lower lung neoplasm incidences at 2 years in mice but not in rats. He did not know whether or not this association was biologically significant.

Dr. Ryan, the third principal reviewer, agreed with the proposed conclusions. She thought it would be useful to state more clearly why inhalation was chosen as the route of exposure since intake from food is likely to be much higher in humans. Dr. Dunnick noted that inhalation is the predominant route of exposure in the workplace. Dr. Ryan asked why only two exposure groups were used instead of the usual three. Dr. Dunnick replied that when nickel subsulfide was included for this series of studies it was considered a positive control based on results of a previously published study. To reduce the number of animals, exposure groups, and costs, the nickel subsulfide study was limited to two exposure groups.

Ms. D. Sivulka, executive director of the Nickel Producers Environmental Research Association, Inc. (NiPERA), commented on the discussion of evidence for nickel toxicity and carcinogenesis in humans and the presentation of the significance of findings relative to existing threshold limit values (TLVs). Ms. Sivulka said that because conclusions in the report were based on existing TLVs, an implication could be made that current regulations are not protective of workers exposed to nickel compounds. Ms. Sivulka discussed the cohorts of workers exposed to nickel compounds that have been examined, and she said that the information obtained from these examinations shows no evidence of nickel-related increases in the incidence of nonneoplastic lesions in workers exposed to low nickel levels.

Dr. Klaassen moved that the Technical Report on nickel subsulfide be accepted with the revisions discussed and with the conclusions as written for male and female rats, *clear evidence of carcinogenic activity*, and for male and female mice, *no evidence of carcinogenic activity*. Dr. Ryan seconded the motion, which was accepted unanimously with six votes.

# INTRODUCTION

# $Ni_3S_2$

## NICKEL SUBSULFIDE

CAS No. 12035-72-2

Chemical Formula: $Ni_3S_2$ Molecular Weight: 240.25

**Synonyms:** Heazlewoodite, nickel subsulphide, nickel sulfide (3:2), α-nickel sulfide (3:2) crystalline, nickel sulphide, nickel tritadisulphide, trinickel disulfide

## CHEMICAL AND PHYSICAL PROPERTIES

Nickel subsulfide is a black powder with a melting point of 790° C and a density of 5.82 g/cm$^3$. It is insoluble in water but soluble in acid (USEPA, 1986). The mean value for the mass median aerodynamic diameter at each exposure concentration of nickel subsulfide used in these 2-year studies ranged from 2.0 to 2.2 μm.

## PRODUCTION, USE, AND HUMAN EXPOSURE

Nickel was first isolated in 1751 and is found primarily as an oxide (laterite) or sulfide ore (pentlandite) (NIOSH, 1977; Warner, 1984; U.S. Bureau of Mines, 1984, 1985a). In 1991, the six largest nickel producing countries were the Soviet Union, Canada, Australia, New Caledonia, Indonesia, and Cuba. Approximately 55% of the nickel currently used is extracted from sulfide ore, and the remainder is extracted from oxide ore. The total annual world production of nickel is estimated at 1,000,000 tons (900,000 metric tons) (U.S. Bureau of Mines, 1991).

The United States consumption of nickel is approximately 200,000 tons (180,000 metric tons) annually (U.S. Bureau of Mines, 1991). The United States consumes unwrought nickel (68%), ferronickel (17.3%), nickel oxide (11.4%), nickel salts (1.2%), and other forms (2.1%) (U.S. Bureau of Mines, 1984, 1985b). The National Occupational Exposure Survey reported that 56,843 United States workers are potentially exposed to nickel sulfate and 18,165 to nickel oxide (information on nickel subsulfide exposure not reported) (NIOSH, 1991).

Half of the nickel sold per year is used to make stainless steel (Warner, 1984), which contains up to 8% nickel. The ability of nickel to impart corrosion resistance and strength leads to its wide use in chemicals and allied products and in petroleum refining, electrical equipment and supplies, aircraft and parts, construction, fabricated metal products, household appliances, machinery, and ships and boats (U.S. Bureau of Mines, 1984).

Nickel constitutes about 0.008% of the earth's crust. Low levels of nickel are found in air, soil, water, food, and household objects. The average concentration of nickel in finished drinking water is less than 10 ppb. Nickel concentration in United States air has been found to range from 1 to 86 ng/m$^3$. The most probable nickel species present in the atmosphere include complex nickel, nickel oxide, and nickel sulfate, and the most probable species found in water include hydrated nickels (ATSDR, 1992). The

average amount of nickel in mainstream particulate fractions of cigarette smoke is 79 ng/cigarette (Bache *et al.*, 1985). Dietary intake of nickel per person from foods is estimated at 170 μg per day, intake from inhalation is estimated at 0.1 to 1 μg nickel per day (excluding cigarette smoke), and intake from drinking water is estimated at 2 μg per day (ATSDR, 1992). Nickel is listed as a frequently occurring chemical in waste deposit sites in the United States (*Fed. Regist.*, 1987).

The threshold limit values adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) are 1 mg/m$^3$ for nickel metal and water-insoluble salts and 0.1 mg/m$^3$ for water-soluble salts, but the ACGIH published notice of an intended change to 0.05 mg nickel/m$^3$ for water-soluble and water-insoluble nickel compounds (ACGIH, 1993). The National Institute for Occupational Safety and Health recommended that the permissible exposure limit for nickel be reduced to 0.015 mg nickel/m$^3$ averaged over a work shift of up to 10 hours per day, 40 hours per week (NIOSH, 1977).

Atomic absorption spectroscopy is a widely used method for quantifying nickel in the environment and in the workplace. This method of analysis measures total nickel without discerning the forms of nickel present, and most studies of environmental or industrial exposure report total nickel and not the occurrence of individual nickel species (ATSDR, 1992).

## ABSORPTION, DISTRIBUTION, AND EXCRETION

### *Experimental Animals*

Animal model systems have been used to obtain information on the absorption, distribution, and excretion of nickel after inhalation exposure (water-soluble and water-insoluble forms of nickel), oral exposure (water-soluble forms of nickel), and dermal exposure (water-soluble forms of nickel).

Intratracheal administration of nickel compounds was one method used by several investigators to study the fate of specific forms of nickel in the lung. English *et al.* (1981) reported on a comparative toxicokinetic study after intratracheal administration of [$^{63}$Ni]-labeled nickel chloride or nickel oxide (low temperature nickel oxide calcined at 250° C) in Wistar rats. Nickel, after nickel chloride administration, was excreted primarily in the urine. After nickel oxide administration, nickel was equally excreted in the feces and urine. Nickel oxide persisted in the lung for more than 90 days, while nickel chloride was rapidly excreted from the lung with greater than 50% of the nickel cleared from the lungs within 3 days.

Nickel chloride administered as an intratracheal dose to Sprague-Dawley rats was excreted primarily in the urine. By day 3, 90% of the instilled chemical was eliminated from the lungs. The lungs retained 29% of their initial burden at day 1, and this decreased to 0.1% on day 21; 96% of the chemical was excreted in the urine (Carvalho and Ziemer, 1982).

The pulmonary clearance of intratracheally administered nickel subsulfide ($Ni_3S_2$) in mice has two distinct components with initial and final biological half-lives corresponding to 1.2 and 12.4 days, respectively. The excretion of the chemical (measured as $^{63}$Ni) was 60% in the urine and 40% in the feces; 57% of the administered dose was excreted after 3 days with 33% appearing in the urine (Valentine and Fisher, 1984). In another experiment, the calculated clearance times of nickel subsulfide administered intratracheally to mice was also biphasic with a clearance half-life of 2 hours for the first phase and 119 hours for the second phase (Finch *et al.*, 1987).

In F344/N rats administered [$^{63}$Ni]-labeled nickel oxide (high temperature, green oxide) or nickel subsulfide by pernasal inhalation, the lung half-life was estimated at 120 days for nickel oxide and 5 days for nickel subsulfide (Benson *et al.*, 1994). Following nickel oxide exposure, nickel was not distributed to the extrarespiratory tract tissue, and the material was only excreted in the feces during the first few days after exposure. In contrast, after nickel subsulfide exposure, nickel was detected in extrarespiratory tract tissue including blood and kidney, and nickel was excreted in the urine and the feces. The half-life of [$^{63}$Ni]-labeled nickel sulfate administered to F344/N rats intratracheally was 1 to 3 days, nickel was present in extrarespiratory tract tissues (including blood, kidney, and intestine), and

urine was the major route for excretion of nickel (Medinsky *et al.*, 1987).

Other studies also indicated that nickel oxide has a relatively long half-life in the rodent lung. Nickel oxide (formed at 550° C; mass median aerodynamic diameter [MMAD] of 0.15 $\mu$m, geometric standard deviation [$\sigma_g$] of 1.5) given as an aerosol of 750 $\mu g/m^3$ to Wistar rats had a bronchial clearance half-life of 1 day and an alveolar clearance half-life of 36 days (Hochrainer *et al.*, 1980). Hochrainer *et al.* (1980) estimated that with continuous exposure to nickel oxide, a steady state would be reached after 1 year.

In Wistar rats after exposure to 0.6 or 8.0 mg nickel oxide/$m^3$ (high temperature, green oxide; MMAD of 1.2 $\mu$m, $\sigma_g$ of 2.5) for 6 to 7 hours per day for 1 to 2 months, the lung clearance was estimated to be 100 $\mu g$ per year. There was no apparent deposition of nickel in the liver, kidney, spleen, heart, brain, or blood (Kodama *et al.*, 1985). Lung clearance half-lives for nickel oxide (high temperature, green oxide) in Wistar rats exposed for 1 month were estimated to be 8, 11, and 21 months for nickel oxide with particulate MMADs of 0.6, 1.2, and 4.0 $\mu$m, respectively (Tanaka *et al.*, 1985, 1988).

In summary, in absorption and distribution studies for nickel administered intratracheally or by inhalation exposure, the lung half-life was 1 to 3 days for nickel sulfate, 5 days for nickel subsulfide, and greater than 100 days for nickel oxide. Nickel was detected in extrarespiratory tract tissue after exposure to nickel sulfate or nickel subsulfide, but not after exposure to nickel oxide.

The present studies also report findings on the deposition of nickel sulfate hexahydrate, nickel subsulfide, and nickel oxide in the lungs and tissues of rats and mice after 16 days, 13 weeks, and at 7 and 15 months in the 2-year studies. These data show a relatively short half-life in the lung for nickel sulfate hexahydrate, a longer half-life for nickel subsulfide, and the longest half-life for nickel oxide (Benson *et al.*, 1987; Dunnick *et al.*, 1989).

Studies of other routes of nickel exposure in rats, mice, and dogs indicate that 1% to 10% was absorbed after oral administration of nickel sulfate hexahydrate or nickel chloride, and less than 1% of nickel chloride was absorbed through the skin of guinea pigs within 24 hours (ATSDR, 1992; Nielsen *et al.*, 1993).

### *Humans*

In the industrial setting, a major route of nickel exposure in humans is by inhalation (Sunderman, 1992); it is estimated that 35% of inhaled nickel is absorbed into the blood from the respiratory tract (Bennet, 1984; Grandjean, 1984; Sunderman and Oskarsson, 1991). Nickel was excreted in the urine of refinery workers for periods of up to 6 months after facility closing, indicating that there are storage depots in the body that retain nickel for long periods of time (Morgan and Rouge, 1983). There were elevated nickel concentrations in specimens of urine, plasma, and nasal mucosa biopsies obtained from retired workers years after cessation of employment, although the specific form of nickel to which these workers were exposed was not identified (Torjussen and Andersen, 1979; Boysen *et al.*, 1984).

Andersen and Svenes (1989) found elevated levels of nickel in the lungs of nickel refinery workers, although workers who were diagnosed as having lung cancer had the same concentrations of nickel in the lung at autopsy as those who died of other types of cancer. In the workplace setting, exposure to nickel is monitored by analyzing urine, hair, or fingernails for levels of total nickel.

When nickel sulfate was administered to fasting human volunteers, 27% of the administered dose was absorbed when given in drinking water, while only 0.7% was absorbed when administered in food. The elimination half-life for absorbed nickel averaged 28 hours; 100% of the absorbed nickel was eliminated in either the feces or urine within 4 days (Sunderman, 1989, 1992). In studies in humans, reported absorption of radioactive nickel applied to occluded skin varied from 55% to 77% for nickel sulfate to 3% for nickel chloride (ATSDR, 1992).

## TOXICITY

Studies of nickel toxicity after experimental or industrial exposure have been summarized in various reviews (NAS, 1975; IARC, 1976, 1984, 1987, 1990; NIOSH, 1977; Brown and Sunderman, 1985;

USEPA, 1986; European Chemical Industry, 1989; WHO, 1991; ATSDR, 1992; Nieboer and Nriagu, 1992). In experimental animals and in humans, the primary toxic response to nickel after inhalation occurred in the respiratory system.

Information on the dissolution half-lives for nickel subsulfide and nickel oxide in water and rat serum have been reported. The calculated dissolution half-lives (based on *in vitro* studies) for nickel subsulfide and nickel oxide in water are greater than 7 or 11 years, respectively. In rat serum, the estimated dissolution half-life is 23 days for nickel subsulfide and greater than 11 years for nickel oxide (Sunderman *et al.*, 1987). While nickel subsulfide and nickel oxide are both relatively insoluble in water, nickel subsulfide is more soluble than nickel oxide in biological fluids. Soluble nickel salts (nickel hydroxide) have been shown to be more soluble in human serum than nickel subsulfide (Kasprzak *et al.*, 1983). The comparative toxicity of nickel sulfate hexahydrate, nickel subsulfide, and nickel oxide parallels the solubility of the compounds in biological fluids.

### *Experimental Animals*

The acute toxicity values for selected nickel compounds are summarized in Table 1. Nickel carbonyl [$Ni(CO)_4$] is the most acutely toxic form of nickel, but the use or formation of this nickel compound in manufacturing processes is limited (NAS, 1975). Exposure to nickel oxide, nickel sulfate hexahydrate, or nickel subsulfide is more common in the workplace.

In animals, after inhalation exposure to water-soluble and water-insoluble nickel compounds, the primary toxic response is seen in the respiratory system. Changes in a variety of parameters, including dose-related reduction in body weight, reduced leukocyte count, increase in urine alkaline phosphatase, and increased erythrocyte count, were observed in Wistar rats continuously exposed to nickel oxide at 200, 400, or 800 $\mu g/m^3$ for 120 days (except for daily cleaning and feeding periods) (Weischer *et al.*, 1980).

Alveolar macrophages from lung lavage fluid from rats exposed to nickel oxide at 120 $\mu g/m^3$ for 12 hours per day, 6 days per week, for 28 days or by intratracheal injection (10 mg nickel oxide/mL) were examined by electron microscopy. Compared to controls, alveolar macrophages from exposed animals were increased in number and enlarged. In the cytoplasm of alveolar macrophages, phagosomes contained osmophilic nickel oxide particles as well as membranous and lamellar structures consistent with accumulation of phospholipid material (Migally *et al.*, 1982; Murthy and Niklowitz, 1983).

Respiratory toxicity to F344/Crl rats administered a single dose of either nickel subsulfide, nickel chloride, nickel sulfate, or nickel oxide by intratracheal instillation was evaluated by examining treatment-related changes in lung lavage fluid (Benson *et al.*, 1986). No significant changes in lung lavage fluid were seen after exposure to nickel oxide. After exposure to nickel subsulfide, nickel sulfate hexahydrate, and nickel chloride, there were increases in the following parameters in lung lavage fluid: lactate dehydrogenase, $\beta$-glucuronidase, total protein, glutathione reductase, glutathione peroxidase, and sialic acid. This evaluation was continued by exposing rats or mice to nickel oxide, nickel sulfate hexahydrate, or nickel subsulfide for 13 weeks and looking for treatment-related markers of lung toxicity in lung lavage fluid (Benson *et al.*, 1989). Increases in $\beta$-glucuronidase, total protein, neutrophil number, and macrophage number were observed in the lavage fluid after exposure of rats and mice to all three nickel compounds, although there were quantitative differences in the magnitude of the response. Inflammation was observed histologically in the lung of rats and mice exposed to the three nickel compounds. The severity of lung toxicity as measured by the changes in lung lavage fluid paralleled the severity of histologic changes in the lung. Nickel sulfate hexahydrate was the most toxic, and nickel oxide was the least toxic (Benson *et al.*, 1989).

TABLE 1
**Toxicity Values for Nickel Carbonyl, Nickel Oxide, Nickel Sulfate Hexahydrate, Nickel Sulfate, and Nickel Subsulfide[a]**

| Nickel Compound | Species | Route | Toxicity Value[b] |
|---|---|---|---|
| Nickel carbonyl | Rat | Inhalation | 35 ppm ($LC_{50}$) |
| | | Subcutaneous | 63 mg/kg ($LD_{50}$) |
| | | Intravenous | 66 mg/kg ($LD_{50}$) |
| | | Intraperitoneal | 39 mg/kg ($LD_{50}$) |
| | Mouse | Inhalation | 67 mg/m$^3$ ($LC_{50}$) |
| | Dog | Inhalation | 360 ppm (LCLo) |
| | Cat | Inhalation | 1,890 mg/m$^3$ ($LC_{50}$) |
| | Rabbit | Inhalation | 73 g/m$^3$ (LCLo) |
| Nickel oxide | Rat | Subcutaneous | 25 mg/kg ($LD_{50}$) |
| | | Intramuscular | 180 mg/kg (TDLo) |
| | | Intratracheal | 90 mg/kg (TDLo) |
| | Mouse | Subcutaneous | 50 mg/kg ($LD_{50}$) |
| | | Intraperitoneal | 400 mg/kg (TDLo) |
| Nickel sulfate hexahydrate | Dog | Subcutaneous | 500 mg/kg (LDLo) |
| | | Intravenous | 89 mg/kg (LDLo) |
| | Cat | Subcutaneous | 500 mg/kg (LDLo) |
| | | Intravenous | 72 mg/kg (LDLo) |
| | Rabbit | Subcutaneous | 500 mg/kg (LDLo) |
| | | Intravenous | 36 mg/kg (LDLo) |
| | Guinea pig | Subcutaneous | 62 mg/kg (LDLo) |
| Nickel sulfate | Rat | Intraperitoneal | 500 mg/kg ($LD_{50}$) |
| | Mouse | Intraperitoneal | 21 mg/kg ($LD_{50}$) |
| | | Intravenous | 7 mg/kg (LDLo) |
| | Dog | Subcutaneous | 38 mg/kg (LDLo) |
| | | Intravenous | 38 mg/kg (LDLo) |
| | Cat | Subcutaneous | 24 mg/kg (LDLo) |
| | Rabbit | Subcutaneous | 33 mg/kg (LDLo) |
| | | Intravenous | 33 mg/kg (LDLo) |

(continued)

**TABLE 1**
**Toxicity Values for Nickel Carbonyl, Nickel Oxide, Nickel Sulfate Hexahydrate, Nickel Sulfate, and Nickel Subsulfide** (continued)

| Nickel Compound | Species | Route | Toxicity Value |
|---|---|---|---|
| Nickel subsulfide | Rat | Inhalation | 1 mg/kg (TCLo) |
| | | Subcutaneous | 125 mg/kg (TDLo) |
| | | Intravenous | 10 mg/kg (TDLo) |
| | | Intramuscular | 20 mg/kg (TDLo) |
| | Mouse | Intramuscular | 200 mg/kg (TDLo) |

[a] From RTECS (1987)
[b] $LC_{50}$ = median lethal concentration; LCLo = lowest lethal concentration; $LD_{50}$ = median lethal dose; LDLo = lowest lethal dose; TCLo = lowest toxic concentration; TDLo = lowest toxic dose.

Treatment of rats and mice with water-soluble and water-insoluble nickel salts may cause an alteration of local and systemic immunity, and this toxicity has been studied under various conditions and experiments (Table 2).

Toxic responses to the immune system were measured in $B6C3F_1$ mice after inhalation exposure to nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate for 6 hours per day and 5 days per week for 13 weeks. Exposure concentrations were 0.11, 0.45, and 1.8 mg nickel/$m^3$ for nickel subsulfide; 0.47, 2.0, and 7.9 mg nickel/$m^3$ for nickel oxide; and 0.027, 0.11, and 0.45 mg nickel/$m^3$ for nickel sulfate hexahydrate. Thymic weights in mice exposed to 1.8 mg nickel/$m^3$ of nickel subsulfide were lower than those of the controls. Lung-associated lymph nodes were increased in size after exposure to all compounds. The number of alveolar macrophages in lavage samples was increased in mice exposed to the highest concentrations of nickel sulfate hexahydrate and nickel oxide and to 0.45 and 1.8 mg nickel/$m^3$ nickel subsulfide. Numbers of antibody-forming cells in lung-associated lymph nodes of mice exposed to 2.0 and 7.9 mg nickel/$m^3$ nickel oxide and 1.8 mg nickel/$m^3$ nickel subsulfide were greater than those in the controls. Low numbers of antibody-forming cells were observed in the spleens of mice exposed to nickel oxide and in mice exposed to 1.8 mg nickel/$m^3$ nickel subsulfide. Only mice exposed to 1.8 mg nickel/$m^3$ nickel subsulfide had a low mixed lymphocyte response. All concentrations of nickel oxide resulted in low levels of alveolar macrophage phagocytic activity, as did 0.45 and 1.8 mg nickel/$m^3$ nickel subsulfide. None of the nickel compounds affected the phagocytic activity of peritoneal macrophages.

Only 1.8 mg nickel/$m^3$ nickel subsulfide caused a depressed natural killer cell activity in the spleen. Results indicate that inhalation exposure of mice to nickel can have varying effects on the immune system, depending on dose and physicochemical form of the nickel compound, and these effects were observed at occupationally relevant exposure concentrations (Haley *et al.*, 1990).

Administration of nickel sulfate in the drinking water for 180 days (1 to 10 g/L drinking water, estimated to deliver 116 to 396 mg/kg body weight) resulted in a depressed proliferating response in the bone marrow and spleen of $B6C3F_1$ mice (Dieter *et al.*, 1988).

While experimental studies in animals show the potential of nickel to affect the immune system, the clinical significance of these studies in humans has not been determined (Nicklin and Nielsen, 1992). Further, there are no studies to examine if there is a relationship between effects on the immune system and the carcinogenic effects of nickel.

TABLE 2
Studies on the Immunologic Effects of Nickel Compounds

| Nickel Compound | Species/Route | Treatment | Response | Reference |
|---|---|---|---|---|
| **Cell-Mediated Immunity** | | | | |
| Nickel chloride | CBA/J mice/ intramuscular | Single injection, 18 mg/kg | Reduced T-lymphocyte proliferation | Smialowicz *et al.* (1984) |
| | Guinea pig | *In vitro* study on spleen cells | Inhibited macrophage migration | Hennighausen and Lange (1980) |
| Nickel sulfate | $B6C3F_1$ mice (female)/oral | Up to 4,000 mg/kg/day for 23 weeks | Depressed spleen lymphoproliferative response to LPS (no effect on NK activity; PFC assay; mitogen response in spleen cells; resistance to *Listeria* challenge) | Dieter *et al.* (1988) |
| Nickel subsulfide | Cynomolgus monkey | Intratracheal instillation 0.06 μmol/g lung | No effect on antibody-forming cells (in lung) | Haley *et al.* (1987) |
| **Humoral Immunity** | | | | |
| Nickel chloride | CBA/J mice/ intramuscular | Single injection, 18 mg/kg | Reduced antibody response to T-cell dependent sheep red blood cells | Smialowicz *et al.* (1984) |
| | C57BL/6J mouse spleen cells | *In vitro* exposure to nickel chloride | Decreased response | Lawrence (1981) |
| | Swiss albino mice/ intramuscular | 3-12 μg Ni/kg body weight followed by immunization with sheep red blood cells | Depressed antibody formation | Graham *et al.* (1975a) |
| | Swiss mice/ inhalation | 2-hour inhalation exposure at 250 $\mu g/m^3$ | Depressed antibody response to sheep red blood cells | Graham *et al.* (1978) |
| Nickel acetate | Sprague-Dawley rats/intraperitoneal | 11 mg/kg body weight immunized with *E. coli* bacteriophage | Depressed circulating antibody response | Figoni and Treagan (1975) |
| Nickel oxide | Wistar rats/ inhalation | 25-800 $\mu g/m^3$ for 4 weeks to 4 months | Decreased ability to form spleen antibodies to sheep red blood cells | Spiegelberg *et al.* (1984) |

(continued)

TABLE 2
**Studies on the Immunologic Effects of Nickel Compounds** (continued)

| Nickel Compound | Species/Route | Treatment | Response | Reference |
|---|---|---|---|---|
| **Macrophage Function** | | | | |
| Nickel chloride | CBA/J mice/ intramuscular | Single injection, 18 mg/kg | No effect on phagocytic capacity of peritoneal macrophages | Smialowicz *et al.* (1984) |
| | Rabbits | Alveolar macrophage *in vitro* exposure | Reduced viability of macrophages | Graham *et al.* (1975b) |
| Nickel oxide and nickel chloride | Wistar rats/ inhalation | 12 hours/day, 6 days/week for 2 weeks at 0.1 mg/m$^3$ | Increased number of alveolar macrophages after nickel oxide; no change after nickel chloride | Bingham *et al.* (1972) |
| Nickel oxide | Wistar rats/ inhalation | 800 $\mu$g/m$^3$ for 2 weeks | Decrease in alveolar macrophage phagocytic ability | Spiegelberg *et al.* (1984) |
| Nickel subsulfide | Cynomolgus monkey | Intratracheal instillation 0.06 $\mu$mol/g lung | Lung macrophage activity decreased | Haley *et al.* (1987) |
| **Natural Killer Cell Activity** | | | | |
| Nickel chloride | CBA/J and C57BL/6J mice/ intramuscular | Single injection, 18 mg/kg | Depressed NK activity (against Yac-1 murine lymphoma cells) | Smialowicz *et al.* (1984, 1985, 1986) |
| **Host Resistance** | | | | |
| Nickel chloride and nickel oxide | CD mice and Sprague-Dawley rats/ inhalation | 0.5 mg/m$^3$ for 2 hours | Enhanced respiratory infection to *Streptococcus* | Adkins *et al.* (1979) |

## *Humans*

Most of the toxicity information on nickel and nickel compounds came from studies of workers in nickel refineries where the primary toxicity is to the respiratory system. In the industrial setting, nickel exposures were occasionally associated with rhinitis, sinusitis, and nasal-septal perforations. Hypersensitive allergic asthmatic reactions to nickel are rare (Nemery, 1990). There were also reports of pulmonary fibrosis in workers inhaling nickel dust (WHO, 1991). While respiratory toxicity has been observed in workers exposed to nickel in the industrial setting, these workers are often exposed to other toxic metals and/or cigarette smoke, and it has not always been possible to conclude that nickel is the sole causative agent of toxicity (ATSDR, 1992). Muir *et al.* (1993) reviewed X-rays of 745 former sinter workers and found no evidence of significant inflammatory or fibrogenic responses in the lungs of the exposed workers.

Nickel contact hypersensitivity has been seen in the general population and in exposed workers. In the general population, contact sensitivity to nickel-containing jewelry and/or prosthesis is another form of nickel toxicity (ATSDR, 1992). Other toxic reactions to nickel were reported in humans in isolated cases where exposures to nickel were not well characterized. These reactions included cardiovascular effects in a child ingesting nickel sulfate and gastrointestinal effects, transient increases in blood reticulocytes, or muscular pain in workers exposed to

nickel-contaminated water (ATSDR, 1992). In epidemiologic studies that have shown an association between nickel exposure and cancer, excess mortality from non-malignant respiratory effects or other diseases has not been observed (Doll *et al.*, 1990).

## CARCINOGENICITY

### *Experimental Animals*

The International Agency for Research on Cancer (IARC, 1990) summarized the results of experimental studies on the carcinogenic potential of nickel compounds after local injection (e.g., subcutaneous or intramuscular injection). Nickel oxide, nickel subsulfide, nickel carbonyl, and nickel powder cause neoplasms at the injection site, while the soluble nickel salts such as nickel sulfate have generally not been associated with a carcinogenic response at the injection site. A portion of the IARC (1990) listing and tabulation of over 100 experiments on the carcinogenic potential of nickel compounds is presented in Table 3.

Information on the carcinogenic potential of nickel oxide, nickel subsulfide, and nickel sulfate hexahydrate by inhalation exposure is limited. Ottolenghi *et al.* (1975) reported that nickel subsulfide (70% of particles were smaller than 1 $\mu$m in diameter; 25% of particles were between 1 and 1.5 $\mu$m) caused an increased incidence in lung tumors in F344/N rats exposed to 1 mg/m$^3$ by inhalation (6 hours/day and 5 days/week for 108 weeks). In the exposed groups, 12% to 14% of the 208 animals had lung tumors compared to less than 0.5% of 215 control animals. At the end of the 108-week exposure period, fewer than 5% of the animals in exposed groups were alive compared with a survival of 31% in control groups.

Other experimental studies indicated carcinogenic potential of nickel subsulfide for the respiratory tract mucosa. Yarita and Nettesheim (1978) reported that a single intratracheal dose of 1 or 3 mg nickel subsulfide/kg caused tumors in heterotrophic tracheal transplants in female F344 rats. These authors noted that toxicity might decrease a carcinogenic response resulting in a misleadingly low carcinoma incidence, based on the finding that the more toxic dose (3 mg/kg) caused only a 1.5% incidence of carcinomas (there was a high incidence of tracheal hyperplastic change) versus a 10% carcinoma incidence in the 1 mg/kg group (generally with only a low incidence of toxic lesions).

Hamsters exposed to 53 mg nickel oxide/m$^3$ (median diameter of 0.3 $\mu$m; geometric standard deviation of 2.2) for 2 years did not have an increase in the incidence of lung tumors (Wehner *et al.*, 1975). The hamster may be less sensitive than the rat to the carcinogenic effects of nickel (Furst and Schlauder, 1971).

Sunderman *et al.* (1959) found a low incidence of lung tumors in groups of Wistar rats exposed to nickel carbonyl (0.03 to 0.25 mg/m$^3$ for 30 minutes 3 times/week for 1 year). Follow-up studies also showed a low incidence of lung tumors in rats exposed to nickel carbonyl (Sunderman and Donnelly, 1965).

Information on the carcinogenic potential of nickel after oral administration is limited (IARC, 1990). Lifetime exposure to nickel acetate at low concentrations (5 ppm) induced no lung lesions in Swiss mice (Schroeder *et al.*, 1964; Schroeder and Mitchener, 1975); the maximum tolerated dose was not reached. Ambrose *et al.* (1976) administered nickel sulfate hexahydrate in the diet of Wistar rats or dogs (0, 100, 1,000, 2,500 ppm) for 2 years, and no treatment-related lesions were observed.

### *Humans*

Exposure to nickel in the workplace has been associated with an increase in lung and nasal sinus tumors (IARC, 1976, 1987, 1990; Doll *et al.*, 1990). Based on the finding of lung and/or nasal sinus tumors in nickel refinery workers, IARC classified nickel and nickel compounds as human carcinogens (Group 1), although there was insufficient information available to evaluate the carcinogenic risk for individual nickel compounds or the risk for cancer based on exposure to different concentrations of nickel compound(s) (IARC, 1987).

TABLE 3
**Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals[a]**

| Nickel Compound | Species/Route | Lesion Incidence[b] | Reference |
|---|---|---|---|
| **Nickel oxides and hydroxides** | | | |
| Nickel monoxide (green) | Rat/inhalation | 0.6 mg/m$^3$: 0/6 lung lesion<br>8 mg/m$^3$: 1/8 lung lesion | Horie *et al.* (1985) |
| Nickel monoxide | Rat/inhalation | 0.06 mg/m$^3$: 0/40 lesion<br>0.2 mg/m$^3$: 0/20 lesion | Glaser *et al.* (1986) |
| | Rat/intrapleural | Controls: 0/32 local lesions<br>31/32 local lesions | Skaug *et al.* (1985) |
| | Rat/intratracheal | Controls: 0/40 lesions<br>10 × 5 mg: 10/37 lung lesions<br>10 × 15 mg: 12/38 lung lesions | Pott *et al.* (1987) |
| | Rat/intramuscular | 21/32 local lesions | Gilman (1962) |
| | Rat/intramuscular | 2/20 local lesions | Gilman (1966) |
| | Rat/intramuscular | 0/20 local lesions | Sosiński (1975) |
| | Rat/intramuscular | 14/15 local lesions | Sunderman and McCully (1983) |
| | Rat/intramuscular | 0/20 local lesions | Berry *et al.* (1984) |
| | Rat/subperiosteal | 0/20 local lesions | Berry *et al.* (1984) |
| | Rat/intraperitoneal | 46/47 local lesions | Pott *et al.* (1987) |
| | Rat/intraperitoneal | 25 mg: 12/34 local lesions<br>100 mg: 15/36 local lesions | Pott *et al.* (1989, 1992) |
| Nickel monoxide (green) | Rat/intrarenal | 0/12 local lesions | Sunderman *et al.* (1984) |
| Nickel monoxide | Mouse/intramuscular | 33/50 and 23/52 local lesions | Gilman (1962) |
| | Hamster/inhalation | 1/51 osteosarcoma | Wehner *et al.* (1975, 1979) |
| | Hamster/intratracheal | Controls: 4/50 lung lesions<br>1/49 lung lesions | Farrell and Davis (1974) |
| Nickel hydroxide | Rat/intramuscular | 15/20 local lesions | Gilman (1966) |
| | Rat/intramuscular | Dried gel: 5/19 local lesions<br>Crystalline: 3/20 local lesions<br>Colloidal: 0/13 local lesions | Kasprzak *et al.* (1983) |
| Nickel trioxide | Rat/intramuscular | 0/10 local lesions | Judde *et al.* (1987) |
| | Rat/intracerebral | 3/20 local lesions | Sosiński (1975) |

(continued)

TABLE 3
**Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals** (continued)

| Nickel Compound | Species/Route | Lesion Incidence | Reference |
|---|---|---|---|
| **Nickel sulfides** | | | |
| Nickel disulfide | Rat/intramuscular | 12/14 local lesions | Sunderman (1984) |
| | Rat/intrarenal | 2/10 local lesions | Sunderman *et al.* (1984) |
| Nickel sulfide (amorphous) | Rat/intramuscular | 5.6 mg: 0/10 local lesions<br>22.4 mg: 0/10 local lesions | Sunderman and Maenza (1976) |
| ß-Nickel sulfide | Rat/intramuscular | 14/14 local lesions | Sunderman (1984) |
| Nickel sulfide (amorphous) | Rat/intramuscular | 3/25 local lesions | Sunderman (1984) |
| Nickel sulfide | Rat/intrarenal | 0/18 local lesions | Jasmin and Riopelle (1976) |
| ß-Nickel sulfide | Rat/intrarenal | 8/14 local lesions | Sunderman *et al.* (1984) |
| Nickel sulfide (amorphous) | Rat/intrarenal | 0/15 local lesions | Sunderman *et al.* (1984) |
| Nickel subsulfide | Rat/inhalation | 14/208 malignant lung lesions<br>15/208 benign lung lesions | Ottolenghi *et al.* (1975) |
| | Rat/intratracheal | 0.94 mg: 7/47 lung lesions<br>1.88 mg: 13/45 lung lesions<br>3.75 mg: 12/40 lung lesions | Pott *et al.* (1987) |
| | Rat/intrapleural | 28/32 local lesions | Skaug *et al.* (1985) |
| | Rat/subcutaneous | 3.3 mg: 37/39 local lesions<br>10 mg: 37/40 local lesions | Mason (1972) |
| | Rat/subcutaneous | 18/19 local lesions | Shibata *et al.* (1989) |
| | Rat/intramuscular | 25/28 local lesions | Gilman (1962) |
| | Rat/intramuscular | Controls:<br>1/19 local lesion<br>10 mg powder:<br>19/20 local lesions<br>10 mg diffusion chamber:<br>14/17 local lesions<br>500.mg fragments:<br>5/7 local lesions<br>500 mg discs:<br>14/17 local lesions | Gilman and Herchen (1963) |

(continued)

**TABLE 3**
**Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals** (continued)

| Nickel Compound | Species/Route | Lesion Incidence | Reference |
|---|---|---|---|
| **Nickel sulfides** (continued) | | | |
| Nickel subsulfide (disc) | Rat/intramuscular | Removal of disc after 64 days: 4/10 local lesions<br>Removal of disc after 128 days: 7/10 local lesions<br>Removal of disc after 206 days: 10/10 local lesions | Herchen and Gilman (1964) |
| Nickel subsulfide | Rat/intramuscular | NIH black: 28/28 local lesions<br>Hooded: 14/23 local lesions | Daniel (1966) |
| | Rat/intramuscular | 3.3 mg: 38/39 local lesions<br>10 mg: 34/40 local lesions | Mason (1972) |
| | Rat/intramuscular | 5 mg: 8/20 local lesions<br>20 mg: 9/9 local lesions | Sunderman and Maenza (1976) |
| | Rat/intramuscular | Fischer: 59/63 local lesions<br>Hooded: 11/20 local lesions | Yamashiro *et al.* (1980) |
| | Rat/intramuscular | 0.6 mg: 7/30 local lesions<br>1.2 mg: 23/30 local lesions<br>2.5 mg: 28/30 local lesions<br>5 mg: 29/30 local lesions | Sunderman *et al.* (1976) |
| | Rat/intramuscular | 0.63 mg: 7/29 local lesions<br>20 mg: 9/9 local lesions | Sunderman (1981) |
| α-Nickel subsulfide | Rat/intramuscular | 9/9 local lesions | Sunderman (1984) |
| Nickel subsulfide | Rat/intramuscular | 10/20 local lesions | Berry *et al.* (1984) |
| | Rat/intramuscular | 2/100 local lesions | Judde *et al.* (1987) |
| | Rat/intramuscular | 19/20 local lesions | Shibata *et al.* (1989) |
| | Rat/intraperitoneal | 9/37 local lesions | Gilman (1966) |
| | Rat/intraperitoneal | 27/42 local lesions | Pott *et al.* (1987) |
| | Rat/intraperitoneal | 6 mg: 20/36 local lesions<br>12 mg: 25/35 local lesions<br>25 mg: 25/34 local lesions | Pott *et al.* (1989, 1992) |
| | Rat/subperiosteal | 0/20 local lesions | Berry *et al.* (1984) |
| | Rat/intrafemoral | 10/20 local lesions | Berry *et al.* (1984) |
| | Rat/intrarenal | In glycerin: 7/16 local lesions<br>In saline: 11/24 local lesions | Jasmin and Riopelle (1976) |

(continued)

TABLE 3
**Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals** (continued)

| Nickel Compound | Species/Route | Lesion Incidence | Reference |
|---|---|---|---|
| **Nickel sulfides** (continued) | | | |
| α-Nickel subsulfide | Rat/intrarenal | Wistar Lewis: 7/11 local lesions<br>NIH black: 6/12 local lesions<br>Fischer 344: 9/32 local lesions<br>Long-Evans: 0/12 local lesions | Sunderman *et al.* (1979) |
| Nickel subsulfide | Rat/intratesticular | 16/19 local lesions | Damjanov *et al.* (1978) |
| | Rat/intraocular | 14/15 local lesions | Albert *et al.* (1980); Sunderman (1983a) |
| | Rat/transplacental | No difference in lesion incidence | Sunderman *et al.* (1981) |
| | Rat/pellet implantation into subcutaneous implanted tracheal grafts | 5 mg: 9/60 local lesions<br>15 mg: 45/64 local lesions | Yarita and Nettesheim (1978) |
| | Rat/intra-articular | 16/19 local lesions | Shibata *et al.* (1989) |
| | Rat/intra-fat | 9/20 local lesions | Shibata *et al.* (1989) |
| | Mouse/intratracheal | No increase in lung lesion incidence | Fisher *et al.* (1986) |
| | Mouse/subcutaneous | 5 mg: 4/8 local lesions<br>10 mg: 7/8 local lesions | Oskarsson *et al.* (1979) |
| | Mouse/intramuscular | Swiss: 27/45 local lesions<br>C3H: 9/18 local lesions | Gilman (1962) |
| | Mouse/intramuscular | 5 mg: 4/8 local lesions<br>10 mg: 4/8 local lesions | Oskarsson *et al.* (1979) |
| | Mouse/intramuscular | C57B16: 5/10 local lesions<br>DBA/2: 6/10 local lesions | Sunderman (1983a) |
| α-Nickel subsulfide | Hamster/intratracheal | 0/62 lung lesions | Muhle *et al.* (1992) |
| Nickel subsulfide | Hamster/intramuscular | Controls: 0/14 local lesions<br>5 mg: 4/15 local lesions<br>10 mg: 12/17 local lesions | Sunderman (1983b) |
| α-Nickel subsulfide | Hamster/topical | 54 mg total: 0/6 local lesions<br>108 mg total: 0/7 local lesions<br>540 mg total: 0/15 local lesions<br>1,080 mg total: 0/13 local lesions | Sunderman (1983a) |
| Nickel subsulfide | Rabbit/intramuscular | 16 local lesions | Hildebrand and Biserte (1979a,b) |

(continued)

TABLE 3
**Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals** (continued)

| Nickel Compound | Species/Route | Lesion Incidence | Reference |
|---|---|---|---|
| **Nickel sulfides** (continued) | | | |
| α-Nickel subsulfide | Rabbit/intramuscular | 0/4 local lesions | Sunderman (1983b) |
| Nickel subsulfide | Salamander/intraocular | 7/8 local lesions | Okamoto (1987) |
| Nickel ferrosulfide | Rat/intramuscular | 15/15 local lesions | Sunderman (1984) |
| | Rat/intrarenal | 1/12 local lesions | Sunderman *et al.* (1984) |
| **Nickel salts** | | | |
| Basic nickel carbonate tetrahydrate | Rat/intraperitoneal | Controls: 1/33 lung lesions<br>25 mg: 1/35 lung lesions<br>50 mg: 3/33 lung lesions | Pott *et al.* (1989, 1992) |
| Nickel acetate | Mouse/intraperitoneal | 72 mg: 8/18 lung lesions<br>180 mg: 7/14 lung lesions<br>360 mg: 12/19 lung lesions | Stoner *et al.* (1976) |
| | Rat/intramuscular | 1/35 local lesions | Payne (1964) |
| Nickel acetate tetrahydrate | Mouse/intraperitoneal | Controls: 0.32 lung lesions/animal<br>1.5 lung lesions/animal | Poirier *et al.* (1984) |
| | Rat/intraperitoneal | Controls: 1/33 lung lesions<br>25 mg: 3/35 lung lesions<br>50 mg: 5/31 lung lesions | Pott *et al.* (1989, 1992) |
| Nickel ammonium sulfate | Rat/intramuscular | 0/35 local lesions | Payne (1964) |
| Nickel carbonate | Rat/intramuscular | 6/35 local lesions | Payne (1964) |
| Nickel chloride | Rat/intramuscular | 0/35 local lesions | Payne (1964) |
| Nickel chloride hexahydrate | Rat/intraperitoneal | Controls: 1/33 lung lesions<br>4/32 lung lesions | Pott *et al.* (1989, 1992) |
| Nickel chromate | Rat/intramuscular | 1/16 local lesions | Sunderman (1984) |
| Nickel fluoride | Rat/intramuscular | 3/18 local lesions | Gilman (1966) |
| Nickel sulfate | Rat/intramuscular | 1/35 local lesions | Payne (1964) |
| | Rat/intramuscular | 0/20 local lesions | Gilman (1966) |
| | Rat/intramuscular | 0/20 local lesions | Kasprzak *et al.* (1983) |

(continued)

TABLE 3
**Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals** (continued)

| Nickel Compound | Species/Route | Lesion Incidence | Reference |
|---|---|---|---|
| **Nickel salts** (continued) | | | |
| Nickel sulfate hexahydrate | Rat/intramuscular | 0/32 local lesions | Gilman (1962) |
| Nickel sulfate heptahydrate | Rat/intraperitoneal | Controls: 1/33 lung lesions<br>6/30 lung lesions | Pott *et al.* (1989, 1992) |
| **Other** | | | |
| Nickel carbonyl | Rat/inhalation | 30 mg/m$^3$ for 32 weeks: 1/64 pulmonary lesions<br>60 mg/m$^3$ for 32 weeks: 1/32 pulmonary lesions<br>250 mg/m$^3$ once: 1/80 pulmonary lesion | Sunderman *et al.* (1957, 1959) |
| | Rat/inhalation | Controls: 0/32 lung lesions<br>1/71 lung lesions | Sunderman and Donnelly (1965) |
| | Rat/intravenous | 19/120 lung lesions | Lau *et al.* (1972) |

[a] From IARC (1990)
[b] Number of animals with lesion per effective number

Information on the hazards associated with exposure to nickel came from studies on occupational exposure in nickel refineries and mines in Clydach, South Wales; Kristiansand, Norway; the International Nickel Company (INCO) refineries in Ontario, Canada; or from other studies of nickel refineries, nickel mines, or other nickel industrial operations throughout the world (Doll, 1984).

The United States Environmental Protection Agency (USEPA, 1986) and the International Committee on Nickel Carcinogenesis in Man (Doll *et al.*, 1990) reviewed the epidemiological evidence for cancer after exposure to nickel in mining or refinery operations. A complete analysis on the type of ore mined and the calcining, smelting, and refining operations in 10 different mines or refineries throughout the world can be found in Doll *et al.* (1990) and in other more recent summaries (Courtin, 1994; McIlveen and Negusante, 1994; Nieboer and Templeton, 1994; Norseth, 1994). Doll *et al.* (1990) also estimate the type of nickel exposures encountered based on knowledge of the nickel process procedures used and a few relatively recent measurements of total airborne nickel. This study focused primarily on "high-risk" cohorts of nickel workers, and many of the workers studied did not have nickel-related cancers.

The first indication that some form of nickel can give rise to lung and nasal sinus cancers was obtained from refinery workers at Clydach, South Wales (Bridge, 1933; Doll, 1958; Morgan, 1958). The Clydach Nickel Refinery (Mond Nickel Works) opened in 1902 and used a nickel-copper matte. In 1933, nasal sinus and lung cancers were first noted in workers who were employed prior to 1925. After 1925, the copper and sulfate content of the matte was reduced, the arsenic contamination in sulfuric acid used to extract copper was reduced, the use of respirators and masks was introduced, and improvements were made in factory design that reduced exposure to nickel (USEPA, 1986; Doll *et al.*, 1990). An increased risk for lung and nasal sinus cancers was particularly noted in refinery work involving

roasting, sintering, and calcining processes that converted impure nickel-copper matte to an oxide (Doll *et al.*, 1990).

Peto *et al.* (1984) analyzed the incidence of lung and nasal sinus cancers found in workers in the Clydach plant and found the highest incidence of cancer in those workers employed in the copper sulfate and furnace areas. There was no increased risk to workers in the reduction area where nickel carbonyl concentrations were highest.

Other evidence for nasal sinus and lung cancer come from studies of workers in the INCO (Ontario, Canada) mines and refineries (Roberts *et al.*, 1989a,b; Muir *et al.*, 1994). Facilities operated include the Sudbury area mines (Copper Cliff Smelter and the Port Colborne refinery) that use an ore that is primarily petlandite ($NiFeS_2$). Men working in mining operations in Ontario had an increase in lung cancer risk, but no nasal sinus cancers (Doll *et al.*, 1990).

The Falconbridge refinery in Kristiansand, Norway, receives nickel-copper matte from Canada and uses an electrolysis process to refine the ore. Workers in roasting and smelting operations are exposed to dry dust containing nickel subsulfide and nickel oxide. Electrolysis workers are also exposed to nickel sulfate and nickel chloride. In this cohort, nasal sinus and lung cancer risks were increased in men working in the electrolysis department, thus implicating the soluble forms of nickel as the cause for the cancer (USEPA, 1986; Doll *et al.*, 1990). The electrolysis workers had the highest average plasma and urine nickel concentrations (Høgetveit *et al.*, 1978).

Enterline and Marsh (1982) studied cancer rates in workers at a refinery in Huntington, West Virginia, which received nickel-copper matte from Canada and/or nickel matte from New Caledonia. The Doll Committee reported no clear evidence for an increased incidence in lung cancer in this population, although the data from this cohort provided weak evidence for an increased incidence in lung cancer in men exposed to sulfidic nickel at 4 mg nickel/$m^3$ for more than a year (Doll *et al.*, 1990).

Results of epidemiology studies of workers in the nickel mining, smelting, and refinery operations in New Caledonia showed no increased incidence of lung or upper respiratory tract cancers (Goldberg *et al.*, 1994). Nickel at this site is mined from nickel laterites including silicate and limonite ores. The Doll Committee also reported little evidence for an increased incidence in lung or upper respiratory tract cancer in this group of nickel workers (Doll *et al.*, 1990).

The ten cohorts of nickel workers studied by the Doll Committee include the six cohorts mentioned above (nickel refinery operations, Clydach, South Wales; Falconbridge Nickel Mines, Ontario, Canada; INCO mines and refineries [Copper Cliff, Port Colborne, and Coniston], Ontario, Canada; Falconbridge refinery, Kristiansand, Norway; Huntington Alloys, West Virginia; and New Caledonia mines) as well as the Hanna Nickel Smelting Co., Oregon; Oak Ridge Gaseous Diffusion Plant, Tennessee; Outokumpu Oy nickel refinery, Finland; and Henry Wiggin Alloy Co., England (Doll *et al.*, 1990).

The results within the individual cohorts varied, but the overall conclusion by the Doll Committee suggested that more than one form of nickel gives rise to lung and nasal sinus cancer. Much of the respiratory cancer risk was attributed to exposure to a mixture of oxidic and sulfidic nickel. In the absence of sulfidic nickel, exposure to large concentrations of oxidic nickel was also associated with increased lung and nasal sinus cancer risks. There was evidence that exposure to soluble nickel salts increased the risk of lung and nasal sinus cancer and that it may enhance risks associated with exposure to less soluble forms of nickel. There was no evidence that metallic nickel was associated with increased lung and nasal sinus cancer risks. There was no evidence to suggest that exposure to metallic nickel or any of its compounds was likely to produce cancers elsewhere than in the lung or nose. These investigators were not able to provide exposure-specific estimates of risks for individual nickel species. However, the evidence from these studies suggests that respiratory cancer risks in "high-risk" cohorts are primarily related to exposure to water-soluble nickel compounds at concentrations in excess of 1 mg nickel/$m^3$ and to exposure to less soluble forms at concentrations greater than 10 mg nickel/$m^3$.

There are no studies evaluating the potential carcinogenic effect in humans specifically after oral exposure to nickel (ATSDR, 1992).

While nickel and nickel compounds are classified by the IARC as Group 1 (human) carcinogens, the mechanism for this carcinogenic activity is not fully understood (Sunderman, 1989; Costa, 1991; Snow, 1992). The mechanisms involved in the induction of cancer by nickel compounds may be related to the ability of nickel ions to interact with chromatin proteins and/or the ability of nickel to generate intracellular oxidants (Costa *et al.*, 1994). Recent studies suggest that nickel generates free radicals, and the subsequent oxidative reactions lead to DNA damage and cancer. Studies show that 1) incubation of nickel ions with cysteine under aerobic conditions generates hydroxyl radicals and carbon-centered alkyl radicals, suggesting free radicals are generated by nickel (II)-thiol complexes and molecular oxygen (Shi *et al.*, 1993); 2) in forward mutation assays with bacterial DNA, nickel ions produce tandem double CC → TT mutations consistent with damage to DNA by either ultraviolet irradiation or oxygen-free radicals (Tkeshelashvili *et al.*, 1993); and 3) in *in vitro* studies, nickel ions induce increases in 8-hydroxy-2′-deoxyguanosine (8-OH-dG), a biomarker of oxidatively damaged DNA (Littlefield *et al.*, 1991).

After subcutaneous or intramuscular injection of nickel compounds, the water-insoluble nickel compounds are the most potent carcinogens. These findings may be related to the fact that water-insoluble nickel compounds are more readily phagocytized than are the water-soluble nickel salts, which passively diffuse through the cell membrane. Phagocytized nickel particles are internalized in vacuoles whose acidity accelerates the dissolution of nickel ions and results in a higher concentration of nickel than would be achieved by the cellular uptake of water-soluble nickel salts (Costa *et al.*, 1994).

## Reproductive and Developmental Toxicity

### *Experimental Animals*

Leonard and Jacquet (1984) reviewed studies which show that water-soluble nickel compounds administered orally or by peritoneal routes have the potential to cause embryotoxicity in rodents. In these studies, the nickel compounds were generally administered at higher doses than humans would be exposed to in drinking water or in the diet.

Studies in rodents have indicated that water-soluble nickel compounds can cross the placenta or be excreted in the milk of lactating animals. When [$^{63}$Ni]-labeled nickel chloride was administered as an oral bolus dose (10 μmol or 0.58 mg/kg body weight) to pregnant mice, the label was detected in various fetal tissues including liver, kidney, lung, brain, and heart. In another experiment, when [$^{63}$Ni]-labeled nickel chloride was injected into pregnant mice, nickel was found to cross the placenta, and a marked uptake of nickel was observed in the embryo as measured by whole-body autoradiography (Olsen and Jonsen, 1979). When nickel chloride hexahydrate was given as a single subcutaneous dose (10 to 100 μmol $NiCl_2 \cdot 6H_2O$/kg body weight or 23 mg/kg) to lactating rats, nickel was excreted in the milk and was found in the plasma of the pups (Dostal *et al.*, 1989). The doses used in these studies are higher than the average concentration of nickel found in drinking water in the United States (48 μg/L water) (NAS, 1975).

Nickel chloride administered in the drinking water (50 and 250 ppm, estimated to deliver 7 or 31 mg/kg of nickel compound) to female rats for 11 weeks prior to mating and then during two successive gestation and lactation periods caused an increase in the proportion of dead pups per litter (Smith *et al.*, 1993).

Other studies in rodents administered nickel chloride by intramuscular or intraperitoneal injection during gestation also showed developmental toxicity or fetal death. Nickel chloride injected intraperitoneally (1, 2, or 4 mg/kg body weight) to pregnant Wistar Porton rats on day 8, 12, or 16 of pregnancy caused skeletal retardation (poor ossification), hydrocephalus, hydronephrosis, heart defects, and hemorrhage. At these doses, there was an increase in maternal plasma glucose concentration (Mas *et al.*, 1985).

Nickel chloride injected intramuscularly (16 mg/kg) on day 8 of gestation to Fischer rats reduced the

mean number of live pups per dam and diminished fetal body weights on day 20 (Sunderman *et al.*, 1978). Nickel chloride injected into chicken eggs at doses of 0.02 to 0.8 mg per egg on days 0, 1, 2, 3, and 4 after fertilization caused malformations in the embryo including exencephaly, everted viscera, abnormalities in the limb development, microphthalmia, and reduced body size when examined at day 8 (Gilani and Marano, 1980).

Groups of pregnant hamsters were exposed to nickel carbonyl by inhalation (0.06 mg/L for 15 minutes) on days 4, 5, 6, 7, or 8 of gestation; dams were evaluated on day 15 of gestation. Teratogenic effects observed included cystic lung, exencephaly, cleft palate, and fused ribs. In another series of experiments where dams were allowed to deliver the pups, neonatal mortality was increased in the exposed groups (Sunderman *et al.*, 1980). Nickel carbonyl administered to pregnant dams by intravenous injection (11 mg/kg) on day 7 of gestation caused an increase in fetal mortality, diminished body weight of live pups, and increased incidences of fetal abnormalities including anophthalmia, microphthalmia, cystic lungs, and hydronephrosis (Sunderman *et al.*, 1983).

In a study of nickel oxide, Wistar rats were exposed to 1.6 mg nickel/$m^3$ by inhalation on gestation days 1 through 20. There was no evidence of embryotoxicity (Weischer *et al.*, 1980).

These and other studies show that water-soluble nickel salts have the potential to cause embryotoxicity in rodents. The metal can cross the feto-maternal barrier and enter the fetus. The embryotoxicity of nickel may be related to several factors including the mutagenic properties of nickel, direct effects on the mammalian embryo, or indirect effects through maternal toxicity. Further work is needed to understand the mechanisms for these effects (Leonard and Jacquet, 1984).

### *Humans*

Until recently, there have been few studies of reproductive effects in humans after exposure to nickel (ATSDR, 1992). A preliminary study of nickel refinery workers in Russia who were exposed to water-soluble nickel salts in electrolysis departments noted a suggested increased risk of pregnancy complications in female workers (Chashschin *et al.*, 1994).

## GENETIC TOXICITY

Recent detailed reviews of the mutagenicity of nickel compounds and the possible mechanisms involved in the production of these effects were presented by Coogan *et al.* (1989), Christie and Katisifis (1990), Costa (1991), Snow (1992), and Costa *et al.* (1994). Nickel compounds are not typically detected as bacterial mutagens, but they often give positive results in *in vitro* assays designed to identify compounds that induce chromosomal damage in mammalian cells in the form of sister chromatid exchanges, chromosomal aberrations, and DNA strand breaks. Nickel salts have been shown to inhibit DNA replication and to increase replication errors in mammalian cells *in vitro*, possibly by competing with magnesium for essential binding sites on DNA polymerases (Christie *et al.*, 1991). In addition, positive results were demonstrated in mammalian cell forward mutation assays (TK locus in mouse lymphoma cells and hypoxanthine phosphoribosyl transferase locus in hamster V79 cells), although these responses are usually weak (Nishimura and Umeda, 1979; Amacher and Paillet, 1980; Morita *et al.*, 1991; Lee *et al.*, 1993). Insoluble crystalline nickel compounds are more active in genetic toxicity assays than the soluble or amorphous forms of nickel. Presumably, this differential activity derives from the more efficient entry of insoluble nickels into the cell through phagocytosis (Costa, 1991), longer retention of these compounds within the cell, and the consequent higher intracellular concentration of nickel (II) ions. Soluble nickel salts cannot be efficiently phagocytized and do not accumulate in high concentration within the cell. Based on the results of cell transformation studies in cultured rodent cells, Costa and Heck (1983) concluded that the nickel sulfide compounds must be in the crystalline, rather than in the amorphous state to be efficiently phagocytized into the cell and cause genetic damage. Particle size (Costa and Mollenhauer, 1980) and surface charge (Costa *et al.*, 1982) are also important factors in the phagocytosis of nickel compounds. Insoluble nickel compounds, once inside the cell, aggregate near the nucleus (Bryan, 1981; Evans *et al.*, 1982) where they are

dissolved by lysosomes, releasing nickel (II) ions that proceed to effect DNA damage (Costa *et al.*, 1994).

The DNA damage resulting from nickel exposure has been attributed to one or more of the following mechanisms. It may follow the generation of short-lived reactive oxygen species inside the nucleus, produced by the oxidation of $Ni^{+2}$ to $Ni^{+3}$ by hydrogen peroxide or other oxidants subsequent to the binding of nickel ions to ligands such as amino acids, glutathione, and amino acid side chains of nuclear proteins (Biggart and Costa, 1986; Inoue and Kawanishi, 1989; Nieboer *et al.*, 1989; Cotelle *et al.*, 1992; Tkeshelashvili *et al.*, 1993; Sugiyama, 1994). The formation of persistent DNA-protein crosslinks is implicated in the generation of nickel (II)-induced DNA damage (Ciccarelli and Wetterhahn, 1982; Lee *et al.*, 1982; Patierno and Costa, 1985; Sen and Costa, 1986a). Factors involved in the binding of nickel ions to DNA, nuclear proteins, and other nuclear structures are reviewed by Coogan *et al.* (1989). The binding affinity of nickel to protein is far greater than to purified DNA (Eichorn and Shin, 1968) and therefore, the mutagenic activity of nickel (II) ions probably derives primarily from the binding of nickel to chromosomal protein rather than directly to DNA (Costa, 1991). Nickel binds preferentially to heterochromatic regions of the chromosomes such as the long arm of the X chromosome in cultured Chinese hamster cells (Sen and Costa, 1986a,b; Sen *et al.*, 1987; Costa, 1991); binding of nickel ions to the long arm of the X chromosome and subsequent deletions in this region were postulated to cause the loss of a gene controlling senescence in cultured Chinese hamster cells and to promote immortality in transformed cultured Chinese hamster cell lines (Klein *et al.*, 1991). A schematic representation of some of the proposed mechanisms of nickel-induced genotoxicity, based upon the current understanding of the activities of nickel ions within mammalian cells, is presented in Figure 1. The genetic toxicity data for each of the three nickel compounds under study by the NTP are described below.

The mutagenicity data for nickel oxide are limited; however, there are clear indications of genotoxicity in some *in vitro* test systems. Although exposure to nickel oxide did not result in growth inhibition due to DNA damage in repair-deficient strains of *Bacillus subtilis* (Kanematsu *et al.*, 1980), an S-phase block (determined by flow cytometric analysis) was induced in cycling Chinese hamster ovary cells incubated with 5 μg/mL nickel oxide (Costa *et al.*, 1982). No increase in gene mutations was detected at the ouabain resistance locus in C3H/$10T_{1/2}$ mouse embryo cells (Miura *et al.*, 1989) or at the HPRT locus in hamster V79 cells after exposure to nickel oxide (Kargacin *et al.*, 1993). However, positive effects were reported in mutation assays using a different site, the *gpt* gene, in V79 cells as the target for nickel oxide activity (Kargacin *et al.*, 1993). No induction of chromosomal aberrations was detected in human fibroblast or leukocyte cultures exposed to nickel oxide for 24, 48, or 72 hours (Paton and Allison, 1972); however, the experimental protocol used in this test was designed for water-soluble compounds and may not have been suitable for testing insoluble nickel oxide. Data from human epidemiology studies indicate that exposure to nickel oxide-containing fumes or smelter dusts may induce chromosomal aberrations (Waksvik *et al.*, 1984) and DNA-crosslinks (Costa *et al.*, 1993) in peripheral blood lymphocytes of workers, but the evidence is weak. The link between nickel oxide and these genetic endpoints is confounded because smelter dusts and welding fumes contain other nickel compounds as well as other metals such as chromium and magnesium. Also, the genetic effects noted were not correlated with nickel concentrations in urine or blood, whereas increased DNA-crosslink frequencies noted after exposure to chromium-containing fumes, for example, were correlated with urine concentrations of the metal (Popp *et al.*, 1992).

Nickel sulfate hexahydrate did not induce gene mutations in *Escherichia coli* or *Salmonella typhimurium* (Arlauskas *et al.*, 1985), and (in contrast to results reported for nickel oxide) no increases in *gpt* mutants were observed in hamster V79 cells treated with nickel sulfate hexahydrate (Christie, 1989; Lee *et al.*, 1993). However, nickel sulfate hexahydrate did induce mutations in L5178Y mouse lymphoma $TK^{+/-}$ cells treated with 500 to 1,000 μg/mL in the absence of S9 metabolic activation enzymes (McGregor *et al.*, 1988). In addition, nickel sulfate hexahydrate, administered by injection at doses of 200, 300, and 400 ppm, induced sex-linked recessive lethal mutations in germ cells of male *Drosophila*

(Rodriguez-Arnaiz and Ramos, 1986). The pre- and post-meiotic cell stages were affected; the broods obtained from sperm cells undergoing meiosis at the time of treatment showed no evidence of increased lethal mutations. In another test for germ cell effects in male *Drosophila*, the test for sex chromosome loss, only the highest dose of nickel sulfate hexahydrate (400 ppm) resulted in the production of XO males (Rodriguez-Arnaiz and Ramos, 1986). Induction of sister chromatid exchanges and chromosomal aberrations was observed in hamster cells (Larramendy *et al.*, 1981; Ohno *et al.*, 1982), as well as human peripheral lymphocytes (Larramendy *et al.*, 1981) treated with nickel sulfate hexahydrate *in vitro*. However, no induction of DNA single strand breaks was detected in human xeroderma pigmentosum fibroblasts treated with 250 μg/mL nickel sulfate hexahydrate (Fornace, 1982). *In vivo*, no induction of chromosomal aberrations was observed in rat bone marrow or spermatogonial cells after injection of nickel sulfate hexahydrate at doses that provided 3 or 6 mg nickel/kg body weight. Also, no change in the mitotic index of bone marrow cells was noted in treated animals (Mathur *et al.*, 1978).

As with the two nickel compounds discussed above, there are limited published mutagenicity data for the third nickel compound in the present studies, nickel subsulfide. However, results of *in vitro* tests performed with this insoluble nickel compound were mainly positive. In the *Salmonella typhimurium* gene mutation assay, crystalline nickel subsulfide gave equivocal results in one study that used a preincubation protocol (Zeiger *et al.*, 1992) and negative results in a standard plate incorporation assay (Arrouijal *et al.*, 1990). It induced lethal mutations in *Paramecium tetraurelia*, without S9 (Smith-Sonneborn *et al.*, 1986) and unscheduled DNA repair in cultured Syrian hamster embryo cells (Robison *et al.*, 1983). Treatment of cultured Chinese hamster ovary cells for 24 hours with 10 μg/mL nickel subsulfide resulted in an increase in the number of DNA strand breaks detected by alkaline sucrose gradient techniques (Robison *et al.*, 1982). Nickel subsulfide, in the absence of S9, was a weak inducer of hypoxanthine phosphoribosyl transferase mutations in cultured Chinese hamster ovary cells (Rossetto *et al.*, 1994) and sister chromatid exchanges in cultured human lymphocytes (Saxholm *et al.*, 1981). Nickel subsulfide induced significant dose-related increases in chromosomal aberrations (Arrouijal *et al.*, 1990) and micronuclei (Arrouijal *et al.*, 1992) in human lymphocytes *in vitro*. One reported *in vivo* test with nickel subsulfide, a measure of DNA synthesis inhibition in rats administered 10 μg/rat (6 mg/100 g body weight) by intrarenal injection, was negative (Hui and Sunderman, 1980). A second *in vivo* study, a mouse bone marrow micronucleus test, reportedly produced positive results (Arrouijal *et al.*, 1990). This second study, however, employed only a single dose (250 mg/kg nickel subsulfide administered by intraperitoneal injection), and no confirmatory study was conducted.

## STUDY RATIONALE

The National Cancer Institute nominated nickel compounds for study because there was little information on the toxic and carcinogenic properties of specific nickel compounds after inhalation exposure. Nickel oxide and nickel sulfate hexahydrate were selected as compounds that are commonly found in the workplace in the United States. Nickel subsulfide was selected for study based on a previous study in which lung tumors were observed in rats (Ottolenghi *et al.*, 1975). The NTP toxicity and carcinogenicity studies of nickel oxide (NTP, 1996a), nickel subsulfide, and nickel sulfate hexahydrate (NTP, 1996b) were performed to provide comparative toxicology and carcinogenicity information on these nickel compounds. The results of the nickel subsulfide studies are presented in this Technical Report.

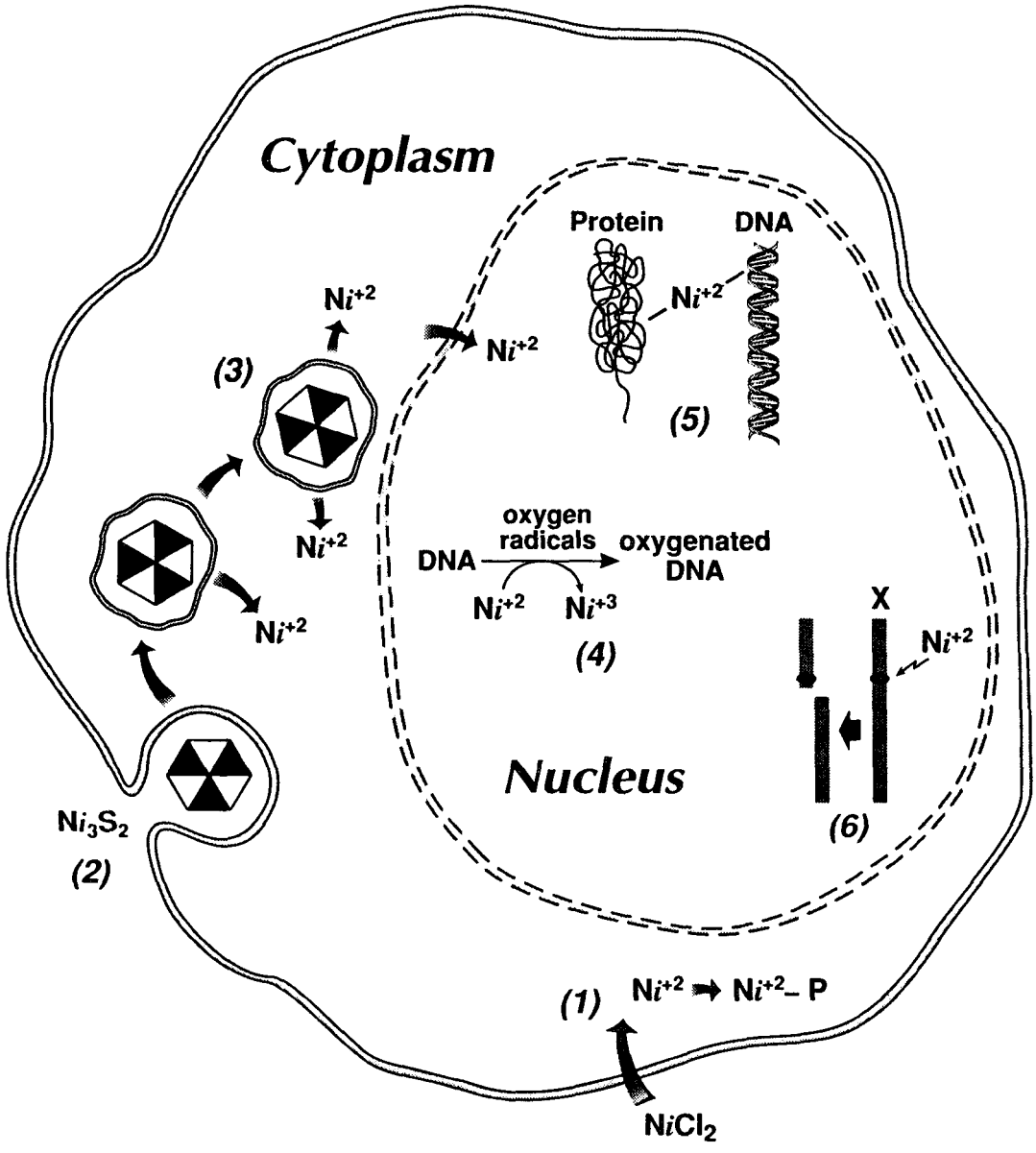


FIGURE 1
**Possible Mechanisms of Nickel-Induced Genotoxicity**

1. Soluble nickel compounds such as nickel chloride diffuse into the cell; $Ni^{+2}$ ions are rapidly bound to cytoplasmic proteins (P) (Lee *et al.*, 1993). 2. Insoluble nickel compounds such as nickel subsulfide are phagocytized into the cell and move toward the nucleus (Costa *et al.*, 1982). 3. Lysosomal breakdown of insoluble nickel compounds releases large quantities of $Ni^{+2}$ ions which concentrate adjacent to the nuclear membrane (Costa and Heck, 1983). 4. Oxidative damage is induced in DNA by nickel ions bound to nuclear proteins ($Ni^{+2} \rightarrow Ni^{+3}$), releasing active oxygen species (Tkeshelashvili *et al.*, 1993; Sugiyama, 1994). 5. DNA-protein crosslinks are produced by $Ni^{+2}$ ions binding to heterochromatin (Lee *et al.*, 1982; Patierno and Costa, 1985; Sen and Costa, 1986a). 6. Binding of nickel ions to the heterochromatic regions of the long arm of the X chromosome, which may contain a senescence gene and a tumor suppressor gene, can cause deletion of all or part of this region, leading to an immortalization of the cell and clonal expansion (Conway and Costa, 1989; Klein *et al.*, 1991).

# MATERIALS AND METHODS

## PROCUREMENT AND CHARACTERIZATION OF NICKEL SUBSULFIDE

Nickel subsulfide was obtained from International Nickel Company, Ltd. (Toronto, Ontario), in three lots (HF-1517, I080786, and I072588). All lots were subject to particle size reduction with a 4-inch micronizer prior to use (Sturtevant Mills, Inc., Boston, MA). Lot HF-1517 was used during the 16-day and 13-week studies, and a blend of the three lots (identified as lot M082288) was used during the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix K). Reports on analyses performed in support of the nickel subsulfide studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a gray or black powder, was characterized as high purity nickel subsulfide by elemental analysis, melting point, spectroscopy, solubility in nitric acid, Karl Fischer water analysis, ion chromatography, and chelometric titration. No absorbance was observed with infrared spectroscopy (Figure K1), and the ultraviolet/visible spectrum was consistent with that expected for the structure. For both lots, elemental analysis values for nickel were slightly low. Elemental analysis results for sulfur were in agreement with the theoretical values for nickel subsulfide. Karl Fischer water analysis indicated approximately 0.08% water. For lot HF-1517, only trace amounts (less than 70 ppm) of sulfate, sulfite, and thiosulfate were detected by ion chromatography. Chelometric titration indicated a purity of 97.0% $\pm$ 1.1% nickel subsulfide. The overall purity of lot HF-1517 was determined to be at least 97%. For lot M082288, spark source mass spectrometry indicated total impurities of less than or equal to 2,620 ppm; the major inorganic impurities were silicon (1,200 ppm), iron (470 ppm), phosphorus (335 ppm), and chromium (300 ppm). Chelometric titration indicated a purity of 98.0% $\pm$ 1.7% nickel subsulfide. The overall purity of lot M082288 was determined to be at least 98%.

A chemical stability study was not performed for nickel subsulfide because of its inert refractory properties as evidenced by the high melting point and extreme conditions necessary for dissolution. To ensure stability, the bulk chemical was stored in amber glass bottles at room temperature.

Periodic monitoring of the bulk chemical by elemental analysis was performed by Huffman Laboratories, Inc. (Golden, CO), prior to and after all studies and every 3 to 4 months during the 2-year studies. No change in purity of the bulk chemical was observed during the studies.

## AEROSOL GENERATION AND EXPOSURE SYSTEM

Nickel subsulfide aerosol was generated from 2-inch fluid bed generators (FBGs) during all studies. A Kr-85 discharger was placed in the generator to reduce the electrical charge on the aerosol. The nickel subsulfide aerosol was mixed with diluting air to achieve the desired concentrations and was delivered to the exposure chambers. The aerosol generation assembly was enclosed in a walk-in hood. Air was circulated through HEPA filters to remove suspended particles in the enclosure. The aerosol delivery system is shown in Figure K3.

Stainless steel, multi-tiered, whole-body exposure chambers (H1000 and H2000, Hazleton Systems, Aberdeen, MD) were used to expose the rats and mice in these studies (Figure K4). The air flow rate was monitored with calibrated rotameters. The air flow rate in the 16-day and 13-week studies corresponded to 10 $\pm$ 2 and 12 $\pm$ 2 air changes per hour, respectively. In the 2-year studies, the air flow rate was 5.99 to 21.63 (rats) and 12.02 to

18.06 (mice) air changes per hour. To reduce the spatial variation of aerosol concentration and to increase the uniformity of mixing, the aerosol was diluted in a radial diluter prior to introduction into the chamber, and a small boxer fan (Model WS 2107FL-1002, Newark Electronics, Chicago, IL) with a flow rate of 60 $ft^3$/min was placed below the aerosol entrance to further mix the aerosol as it entered the chamber. During the 2-year studies, a cyclone device was placed in the aerosol delivery line to reduce the aerosol particle size.

## Aerosol Concentration Monitoring

In the 13-week and 2-year studies, the aerosol concentrations were determined gravimetrically from three 2-hour samples (3 L/min flow rate) from each exposure chamber, except chamber 2 (0.15 mg/$m^3$) was determined from two 3-hour samples (4.5 L/min flow rate), during each 6-hour exposure day. The background concentrations of total suspended particles in the control chambers were monitored each exposure day of the 2-year studies by collecting one 6-hour filter sample. Daily mean exposure concentrations for the 13-week studies are presented in Figures K7 and K8. Weekly mean exposure concentrations for the 2-year studies are presented in Figures K9 and K10. Good control of aerosol concentration was maintained. A continuous aerosol monitor (Model RAM-S, GCA, Co., Bedford, MA) was used to monitor the stability of the aerosol concentrations and to determine the need to adjust the aerosol generation system during exposures. The RAM-S was used to monitor each chamber for at least 10 minutes of every exposure hour during the 16-day studies and at least 5 minutes of every exposure hour during the 13-week and 2-year studies.

## Chamber Atmosphere Characterization

Aerosol size distribution was determined with a cascade impactor once during the 16-day and 13-week studies and monthly during the 2-year studies for each exposure chamber. The particle size as expressed as mass median aerodynamic diameter was similar for all exposure concentrations and ranged from 1.65 to 2.99 $\mu$m with the geometric standard deviation ranging from 1.63 to 3.47 (Tables K1 through K4). Uniformity of aerosol concentration in the exposure chambers was measured prior to the start of the studies without animals in the chambers and with animals during the first week of exposure, and was checked quarterly during the 2-year studies. The spatial variations ranged from 0% to 8.8% for all chambers. The time for the aerosol concentration in the chambers to reach 90% of the target ($T_{90}$), determined with a RAM-S, was 10 minutes during the 16-day studies, 15 minutes during the 13-week studies, and 8 minutes during the 2-year studies.

## 16-Day Studies

Male and female F344/N rats and B6C3$F_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 19 to 20 days (rats) or 21 to 22 days (mice) and were approximately 7 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation, gross observation for evidence of disease, and serologic testing.

Groups of five male and five female rats and mice were exposed to nickel subsulfide by inhalation at concentrations of 0, 0.6, 1.2, 2.5, 5, or 10 mg nickel subsulfide/$m^3$ (equivalent to 0, 0.44, 0.88, 1.83, 3.65, or 7.33 mg nickel/$m^3$). The animals were exposed for 6 hours plus $T_{90}$ (time to reach 90% of target concentration) (10 minutes) per day, 5 days per week for 12 exposure days during a 16-day period. Food was available *ad libitum*, except during exposure periods; water was available *ad libitum* throughout the study. Rats and mice were housed individually. Clinical findings were recorded prior to the start of the study and on day 5 for rats and mice. The animals were weighed initially, on day 4 or 5, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 4.

A tissue burden study was conducted on three male and three female rats and mice exposed to 0, 0.6, 2.5, or 10 mg nickel subsulfide/$m^3$ (equivalent to 0, 0.44, 1.83, or 7.33 mg nickel/$m^3$). The kidney and lung were analyzed to determine nickel content

(Table 4). For determination of nickel concentration, rats and mice were killed using carbon monoxide and exsanguination the morning following the last exposure. Tissue samples were digested with a mixture of nitric and sulfuric acids and hydrogen peroxide and heated in a microwave oven. The digestates were then diluted with deionized water (Millipore Co., Bedford, MA) and analyzed for their nickel content using electrothermal atomic absorption spectroscopy. Limits of detection and quantitation of the analytical method were calculated on a cumulative basis for each set of samples analyzed according to a formula given by Keith *et al.* (1983). Results of the tissue burden studies in the lung and kidney are found in Appendixes H and I.

A necropsy was performed on all animals. The brain, 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, trimmed, embedded in paraffin, sectioned to a thickness of 5 $\mu$m, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on 0, 5 (mice), and 10 mg nickel subsulfide/m$^3$ exposure groups of rats and mice. Selected organs from rats and mice in the other exposure groups were also examined. Table 4 lists the tissues and organs examined.

## 13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to nickel subsulfide 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 Frederick Cancer Research Facility (Frederick, MD). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 19 (males) or 20 days (females) and were approximately 7 weeks old on the first day of exposure. Before initiation of the studies, 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 M).

Groups of 10 male and 10 female rats and mice were exposed to nickel subsulfide by inhalation at concentrations of 0, 0.15, 0.3, 0.6, 1.2, or 2.5 mg nickel subsulfide/m$^3$ (equivalent to 0, 0.11, 0.22, 0.44, 0.88, or 1.83 mg nickel/m$^3$). The animals were exposed for 6 hours plus $T_{90}$ (15 minutes) per day, 5 days per week for 13 weeks (excluding three holidays). Feed was available *ad libitum*, except during exposure periods; water was available *ad libitum* throughout the study. Rats and mice were housed individually. Clinical findings and body weights were recorded prior to the start of the study, weekly thereafter, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 4.

In addition, a tissue burden study was conducted on 18 male and 18 female rats and six male and six female mice exposed to 0, 0.15, 0.6, or 2.5 mg nickel subsulfide/m$^3$ (equivalent to 0, 0.11, 0.44, or 1.83 mg nickel/m$^3$). The lungs of six male rats in each group were examined for nickel burden after 4, 9, and 13 weeks of exposure (Table 4). The kidneys and testes of six male rats in each group were also examined for nickel burden at 13 weeks. The lungs of female rats and male and female mice in each group were examined for nickel burden after 13 weeks of exposure. Tissue burden methodologies used were those described for the 16-day studies. Results of the tissue burden studies in the lung, kidney, and testes of rats and the lung of mice are found in Appendixes H and I.

Sperm morphology and vaginal cytology evaluations were performed at the end of the 13-week studies on 10 male and 10 female rats and mice from the 0, 0.15, 0.6, and 2.5 mg nickel subsulfide/m$^3$ exposure groups. The parameters evaluated are listed in Table 4. Methods used were those described in the NTP General Statement of Work (April, 1987). For 7 consecutive days prior to the end of the studies, 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 rats and mice were evaluated for sperm morphology, count, and motility. The right cauda, right testis, and right 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 right cauda epididymis was placed in buffered saline solution. Cauda 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, 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. Results of reproductive tissue evaluations and estrous cycle characterization are given in Appendix J.

At the end of the 13-week studies, blood was collected from all surviving animals by cardiac puncture for hematology analysis. Blood for hematology determinations was placed in tubes containing potassium EDTA as the anticoagulant. Hematology determinations were performed on a Coulter Electronics model S-550. Leukocyte differential counts and morphologic evaluation of blood cells were determined by light microscopic examination of blood films stained with Wright's stain. Reticulocyte counts were determined by light microscopy, using smears prepared by incubating equal volumes of whole blood and new methylene blue and a Miller disc for reticulocyte quantitation. The hematology parameters measured are listed in Table 4.

A necropsy was performed on all rats and mice in all exposure groups surviving to the end of the studies and on any animals that were killed early due to morbidity or moribundity. The brain, heart, right kidney, liver, lung, right testis, and thymus of rats and mice 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 5 to 6 $\mu$m, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all 0 and 2.5 mg nickel subsulfide/$m^3$ rats and mice and on selected organs from rats and mice in the other exposure groups. Table 4 lists the tissues and organs examined.

## 2-YEAR STUDIES

### Study Design

Groups of 63 male and 63 female rats were exposed to nickel subsulfide by inhalation at concentrations of 0, 0.15, or 1 mg nickel subsulfide/$m^3$ (equivalent to 0, 0.11, or 0.73 mg nickel/$m^3$) and groups of 80 male and 80 female mice were exposed to nickel subsulfide by inhalation at concentrations of 0, 0.6, or 1.2 mg nickel subsulfide/$m^3$ (equivalent to 0, 0.44, or 0.88 mg nickel/$m^3$) for 6 hours plus $T_{90}$ (8 minutes) per day, 5 days per week for 104 (rats) or 105 (mice) weeks, excluding holidays. After 7 months of exposure, five male and five female rats and mice from each exposure group were evaluated for histopathology; seven male and seven female rats and, additionally, as many as five male and five female mice from each exposure group were evaluated for tissue burden. After 15 months of exposure, five male and five female rats were evaluated for hematology parameters, histopathology, and tissue burden; five male and five female mice were evaluated for hematology parameters and histopathology, and another five male and five female mice were evaluated for tissue burden.

### Source and Specification of Animals

Male and female F344/N rats were obtained from Taconic Farms (Germantown, NY) and male and female B6C3$F_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Animals were quarantined for 10 (rats) or 12 days (mice) before the beginning of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation for evidence of disease. Serology samples were collected 4 times during the study for viral screening: prior to study start, at the 7-month and 15-month interim evaluations, and at the end of the studies. Rats were approximately 6 weeks old and mice approximately

7 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 M).

## Animal Maintenance

Rats and mice were housed individually. Cages and chambers were cleaned and rotated weekly. Feed was available *ad libitum*, except during exposure periods; water was available *ad libitum* throughout the study. Further details of animal maintenance are given in Table 4. Information on feed composition and contaminants is provided in Appendix L.

## Clinical Examinations and Pathology

The animals were observed twice daily for signs of toxicity, mortality, or moribundity. Clinical findings and body weights were recorded initially, weekly for the first 13 weeks, monthly thereafter, and at the end of the studies.

At 15 months, five male and five female rats and mice were anesthetized with carbon dioxide and blood was drawn from the retro-orbital sinus and placed in tubes containing potassium EDTA as the anticoagulant. The hematology parameters measured are listed in Table 4.

Lung and kidney samples for determination of tissue burden were collected from rats exposed to 0, 0.15, or 1 mg/m$^3$ and from mice exposed to 0, 0.6, or 1.2 mg/m$^3$ after 7 and 15 months and were analyzed using the same methods used in the 16-day studies. The results of the tissue burden studies are found in Appendixes H and I.

A complete necropsy was performed on all rats and mice. The brain, right kidney, liver, lung, spleen, and thymus of all animals at both interim evaluations 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, trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 $\mu$m, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 4.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic 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 reviewed the lung, bronchial and mediastinal lymph nodes, and adrenal gland medulla in rats and the lung, nose, and bronchial lymph nodes in mice for all neoplastic and nonneoplastic lesions. All diagnosed neoplasms from all organs in rats and mice, with the exception of interstitial cell adenomas of the testis in rats, were also reviewed.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of exposure groups. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists 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 diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

# STATISTICAL METHODS

## Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missexed 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 incidence of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidence 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., skin, intestine, harderian gland, and mammary gland) 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, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

## Analysis of Neoplasm Incidences

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

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

## Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

## 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 have approximately normal distributions, were analyzed

using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, spermatid, epididymal spermatozoa, and tissue burden 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). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the 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 normality assumptions. 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 levels.

### Historical Control Data

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

## Quality Assurance Methods

The 13-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 covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

## Genetic Toxicology

The genetic toxicity of nickel subsulfide was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and the frequency of micronucleated erythrocytes in peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of nickel subsulfide are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 4
**Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Subsulfide**

| 16-Day Studies | 13-Week Studies | 2-Year Studies |
|---|---|---|
| **Study Laboratory** | | |
| Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM) | Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM) | Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM) |
| **Strain and Species** | | |
| Rats: F344/N<br>Mice: $B6C3F_1$ | Rats: F344/N<br>Mice: $B6C3F_1$ | Rats: F344/N<br>Mice: $B6C3F_1$ |
| **Animal Source** | | |
| Frederick Cancer Research Facility (Frederick, MD) | Frederick Cancer Research Facility (Frederick, MD) | Rats: Taconic Farms (Germantown, NY)<br>Mice: Simonsen Laboratories (Gilroy, CA) |
| **Time Held Before Studies** | | |
| Rats: 19 or 20 days<br>Mice: 21 or 22 days | 19 days (males) or 20 days (females) | Rats: 10 days<br>Mice: 12 days |
| **Average Age When Studies Began** | | |
| 7 weeks | 7 weeks | Rats: 6 weeks<br>Mice: 7 weeks |
| **Date of First Dose** | | |
| Rats: 1 or 2 April 1985<br>Mice: 3 or 4 April 1985 | Rats: 25 November (males) or 26 November 1985 (females)<br>Mice: 2 December (males) or 3 December 1985 (females) | Rats: 31 October 1988<br>Mice: 29 September 1988 |
| **Duration of Dosing** | | |
| 6 hours/day, 5 days/week for 16 days | 6 hours/day, 5 days/week (excluding 3 holidays) for 13 weeks | 6 hours/day, 5 days/week for 104 (rats) or 105 weeks (mice) (excluding holidays) |
| **Date of Last Dose** | | |
| Rats: 16 or 17 April 1985<br>Mice: 18 or 19 April 1985 | Rats: 25-26 February (males) or 27-28 February 1985 (females)<br>Mice: 4-6 March (males) or 6-7 March 1986 (females) | Rats: 26 October 1990<br>Mice: 28 September 1990 |

TABLE 4
**Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Subsulfide**
(continued)

| 16-Day Studies | 13-Week Studies | 2-Year Studies |
|---|---|---|
| **Necropsy Dates** | | |
| Rats: 18 or 19 April 1985<br>Mice: 19 or 20 April 1985 | Rats: 26-27 February (males) or 28 February and 1 March 1986 (females)<br>Mice: 5-6 March (males) or 7-8 March 1986 (females) | Rats<br>7-Month interim evaluation: 17-18 May 1989<br>15-Month interim evaluation: 31 January-1 February 1990<br>Terminal sacrifice: 2, 5-6 November 1990 (males) and 29 October-1 November 1990 (females)<br>Mice<br>7-Month interim evaluation: 12-13 April 1989<br>15-Month interim evaluation: 17-18 January 1990<br>Terminal sacrifice: 5-9 October 1990 (males) or 1-4 October 1990 (females) |
| **Average Age at Necropsy** | | |
| 9 weeks | 20 weeks | Rats<br>7-Month interim evaluation: 35 weeks<br>15-Month interim evaluation: 72 weeks<br>Terminal sacrifice: 111-112 weeks<br>Mice<br>7-Month interim evaluation: 35 weeks<br>15-Month interim evaluation: 75 weeks<br>Terminal sacrifice: 112 weeks |
| **Size of Study Groups** | | |
| Core study: 5 males and 5 females<br>Tissue burden study: 3 males and 3 females | Core study: 10 males and 10 females<br>Tissue burden study: 18 male and 18 female rats; 6 male and 6 female mice | Core study:<br>7-Month interim evaluation: 5 males and 5 females<br>15-Month interim evaluation: 5 males and 5 females<br>2-Year study: 53 male and 53 female rats; 61 (0 mg/m$^3$), 60 (0.6 mg/m$^3$), and 60 (1.2 mg/m$^3$) male and 58, 60, and 60 female mice<br>Tissue burden study:<br>7-Month interim evaluation: 7 male and 7 female rats; as many as 5 male and 5 female mice<br>15-Month interim evaluation: 5 males and 5 females |

TABLE 4
**Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Subsulfide**
(continued)

| 16-Day Studies | 13-Week Studies | 2-Year Studies |
|---|---|---|
| **Method of Distribution**<br>Animals were distributed randomly into groups of approximately equal initial mean body weights. | Same as 16-day studies | Same as 16-day studies |
| **Animals per Cage**<br>1 | 1 | 1 |
| **Method of Animal Identification**<br>Toe clip, ear tag, and location within chamber unit | Toe clip, ear tag, and location within chamber unit | Rats: tail tattoo<br>Mice: tail tattoo and ear tag |
| **Diet**<br>NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed at least weekly | Same as 16-day studies | NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods; troughs filled when needed and cleaned weekly |
| **Water Distribution**<br>Tap water (Albuquerque municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum* and checked twice per day | Same as 16-day studies | Same as 16-day studies |
| **Cages**<br>Stainless steel wire cages (Hazleton Systems, Inc., Aberdeen, MD); cage units rotated and changed weekly | Same as 16-day studies | Same as 16-day studies |
| **Bedding/Cage Board**<br>Techboard untreated paper (Shepherd Specialties Paper, Inc., Kalamazoo, MI); changed twice daily | Same as 16-day studies | Same as 16-day studies |
| **Room/Chamber Air Supply Filter**<br>High-efficiency particulate air filter (Flanders, Washington, DC); changed as needed | Same as 16-day studies | Same as 16-day studies |
| **Chambers**<br>Hazleton 1000 and 2000 multitiered, stainless steel inhalation chambers (Lab Products, Maywood, NJ), changed and rotated weekly | Same as 16-day studies | Same as 16-day studies |

**TABLE 4**
**Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Subsulfide**
(continued)

| 16-Day Studies | 13-Week Studies | 2-Year Studies |
|---|---|---|
| **Chamber Environment** | | |
| Temperature: 21.1° to 28.4° C<br>Relative humidity: 13% to 44%<br>Fluorescent light: 12 hours/day<br>Chamber air: 10 ± 2 changes/hour | Temperature: 18.6° to 24.1° C (rats), 18.6° to 24.2° C (mice)<br>Relative humidity: 15% to 38%<br>Fluorescent light: 12 hours/day<br>Chamber air: 12 ± 2 changes/hour | Temperature: 17.6° to 30.5° C<br>Relative humidity: 11% to 93%<br>Fluorescent light: 12 hours/day<br>Chamber air: 5.99 to 21.63 (rats) and 12.02 to 18.06 (mice) changes/hour |
| **Doses** | | |
| Core study: 0, 0.6, 1.2, 2.5, 5, or 10 mg nickel subsulfide/$m^3$ (0, 0.44, 0.88, 1.83, 3.65, or 7.33 mg nickel/$m^3$<br>Tissue burden study: 0, 0.6, 2.5, or 10 mg nickel subsulfide/$m^3$ (0, 0.44, 1.83, or 7.33 mg nickel/$m^3$) | Core study: 0, 0.15, 0.3, 0.6, 1.2, or 2.5 mg nickel subsulfide/$m^3$ (0, 0.11, 0.22, 0.44, 0.88, or 1.83 mg nickel/$m^3$)<br>Tissue burden study: 0, 0.15, 0.6, or 2.5 mg nickel subsulfide/$m^3$ (0, 0.11, 0.44, or 1.83 mg nickel/$m^3$) | Rats: 0, 0.15, or 1 mg nickel subsulfide/$m^3$ (0, 0.11, or 0.73 mg nickel/$m^3$) (core study and tissue burden study)<br>Mice: 0, 0.6, or 1.2 mg nickel subsulfide/$m^3$ (0, 0.44, or 0.88 mg nickel/$m^3$) (core study and tissue burden study) |
| **Type and Frequency of Observation** | | |
| Observed twice daily; animals were weighed initially, after 5 days of exposure, and at the end of the studies. Clinical observations were recorded initially and after 5 days of exposure. | Observed twice daily; animals were weighed and clinical observations were recorded initially, weekly thereafter, and at the end of the studies. | Observed twice daily; animals were weighed and clinical observations were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. |
| **Method of Sacrifice** | | |
| Intraperitoneal $T_{61}$ euthanasia solution | Exsanguination under halothane anesthesia | Exsanguination under carbon dioxide anesthesia |
| **Necropsy** | | |
| Necropsy performed on all animals. Organs weighed were the brain, heart, right kidney, liver, lung, right testis, and thymus. | Necropsy performed on all animals. Organs weighed were the brain, heart, right kidney, liver, lung, right testis, and thymus. | Necropsy performed on all animals. Organs weighed at the 7- and 15-month interim evaluations were brain, right kidney, liver, lung, spleen, and thymus. |
| **Clinical Pathology** | | |
| None | Blood was collected from all animals by cardiac puncture after 13 weeks for hematology analysis.<br>***Hematology:*** eosinophils, erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes, mean cell volume, mean cell hemoglobin concentration, monocytes, nucleated erythrocytes, reticulocytes, and segmented neutrophils. | Blood was collected from the retroorbital sinus of 5 male and 5 female rats and mice in each group after 15 months of exposure.<br>***Hematology:*** eosinophils, erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, monocytes, reticulocytes, and segmented neutrophils. |

**TABLE 4**
**Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Subsulfide**
(continued)

| 16-Day Studies | 13-Week Studies | 2-Year Studies |
|---|---|---|
| **Histopathology** | | |
| Complete histopathology was performed on 0, 5 (mice), and 10 mg/m$^3$ rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (vertebra, spinal cord, bone marrow, nasal, and rib), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, small intestine (duodenum, jejunum, and ileum), large intestine (cecum, colon, and rectum), kidney, larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose (3 sections), ovary and oviduct, pancreas and pancreatic islets, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular portions), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The following organs were examined from all other exposure groups of rats and mice: lung, nose, and respiratory tract lymph nodes. | Complete histopathology was performed on 0 and 2.5 mg/m$^3$ rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (vertebra, spinal cord, and femur and bone marrow and rib of mice), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, small intestine (duodenum, jejunum, and ileum), large intestine (cecum, colon, and rectum), kidneys, larynx, liver, lungs, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose (3 sections), ovary and oviduct, pancreas and pancreatic islets, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary glands, seminal vesicles, skin, spleen, stomach (forestomach and glandular portions), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The following organs were examined from all other exposure groups of rats and mice: lung, nose, and respiratory tract lymph nodes. | Complete histopathology was performed on all rats and mice at the end of the studies and on 5 male and 5 female rats and mice at the 7- and 15-month interim evaluations. At 7 months, only the kidney, lung, lymph nodes (bronchial and mediastinal), and nasal turbinates were examined. For all others, in addition to gross lesions and tissue masses with regional lymph nodes, tissues examined included: adrenal gland, brain (3 sections), clitoral gland, esophagus, eyes (if grossly abnormal), femur, gallbladder (mice), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung and mainstem bronchi, lymph nodes (mandibular, mesenteric, bronchial, and mediastinal), mammary gland and adjacent skin, muscle (rats), nasal cavity and turbinates (3 sections), ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spinal cord and sciatic nerve, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. |
| **Tissue Burden Analyses** | | |
| Lung and/or kidney (see Appendixes H and I) | Lung, kidney, and/or testis (see Appendixes H and I) | Lung and/or kidney (see Appendixes H and I) |
| **Sperm Morphology and Vaginal Cytology Evaluations** | | |
| None | At the end of the studies sperm samples were collected from all male animals in the 0, 0.15, 0.6, and 2.5 mg/m$^3$ groups for sperm morphology evaluations. The parameters evaluated were sperm density, morphology, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal samples were collected for up to 7 consecutive days prior to the end of the studies from all female animals in the 0, 0.15, 0.6, and 2.5 mg/m$^3$ groups for vaginal cytology evaluations. The parameters evaluated were relative frequency of estrous stages and estrous cycle length. | None |

# RESULTS

## RATS

### 16-DAY STUDY

One male exposed to 10 mg nickel subsulfide/m$^3$ died on day 14; all other rats survived until the end of the study (Table 5). Male and female rats exposed to 10 mg/m$^3$ lost weight, and 5 mg/m$^3$ males and females did not gain weight; the final mean body weights of these groups and 2.5 mg/m$^3$ females were significantly lower than those of the controls. On day 5 of exposure, clinical findings of toxicity included labored respiration in 10 mg/m$^3$ males and 5 and 10 mg/m$^3$ females and dehydration in 5 and 10 mg/m$^3$ females.

**TABLE 5**
**Survival and Body Weights of Rats in the 16-Day Inhalation Study of Nickel Subsulfide**

| Dose (mg/m$^3$) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 5/5 | 161 ± 3 | 216 ± 13 | 55 ± 15 | |
| 0.6 | 5/5 | 159 ± 4 | 236 ± 4 | 77 ± 5 | 109 |
| 1.2 | 5/5 | 159 ± 3 | 226 ± 6 | 66 ± 5 | 105 |
| 2.5 | 5/5 | 160 ± 2 | 198 ± 6 | 38 ± 6 | 92 |
| 5 | 5/5 | 155 ± 3 | 155 ± 8** | 0 ± 9** | 72 |
| 10 | 4/5[c] | 158 ± 4 | 113 ± 5** | −45 ± 5** | 52 |
| **Female** | | | | | |
| 0 | 5/5 | 115 ± 3 | 151 ± 4 | 36 ± 3 | |
| 0.6 | 5/5 | 116 ± 1 | 149 ± 4 | 33 ± 3 | 99 |
| 1.2 | 5/5 | 116 ± 2 | 147 ± 5 | 31 ± 3 | 97 |
| 2.5 | 5/5 | 116 ± 2 | 138 ± 1* | 22 ± 1* | 91 |
| 5 | 5/5 | 115 ± 3 | 117 ± 6** | 2 ± 6** | 78 |
| 10 | 5/5 | 113 ± 2 | 86 ± 1** | −28 ± 2** | 57 |

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Day of death: 14. Final weights and weight changes are based on 5 animals.

Absolute and relative lung weights of 2.5, 5, and 10 mg/m$^3$ males and all exposed groups of females were significantly greater than those of the controls; the absolute lung weight of 1.2 mg/m$^3$ males was also significantly greater than that of the controls (Table F1). Absolute brain, liver, and thymus weights of 5 mg/m$^3$ males and 10 mg/m$^3$ males and females and the relative thymus weight of 10 mg/m$^3$ males were significantly less than those of the controls.

At necropsy, the lungs of males and females exposed to 10 mg/m$^3$ did not collapse to the extent normally expected when the thoracic cavity is opened. In addition, gray or red foci up to 1 mm in diameter were present in the lungs of most 10 mg/m$^3$ rats. The only other gross observation in males and females exposed to 5 or 10 mg/m$^3$ was a decrease in thymus size; rats in these groups did not gain weight during the 16-day study. Chemical-related histopathologic lesions were present in the lung and nose of males and females (Table 6). Microscopic lesions in the lung of rats exposed to nickel subsulfide consisted of inflammation with necrosis. At 5 and 10 mg/m$^3$, inflammation was characterized by the presence of necrotic cellular debris, macrophages, and a few neutrophils in the lumen of terminal bronchioles and alveoli. There was mucus in the lumen of bronchioles, and the prominence of goblet cells in the bronchial epithelium was increased. There was also vacuolation, necrosis, and detachment of some of the bronchiolar epithelial cells. At 5 and 10 mg/m$^3$, this inflammatory response involved most of the airways throughout the lung. In rats exposed to 5 or 10 mg/m$^3$, aggregates of black, slightly refractile pigment were present within alveolar macrophages and were considered to be nickel subsulfide. In the 0.6, 1.2, and 2.5 mg/m$^3$ groups, the inflammatory lesions in the lung were less diffuse and consisted primarily of focal increases in the number of alveolar macrophages and interstitial infiltrates consisting of perivascular accumulation of lymphocytes and macrophages. Minimal to mild atrophy of the olfactory epithelium was present in all exposed groups. Atrophy consisted of thinning of the olfactory epithelial layer, primarily in the anterior of the dorsal meatus in the nasal passages. Other histopathologic lesions present in a few animals from the higher exposure groups were considered nonspecific and secondary to generalized toxicity and the marked reduction in body weight gain or body weight loss that occurred during the course of the study. These changes included testicular degeneration and lymphoid depletion in the spleen, thymus, and lymph nodes.

**TABLE 6**
**Incidences of Selected Nonneoplastic Lesions in Rats in the 16-Day Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ | 2.5 mg/m$^3$ | 5 mg/m$^3$ | 10 mg/m$^3$ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Lung[a] | 5 | 5 | 5 | 5 | 5 | 5 |
| Inflammation[b] | 0 | 5** (1.0)[c] | 5** (1.0) | 5** (2.0) | 5** (1.8) | 5** (3.0) |
| Nose | 5 | 5 | 5 | 5 | 5 | 5 |
| Olfactory Epithelium Atrophy | 0 | 4* (1.0) | 4* (1.0) | 5** (1.0) | 5** (1.0) | 5** (1.0) |
| **Female** | | | | | | |
| Lung | 5 | 5 | 5 | 5 | 5 | 5 |
| Inflammation | 0 | 5** (1.0) | 5** (1.0) | 5** (2.4) | 5** (1.2) | 5** (2.6) |
| Nose | 5 | 5 | 5 | 5 | 5 | 5 |
| Olfactory Epithelium Atrophy | 0 | 2 (1.0) | 5** (1.0) | 5** (2.0) | 5** (1.2) | 5** (1.2) |

* Significantly different ($P \leq 0.05$) from the 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 of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Nickel concentrations in the lungs of 0.6, 2.5, and 10 mg/m$^3$ males and females were significantly greater than those of the controls and increased with exposure concentration, and the absolute lung weights of these 2.5 and 10 mg/m$^3$ males and females were significantly greater than those of the controls (Tables 7 and H1). Nickel concentrations in the kidneys of exposed males and females were significantly greater than those of the controls and increased with exposure concentration in 2.5 and 10 mg/m$^3$ males and females; however, the absolute kidney weight of 10 mg/m$^3$ males was significantly less than that of the controls. (Table H2). Because of the severity of lung lesions in rats exposed to 5 and 10 mg/m$^3$, 2.5 mg/m$^3$ was selected as the highest exposure concentration for the 13-week study.

TABLE 7
**Lung Weight and Lung Burden in Rats in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 2.5 mg/m$^3$ | 10 mg/m$^3$ |
|---|---|---|---|---|
| n | 3 | 3 | 3 | 3 |
| **Male** | | | | |
| Absolute lung wt (g) | 0.827 ± 0.009 | 1.000 ± 0.000 | 1.370 ± 0.012** | 1.577 ± 0.150** |
| μg Ni/lung | —[b] | 7 ± 0.9* | 25 ± 0.6** | 103 ± 2.9** |
| μg Ni/g lung | — | 7 ± 0.9* | 18 ± 0.3** | 67 ± 8.7** |
| μg Ni/g control lung | — | 9 ± 1.0* | 30 ± 0.6** | 127 ± 3.3** |
| **Female** | | | | |
| Absolute lung wt (g) | 0.810 ± 0.169 | 0.883 ± 0.041 | 1.263 ± 0.078* | 1.167 ± 0.087 |
| μg Ni/lung | — | 8 ± 1.3* | 24 ± 1.9** | 87 ± 9.3** |
| μg Ni/g lung | — | 9 ± 1.3* | 19 ± 1.6** | 77 ± 12.1** |
| μg Ni/g control lung | — | 12 ± 2.0* | 36 ± 3.0** | 133 ± 13.3** |

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's or Williams' test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.093 μg Ni (the limit of detection).

## 13-WEEK STUDY

All rats survived until the end of the study (Table 8). The final mean body weight and mean body weight gain of 2.5 mg/m$^3$ males were significantly lower than those of the controls; final mean body weights of all other exposure groups were similar to those of the controls. Chemical-related clinical findings included labored respiration in 2.5 mg/m$^3$ males and females during weeks 2 through 7.

Hematology results are presented in Table G1. In general, there were minimal to mild differences, and females were affected more than males. A mature neutrophilia was indicated by greater segmented neutrophil counts in all exposed males and females. There was microscopic evidence of pulmonary inflammation in the exposure groups, and this could account for the neutrophilia. Increased tissue demand for granulocytes due to inflammation causes increased bone marrow production and release and can increase the intravascular life span of neutrophils resulting in neutrophilia. The total leukocyte count in 2.5 mg/m$^3$ males was greater than that in the controls and was a reflection of the increased neutrophil count.

Hematocrit values in 2.5 mg/m$^3$ males and females, hemoglobin concentrations in 1.2 and 2.5 mg/m$^3$ males and females, and erythrocyte counts in 1.2 and 2.5 mg/m$^3$ males and 0.3, 0.6, 1.2, and 2.5 mg/m$^3$ females were minimally greater than those in the controls. These differences were accompanied by mean cell volumes that were minimally less than those of the controls. Mean cell hemoglobin concentrations in 1.2 and 2.5 mg/m$^3$ males and females were minimally greater than those in the controls.

TABLE 8
**Survival and Body Weights of Rats in the 13-Week Inhalation Study of Nickel Subsulfide**

| Dose (mg/m$^3$) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 10/10 | 157 ± 4 | 353 ± 4 | 196 ± 2 | |
| 0.15 | 10/10 | 157 ± 4 | 355 ± 6 | 198 ± 6 | 100 |
| 0.3 | 10/10 | 149 ± 6 | 337 ± 4 | 188 ± 4 | 95 |
| 0.6 | 10/10 | 153 ± 5 | 338 ± 7 | 186 ± 7 | 96 |
| 1.2 | 10/10 | 157 ± 3 | 350 ± 4 | 193 ± 4 | 99 |
| 2.5 | 10/10 | 155 ± 4 | 330 ± 8* | 174 ± 6** | 93 |
| **Female** | | | | | |
| 0 | 10/10 | 118 ± 3 | 200 ± 3 | 83 ± 3 | |
| 0.15 | 10/10 | 121 ± 3 | 203 ± 3 | 82 ± 2 | 101 |
| 0.3 | 10/10 | 121 ± 3 | 209 ± 4 | 87 ± 3 | 104 |
| 0.6 | 10/10 | 118 ± 2 | 202 ± 2 | 84 ± 3 | 101 |
| 1.2 | 10/10 | 118 ± 2 | 201 ± 3 | 83 ± 2 | 100 |
| 2.5 | 10/10 | 119 ± 2 | 198 ± 3 | 79 ± 3 | 99 |

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Increases in mean cell hemoglobin concentration have been related to erythrocyte hemolysis (*in vivo* or *in vitro*), alterations in the hemoglobin concentration or hematocrit, or an artifact (e.g., lipemia, Heinz bodies). The higher hematocrit values, hemoglobin concentrations, and erythrocyte counts could be consistent with dehydration (relative erythrocytosis) or with increased erythropoietin production as the result of tissue hypoxia (secondary erythrocytosis). Secondary erythrocytosis has been observed with pulmonary or cardiovascular disease, altered erythrocyte/hemoglobin oxygen transport, and reduced atmospheric oxygen. In this study, pulmonary lesions were observed microscopically in all exposure groups, and this could account for the observed increases. Reticulocyte counts were not affected, and this is consistent with mild relative erythrocytosis or with a very mild increase in erythropoiesis. Lower mean cell volume has been associated with metabolic alterations related to iron, copper, and pyridoxine deficiency. Total nucleated erythrocyte counts in 1.2 and 2.5 mg/m$^3$ females were greater than those in the controls. Differences in nucleated erythrocyte counts were not accompanied by anemia or by corresponding differences in reticulocyte counts. Nickel is a transition metal, as are cobalt and iron. Cobalt excess can induce erythrocytosis due to increased erythropoietin production, and iron is essential for heme synthesis. Thus, the presence of excess nickel may have altered normal biological activities associated with transition metals and could account for some of the differences that occurred (e.g., the minimal erythrocytosis and lower mean cell volume).

No significant differences in sperm morphology or vaginal cytology between exposed and control rats were observed (Table J1).

Absolute and relative lung weights of all exposed groups were significantly greater than those of the controls (Table F2). At necropsy, chemical-related gross lesions were present in the lung and bronchial and mediastinal lymph nodes. Numerous, 1- to 2-mm, white foci were scattered throughout the lung parenchyma of rats in all exposed groups. The incidence and the severity of this finding increased with exposure concentration. There was enlargement of the bronchial and mediastinal lymph nodes of most rats exposed to 1.2 or 2.5 mg/m$^3$; enlargement of one or both of these lymph nodes was also observed in most males and females exposed to 0.6 mg/m$^3$. Mediastinal and bronchial lymph nodes were enlarged in one 0.3 mg/m$^3$ female. Chemical-related histopathologic lesions were observed in the lungs, bronchial and mediastinal lymph nodes, and noses of males and females (Table 9). There was an exposure-related increase in the incidence and severity of inflammatory lesions in the lung. At 0.15 mg/m$^3$, macrophage hyperplasia consisted primarily of a minimal increase in the number of alveolar macrophages. At 0.3, 0.6, 1.2, and 2.5 mg/m$^3$, there was focal thickening of alveolar septa from an inflammatory cell infiltrate consisting of macrophages and neutrophils. Often within these focal areas of inflammation, the alveolar type II cells were enlarged. Other inflammatory changes in the lung included minimal to mild interstitial infiltrates of lymphocytes around blood vessels. The gross enlargement of the lymph nodes associated with the respiratory tract was attributed to lymphoid hyperplasia and an increase in the number of lymphocytes, primarily in the paracortical region of the lymph nodes. Lymphoid hyperplasia was present in groups exposed to 0.3, 0.6, 1.2, or 2.5 mg/m$^3$. Atrophy of the olfactory epithelium consisted of a minimal to mild reduction in the normal thickness of this neuroepithelial layer, which was attributable primarily to a decrease in the amount of cytoplasm in the apical portion of the cells. Olfactory epithelial atrophy was present in the region of the dorsal meatus of the nasal passages of most 0.6, 1.2, and 2.5 mg/m$^3$ males and females.

TABLE 9
**Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.15 mg/m³ | 0.3 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Lung[a] | 10 | 10 | 10 | 10 | 10 | 10 |
| Alveolar Macrophage Hyperplasia[b] | 0 | 10** (1.1)[c] | 10** (1.5) | 10** (1.6) | 10** (3.4) | 10** (3.8) |
| Interstitial Infiltrate | 0 | 0 | 1 (1.0) | 10** (1.9) | 9** (2.1) | 8** (1.2) |
| Inflammation, Chronic Active | 0 | 2 (1.0) | 9** (1.3) | 10** (1.8) | 10** (2.9) | 10** (3.7) |
| Lymph Node, Bronchial | 6 | 9 | 9 | 10 | 10 | 10 |
| Hyperplasia | 0 | 0 | 1 (1.0) | 10** (1.2) | 10** (2.6) | 10** (3.3) |
| Lymph Node, Mediastinal | 7 | 10 | 9 | 9 | 9 | 9 |
| Hyperplasia | 0 | 0 | 0 | 6* (1.5) | 9** (2.5) | 9** (2.6) |
| Nose | 10 | 10 | 10 | 10 | 10 | 10 |
| Olfactory Epithelium Atrophy | 0 | 0 | 1 (1.0) | 5* (1.0) | 10** (1.0) | 10** (1.6) |
| **Female** | | | | | | |
| Lung | 10 | 10 | 10 | 10 | 10 | 10 |
| Alveolar Macrophage Hyperplasia | 0 | 10** (1.0) | 10** (1.7) | 10** (1.8) | 10** (2.9) | 10** (3.8) |
| Interstitial Infiltrate | 0 | 0 | 2 (1.0) | 9** (1.7) | 10** (2.4) | 5* (1.6) |
| Inflammation, Chronic Active | 0 | 3 (1.0) | 9** (1.0) | 10** (1.9) | 10** (2.6) | 10** (3.8) |
| Lymph Node, Bronchial | 7 | 8 | 8 | 10 | 9 | 9 |
| Hyperplasia | 1 (1.0) | 2 (1.0) | 2 (1.0) | 9** (1.2) | 9** (2.8) | 9** (3.2) |
| Lymph Node, Mediastinal | 8 | 9 | 10 | 10 | 10 | 10 |
| Hyperplasia | 0 | 0 | 1 (1.0) | 8** (1.2) | 10** (2.5) | 10** (3.1) |
| Nose | 10 | 10 | 10 | 10 | 10 | 10 |
| Olfactory Epithelium Atrophy | 0 | 0 | 0 | 8** (1.1) | 9** (1.0) | 10** (2.3) |

* Significantly different ($P \leq 0.05$) from the 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 of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Nickel concentrations in the lung increased with exposure concentration (Tables 10 and H3). At 4, 9, and 13 weeks on study, nickel concentrations in the lungs of 0.15, 0.6, and 2.5 mg/m³ males were significantly greater than those of the controls. However, by 13 weeks, nickel concentrations had reached a steady state. Nickel concentrations in the lungs of 0.15, 0.6, and 2.5 mg/m³ females were also significantly greater than that of the controls at 13 weeks. The nickel concentration in the kidneys of 2.5 mg/m³ males was significantly greater than that of the controls, and the nickel concentration in the testes of 0.6 mg/m³ males was significantly less than that of the controls (Table H4).

TABLE 10
**Lung Weight and Lung Burden in Rats in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 0.6 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 6 | 6 | 6 | 6 |
| 4 weeks | | | | |
| μg Ni/g lung | —[b] | 3 ± 0.2** | 6 ± 0.7** | 15 ± 1.4** |
| μg Ni/g control lung | — | 3 ± 0.2** | 8 ± 0.9** | 23 ± 2.2** |
| 9 weeks | | | | |
| μg Ni/g lung | — | 5 ± 0.2** | 7 ± 0.6** | 16 ± 1.0** |
| μg Ni/g control lung | — | 6 ± 0.2** | 12 ± 1.2** | 31 ± 1.7** |
| 13 weeks | | | | |
| Absolute lung wt (g) | 1.15 ± 0.03 | 1.56 ± 0.01** | 2.23 ± 0.08** | 2.38 ± 0.03** |
| μg Ni/lung | — | 8 ± 0.3** | 17 ± 1.0** | 42 ± 1.3** |
| μg Ni/g lung | — | 5 ± 0.2** | 7 ± 0.4** | 18 ± 0.5** |
| μg Ni/g control lung | — | 7 ± 0.3** | 14 ± 0.9** | 36 ± 1.2** |
| **Female** | | | | |
| n | 6 | 6 | 6 | 5 |
| 13 weeks | | | | |
| Absolute lung wt (g) | 0.849 ± 0.026 | 1.234 ± 0.053** | 1.570 ± 0.034** | 1.607 ± 0.045** |
| μg Ni/lung | — | 6 ± 0.2** | 11 ± 0.3** | 28 ± 1.4** |
| μg Ni/g lung | — | 5 ± 0.1** | 7 ± 0.1** | 17 ± 0.7** |
| μg Ni/g control lung | — | 7 ± 0.3** | 13 ± 0.4** | 33 ± 1.7** |

** Significantly different ($P \leq 0.01$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.218 μg Ni (the limit of detection).

*Dose Selection Rationale:* Based on the increased incidence and severity of chronic active inflammation in the lung at 0.3 mg/m³, 0.15 mg/m³ was selected as the highest nickel subsulfide exposure concentration giving toxicological lesions comparable to the highest exposure concentration in the nickel oxide and nickel sulfate hexahydrate 2-year studies; 1 mg/m³ was selected for the 2-year nickel subsulfide study to replicate the study by Ottolenghi *et al.* (1975).

## 2-YEAR STUDY

### *Survival*

Estimates of 2-year survival probabilities for male and female rats are shown in Table 11 and in the Kaplan-Meier survival curves in Figure 2. Survival of exposed male and female rats was similar to that of the controls.

### *Body Weights and Clinical Findings*

Mean body weights of males and females exposed to 0.15 mg/m$^3$ were similar to those of the controls throughout the study (Tables 12 and 13 and Figure 3). Mean body weights of rats exposed to 1 mg/m$^3$ were lower than those of the controls throughout the second year of the study. Chemical-related clinical findings included rapid and shallow breathing following exposure periods.

### *Hematology*

Hematology results at 15 months are presented in Table G2. Hematocrit values and hemoglobin concentrations in 1 mg/m$^3$ males and females and the erythrocyte count in 1 mg/m$^3$ males were mildly greater than those in the controls. These differences could be consistent with dehydration (relative erythrocytosis) or with increased erythropoietin production as a result of tissue hypoxia (secondary erythrocytosis). Secondary erythrocytosis has been observed with pulmonary or cardiovascular disease, altered erythrocyte/hemoglobin oxygen transport, and reduced atmospheric oxygen.

TABLE 11
**Survival of Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|
| **Male** | | | |
| Animals initially in study | 63 | 63 | 63 |
| 7-Month interim evaluation[a] | 5 | 5 | 5 |
| 15-Month interim evaluation[a] | 5 | 5 | 5 |
| Moribund | 35 | 28 | 33 |
| Natural deaths | 5 | 4 | 2 |
| Animals surviving to study termination | 13 | 21 | 18 |
| Percent probability of survival at end of study[b] | 25 | 40 | 34 |
| Mean survival (days)[c] | 635 | 663 | 658 |
| Survival analysis[d] | P=0.579N | P=0.122N | P=0.260N |
| **Female** | | | |
| Animals initially in study | 63 | 63 | 63 |
| 7-Month interim evaluation[a] | 5 | 5 | 5 |
| 15-Month interim evaluation[a] | 5 | 5 | 5 |
| Accidental death[a] | 0 | 0 | 1 |
| Moribund | 24 | 27 | 23 |
| Natural deaths | 4 | 1 | 1 |
| Animals surviving to study termination | 25 | 25 | 28 |
| Percent probability of survival at end of study | 47 | 47 | 54 |
| Mean survival (days) | 658 | 674 | 670 |
| Survival analysis | P=0.563N | P=1.000N | P=0.633N |

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or a lower mortality in an exposure group is indicated by N.

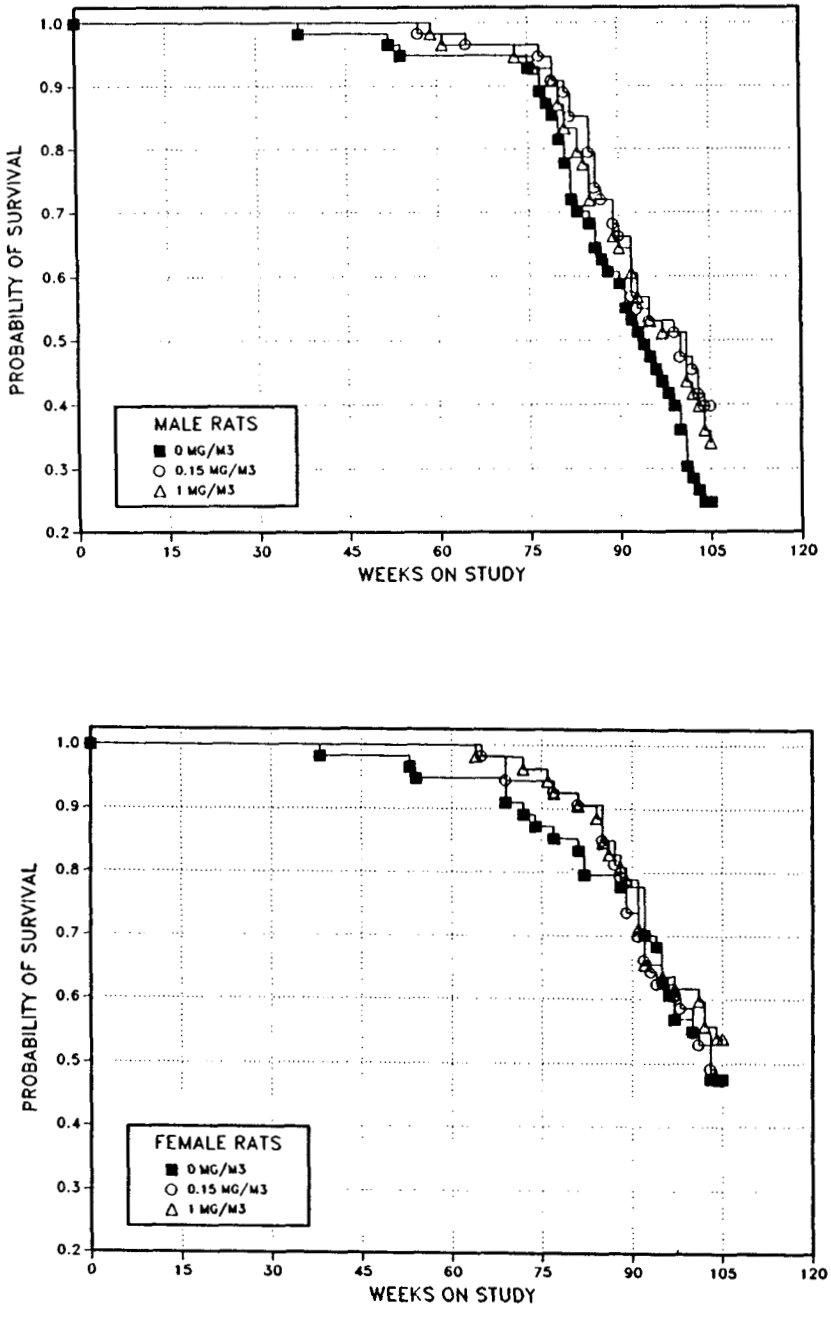


**FIGURE 2**
**Kaplan-Meier Survival Curves for Rats Administered Nickel Subsulfide by Inhalation for 2 Years**

TABLE 12
**Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| Weeks on Study | 0 mg/m³ | | 0.15 mg/m³ | | | 1 mg/m³ | | |
|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls) | Number of Survivors |
| 1 | 120 | 63 | 118 | 98 | 63 | 117 | 98 | 63 |
| 2 | 166 | 63 | 162 | 97 | 63 | 160 | 96 | 63 |
| 3 | 195 | 63 | 190 | 98 | 63 | 187 | 96 | 63 |
| 4 | 217 | 63 | 213 | 98 | 63 | 210 | 97 | 63 |
| 5 | 238 | 63 | 234 | 98 | 63 | 228 | 96 | 63 |
| 6 | 253 | 63 | 249 | 99 | 63 | 242 | 96 | 63 |
| 7 | 268 | 63 | 263 | 98 | 63 | 255 | 95 | 63 |
| 8 | 279 | 63 | 273 | 98 | 63 | 264 | 95 | 63 |
| 9 | 293 | 63 | 286 | 98 | 63 | 279 | 95 | 63 |
| 10 | 304 | 63 | 298 | 98 | 63 | 290 | 95 | 63 |
| 11 | 316 | 63 | 310 | 98 | 63 | 299 | 95 | 63 |
| 12 | 325 | 63 | 314 | 97 | 63 | 305 | 94 | 63 |
| 13 | 333 | 63 | 325 | 97 | 63 | 316 | 95 | 63 |
| 17 | 360 | 63 | 351 | 97 | 63 | 337 | 94 | 63 |
| 21 | 377 | 63 | 366 | 97 | 63 | 353 | 94 | 63 |
| 25 | 401 | 63 | 385 | 96 | 63 | 371 | 93 | 63 |
| 29[a] | 413 | 58 | 394 | 95 | 58 | 383 | 93 | 58 |
| 33 | 433 | 58 | 416 | 96 | 58 | 403 | 93 | 58 |
| 37 | 448 | 57 | 433 | 97 | 58 | 419 | 94 | 58 |
| 41 | 452 | 57 | 436 | 96 | 58 | 424 | 94 | 58 |
| 45 | 468 | 57 | 448 | 96 | 58 | 435 | 93 | 58 |
| 49 | 476 | 57 | 458 | 96 | 58 | 441 | 93 | 58 |
| 53 | 483 | 56 | 466 | 97 | 58 | 448 | 93 | 58 |
| 57 | 487 | 55 | 466 | 96 | 58 | 448 | 92 | 58 |
| 61 | 494 | 55 | 475 | 96 | 57 | 455 | 92 | 56 |
| 65 | 498 | 55 | 473 | 95 | 57 | 451 | 91 | 56 |
| 69[a] | 501 | 50 | 476 | 95 | 51 | 452 | 90 | 51 |
| 73 | 503 | 50 | 478 | 95 | 51 | 451 | 90 | 50 |
| 77 | 503 | 47 | 479 | 95 | 50 | 450 | 90 | 49 |
| 81 | 498 | 41 | 476 | 96 | 47 | 444 | 89 | 44 |
| 85 | 492 | 36 | 468 | 95 | 44 | 435 | 88 | 40 |
| 89 | 487 | 32 | 462 | 95 | 38 | 427 | 88 | 36 |
| 93 | 474 | 28 | 459 | 97 | 30 | 418 | 88 | 31 |
| 97 | 471 | 23 | 458 | 97 | 28 | 405 | 86 | 27 |
| 101 | 455 | 17 | 446 | 98 | 25 | 386 | 85 | 24 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 254 | | 249 | 98 | | 242 | 95 | |
| 14-52 | 425 | | 410 | 96 | | 396 | 93 | |
| 53-101 | 488 | | 468 | 96 | | 436 | 89 | |

[a] Interim evaluations occurred during weeks 29 and 66.

TABLE 13
**Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| Weeks on Study | 0 mg/m³ Av. Wt. (g) | 0 mg/m³ Number of Survivors | 0.15 mg/m³ Av. Wt. (g) | 0.15 mg/m³ Wt. (% of controls) | 0.15 mg/m³ Number of Survivors | 1 mg/m³ Av. Wt. (g) | 1 mg/m³ Wt. (% of controls) | 1 mg/m³ Number of Survivors |
|---|---|---|---|---|---|---|---|---|
| 1 | 100 | 63 | 100 | 100 | 63 | 99 | 99 | 63 |
| 2 | 124 | 63 | 123 | 100 | 63 | 120 | 97 | 63 |
| 3 | 137 | 63 | 136 | 99 | 63 | 134 | 98 | 63 |
| 4 | 146 | 63 | 146 | 100 | 63 | 144 | 99 | 63 |
| 5 | 156 | 63 | 156 | 100 | 63 | 153 | 98 | 63 |
| 6 | 164 | 63 | 163 | 99 | 63 | 160 | 97 | 63 |
| 7 | 170 | 63 | 168 | 99 | 63 | 166 | 97 | 63 |
| 8 | 175 | 63 | 173 | 98 | 63 | 170 | 97 | 63 |
| 9 | 181 | 63 | 178 | 98 | 63 | 175 | 97 | 63 |
| 10 | 186 | 63 | 182 | 98 | 63 | 180 | 97 | 63 |
| 11 | 193 | 63 | 189 | 98 | 63 | 185 | 96 | 63 |
| 12 | 195 | 63 | 190 | 98 | 63 | 188 | 96 | 63 |
| 13 | 200 | 63 | 195 | 98 | 63 | 192 | 96 | 63 |
| 17 | 210 | 63 | 206 | 98 | 63 | 202 | 96 | 63 |
| 21 | 217 | 63 | 213 | 98 | 63 | 208 | 96 | 63 |
| 25 | 228 | 63 | 223 | 98 | 63 | 218 | 96 | 63 |
| 29[a] | 233 | 58 | 228 | 98 | 58 | 222 | 95 | 58 |
| 33 | 238 | 58 | 232 | 97 | 58 | 228 | 96 | 58 |
| 37 | 248 | 58 | 243 | 98 | 58 | 239 | 96 | 58 |
| 41 | 253 | 57 | 250 | 99 | 58 | 243 | 96 | 57 |
| 45 | 265 | 57 | 260 | 98 | 58 | 252 | 95 | 57 |
| 49 | 274 | 57 | 271 | 99 | 58 | 259 | 94 | 57 |
| 53 | 284 | 56 | 277 | 98 | 58 | 266 | 94 | 57 |
| 57 | 287 | 55 | 283 | 99 | 58 | 268 | 94 | 57 |
| 61 | 299 | 55 | 294 | 98 | 58 | 278 | 93 | 57 |
| 65 | 304 | 55 | 298 | 98 | 57 | 281 | 93 | 56 |
| 69[a] | 308 | 48 | 300 | 97 | 50 | 283 | 92 | 51 |
| 73 | 314 | 47 | 306 | 97 | 50 | 285 | 91 | 50 |
| 77 | 318 | 45 | 310 | 98 | 50 | 286 | 90 | 49 |
| 81 | 325 | 44 | 313 | 96 | 49 | 285 | 88 | 47 |
| 85 | 329 | 42 | 318 | 97 | 45 | 282 | 86 | 45 |
| 89 | 331 | 41 | 315 | 95 | 40 | 279 | 84 | 42 |
| 93 | 330 | 37 | 314 | 95 | 34 | 276 | 84 | 34 |
| 97 | 336 | 30 | 324 | 96 | 32 | 274 | 82 | 32 |
| 101 | 332 | 29 | 320 | 96 | 29 | 260 | 78 | 32 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 164 | | 161 | 98 | | 159 | 97 | |
| 14-52 | 241 | | 236 | 98 | | 230 | 95 | |
| 53-101 | 315 | | 306 | 97 | | 277 | 88 | |

[a] Interim evaluations occurred during weeks 29 and 66.

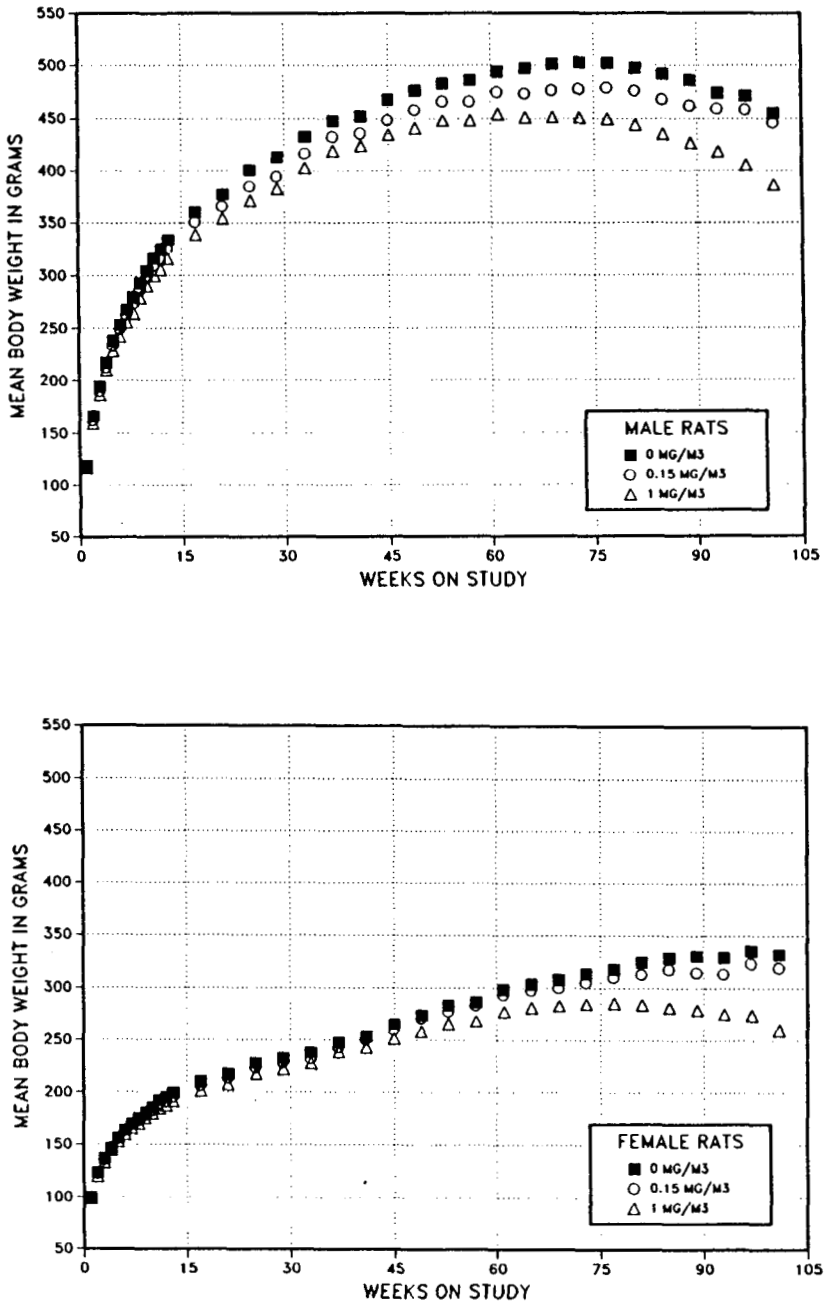


**FIGURE 3**
**Growth Curves for Rats Administered Nickel Subsulfide by Inhalation for 2 Years**

### *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, adrenal medulla, nose, and bronchial lymph node, and other organs. 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:* The absolute and relative lung weights of exposed males and females at 7 and 15 months (except the relative lung weight of 0.15 mg/m$^3$ males at 15 months) were significantly greater than those of the controls (Tables F3 and F4). There were exposure-related increased trends in the incidences of alveolar/bronchiolar adenoma in males, alveolar/bronchiolar carcinoma in males and females, and alveolar/bronchiolar adenoma or carcinoma (combined) in males and females at 2 years (Tables 14, A3, and B3). The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 0.15 and 1 mg/m$^3$ males and females exceeded the historical control ranges for these neoplasms in inhalation and feed studies (Tables 14, A4a, and B4a). The incidences of alveolar epithelial hyperplasia in 1 mg/m$^3$ males and in exposed females were significantly greater than those of the controls.

Most alveolar/bronchiolar carcinomas had cuboidal or low columnar epithelium in mixtures of tubular, papillary, and solid formations. Neoplastic cells in carcinomas were pleomorphic and often stained deeply basophilic. Some of the alveolar/bronchiolar neoplasms in exposed rats differed morphologically from the typical papillary or solid neoplastic proliferations of alveolar/bronchiolar epithelium typically found in control rats. Five alveolar/bronchiolar carcinomas had a prominent (10% or more) fibrous tissue component; four had areas of differentiation to stratified squamous epithelium (Plates 1 and 2). The fibrous tissue component and the squamous differentiation seen in some of the alveolar/bronchiolar neoplasms have been seen in lung neoplasms in rats in other studies of inhaled particulates such as talc (NTP, 1993). Most alveolar/bronchiolar adenomas were discrete proliferations of alveolar, tubular, or solid structures of moderately pleomorphic cuboidal to low columnar epithelial cells. A few adenomas had incorporated inflammatory cells, cellular debris, and areas of squamous differentiation; several had a prominent (10% or more) amount of dense fibrous connective tissue. Adenomas were usually visible macroscopically in histologic specimens. The severity of the inflammatory alterations in the lungs of the exposed rats obscured the gross identification of most of these neoplasms at necropsy. Focal alveolar epithelial hyperplasia was part of the morphologic continuum toward neoplasia and consisted of discrete areas where alveoli were lined by cuboidal cells that occasionally formed small projections within alveolar lumens (Plate 3). Because such proliferative changes can be stimulated by inflammation, this diagnosis was only used when proliferations were either located at a distance from inflammatory cell aggregates or were disproportionately severe compared to the accompanying inflammatory reaction.

At 7 months, the incidences of chronic active inflammation and alveolar macrophage hyperplasia in exposed males and females and the incidences of alveolar proteinosis and bronchial lymphoid hyperplasia in 1 mg/m$^3$ males and females were significantly greater than those of the controls (Tables 14, A5, and B5). At 15 months, the incidences of chronic active inflammation and alveolar macrophage hyperplasia and proteinosis in exposed males and females and interstitial infiltration in exposed females were significantly greater than those of the controls. In exposed males and females at 2 years, the incidences of chronic active inflammation, alveolar macrophage hyperplasia and proteinosis, bronchial lymphoid hyperplasia, and fibrosis were significantly greater than those of the controls. The incidences of interstitial infiltration in exposed males and 1 mg/m$^3$ females were also significantly greater than those of the controls. The severity of macrophage hyperplasia, proteinosis, and bronchial lymphoid hyperplasia increased with increasing exposure concentration. In addition, one squamous cyst was diagnosed in a 1 mg/m$^3$ female and squamous metaplasia was observed in the lungs of three 1 mg/m$^3$ females and two 0.15 mg/m$^3$ males (Tables 14, A5, and B5).

TABLE 14
**Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| **7-Month Interim Evaluation** | | | |
| Lung[a] | 5 | 5 | 5 |
| Inflammation, Chronic Active[b] | 1 (1.0)[c] | 5* (1.2) | 5* (2.0) |
| Alveolus, Hyperplasia, Macrophage | 0 | 5** (2.0) | 5** (3.4) |
| Alveolus, Proteinosis | 0 | 3 (1.0) | 5** (2.2) |
| Bronchus, Hyperplasia, Lymphoid | 0 | 1 (2.0) | 4* (1.0) |
| Interstitium, Infiltration Cellular | 3 (1.0) | 5 (1.0) | 5 (1.8) |
| **15-Month Interim Evaluation** | | | |
| Lung | 5 | 5 | 5 |
| Inflammation, Chronic Active | 0 | 5** (1.4) | 5** (1.2) |
| Alveolus, Hyperplasia, Macrophage | 1 (1.0) | 5* (2.0) | 5* (2.2) |
| Alveolus, Proteinosis | 0 | 5** (1.6) | 5** (4.0) |
| Interstitium, Infiltration Cellular | 2 (1.0) | 4 (1.3) | 4 (2.3) |
| **2-Year Study** | | | |
| Lung | 53 | 53 | 53 |
| Fibrosis | 2 (2.0) | 48** (1.8) | 40** (1.7) |
| Inflammation, Chronic Active | 9 (1.3) | 53** (2.5) | 51** (2.6) |
| Alveolar Epithelium, Hyperplasia, Focal | 2 (3.0) | 6 (2.2) | 11* (2.1) |
| Alveolus, Hyperplasia, Macrophage | 9 (1.1) | 48** (2.4) | 52** (3.0) |
| Alveolus, Proteinosis | 1 (1.0) | 36** (1.3) | 51** (3.6) |
| Bronchus, Hyperplasia, Lymphoid | 0 | 10** (1.7) | 14** (2.1) |
| Interstitium, Infiltration Cellular | 17 (1.2) | 31* (1.6) | 39** (1.9) |
| Squamous Metaplasia | 0 | 2 (1.0) | 0 |
| Alveolar/bronchiolar Adenoma (Multiple) | 0 | 0 | 2 |
| Alveolar/bronchiolar Adenoma (Single or Multiple) | 0 | 3 | 6* |
| Alveolar/bronchiolar Carcinoma | 0 | 3 | 7* |
| Alveolar/bronchiolar Adenoma or Carcinoma[d] | | | |
| Overall rate[e] | 0/53 (0%) | 6/53 (11%) | 11/53 (21%) |
| Adjusted rate[f] | 0.0% | 19.7% | 48.1% |
| Terminal rate[g] | 0/13 (0%) | 1/21 (5%) | 7/18 (39%) |
| First incidence | —[i] | 549 | 621 |
| Logistic regression test[h] | P=0.003 | P=0.020 | P=0.001 |
| **Female** | | | |
| **7-Month Interim Evaluation** | | | |
| Lung | 5 | 5 | 5 |
| Inflammation, Chronic Active | 0 | 5** (1.2) | 5** (1.2) |
| Alveolus, Hyperplasia, Macrophage | 0 | 5** (2.0) | 5** (2.6) |
| Alveolus, Proteinosis | 0 | 2 (1.0) | 5** (3.6) |
| Bronchus, Hyperplasia, Lymphoid | 0 | 1 (1.0) | 4* (1.0) |
| Interstitium, Infiltration Cellular | 2 (1.0) | 5 (1.0) | 5 (1.4) |

(continued)

TABLE 14
**Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Female** (continued) | | | |
| **15-Month Interim Evaluation** | | | |
| Lung | 5 | 5 | 5 |
| Inflammation, Chronic Active | 0 | 5** (2.4) | 5** (1.2) |
| Alveolus, Hyperplasia, Macrophage | 1 (1.0) | 5* (2.6) | 5* (2.6) |
| Alveolus, Proteinosis | 0 | 5** (1.8) | 5** (4.0) |
| Bronchus, Hyperplasia, Lymphoid | 0 | 0 | 1 (1.0) |
| Interstitium, Infiltration Cellular | 0 | 4* (1.0) | 5** (1.8) |
| **2-Year Study** | | | |
| Lung | 53 | 53 | 53 |
| Cyst | 0 | 0 | 1 (1.0) |
| Fibrosis | 0 | 50** (1.7) | 44** (1.9) |
| Inflammation, Chronic Active | 7 (1.3) | 51** (2.5) | 51** (2.3) |
| Alveolar Epithelium, Hyperplasia, Focal | 2 (2.0) | 10* (2.1) | 11** (1.6) |
| Alveolus, Hyperplasia, Macrophage | 8 (1.0) | 51** (2.5) | 52** (2.7) |
| Alveolus, Proteinosis | 2 (1.0) | 49** (2.1) | 53** (3.7) |
| Bronchus, Hyperplasia, Lymphoid | 0 | 15** (1.4) | 18** (1.9) |
| Interstitium, Infiltration Cellular | 28 (1.1) | 36 (1.6) | 43** (1.5) |
| Squamous Metaplasia | 0 | 0 | 3 (2.0) |
| Alveolar/bronchiolar Adenoma[j] | 2 | 5 | 5 |
| Alveolar/bronchiolar Carcinoma (Multiple) | 0 | 0 | 1 |
| Alveolar/bronchiolar Carcinoma (Single or Multiple) | 0 | 0 | 4 |
| Alveolar/bronchiolar Adenoma or Carcinoma[j] | 2 | 5 | 9* |
| Squamous Cell Carcinoma | 0 | 1 | 0 |
| Alveolar/bronchiolar Adenoma or Carcinoma or Squamous Cell Carcinoma[j,k] | | | |
| Overall rate | 2/53 (4%) | 6/53 (11%) | 9/53 (17%) |
| Adjusted rate | 8.0% | 20.0% | 27.2% |
| Terminal rate | 2/25 (8%) | 4/25 (16%) | 6/28 (21%) |
| First incidence | 729 (T) | 594 | 594 |
| Logistic regression test | P=0.030 | P=0.142 | P=0.031 |

(T)Terminal sacrifice
* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[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
[d] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 27/703 (3.8% ± 3.8%); range 0%-10% (includes squamous cell carcinoma). Feed studies: 39/1,200 (3.3% ± 2.0%); range 0%-8%
[e] Number of animals with neoplasm per number of animals with organ examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence in animals surviving until the end of the study
[h] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[i] Not applicable; no neoplasms in animal group
[j] Includes one adenoma NOS, NOS = nonspecified site
[k] Historical incidence for 2-year NTP inhalation studies: 8/700 (1.1% ± 1.5%); range 0%-4%. Feed studies: 25/1,201 (2.1% ± 2.2%); range 0%-10%

Chronic active inflammation was typically of moderate severity in exposed rats and consisted of variably distributed intra-alveolar macrophages, neutrophils, and cell debris, often subjacent to the pleura (Plate 4). Macrophage hyperplasia was typically of moderate severity in exposed rats and consisted of variably distributed large intra-alveolar macrophages containing abundant pale vacuolated cytoplasm. The source of these macrophages was probably the intravascular pool of circulating monocytes. Proteinosis was a moderate to marked presence of eosinophilic granular or flocculent material with alveolar lumens. Severity of proteinosis was judged by the extent of lung affected and by the amount of material present. Bronchial lymphoid hyperplasia was a minimal to mild increase in the number of lymphocytes around major bronchi. Interstitial cellular infiltrates were minimal to mild aggregates of lymphocytes with fewer macrophages forming perivascular cuffs and infiltrating the adjacent alveolar septa. Fibrosis, consisting of varying amounts of dense fibrous tissue within alveolar septa and lumens, occasionally had slit-like spaces typical of cholesterol clefts. The fibrosis was considered to be secondary to the inflammatory processes in the lungs of exposed rats. The squamous cyst in the 1 mg/m$^3$ female had a wall of well-differentiated stratified squamous epithelium without atypia and a lumen containing keratin. Squamous cell metaplasia consisted of a focal replacement of pneumocytes by well-differentiated squamous epithelium.

Chronic active inflammation varied in extent and consisted of infiltrates of neutrophils and lymphocytes, occasionally including plasma cells, in the lamina propria. With increased severity, there were neutrophils and cell debris within the nasal lumen, occasionally accompanied by focal hyperplasia of respiratory epithelium. Atrophy of the olfactory epithelium was minimal in exposed rats and consisted of focal decreased numbers and thickness of the pseudostratified olfactory epithelium in the dorsal meatus.

*Adrenal Medulla:* At 2 years, there were significant exposure-related increases in the incidences of benign pheochromocytoma, malignant pheochromocytoma, and benign or malignant pheochromocytoma (combined) in males (Tables 15 and A3). The incidences of benign pheochromocytoma and of benign or malignant pheochromocytoma (combined) in females also occurred with a significant exposure-related increased trend (Tables 15 and B3). The incidences of benign pheochromocytoma in 0.15 and 1 mg/m$^3$ males, of malignant pheochromocytoma in 1 mg/m$^3$ males, and of benign or malignant pheochromocytoma (combined) in 0.15 and 1 mg/m$^3$ males exceeded the historical control ranges for these neoplasms from NTP inhalation studies (Tables 15 and A4b). In 1 mg/m$^3$ females, the incidences of benign pheochromocytoma and of benign or malignant pheochromocytoma (combined) exceeded the historical controls ranges from inhalation studies (Tables 15 and B4b). Focal hyperplasia and pheochromocytoma were mutually exclusive diagnoses in the medulla of each adrenal gland. Most of the adrenal glands of exposed male rats had one or the other of these diagnoses. The incidence of adrenal medulla hyperplasia in 1 mg/m$^3$ females was significantly greater than that of the controls at 2 years.

Benign pheochromocytomas were discrete masses of adrenal medullary cells producing distinct compression of the adrenal cortex. Many benign pheochromocytomas were bilateral. Malignant pheochromocytomas penetrated the adrenal gland capsule and invaded the periadrenal tissues. Hyperplasias were focal to multifocal clusters of increased numbers of adrenal medullary cells with alterations in size and/or staining characteristics. Hyperplastic lesions did not compress the adjacent parenchyma.

TABLE 15
**Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| **15-Month Interim Evaluation** | | | |
| Adrenal Medulla[a] | 5 | 5 | 5 |
| Hyperplasia[b] | 0 | 0 | 1 (1.0)[c] |
| **2-Year Study** | | | |
| Adrenal Medulla | 53 | 52 | 53 |
| Hyperplasia | 26 (2.2) | 22 (1.9) | 10** (2.4) |
| Pheochromocytoma Benign, Bilateral | 1 | 7* | 23** |
| Pheochromocytoma Benign (Includes Bilateral) | | | |
| Overall rate[d] | 13/53 (25%) | 30/52 (58%) | 37/53 (70%) |
| Adjusted rate[e] | 54.4% | 84.6% | 88.0% |
| Terminal rate[f] | 4/13 (31%) | 16/21 (76%) | 13/18 (72%) |
| First incidence (days) | 559 | 455 | 552 |
| Logistic regression test[g] | P<0.001 | P=0.002 | P<0.001 |
| Pheochromocytoma Malignant, Bilateral | 0 | 0 | 5 |
| Pheochromocytoma Malignant (Includes Bilateral) | | | |
| Overall rate | 0/53 (0%) | 2/52 (4%) | 11/53 (21%) |
| Adjusted rate | 0.0% | 6.9% | 48.6% |
| Terminal rate | 0/13 (0%) | 0/21 (0%) | 7/18 (39%) |
| First incidence | —[h] | 601 | 703 |
| Logistic regression test | P<0.001 | P=0.242 | P=0.002 |
| Pheochromocytoma Benign, Malignant, or Complex[i] | | | |
| Overall rate | 14/53 (26%) | 30/52 (58%) | 42/53 (79%) |
| Adjusted rate | 55.4% | 84.6% | 100.0% |
| Terminal rate | 4/13 (31%) | 16/21 (76%) | 18/18 (100%) |
| First incidence | 553 | 455 | 552 |
| Logistic regression test | P<0.001 | P=0.003 | P<0.001 |

(continued)

TABLE 15
**Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Female** | | | |
| **2-Year Study** | | | |
| Adrenal Medulla | 53 | 53 | 53 |
| *Hyperplasia* | 5 (1.6) | 11 (2.0) | 16** (2.1) |
| Pheochromocytoma Benign, Bilateral | 0 | 1 | 24** |
| Pheochromocytoma Benign (Includes Bilateral) | | | |
| Overall rate | 2/53 (4%) | 7/53 (13%) | 36/53 (68%) |
| Adjusted rate | 7.6% | 24.4% | 85.5% |
| Terminal rate | 1/25 (4%) | 5/25 (20%) | 22/28 (79%) |
| First incidence | 721 | 590 | 563 |
| Logistic regression test | P<0.001 | P=0.083 | P<0.001 |
| Pheochromocytoma Malignant | | | |
| Overall rate | 1/53 (2%) | 0/53 (0%) | 1/53 (2%) |
| Adjusted rate | 3.1% | 0.0% | 3.6% |
| Terminal rate | 0/25 (0%) | 0/25 (0%) | 1/28 (4%) |
| First incidence | 677 | — | 729 (T) |
| *Logistic regression test* | P=0.628 | P=0.497N | P=0.755N |
| Pheochromocytoma Benign, Malignant, or Complex[j] | | | |
| Overall rate | 3/53 (6%) | 7/53 (13%) | 36/53 (68%) |
| Adjusted rate | 10.4% | 24.4% | 85.5% |
| Terminal rate | 1/25 (4%) | 5/25 (20%) | 22/28 (79%) |
| First incidence | 677 | 590 | 563 |
| Logistic regression test | P<0.001 | P=0.166 | P<0.001 |

(T)Terminal sacrifice
** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
[a] Number of animals with adrenal medulla 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] *Number of animals with neoplasm per number of animals with adrenal medulla examined microscopically*
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] *In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to* the pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A lower incidence in an exposure group is indicated by N.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 176/623 (28.3% ± 12.0%); range 8%-50%. Feed studies: 400/1,182 (33.8% ± 10.9%); range 14%-63%
[j] Historical incidence for 2-year NTP inhalation studies: 39/608 (6.4% ± 4.4%); range 2%-14%. Feed studies: 62/1,175 (5.3% ± 2.8%); range 2%-12%

*Nose:* At 2 years, the incidences of chronic active inflammation of the nose in 1 mg/m$^3$ females and of olfactory epithelial atrophy in 1 mg/m$^3$ males and females were significantly greater than those of the controls (Tables 16, A5, and B5).

*Bronchial Lymph Node:* The incidences of lymphoid hyperplasia of the bronchial lymph node in exposed males at 7 and 15 months and in exposed males and females at 2 years were significantly greater than those of the controls (Tables 17, A5, and B5). Incidences of macrophage hyperplasia in the bronchial lymph node of exposed males at 15 months and exposed males and females at 2 years were also significantly greater than those of the controls.

**TABLE 16**
**Incidences of Nonneoplastic Lesions of the Nose in Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | | 0.15 mg/m$^3$ | | 1 mg/m$^3$ | |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| **7-Month Interim Evaluation** | | | | | | |
| Nose[a] | 5 | | 5 | | 5 | |
| Inflammation, Chronic Active[b] | 0 | | 0 | | 3 | (1.0)[c] |
| Olfactory Epithelium, Atrophy | 0 | | 0 | | 1 | (1.0) |
| **15-Month Interim Evaluation** | | | | | | |
| Nose | 5 | | 5 | | 5 | |
| Inflammation, Chronic Active | 1 | (1.0) | 2 | (1.0) | 0 | |
| **2-Year Study** | | | | | | |
| Nose | 53 | | 53 | | 52 | |
| Inflammation, Chronic Active | 12 | (1.8) | 10 | (2.6) | 18 | (2.3) |
| Olfactory Epithelium, Atrophy | 2 | (1.0) | 1 | (1.0) | 9* | (1.1) |
| **Female** | | | | | | |
| **7-Month Interim Evaluation** | | | | | | |
| Nose | 5 | | 5 | | 5 | |
| Inflammation, Chronic Active | 1 | (1.0) | 2 | (1.5) | 4 | (1.0) |
| **15-Month Interim Evaluation** | | | | | | |
| Nose | 5 | | 5 | | 5 | |
| Inflammation, Chronic Active | 3 | (1.3) | 2 | (1.0) | 2 | (1.5) |
| Olfactory Epithelium, Atrophy | 0 | | 0 | | 1 | (1.0) |
| **2-Year Study** | | | | | | |
| Nose | 53 | | 53 | | 52 | |
| Inflammation, Chronic Active | 6 | (1.7) | 9 | (1.7) | 20** | (2.0) |
| Olfactory Epithelium, Atrophy | 0 | | 0 | | 16** | (1.0) |

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression 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

TABLE 17
**Incidences of Nonneoplastic Lesions of the Bronchial Lymph Node in Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| **7-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial[a] | 4 | 5 | 5 |
| Hyperplasia, Lymphoid[b] | 0 | 4* (1.0)[c] | 5** (1.6) |
| **15-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial | 5 | 5 | 4 |
| Hyperplasia, Lymphoid | 0 | 5** (1.6) | 4* (2.0) |
| Hyperplasia, Macrophage | 0 | 4* (1.0) | 4* (1.3) |
| **2-Year Study** | | | |
| Lymph Node, Bronchial | 52 | 51 | 53 |
| Hyperplasia, Lymphoid | 5 (2.2) | 29** (2.1) | 34** (2.4) |
| Hyperplasia, Macrophage | 1 (1.0) | 14** (1.1) | 28** (1.2) |
| **Female** | | | |
| **7-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial | 5 | 5 | 5 |
| Hyperplasia, Lymphoid | 2 (1.0) | 2 (1.0) | 5 (2.4) |
| **15-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial | 5 | 5 | 5 |
| Hyperplasia, Lymphoid | 0 | 1 (2.0) | 2 (1.5) |
| Hyperplasia, Macrophage | 1 (1.0) | 2 (1.0) | 4 (1.0) |
| **2-Year Study** | | | |
| Lymph Node, Bronchial | 50 | 49 | 50 |
| Hyperplasia, Lymphoid | 11 (1.8) | 36** (1.9) | 36** (2.6) |
| Hyperplasia, Macrophage | 0 | 16** (1.3) | 24** (1.3) |

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with bronchial lymph node 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

Lymphoid hyperplasia consisted of an increased number of lymphocytes, mainly in the paracortical region and usually accompanied by enlargement of the lymph node. The lymphocytes were at different stages of differentiation and the overall architecture of the lymph node was maintained. Macrophage hyperplasia consisted of a few to several macrophages with abundant pale granular cytoplasm within the medulla of the lymph node, consistent with a reaction to inflammation in the lung.

*Other Organs:* There were exposure-related decreases in the incidences of fibroadenoma (22/53, 11/53, 10/53; Table B3) and of fibroadenoma, adenoma, and carcinoma (combined) (24/53, 13/53, 10/53; Table B3) of the mammary gland in exposed females.

The incidence of adenoma of the pars distalis of the pituitary gland in 1 mg/m³ females was significantly less than that of the controls (24/52, 30/53, 15/53; Table B3).

### *Tissue Burden Analyses*

In general, nickel concentrations in the lung of exposed rats were significantly greater than those of the controls at 7 and 15 months, and generally increased with increasing exposure concentration (Tables 18 and H5). However, by 15 months, nickel concentrations in the lung had reached a steady state. Absolute lung weights of 0.15 and 1 mg/m³ males and females were significantly greater than those of the controls at 7 and 15 months. Nickel concentrations in the kidney of 0.15 and 1 mg/m³ males and females at 7 months and those of 0.15 and 1 mg/m³ females at 15 months were significantly greater than those of the controls (Table H6).

**TABLE 18**
**Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| n | 7 | 7 | 7 |
| **7-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 1.53 ± 0.13 | 1.97 ± 0.09** | 3.21 ± 0.08** |
| μg Ni/lung | —[b] | 12 ± 0.5** | 28 ± 1.8** |
| μg Ni/g lung | — | 6 ± 0.2** | 9 ± 0.5** |
| μg Ni/g control lung | — | 8 ± 0.3** | 18 ± 1.2** |
| n | 5 | 5 | 5 |
| **15-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 2.27 ± 0.09 | 3.31 ± 0.22** | 6.84 ± 0.70** |
| μg Ni/lung | — | 14 ± 0.6** | 21 ± 1.5** |
| μg Ni/g lung | — | 4 ± 0.2** | 3 ± 0.1 |
| μg Ni/g control lung | — | 6 ± 0.3** | 9 ± 0.7** |
| **Female** | | | |
| n | 7 | 7 | 7 |
| **7-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 1.10 ± 0.03 | 1.48 ± 0.04** | 2.44 ± 0.07** |
| μg Ni/lung | — | 9 ± 0.4** | 23 ± 0.7** |
| μg Ni/g lung | — | 6 ± 0.2** | 9 ± 0.4** |
| μg Ni/g control lung | — | 8 ± 0.4** | 21 ± 0.6** |
| n | 5 | 5 | 5 |
| **15-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 1.52 ± 0.11 | 2.52 ± 0.25** | 4.15 ± 0.10** |
| μg Ni/lung | — | 9 ± 0.8** | 29 ± 1.0** |
| μg Ni/g lung | — | 4 ± 0.5** | 7 ± 0.2** |
| μg Ni/g control lung | — | 6 ± 0.5** | 19 ± 0.6** |

** Significantly different ($P \leq 0.01$) from the control group by Williams' test (lung weight) or Dunn's or Shirley's test (lung burden parameters)

[a] Mean ± standard error; statistical tests were performed on unrounded data.

[b] Results were below 0.035 μg Ni (the limit of detection) for the 7-month interim evaluation and below 0.119 μg Ni for the 15-month interim evaluation.

# MICE
## 16-DAY STUDY

All male and female mice exposed to 10 mg nickel subsulfide/m$^3$ died before the end of the study; the death of one female was accidental (Table 19). One control male, one control female, and one 1.2 mg/m$^3$ male also died before the end of the study. Final mean body weights and mean body weight gains of 5 mg/m$^3$ males were significantly lower than those of the controls. Clinical findings at day 5 included labored respiration in 10 mg/m$^3$ males and females.

**TABLE 19**
**Survival and Body Weights of Mice in the 16-Day Inhalation Study of Nickel Subsulfide**

| Dose (mg/m$^3$) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 4/5[c] | 23.3 ± 0.3 | 25.3 ± 0.3 | 2.0 ± 0.2 | |
| 0.6 | 5/5 | 22.8 ± 1.0 | 25.0 ± 0.4 | 2.2 ± 0.7 | 99 |
| 1.2 | 4/5[d] | 22.4 ± 0.3 | 22.8 ± 1.8 | 0.4 ± 1.7 | 90 |
| 2.5 | 5/5 | 22.6 ± 0.2 | 23.4 ± 0.5 | 0.7 ± 0.3 | 92 |
| 5 | 5/5 | 22.6 ± 0.3 | 21.8 ± 0.5* | −0.8 ± 0.4* | 86 |
| 10 | 0/5[e] | 23.1 ± 0.3 | — | — | — |
| **Female** | | | | | |
| 0 | 4/5[f] | 19.6 ± 0.3 | 20.3 ± 2.0 | 0.7 ± 2.1 | |
| 0.6 | 5/5 | 18.6 ± 0.2 | 21.6 ± 0.2 | 2.9 ± 0.3 | 106 |
| 1.2 | 5/5 | 18.8 ± 0.3 | 21.1 ± 0.4 | 2.3 ± 0.4 | 104 |
| 2.5 | 5/5 | 19.1 ± 0.5 | 20.6 ± 0.4 | 1.5 ± 0.4 | 101 |
| 5 | 5/5 | 19.6 ± 0.4 | 20.1 ± 0.6 | 0.5 ± 0.6 | 99 |
| 10 | 0/5[g] | 18.8 ± 0.5 | — | — | — |

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Day of death: 5.
[d] Day of death: 11. Final weights and weight changes are based on 5 animals.
[e] Day of death: 5, 6, 6, 7, 8.
[f] Day of death: 9. Final weights and weight changes are based on 5 animals.
[g] Day of death: 5, 6 (accidental death), 9, 10, 10.

The absolute lung weight of 5 mg/m³ males, the absolute and relative lung weights of 10 mg/m³ males and 5 mg/m³ females, and the relative lung weight of 10 mg/m³ females were significantly greater than those of the controls (Table F5). Absolute and relative thymus weights of 10 mg/m³ males and females were significantly less than those of the controls. At necropsy, chemical-related gross lesions were limited to mottled or diffusely reddened lungs in a few 5 mg/m³ mice and in most 10 mg/m³ mice, which died before the end of the study. Chemical-related histopathologic lesions were observed in the lung, bronchial lymph node, and nose of males and females (Table 20). Inflammation in the lung occurred in 2.5, 5, and 10 mg/m³ males and females. In 10 mg/m³ mice, inflammation included inflammatory cell infiltration as well as necrosis in the alveolar and bronchiolar epithelium, extensive vascular congestion, and edema throughout the lung. In 2.5 and 5 mg/m³ males and females, all of which survived until the end of the study, there was an increase in the number of alveolar macrophages and interstitial inflammatory cell infiltrates around blood vessels and within alveolar septa. A few granules of black pigment were present in some alveolar macrophages in mice from the 5 mg/m³ group. There were also minimal to mild focal areas of fibrosis within the alveolar septa of 5 mg/m³ mice. Lymphoid hyperplasia was observed in the bronchial lymph node of 1.2, 2.5, and 5 mg/m³ mice. Minimal to marked atrophy of the olfactory epithelium was observed in the nasal passages of males and females exposed to 1.2, 2.5, 5, or 10 mg/m³. Other microscopic lesions observed included atrophy due to lymphoid depletion

**TABLE 20**
**Incidences of Selected Nonneoplastic Lesions in Mice in the 16-Day Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ | 5 mg/m³ | 10 mg/m³ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Lung[a] | 5 | 5 | 5 | 5 | 5 | 5 |
| Inflammation[b] | 0 | 0 | 0 | 5** (1.2)[c] | 5** (1.4) | 5** (3.0) |
| Fibrosis | 0 | 0 | 0 | 0 | 3 (1.3) | 0 |
| Lymph Node, Bronchial | 3 | 2 | 3 | 3 | 3 | 2 |
| Hyperplasia | 0 | 0 | 3* (1.3) | 2 (2.0) | 2 (1.5) | 0 |
| Nose | 5 | 5 | 5 | 5 | 5 | 5 |
| Olfactory Epithelium Atrophy | 0 | 0 | 3 (1.0) | 5** (1.8) | 5** (4.0) | 5** (3.0) |
| **Female** | | | | | | |
| Lung | 5 | 5 | 5 | 5 | 5 | 4 |
| Inflammation | 0 | 0 | 0 | 4* (1.5) | 5** (2.0) | 4** (2.5) |
| Fibrosis | 0 | 0 | 0 | 0 | 2 (2.0) | 0 |
| Lymph Node, Bronchial | 3 | 3 | 2 | 4 | 3 | 2 |
| Hyperplasia | 0 | 0 | 1 (1.0) | 3 (2.0) | 2 (3.0) | 0 |
| Nose | 5 | 5 | 5 | 5 | 5 | 4 |
| Olfactory Epithelium Atrophy | 0 | 0 | 2 (1.0) | 5** (1.0) | 5** (4.0) | 4** (3.0) |

* Significantly different ($P \leq 0.05$) from the 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 of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

in the thymus of 10 mg/m³ males (0 mg/m³, 1/5; 5 mg/m³, 0/5; 10 mg/m³, 5/5) and females (1/5, 0/5, 4/4) and spleen of 10 mg/m³ males (0 mg/m³, 1/5; 2.5 mg/m³, 0/5; 5 mg/m³, 0/5; 10 mg/m³, 5/5) and females (1/5, 0/4, 0/5, 3/4); these lesions were considered to be nonspecific findings typically observed in mice that are killed moribund or mice that lose weight during the study.

Although nickel concentrations in the lung of exposed males and females were generally greater than those of controls, the increase was not exposure related (Tables 21 and I1). Absolute lung weights of these 2.5 and 10 mg/m³ animals were significantly greater than those of the controls. Nickel concentrations in the kidney of 10 mg/m³ males and females were significantly greater than those of the controls; however, absolute kidney weights of these males and females were significantly less than those of the controls (Table I2).

Because of the severity of lung lesions in mice exposed to 5 or 10 mg/m³, 2.5 mg/m³ was selected as the highest exposure concentration for the 13-week study.

**TABLE 21**
**Lung Weight and Lung Burden in Mice in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 2.5 mg/m³ | 10 mg/m³ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 3 | 3 | 3 | 2 |
| Absolute lung wt (g) | 0.138 ± 0.004 | 0.145 ± 0.006 | 0.200 ± 0.014** | 0.335 ± 0.005** |
| μg Ni/lung | —[b] | 1 ± 0.2* | 4 ± 0.9** | 4 ± 0.9* |
| μg Ni/g lung | — | 10 ± 0.7* | 20 ± 3.2** | 13 ± 2.5* |
| μg Ni/g control lung | — | 10 ± 1.0* | 30 ± 6.8** | 31 ± 6.0* |
| **Female** | | | | |
| n | 3 | 3 | 3 | 3 |
| Absolute lung wt (g) | 0.125 ± 0.002 | 0.153 ± 0.011 | 0.197 ± 0.006* | 0.380 ± 0.040** |
| μg Ni/lung | — | 1 ± 0.1* | 4 ± 0.5** | 3 ± 0.5* |
| μg Ni/g lung | — | 8 ± 0.4 | 20 ± 2.6** | 8 ± 1.9 |
| μg Ni/g control lung | — | 10 ± 1.0* | 31 ± 4.1** | 22 ± 3.9* |

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Dunn's or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.155 μg Ni (the limit of detection).

## 13-WEEK STUDY

Two control males, two 0.6 mg/m$^3$ males, one 1.2 mg/m$^3$ male, two 0.15 mg/m$^3$ females, one 0.6 mg/m$^3$ female, and two 2.5 mg/m$^3$ females died before the end of the study (Table 22). Deaths were not related to exposure level or sex of the animal and were not considered to be chemical related. Final mean body weights of all exposure groups were similar to those of the controls. No chemical-related clinical findings were observed.

In general, hematology differences in mice (Table G3) were similar to those reported for rats at 13 weeks. The mice were less affected than the rats, and minimal differences occurred in fewer end points and exposure groups. Lymphocyte counts in 1.2 and 2.5 mg/m$^3$ males were minimally greater than that of the controls. Hemoglobin concentrations and erythrocyte counts in 0.3, 0.6, 1.2, and 2.5 mg/m$^3$ females were minimally greater than those of the controls.

No significant differences in sperm morphology or vaginal cytology between exposed and control mice were observed (Table J2).

TABLE 22
**Survival and Body Weights of Mice in the 13-Week Inhalation Study of Nickel Subsulfide**

| Dose (mg/m$^3$) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 8/10[c] | 23.0 ± 0.3 | 29.8 ± 0.5 | 6.8 ± 0.3 | |
| 0.15 | 10/10 | 21.6 ± 0.4 | 30.5 ± 0.5 | 9.0 ± 0.6 | 102 |
| 0.3 | 10/10 | 23.1 ± 0.6 | 31.6 ± 0.6 | 8.5 ± 0.4 | 106 |
| 0.6 | 8/10[d] | 23.0 ± 0.5 | 30.8 ± 0.5 | 7.7 ± 0.5 | 103 |
| 1.2 | 9/10[e] | 23.0 ± 0.6 | 30.2 ± 0.8 | 7.1 ± 0.5 | 101 |
| 2.5 | 10/10 | 23.7 ± 0.2 | 29.0 ± 0.3 | 5.4 ± 0.4* | 97 |
| **Female** | | | | | |
| 0 | 10/10 | 18.3 ± 0.4 | 25.1 ± 0.5 | 6.8 ± 0.3 | |
| 0.15 | 8/10[f] | 18.0 ± 0.2 | 25.4 ± 0.5 | 7.6 ± 0.4 | 101 |
| 0.3 | 10/10 | 17.8 ± 0.3 | 25.2 ± 0.4 | 7.5 ± 0.5 | 100 |
| 0.6 | 9/10[g] | 18.1 ± 0.3 | 25.4 ± 0.4 | 7.3 ± 0.3 | 101 |
| 1.2 | 10/10[h] | 18.3 ± 0.3 | 25.3 ± 0.4 | 6.9 ± 0.5 | 101 |
| 2.5 | 8/10[i] | 18.1 ± 0.2 | 24.9 ± 0.5 | 6.8 ± 0.4 | 99 |

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Week of death: 4, 4
[d] Week of death: 5, 5
[e] Week of death: 5
[f] Week of death: 5, 7
[g] Week of death: 2
[h] Final weights and weight changes are based on 9 animals.
[i] Week of death: 4, 9. Final weights and weight changes are based on 7 animals.

Absolute and relative lung weights of 1.2 and 2.5 mg/m$^3$ males and females were significantly greater than those of the controls (Table F6). The absolute liver weight of 2.5 mg/m$^3$ males was significantly less than that of the controls. At necropsy, chemical-related gross findings in mice consisted of enlargement of the bronchial lymph nodes in two male and three female mice exposed to 2.5 mg/m$^3$ and four female mice exposed to 1.2 mg/m$^3$. White, pinpoint foci were observed on the pleural surface of the lungs of two 1.2 mg/m$^3$ mice. Chemical-related histopathologic lesions were present in the lung, bronchial lymph node, and nose of male and female mice (Table 23). There was an exposure-related increase in the incidence and severity of inflammatory lesions in the lung. A minimally detectable increase in the number of macrophages within the alveolar spaces occurred in mice exposed to 0.3 mg/m$^3$ or greater. Minimal focal interstitial infiltrates, predominantly lymphocytes around blood vessels, were present in 0.15, 0.6, 1.2, and 2.5 mg/m$^3$ males and in exposed females. In mice exposed to 1.2 or 2.5 mg/m$^3$, there was an increase in the severity of alveolar macrophage accumulation. Perivascular interstitial infiltrates of lymphocytes and focal areas of chronic inflammation, which

**TABLE 23**
**Incidences of Selected Nonneoplastic Lesions in Mice in the 13-Week Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 0.3 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ | 2.5 mg/m$^3$ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Lung[a] | 10 | 10 | 10 | 10 | 10 | 10 |
| Alveolar Macrophage Hyperplasia[b] | 0 | 0 | 8** (1.0)[c] | 8** (1.0) | 9** (2.0) | 10** (2.2) |
| Interstitial Infiltrate | 0 | 1 (1.0) | 0 | 2 (1.0) | 3 (1.2) | 2 (1.5) |
| Inflammation, Chronic Active | 0 | 0 | 0 | 0 | 5* (1.2) | 7** (1.6) |
| Fibrosis | 0 | 0 | 0 | 0 | 5* (1.6) | 10** (2.1) |
| Lymph Node, Bronchial | 3 | —[d] | — | 4 | 5 | 8 |
| Hyperplasia | 0 | | | 0 | 3 (1.0) | 8** (2.1) |
| Nose | 8 | 10 | 10 | 10 | 9 | 10 |
| Olfactory Epithelium Atrophy | 0 | 0 | 0 | 5* (1.0) | 5* (1.0) | 10** (2.8) |
| **Female** | | | | | | |
| Lung | 10 | 10 | 10 | 10 | 10 | 10 |
| Alveolar Macrophage Hyperplasia | 0 | 0 | 4* (1.0) | 9** (1.0) | 10** (2.4) | 10** (2.6) |
| Interstitial Infiltrate | 0 | 2 (1.0) | 3 (1.0) | 4* (1.0) | 9** (1.4) | 8** (1.7) |
| Inflammation, Chronic Active | 0 | 0 | 0 | 0 | 10** (1.5) | 7** (2.0) |
| Fibrosis | 0 | 0 | 0 | 0 | 1 (2.0) | 9** (1.6) |
| Lymph Node, Bronchial | 4 | — | — | 5 | 7 | 6 |
| Hyperplasia | 0 | | | 0 | 5* (1.2) | 5* (2.8) |
| Nose | 8 | 10 | 10 | 9 | 10 | 10 |
| Olfactory Epithelium Atrophy | 0 | 0 | 0 | 1 (1.0) | 6* (1.1) | 10** (2.5) |

* Significantly different ($P \leq 0.05$) from the 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 of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Tissue not examined at this exposure concentration

resulted in thicker alveolar septa, were also present. In some of the foci of chronic inflammation, there was minimal to mild fibrosis characterized by a focal increase in fibroblasts and collagen fibers in the alveolar septa. Microscopically, hyperplasia was observed in the bronchial lymph nodes, corresponding to the enlargement of these nodes observed grossly. This consisted of an increase in lymphocytes, primarily in the paracortical region of the lymph nodes. Atrophy of the olfactory epithelium consisted of a thinner neuroepithelial layer resulting from a decrease in cell number and a decrease in the amount of cytoplasm in the apical portion of the cells. This olfactory lesion was most evident in the dorsal meatus of the nasal passages.

At 13 weeks, nickel concentrations in the lung of 0.15, 0.6, and 2.5 mg/m$^3$ males and females were significantly greater than those of the controls, and these concentrations increased with nickel subsulfide exposure concentration (Tables 24 and I3). Absolute lung weights of these 0.6 mg/m$^3$ males and 2.5 mg/m$^3$ males and females were significantly greater than those of the controls.

*Dose Selection Rationale:* Based on the increased incidences and severities of chronic active inflammation and fibrosis in the lung at 2.5 mg/m$^3$, the highest nickel subsulfide exposure concentration selected for the 2-year inhalation study was 1.2 mg/m$^3$.

**TABLE 24**
**Lung Weight and Lung Burden in Mice in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 0.6 mg/m$^3$ | 2.5 mg/m$^3$ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 6 | 5 | 6 | 6 |
| Absolute lung wt (g) | 0.158 ± 0.005 | 0.178 ± 0.010 | 0.195 ± 0.010* | 0.258 ± 0.013** |
| μg Ni/lung | —[b] | 1 ± 0.2* | 2 ± 0.1** | 4 ± 0.5** |
| μg Ni/g lung | — | 3 ± 0.9* | 11 ± 0.8** | 17 ± 1.6** |
| μg Ni/g control lung | — | 4 ± 1.0* | 14 ± 0.8** | 28 ± 3.2** |
| **Female** | | | | |
| n | 6 | 5 | 5 | 6 |
| Absolute lung wt (g) | 0.163 ± 0.004 | 0.139 ± 0.007 | 0.170 ± 0.011 | 0.298 ± 0.012** |
| μg Ni/lung | — | 1 ± 0.1** | 2 ± 0.1** | 7 ± 0.5** |
| μg Ni/g lung | — | 6 ± 0.4** | 13 ± 1.0** | 23 ± 1.4** |
| μg Ni/g control lung | — | 5 ± 0.4** | 14 ± 0.8** | 41 ± 2.9** |

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.255 μg Ni (the limit of detection).

## 2-YEAR STUDY

### *Survival*

Estimates of 2-year survival probabilities for male and female mice are shown in Table 25 and in the Kaplan-Meier survival curves in Figure 4. Survival of exposed male and female mice was similar to that of the controls.

### *Body Weights and Clinical Findings*

Mean body weights of 0.6 and 1.2 mg/m$^3$ males and females were less than those of the controls throughout the second year of the study (Figure 5 and Tables 26 and 27). Chemical-related clinical findings in male and female mice included labored respiration following exposure periods.

**TABLE 25**
**Survival of Mice in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ |
|---|---|---|---|
| **Male** | | | |
| Animals initially in study | 80 | 80 | 80 |
| 7-Month interim evaluation[a] | 9 | 10 | 10 |
| 15-Month interim evaluation[a] | 10 | 10 | 10 |
| Moribund | 27 | 26 | 25 |
| Natural deaths | 8 | 9 | 9 |
| Animals surviving to study termination | 26 | 25 | 26[e] |
| Percent probability of survival at end of study[b] | 43 | 43 | 43 |
| Mean survival (days)[c] | 563 | 544 | 552 |
| Survival analysis[d] | P=1.000 | P=0.920 | P=1.000 |
| **Female** | | | |
| Animals initially in study | 80 | 80 | 80 |
| 7-Month interim evaluation[a] | 10 | 10 | 10 |
| 15-Month interim evaluation[a] | 10 | 10 | 10 |
| Missexed[a] | 2 | 0 | 0 |
| Moribund | 14 | 15 | 13 |
| Natural deaths | 8 | 11 | 9 |
| Animals surviving to study termination | 36 | 34 | 38 |
| Percent probability of survival at end of study | 63 | 58 | 64 |
| Mean survival (days) | 590 | 580 | 587 |
| Survival analysis | P=0.979N | P=0.658 | P=1.000N |

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or a lower mortality in an exposure group is indicated by N.
[e] Includes one animal that died during the last week of the study.

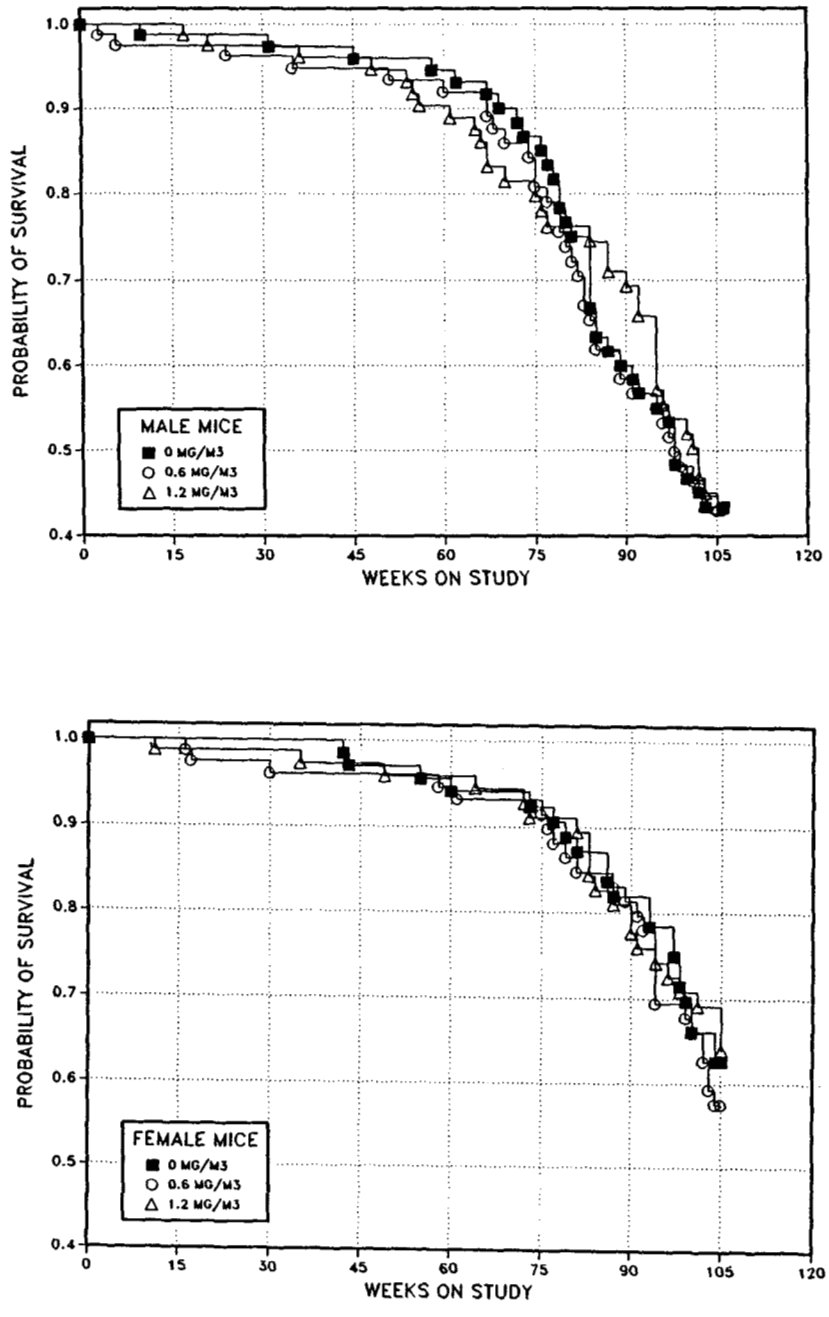


**FIGURE 4**
**Kaplan-Meier Survival Curves for Mice Administered Nickel Subsulfide by Inhalation for 2 Years**

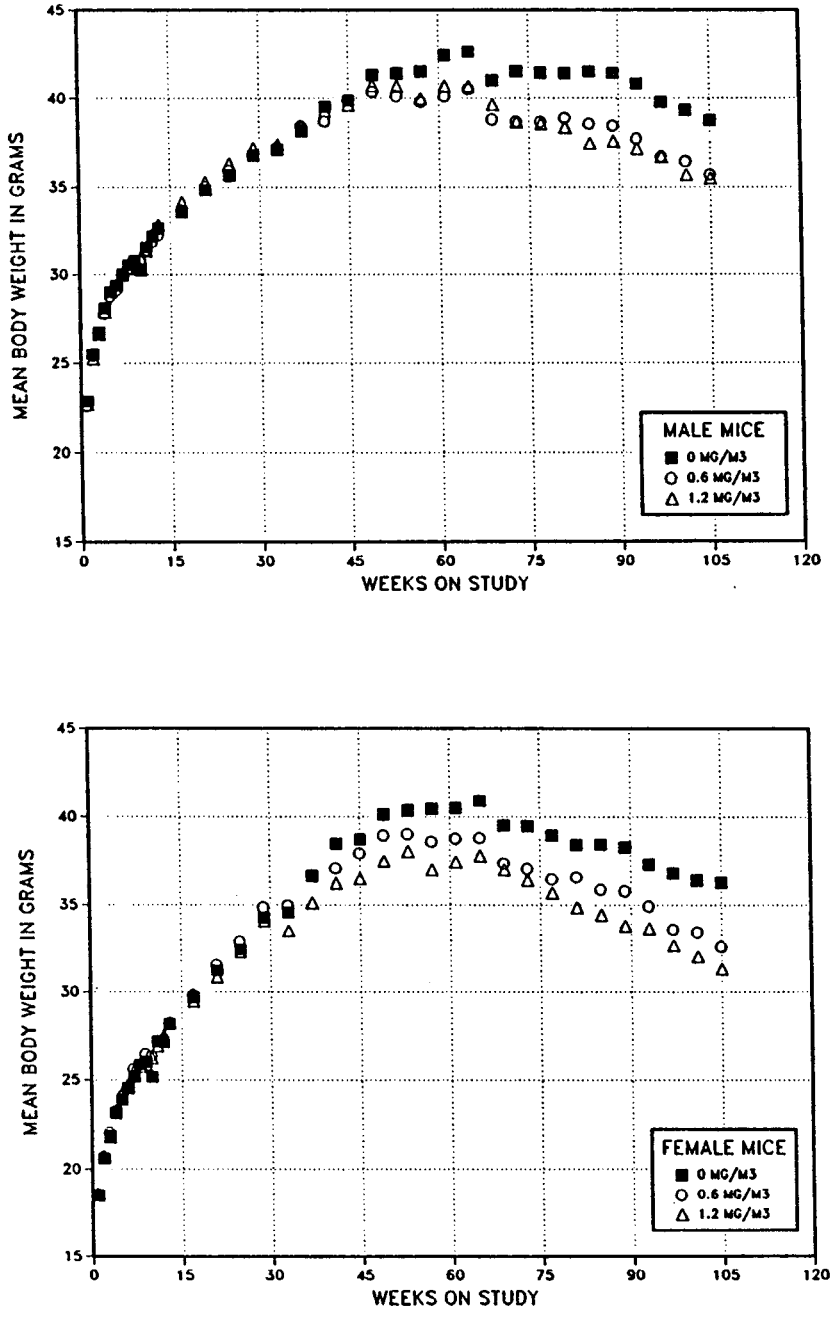


**FIGURE 5**
**Growth Curves for Mice Administered Nickel Subsulfide by Inhalation for 2 Years**

TABLE 26
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide

| Weeks on Study | 0 mg/m³ Av. Wt. (g) | 0 mg/m³ Number of Survivors | 0.6 mg/m³ Av. Wt. (g) | 0.6 mg/m³ Wt. (% of controls) | 0.6 mg/m³ Number of Survivors | 1.2 mg/m³ Av. Wt. (g) | 1.2 mg/m³ Wt. (% of controls) | 1.2 mg/m³ Number of Survivors |
|---|---|---|---|---|---|---|---|---|
| 1 | 22.9 | 80 | 22.6 | 99 | 80 | 22.7 | 99 | 80 |
| 2 | 25.5 | 80 | 25.4 | 100 | 80 | 25.2 | 99 | 80 |
| 3 | 26.7 | 80 | 26.6 | 100 | 80 | 26.6 | 100 | 80 |
| 4 | 28.1 | 80 | 27.8 | 99 | 79 | 27.9 | 99 | 80 |
| 5 | 29.0 | 80 | 28.8 | 99 | 79 | 29.1 | 100 | 80 |
| 6 | 29.4 | 80 | 29.1 | 99 | 78 | 29.4 | 100 | 80 |
| 7 | 30.1 | 80 | 30.0 | 100 | 78 | 30.0 | 100 | 80 |
| 8 | 30.6 | 80 | 30.3 | 99 | 78 | 30.3 | 99 | 80 |
| 9 | 30.8 | 80 | 30.7 | 100 | 78 | 30.8 | 100 | 80 |
| 10 | 30.3 | 80 | 30.8 | 102 | 78 | 31.0 | 102 | 80 |
| 11 | 31.6 | 79 | 31.4 | 99 | 78 | 31.4 | 99 | 80 |
| 12 | 32.2 | 79 | 31.9 | 99 | 78 | 32.4 | 101 | 80 |
| 13 | 32.7 | 79 | 32.3 | 99 | 78 | 32.9 | 101 | 80 |
| 17 | 33.6 | 79 | 33.7 | 100 | 78 | 34.1 | 102 | 80 |
| 21 | 34.8 | 79 | 35.0 | 101 | 78 | 35.3 | 101 | 79 |
| 25 | 35.7 | 79 | 35.9 | 101 | 77 | 36.3 | 102 | 78 |
| 29[a] | 36.8 | 70 | 36.8 | 100 | 67 | 37.2 | 101 | 68 |
| 33 | 37.1 | 69 | 37.2 | 100 | 67 | 37.4 | 101 | 68 |
| 37 | 38.2 | 69 | 38.4 | 101 | 66 | 38.4 | 101 | 67 |
| 41 | 39.5 | 69 | 38.7 | 98 | 66 | 39.3 | 100 | 67 |
| 45 | 39.9 | 69 | 39.9 | 100 | 66 | 39.6 | 99 | 67 |
| 49 | 41.3 | 68 | 40.4 | 98 | 66 | 40.7 | 99 | 66 |
| 53 | 41.4 | 68 | 40.1 | 97 | 65 | 40.7 | 98 | 66 |
| 57 | 41.5 | 68 | 39.8 | 96 | 65 | 40.0 | 96 | 63 |
| 61 | 42.4 | 67 | 40.1 | 95 | 64 | 40.7 | 96 | 62 |
| 65 | 42.6 | 66 | 40.5 | 95 | 64 | 40.7 | 96 | 61 |
| 69[a] | 41.0 | 55 | 38.8 | 95 | 51 | 39.7 | 97 | 48 |
| 73 | 41.5 | 53 | 38.7 | 93 | 50 | 38.7 | 93 | 47 |
| 77 | 41.4 | 50 | 38.7 | 94 | 46 | 38.6 | 93 | 45 |
| 81 | 41.4 | 45 | 38.9 | 94 | 42 | 38.4 | 93 | 44 |
| 85 | 41.5 | 38 | 38.6 | 93 | 36 | 37.5 | 90 | 43 |
| 89 | 41.4 | 37 | 38.5 | 93 | 35 | 37.6 | 91 | 41 |
| 93 | 40.8 | 34 | 37.7 | 92 | 33 | 37.2 | 91 | 38 |
| 97 | 39.8 | 33 | 36.7 | 92 | 30 | 36.7 | 92 | 31 |
| 101 | 39.3 | 28 | 36.5 | 93 | 28 | 35.7 | 91 | 30 |
| 105 | 38.8 | 26 | 35.7 | 92 | 25 | 35.5 | 92 | 26 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 29.2 | | 29.1 | 100 | | 29.2 | 100 | |
| 14-52 | 37.4 | | 37.3 | 100 | | 37.6 | 101 | |
| 53-105 | 41.1 | | 38.5 | 94 | | 38.4 | 93 | |

[a] Interim evaluations occurred during weeks 28 and 68.

TABLE 27
**Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide**

| Weeks on Study | 0 mg/m³ Av. Wt. (g) | 0 mg/m³ Number of Survivors | 0.6 mg/m³ Av. Wt. (g) | 0.6 mg/m³ Wt. (% of controls) | 0.6 mg/m³ Number of Survivors | 1.2 mg/m³ Av. Wt. (g) | 1.2 mg/m³ Wt. (% of controls) | 1.2 mg/m³ Number of Survivors |
|---|---|---|---|---|---|---|---|---|
| 1 | 18.5 | 80 | 18.6 | 101 | 80 | 18.6 | 101 | 80 |
| 2 | 20.6 | 80 | 20.7 | 101 | 80 | 20.8 | 101 | 80 |
| 3 | 21.8 | 80 | 22.0 | 101 | 80 | 21.8 | 100 | 80 |
| 4 | 23.1 | 80 | 23.2 | 100 | 80 | 23.3 | 101 | 80 |
| 5 | 23.9 | 80 | 24.1 | 101 | 80 | 24.3 | 102 | 80 |
| 6 | 24.5 | 80 | 24.5 | 100 | 80 | 24.7 | 101 | 80 |
| 7 | 25.2 | 80 | 25.6 | 102 | 80 | 25.5 | 101 | 80 |
| 8 | 25.9 | 80 | 25.9 | 100 | 80 | 25.7 | 99 | 80 |
| 9 | 26.0 | 78 | 26.5 | 102 | 80 | 25.9 | 100 | 80 |
| 10 | 25.2 | 78 | 26.3 | 104 | 80 | 26.3 | 104 | 80 |
| 11 | 27.2 | 78 | 27.2 | 100 | 80 | 26.9 | 99 | 80 |
| 12 | 27.2 | 78 | 27.3 | 100 | 80 | 27.5 | 101 | 79 |
| 13 | 28.2 | 78 | 28.2 | 100 | 80 | 28.3 | 100 | 79 |
| 17 | 29.7 | 78 | 29.8 | 100 | 79 | 29.5 | 99 | 79 |
| 21 | 31.2 | 78 | 31.6 | 101 | 78 | 30.9 | 99 | 79 |
| 25 | 32.4 | 78 | 32.9 | 102 | 78 | 32.3 | 100 | 79 |
| 29[a] | 34.3 | 68 | 34.9 | 102 | 68 | 34.1 | 99 | 69 |
| 33 | 34.6 | 68 | 35.0 | 101 | 67 | 33.6 | 97 | 69 |
| 37 | 36.7 | 68 | 36.7 | 100 | 67 | 35.1 | 96 | 68 |
| 41 | 38.5 | 68 | 37.1 | 96 | 67 | 36.3 | 94 | 68 |
| 45 | 38.7 | 66 | 37.9 | 98 | 67 | 36.5 | 94 | 68 |
| 49 | 40.2 | 66 | 38.9 | 97 | 67 | 37.5 | 93 | 68 |
| 53 | 40.4 | 66 | 39.0 | 97 | 67 | 38.0 | 94 | 67 |
| 57 | 40.5 | 65 | 38.6 | 95 | 67 | 37.0 | 91 | 67 |
| 61 | 40.5 | 64 | 38.7 | 96 | 66 | 37.5 | 93 | 67 |
| 65 | 40.9 | 64 | 38.8 | 95 | 65 | 37.8 | 92 | 66 |
| 69[a] | 39.5 | 54 | 37.3 | 94 | 55 | 37.0 | 94 | 56 |
| 73 | 39.5 | 53 | 37.0 | 94 | 55 | 36.4 | 92 | 54 |
| 77 | 39.0 | 53 | 36.5 | 94 | 53 | 35.7 | 92 | 54 |
| 81 | 38.4 | 50 | 36.6 | 95 | 50 | 34.8 | 91 | 53 |
| 85 | 38.4 | 50 | 35.9 | 94 | 50 | 34.4 | 90 | 49 |
| 89 | 38.3 | 47 | 35.8 | 94 | 49 | 33.8 | 88 | 48 |
| 93 | 37.3 | 46 | 34.9 | 94 | 46 | 33.7 | 90 | 45 |
| 97 | 36.8 | 44 | 33.6 | 91 | 41 | 32.7 | 89 | 43 |
| 101 | 36.4 | 38 | 33.4 | 92 | 39 | 32.1 | 88 | 41 |
| 105 | 36.3 | 36 | 32.6 | 90 | 34 | 31.3 | 86 | 40 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 24.4 | | 24.6 | 101 | | 24.6 | 101 | |
| 14-52 | 35.1 | | 35.0 | 100 | | 34.0 | 97 | |
| 53-105 | 38.7 | | 36.3 | 94 | | 35.2 | 91 | |

[a] Interim evaluations occurred during weeks 29 and 69.

### *Hematology*

Hematology results are presented in Table G4. In 1.2 mg/m$^3$ females, the segmented neutrophil count was greater than in the controls, and the monocyte count was mildly greater than in the controls. Increased neutrophil counts can occur due to altered granulopoiesis and/or rate of release from the bone marrow; neutrophils redistributed between the marginal and the circulating pools, or increased intravascular neutrophil life span. Increases in monocyte numbers can accompany increases in neutrophils, particularly if the increases are a result of an inflammatory process. The lymphocyte count in 1.2 mg/m$^3$ females was greater than that in the controls. Increased lymphocyte numbers may reflect stimulation of lymphopoiesis or mechanisms involving altered lymphocyte migration or homing, tissue migration, and recirculation. The total leukocyte count in 1.2 mg/m$^3$ females was greater than that in the controls, and this difference reflected the differences in neutrophil, lymphocyte, and monocyte numbers.

The hematocrit value in 1.2 mg/m$^3$ females was mildly greater than that of the controls; this difference could be consistent with dehydration (relative erythrocytosis) or with increased erythropoietin production as a result of tissue hypoxia (secondary erythrocytosis).

### *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, nose, and bronchial lymph node. 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:* Absolute and relative lung weights of exposed males (except 0.6 mg/m$^3$ group at 7 months) and females were significantly greater than those of the controls at 7 and 15 months (Tables F7 and F8). The incidences of alveolar/bronchiolar carcinoma in females and the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in males and females occurred with a significant negative trend at 2 years (Tables 28, C3, and D3). The incidence of alveolar/bronchiolar carcinoma in 0.6 mg/m$^3$ females and the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 0.6 mg/m$^3$ males and 0.6 and 1.2 mg/m$^3$ females were significantly less than those of the controls. However, the incidences of alveolar/bronchiolar carcinoma and of alveolar/bronchiolar adenoma or carcinoma (combined) in female controls exceeded the ranges in historical controls from inhalation studies (Tables 28 and D4). The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in male controls was within the historical control range from inhalation studies (Tables 28 and C4).

At 7 months, the incidences of chronic active inflammation in 1.2 mg/m$^3$ males and females, of alveolar macrophage hyperplasia and proteinosis in 0.6 and 1.2 mg/m$^3$ males and females, and of interstitial infiltration in 0.6 mg/m$^3$ males and females were significantly greater than those of the controls (Tables 28, C5, and D5). At 15 months, the incidences of chronic active inflammation, bronchialization (except in 0.6 mg/m$^3$ females), macrophage hyperplasia, proteinosis, and interstitial infiltration in all exposed groups were significantly greater than those of the controls. Except for fibrosis in 0.6 mg/m$^3$ males, the incidences of fibrosis, chronic active inflammation, bronchialization, macrophage hyperplasia, proteinosis, and interstitial infiltration in exposed groups were significantly greater than those of the controls at 2 years. Chronic active inflammation, macrophage hyperplasia, proteinosis, and bronchialization were more severe in 1.2 mg/m$^3$ mice than in 0.6 mg/m$^3$ mice.

Chronic active inflammation consisted of multifocal to locally extensive accumulations of inflammatory cells within alveolar lumens. Typically, these were macrophages and lymphocytes; rarely, there were admixed neutrophils, cellular debris, and/or brightly eosinophilic, rod-shaped crystalline material. Macrophage hyperplasia consisted of a widespread increase in intra-alveolar macrophages, the number of which varied, typically with abundant eosinophilic granular to vacuolated cytoplasm (Plate 5). Most probably, these macrophages were from the intravascular pool of circulating monocytes. Proteinosis consisted of accumulations of varying amounts of eosinophilic granular to hyaline material within alveolar lumens. Interstitial infiltrating cells were lymphocytes with occasional macrophages in alveolar septa adjacent to a focus of inflammation and/or an increased number of lymphocytes in alveolar septa adjacent to peribronchiolar lymphoid tissue. Bronchialization in this study consisted of multiple foci where cuboidal cells extended from terminal bronchioles into adjacent alveoli. This hyperplastic change, unlike focal alveolar epithelial hyperplasia, is not considered a part of the morphologic continuum toward neoplasia and therefore was not termed alveolar epithelial hyperplasia. Because these cuboidal cells were not observed to have cilia and no attempts were made to determine their cell of origin, the term bronchialization in this study corresponds to the overall light microscopic appearance only. Fibrosis, a minimal change considered secondary to inflammation, consisted of foci of loosely arranged fibroblasts within the lung parenchyma.

TABLE 28
**Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| **7-Month Interim Evaluation** | | | |
| Lung[a] | 5 | 5 | 5 |
| Inflammation, Chronic Active[b] | 0 | 3 (1.3)[c] | 5** (1.6) |
| Alveolus, Hyperplasia, Macrophage | 0 | 5** (1.0) | 5** (1.4) |
| Alveolus, Proteinosis | 0 | 5** (1.0) | 5** (1.6) |
| Interstitium, Infiltration Cellular | 0 | 5** (1.0) | 3 (1.0) |
| **15-Month Interim Evaluation** | | | |
| Lung | 5 | 5 | 5 |
| Inflammation, Chronic Active | 0 | 5** (1.2) | 5** (1.8) |
| Bronchialization | 0 | 4* (1.5) | 5** (2.6) |
| Alveolus, Hyperplasia, Macrophage | 0 | 5** (1.4) | 5** (2.2) |
| Alveolus, Proteinosis | 0 | 5** (3.4) | 5** (3.0) |
| Interstitium, Infiltration Cellular | 0 | 4* (1.8) | 5** (1.4) |
| **2-Year Study** | | | |
| Lung | 61 | 59 | 58 |
| Fibrosis | 0 | 3 (1.0) | 16** (1.0) |
| Inflammation, Chronic Active | 1 (1.0) | 52** (1.7) | 53** (2.0) |
| Bronchialization | 3 (2.7) | 53** (1.8) | 54** (2.1) |
| Alveolus, Hyperplasia, Macrophage | 6 (2.7) | 57** (2.2) | 58** (2.5) |
| Alveolus, Proteinosis | 0 | 57** (2.9) | 57** (3.0) |
| Interstitium, Infiltration Cellular | 10 (1.0) | 55** (1.7) | 55** (1.8) |
| Alveolar/bronchiolar Adenoma | 6 | 3 | 2 |
| Alveolar/bronchiolar Carcinoma | 7 | 2 | 4 |
| Alveolar/Bronchiolar Adenoma or Carcinoma[d] | | | |
| Overall rate[e] | 13/61 (21%) | 5/59 (8%) | 6/58 (10%) |
| Adjusted rate[f] | 40.7% | 18.5% | 21.4% |
| Terminal rate[g] | 8/26 (31%) | 4/25 (16%) | 4/25 (16%) |
| First incidence (days) | 552 | 661 | 661 |
| Logistic regression test[h] | P=0.035N | P=0.038N | P=0.058N |
| **Female** | | | |
| **7-Month Interim Evaluation** | | | |
| Lung | 5 | 5 | 5 |
| Inflammation, Chronic Active | 0 | 2 (1.0) | 5** (1.2) |
| Alveolus, Hyperplasia, Macrophage | 1 (1.0) | 5* (1.0) | 5* (1.2) |
| Alveolus, Proteinosis | 0 | 4* (1.0) | 5** (1.4) |
| Interstitium, Infiltration Cellular | 1 (1.0) | 5* (1.4) | 4 (1.5) |

(continued)

TABLE 28
**Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Female** (continued) | | | |
| **15-Month Interim Evaluation** | | | |
| Lung | 5 | 5 | 5 |
| Inflammation, Chronic Active | 0 | 4* (2.5) | 5** (1.4) |
| Bronchialization | 0 | 2 (1.0) | 5** (1.6) |
| Alveolus, Hyperplasia, Macrophage | 0 | 5** (1.6) | 5** (2.8) |
| Alveolus, Proteinosis | 0 | 5** (2.8) | 5** (3.6) |
| Interstitium, Infiltration Cellular | 1 (1.0) | 5* (2.2) | 5* (1.8) |
| **2-Year Study** | | | |
| Lung | 58 | 59 | 60 |
| Fibrosis | 0 | 7** (1.0) | 17** (1.1) |
| Inflammation, Chronic Active | 1 (2.0) | 46** (1.7) | 58** (2.0) |
| Bronchialization | 3 (2.3) | 53** (1.8) | 58** (2.1) |
| Alveolus, Hyperplasia, Macrophage | 5 (1.8) | 57** (2.6) | 60** (2.9) |
| Alveolus, Proteinosis | 0 | 54** (2.8) | 59** (3.4) |
| Interstitium, Infiltration Cellular | 19 (1.2) | 53** (2.6) | 58** (2.2) |
| Alveolar/bronchiolar Adenoma | 3 | 1 | 1 |
| Alveolar/bronchiolar Carcinoma | 7 | 1 | 2 |
| Alveolar/bronchiolar Adenoma or Carcinoma[i] | | | |
| Overall rate | 9/58 (16%) | 2/59 (3%) | 3/60 (5%) |
| Adjusted rate | 24.1% | 4.8% | 7.9% |
| Terminal rate | 8/36 (22%) | 1/34 (3%) | 3/38 (8%) |
| First incidence (days) | 683 | 552 | 733 (T) |
| Logistic regression test | P=0.027N | P=0.028N | P=0.050N |

(T)Terminal sacrifice
* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[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
[d] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 205/952 (21.5% ± 8.0%); range 10%-42%. Feed studies: 249/1,319 (18.9% ± 7.6%); range 4%-32%
[e] Number of animals with neoplasm per number of animals with organ examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence in animals surviving until the end of the study
[h] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[i] Historical incidence for 2-year NTP inhalation studies: 97/944 (10.3% ± 3.7%); range 0%-16%. Feed studies: 102/1,319 (7.7% ± 5.3%); range 2%-26%

*Nose:* The incidences of atrophy of the olfactory epithelium in 1.2 mg/m$^3$ males at 7 and 15 months and in 0.6 and 1.2 mg/m$^3$ males and females at 2 years were significantly greater than those of the controls (Tables 29, C5, and D5). The incidences of acute inflammation of the nose in 0.6 and 1.2 mg/m$^3$ females were significantly greater than that of the controls at 2 years. At 2 years, the incidences of degeneration of olfactory epithelium in exposed females were significantly less than that of the controls.

Acute inflammation consisted of focal aggregates of neutrophils, sometimes admixed with cellular debris, on or adjacent to the surface respiratory epithelium.

Atrophy of olfactory epithelium was a minimal focal decrease in the thickness of olfactory epithelial cells (Plate 6). Degeneration, a normal age-related lesion in B6C3F$_1$ mice, was a minimal accumulation of droplets of brightly eosinophilic homogenous material within the cytoplasm of olfactory epithelial cells.

TABLE 29
**Incidences of Nonneoplastic Lesions of the Nose in Mice in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | | 0.6 mg/m$^3$ | | 1.2 mg/m$^3$ | |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| **7-Month Interim Evaluation** | | | | | | |
| Nose[a] | 5 | | 5 | | 5 | |
| Olfactory Epithelium, Atrophy[b] | 0 | | 1 | (1.0)[c] | 4* | (1.0) |
| Olfactory Epithelium, Degeneration | 1 | (1.0) | 0 | | 0 | |
| **15-Month Interim Evaluation** | | | | | | |
| Nose | 5 | | 5 | | 5 | |
| Olfactory Epithelium, Atrophy | 0 | | 3 | (1.0) | 4* | (1.0) |
| **2-Year Study** | | | | | | |
| Nose | 61 | | 59 | | 59 | |
| Inflammation, Acute | 0 | | 0 | | 3 | (2.0) |
| Olfactory Epithelium, Atrophy | 1 | (1.0) | 27** | (1.1) | 55** | (1.2) |
| Olfactory Epithelium, Degeneration | 3 | (1.0) | 8 | (1.0) | 6 | (1.0) |
| **Female** | | | | | | |
| **7-Month Interim Evaluation** | | | | | | |
| Nose | 5 | | 5 | | 5 | |
| Olfactory Epithelium, Atrophy | 0 | | 0 | | 1 | (1.0) |
| Olfactory Epithelium, Degeneration | 4 | (1.0) | 0* | | 0* | |
| **15-Month Interim Evaluation** | | | | | | |
| Nose | 5 | | 5 | | 5 | |
| Olfactory Epithelium, Degeneration | 1 | (2.0) | 0 | | 0 | |
| **2-Year Study** | | | | | | |
| Nose | 58 | | 59 | | 60 | |
| Inflammation, Acute | 0 | | 11** | (1.8) | 14** | (1.7) |
| Olfactory Epithelium, Atrophy | 1 | (1.0) | 11** | (1.0) | 41** | (1.1) |
| Olfactory Epithelium, Degeneration | 27 | (1.1) | 3** | (1.0) | 12** | (1.0) |

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[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

*Bronchial Lymph Node:* The incidences of lymphoid hyperplasia in 1.2 mg/m$^3$ males at 15 months, in 0.6 and 1.2 mg/m$^3$ females at 15 months, and in 0.6 and 1.2 mg/m$^3$ males and females at 2 years were significantly greater than those of the controls (Tables 30, C5, and D5). The incidences of macrophage hyperplasia in 1.2 mg/m$^3$ males at 7 and 15 months, in 0.6 and 1.2 mg/m$^3$ females at 15 months, and in 0.6 and 1.2 mg/m$^3$ males and females at 2 years were significantly greater than those of the controls.

Lymphoid hyperplasia was characterized by an increased number of cortical lymphocytes resulting in an increase in the size and cellularity of the lymph node. The lymphocytes were at different stages of differentiation and the overall architecture of the lymph node was maintained. Macrophage hyperplasia consisted of scattered aggregates of macrophages with abundant pale foamy cytoplasm typically within the medulla of the lymph node. Increased macrophages in the bronchial lymph node were probably secondary to inflammation in the lung.

**TABLE 30**
**Incidences of Nonneoplastic Lesions of the Bronchial Lymph Node in Mice in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ |
|---|---|---|---|
| **Male** | | | |
| **7-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial[a] | 3 | 4 | 5 |
| Hyperplasia, Lymphoid[b] | 0 | 2 (1.0)[c] | 3 (1.0) |
| Hyperplasia, Macrophage | 0 | 2 (1.0) | 5* (1.0) |
| **15-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial | 4 | 3 | 5 |
| Hyperplasia, Lymphoid | 0 | 3 (1.7) | 5** (2.2) |
| Hyperplasia, Macrophage | 0 | 3 (1.0) | 4* (1.3) |
| **2-Year Study** | | | |
| Lymph Node, Bronchial | 40 | 53 | 54 |
| Hyperplasia, Lymphoid | 4 (2.3) | 40** (2.1) | 49** (2.2) |
| Hyperplasia, Macrophage | 1 (3.0) | 47** (1.7) | 50** (1.8) |
| **Female** | | | |
| **7-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial | 5 | 4 | 5 |
| Hyperplasia, Lymphoid | 0 | 1 (1.0) | 0 |
| Hyperplasia, Macrophage | 0 | 1 (1.0) | 1 (1.0) |
| **15-Month Interim Evaluation** | | | |
| Lymph Node, Bronchial | 5 | 5 | 5 |
| Hyperplasia, Lymphoid | 0 | 5** (2.6) | 5** (2.4) |
| Hyperplasia, Macrophage | 0 | 5** (1.2) | 5** (1.0) |
| **2-Year Study** | | | |
| Lymph Node, Bronchial | 50 | 57 | 59 |
| Hyperplasia, Lymphoid | 10 (1.9) | 46** (2.2) | 52** (2.4) |
| Hyperplasia, Macrophage | 0 | 44** (1.5) | 47** (1.8) |

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with bronchial lymph node 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

### *Tissue Burden Analyses*

Nickel concentrations in the lung of exposed groups of mice were significantly greater than those of the controls at 7 and 15 months, and these concentrations increased with increasing exposure concentration and with time (Tables 31 and I4). In these groups, absolute lung weights of 0.6 and 1.2 mg/m$^3$ males and females at 7 and 15 months were significantly greater than those of the controls. Nickel concentrations in the kidney of 0.6 mg/m$^3$ males and 1.2 mg/m$^3$ males and females were significantly greater than those of the controls at 15 months (Table I5).

TABLE 31
**Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ |
|---|---|---|---|
| n | 5 | 5 | 5 |
| **Male** | | | |
| **7-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 0.219 ± 0.015[b] | 0.311 ± 0.016** | 0.406 ± 0.018** |
| μg Ni/lung | —[c] | 3 ± 0.1** | 4 ± 0.3** |
| μg Ni/g lung | — | 10 ± 0.2** | 11 ± 1.2* |
| μg Ni/g control lung | — | 15 ± 0.5** | 20 ± 1.6** |
| **15-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 0.184 ± 0.009 | 0.354 ± 0.017** | 0.410 ± 0.017** |
| μg Ni/lung | — | 4 ± 0.3** | 8 ± 0.7** |
| μg Ni/g lung | — | 12 ± 0.7** | 20 ± 0.9** |
| μg Ni/g control lung | — | 24 ± 1.9** | 44 ± 4.0** |
| **Female** | | | |
| **7-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 0.247 ± 0.026 | 0.325 ± 0.020* | 0.358 ± 0.012** |
| μg Ni/lung | — | 3 ± 0.1** | 5 ± 0.2** |
| μg Ni/g lung | — | 10 ± 0.6** | 14 ± 1.0** |
| μg Ni/g control lung | — | 13 ± 0.4** | 19 ± 1.0** |
| **15-Month Interim Evaluation** | | | |
| Absolute lung wt (g) | 0.178 ± 0.011 | 0.346 ± 0.019** | 0.414 ± 0.020** |
| μg Ni/lung | — | 5 ± 0.9** | 11 ± 1.3** |
| μg Ni/g lung | — | 15 ± 1.8** | 26 ± 2.2** |
| μg Ni/g control lung | — | 30 ± 4.9** | 61 ± 7.4** |

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Dunn's or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] n=4
[c] Results were below 0.0037 μg Ni (the limit of detection) for the 7-month interim evaluation and below 0.0034 μg Ni for the 15-month interim evaluation.

## GENETIC TOXICOLOGY

Nickel subsulfide was tested for induction of gene mutations in five strains of *Salmonella typhimurium* (Table E1). Results of these tests were considered to be equivocal overall due to the response seen in strain TA100. Varied indications of mutagenic activity were observed with and without S9 in TA100, with the most consistent demonstration of mutagenicity noted in the presence of 10% rat liver S9. No mutagenic responses were observed in strains TA97, TA98, TA102, or TA1535, with or without S9. Nickel subsulfide was also tested for induction of micronuclei in normochromatic erythrocytes of male and female mice exposed by inhalation for 13 weeks. Nickel subsulfide did not induce an increase in the frequency of micronucleated normochromatic erythrocytes in peripheral blood samples (Table E2).

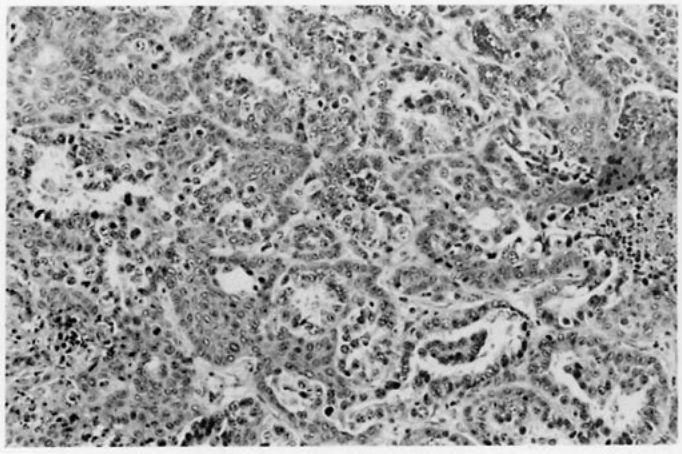

**PLATE 1**
Squamous differentiation within an alveolar/bronchiolar carcinoma in the lung of a male F344/N rat exposed to 1 mg nickel subsulfide/$m^3$ by inhalation for 2 years. H&E; 120×

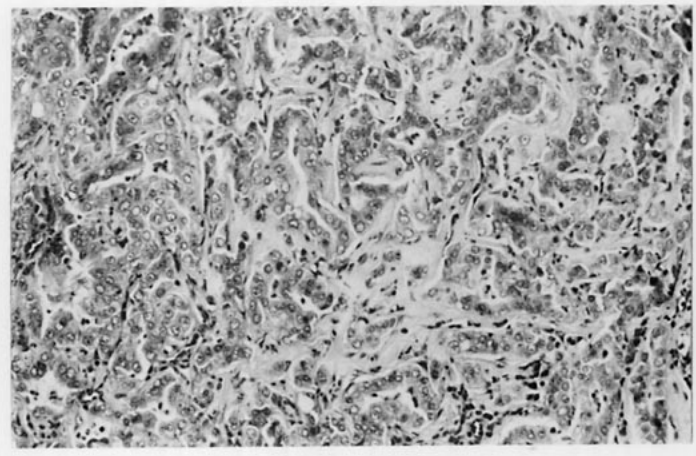

**PLATE 2**
Connective (scirrhous) tissue within an alveolar/bronchiolar carcinoma in the lung of a male F344/N rat exposed to 0.15 mg nickel subsulfide/$m^3$ by inhalation for 2 years. H&E; 120×

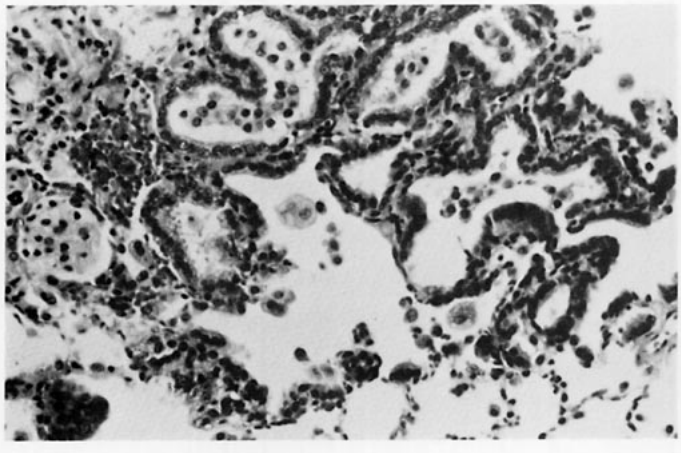

**PLATE 3**
Focal alveolar epithelial hyperplasia in the lung of a male F344/N rat exposed to 0.15 mg nickel subsulfide/$m^3$ by inhalation for 2 years. H&E; 180×

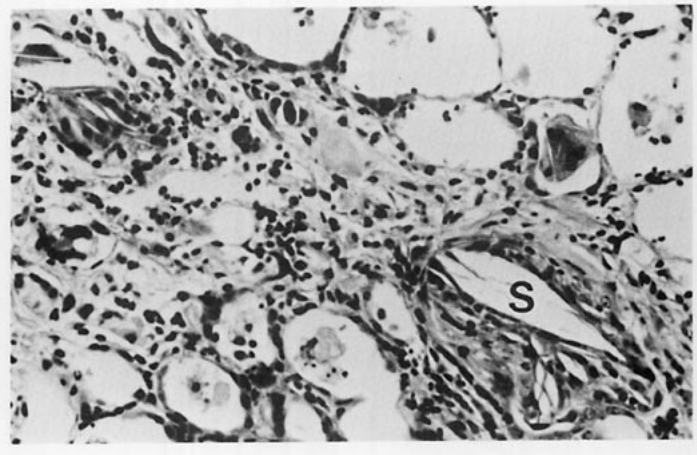


**PLATE 4**
Fibrosis and chronic active inflammation in the lung of a male F344/N rat exposed to 0.15 mg nickel subsulfide/$m^3$ by inhalation for 2 years. Connective tissue with slit-like spaces (S) that may have contained cholesterol or phospholipid. H&E; 180×

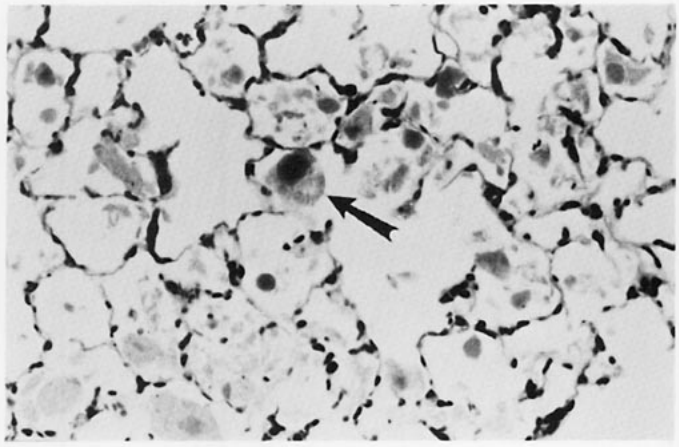

**PLATE 5**
Protein and macrophages (arrow) in alveolar spaces in the lung of a male B6C3F$_1$ mouse exposed to 1.2 mg nickel subsulfide/m$^3$ by inhalation for 2 years. H&E; 215×

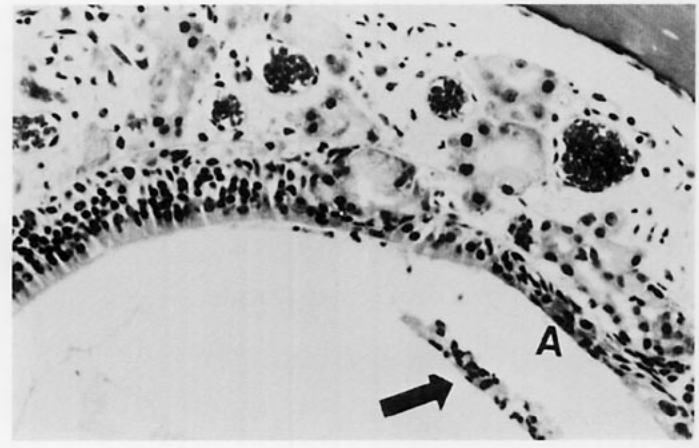


**PLATE 6**
Atrophy of olfactory epithelium (A) in the nose of a male B6C3F$_1$ mouse exposed to 1.2 mg nickel subsulfide/m$^3$ by inhalation for 2 years. Note inflammatory exudate (arrow) within the lumen. H&E; 215×

# DISCUSSION AND CONCLUSIONS

Workplace exposure to nickel subsulfide can occur during the unloading and crushing of nickel matte, and during roasting, sintering, calcining, and smelting operations (Doll *et al.*, 1990). These NTP studies were performed to determine the toxicologic and carcinogenic properties of nickel subsulfide in rats and mice exposed by inhalation.

In the 16-day studies [0.6 to 10 mg/m$^3$ (equivalent to 0.44 to 7.33 mg nickel/m$^3$)], one male rat and all male and female mice exposed to 10 mg nickel subsulfide/m$^3$ died before the end of the studies; these deaths were attributed to respiratory toxicity. In the 13-week studies, where the highest exposure concentration was 2.5 mg nickel subsulfide/m$^3$ (1.8 mg nickel/m$^3$), there were no chemical-related deaths. In the 16-day and 13-week studies, general indications of respiratory toxicity included lung weights greater than those of the controls and incidences of inflammation, hyperplasia, and/or fibrosis in the lungs, atrophy of the olfactory epithelium, and lymphoid hyperplasia in the respiratory tract lymph nodes that were greater than those in the controls. The biochemical indices for lung toxicity (as measured in lung lavage fluid) paralleled the toxicity identified by histopathologic analysis of the lung tissue (Benson *et al.*, 1989), and increased numbers of macrophages and neutrophils within lavage samples were consistent with the pulmonary chronic active inflammation.

In the companion 16-day and 13-week nickel compound studies, nickel sulfate hexahydrate was more toxic and nickel oxide was less toxic than nickel subsulfide (Tables 32 and 33). The lung and nasal toxicity reflects the relative solubility of the nickel compounds in water and biological fluids, with the most soluble nickel compound (nickel sulfate hexahydrate) being the most toxic. The soluble nickel compounds may be more toxic than the insoluble nickel compounds because the nickel ions can diffuse across the cell membrane and interact with cytoplasmic proteins, thereby causing toxicity. Alternatively, the water-insoluble nickel compounds may be phagocytized and may not cause as extensive damage to cytoplasmic components of the alveolar/bronchiolar epithelium (Lee *et al.*, 1993; Costa *et al.*, 1994).

The spectrum of inflammatory lesions in the lungs of rats and mice after 13 weeks of exposure to nickel subsulfide was similar to that observed with other particles including nickel sulfate hexahydrate, nickel oxide, gallium arsenide (NTP, unpublished data), gallium oxide (NTP, unpublished data), and cadmium oxide (NTP, 1995). Lymphoid hyperplasia with or without inflammation was present in the respiratory tract lymph nodes of rats and mice from all of these studies. Nickel oxide pigment granules were also present in the lung and respiratory tract lymph nodes; although pigment granules were not present in the lymph nodes of animals from the nickel sulfate hexahydrate, nickel subsulfide, or cadmium oxide studies, the morphologic appearance of the hyperplasia in the paracortical region of the lymph nodes was otherwise generally similar in each study.

In nickel subsulfide immunotoxicity studies, a decrease in cell-mediated immunity occurred in mice exposed to 2.5 mg/m$^3$ for 13 weeks, although there was no evidence for suppression of the humoral immune response (Haley *et al.*, 1990). No significant effects of nickel subsulfide on sperm morphology or vaginal cytology occurred in rats or mice.

The highest exposure concentrations for these 2-year studies were limited to 1 mg/m$^3$ for rats and 1.2 mg/m$^3$ for mice because of increased lung weights and incidences and severity of inflammatory lesions in the lung at the higher exposure concentrations in the 13-week studies. The nickel compound exposure concentrations for the 16-day, 13-week, and 2-year nickel studies and their nickel equivalents are presented in Table 34.

In the 2-year nickel subsulfide studies, there were no exposure-related effects on survival. Body weights

were reduced in 1 mg/m$^3$ male and female rats and in 0.6 and 1.2 mg/m$^3$ male and female mice. Respiratory toxicity was manifested by clinical findings of respiratory stress (labored breathing patterns compared to controls), lung weights greater than those of the controls, and increased incidences of lesions in the lungs of rats and mice including inflammation, hyperplasia, and/or fibrosis, and atrophy of the olfactory epithelium.

Nickel subsulfide exposure caused lung neoplasms in male and female rats. This was considered clear evidence of a carcinogenic response in rats because there were exposure-related increases in the incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined) in males and of alveolar/bronchiolar carcinoma and adenoma or carcinoma (combined) in females. The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in females exceeded the historical control range for this neoplasm in NTP inhalation studies.

The level of nickel in the lung was measured at various time points in the 2-year studies (Table 32), and this measurement represents the difference between the amount of nickel deposited and cleared over time. In the 2-year study of nickel oxide, there was approximately 300 to 1,100 $\mu$g nickel/g lung at 15 months; in the 2-year nickel subsulfide study, there was 3 to 7 $\mu$g nickel/g lung. Thus, the amount of nickel in the lung (as measured in these studies), does not predict or parallel the lung tumor response. The type of nickel compound is important in the eventual carcinogenic response, and under the conditions of these studies, the nickel compound that was more rapidly cleared from the lungs (nickel subsulfide) gave a stronger carcinogenic response than the nickel compound retained in the lungs (nickel oxide).

The pulmonary and lung neoplasm responses observed in the nickel oxide and nickel subsulfide studies were chemically related; these responses occurred at exposure concentrations of 1.25 and 2.5 mg/m$^3$ nickel oxide and 0.15 and 1 mg/m$^3$ nickel subsulfide. There is no evidence for particle overload; nickel subsulfide levels at 15 months remained below 30 $\mu$g nickel/g lung, and while lung nickel levels increased in the nickel oxide studies to 1,000 $\mu$g/g lung, the levels approached steady state. In contrast, rat carcinogenicity studies with other relatively nontoxic particles (i.e., titanium dioxide, talc, or chromium dioxide) required higher aerosol concentrations (10 mg/m$^3$ or greater) to produce a lung neoplasm response. For example, the carcinogenic response in the rat lung reported in the NTP talc studies (NTP, 1993) was seen at 18 mg/m$^3$; and at this exposure concentration, approximately 25 mg talc/g lung was recorded at 18 months and 2 years. Similarly, in the titanium dioxide inhalation studies in rats (Lee *et al.*, 1985), a lung neoplasm response was observed only at an exposure level of 250 mg/m$^3$, suggesting that the response may be related to accumulation of nontoxic particles.

Comparisons could be made of the types of lung neoplasms observed after inhalation exposure to various chemicals at various levels of concentration. For example, relatively low levels of exposure to nickel (NTP, 1996a,b) or cadmium (NTP, 1995) produced neoplastic responses in rats. Intermediate exposure levels to diesel exhaust (3.5 to 7 mg/m$^3$; Mauderly *et al.*, 1987; Mauderly, 1994) and talc (18 mg/m$^3$; NTP, 1993) produced carcinogenic effects in the lungs of rats. Higher exposure concentrations of antimony trioxide (45 mg/m$^3$; Groth *et al.*, 1986) and titanium dioxide (250 mg/m$^3$; Lee *et al.*, 1988) are required to produce similar effects in rats. Comparisons could also be made of the histopathologic nature of lung neoplasms and of the molecular changes involved in the response.

Some generalities can be made about the comparative lung pathology in rats and mice after 2 years of exposure to nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate. Incidence, appearance, and severity of spontaneous lung lesions in control rats were similar for all three compounds; lung lesions in control mice were similar for all three compounds. The alveolar/bronchiolar neoplasms in rats exposed to nickel sulfate hexahydrate and of mice exposed to each of the three nickel compounds occurred with no greater incidence than the controls and were typical of spontaneously occurring neoplasms. Although the difference in the proliferative responses (focal alveolar epithelial hyperplasia and alveolar/bronchiolar neoplasms) between rats and mice were not marked, all three studies were similar in that mice were less susceptible to proliferative and fibrotic lung lesions than rats exposed to the same compound. Five of

the alveolar/bronchiolar carcinomas in rats exposed to nickel oxide and four of the alveolar/bronchiolar carcinomas and two of the alveolar/bronchiolar adenomas in rats exposed to nickel subsulfide had marked squamous differentiation. Such proliferative squamous differentiation is not characteristic of spontaneous alveolar/bronchiolar neoplasms in rats, but has been observed in rats exposed to inhaled particulates such as talc (NTP, 1993).

The increases in the incidences of proliferative lesions and severity of inflammation in the lungs of rats exposed to nickel subsulfide or nickel oxide were more severe than those in rats exposed to nickel sulfate hexahydrate. The lungs of rats exposed to nickel subsulfide and nickel oxide had significant parenchymal damage secondary to inflammation. The lungs of rats exposed to 1 mg nickel subsulfide/$m^3$ and 2.5 mg nickel oxide/$m^3$ had abundant protein accumulations and variable numbers of foamy macrophages in alveoli and multifocally extensive fibrosis. Foci of necrotic cellular debris, regenerative alveolar epithelial proliferation, and collapse or filling of air spaces were somewhat more prominent in rats exposed to nickel subsulfide than in rats exposed to nickel oxide. Exposure-related pigment in the lungs and bronchial lymph nodes was observed only in rats and mice exposed to nickel oxide.

With the exception of the pigment observed only in the nickel oxide study, the nonneoplastic lesions in the lungs of exposed mice were similar in all three nickel compound studies. The components of the inflammatory reaction (intra-alveolar protein and macrophages, mononuclear inflammatory cells around vessels, and multifocal intra-alveolar aggregates of inflammatory cells) were similar in exposed mice in all three studies. Inflammatory foci with neutrophils and necrotic cell debris were relatively common in mice exposed to nickel sulfate hexahydrate, while inflammatory foci in mice exposed to nickel oxide and nickel subsulfide were predominantly mononuclear cells with little evidence of necrotic cell debris.

The inflammatory alterations of proteinosis, macrophage hyperplasia, and fibrosis of the lung in rats exposed to nickel subsulfide and nickel oxide were similar to those reported after chronic inhalation exposure to talc (NTP, 1993). In the talc study, it was concluded that these lesions resulted in impaired pulmonary function. Rats in the lifetime talc study, like rats in the current 2-year studies of nickel subsulfide and nickel oxide, had significantly increased incidences of adrenal medullary hyperplasia and pheochromocytoma. Pheochromocytomas are relatively common spontaneous neoplasms in chronic studies with F344 rats, especially in males. The cells of the adrenal medulla secrete the catecholamines, epinephrine and norepinephrine, and are derived from the same embryonic population as sympathetic ganglia cells. Proliferation of the catecholamine-synthesizing cells of the adrenal medulla in studies in which treated rats have marked inflammatory alterations in the lungs suggests that these two findings might be related. Factors that could act as stimuli for adrenal medullary proliferative lesions include an increased demand for catecholamines to overcome increased pulmonary vascular resistance or impaired pulmonary function, and cytokines released by inflammatory cells in the lungs.

Nasopharyngeal carcinoma in humans has been attributed to nickel exposure. The preponderance of these sinonasal neoplasms in humans have been classified as anaplastic, undifferentiated, or squamous cell carcinoma (Sunderman *et al.*, 1989). In the present rodent studies, the olfactory epithelium, rather than the respiratory or squamous mucosa, was the target site for chemical-related toxicity. Although the atrophic changes were present in the olfactory epithelium of rats and mice in the 13-week and 2-year studies of nickel subsulfide and nickel sulfate hexahydrate, the nasal mucosa was not affected in the nickel oxide study. In the nickel subsulfide studies, there was no evidence for nasal sinus neoplasms in either rats or mice. Furthermore, after 2 years, there was no evidence of a chemical-related increase in the incidences of proliferative lesions in the nasal cavity of rats or mice exposed to any of the three nickel compounds tested.

In this 2-year rat study, there were exposure-related increased incidences of benign and malignant pheochromocytomas in male rats and benign pheochromocytoma in female rats. There were also increased incidences of benign or malignant pheochromocytoma (combined) of the adrenal medulla in male and female rats in the talc study (NTP, 1993) and of benign or malignant pheochromocytoma in male and

of benign pheochromocytoma in female rats exposed to nickel oxide. However, similar increases were not observed in rats exposed to nickel sulfate hexahydrate or to other particulates including antimony trioxide or trisulfide (Groth *et al.*, 1986) and titanium dioxide (Lee *et al.*, 1988). Chemical-related increases in the incidences of pheochromocytoma have also been reported in rats exposed by inhalation to bromoethane (NTP, 1990) and orally to 2-mercaptobenzothiazole (NTP, 1988) and reserpine (NCI, 1982).

Other studies have shown that nickel subsulfide causes tumors after local injection (Table 3) and demonstrated the carcinogenic potential of this chemical. A chemical-related increase in lung tumors in 1 mg/m$^3$ rats was observed in the one previous nickel subsulfide inhalation study (Ottolenghi *et al.*, 1975). Multiple intratracheal instillations of nickel subsulfide induced malignant lung tumors in female Wistar rats (Pott *et al.*, 1987) and in female Fisher 344 rats (Yarita and Nettesheim, 1978), while intratracheally instilled nickel subsulfide did not induce lung tumors in Syrian hamsters (Muhle *et al.*, 1992).

Previous studies of nickel pulmonary carcinogenesis have not shown evidence of carcinogenicity in mice. Hueper (1958) observed no abnormalities of the bronchial mucosa in female C57B1 mice exposed to 15 mg nickel/m$^3$, although only three of 12 mice lived longer than 12 months. In earlier studies, Hueper (1955) did not observe chemical-related neoplasms in mice after a single intrapleural injection of nickel metal powder. A study of the pulmonary carcinogenesis of nickel subsulfide, administered intratracheally or intraperitoneally, provided no evidence of an exposure-related increase in lung tumor response in strain A/J mice (McNeill *et al.*, 1990). Results from these nickel subsulfide studies, and from carcinogenicity studies of other metal compounds such as cadmium, suggest that the rat is more susceptible than the mouse to a carcinogenic response in the lung after exposure to certain metals by inhalation.

Recent studies have shown that nickel subsulfide produces a high level of oxidants in the nuclei of cells, which could cause oxidative damage to proteins and DNA (Huang *et al.*, 1994). This damage may lead to specific alterations in oncogene or suppressor gene patterns in *in vitro* studies (Haugen *et al.*, 1989; Higinbotham *et al.*, 1992; Mæhle *et al.*, 1992; Lin *et al.*, 1994). Nickel subsulfide transforms rat tracheal epithelial cells more readily than nickel oxide or nickel sulfate (Patierno *et al.*, 1993). Recent studies have also suggested that the carcinogenic properties of nickel subsulfide may be due to the ability of the metal and sulfide portions of the molecule to enhance the generation of genotoxic free radicals (Shi *et al.*, 1994; Tajmir-Riahi *et al.*, 1994). These studies suggest that the mechanism involved in nickel subsulfide carcinogenesis includes specific genetic alterations, and further studies should help elucidate the molecular changes that occur in the rat lung after nickel subsulfide exposures.

The findings of the carcinogenic response in the rat lung after nickel subsulfide exposure agree with epidemiology findings that show that exposure of workers in nickel industries may lead to an increased risk of lung neoplasms (Doll *et al.*, 1990). Studies from the Sudbury sinter plant (Copper Cliff) show a strong association between exposure to sulfidic nickel and lung cancer at estimated exposure concentrations of 2 to 8 mg nickel/m$^3$. Oxidic nickel levels and soluble nickel levels were also at their highest in the areas of sulfidic nickel exposure, and it was not possible to separate the types of exposure and cancer risk.

Lung tissue specimens from 39 nickel refinery workers showed increased lung nickel levels (Andersen and Svenes, 1989). The average nickel concentration for workers in roasting and smelting operations was 330 $\pm$ 380 $\mu$g nickel/g dry lung weight; for workers in electrolysis departments, 34 $\pm$ 48 $\mu$g/g; and for lung tissue from unexposed people, 0.76 $\pm$ 0.39 $\mu$g/g. Dry lung represents approximately 20% "wet" lung weight (Henderson and Escobedo, 1976). Workers who were diagnosed with lung cancer (14 cases) had the same lung nickel concentrations at autopsy as nickel workers (25 cases) who died of other causes. The lung nickel concentration was independent of smoking habits. Anderson and Svenes (1989) felt that the retained nickel in the lung was probably nickel oxide because an earlier study using energy dispersive X-ray analysis did not detect sulfides (e.g., $Ni_3S_2$) in the lung. This study also found that lung cancer occurred in workers from the electrolysis department (8/24) as well as those from the roasting and smelting

operations (6/15) even though those from the electrolysis department had lower lung nickel levels.

The current threshold limit value (TLV) for water-insoluble nickel compounds is 1 mg/m$^3$, and in these 13-week studies, chemical-related toxic lesions were found in the respiratory tract of rodents at exposure concentrations below the TLV. A no-observed-adverse-effect level (NOAEL) for lung toxicity was not reached for rats; exposure-related lung lesions occurred even at the lowest exposure concentration of 0.15 mg/m$^3$ (0.11 mg nickel/m$^3$). The NOAEL for lung toxicity in mice was 0.15 mg/m$^3$. The NOAEL for nasal toxicity was approximately 0.3 mg/m$^3$ for rats and mice. Lung neoplasms occurred below the TLV in rats in the current 2-year study of nickel subsulfide.

## CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of nickel subsulfide in male F344/N rats based on increased incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined) and on increased incidences of benign, malignant, and benign or malignant (combined) pheochromocytoma of the adrenal medulla. There was *clear evidence of carcinogenic activity* of nickel subsulfide in female F344/N rats based on increased incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) and an increased incidence of benign pheochromocytoma of the adrenal medulla. There was *no evidence of carcinogenic activity* of nickel subsulfide in male or female B6C3F$_1$ mice exposed to 0.6 or 1.2 mg/m$^3$.

Exposure of male and female rats to nickel subsulfide by inhalation for 2 years resulted in inflammation, hyperplasia, and fibrosis in the lung; inflammation and atrophy of the olfactory epithelium in the nose; and hyperplasia in the adrenal medulla (females). Exposure of male and female mice to nickel subsulfide by inhalation for 2 years resulted in inflammation, bronchialization, hyperplasia, and fibrosis in the lung and inflammation and atrophy of the olfactory epithelium in the nose.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this report appears on page 13.

TABLE 32
**Selected Results in the 16-Day Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]**

| Dose mg/m³ (mg Ni/m³) | Nickel Sulfate Hexahydrate | | | | | | Nickel Subsulfide | | | | | | Nickel Oxide | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 3.5 (0.7) | 7 (1.4) | 15 (3.1) | 30 (6.1) | 60 (12.2) | 0 | 0.6 (0.44) | 1.2 (0.88) | 2.5 (1.83) | 5 (3.65) | 10 (7.33) | 0 | 1.2 (0.9) | 2.5 (2.0) | 5 (3.9) | 10 (7.9) | 30 (23.6) |
| **Male Rats** | | | | | | | | | | | | | | | | | | |
| Survival | 5 | 5 | 5 | 5 | 5 | 3 | 5 | 5 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| Final Mean Body Weights (Relative to Controls) | — | 72% | 60% | 56% | 55% | 45% | — | 109% | 105% | 92% | 72% | 52% | — | 99% | 101% | 99% | 99% | 96% |
| Absolute Lung Weights[b] | 0.98 | 1.44** | 1.45** | 1.40* | 1.40* | 1.62** | 1.13 | 1.41 | 1.60* | 1.59* | 1.82** | 1.54** | 1.06 | 1.00 | 1.06 | 0.96 | 1.20* | 1.36** |
| **Female Rats** | | | | | | | | | | | | | | | | | | |
| Survival | 5 | 5 | 5 | 5 | 4 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Final Mean Body Weights (Relative to Controls) | — | 82% | 71% | 68% | 63% | — | — | 99% | 97% | 91% | 78% | 57% | — | 103% | 103% | 104% | 101% | 99% |
| Absolute Lung Weights | 0.76 | 1.28* | 1.28* | 1.32* | 1.40** | 1.52** | 0.82 | 1.12** | 1.12** | 1.36** | 1.42** | 1.25** | 0.78 | 0.86 | 0.90 | 0.82 | 1.04** | 1.12** |

(continued)

TABLE 32
**Selected Results in the 16-Day Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| Dose mg/m³ (mg Ni/m³) | Nickel Sulfate Hexahydrate | | | | | | Nickel Subsulfide | | | | | | Nickel Oxide | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 3.5 (0.7) | 7 (1.4) | 15 (3.1) | 30 (6.1) | 60 (12.2) | 0 | 0.6 (0.44) | 1.2 (0.88) | 2.5 (1.83) | 5 (3.65) | 10 (7.33) | 0 | 1.2 (0.9) | 2.5 (2.0) | 5 (3.9) | 10 (7.9) | 30 (23.6) |
| **Male Mice** | | | | | | | | | | | | | | | | | | |
| Survival | 5 | 5 | 0 | 0 | 0 | 0 | 4 | 5 | 4 | 5 | 5 | 0 | 5 | 5 | 5 | 4 | 5 | 5 |
| Final Mean Body Weights (Relative to Controls) | — | 95% | — | — | — | — | — | 99% | 90% | 92% | 86% | — | — | 100% | 100% | 98% | 102% | 94% |
| Absolute Lung Weights | 0.20 | 0.24 | 0.40** | 0.36** | 0.36** | 0.38** | 0.22 | 0.20 | 0.22 | 0.28 | 0.31** | 0.38** | 0.20 | 0.16 | 0.20 | 0.13** | 0.20 | 0.20 |
| **Female Mice** | | | | | | | | | | | | | | | | | | |
| Survival | 5 | 5 | 0 | 0 | 0 | 0 | 4 | 5 | 5 | 5 | 5 | 0 | 5 | 5 | 5 | 5 | 5 | 5 |
| Final Mean Body Weights (Relative to Controls) | — | 96% | — | — | — | — | — | 106% | 104% | 101% | 99% | — | — | 100% | 96% | 100% | 95% | 95% |
| Absolute Lung Weights | 0.16 | 0.22 | 0.36** | 0.36** | 0.38** | 0.40** | 0.20 | 0.21 | 0.22 | 0.27 | 0.36* | 0.25 | 0.16 | 0.16 | 0.14 | 0.18 | 0.12 | 0.20 |

* Significantly different ($P \leq 0.05$) from the control by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Survival data indicate number of animals surviving. Five animals initially in group. Final mean body weights are not presented for groups with 100% mortality.
[b] Organ weights are given in grams.

**TABLE 33**
**Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]**

| | Nickel Sulfate Hexahydrate | | | | | | Nickel Subsulfide | | | | | | Nickel Oxide | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose mg/m³** | **0** | **0.12** | **0.25** | **0.5** | **1** | **2** | **0** | **0.15** | **0.3** | **0.6** | **1.2** | **2.5** | **0** | **0.6** | **1.2** | **2.5** | **5** | **10** |
| **(mg Ni/m³)** | | **(0.03)** | **(0.06)** | **(0.11)** | **(0.22)** | **(0.44)** | | **(0.11)** | **(0.22)** | **(0.44)** | **(0.88)** | **(1.83)** | | **(0.4)** | **(0.9)** | **(2.0)** | **(3.9)** | **(7.9)** |
| **Male Rats** | | | | | | | | | | | | | | | | | | |
| *Survival* | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Final Mean Body Weights | | | | | | | | | | | | | | | | | | |
| (Relative to Controls) | — | 99% | 103% | 96% | 102% | 95% | — | 100% | 95% | 96% | 99% | 93% | — | 103% | 104% | 99% | 102% | 100% |
| Absolute Lung Weights | 1.35 | 1.25 | 1.51* | 1.64** | 2.14** | 2.22** | 1.33 | 1.74** | 1.83** | 2.30** | 2.63** | 2.42** | 1.18 | 1.35** | 1.47** | 1.70** | 1.91** | 2.47** |
| Nonneoplastic Lung Lesions | | | | | | | | | | | | | | | | | | |
| Alveolar Macrophage, | | | | | | | | | | | | | | | | | | |
| Hyperplasia | 0 | 10 | 10 | 10 | 10 | 9 | 0 | 10 | 10 | 10 | 10 | 10 | 0 | 10 | 10 | 9 | 10 | 10 |
| (Severity)[b] | | (1.0) | (1.0) | (1.0) | (2.4) | (3.6) | | (1.1) | (1.5) | (1.6) | (3.4) | (3.8) | | (1.0) | (1.0) | (1.0) | (1.5) | (2.5) |
| Inflammation, Chronic Active | 0 | 0 | 0 | 2 | 10 | 8 | 0 | 2 | 9 | 10 | 10 | 10 | 0 | 0 | 0 | 2 | 10 | 10 |
| (Severity) | | | | (1.0) | (1.5) | (1.3) | | (1.0) | (1.3) | (1.8) | (2.9) | (3.7) | | | | (1.0) | (1.7) | (3.0) |
| Inflammation, Granulomatous | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 |
| (Severity) | | | | | | | | | | | | | | | | | (2.0) | (3.0) |
| Interstitial Infiltrate | 1 | 0 | 1 | 5 | 10 | 9 | 0 | 0 | 1 | 10 | 9 | 8 | 0 | 0 | 1 | 2 | 10 | 10 |
| (Severity) | (1.0) | | (1.0) | (1.0) | (1.0) | (1.1) | | | (1.0) | (1.9) | (2.1) | (1.2) | | | (1.0) | (1.0) | (1.4) | (2.1) |
| Pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 7 | 9 | 9 | 10 |
| (Severity) | | | | | | | | | | | | | | (1.0) | (1.0) | (1.0) | (1.0) | (1.8) |
| Nonneoplastic Nasal Lesions | | | | | | | | | | | | | | | | | | |
| Atrophy, Olfactory Epithelium | 0 | 0 | 0 | 1 | 10 | 9 | 0 | 0 | 1 | 5 | 10 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |

*(continued)*

TABLE 33
**Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| | Nickel Sulfate Hexahydrate | | | | | | Nickel Subsulfide | | | | | | Nickel Oxide | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose mg/m³** | **0** | **0.12** | **0.25** | **0.5** | **1** | **2** | **0** | **0.15** | **0.3** | **0.6** | **1.2** | **2.5** | **0** | **0.6** | **1.2** | **2.5** | **5** | **10** |
| **(mg Ni/m³)** | | **(0.03)** | **(0.06)** | **(0.11)** | **(0.22)** | **(0.44)** | | **(0.11)** | **(0.22)** | **(0.44)** | **(0.88)** | **(1.83)** | | **(0.4)** | **(0.9)** | **(2.0)** | **(3.9)** | **(7.9)** |
| **Female Rats** | | | | | | | | | | | | | | | | | | |
| Survival | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Final Mean Body Weights (Relative to Controls) | — | 96% | 98% | 98% | 101% | 95% | — | 101% | 104% | 101% | 100% | 99% | — | 101% | 101% | 98% | 98% | 100% |
| Absolute Lung Weights | 1.02 | 1.02 | 1.16** | 1.34** | 1.72** | 1.72** | 1.01 | 1.29** | 1.39** | 1.82** | 1.85** | 1.81** | 0.98 | 1.03 | 1.13* | 1.55** | 1.61** | 2.11** |
| Nonneoplastic Lung Lesions | | | | | | | | | | | | | | | | | | |
| Alveolar Macrophage, Hyperplasia | 0 | 8 | 10 | 10 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 10 | 0 | 10 | 8 | 10 | 10 | 10 |
| (Severity) | | (1.0) | (1.0) | (1.1) | (2.2) | (3.6) | | (1.0) | (1.7) | (1.8) | (2.9) | (3.8) | | (1.0) | (1.0) | (1.0) | (1.4) | (2.2) |
| Inflammation, Chronic Active | 0 | 0 | 0 | 4 | 10 | 10 | 0 | 3 | 9 | 10 | 10 | 10 | 0 | 0 | 0 | 1 | 7 | 7 |
| (Severity) | | | | (1.0) | (1.3) | (1.0) | | (1.0) | (1.0) | (1.9) | (2.6) | (3.8) | | | | (1.0) | (1.3) | (2.7) |
| Inflammation, Granulomatous | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 4 |
| (Severity) | | | | | | | | | | | | | | | | | (2.1) | (2.0) |
| Interstitial Infiltrate | 0 | 0 | 0 | 6 | 10 | 10 | 0 | 0 | 2 | 9 | 10 | 5 | 0 | 0 | 0 | 2 | 10 | 10 |
| (Severity) | | | | (1.0) | (1.0) | (1.0) | | | (1.0) | (1.7) | (2.4) | (1.6) | | | | (1.0) | (1.2) | (1.8) |
| Pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 8 | 8 | 10 |
| (Severity) | | | | | | | | | | | | | | | (1.0) | (1.0) | (1.0) | (1.2) |
| Nonneoplastic Nasal Lesions | | | | | | | | | | | | | | | | | | |
| Atrophy, Olfactory Epithelium | 0 | 0 | 1 | 2 | 10 | 10 | 0 | 0 | 0 | 8 | 9 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |

(continued)

TABLE 33
**Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| | Nickel Sulfate Hexahydrate | | | | | | Nickel Subsulfide | | | | | | Nickel Oxide | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose mg/m³ (mg Ni/m³)** | **0** | **0.12 (0.03)** | **0.25 (0.06)** | **0.5 (0.11)** | **1 (0.22)** | **2 (0.44)** | **0** | **0.15 (0.11)** | **0.3 (0.22)** | **0.6 (0.44)** | **1.2 (0.88)** | **2.5 (1.83)** | **0** | **0.6 (0.4)** | **1.2 (0.9)** | **2.5 (2.0)** | **5 (3.9)** | **10 (7.9)** |
| **Male Mice** | | | | | | | | | | | | | | | | | | |
| Survival | 6 | 8[c] | 10 | 10 | 10 | 10 | 8 | 10 | 10 | 8 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 9 |
| Final Mean Body Weights (Relative to Controls) | — | 105% | 100% | 104% | 104% | 102% | — | 102% | 106% | 103% | 101% | 97% | — | 101% | 99% | 97% | 98% | 97% |
| Absolute Lung Weights | 0.20 | 0.20 | 0.20 | 0.21 | 0.25** | 0.31** | 0.19 | 0.20 | 0.22 | 0.21 | 0.23* | 0.28** | 0.21 | 0.22 | 0.21 | 0.21 | 0.24 | 0.29** |
| Nonneoplastic Lung Lesions | | | | | | | | | | | | | | | | | | |
| Alveolar Macrophage, Hyperplasia | 0 | 0 | 0 | 10 | 10 | 10 | 0 | 0 | 8 | 8 | 9 | 10 | 0 | 10 | 10 | 10 | 10 | 9 |
| (Severity) | | | | (1.0) | (1.0) | (1.0) | | | (1.0) | (1.0) | (2.0) | (2.2) | | (1.0) | (1.0) | (1.0) | (1.0) | (1.1) |
| Fibrosis, Focal | 0 | 0 | 0 | 0 | 2 | 10 | 0 | 0 | 0 | 0 | 5 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| (Severity) | | | | | (1.5) | (2.0) | | | | | (1.6) | (2.1) | | | | | | |
| Inflammation, Chronic Active | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 5 | 7 | 0 | 0 | 0 | 0 | 0 | 3 |
| (Severity) | | | | | (1.0) | (1.5) | | | | | (1.2) | (1.6) | | | | | | (1.0) |
| Inflammation, Granulomatous | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| (Severity) | | | | | | | | | | | | | | | | | | (1.0) |
| Interstitial Infiltrate | 0 | 0 | 0 | 0 | 2 | 8 | 0 | 1 | 0 | 2 | 3 | 2 | 0 | 0 | 0 | 1 | 3 | 8 |
| (Severity) | | | | | (1.0) | (1.0) | | (1.0) | | (1.0) | (1.2) | (1.5) | | | | (1.0) | (1.0) | (1.0) |
| Pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 9 |
| (Severity) | | | | | | | | | | | | | | (1.0) | (1.0) | (1.0) | (1.0) | (1.0) |
| Nonneoplastic Nasal Lesions | | | | | | | | | | | | | | | | | | |
| Atrophy, Olfactory Epithelium | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 5 | 5 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |

(continued)

TABLE 33
**Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| Dose mg/m³ (mg Ni/m³) | Nickel Sulfate Hexahydrate | | | | | | Nickel Subsulfide | | | | | | Nickel Oxide | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.12 (0.03) | 0.25 (0.06) | 0.5 (0.11) | 1 (0.22) | 2 (0.44) | 0 | 0.15 (0.11) | 0.3 (0.22) | 0.6 (0.44) | 1.2 (0.88) | 2.5 (1.83) | 0 | 0.6 (0.4) | 1.2 (0.9) | 2.5 (2.0) | 5 (3.9) | 10 (7.9) |
| **Female Mice** | | | | | | | | | | | | | | | | | | |
| Survival | 7 | 10 | 10 | 10 | 10 | 10 | 10 | 8 | 10 | 9 | 10 | 8 | 9 | 10 | 7 | 10 | 10 | 9 |
| *Final Mean Body Weights* | | | | | | | | | | | | | | | | | | |
| (Relative to Controls) | — | 105% | 104% | 105% | 103% | 97% | — | 101% | 100% | 101% | 101% | 99% | — | 97% | 100% | 96% | 94% | 97% |
| *Absolute Lung Weights* | *0.20* | *0.20* | *0.20* | *0.20* | *0.22* | *0.27*** | *0.19* | *0.18* | *0.20* | *0.21* | *0.26*** | *0.29*** | *0.20* | *0.20* | *0.19* | *0.21* | *0.22* | *0.27*** |
| Nonneoplastic Lung Lesions | | | | | | | | | | | | | | | | | | |
| Alveolar Macrophage, Hyperplasia | 0 | 0 | 0 | 10 | 10 | 10 | 0 | 0 | 4 | 9 | 10 | 10 | 0 | 10 | 7 | 10 | 10 | 9 |
| (Severity) | | | | (1.0) | (1.0) | (1.0) | | | (1.0) | (1.0) | (2.4) | (2.6) | | (1.0) | (1.0) | (1.0) | (1.1) | (1.0) |
| Fibrosis, Focal | 0 | 0 | 0 | 0 | 1 | 8 | 0 | 0 | 0 | 0 | 1 | 9 | 0 | 0 | 0 | 0 | 0 | 0 |
| (Severity) | | | | | (1.0) | (1.5) | | | | | (2.0) | (1.6) | | | | | | |
| Inflammation, Chronic Active | 0 | 0 | 0 | 0 | 1 | 9 | 0 | 0 | 0 | 0 | 10 | 7 | 0 | 0 | 0 | 0 | 1 | 3 |
| (Severity) | | | | | (1.0) | (1.9) | | | | | (1.5) | (2.0) | | | | | (1.0) | (1.1) |
| Inflammation, Granulomatous | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| (Severity) | | | | | | | | | | | | | | | | | | (1.0) |
| Interstitial Infiltrate | 1 | 0 | 0 | 1 | 1 | 8 | 0 | 2 | 3 | 4 | 9 | 8 | 0 | 1 | 0 | 4 | 6 | 8 |
| (Severity) | (1.0) | | | (1.0) | (1.0) | (1.3) | | (1.0) | (1.0) | (1.0) | (1.4) | (1.7) | | (1.0) | | (1.0) | (1.1) | (1.1) |
| Pigment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 7 | 10 | 10 | 9 |
| (Severity) | | | | | | | | | | | | | | (1.0) | (1.0) | (1.0) | (1.0) | (1.0) |
| Nonneoplastic Nasal Lesions | | | | | | | | | | | | | | | | | | |
| Atrophy, Olfactory Epithelium | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 1 | 6 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |

* *Significantly different ($P \leq 0.05$) from the control by Williams' or Dunnett's test*
** $P \leq 0.01$
[a] Survival data indicate number of animals surviving. Ten animals initially in group. Final mean body weights are not presented for groups with 100% mortality.
[b] *Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked*
[c] Nine animals initially in group.

TABLE 34
**Comparison of Exposure Concentrations in the 16-Day, 13-Week, and 2-Year Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide**[a]

| | Amount of Compound | Amount of Nickel |
|---|---|---|
| **16-Day Studies** | | |
| **Nickel Sulfate Hexahydrate (22.3% Ni)** | 0, 3.5, 7, 15, 30, 60 | 0, 0.7, 1.4, 3.1, 6.1, 12.2 |
| **Nickel Subsulfide (73.3% Ni)** | 0, 0.6, 1.2, 2.5, 5, 10 | 0, 0.44, 0.88, 1.83, 3.65, 7.33 |
| **Nickel Oxide (78.6% Ni)** | 0, 1.2, 2.5, 5, 10, 30 | 0, 0.9, 2.0, 3.9, 7.9, 23.6 |
| **13-Week Studies** | | |
| **Nickel Sulfate Hexahydrate (22.3% Ni)** | 0, 0.12, 0.25, 0.5, 1, 2 | 0, 0.03, 0.06, 0.11, 0.22, 0.44 |
| **Nickel Subsulfide (73.3% Ni)** | 0, 0.15, 0.3, 0.6, 1.2, 2.5 | 0, 0.11, 0.22, 0.44, 0.88, 1.83 |
| **Nickel Oxide (78.6% Ni)** | 0, 0.6, 1.2, 2.5, 5, 10 | 0, 0.4, 0.9, 2.0, 3.9, 7.9 |
| **2-Year Studies** | | |
| **Nickel Sulfate Hexahydrate (22.3% Ni)** | | |
| Rats | 0, 0.12, 0.25, 0.5 | 0, 0.03, 0.06, 0.11 |
| Mice | 0, 0.25, 0.5, 1 | 0, 0.06, 0.11, 0.22 |
| **Nickel Subsulfide (73.3% Ni)** | | |
| Rats | 0, 0.15, 1 | 0, 0.11, 0.73 |
| Mice | 0, 0.6, 1.2 | 0, 0.44, 0.88 |
| **Nickel Oxide (78.6% Ni)** | | |
| Rats | 0, 0.62, 1.25, 2.5 | 0, 0.5, 1.0, 2.0 |
| Mice | 0, 1.25, 2.5, 5 | 0, 1.0, 2.0, 3.9 |

[a] Amounts of nickel and nickel compounds are expressed in mg/m$^3$. Occupational exposure limits in the United States: 1 mg Ni/m$^3$ for nickel metals, 0.1 mg Ni/m$^3$ for soluble nickel compounds.

TABLE 35
**Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]**

| | Nickel Sulfate Hexahydrate (22.3% Ni) | | | | Nickel Subsulfide (73.3% Ni) | | | Nickel Oxide (78.6% Ni) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose mg/m³ | 0 | 0.12 | 0.25 | 0.5 | 0 | 0.15 | 1 | 0 | 0.62 | 1.25 | 2.5 |
| (mg Ni/m³) | | (0.03) | (0.06) | (0.11) | | (0.11) | (0.73) | | (0.5) | (1.0) | (2.0) |
| **Male Rats** | | | | | | | | | | | |
| Survival | 16/54 | 16/55 | 18/55 | 21/55 | 13/53 | 21/53 | 18/53 | 14/54 | 15/53 | 15/53 | 12/52 |
| Final Mean Body Weights | | | | | | | | | | | |
| (Relative to Controls) | — | 99% | 101% | 98% | — | 98% | 85% | — | 100% | 95% | 93% |
| Absolute Lung Weights | | | | | | | | | | | |
| 7-Month Interim Evaluation | 1.67 | 1.62 | 1.65 | 1.89 | 1.87 | 2.38** | 3.48** | 1.72 | 1.85 | 2.43** | 2.59** |
| 15-Month Interim Evaluation | 2.12 | 2.48 | 2.50 | 3.00** | 2.27 | 3.31** | 6.84** | 2.20 | 2.15 | 3.30** | 4.09** |
| Alveolar/bronchiolar Proliferative Lesions and Neoplasms | | | | | | | | | | | |
| Alveolar Epithelial | | | | | | | | | | | |
| Hyperplasia, Focal or Atypical | 3 | 2 | 3 | 2 | 2 | 6 | 11** | 0 | 2 | 5* | 3 |
| Adenoma | 0 | 0 | 0 | 2 | 0 | 3 | 6* | 0 | 1 | 3 | 2 |
| Carcinoma | 2[b] | 0 | 1 | 1 | 0 | 3 | 7* | 1[b] | 0 | 3 | 2 |
| Adenoma or Carcinoma (Combined) | 2[b] | 0 | 1 | 3 | 0 | 6* | 11** | 1[b] | 1 | 6[c] | 4[c] |
| Adrenal Medulla Proliferative Lesions and Neoplasms | | | | | | | | | | | |
| Hyperplasia | 28 | 20 | 18 | 26 | 26 | 22 | 10 | 25 | 27 | 26 | 24 |
| Benign Pheochromocytoma | 16 | 16 | 12 | 11 | 13 | 30** | 37** | 27 | 24 | 26 | 32 |
| Malignant Pheochromocytoma | 0 | 3 | 2 | 1 | 0 | 2 | 11** | 0 | 0 | 1 | 6* |
| Benign or Malignant Pheochromocytoma | 16 | 19 | 13 | 12 | 14 | 30** | 42** | 27 | 24 | 27 | 35** |
| Carcinogenic Activity | | No evidence | | | | Clear evidence | | | Some evidence | | |

(continued)

TABLE 35
**Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| | Nickel Sulfate Hexahydrate (22.3% Ni) | | | | Nickel Subsulfide (73.3% Ni) | | | Nickel Oxide (78.6% Ni) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose mg/m³** | **0** | **0.12** | **0.25** | **0.5** | **0** | **0.15** | **1** | **0** | **0.62** | **1.25** | **2.5** |
| **(mg Ni/m³)** | | **(0.03)** | **(0.06)** | **(0.11)** | | **(0.11)** | **(0.73)** | | **(0.5)** | **(1.0)** | **(2.0)** |
| **Female Rats** | | | | | | | | | | | |
| Survival | 22/52 | 17/53 | 28/53 | 29/54 | 25/53 | 25/53 | 28/52 | 21/53 | 26/53 | 20/53 | 26/54 |
| Final Mean Body Weights | | | | | | | | | | | |
| (Relative to Controls) | — | 97% | 97% | 94% | — | 96% | 78% | — | 96% | 92% | 90% |
| Absolute Lung Weights | | | | | | | | | | | |
| 7-Month Interim Evaluation | 1.25 | 1.22 | 1.22 | 1.45* | 1.31 | 1.75** | 2.59** | 1.14 | 1.31* | 1.65** | 1.78** |
| 15-Month Interim Evaluation | 1.37 | 1.57 | 1.49 | 1.82** | 1.52 | 2.52** | 4.14** | 1.56 | 1.79 | 2.41** | 3.02** |
| Alveolar/bronchiolar Proliferative Lesions and Neoplasms | | | | | | | | | | | |
| Alveolar Epithelial | | | | | | | | | | | |
| Hyperplasia, Focal or Atypical | 5 | 3 | 7 | 9 | 2 | 10* | 11** | 2 | 1 | 6 | 6 |
| Adenoma | 0 | 0 | 0 | 1 | 2 | 5 | 5 | 1 | 0 | 1 | 4 |
| Carcinoma | 0 | 0 | 0 | 0 | 0 | 1[b] | 4 | 0 | 0 | 5* | 1 |
| Adenoma or Carcinoma (Combined) | 0 | 0 | 0 | 1 | 2 | 6[b,d] | 9* | 1 | 0 | 6[d] | 5[d] |
| Adrenal Medulla Proliferative Lesions and Neoplasms | | | | | | | | | | | |
| Hyperplasia | 6 | 4 | 8 | 8 | 5 | 11 | 16** | 8 | 12 | 14 | 22** |
| Benign Pheochromocytoma | 2 | 4 | 2 | 3 | 2 | 7 | 36** | 4 | 7 | 6 | 18** |
| Malignant Pheochromocytoma | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Benign or Malignant Pheochromocytoma | 2 | 4 | 2 | 3 | 3 | 7 | 36** | 4 | 7 | 6 | 18** |
| Carcinogenic Activity | | No evidence | | | | Clear evidence | | | Some evidence | | |

(continued)

TABLE 35
**Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| | Nickel Sulfate Hexahydrate (22.3% Ni) | | | | Nickel Subsulfide (73.3% Ni) | | | Nickel Oxide (78.6% Ni) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose mg/m³** | **0** | **0.25** | **0.5** | **1** | **0** | **0.6** | **1.2** | **0** | **1.25** | **2.5** | **5** |
| **(mg Ni/m³)** | | **(0.06)** | **(0.11)** | **(0.22)** | | **(0.44)** | **(0.88)** | | **(1.0)** | **(2.0)** | **(3.9)** |
| **Male Mice** | | | | | | | | | | | |
| Survival | 26/61 | 23/61 | 24/62 | 25/61 | 26/61 | 25/59 | 26/58 | 19/57 | 23/67 | 29/66 | 23/69 |
| Final Mean Body Weights | | | | | | | | | | | |
| (Relative to Controls) | — | 94% | 97% | 91% | — | 92% | 92% | — | 93% | 93% | 93% |
| Absolute Lung Weights | | | | | | | | | | | |
| 7-Month Interim Evaluation | 0.21 | 0.20 | 0.22 | 0.23 | 0.24 | 0.27 | 0.34** | 0.19 | 0.21 | 0.24** | 0.24** |
| 15-Month Interim Evaluation | 0.24 | 0.25 | 0.26 | 0.31** | 0.23 | 0.40** | 0.41** | 0.23 | 0.25 | 0.31* | 0.38** |
| Alveolar/bronchiolar Proliferative Lesions and Neoplasms | | | | | | | | | | | |
| Alveolar Epithelial | | | | | | | | | | | |
| Hyperplasia, Focal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 |
| Adenoma | 5 | 5 | 3 | 5 | 6 | 3 | 2 | 7 | 5 | 6 | 11 |
| Carcinoma | 9 | 13 | 4 | 3 | 7 | 2 | 4 | 4 | 10 | 9 | 6 |
| Adenoma or Carcinoma (Combined) | 13 | 18 | 7 | 8 | 13 | 5 | 6 | 9 | 14 | 15 | 14 |
| Carcinogenic Activity | | No evidence | | | | No evidence | | | No evidence | | |

(continued)

TABLE 35
**Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| | Nickel Sulfate Hexahydrate (22.3% Ni) | | | | Nickel Subsulfide (73.3% Ni) | | | Nickel Oxide (78.6% Ni) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose mg/m³ (mg Ni/m³)** | **0** | **0.25 (0.06)** | **0.5 (0.11)** | **1 (0.22)** | **0** | **0.6 (0.44)** | **1.2 (0.88)** | **0** | **1.25 (1.0)** | **2.5 (2.0)** | **5 (3.9)** |
| **Female Mice** | | | | | | | | | | | |
| Survival | 34/61 | 39/60 | 45/60 | 37/60 | 36/58 | 34/59 | 38/60 | 41/64 | 40/66 | 42/63 | 38/64 |
| Final Mean Body Weights (Relative to Controls) | — | 91% | 94% | 88% | — | 90% | 86% | — | 96% | 94% | 90% |
| Absolute Lung Weights | | | | | | | | | | | |
| 7-Month Interim Evaluation | 0.22 | 0.21 | 0.22 | 0.25 | 0.19 | 0.26* | 0.29** | 0.18 | 0.21 | 0.23 | 0.23 |
| 15-Month Interim Evaluation | 0.24 | 0.24 | 0.28 | 0.33** | 0.26 | 0.39** | 0.50** | 0.25 | 0.26 | 0.29 | 0.34** |
| Alveolar/bronchiolar Proliferative Lesions and Neoplasms | | | | | | | | | | | |
| Alveolar Epithelial Hyperplasia, Focal | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Adenoma | 3 | 3 | 2 | 0 | 3 | 1 | 1 | 2 | 4 | 10* | 3 |
| Carcinoma | 4 | 3 | 9 | 2 | 7 | 1 | 2 | 4 | 11 | 4 | 5 |
| Adenoma or Carcinoma (Combined) | 7 | 6 | 10 | 2 | 9 | 2 | 3 | 6 | 15* | 12 | 8 |
| Carcinogenic Activity | | No evidence | | | | No evidence | | | Equivocal evidence | | |

* Significantly different ($P \leq 0.05$) from the control by Williams' or Dunnett's test (lung weights) or the logistic regression test (incidences).
** $P \leq 0.01$
[a] Survival data indicate number of animals surviving/number initially in group.
[b] Includes data for squamous cell carcinoma
[c] Significantly different ($P < 0.05$) from the Lovelace Inhalation Toxicology Research Institute historical controls [3/210 (1.4%)]
[d] Significantly different ($P < 0.05$) from the Lovelace Inhalation Toxicology Research Institute historical controls [4/208 (1.9%)]

TABLE 36
**Lung Burden Analyses in the 16-Day, 13-Week, and 2-Year Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]**

| Dose mg/m³ (mg Ni/m³) | Nickel Sulfate Hexahydrate (22.3% Ni) | | | | | | | Nickel Subsulfide (73.3% Ni) | | | | | Nickel Oxide (78.6% Ni) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.12 (0.03) | 0.5 (0.06) | 2 (0.44) | 3.5 (0.7) | 15 (3.1) | 30 (6.1) | 0 | 0.15 (0.11) | 0.6 (0.44) | 2.5 (1.83) | 10 (7.33) | 0 | 0.6 (0.4) | 1.2 (0.9) | 2.5 (2.0) | 5 (3.9) | 10 (7.9) |
| **16-Day Studies** | | | | | | | | | | | | | | | | | | |
| Male Rats | –[b] | | | | 5 | 9 | 8 | – | | 7 | 18 | 67 | – | | 42 | | 108 | 267 |
| Female Rats | – | | | | 8 | 11 | 9 | – | | 9 | 19 | 77 | – | | 54 | | 122 | 340 |
| Male Mice | – | | | | 3 | | | – | | 10 | 20 | 13 | – | | 32 | 46 | 84 | |
| Female Mice | – | | | | 4 | | | – | | 8 | 20 | 8 | – | | 31 | 43 | 71 | |
| **13-Week Studies** | | | | | | | | | | | | | | | | | | |
| Male Rats | – | – | 1 | 6 | | | | – | 5 | 7 | 18 | | – | 80 | | 181 | | 524 |
| Female Rats | – | – | 2 | 7 | | | | – | 5 | 7 | 17 | | | | | | | |
| Male Mice | – | – | – | 1 | | | | – | 3 | 11 | 17 | | – | 42 | | 202 | | 736 |
| Female Mice | – | – | – | 4 | | | | – | 6 | 13 | 23 | | | | | | | |

(continued)

TABLE 36
**Lung Burden Analyses in the 16-Day, 13-Week, and 2-Year Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide** (continued)

| Dose mg/m³ (mg Ni/m³) | Nickel Sulfate Hexahydrate (22.3% Ni) | | | | | | Nickel Subsulfide (73.3% Ni) | | | | | Nickel Oxide (78.6% Ni) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.12 (0.03) | 0.25 (0.06) | 0.5 (0.11) | 1 (0.22) | 2 (0.44) | 0 | 0.15 (0.11) | 0.6 (0.44) | 1 (0.73) | 1.2 (0.88) | 0 | 0.62 (0.5) | 1.25 (1.0) | 2.5 (2.0) | 5 (3.9) | 10 (7.9) |
| **7-Month Interim Evaluation** | | | | | | | | | | | | | | | | | |
| Male Rats | – | – | – | 1 | | | – | 6 | | 9 | | – | 175 | 388 | 701 | | |
| Female Rats | – | – | – | 1 | | | – | 6 | | 9 | | – | 173 | 477 | 713 | | |
| Male Mice | – | | 1 | 1 | 2 | | – | | 10 | | 11 | – | | 162 | 442 | 1,034 | |
| Female Mice | – | | 1 | 2 | 2 | | – | | 10 | | 14 | – | | 169 | 533 | 861 | |
| **15-Month Interim Evaluation** | | | | | | | | | | | | | | | | | |
| Male Rats | – | – | – | 1 | | | – | 4 | | 3 | | – | 328 | 746 | 1,116 | | |
| Female Rats | – | – | – | 2 | | | – | 4 | | 7 | | – | 262 | 706 | 949 | | |
| Male Mice | – | | 1 | 1 | 2 | | – | | 12 | | 20 | – | | 331 | 959 | 1,798 | |
| Female Mice | – | | 1 | 2 | 2 | | – | | 15 | | 26 | – | | 451 | 1,237 | 2,258 | |

[a] Values represent mean amounts of nickel (μg Ni/g lung). Lung burden groups included five to seven animals.
[b] Results were below the limit of detection.

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# APPENDIX A
# SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF NICKEL SUBSULFIDE

TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 63 | 63 | 63 |
| *7-Month interim evaluation* | 5 | 5 | 5 |
| *15-Month interim evaluation* | 5 | 5 | 5 |
| Early deaths | | | |
| Moribund | 35 | 28 | 33 |
| Natural deaths | 5 | 4 | 2 |
| Survivors | | | |
| Terminal sacrifice | 13 | 21 | 18 |
| Animals examined microscopically | 63 | 63 | 63 |
| ***Systems Examined At 7 Months With No Neoplasms Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Genital System** | | | |
| **Hematopoitic System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Respiratory System** | | | |
| **Special Scenes System** | | | |
| **Urinary System** | | | |
| ***15-Month Interim Evaluation*** | | | |
| **Genital System** | | | |
| Testes | (5) | (5) | (5) |
| Interstitial cell, adenoma | 4 (80%) | 1 (20%) | 2 (40%) |
| **Systemic Lesions** | | | |
| Multiple organs[b] | (5) | (5) | (5) |
| Leukemia mononuclear | | | 1 (20%) |
| ***Systems Examined With No Neoplasms Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Hematopoitic System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Respiratory System** | | | |
| **Special Scenes System** | | | |
| **Urinary System** | | | |

TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Intestine large, colon | (51) | (51) | (53) |
| Intestine large, rectum | (46) | (45) | (52) |
| Fibrosarcoma, metastatic, testes | | | 1 (2%) |
| Intestine small, duodenum | (52) | (52) | (53) |
| Adenocarcinoma | | 1 (2%) | |
| Intestine small, jejunum | (51) | (51) | (52) |
| Intestine small, ileum | (51) | (51) | (52) |
| Liver | (53) | (53) | (53) |
| Hepatocellular adenoma | 4 (8%) | 1 (2%) | 3 (6%) |
| Histiocytic sarcoma | 1 (2%) | | |
| Mesentery | (1) | (1) | (1) |
| Pancreas | (53) | (53) | (53) |
| Adenoma | 1 (2%) | 1 (2%) | |
| Pharynx | | | (1) |
| Squamous cell papilloma | | | 1 (100%) |
| Salivary glands | (53) | (52) | (53) |
| Stomach, forestomach | (53) | (53) | (53) |
| Squamous cell papilloma | | | 1 (2%) |
| Stomach, glandular | (53) | (53) | (53) |
| Tongue | (1) | | |
| Squamous cell papilloma | 1 (100%) | | |
| Tooth | (1) | (1) | (1) |
| Gingiva, squamous cell carcinoma | | | 1 (100%) |
| **Cardiovascular System** | | | |
| Heart | (53) | (53) | (53) |
| **Endocrine System** | | | |
| Adrenal cortex | (53) | (53) | (53) |
| Adrenal medulla | (53) | (52) | (53) |
| Pheochromocytoma malignant | | 2 (4%) | 6 (11%) |
| Pheochromocytoma complex | 1 (2%) | | |
| Pheochromocytoma benign | 12 (23%) | 23 (44%) | 14 (26%) |
| Bilateral, pheochromocytoma malignant | | | 5 (9%) |
| Bilateral, pheochromocytoma benign | 1 (2%) | 7 (13%) | 23 (43%) |
| Islets, pancreatic | (53) | (53) | (53) |
| Adenoma | 2 (4%) | 4 (8%) | 4 (8%) |
| Carcinoma | | 1 (2%) | 2 (4%) |
| Parathyroid gland | (50) | (50) | (51) |
| Adenoma | 1 (2%) | 1 (2%) | |
| Pituitary gland | (53) | (52) | (53) |
| Pars distalis, adenoma | 20 (38%) | 17 (33%) | 17 (32%) |
| Thyroid gland | (52) | (53) | (53) |
| C-cell, adenoma | 4 (8%) | 2 (4%) | 9 (17%) |
| C-cell, carcinoma | 2 (4%) | 1 (2%) | |

TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **General Body System** | | | |
| Tissue NOS | (2) | (1) | (1) |
| Abdominal, fibrosarcoma | | | 1 (100%) |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (100%) | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (100%) | |
| Thoracic, fibrosarcoma | 1 (50%) | | |
| **Genital System** | | | |
| Preputial gland | (53) | (53) | (53) |
| Adenoma | 1 (2%) | 2 (4%) | |
| Carcinoma | 2 (4%) | | |
| Prostate | (53) | (53) | (53) |
| Seminal vesicle | (52) | (53) | (52) |
| Testes | (53) | (53) | (53) |
| Bilateral, interstitial cell, adenoma | 28 (53%) | 30 (57%) | 15 (28%) |
| Interstitial cell, adenoma | 11 (21%) | 15 (28%) | 20 (38%) |
| Tunic, fibrosarcoma | | | 1 (2%) |
| **Hematopoietic System** | | | |
| Bone marrow | (53) | (52) | (53) |
| Lymph node | (5) | (16) | (6) |
| Iliac, fibrosarcoma, metastatic, testes | | | 1 (17%) |
| Lymph node, bronchial | (52) | (51) | (53) |
| Lymph node, mandibular | (50) | (51) | (50) |
| Lymph node, mesenteric | (53) | (53) | (53) |
| Lymph node, mediastinal | (49) | (49) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (2%) | |
| Histiocytic sarcoma | 1 (2%) | | |
| Spleen | (53) | (53) | (53) |
| Thymus | (50) | (49) | (49) |
| **Integumentary System** | | | |
| Mammary gland | (49) | (48) | (43) |
| Adenoma | 1 (2%) | | |
| Fibroadenoma | | 1 (2%) | |

TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Integumentary System** (continued) | | | |
| Skin | (53) | (53) | (53) |
| Basal cell adenoma | | | 1 (2%) |
| Basal cell carcinoma | | 1 (2%) | |
| Carcinoma, metastatic, preputial gland | 1 (2%) | | |
| Fibroma | 2 (4%) | 2 (4%) | 3 (6%) |
| Keratoacanthoma | 4 (8%) | 4 (8%) | 1 (2%) |
| Squamous cell papilloma | 1 (2%) | | |
| Nose, squamous cell papilloma | | | 1 (2%) |
| Pinna, keratoacanthoma | 1 (2%) | | |
| Pinna, squamous cell papilloma | 1 (2%) | | |
| Subcutaneous tissue, fibrosarcoma | 1 (2%) | | |
| Subcutaneous tissue, lipoma | 1 (2%) | | 1 (2%) |
| Tail, fibroma | 1 (2%) | | |
| Tail, squamous cell papilloma | | 1 (2%) | |
| **Musculoskeletal System** | | | |
| Bone | (53) | (52) | (53) |
| Cranium, osteosarcoma | 1 (2%) | | |
| Maxilla, osteosarcoma | | | 1 (2%) |
| **Nervous System** | | | |
| Brain | (53) | (53) | (53) |
| Astrocytoma NOS | | | 1 (2%) |
| Oligodendroglioma NOS | | 1 (2%) | |
| Spinal cord | (1) | (1) | |
| Astrocytoma benign | 1 (100%) | | |
| **Respiratory System** | | | |
| Lung | (53) | (53) | (53) |
| Alveolar/bronchiolar adenoma | | 3 (6%) | 4 (8%) |
| Alveolar/bronchiolar adenoma, multiple | | | 2 (4%) |
| Alveolar/bronchiolar carcinoma | | 3 (6%) | 7 (13%) |
| Carcinoma, metastatic, preputial gland | 1 (2%) | | |
| Chordoma, metastatic, tissue NOS | | | 1 (2%) |
| Fibrosarcoma, metastatic, testes | | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | |
| Osteosarcoma, metastatic, bone | 1 (2%) | | 1 (2%) |
| Pheochromocytoma malignant, metastatic, adrenal medulla | | | 1 (2%) |
| Nose | (53) | (53) | (52) |
| Trachea | (53) | (53) | (53) |

TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Special Senses System** | | | |
| None | | | |
| **Urinary System** | | | |
| Kidney | (52) | (53) | (53) |
| Urinary bladder | (53) | (53) | (53) |
| **Systemic Lesions** | | | |
| Multiple organs | (53) | (53) | (53) |
| Histiocytic sarcoma | 1 (2%) | | |
| Leukemia mononuclear | 28 (53%) | 32 (60%) | 35 (66%) |
| Mesothelioma NOS | 1 (2%) | 1 (2%) | |
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[c] | | | |
| 15-Month interim evaluation | 4 | 1 | 3 |
| 2-Year study | 52 | 52 | 53 |
| Total primary neoplasms | | | |
| 15-Month interim evaluation | 4 | 1 | 3 |
| 2-Year study | 137 | 157 | 180 |
| Total animals with benign neoplasms | | | |
| 15-Month interim evaluation | 4 | 1 | 2 |
| 2-Year study | 49 | 52 | 50 |
| Total benign neoplasms | | | |
| 15-Month interim evaluation | 4 | 1 | 2 |
| 2-Year study | 99 | 114 | 120 |
| Total animals with malignant neoplasms | | | |
| 15-Month interim evaluation | | | 1 |
| 2-Year study | 33 | 37 | 45 |
| Total malignant neoplasms | | | |
| 15-Month interim evaluation | | | 1 |
| 2-Year study | 37 | 41 | 59 |
| Total animals with metastatic neoplasms | | | |
| 2-Year study | 2 | 2 | 4 |
| Total metastatic neoplasms | | | |
| 2-Year study | 3 | 4 | 6 |
| Total animals with uncertain neoplasms-benign or malignant | | | |
| 2-Year study | 1 | 2 | 1 |
| Total uncertain neoplasms | | | |
| 2-Year study | 9 | 2 | 1 |

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**

| Number of Days on Study | 2 5 7 | 3 6 1 | 3 7 3 | 5 2 1 | 5 3 7 | 5 3 9 | 5 4 2 | 5 5 3 | 5 5 9 | 5 5 9 | 5 6 5 | 5 6 5 | 5 7 2 | 5 7 3 | 5 7 4 | 5 7 8 | 5 9 4 | 5 9 6 | 5 9 9 | 6 0 8 | 6 1 5 | 6 2 4 | 6 3 4 | 6 3 5 | 6 3 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 2 | 0 0 3 | 0 2 9 | 0 3 6 | 0 6 5 | 0 7 0 | 0 4 8 | 0 4 3 | 0 1 2 | 0 3 6 | 0 0 9 | 0 6 7 | 0 5 7 | 0 1 6 | 0 4 1 | 0 0 7 | 0 0 8 | 0 6 0 | 0 3 8 | 0 0 4 | 0 2 6 | 0 1 8 | 0 4 5 | 0 5 6 | 0 6 2 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | I | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Intestine large, cecum | + | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | X | | | | | | | | | X | |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | + | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tooth | + | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma complex | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | | | X | X | | | | | | | | | | | | | | | |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Parathyroid gland | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | X | X | | | | | | X | X | | | X | X | X | X | | X | | | X | X | X |
| Thyroid gland | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | | X | X | | | | | | | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | + | | | | | | | | | | | | | | | | | | | | | | |
| Thoracic, fibrosarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | |

+: 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 Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 6 5 1 | 6 5 7 | 6 6 4 | 6 7 1 | 6 7 8 | 6 8 3 | 6 9 1 | 6 9 6 | 6 9 9 | 7 0 1 | 7 0 5 | 7 0 6 | 7 1 3 | 7 1 5 | 7 2 8 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 6 6 3 | 0 2 9 9 | 0 1 9 1 | 0 5 1 7 | 0 4 7 0 | 0 3 0 1 | 0 2 1 3 | 0 1 3 4 | 0 5 4 5 | 0 5 5 4 | 0 3 4 5 | 0 2 5 0 | 0 4 0 3 | 0 3 7 9 | 0 6 9 0 | 0 1 0 7 | 0 2 7 2 | 0 4 2 9 | 0 4 9 6 | 0 0 6 7 | 0 1 7 3 | 0 2 3 1 | 0 3 1 4 | 0 6 4 6 | 0 6 6 5 | 0 1 5 3 | 0 5 3 1 | 0 6 1 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | I | + | + | + | + | 46 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Hepatocellular adenoma | | | | | | | | | | | | | X | | | X | | | | | | | | | | | | | 4 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Tongue | | | | | | | | | | | | | | | | | | | | | + | | | | | | | | 1 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | | | | | | | | | + | | | | | | | | | | | | | | | 1 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pheochromocytoma complex | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma benign | X | | X | | | | | | X | X | X | | X | X | | | | X | | | | | | | | | X | X | 12 |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| Parathyroid gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pars distalis, adenoma | X | | | | | | X | | | | | X | | | X | | | | X | | | | X | | X | | X | | 20 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| C-cell, adenoma | | | | | | | | | | | | | X | | | X | | | | | | | | | | | | | 4 |
| C-cell, carcinoma | X | | | | | | | | X | | | | | | | | | | | | | | | | | | | | 2 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | + | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Thoracic, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 2 5 7 | 3 6 1 | 3 7 3 | 5 2 1 | 5 3 7 | 5 3 9 | 5 4 2 | 5 5 3 | 5 5 9 | 5 5 9 | 5 6 5 | 5 6 5 | 5 7 2 | 5 7 3 | 5 7 4 | 5 7 8 | 5 9 4 | 5 9 6 | 5 9 9 | 6 0 8 | 6 1 5 | 6 2 4 | 6 3 4 | 6 3 5 | 6 3 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 2 | 0 3 3 | 0 2 2 | 0 3 9 | 0 6 5 | 0 7 0 | 0 4 8 | 0 4 3 | 0 1 2 | 0 3 6 | 0 0 9 | 0 6 7 | 0 5 7 | 0 1 6 | 0 4 1 | 0 0 7 | 0 0 8 | 0 6 0 | 0 3 8 | 0 0 4 | 0 2 6 | 0 1 8 | 0 4 5 | 0 5 6 | 0 6 2 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Coagulating gland | | | | + | + | + | | + | | + | + | + | + | | + | | | + | + | | + | + | + | + | + |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Penis | | | | | | + | | | | | | | | | | | | | | | | | | | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | X |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | X | | | | | | X | | | | | | | | X | X | | X | X | | | X |
| Interstitial cell, adenoma | | | | | | | X | X | | | | | X | X | | X | | | | | | | X | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | + | | | | | | | | | | | | + | | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mediastinal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | M | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | I | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, preputial gland | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Fibroma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Squamous cell papilloma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Pinna, keratoacanthoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Pinna, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tail, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cranium, osteosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | | + | | | | | | | | | | | | | | | |
| Astrocytoma benign | | | | | | | | | | X | | | | | | | | | | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 6 5 1 | 6 5 7 | 6 6 4 | 6 7 1 | 6 7 8 | 6 8 3 | 6 9 1 | 6 9 6 | 6 9 9 | 7 0 1 | 7 0 5 | 7 0 6 | 7 1 3 | 7 1 5 | 7 2 8 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 0 6 3 | 0 2 9 | 0 1 9 | 0 5 1 | 0 4 7 | 0 3 0 | 0 2 1 | 0 1 3 | 0 5 4 | 0 5 5 | 0 3 4 | 0 2 5 | 0 4 0 | 0 3 7 | 0 6 9 | 0 1 0 | 0 2 7 | 0 4 2 | 0 4 9 | 0 0 6 | 0 1 7 | 0 2 3 | 0 3 1 | 0 6 4 | 0 6 6 | 0 1 5 | 0 5 3 | 0 6 1 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Coagulating gland | | + | + | | + | + | + | + | + | | + | + | + | | | + | + | + | + | + | + | + | + | + | + | + | + | 39 |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Penis | | | | | | | | | | | | | | | + | | | | | | | | | | | | | 2 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Bilateral, interstitial cell, adenoma | X | X | X | X | X | X | | X | | | X | | X | | | X | X | X | | X | X | X | X | X | X | X | X | X | 28 |
| Interstitial cell, adenoma | | | | | | | X | | X | X | | | | X | | | | | X | | | | | | | | | | 11 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Lymph node | | + | | | | | | | + | + | | | | | | | | | | | | | | | | | | | 5 |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | 52 |
| Lymph node, mandibular | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Lymph node, mediastinal | + | + | + | + | I | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | 50 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Carcinoma, metastatic, preputial gland | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Fibroma | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | 2 |
| Keratoacanthoma | | | | | | | | | | | | | | | X | | | | | X | | | | | | X | | | 4 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pinna, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pinna, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Tail, fibroma | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Cranium, osteosarcoma | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Astrocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 2 5 7 | 3 6 1 | 3 7 3 | 5 2 1 | 5 3 7 | 5 3 9 | 5 4 2 | 5 5 3 | 5 5 9 | 5 5 9 | 5 6 9 | 5 6 5 | 5 6 5 | 5 7 2 | 5 7 3 | 5 7 4 | 5 7 8 | 5 9 4 | 5 9 6 | 5 9 9 | 6 0 8 | 6 1 5 | 6 2 4 | 6 3 4 | 6 3 5 | 6 3 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 2 | 0 3 2 | 0 2 2 | 0 3 9 | 0 6 5 | 0 7 0 | 0 4 8 | 0 4 3 | 0 1 2 | 0 3 6 | 0 0 9 | 0 6 7 | 0 5 7 | 0 1 6 | 0 4 1 | 0 0 7 | 0 0 8 | 0 6 0 | 0 3 8 | 0 0 4 | 0 2 6 | 0 1 8 | 0 4 5 | 0 5 6 | 0 6 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | I | + | + | + | + | I | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, preputial gland | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Osteosarcoma, metastatic, bone | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | + | | | | + | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Leukemia mononuclear | | | | | | X | X | | X | | X | | X | | | | | | X | X | | X | X | | X | X |
| Mesothelioma NOS | | | | | | | | | | | | | | | | | | | | | | | X | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 6 5 1 | 6 5 7 | 6 6 4 | 6 7 1 | 6 7 8 | 6 8 3 | 6 9 1 | 6 9 6 | 6 9 9 | 7 0 1 | 7 0 5 | 7 0 6 | 7 1 3 | 7 1 5 | 7 2 8 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 6 3 | 0 2 9 | 0 1 9 | 0 5 1 | 0 4 7 | 0 3 0 | 0 2 1 | 0 1 3 | 0 5 4 | 0 5 5 | 0 3 4 | 0 2 5 | 0 4 0 | 0 3 7 | 0 6 9 | 0 1 0 | 0 2 7 | 0 4 2 | 0 4 9 | 0 0 6 | 0 1 7 | 0 2 3 | 0 3 1 | 0 6 4 | 0 6 6 | 0 1 5 | 0 5 3 | 0 6 1 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | 49 |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Carcinoma, metastatic, preputial gland | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Osteosarcoma, metastatic, bone | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | + | | | | | | | | | | | | | | | | | | | + | | | | | | | | | 4 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Leukemia mononuclear | | X | X | X | X | X | | X | X | X | X | | X | | | X | X | | | X | X | X | | | X | | X | 28 |
| Mesothelioma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**

| Number of Days on Study | 3 9 8 | 4 5 5 | 5 3 8 | 5 4 9 | 5 5 2 | 5 6 3 | 5 6 9 | 5 7 0 | 5 9 4 | 5 9 4 | 5 9 5 | 5 9 9 | 5 9 9 | 6 0 1 | 6 0 8 | 6 2 3 | 6 2 3 | 6 2 4 | 6 3 8 | 6 3 8 | 6 3 9 | 6 3 9 | 6 4 2 | 6 5 0 | 6 6 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 6 0 2 | 1 8 7 8 | 1 7 4 4 | 1 7 0 0 | 1 6 4 4 | 1 6 3 3 | 1 7 3 3 | 2 0 8 8 | 1 6 0 8 | 2 0 7 7 | 1 7 4 2 | 1 1 4 5 | 1 5 9 9 | 1 9 0 1 | 1 5 7 8 | 1 5 1 3 | 1 6 6 1 | 1 7 7 6 | 1 4 2 4 | 1 9 4 0 | 1 6 0 7 | 1 8 7 9 | 1 9 7 7 | 1 8 4 4 | 2 0 1 1 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | M | + | M | M | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | A | + | + | + | + | + | + | + | A |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | + | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | + | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma malignant | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Pheochromocytoma benign | | X | | X | X | | | | X | | | | | X | | X | | | | | | | | | X |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | X | | | | | | | X | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary gland | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | X | X | | X | | | X | | | | | | X | | | | X | | | X | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | + | | | | | | | | |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 6 9 0 | 6 9 5 | 7 0 0 | 7 1 3 | 7 1 7 | 7 1 8 | 7 2 7 | 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 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 8 | 1 4 3 | 1 5 4 | 1 9 9 | 2 0 5 | 1 4 9 | 1 4 1 | 1 4 4 | 1 4 6 | 1 5 5 | 1 6 9 | 1 9 1 | 1 9 2 | 2 0 3 | 2 0 6 | 2 0 9 | 1 5 2 | 1 5 6 | 1 6 5 | 1 6 7 | 1 7 9 | 1 8 0 | 1 8 1 | 1 9 3 | 2 0 2 | 1 6 1 | 1 9 5 | 2 1 0 | Total Tissues/ Tumors | |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Intestine large, colon | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 | |
| Intestine large, rectum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | M | M | + | + | 45 | |
| Intestine large, cecum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Intestine small, duodenum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 | |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 | |
| Intestine small, jejunum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 | |
| Intestine small, ileum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 | |
| Pheochromocytoma malignant | | | | | | | X | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Pheochromocytoma benign | | X | X | | | | X | X | X | X | X | | X | X | | | | | | X | X | | X | | X | | X | X | X | 23 | |
| Bilateral, pheochromocytoma benign | X | | | | X | | | | | | | | | | | | | X | | | | X | | | | X | | | | 7 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Adenoma | X | | | | | | X | | | | | | | | | | | X | | | | X | | | | | | | 4 | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 | |
| Pars distalis, adenoma | | | | X | | | | | X | | | | X | | | | | | X | | X | | | X | X | X | | X | X | 17 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | 2 | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 3 9 8 | 4 5 5 | 5 3 8 | 5 4 9 | 5 5 2 | 5 6 3 | 5 6 9 | 5 7 0 | 5 9 4 | 5 9 4 | 5 9 5 | 5 9 9 | 5 9 9 | 6 0 1 | 6 0 8 | 6 2 3 | 6 2 3 | 6 2 4 | 6 3 8 | 6 3 8 | 6 3 9 | 6 3 9 | 6 4 2 | 6 5 0 | 6 6 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 6 2 | 1 8 8 | 1 7 4 | 1 7 0 | 1 6 4 | 1 6 3 | 1 7 3 | 2 0 8 | 1 6 8 | 2 0 7 | 1 7 2 | 1 4 5 | 1 5 9 | 1 9 0 | 1 5 7 | 1 5 1 | 1 6 6 | 1 7 7 | 1 4 2 | 1 9 4 | 1 6 0 | 1 8 7 | 1 9 7 | 1 8 4 | 2 0 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Coagulating gland | | | + | + | + | + | + | + | | + | + | + | + | + | + | + | | + | + | + | | + | + | + | + |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| *Bilateral, interstitial cell, adenoma* | | | | | | | | | X | X | X | X | X | 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 | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mediastinal | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma NOS, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Mammary gland* | I | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibroma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Tail, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Oligodendroglioma NOS | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Spinal cord | | | + | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | X | | | | | | X | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 6 9 0 | 6 9 5 | 7 0 0 | 7 1 3 | 7 1 7 | 7 1 8 | 7 2 7 | 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 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 4 8 | 1 4 3 | 1 5 4 | 1 9 9 | 2 0 5 | 1 4 9 | 1 4 1 | 1 4 4 | 1 4 6 | 1 5 5 | 1 6 9 | 1 9 1 | 1 9 2 | 2 0 3 | 2 0 6 | 2 0 9 | 1 5 2 | 1 5 6 | 1 6 5 | 1 6 7 | 1 7 9 | 1 8 0 | 1 8 1 | 1 9 3 | 2 0 2 | 1 6 1 | 1 9 5 | 2 1 0 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Coagulating gland | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | X | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Bilateral, interstitial cell, adenoma | | | X | | X | | X | X | | | X | X | X | X | X | X | | X | X | | | X | X | | X | | | | 30 |
| Interstitial cell, adenoma | | X | | X | | X | | | X | X | | | | | | | X | | | X | X | | | X | | X | X | | 15 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Lymph node | + | | + | + | + | | + | | | | | | | | | | | | | | | | | | | | | | 16 |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Lymph node, mediastinal | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | + | + | + | M | + | + | + | + | + | + | 49 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Mesothelioma NOS, metastatic | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Thymus | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | 49 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | 48 |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Basal cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Fibroma | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | 2 |
| Keratoacanthoma | | | | | | | | | | | | X | | | | | | | | X | | X | | | | | | | 4 |
| Tail, squamous cell papilloma | | | | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Oligodendroglioma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Alveolar/bronchiolar adenoma | | | | | | X | X | | | | | | | | | | | | | | | | | | | | | | 3 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | 3 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m$^3$**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 3 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | 9 | 5 | 3 | 4 | 5 | 6 | 6 | 7 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 4 | 5 | 6 |
| | 8 | 5 | 8 | 9 | 2 | 3 | 9 | 0 | 4 | 4 | 5 | 9 | 9 | 1 | 8 | 3 | 3 | 4 | 8 | 8 | 9 | 9 | 2 | 0 | 1 |
| **Carcass ID Number** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| | 6 | 8 | 7 | 7 | 6 | 6 | 7 | 0 | 6 | 0 | 7 | 4 | 5 | 9 | 5 | 5 | 6 | 7 | 4 | 9 | 6 | 8 | 9 | 8 | 0 |
| | 2 | 8 | 4 | 0 | 4 | 3 | 3 | 8 | 8 | 7 | 2 | 5 | 9 | 0 | 7 | 1 | 6 | 7 | 2 | 4 | 0 | 7 | 7 | 4 | 1 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | + | + | | | | | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urethra | | | | | | + | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | X | | | X | | X | | | X | X | X | X | | X | X | | X | X | X | X | X | X | X | X |
| Mesothelioma NOS | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 6 9 0 | 6 9 5 | 7 0 0 | 7 1 3 | 7 1 7 | 7 1 8 | 7 2 7 | 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 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 8 | 1 4 3 | 1 5 4 | 1 9 9 | 2 0 5 | 1 4 9 | 1 4 1 | 1 4 4 | 1 4 6 | 1 5 5 | 1 6 9 | 1 9 1 | 1 9 2 | 2 0 3 | 2 0 6 | 2 0 9 | 1 5 2 | 1 5 6 | 1 6 5 | 1 6 7 | 1 7 9 | 1 8 0 | 1 8 1 | 1 9 3 | 2 0 2 | 1 6 1 | 1 9 5 | 2 1 0 | Total Tissues/ Tumors |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | + | | | | | | | | | | | | | | | | | | 4 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Urethra | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Leukemia mononuclear | X | | X | X | X | X | X | X | X | X | | | | X | | | | | X | | X | | X | X | X | | | | 32 |
| Mesothelioma NOS | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**

| Number of Days on Study | 4 0 8 | 4 2 4 | 5 0 9 | 5 2 7 | 5 5 2 | 5 5 9 | 5 6 0 | 5 6 4 | 5 6 4 | 5 7 7 | 5 7 8 | 5 8 4 | 5 9 0 | 5 9 4 | 5 9 5 | 6 2 1 | 6 2 1 | 6 2 3 | 6 2 9 | 6 4 2 | 6 4 3 | 6 4 8 | 6 5 0 | 6 6 3 | 6 6 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 4 7 | 3 1 4 | 3 1 0 | 3 0 2 | 2 9 0 | 3 0 0 | 3 4 0 | 3 3 8 | 3 5 0 | 3 2 1 | 3 1 6 | 3 4 8 | 2 8 2 | 2 8 9 | 3 3 7 | 3 1 5 | 2 0 3 | 3 0 5 | 3 1 2 | 3 2 5 | 2 8 3 | 2 8 4 | 3 2 0 | 3 0 4 | 3 3 7 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrosarcoma, metastatic, testes | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pharynx | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | + | | | | | | | | |
| Gingiva, squamous cell carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | X | | | | | | | | X | | X | | X | | | X | | | X | | |
| Bilateral, pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bilateral, pheochromocytoma benign | | | | | | | X | | | | | | | X | | X | | | X | | X | X | | X | X |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | X | | | | | | | | | | | X | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Parathyroid gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | X | X | | X | | | X | X | | X | | X | X | | X | | X | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | X | | | | | | | | X | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | + | | |
| Abdominal, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 | Carcass ID Number | 2 2 2 3 3 2 3 2 3 3 2 3 3 3 3 3 3 2 2 3 3 3 3 3 3 3 | Total Tissues/ Tumors |
|---|---|---|---|---|
| | 7 0 0 0 0 1 1 2 2 3 3 3 3 3 3 3 3 3 6 6 6 6 6 6 6 7 7 7 | | 9 9 9 4 3 8 3 9 4 4 9 0 0 0 1 1 1 2 9 9 0 1 3 3 4 2 3 3 | |
| | 8 3 3 3 7 1 6 3 6 1 3 3 3 3 3 3 3 3 6 6 6 6 6 6 6 7 7 7 | | 7 5 8 9 3 8 0 6 2 1 4 7 8 9 1 3 8 9 1 9 3 7 5 9 6 8 4 6 | |
| **Alimentary System** | | | | |
| Esophagus | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Intestine large, colon | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Intestine large, rectum | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 52 |
| Fibrosarcoma, metastatic, testes | | | | 1 |
| Intestine large, cecum | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 52 |
| Intestine small, duodenum | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Intestine small, jejunum | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 52 |
| Intestine small, ileum | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 52 |
| Liver | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Hepatocellular adenoma | X X X | | | 3 |
| Mesentery | + | | | 1 |
| Pancreas | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Pharynx | + | | | 1 |
| Squamous cell papilloma | X | | | 1 |
| Salivary glands | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Stomach, forestomach | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Squamous cell papilloma | X | | | 1 |
| Stomach, glandular | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Tooth | | | | 1 |
| Gingiva, squamous cell carcinoma | | | | 1 |
| **Cardiovascular System** | | | | |
| Blood vessel | + | | | 1 |
| Heart | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| **Endocrine System** | | | | |
| Adrenal cortex | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Adrenal medulla | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Pheochromocytoma malignant | X X X X X X | | | 6 |
| Pheochromocytoma benign | X X X X X X X | | | 14 |
| Bilateral, pheochromocytoma malignant | X X X X X | | | 5 |
| Bilateral, pheochromocytoma benign | X X X X X X X X X X X X X X X X X X X X X X X X X | | | 23 |
| Islets, pancreatic | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Adenoma | X X X X | | | 4 |
| Carcinoma | X X | | | 2 |
| Parathyroid gland | + + + + + + + + + + + + + + M + + + + + + + + + + + + | | | 51 |
| Pituitary gland | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| Pars distalis, adenoma | X X X X X X X X X X X X X | | | 17 |
| Thyroid gland | + + + + + + + + + + + + + + + + + + + + + + + + + + + | | | 53 |
| C-cell, adenoma | X X X X X X X X X | | | 9 |
| **General Body System** | | | | |
| Tissue NOS | | | | 1 |
| Abdominal, fibrosarcoma | | | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 4 0 8 | 4 2 4 | 5 0 9 | 5 2 7 | 5 5 2 | 5 5 9 | 5 6 0 | 5 6 4 | 5 6 4 | 5 7 7 | 5 7 8 | 5 8 4 | 5 9 0 | 5 9 4 | 5 9 5 | 6 2 1 | 6 2 1 | 6 2 3 | 6 2 9 | 6 4 2 | 6 4 3 | 6 4 8 | 6 5 0 | 6 6 3 | 6 6 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 4 7 | 3 1 4 | 3 1 0 | 3 0 2 | 2 9 0 | 3 0 0 | 3 4 0 | 3 3 8 | 3 5 0 | 3 2 1 | 3 1 6 | 3 4 8 | 2 8 2 | 2 8 9 | 3 3 7 | 3 1 5 | 3 2 3 | 3 0 5 | 3 1 2 | 3 2 5 | 2 8 3 | 2 8 4 | 3 2 0 | 3 0 4 | 3 3 7 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Coagulating gland | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | + |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | + | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | | | | | | | | X | | | | | | | | | | | | X | X | |
| Interstitial cell, adenoma | | | | X | X | | X | | | | | | X | X | | | | X | X | | X | | | | |
| Tunic, fibrosarcoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | + | | | | + | | | | | + | | | | | | | | | | | | | | + | |
| Iliac, fibrosarcoma, metastatic, testes | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Lymph node, *mesenteric* | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mediastinal | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | M | + | + | + | M | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Fibroma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Maxilla, osteosarcoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| *Astrocytoma NOS* | | | | | | | | | | | | | | | | | | | X | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 | |
|---|---|---|
| | 7 0 0 0 0 1 1 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 | |
| | 8 3 3 3 7 1 6 3 6 1 3 3 3 3 3 3 3 3 6 6 6 6 6 6 7 7 7 | |
| **Carcass ID Number** | 2 2 2 3 3 2 3 2 3 3 2 3 3 3 3 3 3 3 2 2 3 3 3 3 3 3 3 | Total |
| | 9 9 9 4 3 8 3 9 4 4 9 0 0 0 1 1 1 2 9 9 0 1 3 3 4 2 3 3 | Tissues/ |
| | 7 5 8 9 3 8 0 6 2 1 4 7 8 9 1 3 8 9 1 9 3 7 5 9 6 8 4 6 | Tumors |
| **Genital System** | | |
| Coagulating gland | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 48 |
| Epididymis | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Penis | | 1 |
| Preputial gland | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Prostate | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Seminal vesicle | + + M + + + + + + + + + + + + + + + + + + + + + + + + | 52 |
| Testes | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Bilateral, interstitial cell, adenoma | X X X X X X X | 15 |
| Interstitial cell, adenoma | X X X X X X X X X X | 20 |
| Tunic, fibrosarcoma | | 1 |
| **Hematopoietic System** | | |
| Bone marrow | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Lymph node | + + + | 6 |
| Iliac, fibrosarcoma, metastatic, testes | | 1 |
| Lymph node, bronchial | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Lymph node, mandibular | + + + + + + + + + + + + + + + + M + + + + M + + + + + | 50 |
| Lymph node, mesenteric | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Lymph node, mediastinal | + + + + + M + + + + + + + + + + + + + + + + + + M + + + | 50 |
| Spleen | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Thymus | + + + + + + + + + + + M + + + + + + + + + + + + + + + | 49 |
| **Integumentary System** | | |
| Mammary gland | + + + + + + + I M + + + + M M M + + M M + + M M + + + M | 43 |
| Skin | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Basal cell adenoma | | 1 |
| Fibroma | X X | 3 |
| Keratoacanthoma | X | 1 |
| Nose, squamous cell papilloma | X | 1 |
| Subcutaneous tissue, lipoma | X | 1 |
| **Musculoskeletal System** | | |
| Bone | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Maxilla, osteosarcoma | | 1 |
| **Nervous System** | | |
| Brain | + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Astrocytoma NOS | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | | |
| | 0 | 2 | 0 | 2 | 5 | 5 | 6 | 6 | 6 | 7 | 7 | 8 | 9 | 9 | 9 | 2 | 2 | 2 | 2 | 4 | 4 | 4 | 5 | 6 | 6 |
| | 8 | 4 | 9 | 7 | 2 | 9 | 0 | 4 | 4 | 7 | 8 | 4 | 0 | 4 | 5 | 1 | 1 | 3 | 9 | 2 | 3 | 8 | 0 | 3 | 3 |
| **Carcass ID Number** | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 3 | 3 | 3 |
| | 4 | 1 | 1 | 0 | 9 | 0 | 4 | 3 | 5 | 2 | 1 | 4 | 8 | 8 | 3 | 1 | 2 | 0 | 1 | 2 | 8 | 8 | 2 | 0 | 2 |
| | 7 | 4 | 0 | 2 | 0 | 0 | 0 | 8 | 0 | 1 | 6 | 8 | 2 | 9 | 7 | 5 | 3 | 5 | 2 | 5 | 3 | 4 | 0 | 4 | 7 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | X | | | | | | X | | | |
| Chordoma, metastatic, tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrosarcoma, metastatic, testes | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Osteosarcoma, metastatic, bone | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Pheochromocytoma malignant, metastatic, adrenal medulla | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | + | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | X | X | X | X | X | | X | X | | | X | | X | X | | X | | X | X | X | X | X | | X | X |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 | |
|---|---|---|
| | 7 0 0 0 0 1 1 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 | |
| | 8 3 3 3 7 1 6 3 6 1 3 3 3 3 3 3 3 6 6 6 6 6 6 6 7 7 7 | |
| **Carcass ID Number** | 2 2 2 3 3 2 3 2 3 3 2 3 3 3 3 3 3 3 2 2 3 3 3 3 3 3 3 3 | Total |
| | 9 9 9 4 3 8 3 9 4 4 9 0 0 0 1 1 1 2 9 9 0 1 3 3 4 2 3 3 | Tissues/ |
| | 7 5 8 9 3 8 0 6 2 1 4 7 8 9 1 3 8 9 1 9 3 7 5 9 6 8 4 6 | Tumors |
| **Respiratory System** | | |
| Larynx | + + + + + + + + + + + + + + + + + + + + + + + + + + + + | 52 |
| Lung | + + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Alveolar/bronchiolar adenoma | X X | 4 |
| Alveolar/bronchiolar adenoma, multiple | X X | 2 |
| Alveolar/bronchiolar carcinoma | X X X X X | 7 |
| Chordoma, metastatic, tissue NOS | X | 1 |
| Fibrosarcoma, metastatic, testes | | 1 |
| Osteosarcoma, metastatic, bone | | 1 |
| Pheochromocytoma malignant, metastatic, adrenal medulla | X | 1 |
| Nose | + + + + + + + + + + + + + + + + + + + + + + + + + + + + | 52 |
| Trachea | + + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| **Special Senses System** | | |
| Eye | + + | 3 |
| **Urinary System** | | |
| Kidney | + + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Urinary bladder | + + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| **Systemic Lesions** | | |
| Multiple organs | + + + + + + + + + + + + + + + + + + + + + + + + + + + + | 53 |
| Leukemia mononuclear | X X X X X X X X X X X X X X X X X X X X X X X X X X X | 35 |

TABLE A3
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|
| **Adrenal Medulla: Benign Pheochromocytoma** | | | |
| Overall rate[a] | 13/53 (25%) | 30/52 (58%) | 37/53 (70%) |
| Adjusted rate[b] | 54.4% | 84.6% | 88.0% |
| Terminal rate[c] | 4/13 (31%) | 16/21 (76%) | 13/18 (72%) |
| First incidence (days) | 559 | 455 | 552 |
| Life table test[d] | P=0.006 | P=0.054 | P=0.004 |
| Logistic regression test[d] | P<0.001 | P=0.002 | P<0.001 |
| Cochran-Armitage test[d] | P<0.001 | | |
| Fisher exact test[d] | | P<0.001 | P<0.001 |
| **Adrenal Medulla: Malignant Pheochromocytoma** | | | |
| Overall rate | 0/53 (0%) | 2/52 (4%) | 11/53 (21%) |
| Adjusted rate | 0.0% | 6.9% | 48.6% |
| Terminal rate | 0/13 (0%) | 0/21 (0%) | 7/18 (39%) |
| First incidence (days) | —[e] | 601 | 703 |
| Life table test | P<0.001 | P=0.309 | P=0.004 |
| Logistic regression test | P<0.001 | P=0.242 | P=0.002 |
| Cochran-Armitage test | P<0.001 | | |
| Fisher exact test | | P=0.243 | P<0.001 |
| **Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma** | | | |
| Overall rate | 14/53 (26%) | 30/52 (58%) | 42/53 (79%) |
| Adjusted rate | 55.4% | 84.6% | 100.0% |
| Terminal rate | 4/13 (31%) | 16/21 (76%) | 18/18 (100%) |
| First incidence (days) | 553 | 455 | 552 |
| Life table test | P<0.001 | P=0.081 | P<0.001 |
| Logistic regression test | P<0.001 | P=0.003 | P<0.001 |
| Cochran-Armitage test | P<0.001 | | |
| Fisher exact test | | P=0.001 | P<0.001 |
| **Liver: Hepatocellular Adenoma** | | | |
| Overall rate | 4/53 (8%) | 1/53 (2%) | 3/53 (6%) |
| Adjusted rate | 18.5% | 2.2% | 14.4% |
| Terminal rate | 1/13 (8%) | 0/21 (0%) | 2/18 (11%) |
| First incidence (days) | 574 | 570 | 703 |
| Life table test | P=0.604N | P=0.114N | P=0.354N |
| Logistic regression test | P=0.629 | P=0.181N | P=0.437N |
| Cochran-Armitage test | P=0.611 | | |
| Fisher exact test | | P=0.181N | P=0.500N |
| **Lung: Alveolar/bronchiolar Adenoma** | | | |
| Overall rate | 0/53 (0%) | 3/53 (6%) | 6/53 (11%) |
| Adjusted rate | 0.0% | 10.5% | 31.6% |
| Terminal rate | 0/13 (0%) | 0/21 (0%) | 5/18 (28%) |
| First incidence (days) | — | 549 | 731 |
| Life table test | P=0.033 | P=0.190 | P=0.039 |
| Logistic regression test | P=0.029 | P=0.128 | P=0.036 |
| Cochran-Armitage test | P=0.022 | | |
| Fisher exact test | | P=0.121 | P=0.013 |

TABLE A3
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Lung: Alveolar/bronchiolar Carcinoma** | | | |
| Overall rate | 0/53 (0%) | 3/53 (6%) | 7/53 (13%) |
| Adjusted rate | 0.0% | 10.3% | 30.3% |
| Terminal rate | 0/13 (0%) | 1/21 (5%) | 4/18 (22%) |
| First incidence (days) | — | 623 | 621 |
| Life table test | P=0.015 | P=0.171 | P=0.024 |
| Logistic regression test | P=0.011 | P=0.129 | P=0.015 |
| Cochran-Armitage test | P=0.009 | | |
| Fisher exact test | | P=0.121 | P=0.006 |
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | |
| Overall rate | 0/53 (0%) | 6/53 (11%) | 11/53 (21%) |
| Adjusted rate | 0.0% | 19.7% | 48.1% |
| Terminal rate | 0/13 (0%) | 1/21 (5%) | 7/18 (39%) |
| First incidence (days) | — | 549 | 621 |
| Life table test | P=0.005 | P=0.044 | P=0.003 |
| Logistic regression test | P=0.003 | P=0.020 | P=0.001 |
| Cochran-Armitage test | P=0.002 | | |
| Fisher exact test | | P=0.013 | P<0.001 |
| **Pancreatic Islets: Adenoma** | | | |
| Overall rate | 2/53 (4%) | 4/53 (8%) | 4/53 (8%) |
| Adjusted rate | 9.9% | 16.7% | 13.3% |
| Terminal rate | 1/13 (8%) | 2/21 (10%) | 1/18 (6%) |
| First incidence (days) | 572 | 690 | 559 |
| Life table test | P=0.468 | P=0.516 | P=0.447 |
| Logistic regression test | P=0.425 | P=0.413 | P=0.344 |
| Cochran-Armitage test | P=0.400 | | |
| Fisher exact test | | P=0.339 | P=0.339 |
| **Pancreatic Islets: Adenoma or Carcinoma** | | | |
| Overall rate | 2/53 (4%) | 5/53 (9%) | 6/53 (11%) |
| Adjusted rate | 9.9% | 18.4% | 21.0% |
| Terminal rate | 1/13 (8%) | 2/21 (10%) | 2/18 (11%) |
| First incidence (days) | 572 | 538 | 559 |
| Life table test | P=0.246 | P=0.367 | P=0.223 |
| Logistic regression test | P=0.203 | P=0.250 | P=0.147 |
| Cochran-Armitage test | P=0.189 | | |
| Fisher exact test | | P=0.219 | P=0.135 |
| **Pituitary Gland (Pars Distalis): Adenoma** | | | |
| Overall rate | 20/53 (38%) | 17/52 (33%) | 17/53 (32%) |
| Adjusted rate | 59.9% | 54.1% | 46.2% |
| Terminal rate | 4/13 (31%) | 9/21 (43%) | 4/18 (22%) |
| First incidence (days) | 521 | 552 | 509 |
| Life table test | P=0.300N | P=0.109N | P=0.187N |
| Logistic regression test | P=0.388N | P=0.340N | P=0.389N |
| Cochran-Armitage test | P=0.380N | | |
| Fisher exact test | | P=0.368N | P=0.342N |

TABLE A3
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Preputial Gland: Adenoma or Carcinoma** | | | |
| Overall rate | 3/53 (6%) | 2/53 (4%) | 0/53 (0%) |
| Adjusted rate | 12.8% | 6.4% | 0.0% |
| Terminal rate | 1/13 (8%) | 0/21 (0%) | 0/18 (0%) |
| First incidence (days) | 553 | 599 | — |
| Life table test | P=0.096N | P=0.380N | P=0.095N |
| Logistic regression test | P=0.110N | P=0.501N | P=0.121N |
| Cochran-Armitage test | P=0.109N | | |
| Fisher exact test | | P=0.500N | P=0.121N |
| **Skin: Fibroma** | | | |
| Overall rate | 3/53 (6%) | 2/53 (4%) | 3/53 (6%) |
| Adjusted rate | 13.2% | 6.7% | 12.9% |
| Terminal rate | 0/13 (0%) | 1/21 (5%) | 2/18 (11%) |
| First incidence (days) | 573 | 549 | 527 |
| Life table test | P=0.610 | P=0.378N | P=0.552N |
| Logistic regression test | P=0.568 | P=0.493N | P=0.644N |
| Cochran-Armitage test | P=0.563 | | |
| Fisher exact test | | P=0.500N | P=0.661N |
| **Skin: Keratoacanthoma** | | | |
| Overall rate | 5/53 (9%) | 4/53 (8%) | 1/53 (2%) |
| Adjusted rate | 25.8% | 16.7% | 5.6% |
| Terminal rate | 2/13 (15%) | 3/21 (14%) | 1/18 (6%) |
| First incidence (days) | 574 | 638 | 733 (T) |
| Life table test | P=0.067N | P=0.287N | P=0.059N |
| Logistic regression test | P=0.072N | P=0.412N | P=0.078N |
| Cochran-Armitage test | P=0.090N | | |
| Fisher exact test | | P=0.500N | P=0.103N |
| **Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Adenoma or Carcinoma** | | | |
| Overall rate | 7/53 (13%) | 6/53 (11%) | 3/53 (6%) |
| Adjusted rate | 34.0% | 24.9% | 13.7% |
| Terminal rate | 3/13 (23%) | 4/21 (19%) | 2/18 (11%) |
| First incidence (days) | 542 | 638 | 642 |
| Life table test | P=0.100N | P=0.245N | P=0.084N |
| Logistic regression test | P=0.111N | P=0.399N | P=0.126N |
| Cochran-Armitage test | P=0.139N | | |
| Fisher exact test | | P=0.500N | P=0.160N |
| **Testes: Adenoma** | | | |
| Overall rate | 39/53 (74%) | 45/53 (85%) | 35/53 (66%) |
| Adjusted rate | 100.0% | 97.8% | 91.6% |
| Terminal rate | 13/13 (100%) | 20/21 (95%) | 15/18 (83%) |
| First incidence (days) | 521 | 455 | 527 |
| Life table test | P=0.061N | P=0.222N | P=0.046N |
| Logistic regression test | P=0.024N | P=0.283 | P=0.091N |
| Cochran-Armitage test | P=0.077N | | |
| Fisher exact test | | P=0.115 | P=0.263N |

TABLE A3
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Thyroid Gland (C-cell): Adenoma** | | | |
| Overall rate | 4/52 (8%) | 2/53 (4%) | 9/53 (17%) |
| Adjusted rate | 18.1% | 7.0% | 34.9% |
| Terminal rate | 1/13 (8%) | 1/21 (5%) | 4/18 (22%) |
| First incidence (days) | 594 | 599 | 564 |
| Life table test | P=0.047 | P=0.208N | P=0.259 |
| Logistic regression test | P=0.032 | P=0.314N | P=0.156 |
| Cochran-Armitage test | P=0.029 | | |
| Fisher exact test | | P=0.330N | P=0.125 |
| **Thyroid Gland (C-cell): Adenoma or Carcinoma** | | | |
| Overall rate | 6/52 (12%) | 3/53 (6%) | 9/53 (17%) |
| Adjusted rate | 25.0% | 11.7% | 34.9% |
| Terminal rate | 1/13 (8%) | 2/21 (10%) | 4/18 (22%) |
| First incidence (days) | 594 | 599 | 564 |
| Life table test | P=0.173 | P=0.127N | P=0.493 |
| Logistic regression test | P=0.133 | P=0.204N | P=0.358 |
| Cochran-Armitage test | P=0.118 | | |
| Fisher exact test | | P=0.235N | P=0.303 |
| **All Organs: Mononuclear Cell Leukemia** | | | |
| Overall rate | 28/53 (53%) | 32/53 (60%) | 35/53 (66%) |
| Adjusted rate | 78.9% | 71.9% | 81.1% |
| Terminal rate | 7/13 (54%) | 9/21 (43%) | 11/18 (61%) |
| First incidence (days) | 539 | 455 | 408 |
| Life table test | P=0.388 | P=0.347N | P=0.522 |
| Logistic regression test | P=0.151 | P=0.357 | P=0.142 |
| Cochran-Armitage test | P=0.139 | | |
| Fisher exact test | | P=0.278 | P=0.118 |
| **All Organs: Benign Neoplasms** | | | |
| Overall rate | 49/53 (92%) | 52/53 (98%) | 50/53 (94%) |
| Adjusted rate | 100.0% | 100.0% | 100.0% |
| Terminal rate | 13/13 (100%) | 21/21 (100%) | 18/18 (100%) |
| First incidence (days) | 521 | 455 | 509 |
| Life table test | P=0.278N | P=0.111N | P=0.148N |
| Logistic regression test | P=0.466N | P=0.398 | P=0.724N |
| Cochran-Armitage test | P=0.611N | | |
| Fisher exact test | | P=0.181 | P=0.500 |
| **All Organs: Malignant Neoplasms** | | | |
| Overall rate | 33/53 (62%) | 37/53 (70%) | 44/53 (83%) |
| Adjusted rate | 81.4% | 78.2% | 93.2% |
| Terminal rate | 7/13 (54%) | 11/21 (52%) | 15/18 (83%) |
| First incidence (days) | 361 | 455 | 408 |
| Life table test | P=0.220 | P=0.318N | P=0.386 |
| Logistic regression test | P=0.015 | P=0.268 | P=0.016 |
| Cochran-Armitage test | P=0.015 | | |
| Fisher exact test | | P=0.269 | P=0.014 |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|
| **All Organs: Benign or Malignant Neoplasms** | | | |
| Overall rate | 52/53 (98%) | 52/53 (98%) | 53/53 (100%) |
| Adjusted rate | 100.0% | 100.0% | 100.0% |
| Terminal rate | 13/13 (100%) | 21/21 (100%) | 18/18 (100%) |
| First incidence (days) | 361 | 455 | 408 |
| Life table test | P=0.337N | P=0.059N | P=0.155N |
| *Logistic regression test* | P=0.845 | P=0.269N | —[f] |
| Cochran-Armitage test | P=0.378 | | |
| Fisher exact test | | P=0.752N | P=0.500 |

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in 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 Untreated Male F344/N Rats[a]

| Study | Incidence in Controls | | | |
|---|---|---|---|---|
| | Alveolar/bronchiolar Adenoma | Alveolar/bronchiolar Carcinoma | Squamous Cell Carcinoma | Alveolar/bronchiolar Adenoma or Carcinoma or Squamous Cell Carcinoma |
| **Historical Incidence at Lovelace Inhalation Toxicology Research Institute** | | | | |
| Nickel Oxide | 0/54 | 0/54 | 1/54 | 1/54 |
| Nickel Subsulfide | 0/53 | 0/53 | 0/53 | 0/53 |
| Nickel Sulfate Hexahydrate | 0/54 | 1/54 | 1/54 | 2/54 |
| Talc[b] | 0/49 | 0/49 | 0/49 | 0/49 |
| **Overall Historical Incidence in Inhalation Studies** | | | | |
| Total | 17/703 (2.4%) | 6/703 (0.9%) | 4/703 (0.6%) | 27/703 (3.8%) |
| Standard deviation | 3.5% | 1.0% | 0.9% | 3.8% |
| Range | 0%-10% | 0%-2% | 0%-2% | 0%-10% |
| **Overall Historical Incidence in Feed Studies** | | | | |
| Total | 28/1,200 (2.3%) | 11/1,200 (0.9%) | 0/1,200 (0%) | 39/1,200 (3.3%) |
| Standard deviation | 2.0% | 1.2% | | 2.0% |
| Range | 0%-6% | 0%-4% | | 0%-8% |

[a] Data as of 17 June 1994
[b] Results of lifetime study

TABLE A4b
**Historical Incidence of Pheochromocytomas of the Adrenal Medulla in Untreated Male F344/N Rats[a]**

| Study | Incidence in Controls | | | | |
|---|---|---|---|---|---|
| | Benign | Complex | Malignant | NOS | Benign, Complex, Malignant or NOS |
| **Historical Incidence at Lovelace Inhalation Toxicology Research Institute** | | | | | |
| Nickel Oxide | 27/54 | 0/54 | 0/54 | 0/54 | 27/54 |
| Nickel Subsulfide | 13/53 | 1/53 | 0/53 | 0/53 | 14/53 |
| Nickel Sulfate Hexahydrate | 16/54 | 0/54 | 0/54 | 0/54 | 16/54 |
| **Overall Historical Incidence in Inhalation Studies** | | | | | |
| Total | 163/623 (26.2%) | 2/623 (0.3%) | 11/623 (1.8%) | 7/623 (1.1%) | 176/623 (28.3%) |
| Standard deviation | 13.1% | 0.8% | 2.9% | 3.9% | 12.0% |
| Range | 0%-50% | 0%-2% | 0%-10% | 0%-14% | 8%-50% |
| **Overall Historical Incidence in Feed Studies** | | | | | |
| Total | 379/1,182 (32.1%) | 2/1,182 (0.2%) | 33/1,182 (2.8%) | 0/1,182 (0%) | 400/1,182 (33.8%) |
| Standard deviation | 11.7% | 0.6% | 3.2% | | 10.9% |
| Range | 10%-63% | 0%-2% | 0%-12% | | 14%-63% |

[a] Data as of 17 June 1994; data from lifetime talc study not included because incidences of adrenal medulla pheochromocytomas increase significantly in aging rats, and this data would not be comparable to that in the 2-year nickel subsulfide study.

TABLE A5
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide**[a]

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 63 | 63 | 63 |
| *7-Month interim evaluation* | 5 | 5 | 5 |
| *15-Month interim evaluation* | 5 | 5 | 5 |
| Early deaths | | | |
| Moribund | 35 | 28 | 33 |
| Natural deaths | 5 | 4 | 2 |
| Survivors | | | |
| Terminal sacrifice | 13 | 21 | 18 |
| Animals examined microscopically | 63 | 63 | 63 |
| ***7-Month Interim Evaluation*** | | | |
| **Genital System** | | | |
| Preputial gland | | | (1) |
| Ectasia | | | 1 (100%) |
| **Hematopoietic System** | | | |
| Lymph node, bronchial | (4) | (5) | (5) |
| Hyperplasia, lymphoid | | 4 (80%) | 5 (100%) |
| Lymph node, mediastinal | (5) | (5) | (5) |
| Hyperplasia, lymphoid | | 5 (100%) | 3 (60%) |
| **Respiratory System** | | | |
| Lung | (5) | (5) | (5) |
| Inflammation, chronic active | 1 (20%) | 5 (100%) | 5 (100%) |
| Metaplasia, osseous | | 1 (20%) | |
| Alveolus, hyperplasia, macrophage | | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 3 (60%) | 5 (100%) |
| Bronchus, hyperplasia, lymphoid | | 1 (20%) | 4 (80%) |
| Interstitium, infiltration cellular | 3 (60%) | 5 (100%) | 5 (100%) |
| Nose | (5) | (5) | (5) |
| Inflammation, chronic active | | | 3 (60%) |
| Olfactory epithelium, atrophy | | | 1 (20%) |
| Respiratory epithelium, hyperplasia | | | 1 (20%) |
| **Urinary System** | | | |
| Urinary bladder | (3) | (4) | (5) |
| Calculus, microscopic observation only | 2 (67%) | 4 (100%) | 5 (100%) |

[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 Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***7-Month Interim Evaluation*** (continued) | | | |
| ***Systems Examined With No Lesions Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Special Senses System** | | | |
| ***15-Month Interim Evaluation*** | | | |
| **Alimentary System** | | | |
| Intestine large, rectum | (5) | (5) | (5) |
| Parasite metazoan | 1 (20%) | | |
| Intestine large, cecum | (5) | (5) | (5) |
| Parasite metazoan | | 1 (20%) | |
| Liver | (5) | (5) | (5) |
| Basophilic focus | 2 (40%) | 4 (80%) | 4 (80%) |
| Clear cell focus | | 1 (20%) | |
| Hepatodiaphragmatic nodule | | | 1 (20%) |
| Infiltration cellular, mononuclear cell | | | 1 (20%) |
| Bile duct, hyperplasia | | 1 (20%) | 1 (20%) |
| **Cardiovascular System** | | | |
| Heart | (5) | (5) | (5) |
| Cardiomyopathy | 1 (20%) | | |
| **Endocrine System** | | | |
| Adrenal medulla | (5) | (5) | (5) |
| Hyperplasia | | | 1 (20%) |
| Pituitary gland | (5) | (5) | (5) |
| Cyst | | | 1 (20%) |
| Pars distalis, hyperplasia | 1 (20%) | | 1 (20%) |
| **Genital System** | | | |
| Preputial gland | (5) | (5) | (5) |
| Inflammation | 1 (20%) | 1 (20%) | 1 (20%) |
| Testes | (5) | (5) | (5) |
| Interstitial cell, hyperplasia | 3 (60%) | 3 (60%) | 2 (40%) |

TABLE A5
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | |
| **Hematopoietic System** | | | |
| Bone marrow | (5) | (5) | (5) |
| Granuloma | | | 1 (20%) |
| Lymph node, bronchial | (5) | (5) | (4) |
| Hyperplasia, lymphoid | | 5 (100%) | 4 (100%) |
| Hyperplasia, macrophage | | 4 (80%) | 4 (100%) |
| Lymph node, mediastinal | (4) | (5) | (3) |
| Hyperplasia, lymphoid | | | 1 (33%) |
| Hyperplasia, macrophage | | 1 (20%) | |
| Spleen | (5) | (5) | (5) |
| Hyperplasia, lymphoid | | | 1 (20%) |
| **Respiratory System** | | | |
| Lung | (5) | (5) | (5) |
| Hemorrhage, acute | 3 (60%) | 1 (20%) | |
| Inflammation, chronic active | | 5 (100%) | 5 (100%) |
| Metaplasia, osseous | | 1 (20%) | 1 (20%) |
| Alveolus, emphysema | | | 1 (20%) |
| Alveolus, hyperplasia, macrophage | 1 (20%) | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 5 (100%) | 5 (100%) |
| Interstitium, infiltration cellular | 2 (40%) | 4 (80%) | 4 (80%) |
| Nose | (5) | (5) | (5) |
| Inflammation, chronic active | 1 (20%) | 2 (40%) | |
| **Urinary System** | | | |
| Kidney | (5) | (5) | (5) |
| Nephropathy | 5 (100%) | 5 (100%) | 5 (100%) |
| Urinary bladder | (5) | (5) | (5) |
| Calculus, gross observation | 2 (40%) | 1 (20%) | |
| Calculus, microscopic observation only | 1 (20%) | 2 (40%) | 1 (20%) |
| Congestion | 1 (20%) | | |
| ***Systems Examined With No Lesions Observed*** | | | |
| **General Body System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Special Senses System** | | | |

TABLE A5
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Intestine large, colon | (51) | (51) | (53) |
| Inflammation | 3 (6%) | | |
| Mineralization | 1 (2%) | | |
| Parasite metazoan | | 1 (2%) | 1 (2%) |
| Intestine large, rectum | (46) | (45) | (52) |
| Inflammation | 1 (2%) | | |
| Parasite metazoan | 3 (7%) | 1 (2%) | 2 (4%) |
| Intestine large, cecum | (51) | (49) | (52) |
| Hyperplasia, lymphoid | 1 (2%) | | 1 (2%) |
| Inflammation | 2 (4%) | | 4 (8%) |
| Parasite metazoan | 1 (2%) | 1 (2%) | 1 (2%) |
| Intestine small, duodenum | (52) | (52) | (53) |
| Ulcer | | | 2 (4%) |
| Intestine small, jejunum | (51) | (51) | (52) |
| Hyperplasia, lymphoid | 1 (2%) | | |
| Intestine small, ileum | (51) | (51) | (52) |
| Hyperplasia, lymphoid | 4 (8%) | 5 (10%) | 3 (6%) |
| Liver | (53) | (53) | (53) |
| Angiectasis | 3 (6%) | 1 (2%) | |
| Basophilic focus | 27 (51%) | 31 (58%) | 31 (58%) |
| Clear cell focus | 1 (2%) | | |
| Degeneration, cystic | 11 (21%) | 15 (28%) | 15 (28%) |
| Degeneration, fatty | 9 (17%) | 2 (4%) | 7 (13%) |
| Eosinophilic focus | 6 (11%) | 6 (11%) | 6 (11%) |
| Hepatodiaphragmatic nodule | 3 (6%) | 2 (4%) | 3 (6%) |
| Inflammation, focal, granulomatous | 1 (2%) | 2 (4%) | 1 (2%) |
| Pigmentation, hemosiderin | | | 1 (2%) |
| Thrombosis | | | 1 (2%) |
| Bile duct, hyperplasia | 40 (75%) | 44 (83%) | 38 (72%) |
| Biliary tract, hyperplasia | 1 (2%) | | |
| Centrilobular, atrophy | 12 (23%) | 16 (30%) | 13 (25%) |
| Hepatocyte, hyperplasia | 3 (6%) | 1 (2%) | 2 (4%) |
| Hepatocyte, necrosis | 4 (8%) | 7 (13%) | 4 (8%) |
| Mesentery | (1) | (1) | (1) |
| Inflammation | | | 1 (100%) |
| Fat, necrosis | | 1 (100%) | |
| Pancreas | (53) | (53) | (53) |
| Atrophy | 15 (28%) | 15 (28%) | 25 (47%) |
| Hyperplasia | | 1 (2%) | |
| Salivary glands | (53) | (52) | (53) |
| Infarct | | 1 (2%) | 1 (2%) |
| Stomach, forestomach | (53) | (53) | (53) |
| Diverticulum | | 1 (2%) | |
| Hyperkeratosis | 1 (2%) | 3 (6%) | |
| Hyperplasia, squamous | 1 (2%) | | 5 (9%) |
| Mineralization | 1 (2%) | | |
| Ulcer | 4 (8%) | 1 (2%) | 6 (11%) |

TABLE A5
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Alimentary System** (continued) | | | |
| Stomach, glandular | (53) | (53) | (53) |
| Necrosis, focal | 1 (2%) | 2 (4%) | 3 (6%) |
| Epithelium, mineralization | 1 (2%) | 1 (2%) | |
| Tooth | (1) | (1) | (1) |
| Dysplasia | 1 (100%) | 1 (100%) | |
| **Cardiovascular System** | | | |
| Blood vessel | (1) | | (1) |
| Inflammation | | | 1 (100%) |
| Mineralization | 1 (100%) | | |
| Heart | (53) | (53) | (53) |
| Cardiomyopathy | 36 (68%) | 37 (70%) | 36 (68%) |
| Embolus | 1 (2%) | | |
| Inflammation | 2 (4%) | | |
| Mineralization | 1 (2%) | | 1 (2%) |
| Atrium, thrombosis | 7 (13%) | 6 (11%) | 4 (8%) |
| Valve, thrombosis | | | 1 (2%) |
| **Endocrine System** | | | |
| Adrenal cortex | (53) | (53) | (53) |
| Atrophy | | 1 (2%) | |
| Degeneration, cystic | 2 (4%) | 3 (6%) | 5 (9%) |
| Hyperplasia, diffuse | 1 (2%) | | |
| Hyperplasia, focal | 3 (6%) | 2 (4%) | 2 (4%) |
| Necrosis | 2 (4%) | | 1 (2%) |
| Vacuolization cytoplasmic | 23 (43%) | 7 (13%) | 12 (23%) |
| Adrenal medulla | (53) | (52) | (53) |
| Hyperplasia | 26 (49%) | 22 (42%) | 10 (19%) |
| Bilateral, thrombosis | | | 1 (2%) |
| Islets, pancreatic | (53) | (53) | (53) |
| Hyperplasia | 1 (2%) | | 1 (2%) |
| Parathyroid gland | (50) | (50) | (51) |
| Hyperplasia | 8 (16%) | 6 (12%) | 1 (2%) |
| Pituitary gland | (53) | (52) | (53) |
| Pars distalis, angiectasis | 4 (8%) | 9 (17%) | 3 (6%) |
| Pars distalis, cyst | 1 (2%) | 1 (2%) | 3 (6%) |
| Pars distalis, hyperplasia | 16 (30%) | 12 (23%) | 12 (23%) |
| Thyroid gland | (52) | (53) | (53) |
| C-cell, hyperplasia | 7 (13%) | 8 (15%) | 7 (13%) |
| Follicle, hyperplasia | 1 (2%) | | |
| Follicular cell, hyperplasia | 1 (2%) | | |
| **General Body System** | | | |
| None | | | |

TABLE A5
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Genital System** | | | |
| Coagulating gland | (39) | (47) | (48) |
| Inflammation | 1 (3%) | 3 (6%) | 1 (2%) |
| Epididymis | (53) | (53) | (53) |
| Granuloma sperm | | 3 (6%) | |
| Inflammation | | | 1 (2%) |
| Penis | (2) | | (1) |
| Concretion | 2 (100%) | | |
| Preputial gland | (53) | (53) | (53) |
| Ectasia | 2 (4%) | 1 (2%) | 2 (4%) |
| Hyperplasia | 3 (6%) | 1 (2%) | 1 (2%) |
| Inflammation | 1 (2%) | 5 (9%) | 3 (6%) |
| Prostate | (53) | (53) | (53) |
| Inflammation | 2 (4%) | 3 (6%) | |
| Seminal vesicle | (52) | (53) | (52) |
| Atrophy | 1 (2%) | 2 (4%) | 2 (4%) |
| Epithelium, hyperplasia | | | 1 (2%) |
| Testes | (53) | (53) | (53) |
| Germinal epithelium, degeneration | 7 (13%) | 13 (25%) | 13 (25%) |
| Interstitial cell, hyperplasia | 11 (21%) | 13 (25%) | 16 (30%) |
| **Hematopoietic System** | | | |
| Bone marrow | (53) | (52) | (53) |
| Atrophy | 4 (8%) | 3 (6%) | 2 (4%) |
| Fibrosis | 2 (4%) | | 1 (2%) |
| Inflammation, focal, granulomatous | 1 (2%) | 1 (2%) | |
| Inflammation, suppurative | | | 1 (2%) |
| Necrosis | 1 (2%) | 1 (2%) | |
| Myeloid cell, hyperplasia | 1 (2%) | 1 (2%) | 5 (9%) |
| Lymph node | (5) | (16) | (6) |
| Iliac, hyperplasia, lymphoid | | 1 (6%) | |
| Pancreatic, hyperplasia, lymphoid | | | 1 (17%) |
| Renal, angiectasis | 1 (20%) | | |
| Renal, pigmentation | | 1 (6%) | |
| Lymph node, bronchial | (52) | (51) | (53) |
| Angiectasis | 1 (2%) | | |
| Ectasia | | 1 (2%) | |
| Hyperplasia, lymphoid | 5 (10%) | 29 (57%) | 34 (64%) |
| Hyperplasia, macrophage | 1 (2%) | 14 (27%) | 28 (53%) |
| Hyperplasia, plasma cell | 1 (2%) | 1 (2%) | 1 (2%) |
| Lymph node, mandibular | (50) | (51) | (50) |
| Hyperplasia, lymphoid | 4 (8%) | 7 (14%) | 3 (6%) |
| Hyperplasia, plasma cell | 6 (12%) | 10 (20%) | 4 (8%) |
| Inflammation | 2 (4%) | | |
| Lymph node, mesenteric | (53) | (53) | (53) |
| Angiectasis | 1 (2%) | | |
| Atrophy | 1 (2%) | | |
| Hyperplasia, lymphoid | 5 (9%) | 11 (21%) | 6 (11%) |
| Hyperplasia, macrophage | | | 1 (2%) |
| Inflammation | 1 (2%) | | |

TABLE A5
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Hematopoietic System** (continued) | | | |
| Lymph node, mediastinal | (49) | (49) | (50) |
| Angiectasis | 1 (2%) | | |
| Hyperplasia, lymphoid | 1 (2%) | 15 (31%) | 8 (16%) |
| Hyperplasia, macrophage | | 1 (2%) | |
| Inflammation | 1 (2%) | | |
| Spleen | (53) | (53) | (53) |
| Atrophy | 3 (6%) | 2 (4%) | 1 (2%) |
| Fibrosis | 10 (19%) | 13 (25%) | 12 (23%) |
| Hematopoietic cell proliferation | 2 (4%) | | |
| Hemorrhage | | | 1 (2%) |
| Hyperplasia, lymphoid | | 4 (8%) | |
| Infarct | | 2 (4%) | |
| Pigmentation, hemosiderin | | 2 (4%) | 3 (6%) |
| Thymus | (50) | (49) | (49) |
| Degeneration | 17 (34%) | 3 (6%) | 10 (20%) |
| **Integumentary System** | | | |
| Mammary gland | (49) | (48) | (43) |
| Hyperplasia, cystic | 8 (16%) | 2 (4%) | 2 (5%) |
| Skin | (53) | (53) | (53) |
| Cyst epithelial inclusion | 2 (4%) | 1 (2%) | 1 (2%) |
| Conjunctiva, inflammation | 1 (2%) | | |
| Dermis, inflammation | 1 (2%) | | |
| Subcutaneous tissue, inflammation | | | 1 (2%) |
| Tail, hyperkeratosis | | 1 (2%) | 1 (2%) |
| **Musculoskeletal System** | | | |
| Bone | (53) | (52) | (53) |
| Fibrous osteodystrophy | 1 (2%) | | |
| Hyperostosis | 1 (2%) | 4 (8%) | 1 (2%) |
| Mandible, necrosis | | | 1 (2%) |
| **Nervous System** | | | |
| Brain | (53) | (53) | (53) |
| Compression | 1 (2%) | | |
| Cyst | | | 1 (2%) |
| Embolus | 1 (2%) | | |
| Necrosis | 1 (2%) | | |
| Cerebrum, atrophy, focal | | | 1 (2%) |
| Cerebrum, compression | 6 (11%) | 4 (8%) | 4 (8%) |
| Gray matter, necrosis | 1 (2%) | | |
| **Respiratory System** | | | |
| Larynx | (49) | (53) | (52) |
| Hyperplasia | 4 (8%) | | |
| Inflammation | 3 (6%) | 2 (4%) | 2 (4%) |

**TABLE A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Respiratory System** (continued) | | | |
| Lung | (53) | (53) | (53) |
| Embolus | 1 (2%) | | |
| Emphysema | | 1 (2%) | 1 (2%) |
| Fibrosis | 2 (4%) | 48 (91%) | 40 (75%) |
| Hemorrhage, acute | 4 (8%) | | |
| Inflammation, chronic active | 9 (17%) | 53 (100%) | 51 (96%) |
| Metaplasia, osseous | 2 (4%) | 1 (2%) | 1 (2%) |
| Metaplasia, squamous | | 2 (4%) | |
| Mineralization | 1 (2%) | | 1 (2%) |
| Alveolar epithelium, hyperplasia, focal | 2 (4%) | 6 (11%) | 11 (21%) |
| Alveolus, hyperplasia, macrophage | 9 (17%) | 48 (91%) | 52 (98%) |
| Alveolus, proteinosis | 1 (2%) | 36 (68%) | 51 (96%) |
| Bronchus, hyperplasia, lymphoid | | 10 (19%) | 14 (26%) |
| Interstitium, infiltration cellular | 17 (32%) | 31 (58%) | 39 (74%) |
| Nose | (53) | (53) | (52) |
| Inflammation, acute | | 1 (2%) | |
| Inflammation, chronic active | 12 (23%) | 10 (19%) | 18 (35%) |
| Thrombosis | 3 (6%) | 3 (6%) | 4 (8%) |
| Nasolacrimal duct, inflammation | | | 3 (6%) |
| Olfactory epithelium, atrophy | 2 (4%) | 1 (2%) | 9 (17%) |
| Olfactory epithelium, mineralization, focal | 1 (2%) | | 3 (6%) |
| **Special Senses System** | | | |
| Eye | (4) | (4) | (3) |
| Cataract | 1 (25%) | 2 (50%) | |
| Inflammation | 1 (25%) | | |
| Phthisis bulbi | 1 (25%) | | |
| Anterior chamber, hemorrhage, chronic | | 1 (25%) | |
| Iris, inflammation | | 1 (25%) | |
| Retina, degeneration | | 3 (75%) | |
| **Urinary System** | | | |
| Kidney | (52) | (53) | (53) |
| Cyst | 1 (2%) | 2 (4%) | 2 (4%) |
| Embolus | 1 (2%) | | |
| Hydronephrosis | | | 1 (2%) |
| Infarct | 1 (2%) | | 1 (2%) |
| Inflammation | 1 (2%) | | |
| Mineralization | 1 (2%) | | 1 (2%) |
| Nephropathy | 51 (98%) | 53 (100%) | 53 (100%) |
| Cortex, infarct | | | 2 (4%) |
| Papilla, necrosis | | | 1 (2%) |
| Renal tubule, pigmentation | 20 (38%) | 35 (66%) | 35 (66%) |
| Urethra | | (1) | |
| Calculus, microscopic observation only | | 1 (100%) | |
| Urinary bladder | (53) | (53) | (53) |
| Calculus, gross observation | 2 (4%) | 1 (2%) | |
| Calculus, microscopic observation only | 4 (8%) | 1 (2%) | 2 (4%) |
| Inflammation | | | 3 (6%) |

# APPENDIX B
# SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF NICKEL SUBSULFIDE

TABLE B1
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 63 | 63 | 63 |
| *7-Month interim evaluation* | 5 | 5 | 5 |
| *15-Month interim evaluation* | 5 | 5 | 5 |
| Early deaths | | | |
| Accidental death | | | 1 |
| Moribund | 24 | 27 | 23 |
| Natural deaths | 4 | 1 | 1 |
| Survivors | | | |
| Terminal sacrifice | 25 | 25 | 28 |
| Animals examined microscopically | 63 | 63 | 63 |
| ***Systems Examined At 7 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** | | | |
| ***15-Month Interim Evaluation*** | | | |
| **Endocrine System** | | | |
| Pituitary gland | (5) | (5) | (5) |
| Pars distalis, adenoma | | 1 (20%) | 2 (40%) |
| **Genital System** | | | |
| Clitoral gland | (5) | (5) | (5) |
| Carcinoma | 1 (20%) | | |
| Uterus | (5) | (5) | (5) |
| Sarcoma stromal | | | 1 (20%) |
| Vagina | | | (1) |
| Polyp | | | 1 (100%) |
| **Special Senses System** | | | |
| Zymbal's gland | | (1) | |
| Carcinoma | | 1 (100%) | |

**TABLE B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | |
| ***Systems Examined With No Neoplasms Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **General Body System** | | | |
| **Hematopoietic System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Respiratory System** | | | |
| **Urinary System** | | | |
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Liver | (53) | (53) | (53) |
| Histiocytic sarcoma | | | 1 (2%) |
| Mesentery | (1) | | (2) |
| Histiocytic sarcoma | | | 1 (50%) |
| Pancreas | (53) | (52) | (53) |
| Histiocytic sarcoma | | | 1 (2%) |
| Stomach, forestomach | (53) | (53) | (53) |
| Stomach, glandular | (53) | (53) | (53) |
| Tooth | (1) | (1) | |
| Gingiva, squamous cell carcinoma | | 1 (100%) | |
| **Cardiovascular System** | | | |
| Heart | (53) | (53) | (53) |
| Schwannoma NOS | 1 (2%) | 2 (4%) | |
| **Endocrine System** | | | |
| Adrenal cortex | (53) | (53) | (53) |
| Adrenal medulla | (53) | (53) | (53) |
| Histiocytic sarcoma | | | 1 (2%) |
| Pheochromocytoma malignant | 1 (2%) | | 1 (2%) |
| Pheochromocytoma benign | 2 (4%) | 6 (11%) | 12 (23%) |
| Bilateral, pheochromocytoma benign | | 1 (2%) | 24 (45%) |
| Islets, pancreatic | (53) | (53) | (53) |
| Adenoma | | 1 (2%) | 1 (2%) |
| Carcinoma | 1 (2%) | 1 (2%) | |
| Parathyroid gland | (48) | (50) | (49) |
| Pituitary gland | (52) | (53) | (53) |
| Pars distalis, adenoma | 24 (46%) | 30 (57%) | 15 (28%) |
| Thyroid gland | (51) | (53) | (52) |
| C-cell, adenoma | 3 (6%) | 4 (8%) | 4 (8%) |
| C-cell, carcinoma | | 3 (6%) | |
| Follicular cell, carcinoma | | 1 (2%) | |

TABLE B1
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **General Body System** | | | |
| Tissue NOS | | (2) | (1) |
| Mediastinum, squamous cell carcinoma, metastatic, lung | | 1 (50%) | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (100%) |
| Thoracic, squamous cell carcinoma, metastatic, lung | | 1 (50%) | |
| **Genital System** | | | |
| Clitoral gland | (52) | (52) | (52) |
| Adenoma | | 2 (4%) | 1 (2%) |
| Carcinoma | 1 (2%) | 3 (6%) | 3 (6%) |
| Ovary | (53) | (53) | (53) |
| Cystadenoma | | | 1 (2%) |
| Granulosa cell tumor benign | 2 (4%) | | |
| Granulosa-theca tumor benign | | 1 (2%) | |
| Histiocytic sarcoma | | | 1 (2%) |
| Uterus | (53) | (53) | (53) |
| Adenoma | | 1 (2%) | |
| Polyp stromal | 2 (4%) | 1 (2%) | 3 (6%) |
| Vagina | | (1) | (1) |
| Schwannoma malignant | | 1 (100%) | |
| **Hematopoietic System** | | | |
| Bone marrow | (53) | (53) | (53) |
| Histiocytic sarcoma | | | 1 (2%) |
| Lymph node | (5) | (3) | (10) |
| Iliac, histiocytic sarcoma | | | 1 (10%) |
| Renal, histiocytic sarcoma | | | 1 (10%) |
| Lymph node, bronchial | (50) | (49) | (50) |
| Histiocytic sarcoma | | | 1 (2%) |
| Lymph node, mandibular | (44) | (50) | (51) |
| Lymph node, mesenteric | (52) | (53) | (52) |
| Lymph node, mediastinal | (46) | (50) | (47) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) |
| Spleen | (53) | (53) | (53) |
| Histiocytic sarcoma | | | 1 (2%) |
| Thymus | (49) | (51) | (51) |
| **Integumentary System** | | | |
| Mammary gland | (53) | (53) | (53) |
| Adenoma | 1 (2%) | | |
| Carcinoma | 1 (2%) | 3 (6%) | |
| Fibroadenoma | 22 (42%) | 11 (21%) | 10 (19%) |

**TABLE B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Integumentary System** (continued) | | | |
| Skin | (53) | (53) | (53) |
| Fibrosarcoma | | 1 (2%) | |
| Histiocytic sarcoma | | | 1 (2%) |
| Keratoacanthoma | | | 1 (2%) |
| Pinna, fibrosarcoma | 1 (2%) | | 1 (2%) |
| Subcutaneous tissue, lipoma | | 1 (2%) | |
| **Musculoskeletal System** | | | |
| Bone | (53) | (53) | (53) |
| Squamous cell carcinoma, metastatic, tooth | | 1 (2%) | |
| Skeletal muscle | | (1) | |
| Squamous cell carcinoma, metastatic, tooth | | 1 (100%) | |
| **Nervous System** | | | |
| Brain | (53) | (53) | (53) |
| Astrocytoma NOS | | 1 (2%) | |
| **Respiratory System** | | | |
| Lung | (53) | (53) | (53) |
| Adenoma | 1 (2%) | | |
| Alveolar/bronchiolar adenoma | 1 (2%) | 5 (9%) | 5 (9%) |
| Alveolar/bronchiolar carcinoma | | | 3 (6%) |
| Alveolar/bronchiolar carcinoma, multiple | | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) |
| Squamous cell carcinoma | | 1 (2%) | |
| Nose | (53) | (53) | (52) |
| **Special Senses System** | | | |
| None | | | |
| **Urinary System** | | | |
| Kidney | (53) | (53) | (53) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) |
| Nephroblastoma | 1 (2%) | | |
| Urinary bladder | (53) | (53) | (53) |
| **Systemic Lesions** | | | |
| Multiple organs[b] | (53) | (53) | (53) |
| Histiocytic sarcoma | | | 1 (2%) |
| Leukemia mononuclear | 19 (36%) | 18 (34%) | 22 (42%) |

TABLE B1
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[c] | | | |
| 15-Month interim evaluation | 1 | 2 | 4 |
| 2-Year study | 48 | 51 | 48 |
| Total primary neoplasms | | | |
| 15-Month interim evaluation | 1 | 2 | 4 |
| 2-Year study | 84 | 100 | 109 |
| Total animals with benign neoplasms | | | |
| 15-Month interim evaluation | | 1 | 3 |
| 2-Year study | 37 | 45 | 45 |
| Total benign neoplasms | | | |
| 15-Month interim evaluation | | 1 | 3 |
| 2-Year study | 58 | 64 | 77 |
| Total animals with malignant neoplasms | | | |
| 15-Month interim evaluation | 1 | 1 | 1 |
| 2-Year study | 24 | 30 | 28 |
| Total malignant neoplasms | | | |
| 15-Month interim evaluation | 1 | 1 | 1 |
| 2-Year study | 25 | 33 | 32 |
| Total animals with metastatic neoplasms | | | |
| 2-Year study | | 2 | 1 |
| Total metastatic neoplasms | | | |
| 2-Year study | | 4 | 3 |
| Total animals with uncertain neoplasms-benign or malignant | | | |
| 2-Year study | 1 | 3 | |
| Total uncertain neoplasms | | | |
| 2-Year study | 1 | 3 | |

[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 Nickel Subsulfide: 0 mg/m³

| Number of Days on Study | 2 6 3 | 3 6 9 | 3 7 7 | 4 7 7 | 4 7 7 | 5 0 0 | 5 1 3 | 5 3 8 | 5 6 3 | 5 7 4 | 5 7 4 | 6 1 3 | 6 4 0 | 6 4 0 | 6 4 0 | 6 4 2 | 6 5 7 | 6 6 4 | 6 6 5 | 6 6 5 | 6 6 7 | 6 7 7 | 6 7 8 | 6 9 6 | 7 1 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 9 2 | 0 8 1 | 1 2 4 | 1 3 4 | 1 3 9 | 0 8 3 | 0 7 7 | 1 1 0 | 0 8 9 | 0 9 6 | 1 3 0 | 0 9 4 | 0 7 2 | 0 8 7 | 1 0 2 | 1 2 9 | 1 8 3 | 0 9 4 | 0 0 0 | 1 0 2 | 1 2 0 | 1 1 6 | 0 7 6 | 1 2 6 | 1 1 3 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | A | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | A | A | + | A | + | + | + | I | + | + | + | + | + | + | + | M | M | + | + | I | + | + | + | + | + |
| Intestine large, cecum | A | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + |
| Intestine small, duodenum | A | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + |
| Intestine small, jejunum | A | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | A | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesentery | | | | | | | | | | | | | | | | | | + | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Schwannoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | M | M | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | X | | | | | | X | | X | | X | | X | | | | | X | X | | | X |
| Thyroid gland | M | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Granulosa cell tumor benign | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp stromal | | | | | | 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 Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 7 1 7 | 7 2 1 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 7 3 | 1 2 5 | 1 3 3 | 1 0 9 | 1 2 2 | 1 2 7 | 1 2 9 | 0 7 1 | 0 8 0 | 0 8 5 | 0 8 6 | 0 9 7 | 0 9 8 | 0 9 9 | 0 0 1 | 1 2 1 | 1 4 0 | 1 8 2 | 0 9 5 | 0 0 3 | 1 0 7 | 1 1 4 | 1 1 5 | 1 3 5 | 0 9 3 | 1 1 1 | 1 1 7 | 1 1 8 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | M | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | I | + | 41 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Tooth | | | | | | | | | | | | | + | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Schwannoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma benign | | | X | | | | | X | | | | | | | | | | | | | | | | | | | | | 2 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | 48 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Pars distalis, adenoma | X | | X | X | X | X | | | X | X | | | | X | X | X | X | X | | | X | | | X | X | | X | X | 24 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | | 3 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Granulosa cell tumor benign | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | 2 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Polyp stromal | | | | X | | | | | | | | | | | | | | | | | | | | | | | | | 2 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 2 | 3 | 3 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 | 6 | 7 | 7 | 7 | 0 | 1 | 3 | 6 | 7 | 7 | 1 | 4 | 4 | 4 | 4 | 5 | 6 | 6 | 6 | 6 | 7 | 7 | 9 | 1 |
| | 3 | 9 | 7 | 7 | 7 | 0 | 3 | 8 | 3 | 4 | 4 | 3 | 0 | 0 | 0 | 2 | 7 | 4 | 5 | 5 | 7 | 7 | 8 | 6 | 6 |
| **Carcass ID Number** | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 |
| | 9 | 8 | 2 | 3 | 3 | 8 | 7 | 1 | 8 | 9 | 3 | 9 | 7 | 8 | 0 | 1 | 2 | 8 | 9 | 0 | 2 | 1 | 7 | 2 | 1 |
| | 2 | 1 | 4 | 4 | 9 | 3 | 7 | 0 | 9 | 6 | 0 | 4 | 2 | 7 | 2 | 9 | 3 | 4 | 0 | 0 | 0 | 6 | 6 | 6 | 3 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | + | | + | | | | | + | | | | | | | | + | | + | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | + | + | M | + | + | + | I | + | + | + | + | + | + | + | + | + | I | + | M | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mediastinal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | M | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | X | | X | | X | | | X | X | | X | X | X | | | | X | | | | | | X |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pinna, fibrosarcoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nephroblastoma | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | 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 Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 7 1 7 | 7 2 1 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 7 3 | 1 2 5 | 1 3 3 | 1 0 9 | 1 2 2 | 1 2 7 | 1 2 9 | 0 7 1 | 0 8 0 | 0 8 5 | 0 8 6 | 0 9 7 | 0 9 8 | 0 9 9 | 0 9 9 | 1 0 1 | 1 2 1 | 1 4 0 | 0 8 2 | 0 9 5 | 1 0 3 | 1 0 7 | 1 1 4 | 1 1 5 | 1 3 5 | 0 9 3 | 1 1 1 | 1 1 7 | 1 1 8 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | I | + | + | + | 50 |
| Lymph node, mandibular | + | + | M | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | M | 44 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Lymph node, mediastinal | + | + | + | + | + | M | + | M | + | I | + | + | + | + | + | + | + | M | M | + | + | + | + | + | I | + | + | + | 46 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Thymus | + | + | + | + | + | + | + | I | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| Fibroadenoma | | | X | X | | | | X | X | | | | | | | X | X | | X | | | | | X | X | | X | X | X | 22 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pinna, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | + | | | | | | | | | | | | | | + | | | | | | 2 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Nephroblastoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Leukemia mononuclear | X | X | | | | | | | X | | | | X | | | | | | | X | X | | X | | | X | | | 19 |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**

| Number of Days on Study | 4 5 2 | 4 8 2 | 4 8 2 | 5 3 8 | 5 6 6 | 5 9 0 | 5 9 4 | 5 9 4 | 6 0 9 | 6 0 9 | 6 1 2 | 6 2 0 | 6 2 0 | 6 2 2 | 6 3 5 | 6 3 6 | 6 4 0 | 6 4 2 | 6 4 9 | 5 7 3 | 6 8 1 | 6 9 5 | 6 9 9 | 7 0 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 4 6 | 2 2 2 | 2 2 7 | 2 3 8 | 2 7 5 | 2 3 2 | 2 6 2 | 2 7 7 | 2 2 9 | 2 7 2 | 2 4 0 | 2 6 3 | 2 7 4 | 2 1 8 | 2 7 9 | 2 4 2 | 2 5 7 | 2 5 5 | 2 4 3 | 2 3 4 | 2 7 3 | 2 7 0 | 2 6 9 | 2 3 1 | 2 4 7 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | A | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | M | + | M | + | + | M | + |
| Intestine large, cecum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | + | | | | | | | | |
| Gingiva, squamous cell carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Schwannoma NOS | | | | | | | | | | X | | | | | | X | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | X | | | | | | | | | | | | | | | | | | | X |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | X | | | | | X | X | | | X | X | X | | | X | | X | X | X | X | X | X | X | X |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | X | | | | | | | | | | | X | | | |
| C-cell, carcinoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | + | | + | | | | | | | |
| Mediastinum, squamous cell carcinoma, metastatic, lung | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Thoracic, squamous cell carcinoma, metastatic, lung | | | | | | | | | | | | | | | | X | | | | | | | | | |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 7 1 8 | 7 2 1 | 7 2 7 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 7 8 | 2 2 0 | 2 4 5 | 2 1 2 | 2 1 9 | 2 1 1 | 2 2 5 | 2 2 8 | 2 3 5 | 2 3 6 | 2 3 9 | 2 5 1 | 2 5 3 | 2 5 8 | 2 1 1 | 2 3 0 | 2 3 3 | 2 6 5 | 2 6 8 | 2 3 7 | 2 4 4 | 2 5 4 | 2 5 6 | 2 6 0 | 2 8 0 | 2 2 3 | 2 2 6 | 2 6 7 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine large, rectum | M | + | + | M | M | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | M | + | + | M | + | I | + | 40 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | 52 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Gingiva, squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Schwannoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pheochromocytoma benign | | | | | | | | X | X | | | | | | | | | | X | | | | | | | X | | 6 |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | M | 50 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pars distalis, adenoma | X | X | | | X | X | | | | X | | X | X | X | X | | X | | | X | | | X | | X | X | | X | 30 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | | X | 4 |
| C-cell, carcinoma | | | | | | | | | | | | | | | | X | | | | | | | X | | | | | | 3 |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Mediastinum, squamous cell carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thoracic, squamous cell carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 4 5 2 | 4 8 2 | 4 8 2 | 5 3 8 | 5 6 6 | 5 9 0 | 5 9 4 | 5 9 4 | 6 0 9 | 6 0 9 | 6 1 2 | 6 2 0 | 6 2 0 | 6 2 2 | 6 3 5 | 6 3 6 | 6 4 0 | 6 4 2 | 6 4 9 | 6 5 3 | 6 7 8 | 6 8 1 | 6 9 5 | 6 9 9 | 7 0 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 4 6 | 2 2 2 | 2 2 7 | 2 3 8 | 2 7 5 | 2 3 2 | 2 6 2 | 2 7 7 | 2 2 9 | 2 7 2 | 2 4 0 | 2 6 3 | 2 7 4 | 2 1 8 | 2 7 9 | 2 4 2 | 2 5 7 | 2 5 5 | 2 4 3 | 2 3 4 | 2 7 3 | 2 7 0 | 2 6 9 | 2 3 1 | 2 4 7 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Clitoral gland* | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Carcinoma | | | | | | | | | | | | X | | | | | | | | | | X | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Granulosa-theca tumor benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | |
| Vagina | | | | | | | | | | | + | | | | | | | | | | | | | | |
| Schwannoma malignant | | | | | | | | | | | X | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | + | | | | | | | | | | | | | | | | | + | | | | | | | |
| Lymph node, bronchial | + | + | M | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | + | M | + | + | + | + | + | + | M | + | + | I | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mediastinal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | M | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | | | | | X | | X | X | | | | | | | | | | | | | | | X |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrosarcoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | X | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma, metastatic, tooth | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Skeletal muscle | | | | | | | | | | | | | | | | | + | | | | | | | | |
| Squamous cell carcinoma, metastatic, tooth | | | | | | | | | | | | | | | | | X | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Astrocytoma NOS | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | | | | | | | | | | + | | | | | | | | | | |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 7 1 8 | 7 2 1 | 7 2 7 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 7 8 | 2 2 0 | 2 4 5 | 2 1 2 | 2 1 9 | 2 2 1 | 2 2 5 | 2 2 8 | 2 3 5 | 2 3 6 | 2 3 9 | 2 5 1 | 2 5 3 | 2 5 8 | 2 1 1 | 2 3 0 | 2 3 3 | 2 6 5 | 2 6 8 | 3 4 7 | 4 4 4 | 5 5 6 | 5 6 0 | 6 8 0 | 2 2 3 | 2 2 6 | 2 6 7 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Adenoma | | | | | | | | | | | | | | | X | | | | | | | | | | | | | 2 |
| Carcinoma | | | | | | | | | | | | | | X | | | | | | | | | | | | | | 3 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Granulosa-theca tumor benign | | | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Vagina | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | + | | | | 3 |
| Lymph node, bronchial | M | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Lymph node, mediastinal | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Thymus | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Carcinoma | X | | | | | | | | X | | | | | | | | | | | | | | | | | | | 3 |
| Fibroadenoma | | | X | X | | | | | X | X | X | | | | X | | | | | | | | | | | X | | 11 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Squamous cell carcinoma, metastatic, tooth | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, tooth | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Astrocytoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | 8 | 8 | 3 | 6 | 9 | 9 | 9 | 0 | 0 | 1 | 2 | 2 | 2 | 3 | 3 | 4 | 4 | 4 | 5 | 7 | 8 | 9 | 0 |
| | 2 | 2 | 2 | 8 | 6 | 0 | 4 | 4 | 9 | 9 | 2 | 0 | 0 | 2 | 5 | 6 | 0 | 2 | 9 | 3 | 8 | 1 | 5 | 9 | 6 |
| **Carcass ID Number** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 4 | 2 | 2 | 3 | 7 | 3 | 6 | 7 | 2 | 7 | 4 | 6 | 7 | 1 | 7 | 4 | 5 | 5 | 4 | 3 | 7 | 7 | 6 | 3 | 4 |
| | 6 | 2 | 7 | 8 | 5 | 2 | 2 | 7 | 9 | 2 | 0 | 3 | 4 | 8 | 9 | 2 | 7 | 5 | 3 | 4 | 3 | 0 | 9 | 1 | 7 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | X | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | X | | | | | | | | |
| Alveolar epithelium, alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | + | | | | | | | | | | | | + | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | X | | X | | | X | | | | | | | X | | | | X | X | X | | | | X | X |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 0.15 mg/m³**
(continued)

| Number of Days on Study | 7 1 8 | 7 2 1 | 7 2 7 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 7 8 | 2 2 0 | 2 4 5 | 2 1 2 | 2 1 9 | 2 2 1 | 2 2 5 | 2 2 8 | 2 3 5 | 2 3 6 | 2 3 9 | 2 5 1 | 2 5 3 | 2 5 8 | 2 1 1 | 2 3 0 | 2 3 3 | 2 6 5 | 2 6 8 | 2 3 7 | 2 4 4 | 2 5 4 | 2 5 6 | 2 6 0 | 2 8 0 | 2 2 3 | 2 2 6 | 2 6 7 | Total Tissues/ Tumors | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Alveolar/bronchiolar adenoma | | | | | | | X | | | | | | | | | | X | X | | | X | | | | | | | | 5 | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 | |
| Leukemia mononuclear | | | X | | | | X | | | | X | | | | X | | X | | | X | | | X | | X | X | | | 18 | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**

| Number of Days on Study | 2 8 1 | 4 4 4 | 5 0 1 | 5 2 6 | 5 3 8 | 5 6 3 | 5 8 2 | 5 9 0 | 5 9 4 | 6 0 2 | 6 1 5 | 6 2 2 | 6 3 3 | 6 3 4 | 6 3 4 | 6 3 5 | 6 4 1 | 6 4 1 | 6 4 3 | 6 6 3 | 6 7 3 | 7 0 6 | 7 0 9 | 7 1 2 | 7 2 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 0 8 | 3 7 5 | 3 9 0 | 3 9 5 | 3 7 2 | 4 1 6 | 4 1 8 | 3 7 1 | 4 1 7 | 3 6 4 | 3 7 0 | 3 8 8 | 3 6 7 | 3 7 6 | 3 9 2 | 3 6 1 | 3 5 8 | 4 0 4 | 3 5 4 | 3 7 7 | 3 5 1 | 3 8 1 | 4 0 1 | 3 9 4 | 3 6 5 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | M | M | + | M | M | M | + | M | + | + | + | + | + | M | + | + | + | M | + | + | + | M | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | + | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | X | | | | | | | X | X | | | X | X | X | X | | | | |
| Bilateral, pheochromocytoma benign | | | | | | X | | X | | | | | | | | X | X | | | | | | X | X | X |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | M | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | X | | X | | X | X | | | | | | | | | | | | X | | X |
| Thyroid gland | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | X | | | X | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | + | | | | | | | | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | | | |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 5 7 | 3 6 9 | 3 8 0 | 3 8 3 | 3 8 7 | 4 0 9 | 4 1 1 | 4 1 9 | 3 7 3 | 3 7 4 | 3 8 4 | 3 9 3 | 3 9 8 | 3 9 9 | 4 0 0 | 4 0 3 | 3 5 6 | 3 6 0 | 3 7 8 | 3 8 2 | 3 8 6 | 3 8 9 | 4 0 2 | 4 0 7 | 4 1 2 | 4 1 5 | 3 5 2 | 3 6 8 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine large, rectum | + | + | + | + | M | + | I | M | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | + | + | 38 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | | | | | | | + | | | | | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | + | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma malignant | | | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma benign | | | | X | | | X | | | | X | | | | | | | X | | | | | | | | | X | 12 |
| Bilateral, pheochromocytoma benign | | X | X | | | X | | X | X | X | | X | X | X | X | | X | | X | X | X | | | X | X | | | 24 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | M | 49 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Pars distalis, adenoma | | X | | X | | | | X | X | | | X | X | | | X | | X | | | | | | | | | X | 15 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| C-cell, adenoma | | | | | | | | | | | | X | | X | | | | | | | | | | | | | | 4 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 2 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 | 4 | 0 | 2 | 3 | 6 | 8 | 9 | 9 | 0 | 1 | 2 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 6 | 7 | 0 | 0 | 1 | 2 |
| | 1 | 4 | 1 | 6 | 8 | 3 | 2 | 0 | 4 | 2 | 5 | 2 | 3 | 4 | 4 | 5 | 1 | 1 | 3 | 3 | 3 | 6 | 9 | 2 | 6 |
| **Carcass ID Number** | 4 | 3 | 3 | 3 | 3 | 4 | 4 | 3 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 4 | 3 | 3 |
| | 0 | 7 | 9 | 9 | 7 | 1 | 1 | 7 | 1 | 6 | 7 | 8 | 6 | 7 | 9 | 6 | 5 | 0 | 5 | 7 | 5 | 8 | 0 | 9 | 6 |
| | 8 | 5 | 0 | 5 | 2 | 6 | 8 | 1 | 7 | 4 | 0 | 8 | 7 | 6 | 2 | 1 | 8 | 4 | 4 | 7 | 1 | 1 | 1 | 4 | 5 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp stromal | | X | | | | | | | | X | | | | X | | | | | | | | | | | |
| Vagina | | + | | | | | | | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Lymph node | | | | + | | + | + | + | | | | | | | | + | | | + | + | | | | | |
| Iliac, histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Renal, histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mediastinal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | X | | | | | | | | | X | | | X | | | | X |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Pinna, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 5 7 | 3 6 9 | 3 8 0 | 3 8 3 | 3 8 7 | 4 0 9 | 4 1 1 | 4 1 9 | 3 7 3 | 3 7 4 | 3 8 4 | 3 9 3 | 3 9 8 | 3 9 9 | 4 0 0 | 4 0 3 | 3 5 6 | 3 6 0 | 3 7 8 | 3 8 2 | 3 8 6 | 3 8 9 | 4 0 2 | 4 0 7 | 4 1 2 | 4 1 5 | 3 5 2 | 3 6 8 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Adenoma | | | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | X | | | | 3 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Cystadenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Vagina | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node | | | + | | | | | | | | | | | | + | | + | | | | | | | | | | | 10 |
| Iliac, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Renal, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, bronchial | + | + | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | 51 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | 52 |
| Lymph node, mediastinal | + | + | + | M | + | + | + | + | + | + | + | M | M | + | + | + | + | + | + | M | M | I | + | + | + | + | + | 47 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 51 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Fibroadenoma | | X | | | | | | | | | | X | | X | X | | | X | | | X | | | | | | | 10 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pinna, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 2 8 1 | 4 4 4 | 5 0 1 | 5 2 6 | 5 3 8 | 5 6 3 | 5 8 2 | 5 9 0 | 5 9 4 | 6 0 2 | 6 1 5 | 6 2 2 | 6 3 3 | 6 3 4 | 6 3 4 | 6 3 5 | 6 4 1 | 6 4 1 | 6 4 3 | 6 6 3 | 6 7 3 | 7 0 6 | 7 0 9 | 7 1 2 | 7 2 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 0 8 | 3 7 5 | 3 9 0 | 3 9 5 | 3 7 2 | 4 1 6 | 4 1 8 | 3 7 1 | 4 1 7 | 3 6 4 | 3 7 0 | 3 8 8 | 3 6 7 | 3 7 6 | 3 9 2 | 3 6 1 | 3 5 8 | 4 0 4 | 3 5 4 | 3 7 7 | 3 5 1 | 3 8 1 | 4 0 1 | 3 9 4 | 3 6 5 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lacrimal gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Leukemia mononuclear | | | 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 Nickel Subsulfide: 1 mg/m³**
(continued)

| Number of Days on Study | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 35 7 | 36 9 | 38 0 | 38 3 | 38 7 | 40 9 | 41 1 | 41 9 | 37 3 | 37 4 | 38 4 | 39 3 | 39 8 | 39 9 | 40 0 | 40 3 | 40 6 | 56 0 | 67 8 | 82 2 | 86 6 | 89 9 | 40 2 | 40 7 | 41 2 | 41 5 | 52 2 | 63 8 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | 51 |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | X | | | | | | | X | | X | | | | | X | 5 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | X | | | | | | | | | | X | | | | | | | | | | 3 |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 52 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | + | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lacrimal gland | | | | | | | | | | | | | | | | | | | | | | | | | | | | + | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 53 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Leukemia mononuclear | | | X | X | | | | X | | | | X | | | X | X | X | | | | | | | | X | | | | 22 |

**TABLE B3**
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|
| **Adrenal Medulla: Benign Pheochromocytoma** | | | |
| Overall rate[a] | 2/53 (4%) | 7/53 (13%) | 36/53 (68%) |
| Adjusted rate[b] | 7.6% | 24.4% | 85.5% |
| Terminal rate[c] | 1/25 (4%) | 5/25 (20%) | 22/28 (79%) |
| First incidence (days) | 721 | 590 | 563 |
| Life table test[d] | P<0.001 | P=0.087 | P<0.001 |
| Logistic regression test[d] | P<0.001 | P=0.083 | P<0.001 |
| Cochran-Armitage test[d] | P<0.001 | | |
| Fisher exact test[d] | | P=0.080 | P<0.001 |
| **Adrenal Medulla: Benign or Malignant Pheochromocytoma** | | | |
| Overall rate | 3/53 (6%) | 7/53 (13%) | 36/53 (68%) |
| Adjusted rate | 10.4% | 24.4% | 85.5% |
| Terminal rate | 1/25 (4%) | 5/25 (20%) | 22/28 (79%) |
| First incidence (days) | 677 | 590 | 563 |
| Life table test | P<0.001 | P=0.170 | P<0.001 |
| Logistic regression test | P<0.001 | P=0.166 | P<0.001 |
| Cochran-Armitage test | P<0.001 | | |
| Fisher exact test | | P=0.160 | P<0.001 |
| **Clitoral Gland: Carcinoma** | | | |
| Overall rate | 1/52 (2%) | 3/52 (6%) | 3/52 (6%) |
| Adjusted rate | 2.3% | 9.2% | 10.1% |
| Terminal rate | 0/25 (0%) | 1/25 (4%) | 2/28 (7%) |
| First incidence (days) | 574 | 620 | 709 |
| Life table test | P=0.420 | P=0.324 | P=0.340 |
| Logistic regression test | P=0.385 | P=0.294 | P=0.310 |
| Cochran-Armitage test | P=0.382 | | |
| Fisher exact test | | P=0.309 | P=0.309 |
| **Clitoral Gland: Adenoma or Carcinoma** | | | |
| Overall rate | 1/52 (2%) | 5/52 (10%) | 4/52 (8%) |
| Adjusted rate | 2.3% | 15.4% | 13.6% |
| Terminal rate | 0/25 (0%) | 2/25 (8%) | 3/28 (11%) |
| First incidence (days) | 574 | 620 | 709 |
| Life table test | P=0.400 | P=0.114 | P=0.212 |
| Logistic regression test | P=0.363 | P=0.101 | P=0.185 |
| Cochran-Armitage test | P=0.358 | | |
| Fisher exact test | | P=0.102 | P=0.181 |
| **Lung: Alveolar/bronchiolar Adenoma (includes NOS)** | | | |
| Overall rate | 2/53 (4%) | 5/53 (9%) | 5/53 (9%) |
| Adjusted rate | 8.0% | 17.8% | 16.2% |
| Terminal rate | 2/25 (8%) | 4/25 (16%) | 4/28 (14%) |
| First incidence (days) | 729 (T) | 594 | 594 |
| Life table test | P=0.372 | P=0.221 | P=0.260 |
| Logistic regression test | P=0.325 | P=0.223 | P=0.230 |
| Cochran-Armitage test | P=0.311 | | |
| Fisher exact test | | P=0.219 | P=0.219 |

TABLE B3
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Lung: Alveolar/bronchiolar Carcinoma** | | | |
| Overall rate | 0/53 (0%) | 0/53 (0%) | 4/53 (8%) |
| Adjusted rate | 0.0% | 0.0% | 12.0% |
| Terminal rate | 0/25 (0%) | 0/25 (0%) | 2/28 (7%) |
| First incidence (days) | —[e] | — | 635 |
| Life table test | P=0.012 | — | P=0.070 |
| Logistic regression test | P=0.010 | — | P=0.066 |
| Cochran-Armitage test | P=0.009 | — | |
| Fisher exact test | | | P=0.059 |
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma (includes NOS)** | | | |
| Overall rate | 2/53 (4%) | 5/53 (9%) | 9/53 (17%) |
| Adjusted rate | 8.0% | 17.8% | 27.2% |
| Terminal rate | 2/25 (8%) | 4/25 (16%) | 6/28 (21%) |
| First incidence (days) | 729 (T) | 594 | 594 |
| Life table test | P=0.042 | P=0.221 | P=0.038 |
| Logistic regression test | P=0.030 | P=0.223 | P=0.031 |
| Cochran-Armitage test | P=0.028 | | |
| Fisher exact test | | P=0.219 | P=0.026 |
| **Mammary Gland: Fibroadenoma** | | | |
| Overall rate | 22/53 (42%) | 11/53 (21%) | 10/53 (19%) |
| Adjusted rate | 57.9% | 34.0% | 30.0% |
| Terminal rate | 11/25 (44%) | 6/25 (24%) | 6/28 (21%) |
| First incidence (days) | 377 | 594 | 594 |
| Life table test | P=0.030N | P=0.027N | P=0.010N |
| Logistic regression test | P=0.034N | P=0.016N | P=0.009N |
| Cochran-Armitage test | P=0.037N | | |
| Fisher exact test | | P=0.018N | P=0.010N |
| **Mammary Gland: Carcinoma** | | | |
| Overall rate | 1/53 (2%) | 3/53 (6%) | 0/53 (0%) |
| Adjusted rate | 4.0% | 9.4% | 0.0% |
| Terminal rate | 1/25 (4%) | 1/25 (4%) | 0/28 (0%) |
| First incidence (days) | 729 (T) | 594 | — |
| Life table test | P=0.207N | P=0.321 | P=0.477N |
| Logistic regression test | P=0.219N | P=0.315 | P=0.477N |
| Cochran-Armitage test | P=0.224N | | |
| Fisher exact test | | P=0.309 | P=0.500N |
| **Mammary Gland: Fibroadenoma or Adenoma** | | | |
| Overall rate | 23/53 (43%) | 11/53 (21%) | 10/53 (19%) |
| Adjusted rate | 59.2% | 34.0% | 30.0% |
| Terminal rate | 11/25 (44%) | 6/25 (24%) | 6/28 (21%) |
| First incidence (days) | 377 | 594 | 594 |
| Life table test | P=0.023N | P=0.019N | P=0.007N |
| Logistic regression test | P=0.025N | P=0.010N | P=0.005N |
| Cochran-Armitage test | P=0.027N | | |
| Fisher exact test | | P=0.011N | P=0.006N |

**TABLE B3**
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Mammary Gland: Adenoma or Carcinoma** | | | |
| Overall rate | 2/53 (4%) | 3/53 (6%) | 0/53 (0%) |
| Adjusted rate | 6.7% | 9.4% | 0.0% |
| Terminal rate | 1/25 (4%) | 1/25 (4%) | 0/28 (0%) |
| First incidence (days) | 665 | 594 | — |
| Life table test | P=0.133N | P=0.508 | P=0.234N |
| Logistic regression test | P=0.138N | P=0.512 | P=0.231N |
| Cochran-Armitage test | P=0.141N | | |
| Fisher exact test | | P=0.500 | P=0.248N |
| **Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma** | | | |
| Overall rate | 24/53 (45%) | 13/53 (25%) | 10/53 (19%) |
| Adjusted rate | 62.1% | 37.8% | 30.0% |
| Terminal rate | 12/25 (48%) | 6/25 (24%) | 6/28 (21%) |
| First incidence (days) | 377 | 594 | 594 |
| Life table test | P=0.012N | P=0.033N | P=0.004N |
| Logistic regression test | P=0.012N | P=0.018N | P=0.003N |
| Cochran-Armitage test | P=0.013N | | |
| Fisher exact test | | P=0.020N | P=0.003N |
| **Pituitary Gland (Pars Distalis): Adenoma** | | | |
| Overall rate | 24/52 (46%) | 30/53 (57%) | 15/53 (28%) |
| Adjusted rate | 67.1% | 70.5% | 42.0% |
| Terminal rate | 14/25 (56%) | 13/25 (52%) | 9/28 (32%) |
| First incidence (days) | 477 | 482 | 563 |
| Life table test | P=0.010N | P=0.220 | P=0.038N |
| Logistic regression test | P=0.006N | P=0.209 | P=0.037N |
| Cochran-Armitage test | P=0.007N | | |
| Fisher exact test | | P=0.191 | P=0.045N |
| **Thyroid Gland (C-cell): Adenoma** | | | |
| Overall rate | 3/51 (6%) | 4/53 (8%) | 4/52 (8%) |
| Adjusted rate | 10.6% | 12.9% | 12.2% |
| Terminal rate | 2/25 (8%) | 2/25 (8%) | 2/28 (7%) |
| First incidence (days) | 665 | 612 | 635 |
| Life table test | P=0.546 | P=0.502 | P=0.520 |
| Logistic regression test | P=0.524 | P=0.519 | P=0.518 |
| Cochran-Armitage test | P=0.515 | | |
| Fisher exact test | | P=0.522 | P=0.511 |
| **Thyroid Gland (C-cell): Carcinoma** | | | |
| Overall rate | 0/51 (0%) | 3/53 (6%) | 0/52 (0%) |
| Adjusted rate | 0.0% | 9.8% | 0.0% |
| Terminal rate | 0/25 (0%) | 2/25 (8%) | 0/28 (0%) |
| First incidence (days) | — | 538 | — |
| Life table test | P=0.334N | P=0.127 | — |
| Logistic regression test | P=0.359N | P=0.127 | — |
| Cochran-Armitage test | P=0.356N | | |
| Fisher exact test | | P=0.129 | — |

TABLE B3
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Thyroid Gland (C-cell): Adenoma or Carcinoma** | | | |
| Overall rate | 3/51 (6%) | 7/53 (13%) | 4/52 (8%) |
| Adjusted rate | 10.6% | 22.1% | 12.2% |
| Terminal rate | 2/25 (8%) | 4/25 (16%) | 2/28 (7%) |
| First incidence (days) | 665 | 538 | 635 |
| Life table test | P=0.482N | P=0.168 | P=0.520 |
| Logistic regression test | P=0.517N | P=0.175 | P=0.518 |
| Cochran-Armitage test | P=0.524N | | |
| Fisher exact test | | P=0.176 | P=0.511 |
| **Uterus: Stromal Polyp** | | | |
| Overall rate | 2/53 (4%) | 1/53 (2%) | 3/53 (6%) |
| Adjusted rate | 6.0% | 4.0% | 6.5% |
| Terminal rate | 1/25 (4%) | 1/25 (4%) | 0/28 (0%) |
| First incidence (days) | 500 | 729 (T) | 444 |
| Life table test | P=0.369 | P=0.495N | P=0.521 |
| Logistic regression test | P=0.322 | P=0.510N | P=0.442 |
| Cochran-Armitage test | P=0.344 | | |
| Fisher exact test | | P=0.500N | P=0.500 |
| **All Organs: Mononuclear Cell Leukemia** | | | |
| Overall rate | 19/53 (36%) | 18/53 (34%) | 22/53 (42%) |
| Adjusted rate | 46.8% | 48.4% | 50.0% |
| Terminal rate | 6/25 (24%) | 8/25 (32%) | 8/28 (29%) |
| First incidence (days) | 263 | 452 | 501 |
| Life table test | P=0.375 | P=0.498N | P=0.437 |
| Logistic regression test | P=0.252 | P=0.534N | P=0.313 |
| Cochran-Armitage test | P=0.268 | | |
| Fisher exact test | | P=0.500N | P=0.345 |
| **All Organs: Benign Neoplasms** | | | |
| Overall rate | 37/53 (70%) | 45/53 (85%) | 45/53 (85%) |
| Adjusted rate | 83.1% | 97.8% | 93.7% |
| Terminal rate | 18/25 (72%) | 24/25 (96%) | 25/28 (89%) |
| First incidence (days) | 377 | 482 | 444 |
| Life table test | P=0.407 | P=0.162 | P=0.266 |
| Logistic regression test | P=0.134 | P=0.078 | P=0.065 |
| Cochran-Armitage test | P=0.118 | | |
| Fisher exact test | | P=0.052 | P=0.052 |
| **All Organs: Malignant Neoplasms** | | | |
| Overall rate | 24/53 (45%) | 31/53 (58%) | 28/53 (53%) |
| Adjusted rate | 56.3% | 68.7% | 61.9% |
| Terminal rate | 8/25 (32%) | 12/25 (48%) | 12/28 (43%) |
| First incidence (days) | 263 | 452 | 501 |
| Life table test | P=0.537N | P=0.200 | P=0.406 |
| Logistic regression test | P=0.424 | P=0.102 | P=0.261 |
| Cochran-Armitage test | P=0.441 | | |
| Fisher exact test | | P=0.122 | P=0.280 |

**TABLE B3**
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|
| **All Organs: Benign or Malignant Neoplasms** | | | |
| Overall rate | 48/53 (91%) | 51/53 (96%) | 48/53 (91%) |
| Adjusted rate | 90.6% | 98.1% | 94.1% |
| Terminal rate | 20/25 (80%) | 24/25 (96%) | 25/28 (89%) |
| First incidence (days) | 263 | 452 | 444 |
| Life table test | P=0.299N | P=0.418 | P=0.398N |
| Logistic regression test | P=0.442N | P=0.209 | P=0.629N |
| Cochran-Armitage test | P=0.426N | | |
| Fisher exact test | | P=0.219 | P=0.629N |

(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, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Lung Neoplasms in Untreated Female F344/N Rats[a]

| Study | Incidence in Controls | | | |
|---|---|---|---|---|
| | Alveolar/bronchiolar Adenoma | Alveolar/bronchiolar Carcinoma | Squamous Cell Carcinoma | Alveolar/bronchiolar Adenoma or Carcinoma or Squamous Cell Carcinoma |
| **Historical Incidence at Lovelace Inhalation Toxicology Research Institute** | | | | |
| Nickel Oxide | 1/53 | 0/53 | 0/53 | 1/53 |
| Nickel Subsulfide | 2/53 | 0/53 | 0/53 | 2/53 |
| Nickel Sulfate Hexahydrate | 0/52 | 0/52 | 0/52 | 0/52 |
| Talc[b] | 1/50 | 0/50 | 0/50 | 1/50 |
| **Overall Historical Incidence in Inhalation Studies** | | | | |
| Total | 7/700 (1.1%) | 0/700 (0%) | 0/700 (0%) | 8/700 (1.1%) |
| Standard deviation | 1.5% | | | 1.5% |
| Range | 0%-4% | | | 0%-4% |
| **Overall Historical Incidence in Feed Studies** | | | | |
| Total | 20/1,201 (1.7%) | 5/1,201 (0.4%) | 0/1,201 (0%) | 25/1,201 (2.1%) |
| Standard deviation | 2.2% | 0.8% | | 2.2% |
| Range | 0%-10% | 0%-2% | | 0%-10% |

[a] Data as of 17 June 1994
[b] Results of lifetime study

**TABLE B4b**
**Historical Incidence of Pheochromocytomas of the Adrenal Medulla in Untreated Female F344/N Rats[a]**

| Study | Incidence in Controls | | | | |
|---|---|---|---|---|---|
| | Benign | Complex | Malignant | NOS | Benign, Complex, Malignant, or NOS |
| **Historical Incidence at Lovelace Inhalation Toxicology Research Institute** | | | | | |
| Nickel Oxide | 4/51 | 0/51 | 0/51 | 0/51 | 4/51 |
| Nickel Subsulfide | 2/53 | 0/53 | 1/53 | 0/53 | 3/53 |
| Nickel Sulfate Hexahydrate | 2/51 | 0/51 | 0/51 | 0/51 | 2/51 |
| **Overall Historical Incidence in Inhalation Studies** | | | | | |
| Total | 35/608 (5.8%) | 2/608 (0.3%) | 1/608 (0.2%) | 1/608 (0.2%) | 39/608 (6.4%) |
| Standard deviation | 4.9% | 1.1% | 0.6% | 0.6% | 4.4% |
| Range | 0%-14% | 0%-4% | 0%-2% | 0%-2% | 2%-14% |
| **Overall Historical Incidence in Feed Studies** | | | | | |
| Total | 49/1,175 (4.2%) | 2/1,175 (0.2%) | 6/1,175 (0.5%) | 6/1,175 (0.5%) | 62/1,175 (5.3%) |
| Standard deviation | 2.5% | 0.6% | 0.9% | 2.5% | 2.8% |
| Range | 0%-8% | 0%-2% | 0%-2% | 0%-12% | 2%-12% |

[a] Data as of 17 June 1994; data from lifetime talc study not included because incidences of adrenal medulla pheochromocytomas increase significantly in aging rats, and this data would not be comparable to that in the 2-year nickel subsulfide study.

TABLE B5
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide**[a]

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Disposition summary** | | | |
| Animals initially in study | 63 | 63 | 63 |
| *7-Month interim evaluation* | 5 | 5 | 5 |
| *15-Month interim evaluation* | 5 | 5 | 5 |
| Early deaths | | | |
| Accidental death | | | 1 |
| Moribund | 24 | 27 | 23 |
| Natural deaths | 4 | 1 | 1 |
| Survivors | | | |
| Terminal sacrifice | 25 | 25 | 28 |
| Animals examined microscopically | 63 | 63 | 63 |
| ***7-Month Interim Evaluation*** | | | |
| **Genital System** | | | |
| Ovary | (1) | (1) | (1) |
| Cyst | 1 (100%) | 1 (100%) | 1 (100%) |
| **Hematopoietic System** | | | |
| Lymph node, bronchial | (5) | (5) | (5) |
| Hyperplasia, lymphoid | 2 (40%) | 2 (40%) | 5 (100%) |
| Lymph node, mediastinal | (5) | (4) | (5) |
| Hyperplasia, lymphoid | 1 (20%) | 1 (25%) | 5 (100%) |
| **Respiratory System** | | | |
| Lung | (5) | (5) | (5) |
| Inflammation, chronic active | | 5 (100%) | 5 (100%) |
| Metaplasia, osseous | 1 (20%) | | |
| Alveolus, hyperplasia, macrophage | | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 2 (40%) | 5 (100%) |
| Bronchus, hyperplasia, lymphoid | | 1 (20%) | 4 (80%) |
| Interstitium, infiltration cellular | 2 (40%) | 5 (100%) | 5 (100%) |
| Nose | (5) | (5) | (5) |
| Inflammation, chronic active | 1 (20%) | 2 (40%) | 4 (80%) |
| Olfactory epithelium, erosion, focal | 1 (20%) | 2 (40%) | |
| ***Systems Examined With No Lesions Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Special Senses System** | | | |
| **Urinary System** | | | |

[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 Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** | | | |
| **Alimentary System** | | | |
| Liver | (5) | (5) | (5) |
| Basophilic focus | 3 (60%) | 3 (60%) | 5 (100%) |
| Granuloma | | | 1 (20%) |
| Hepatodiaphragmatic nodule | 1 (20%) | 1 (20%) | |
| Inflammation, granulomatous | 4 (80%) | 2 (40%) | 5 (100%) |
| Mixed cell focus | | | 1 (20%) |
| **Endocrine System** | | | |
| Adrenal cortex | (5) | (5) | (5) |
| Hyperplasia | | | 1 (20%) |
| Pituitary gland | (5) | (5) | (5) |
| Cyst | | 1 (20%) | |
| Thyroid gland | (5) | (5) | (5) |
| C-cell, hyperplasia | 1 (20%) | 1 (20%) | 1 (20%) |
| **Hematopoietic System** | | | |
| Lymph node, bronchial | (5) | (5) | (5) |
| Hemorrhage, acute | | 1 (20%) | |
| Hyperplasia, lymphoid | | 1 (20%) | 2 (40%) |
| Hyperplasia, macrophage | 1 (20%) | 2 (40%) | 4 (80%) |
| Lymph node, mediastinal | (5) | (5) | (5) |
| Hyperplasia, lymphoid | | | 1 (20%) |
| Hyperplasia, macrophage | 1 (20%) | 1 (20%) | 2 (40%) |
| **Respiratory System** | | | |
| Lung | (5) | (5) | (5) |
| Hemorrhage, acute | 2 (40%) | 3 (60%) | 2 (40%) |
| Inflammation, chronic active | | 5 (100%) | 5 (100%) |
| Alveolus, hyperplasia, macrophage | 1 (20%) | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 5 (100%) | 5 (100%) |
| Bronchus, hyperplasia, lymphoid | | | 1 (20%) |
| Interstitium, infiltration cellular | | 4 (80%) | 5 (100%) |
| Nose | (5) | (5) | (5) |
| Inflammation, chronic active | 3 (60%) | 2 (40%) | 2 (40%) |
| Nasolacrimal duct, hyperplasia | | 1 (20%) | |
| Olfactory epithelium, atrophy | | | 1 (20%) |
| **Special Senses System** | | | |
| Eye | | | (1) |
| Cataract | | | 1 (100%) |

TABLE B5
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | |
| **Urinary System** | | | |
| Kidney | (5) | (5) | (5) |
| Nephropathy | 1 (20%) | 2 (40%) | 2 (40%) |
| ***Systems Examined With No Lesions Observed*** | | | |
| **Cardiovascular System** | | | |
| **General Body System** | | | |
| **Genital System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Intestine large, colon | (50) | (52) | (53) |
| Parasite metazoan | | | 1 (2%) |
| Intestine large, rectum | (41) | (40) | (38) |
| Parasite metazoan | | 2 (5%) | |
| Intestine large, cecum | (49) | (52) | (52) |
| Inflammation | 1 (2%) | | |
| Parasite metazoan | 2 (4%) | 2 (4%) | 3 (6%) |
| Intestine small, jejunum | (50) | (52) | (52) |
| Hyperplasia, lymphoid | | 1 (2%) | |
| Intestine small, ileum | (50) | (52) | (53) |
| Hyperplasia, lymphoid | 3 (6%) | 5 (10%) | 3 (6%) |
| Liver | (53) | (53) | (53) |
| Angiectasis | 1 (2%) | | |
| Basophilic focus | 44 (83%) | 46 (87%) | 40 (75%) |
| Clear cell focus | | 1 (2%) | |
| Degeneration, cystic | 1 (2%) | 4 (8%) | 2 (4%) |
| Degeneration, fatty | 16 (30%) | 12 (23%) | 11 (21%) |
| Eosinophilic focus | 3 (6%) | 2 (4%) | 5 (9%) |
| Hematopoietic cell proliferation | | 1 (2%) | 1 (2%) |
| Hepatodiaphragmatic nodule | 6 (11%) | 3 (6%) | 2 (4%) |
| Inflammation, focal, granulomatous | 24 (45%) | 22 (42%) | 13 (25%) |
| Mixed cell focus | 3 (6%) | 1 (2%) | |
| Pigmentation, hemosiderin | 3 (6%) | 1 (2%) | 7 (13%) |
| Regeneration | | | 2 (4%) |
| Bile duct, hyperplasia | 18 (34%) | 13 (25%) | 14 (26%) |
| Biliary tract, hyperplasia | 1 (2%) | | |
| Centrilobular, atrophy | 9 (17%) | 5 (9%) | 14 (26%) |
| Hepatocyte, atrophy | | | 1 (2%) |
| Hepatocyte, hyperplasia | 4 (8%) | 1 (2%) | 1 (2%) |
| Hepatocyte, necrosis | 1 (2%) | 1 (2%) | |
| Vein, thrombosis | | | 1 (2%) |
| Mesentery | (1) | | (2) |
| Necrosis | | | 1 (50%) |
| Fat, necrosis | 1 (100%) | | |

**TABLE B5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Alimentary System** (continued) | | | |
| Pancreas | (53) | (52) | (53) |
| Atrophy | 10 (19%) | 4 (8%) | 14 (26%) |
| Stomach, forestomach | (53) | (53) | (53) |
| Hyperplasia, squamous | 2 (4%) | 5 (9%) | 2 (4%) |
| Inflammation | 1 (2%) | | |
| Ulcer | 3 (6%) | 1 (2%) | |
| Tooth | (1) | (1) | |
| Peridontal tissue, inflammation | 1 (100%) | | |
| **Cardiovascular System** | | | |
| Blood vessel | | | (1) |
| Inflammation | | | 1 (100%) |
| Heart | (53) | (53) | (53) |
| Cardiomyopathy | 25 (47%) | 17 (32%) | 18 (34%) |
| Atrium, thrombosis | 2 (4%) | 1 (2%) | |
| **Endocrine System** | | | |
| Adrenal cortex | (53) | (53) | (53) |
| Degeneration, cystic | 11 (21%) | 11 (21%) | 19 (36%) |
| Hyperplasia | | | 1 (2%) |
| Hyperplasia, focal | 1 (2%) | | 5 (9%) |
| Necrosis | | | 2 (4%) |
| Vacuolization cytoplasmic | 4 (8%) | 3 (6%) | 6 (11%) |
| Adrenal medulla | (53) | (53) | (53) |
| Hyperplasia | 5 (9%) | 11 (21%) | 16 (30%) |
| Islets, pancreatic | (53) | (53) | (53) |
| Hyperplasia | | 1 (2%) | 1 (2%) |
| Parathyroid gland | (48) | (50) | (49) |
| Hyperplasia | 1 (2%) | 2 (4%) | 3 (6%) |
| Pituitary gland | (52) | (53) | (53) |
| Pars distalis, angiectasis | 21 (40%) | 11 (21%) | 16 (30%) |
| Pars distalis, cyst | 3 (6%) | 3 (6%) | |
| Pars distalis, hyperplasia | 13 (25%) | 5 (9%) | 14 (26%) |
| Thyroid gland | (51) | (53) | (52) |
| C-cell, hyperplasia | 15 (29%) | 11 (21%) | 11 (21%) |
| **General Body System** | | | |
| None | | | |
| **Genital System** | | | |
| Clitoral gland | (52) | (52) | (52) |
| Hyperplasia, cystic | 6 (12%) | 5 (10%) | 5 (10%) |
| Inflammation | | 1 (2%) | |

TABLE B5
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Genital System** (continued) | | | |
| Ovary | (53) | (53) | (53) |
| Atrophy | | | 1 (2%) |
| Cyst | 5 (9%) | 3 (6%) | 6 (11%) |
| Inflammation | | | 2 (4%) |
| Uterus | (53) | (53) | (53) |
| Cyst | 1 (2%) | | |
| Inflammation | | | 1 (2%) |
| Endometrium, hyperplasia, cystic | 3 (6%) | 1 (2%) | 1 (2%) |
| **Hematopoietic System** | | | |
| Bone marrow | (53) | (53) | (53) |
| Atrophy | 2 (4%) | | |
| Fibrosis | 2 (4%) | | 3 (6%) |
| Inflammation, focal, granulomatous | 4 (8%) | | 1 (2%) |
| Necrosis | | | 1 (2%) |
| Erythroid cell, hyperplasia | | 1 (2%) | |
| Myeloid cell, hyperplasia | | 2 (4%) | 2 (4%) |
| Lymph node | (5) | (3) | (10) |
| Pancreatic, hyperplasia, lymphoid | | 1 (33%) | 1 (10%) |
| Pancreatic, hyperplasia, macrophage | | | 1 (10%) |
| Renal, hyperplasia, lymphoid | 1 (20%) | | |
| Lymph node, bronchial | (50) | (49) | (50) |
| Hyperplasia, lymphoid | 11 (22%) | 36 (73%) | 36 (72%) |
| Hyperplasia, macrophage | | 16 (33%) | 24 (48%) |
| Hyperplasia, plasma cell | | | 2 (4%) |
| Inflammation | | | 1 (2%) |
| Lymph node, mandibular | (44) | (50) | (51) |
| Hyperplasia, lymphoid | 3 (7%) | 5 (10%) | 1 (2%) |
| Hyperplasia, plasma cell | 3 (7%) | 6 (12%) | 4 (8%) |
| Lymph node, mesenteric | (52) | (53) | (52) |
| Atrophy | | 1 (2%) | |
| Hyperplasia, lymphoid | 3 (6%) | 5 (9%) | 6 (12%) |
| Hyperplasia, macrophage | 1 (2%) | | 3 (6%) |
| Lymph node, mediastinal | (46) | (50) | (47) |
| Hyperplasia, lymphoid | | 11 (22%) | 20 (43%) |
| Hyperplasia, macrophage | | 4 (8%) | 5 (11%) |
| Spleen | (53) | (53) | (53) |
| Atrophy | | 1 (2%) | |
| Fibrosis | 2 (4%) | | 2 (4%) |
| Hematopoietic cell proliferation | | 3 (6%) | 3 (6%) |
| Hemorrhage | 1 (2%) | | |
| Hyperplasia, lymphoid | 1 (2%) | 1 (2%) | |
| Pigmentation, hemosiderin | 7 (13%) | 12 (23%) | 2 (4%) |
| Thymus | (49) | (51) | (51) |
| Degeneration | 2 (4%) | | |

TABLE B5
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Integumentary System** | | | |
| Mammary gland | (53) | (53) | (53) |
| Fibrosis | | 1 (2%) | |
| Hyperplasia, cystic | 11 (21%) | 14 (26%) | 16 (30%) |
| Skin | (53) | (53) | (53) |
| Hyperkeratosis | 1 (2%) | | |
| Inflammation | 1 (2%) | | 1 (2%) |
| Ulcer | | 1 (2%) | 1 (2%) |
| Tail, hyperkeratosis | 1 (2%) | | |
| Tail, inflammation | 1 (2%) | 1 (2%) | |
| **Musculoskeletal System** | | | |
| Bone | (53) | (53) | (53) |
| Hyperostosis | 5 (9%) | 3 (6%) | 7 (13%) |
| Cranium, hyperostosis | | | 3 (6%) |
| **Nervous System** | | | |
| Brain | (53) | (53) | (53) |
| Cyst | 1 (2%) | | |
| Hemorrhage | 1 (2%) | | |
| Hydrocephalus | 1 (2%) | 1 (2%) | 2 (4%) |
| Cerebrum, compression | 5 (9%) | 10 (19%) | 5 (9%) |
| Gray matter, necrosis | | | 1 (2%) |
| Spinal cord | | (1) | |
| Degeneration, secondary wallerian | | 1 (100%) | |
| **Respiratory System** | | | |
| Larynx | (52) | (53) | (51) |
| Hyperplasia, squamous | 1 (2%) | | |
| Inflammation | 2 (4%) | 2 (4%) | 3 (6%) |
| Lung | (53) | (53) | (53) |
| Cyst | | | 1 (2%) |
| Emphysema | | | 1 (2%) |
| Fibrosis | | 50 (94%) | 44 (83%) |
| Inflammation, chronic active | 7 (13%) | 51 (96%) | 51 (96%) |
| Metaplasia, osseous | 1 (2%) | 1 (2%) | |
| Metaplasia, squamous | | | 3 (6%) |
| Alveolar epithelium, hyperplasia, focal | 2 (4%) | 10 (19%) | 11 (21%) |
| Alveolus, hyperplasia, macrophage | 8 (15%) | 51 (96%) | 52 (98%) |
| Alveolus, proteinosis | 2 (4%) | 49 (92%) | 53 (100%) |
| Bronchus, hyperplasia, lymphoid | | 15 (28%) | 18 (34%) |
| Interstitium, infiltration cellular | 28 (53%) | 36 (68%) | 43 (81%) |

TABLE B5
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Respiratory System** (continued) | | | |
| Nose | (53) | (53) | (52) |
| Inflammation, chronic active | 6 (11%) | 9 (17%) | 20 (38%) |
| Thrombosis | 2 (4%) | | 1 (2%) |
| Nasolacrimal duct, inflammation | 1 (2%) | 2 (4%) | 2 (4%) |
| Olfactory epithelium, atrophy | | | 16 (31%) |
| Olfactory epithelium, metaplasia | | 1 (2%) | 1 (2%) |
| **Special Senses System** | | | |
| Eye | (2) | (2) | (1) |
| Cataract | 2 (100%) | 2 (100%) | 1 (100%) |
| Retina, degeneration | 2 (100%) | 1 (50%) | |
| Lacrimal gland | | | (1) |
| Metaplasia, squamous | | | 1 (100%) |
| **Urinary System** | | | |
| Kidney | (53) | (53) | (53) |
| Cyst | 1 (2%) | | |
| Hydronephrosis | | | 1 (2%) |
| Nephropathy | 51 (96%) | 52 (98%) | 50 (94%) |
| Renal tubule, pigmentation | 40 (75%) | 43 (81%) | 43 (81%) |

# APPENDIX C
# SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF NICKEL SUBSULFIDE

TABLE C1
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 80 | 80 | 80 |
| *7-Month interim evaluation*[b] | 9 | 10 | 10 |
| *15-Month interim evaluation*[b] | 10 | 10 | 10 |
| Early deaths | | | |
| Moribund | 27 | 26 | 25 |
| Natural deaths | 8 | 9 | 9 |
| Survivors | | | |
| Died last week of study | | | 1 |
| Terminal sacrifice | 26 | 25 | 25 |
| Animals examined microscopically | 71 | 70 | 70 |
| ***Systems Examined At 7 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** | | | |
| ***15-Month Interim Evaluation*** | | | |
| **Alimentary System** | | | |
| Liver | (5) | (5) | (5) |
| Hepatocellular carcinoma | | | 1 (20%) |
| Hepatocellular adenoma | 1 (20%) | 2 (40%) | 1 (20%) |
| ***Systems Examined With No Neoplasms Observed*** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Genital System** | | | |
| **Hematopoietic System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Respiratory System** | | | |
| **Special Senses System** | | | |
| **Urinary System** | | | |

TABLE C1
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Gallbladder | (57) | (50) | (54) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Intestine small, duodenum | (56) | (51) | (54) |
| Adenoma | 1 (2%) | | |
| Intestine small, jejunum | (56) | (51) | (54) |
| Intestine small, ileum | (55) | (51) | (55) |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) |
| Liver | (61) | (59) | (59) |
| Fibrous histiocytoma | 1 (2%) | | |
| Hemangioma | | 1 (2%) | |
| Hemangiosarcoma | | | 1 (2%) |
| Hepatoblastoma | | | 1 (2%) |
| Hepatocellular carcinoma | 11 (18%) | 15 (25%) | 12 (20%) |
| Hepatocellular carcinoma, multiple | | 2 (3%) | |
| Hepatocellular adenoma | 11 (18%) | 8 (14%) | 11 (19%) |
| Hepatocellular adenoma, multiple | 2 (3%) | 1 (2%) | 3 (5%) |
| Hepatocholangiocarcinoma | 1 (2%) | | |
| Mesentery | (1) | | |
| Fibrous histiocytoma, metastatic, liver | 1 (100%) | | |
| Pancreas | (61) | (59) | (58) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Salivary glands | (61) | (59) | (59) |
| Stomach, glandular | (61) | (59) | (57) |
| Adenocarcinoma | | | 1 (2%) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Tooth | (4) | (1) | (4) |
| Odontoma | | | 2 (50%) |
| **Cardiovascular System** | | | |
| Heart | (61) | (59) | (60) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | 1 (2%) | | |
| **Endocrine System** | | | |
| Adrenal cortex | (61) | (59) | (58) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Capsule, adenoma | 2 (3%) | | 1 (2%) |
| Adrenal medulla | (60) | (59) | (56) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Pheochromocytoma complex | 1 (2%) | | |
| Islets, pancreatic | (61) | (59) | (58) |
| Adenoma | 1 (2%) | 1 (2%) | |
| Pituitary gland | (58) | (58) | (55) |
| Pars distalis, adenoma | | | 1 (2%) |
| Thyroid gland | (61) | (59) | (59) |
| Follicular cell, adenoma | 4 (7%) | 1 (2%) | 1 (2%) |

TABLE C1
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **General Body System** | | | |
| Tissue NOS | (1) | | (1) |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic | | | 1 (100%) |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic | | | 1 (100%) |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | 1 (100%) | | |
| **Genital System** | | | |
| Coagulating gland | | | (1) |
| Interstitium, granular cell tumor NOS | | | 1 (100%) |
| Epididymis | (61) | (59) | (59) |
| Fibrous histiocytoma | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Leiomyoma | | 1 (2%) | |
| Seminal vesicle | (61) | (59) | (59) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Testes | (61) | (59) | (59) |
| Interstitial cell, adenoma | 1 (2%) | | |
| **Hematopoietic System** | | | |
| Lymph node | (18) | (11) | (11) |
| Axillary, fibrosarcoma, metastatic, skin | 1 (6%) | | |
| Pancreatic, fibrous histiocytoma, metastatic, liver | 1 (6%) | | |
| Lymph node, bronchial | (40) | (53) | (54) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | 1 (3%) | | |
| Hepatocellular carcinoma, metastatic | | | 1 (2%) |
| Lymph node, mesenteric | (58) | (57) | (55) |
| Adenocarcinoma, metastatic, stomach, glandular | | | 1 (2%) |
| Fibrous histiocytoma | | | 1 (2%) |
| Hemangioma | 1 (2%) | | 1 (2%) |
| Hemangiosarcoma | | 1 (2%) | |
| Lymph node, mediastinal | (12) | (18) | (17) |
| Spleen | (61) | (58) | (57) |
| Hemangioma | | | 1 (2%) |
| Hemangiosarcoma | | 1 (2%) | |
| Thymus | (48) | (51) | (41) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | 1 (2%) | | |

TABLE C1
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Integumentary System** | | | |
| Skin | (61) | (57) | (59) |
| Fibrosarcoma | 1 (2%) | | |
| Fibrous histiocytoma | | | 1 (2%) |
| Pinna, hemangiosarcoma | | | 1 (2%) |
| Prepuce, fibrous histiocytoma | | 1 (2%) | |
| Tail, hemangiosarcoma | | 1 (2%) | |
| **Musculoskeletal System** | | | |
| None | | | |
| **Nervous System** | | | |
| None | | | |
| **Respiratory System** | | | |
| Lung | (61) | (59) | (58) |
| Alveolar/bronchiolar adenoma | 5 (8%) | 3 (5%) | 2 (3%) |
| Alveolar/bronchiolar adenoma, two | 1 (2%) | | |
| Alveolar/bronchiolar carcinoma | 7 (11%) | 2 (3%) | 4 (7%) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Hepatoblastoma, metastatic, liver | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | 2 (3%) | 6 (10%) | 2 (3%) |
| Hepatocholangiocarcinoma, metastatic, liver | 1 (2%) | | |
| Pheochromocytoma complex, metastatic, adrenal medulla | 1 (2%) | | |
| **Special Senses System** | | | |
| Harderian gland | (1) | | |
| Adenoma | 1 (100%) | | |
| **Urinary System** | | | |
| Kidney | (61) | (59) | (59) |
| Fibrous histiocytoma, metastatic, liver | 1 (2%) | | |
| Hepatoblastoma, metastatic, liver | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) |
| Pelvis, hemangiosarcoma | 1 (2%) | | |
| Urinary bladder | (61) | (59) | (58) |
| Leiomyosarcoma | 1 (2%) | | |
| **Systemic Lesions** | | | |
| Multiple organs[c] | (61) | (60) | (60) |
| Lymphoma malignant | 1 (2%) | 1 (2%) | |

**TABLE C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ |
|---|---|---|---|
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[d] | | | |
| 15-Month interim evaluation | 1 | 2 | 1 |
| 2-Year study | 40 | 31 | 35 |
| Total primary neoplasms | | | |
| 15-Month interim evaluation | 1 | 2 | 2 |
| 2-Year study | 56 | 40 | 46 |
| Total animals with benign neoplasms | | | |
| 15-Month interim evaluation | 1 | 2 | 1 |
| 2-Year study | 27 | 15 | 19 |
| Total benign neoplasms | | | |
| 15-Month interim evaluation | 1 | 2 | 1 |
| 2-Year study | 30 | 16 | 23 |
| Total animals with malignant neoplasms | | | |
| 15-Month interim evaluation | | | 1 |
| 2-Year study | 21 | 23 | 20 |
| Total malignant neoplasms | | | |
| 15-Month interim evaluation | | | 1 |
| 2-Year study | 26 | 24 | 22 |
| Total animals with metastatic neoplasms | | | |
| 2-Year study | 7 | 6 | 4 |
| Total metastatic neoplasms | | | |
| 2-Year study | 20 | 6 | 10 |
| Total animals with uncertain neoplasms-benign or malignant | | | |
| 2-Year study | | | 1 |
| Total uncertain neoplasms | | | |
| 2-Year study | | | 1 |

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Five animals in each exposure group were histopathologically examined at the interim evaluations.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**

| Number of Days on Study | 0 6 7 | 2 1 2 | 3 1 3 | 4 0 6 | 4 3 4 | 4 6 3 | 4 8 0 | 4 9 9 | 5 0 8 | 5 2 6 | 5 3 6 | 5 4 4 | 5 5 2 | 5 5 2 | 5 5 7 | 5 6 1 | 5 8 4 | 5 8 4 | 5 8 5 | 5 8 6 | 5 8 8 | 5 8 9 | 5 9 1 | 6 0 5 | 6 2 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 4 2 | 0 4 6 | 0 4 9 | 0 2 5 | 0 6 6 | 0 7 3 | 0 1 6 | 0 2 1 | 0 3 7 | 0 4 7 | 0 2 6 | 0 0 4 | 0 4 8 | 0 6 0 | 0 1 4 | 0 0 5 | 0 0 2 | 0 2 0 | 0 7 7 | 0 0 3 | 0 7 6 | 0 3 6 | 0 6 1 | 0 3 5 | 0 4 9 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Intestine large, colon | A | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Intestine large, rectum | + | + | + | A | A | + | + | + | M | M | + | + | + | M | + | + | + | M | + | M | + | M | M | + | + |
| Intestine large, cecum | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | A | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | A | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | A | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Hepatocellular carcinoma | | | | | X | X | X | | | | X | | | | | X | | | | | | X | | | |
| Hepatocellular adenoma | | | | | | | | | X | | | | | | | | | | X | | | | X | X | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Hepatocholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | + | | | |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Tooth | | | | | | | | | | | | | | + | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, Metastatic, lung | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Capsule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Pheochromocytoma complex | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + |
| Pituitary gland | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | |

+: 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 Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 6 3 1 | 6 4 1 | 6 6 2 | 6 7 9 | 6 8 1 | 6 8 1 | 6 8 1 | 6 9 4 | 7 1 3 | 7 1 9 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 4 7 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 8 0 | 0 3 9 | 0 4 0 | 0 0 8 | 0 1 0 | 0 2 9 | 0 6 3 | 0 5 9 | 0 5 2 | 0 2 4 | 0 1 1 | 0 3 1 | 0 3 2 | 0 3 8 | 0 6 2 | 0 6 4 | 0 7 1 | 0 7 4 | 0 0 1 | 0 0 9 | 0 1 2 | 0 1 5 | 0 1 9 | 0 2 7 | 0 3 4 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine large, colon | + | + | + | + | + | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | M | + | + | + | + | + | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | A | A | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | X | X | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | X | | | | X | X | | | | | | | X | X | X |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | X | | | | | | | | |
| Hepatocholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | + | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Capsule, adenoma | | | | X | | | | | | | | X | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma complex | | X | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | X | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | M | M | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | X | | | | | X | | | | | | | | | | | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 5 0 | 0 5 3 | 0 7 0 | 0 1 7 | 0 2 2 | 0 3 3 | 0 5 6 | 0 5 7 | 0 6 7 | 0 7 8 | 0 7 9 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | 60 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | 57 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | 55 |
| Intestine large, rectum | + | + | + | + | M | + | + | M | + | M | M | 45 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | 57 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | 56 |
| Adenoma | | | | | | X | | | | | | 1 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | 56 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | 55 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrous histiocytoma | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | X | | | X | | | | X | | 11 |
| Hepatocellular adenoma | X | | | | | | | | | | | 11 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | 2 |
| Hepatocholangiocarcinoma | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | | 1 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Tooth | | | | | | | | + | + | | | 4 |
| **Cardiovascular System** | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | 1 |
| **Endocrine System** | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Capsule, adenoma | | | | | | | | | | | | 2 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | 60 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Pheochromocytoma complex | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Adenoma | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | 56 |
| Pituitary gland | + | + | + | + | + | + | M | + | + | + | + | 58 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Follicular cell, adenoma | | | | | | | X | | | | | 4 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 0 6 7 | 2 1 2 | 3 1 3 | 4 0 6 | 4 3 4 | 4 6 3 | 4 8 0 | 4 9 9 | 5 0 8 | 5 2 6 | 5 3 6 | 5 4 4 | 5 5 2 | 5 5 2 | 5 5 7 | 5 6 1 | 5 8 4 | 5 8 4 | 5 8 5 | 5 8 6 | 5 8 8 | 5 8 9 | 5 9 1 | 6 0 5 | 6 2 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 4 2 | 0 4 6 | 0 6 9 | 0 2 5 | 0 6 6 | 0 7 3 | 0 1 6 | 0 2 1 | 0 3 7 | 0 4 7 | 0 2 6 | 0 0 4 | 0 4 8 | 0 6 0 | 0 1 4 | 0 0 5 | 0 0 2 | 0 2 0 | 0 7 7 | 0 0 3 | 0 7 6 | 0 3 6 | 0 6 1 | 0 3 5 | 0 4 9 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | + | | | | | | | | | | | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Penis | | | + | + | | | | | + | | | | | | + | + | + | | | + | | | | | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | + | + | + | | | | + | + | + | | | + | | + | + | | + | | + | | + | + | | |
| Axillary, fibrosarcoma, metastatic, skin | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Pancreatic, fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Lymph node, bronchial | M | I | + | + | + | + | + | + | + | M | M | + | + | + | + | + | + | + | I | M | M | + | M | + | M |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Lymph node, mandibular | M | M | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + |
| Lymph node, mesenteric | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mediastinal | M | M | M | M | M | M | + | M | M | M | + | M | M | M | + | M | M | + | M | M | M | + | M | M | M |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | M | + | + | + | + | + | + | M | M | + | + | + | + | + | + | M | + | + | + | + | I | + | + | 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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrosarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 6 3 1 | 6 4 1 | 6 6 2 | 6 7 9 | 6 8 1 | 6 8 1 | 6 8 1 | 6 9 4 | 7 1 3 | 7 1 9 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 4 7 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 8 0 | 0 3 9 | 0 4 0 | 0 0 8 | 0 1 0 | 0 2 9 | 0 6 3 | 0 5 9 | 0 5 2 | 0 2 4 | 0 1 1 | 0 3 1 | 0 3 2 | 0 3 8 | 0 6 2 | 0 6 4 | 0 7 1 | 0 7 4 | 0 0 1 | 0 0 9 | 0 1 2 | 0 1 5 | 0 1 9 | 0 2 7 | 0 3 4 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Penis | | | + | | + | + | | | | | | | | | | | | | | | | | | | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | + | | | | | + | | | | + | | | | | | | | | | | | | |
| Axillary, fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreatic, fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, bronchial | + | | + | M | + | + | I | + | + | + | + | M | + | + | I | + | + | + | M | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | M | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Lymph node, mediastinal | M | + | M | M | + | M | M | M | I | M | M | M | M | M | M | M | M | M | + | + | M | M | M | M | M |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | M | M | M | + | M | M | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| **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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 5 0 | 0 5 3 | 0 5 7 0 | 0 1 7 | 0 2 2 | 0 3 3 | 0 5 6 | 0 5 7 | 0 6 7 | 0 7 8 | 0 7 9 | Total Tissues/ Tumors |
| **General Body System** | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | 1 |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | 1 |
| **Genital System** | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrous histiocytoma | | | | | | | | | | | | 1 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Penis | | | | | | + | | | | | | 12 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Interstitial cell, adenoma | | | | | X | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Lymph node | | | | | | + | | | | + | | 18 |
| Axillary, fibrosarcoma, metastatic, skin | | | | | | | | | | | | 1 |
| Pancreatic, fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Lymph node, bronchial | + | + | M | M | M | + | M | M | + | + | M | 40 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | M | + | + | + | + | + | + | M | + | 52 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | 58 |
| Hemangioma | | | | | | | | | | | | 1 |
| Lymph node, mediastinal | M | + | M | M | M | I | M | M | M | + | + | 12 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Thymus | + | M | + | + | + | + | + | + | + | + | + | 48 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrosarcoma | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | 61 |
| **Nervous System** | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | 61 |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 0 6 7 | 2 1 2 | 3 1 3 | 4 0 6 | 4 3 4 | 4 6 3 | 4 8 0 | 4 9 9 | 5 0 8 | 5 2 6 | 5 3 6 | 5 4 4 | 5 5 2 | 5 5 2 | 5 5 7 | 5 6 1 | 5 8 4 | 5 8 4 | 5 8 5 | 5 8 6 | 5 8 8 | 5 8 9 | 5 9 1 | 6 0 5 | 6 2 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 4 2 | 0 4 6 | 0 6 9 | 0 2 5 | 0 6 6 | 0 7 3 | 0 1 6 | 0 2 1 | 0 3 7 | 0 4 7 | 0 2 6 | 0 0 4 | 0 4 8 | 0 6 0 | 0 1 4 | 0 0 5 | 0 0 2 | 0 2 0 | 0 7 7 | 0 0 3 | 0 7 6 | 0 3 6 | 0 6 1 | 0 3 5 | 0 4 9 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma, two | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Pheochromocytoma complex, metastatic, adrenal medulla | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Pelvis, hemangiosarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Ureter | | | + | + | | | | | | | | | | | | | | | | | | | | | |
| Urethra | | | | | | | | | | | | | | | | | + | + | + | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 6 3 1 | 6 4 1 | 6 6 2 | 6 7 9 | 6 8 1 | 6 8 1 | 6 8 1 | 6 9 4 | 7 1 3 | 7 1 9 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 4 7 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 8 0 | 0 3 9 | 0 4 0 | 0 0 8 | 0 1 0 | 0 2 9 | 0 6 3 | 0 5 9 | 0 5 2 | 0 2 4 | 0 1 1 | 0 3 1 | 0 3 2 | 0 3 8 | 0 6 2 | 0 6 4 | 0 7 1 | 0 7 4 | 0 0 1 | 0 0 9 | 0 1 2 | 0 1 5 | 0 1 9 | 0 2 7 | 0 3 4 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | X | | | | X | | | | | | X | | X | | | | | | |
| Alveolar/bronchiolar adenoma, two | | X | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | X | | X | | | | | | | | | | X | | X | |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma complex, metastatic, adrenal medulla | | X | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | X |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Pelvis, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Ureter | | | | | | | | | | | | | | | | | | | | | | | | |
| Urethra | | | + | | | | + | + | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 5 0 | 0 5 3 | 0 7 0 | 0 1 7 | 0 2 2 | 0 3 3 | 0 5 6 | 0 5 7 | 0 6 7 | 0 7 8 | 0 7 9 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | M | + | 59 |
| Lung | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Alveolar/bronchiolar adenoma | | | X | | | | | | | | | 5 |
| Alveolar/bronchiolar adenoma, two | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma | | | | | | | | X | | | | 7 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | X | | | X | | | | | | 2 |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | 1 |
| Pheochromocytoma complex, metastatic, adrenal medulla | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | 60 |
| **Special Senses System** | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | 1 |
| Adenoma | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Fibrous histiocytoma, metastatic, liver | | | | | | | | | | | | 1 |
| Pelvis, hemangiosarcoma | | | | | | | | | | | | 1 |
| Ureter | | | | | | | | | | | | 2 |
| Urethra | | | | | | | | | | | | 6 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Leiomyosarcoma | | | | | | | | | | | | 1 |
| **Systemic Lesions** | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | 61 |
| Lymphoma malignant | | | | | | | | | | X | | 1 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**

| Number of Days on Study | 0 2 0 | 0 3 7 | 1 6 3 | 2 4 4 | 3 5 5 | 4 1 5 | 4 6 9 | 4 6 9 | 4 7 5 | 4 8 4 | 5 1 3 | 5 2 1 | 5 2 5 | 5 3 3 | 5 4 9 | 5 4 9 | 5 5 9 | 5 6 3 | 5 7 0 | 5 8 0 | 5 8 1 | 5 8 8 | 5 9 0 | 5 9 2 | 6 1 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 8 4 | 2 2 3 | 2 3 8 | 1 9 6 | 2 3 7 | 1 9 9 | 2 0 9 | 2 1 2 | 1 9 3 | 2 1 0 | 2 0 0 | 1 8 6 | 2 1 4 | 1 8 1 | 1 7 8 | 1 8 3 | 1 8 9 | 2 0 6 | 1 9 5 | 1 6 9 | 2 2 7 | 1 6 6 | 2 6 0 | 2 1 8 | 1 6 2 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | A | A | + | M | + | A | + | M | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | A | M |
| Intestine large, colon | A | + | + | A | + | + | + | + | + | + | + | + | + | A | + | M | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | A | A | M | A | + | A | M | M | + | M | + | + | M | A | + | M | + | M | + | + | + | + | M | + | + |
| Intestine large, cecum | A | A | + | A | + | A | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | A | A | + | A | + | A | + | A | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | A | A |
| Intestine small, jejunum | A | A | + | A | + | A | + | A | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | A | A |
| Intestine small, ileum | A | A | + | A | + | A | + | A | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | A | A |
| Liver | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | X | | | | | X | | | X | | | X | | | X | X | | X | X | |
| Hepatocellular carcinoma, multiple | | | | | | | | X | | | | | | | | X | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | | | | X | | | | | | | | X | | X | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Pancreas | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Parathyroid gland | M | M | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | M | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Penis | | | | | | + | | | | | | | | | | | + | | + | | | | + | | + |
| Preputial gland | + | M | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 6 2 0 | 6 3 6 | 6 3 1 | 6 4 1 | 6 4 7 | 6 4 6 | 6 5 2 | 7 0 4 | 7 1 6 | 7 1 3 | 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 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 8 0 | 2 0 7 | 2 1 6 | 2 1 1 | 1 6 4 | 2 2 4 | 2 2 8 | 1 9 1 | 1 8 8 | 2 2 9 | 1 7 0 | 1 7 3 | 1 9 0 | 1 9 4 | 2 0 4 | 2 0 5 | 2 3 3 | 2 4 0 | 1 7 1 | 1 7 6 | 1 8 2 | 1 8 5 | 2 0 1 | 2 1 9 | 2 2 1 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | M | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | M | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | M | + |
| Intestine large, cecum | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | X | X | | | | | X | | X | | | | X | | | | | | | | |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | X | X | | | | | | | | | X | | | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Penis | | + | | | + | | + | + | | | | | | | | | | | | | | | | | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 2 2 | 2 2 5 | 2 2 6 | 2 3 4 | 1 6 3 | 1 6 8 | 2 1 7 | 2 3 1 | 2 3 2 | 2 3 6 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | 59 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | 56 |
| Intestine large, rectum | M | + | + | + | + | M | + | + | M | + | 39 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | 51 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | 51 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | 51 |
| Liver | + | + | + | + | + | + | + | + | + | + | 59 |
| Hemangioma | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | X | X | | | | | | | | 15 |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | 2 |
| Hepatocellular adenoma | | X | | | | | | X | | | 8 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | 59 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | 59 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | 59 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | 59 |
| Tooth | | | | | | | + | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | 59 |
| **Endocrine System** | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | 59 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | 59 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | 59 |
| Adenoma | | | | | | | | | | | 1 |
| Parathyroid gland | + | M | + | + | + | + | + | + | + | + | 55 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | 58 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | 59 |
| Follicular cell, adenoma | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | |
| None | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | 59 |
| Leiomyoma | | | | X | | | | | | | 1 |
| Penis | | | | | | | | | | | 9 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | 58 |
| Prostate | + | + | + | + | + | + | + | + | + | + | 59 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | 59 |
| Testes | + | + | + | + | + | + | + | + | + | + | 59 |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 0 2 0 | 0 3 7 | 1 6 3 | 2 4 4 | 3 5 5 | 4 1 5 | 4 6 9 | 4 6 9 | 4 7 5 | 4 8 4 | 5 1 3 | 5 2 1 | 5 2 5 | 5 3 3 | 5 4 9 | 5 4 9 | 5 5 9 | 5 6 3 | 5 7 0 | 5 8 0 | 5 8 1 | 5 8 8 | 5 9 0 | 5 9 2 | 6 1 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 8 4 | 2 2 3 | 2 3 8 | 1 9 6 | 2 3 7 | 1 9 9 | 2 0 9 | 2 1 2 | 1 9 3 | 2 1 0 | 2 0 0 | 1 0 6 | 2 8 4 | 1 1 8 | 1 8 3 | 1 7 9 | 1 8 8 | 1 8 9 | 2 0 6 | 1 9 5 | 1 6 9 | 2 2 7 | 1 6 6 | 2 6 0 | 2 1 8 | 1 6 2 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | + | | | | + | | | + | | + | | | | | | + | | | | + | | | + |
| Lymph node, bronchial | M | M | + | A | + | + | + | + | + | I | + | + | + | + | + | I | M | + | I | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M |
| Lymph node, mesenteric | M | + | + | A | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mediastinal | M | M | M | A | M | M | M | M | I | + | + | M | M | M | M | + | M | I | M | M | M | + | + | + | M |
| Spleen | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | M | + | I | + | + | M | + | + | M | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | A | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M |
| Skin | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prepuce, fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tail, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | + | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | X | | | X | | | | | | X | | | | | |
| Nose | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | + | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urethra | | + | | | | | | | | | | | | | | | | + | + | + | | | + | | |
| Urinary bladder | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 6 2 0 | 6 3 6 | 6 6 1 | 6 7 1 | 6 7 4 | 6 8 6 | 6 9 2 | 7 0 4 | 7 1 6 | 7 3 1 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 4 7 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 8 0 | 2 0 7 | 2 1 6 | 2 1 1 | 1 6 4 | 2 2 4 | 2 2 8 | 1 9 1 | 1 8 8 | 2 2 9 | 1 7 0 | 1 7 3 | 1 9 0 | 1 9 4 | 2 0 4 | 2 0 5 | 2 3 3 | 2 4 0 | 1 7 1 | 1 7 6 | 1 8 2 | 1 8 5 | 2 0 1 | 2 1 9 | 2 2 1 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | + | | + | | | + | | | | | | + | | | | | | | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | I |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| *Hemangiosarcoma* | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Lymph node, mediastinal | M | M | + | + | + | M | + | M | M | M | I | I | I | I | I | + | + | M | I | I | I | + | I | + | + |
| Spleen | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | I | + | M | + | + | + | + | + | + | + | + | + | I | + | + |
| **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 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + |
| Prepuce, fibrous histiocytoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Tail, hemangiosarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | X | | | | | | | | X | | | | | | | | | | | X | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | X | X | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urethra | + | | | | | | + | | | + | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | X |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | 7 4 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 2 2 | 2 2 5 | 2 2 6 | 2 3 4 | 1 6 3 | 1 6 8 | 2 1 7 | 2 3 1 | 3 3 2 | 3 3 6 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | 59 |
| Lymph node | | | | | | | | | | | 11 |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | 53 |
| Lymph node, mandibular | M | M | + | + | + | M | + | + | + | + | 52 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | 57 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Lymph node, mediastinal | + | M | I | I | M | + | I | M | + | M | 18 |
| Spleen | + | + | + | + | + | + | + | + | + | + | 58 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | M | + | 51 |
| **Integumentary System** | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | 2 |
| Skin | + | + | + | + | + | + | I | + | + | + | 57 |
| Prepuce, fibrous histiocytoma | | | | | | | | | | | 1 |
| Tail, hemangiosarcoma | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | 59 |
| **Nervous System** | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | 59 |
| Spinal cord | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | |
| Larynx | I | M | + | + | M | + | + | + | + | + | 56 |
| Lung | + | + | + | + | + | + | + | + | + | + | 59 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | 3 |
| Alveolar/bronchiolar carcinoma | | | | | | X | | X | | | 2 |
| Hepatocellular carcinoma, metastatic, liver | | | X | | | | | | | | 6 |
| Nose | + | + | + | + | + | + | + | + | + | + | 59 |
| Trachea | + | + | + | + | + | + | + | + | + | + | 59 |
| **Special Senses System** | | | | | | | | | | | |
| Ear | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | 59 |
| Urethra | | | | | | | | | | | 8 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | 59 |
| **Systemic Lesions** | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | 59 |
| Lymphoma malignant | | | | | | | | | | | 1 |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**

| Number of Days on Study | 1 1 2 3 3 3 3 4 4 4 4 4 4 5 5 5 5 6 6 6 6 6 6 6 6<br>1 4 5 3 7 8 9 2 5 5 6 6 8 2 3 3 8 0 0 2 4 4 6 6 6<br>8 4 0 5 4 5 1 4 0 9 3 9 5 4 2 9 5 7 7 6 2 4 1 1 1 |
|---|---|
| **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<br>9 3 5 8 2 6 5 6 4 2 4 7 4 7 8 9 5 3 5 8 6 7 5 6 8<br>9 3 6 9 3 2 8 8 3 2 6 6 0 4 6 5 9 1 1 0 3 2 3 5 5 |
| **Alimentary System** | |
| Esophagus | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Gallbladder | + + A + + + A + A + + + + + A + + + + + + + + + + |
| Intestine large, colon | + + A + + + + + + + + + + + + + + + + + + + + + + |
| Intestine large, rectum | + + A + + M M M + + + + + + + + + + + + + + + + + |
| Intestine large, cecum | + + A + + + A + A + + + + + + + + + + + + + + + + |
| Intestine small, duodenum | + + A + + + A + A + + + + + A + + + + + + + + + + |
| Intestine small, jejunum | + + A + + + A + + + + + + + A + + + + + + + + + + |
| Intestine small, ileum | + + A + + + A + + + + + + + A + + + + + + + + + + |
| Hepatocellular carcinoma, metastatic, liver | |
| Liver | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Hemangiosarcoma | X |
| Hepatoblastoma | |
| Hepatocellular carcinoma | X X X X X X X |
| Hepatocellular adenoma | X X X |
| Hepatocellular adenoma, multiple | X |
| Pancreas | + + A + + + + + + + + + + + + + + + + + + + + + + |
| Salivary glands | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Stomach, forestomach | + + A + + + + + + + + + + + + + + + + + + + + + + |
| Stomach, glandular | + + A + + + + + + + + + + + + + + + + + + + + + + |
| Adenocarcinoma | |
| Tooth | + |
| Odontoma | X |
| **Cardiovascular System** | |
| Heart | + + + + + + + + + + + + + + + + + + + + + + + + + |
| **Endocrine System** | |
| Adrenal cortex | + + + + M + + + + + + + + + + + + + + + + + + + + |
| Capsule, adenoma | X |
| Adrenal medulla | + + M + M + + + + + + + + + + + + + + + + + + + + |
| Islets, pancreatic | + + A + + + + + + + + + + + + + + + + + + + + + + |
| Parathyroid gland | M M + + + M + M + + + M + + + + + + + + + + + + M |
| Pituitary gland | + + + + + + + M + + + + + + + + + + + + + + + + + |
| Pars distalis, adenoma | |
| Thyroid gland | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Follicular cell, adenoma | |
| **General Body System** | |
| Tissue NOS | + |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic | X |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic | X |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7<br>6 6 6 7 9 0 1 1 1 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4<br>5 5 6 6 5 5 1 3 6 4 7 7 7 7 7 7 7 7 7 7 7 7 0 0 |
|---|---|
| **Carcass ID Number** | 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 3 3<br>3 7 7 9 4 3 4 9 3 6 2 2 2 3 4 5 7 8 8 8 9 9 0 2 4<br>7 1 9 8 5 9 2 4 6 6 7 8 9 4 4 0 8 3 4 7 1 6 0 5 7 |
| **Alimentary System** | |
| Esophagus | + + + + + + + + + + + + + + + + + + + + + + + + |
| Gallbladder | + + + A + A + + + + + + + + + + + + + + + + + + |
| Intestine large, colon | + + + A + A + + + + + + + + + + + + + + + + + + |
| Intestine large, rectum | M + M A + M + + + + + + + + + + + + + + M + M + + |
| Intestine large, cecum | + + + A + A + + + + + + + + + + + + + + + + + + |
| Intestine small, duodenum | + + + A + A + + + + + + + + + + + + + + + + + + |
| Intestine small, jejunum | + + + A + A + + + M + + + + + + + + + + + + + + |
| Intestine small, ileum | + + + A + A + + + + + + + + + + + + + + + + + + |
| Hepatocellular carcinoma, metastatic, liver | X |
| Liver | + + + A + + + + + + + + + + + + + + + + + + + + |
| Hemangiosarcoma | |
| Hepatoblastoma | X |
| Hepatocellular carcinoma | X X X X X |
| Hepatocellular adenoma | X X X X |
| Hepatocellular adenoma, multiple | X X |
| Pancreas | + + + A + + + + + + + + + + + + + + + + + + + + |
| Salivary glands | + + + A + + + + + + + + + + + + + + + + + + + + |
| Stomach, forestomach | + + + A + A + + + + + + + + + + + + + + + + + + |
| Stomach, glandular | + + + A + A + + + + + + + + + + + + + + + + + + |
| Adenocarcinoma | X |
| Tooth | + |
| Odontoma | |
| **Cardiovascular System** | |
| Heart | + + + + + + + + + + + + + + + + + + + + + + + + |
| **Endocrine System** | |
| Adrenal cortex | + + + A + + + + + + + + + + + + + + + + + + + + |
| Capsule, adenoma | |
| Adrenal medulla | M + + A + + + + + + + + + + + + + + + + + + + + |
| Islets, pancreatic | + + + A + + + + + + + + + + + + + + + + + + + + |
| Parathyroid gland | + + M A + + + + + + + + + + + + + + M + + + + + |
| Pituitary gland | + + + A + I + + + + + + + + + + + + + + + + M M + |
| Pars distalis, adenoma | |
| Thyroid gland | + + + A + + + + + + + + + + + + + + + + + + + + |
| Follicular cell, adenoma | X |
| **General Body System** | |
| Tissue NOS | |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 5 2 | 3 6 1 | 3 7 0 | 3 8 1 | 3 8 2 | 3 9 3 | 3 9 7 | 3 2 4 | 3 3 0 | 3 4 8 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | 60 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | 57 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | 55 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | 55 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | 1 |
| Liver | + | + | + | + | + | + | + | + | + | + | 59 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Hepatoblastoma | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | | | | | | | | | 12 |
| Hepatocellular adenoma | | | X | | | | | | | X | 11 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | 3 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | 58 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | 59 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | 57 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | 57 |
| Adenocarcinoma | | | | | | | | | | | 1 |
| Tooth | | | | | + | + | | | | | 4 |
| Odontoma | | | | | | X | | | | | 2 |
| **Cardiovascular System** | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | 60 |
| **Endocrine System** | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | 58 |
| Capsule, adenoma | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | 56 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | 58 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | 51 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | 55 |
| Pars distalis, adenoma | | X | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | 59 |
| Follicular cell, adenoma | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | 1 |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic | | | | | | | | | | | 1 |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic | | | | | | | | | | | 1 |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 1 1 2 3 3 3 3 4 4 4 4 4 4 5 5 5 5 6 6 6 6 6 6 6 |
|---|---|
| | 1 4 5 3 7 8 9 2 5 5 6 6 8 2 3 3 8 0 0 2 4 4 6 6 6 |
| | 1 8 4 0 5 4 5 1 4 0 9 3 9 5 4 2 9 5 7 7 6 2 4 1 1 1 |
| **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 |
| | 9 3 5 8 2 6 5 6 4 2 4 7 4 7 8 9 5 3 5 8 6 7 5 6 8 |
| | 9 3 6 9 3 2 8 8 3 2 6 6 0 4 6 5 9 1 1 0 3 2 3 5 5 |
| **Genital System** | |
| Coagulating gland | |
| Interstitium, granular cell tumor NOS | |
| Epididymis | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Penis | + + + + + + |
| Preputial gland | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Prostate | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Seminal vesicle | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Testes | + + + + + + + + + + + + + + + + + + + + + + + + + |
| **Hematopoietic System** | |
| Blood | A |
| Bone marrow | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Lymph node | + + + + + + + + + + + + + + + + + |
| Lymph node, bronchial | M + + + I + + + + I + + + + + + + + + + I + + + + + |
| Hepatocellular carcinoma, metastatic | |
| Lymph node, mandibular | + + + + + + M + + + + + + + + + + + + + M + + + + + |
| Lymph node, mesenteric | + + A + + + + + + + + + + + + + + + + + M + + + + + |
| Adenocarcinoma, metastatic, stomach, glandular | |
| Fibrous histiocytoma | |
| Hemangioma | |
| Lymph node, mediastinal | M I M M M A A M M I M M + + + + M + M I M M M M I |
| Spleen | + + A + + + + + + + + + + + + + + + + + M + + + + + |
| Hemangioma | |
| Thymus | + M + M + + + + I M + + + M + M + M + + M + + + + |
| **Integumentary System** | |
| Mammary gland | M M M M M M M M M M M M M M M M M M M M M M M M M |
| Skin | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Fibrous histiocytoma | |
| Pinna, hemangiosarcoma | |
| **Musculoskeletal System** | |
| Bone | + + + + + + + + + + + + + + + + + + + + + + + + + |
| **Nervous System** | |
| Brain | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Spinal cord | + |
| **Respiratory System** | |
| Larynx | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Lung | + + A + + + + + + + + + + + + + + + + + + + + + + |
| Alveolar/bronchiolar adenoma | |
| Alveolar/bronchiolar carcinoma | X |
| Hepatoblastoma, metastatic, liver | |
| Hepatocellular carcinoma, metastatic, liver | |
| Nose | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Trachea | + + + + + + + + + + + + + + + + M + + + + + + + + |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7<br>6 6 6 7 9 0 1 1 1 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4<br>5 5 6 6 5 5 1 3 6 4 7 7 7 7 7 7 7 7 7 7 7 7 0 0 |
|---|---|
| **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 4 3 3<br>3 7 7 9 4 3 4 9 3 6 2 2 2 3 4 5 7 8 8 8 9 9 0 2 4<br>7 1 9 8 5 9 2 4 6 6 7 8 9 4 4 0 8 3 4 7 1 6 0 5 7 |
| **Genital System** | |
| Coagulating gland | + |
| Interstitium, granular cell tumor NOS | X |
| Epididymis | + + + A + + + + + + + + + + + + + + + + + + + + |
| Penis | + + |
| Preputial gland | + + + + + + + + + + + + + + + + + + + + + + + + |
| Prostate | + + + A + + + + + + + + + + + + + + + + + + + + |
| Seminal vesicle | + + + A + + + + + + + + + + + + + + + + + + + + |
| Testes | + + + A + + + + + + + + + + + + + + + + + + + + |
| **Hematopoietic System** | |
| Blood | |
| Bone marrow | + + + A + + + + + + + + + + + + + + + + + + + + |
| Lymph node | + + + |
| Lymph node, bronchial | + + + A + + + + + + + + + + + + + + + + + + + + |
| Hepatocellular carcinoma, metastatic | X |
| Lymph node, mandibular | + + M A + + + + + + + + + + + + + + + + + + + + |
| Lymph node, mesenteric | + + + A + + M + + + + + + + + + + + + + + + + + |
| Adenocarcinoma, metastatic, stomach, glandular | X |
| Fibrous histiocytoma | X |
| Hemangioma | X |
| Lymph node, mediastinal | + + M A + + + M + + I + M I I M I + + I I I M M I |
| Spleen | + + + A + + + + + + + + + + + + + + + + + + + + |
| Hemangioma | |
| Thymus | M M + A + + M + + + M I + M M + I + + M + + + M + |
| **Integumentary System** | |
| Mammary gland | M M M M M M M M M M M M M M M M M M M M M M M M |
| Skin | + + + A + + + + + + + + + + + + + + + + + + + + |
| Fibrous histiocytoma | X |
| Pinna, hemangiosarcoma | X |
| **Musculoskeletal System** | |
| Bone | + + + A + + + + + + + + + + + + + + + + + + + + |
| **Nervous System** | |
| Brain | + + + A + + + + + + + + + + + + + + + + + + + + |
| Spinal cord | |
| **Respiratory System** | |
| Larynx | + + + A + + + + + + + + + + + + + + + + + + + + |
| Lung | + + + A + + + + + + + + + + + + + + + + + + + + |
| Alveolar/bronchiolar adenoma | X X |
| Alveolar/bronchiolar carcinoma | X |
| Hepatoblastoma, metastatic, liver | X |
| Hepatocellular carcinoma, metastatic, liver | X X |
| Nose | + + + A + + + + + + + + + + + + + + + + + + + + |
| Trachea | + + + M + + + + + + + + + + + + + + + + + + + + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 5 2 | 3 6 1 | 3 7 0 | 3 8 1 | 3 8 2 | 3 9 3 | 3 9 7 | 3 2 4 | 3 3 0 | 3 3 4 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | |
| Coagulating gland | | | | | | | | | | | 1 |
| Interstitium, granular cell tumor NOS | | | | | | | | | | | 1 |
| Epididymis | + | + | + | + | + | + | + | + | + | + | 59 |
| Penis | | | | | | | | | | | 8 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | 60 |
| Prostate | + | + | + | + | + | + | + | + | + | + | 59 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | 59 |
| Testes | + | + | + | + | + | + | + | + | + | + | 59 |
| **Hematopoietic System** | | | | | | | | | | | |
| Blood | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | 59 |
| Lymph node | | | | | | | | | | | 11 |
| Lymph node, bronchial | + | + | + | + | + | + | + | M | + | + | 54 |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | 56 |
| Lymph node, mesenteric | + | M | + | + | + | + | + | + | + | + | 55 |
| Adenocarcinoma, metastatic, stomach, glandular | | | | | | | | | | | 1 |
| Fibrous histiocytoma | | | | | | | | | | | 1 |
| Hemangioma | | | | | | | | | | | 1 |
| Lymph node, mediastinal | M | I | I | + | + | I | I | M | I | M | 17 |
| Spleen | + | + | + | + | + | + | + | + | + | + | 57 |
| Hemangioma | | X | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | 41 |
| **Integumentary System** | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | |
| Skin | + | + | + | + | + | + | + | + | + | + | 59 |
| Fibrous histiocytoma | | | | | | | | | | | 1 |
| Pinna, hemangiosarcoma | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | 59 |
| **Nervous System** | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | 59 |
| Spinal cord | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | 59 |
| Lung | + | + | + | + | + | + | + | + | + | + | 58 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | 2 |
| Alveolar/bronchiolar carcinoma | | | | | X | | | X | | | 4 |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | 2 |
| Nose | + | + | + | + | + | + | + | + | + | + | 59 |
| Trachea | + | + | + | + | + | + | + | + | + | + | 58 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 1 | 1 | 2 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | 1 | 4 | 5 | 3 | 7 | 8 | 9 | 2 | 5 | 5 | 6 | 6 | 8 | 2 | 3 | 3 | 8 | 0 | 0 | 2 | 4 | 4 | 6 | 6 | 6 |
| | 8 | 4 | 0 | 5 | 4 | 5 | 1 | 4 | 0 | 9 | 3 | 9 | 5 | 4 | 2 | 9 | 5 | 7 | 7 | 6 | 2 | 4 | 1 | 1 | 1 |
| **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 |
| | 9 | 3 | 5 | 8 | 2 | 6 | 5 | 6 | 4 | 2 | 4 | 7 | 4 | 7 | 8 | 9 | 5 | 3 | 5 | 8 | 6 | 7 | 5 | 6 | 8 |
| | 9 | 3 | 6 | 9 | 3 | 2 | 8 | 8 | 3 | 2 | 6 | 6 | 0 | 4 | 6 | 5 | 9 | 1 | 1 | 0 | 3 | 2 | 3 | 5 | 5 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urethra | | | | + | + | | | | | + | | | | | | | + | | + | | | | | | + |
| Urinary bladder | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | 6 | 6 | 6 | 7 | 9 | 0 | 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | |
| | 5 | 5 | 6 | 6 | 5 | 5 | 1 | 3 | 6 | 4 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 0 | 0 | |
| **Carcass ID Number** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | |
| | 3 | 7 | 7 | 9 | 4 | 3 | 4 | 9 | 3 | 6 | 2 | 2 | 2 | 3 | 4 | 5 | 7 | 8 | 8 | 8 | 9 | 9 | 0 | 2 | 4 |
| | 7 | 1 | 9 | 8 | 5 | 9 | 2 | 4 | 6 | 6 | 7 | 8 | 9 | 4 | 4 | 0 | 8 | 3 | 4 | 7 | 1 | 6 | 0 | 5 | 7 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatoblastoma, metastatic, liver | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Urethra | + | + | | | + | + | + | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m$^3$**
(continued)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 0 | 7 4 1 | 7 4 1 | 7 4 1 | |
| **Carcass ID Number** | 3 5 2 | 3 6 1 | 3 7 0 | 3 8 1 | 3 8 2 | 3 9 3 | 3 9 7 | 3 2 4 | 3 3 0 | 3 4 8 | Total Tissues/ Tumors |
| **Special Senses System** | | | | | | | | | | | |
| None | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | 59 |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | 1 |
| Urethra | | | | | | | | | | | 11 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | 58 |
| **Systemic Lesions** | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | 60 |

TABLE C3
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Liver: Hepatocellular Adenoma** | | | |
| Overall rate[a] | 13/61 (21%) | 9/59 (15%) | 14/59 (24%) |
| Adjusted rate[b] | 37.4% | 25.6% | 41.7% |
| Terminal rate[c] | 7/26 (27%) | 3/25 (12%) | 8/25 (32%) |
| First incidence (days) | 508 | 525 | 485 |
| Life table test[d] | P=0.450 | P=0.293N | P=0.492 |
| Logistic regression test[d] | P=0.410 | P=0.278N | P=0.454 |
| Cochran-Armitage test[d] | P=0.419 | | |
| Fisher exact test[d] | | P=0.268N | P=0.461 |
| **Liver: Hepatocellular Carcinoma** | | | |
| Overall rate | 11/61 (18%) | 17/59 (29%) | 12/59 (20%) |
| Adjusted rate | 27.0% | 40.4% | 28.2% |
| Terminal rate | 3/26 (12%) | 5/25 (20%) | 1/25 (4%) |
| First incidence (days) | 434 | 415 | 450 |
| Life table test | P=0.442 | P=0.137 | P=0.492 |
| Logistic regression test | P=0.242 | P=0.123 | P=0.272 |
| Cochran-Armitage test | P=0.418 | | |
| Fisher exact test | | P=0.119 | P=0.464 |
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | |
| Overall rate | 24/61 (39%) | 22/59 (37%) | 25/59 (42%) |
| Adjusted rate | 56.6% | 49.6% | 58.0% |
| Terminal rate | 10/26 (38%) | 6/25 (24%) | 9/25 (36%) |
| First incidence (days) | 434 | 415 | 450 |
| Life table test | P=0.449 | P=0.507N | P=0.487 |
| Logistic regression test | P=0.222 | P=0.489N | P=0.257 |
| Cochran-Armitage test | P=0.405 | | |
| Fisher exact test | | P=0.483N | P=0.440 |
| **Lung: Alveolar/bronchiolar Adenoma** | | | |
| Overall rate | 6/61 (10%) | 3/59 (5%) | 2/58 (3%) |
| Adjusted rate | 19.8% | 10.8% | 7.7% |
| Terminal rate | 3/26 (12%) | 2/25 (8%) | 1/25 (4%) |
| First incidence (days) | 641 | 661 | 734 |
| Life table test | P=0.097N | P=0.269N | P=0.144N |
| Logistic regression test | P=0.088N | P=0.261N | P=0.131N |
| Cochran-Armitage test | P=0.103N | | |
| Fisher exact test | | P=0.262N | P=0.153N |
| **Lung: Alveolar/bronchiolar Carcinoma** | | | |
| Overall rate | 7/61 (11%) | 2/59 (3%) | 4/58 (7%) |
| Adjusted rate | 23.7% | 8.0% | 14.3% |
| Terminal rate | 5/26 (19%) | 2/25 (8%) | 3/25 (12%) |
| First incidence (days) | 552 | 737 (T) | 661 |
| Life table test | P=0.200N | P=0.092N | P=0.279N |
| Logistic regression test | P=0.184N | P=0.088N | P=0.261N |
| Cochran-Armitage test | P=0.211N | | |
| Fisher exact test | | P=0.090N | P=0.294N |

TABLE C3
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | |
| Overall rate | 13/61 (21%) | 5/59 (8%) | 6/58 (10%) |
| Adjusted rate | 40.7% | 18.5% | 21.4% |
| Terminal rate | 8/26 (31%) | 4/25 (16%) | 4/25 (16%) |
| First incidence (days) | 552 | 661 | 661 |
| Life table test | P=0.045N | P=0.046N | P=0.076N |
| Logistic regression test | P=0.035N | P=0.038N | P=0.058N |
| Cochran-Armitage test | P=0.051N | | |
| Fisher exact test | | P=0.042N | P=0.083N |
| **Thyroid Gland (Follicular Cell): Adenoma** | | | |
| Overall rate | 4/61 (7%) | 1/59 (2%) | 1/59 (2%) |
| Adjusted rate | 12.4% | 3.6% | 4.0% |
| Terminal rate | 2/26 (8%) | 0/25 (0%) | 1/25 (4%) |
| First incidence (days) | 313 | 704 | 737 (T) |
| Life table test | P=0.106N | P=0.195N | P=0.188N |
| Logistic regression test | P=0.110N | P=0.192N | P=0.192N |
| Cochran-Armitage test | P=0.109N | | |
| Fisher exact test | | P=0.193N | P=0.193N |
| **All Organs: Hemangiosarcoma** | | | |
| Overall rate | 1/61 (2%) | 3/60 (5%) | 2/60 (3%) |
| Adjusted rate | 1.8% | 10.9% | 6.5% |
| Terminal rate | 0/26 (0%) | 2/25 (8%) | 1/25 (4%) |
| First incidence (days) | 480 | 671 | 661 |
| Life table test | P=0.390 | P=0.291 | P=0.493 |
| Logistic regression test | P=0.392 | P=0.292 | P=0.494 |
| Cochran-Armitage test | P=0.393 | | |
| Fisher exact test | | P=0.303 | P=0.494 |
| **All Organs: Hemangioma or Hemangiosarcoma** | | | |
| Overall rate | 2/61 (3%) | 4/60 (7%) | 4/60 (7%) |
| Adjusted rate | 5.6% | 14.2% | 13.6% |
| Terminal rate | 1/26 (4%) | 2/25 (8%) | 2/25 (8%) |
| First incidence (days) | 480 | 671 | 661 |
| Life table test | P=0.268 | P=0.323 | P=0.329 |
| Logistic regression test | P=0.271 | P=0.317 | P=0.328 |
| Cochran-Armitage test | P=0.268 | | |
| Fisher exact test | | P=0.332 | P=0.332 |
| **All Organs: Benign Neoplasms** | | | |
| Overall rate | 28/61 (46%) | 16/60 (27%) | 19/60 (32%) |
| Adjusted rate | 72.2% | 42.8% | 53.1% |
| Terminal rate | 16/26 (62%) | 6/25 (24%) | 10/25 (40%) |
| First incidence (days) | 313 | 475 | 144 |
| Life table test | P=0.076N | P=0.045N | P=0.092N |
| Logistic regression test | P=0.060N | P=0.025N | P=0.077N |
| Cochran-Armitage test | P=0.060N | | |
| Fisher exact test | | P=0.022N | P=0.078N |

TABLE C3
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **All Organs: Malignant Neoplasms** | | | |
| Overall rate | 21/61 (34%) | 23/60 (38%) | 21/60 (35%) |
| Adjusted rate | 49.1% | 55.2% | 50.6% |
| Terminal rate | 8/26 (31%) | 9/25 (36%) | 7/25 (28%) |
| First incidence (days) | 434 | 415 | 450 |
| Life table test | P=0.510 | P=0.369 | P=0.551 |
| Logistic regression test | P=0.348 | P=0.384 | P=0.375 |
| Cochran-Armitage test | P=0.511 | | |
| Fisher exact test | | P=0.398 | P=0.549 |
| **All Organs: Benign or Malignant Neoplasms** | | | |
| Overall rate | 41/61 (67%) | 32/60 (53%) | 35/60 (58%) |
| Adjusted rate | 84.3% | 68.0% | 76.6% |
| Terminal rate | 19/26 (73%) | 11/25 (44%) | 15/25 (60%) |
| First incidence (days) | 313 | 415 | 144 |
| Life table test | P=0.255N | P=0.201N | P=0.272N |
| Logistic regression test | P=0.193N | P=0.100N | P=0.221N |
| Cochran-Armitage test | P=0.182N | | |
| Fisher exact test | | P=0.085N | P=0.206N |

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

TABLE C4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| **Historical Incidence at Lovelace Inhalation Toxicology Research Institute** | | | |
| Nickel Oxide | 7/57 | 4/57 | 9/57 |
| Nickel Subsulfide | 6/61 | 7/61 | 13/61 |
| Nickel Sulfate Hexahydrate | 5/61 | 9/61 | 13/61 |
| Talc | 6/45 | 7/45 | 12/45 |
| **Overall Historical Incidence in Inhalation Studies** | | | |
| Total | 141/952 (14.8%) | 75/952 (7.9%) | 205/952 (21.5%) |
| Standard deviation | 7.0% | 5.7% | 8.0% |
| Range | 6%-36% | 0%-16% | 10%-42% |
| **Overall Historical Incidence in Feed Studies** | | | |
| Total | 194/1,319 (14.7%) | 64/1,319 (4.9%) | 249/1,319 (18.9%) |
| Standard deviation | 6.4% | 3.9% | 7.6% |
| Range | 4%-28% | 0%-14% | 4%-32% |

[a] Data as of 17 June 1994

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 80 | 80 | 80 |
| *7-Month interim evaluation*[b] | 9 | 10 | 10 |
| *15-Month interim evaluation*[b] | 10 | 10 | 10 |
| Early deaths | | | |
| Moribund | 27 | 26 | 25 |
| Natural deaths | 8 | 9 | 9 |
| Survivors | | | |
| Died last week of study | | | 1 |
| Terminal sacrifice | 26 | 25 | 25 |
| Animals examined microscopically | 71 | 70 | 70 |
| ***7-Month Interim Evaluation*** | | | |
| **Hematopoietic System** | | | |
| Lymph node | (1) | (1) | |
| Lumbar, hyperplasia, lymphoid | 1 (100%) | 1 (100%) | |
| Lumbar, pigmentation | 1 (100%) | 1 (100%) | |
| Lymph node, bronchial | (3) | (4) | (5) |
| Hyperplasia, lymphoid | | 2 (50%) | 3 (60%) |
| Hyperplasia, macrophage | | 2 (50%) | 5 (100%) |
| Lymph node, mediastinal | (2) | (2) | (3) |
| Hyperplasia | | 1 (50%) | |
| **Respiratory System** | | | |
| Lung | (5) | (5) | (5) |
| Inflammation, chronic active | | 3 (60%) | 5 (100%) |
| Alveolus, hyperplasia, macrophage | | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 5 (100%) | 5 (100%) |
| Interstitium, infiltration cellular | | 5 (100%) | 3 (60%) |
| Nose | (5) | (5) | (5) |
| Olfactory epithelium, atrophy | | 1 (20%) | 4 (80%) |
| Olfactory epithelium, respiratory epithelium, degeneration | 1 (20%) | | |
| **Urinary System** | | | |
| Urinary bladder | | (1) | |
| Calculus, microscopic observation only | | 1 (100%) | |

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Five animals in each exposure group were histopathologically examined at the interim evaluations.

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***7-Month Interim Evaluation*** (continued) | | | |
| ***Systems Examined With No Lesions Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Genital System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Special Senses System** | | | |
| ***15-Month Interim Evaluation*** | | | |
| **Alimentary System** | | | |
| Intestine large, cecum | (5) | (5) | (5) |
| Hyperplasia, focal, lymphoid | | 2 (40%) | |
| Liver | (5) | (5) | (5) |
| Basophilic focus | | | 1 (20%) |
| Mixed cell focus | | | 1 (20%) |
| Stomach, forestomach | (3) | (5) | (5) |
| Hyperplasia, focal | | 1 (20%) | |
| Stomach, glandular | (5) | (5) | (5) |
| Hyperplasia, focal | | 1 (20%) | |
| **Endocrine System** | | | |
| Adrenal cortex | (5) | (5) | (5) |
| Hypertrophy | 1 (20%) | | |
| Thyroid gland | (5) | (5) | (5) |
| Follicular cell, hyperplasia | | | 1 (20%) |
| **Genital System** | | | |
| Preputial gland | (5) | (5) | (5) |
| Ectasia | 4 (80%) | 5 (100%) | 3 (60%) |
| Inflammation, chronic | 1 (20%) | 1 (20%) | 1 (20%) |
| **Hematopoietic System** | | | |
| Lymph node, inguinal | | (1) | |
| Hyperplasia, lymphoid | | 1 (100%) | |
| Lymph node, bronchial | (4) | (3) | (5) |
| Hyperplasia, lymphoid | | 3 (100%) | 5 (100%) |
| Hyperplasia, macrophage | | 3 (100%) | 4 (80%) |
| Lymph node, mandibular | (2) | (3) | (4) |
| Hyperplasia, lymphoid | | | 1 (25%) |

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | |
| **Hematopoietic System** (continued) | | | |
| Lymph node, mesenteric | (5) | (5) | (5) |
| Hemorrhage, chronic | 1 (20%) | | |
| Hyperplasia, lymphoid | 1 (20%) | | |
| Spleen | (5) | (5) | (5) |
| Hematopoietic cell proliferation | | 1 (20%) | |
| **Integumentary System** | | | |
| Skin | (5) | (5) | (5) |
| Ulcer | | 1 (20%) | |
| Subcutaneous tissue, abscess | | | 1 (20%) |
| **Musculoskeletal System** | | | |
| Bone | (5) | (5) | (5) |
| Femur, hyperostosis | | | 1 (20%) |
| **Respiratory System** | | | |
| Lung | (5) | (5) | (5) |
| Inflammation, chronic active | | 5 (100%) | 5 (100%) |
| Bronchialization | | 4 (80%) | 5 (100%) |
| Alveolus, hyperplasia, macrophage | | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 5 (100%) | 5 (100%) |
| Bronchus, hyperplasia, lymphoid | 2 (40%) | 1 (20%) | 2 (40%) |
| Interstitium, infiltration cellular | | 4 (80%) | 5 (100%) |
| Nose | (5) | (5) | (5) |
| Olfactory epithelium, atrophy | | 3 (60%) | 4 (80%) |
| Trachea | (5) | (5) | (5) |
| Inflammation, focal | 3 (60%) | | |
| **Urinary System** | | | |
| Kidney | (5) | (5) | (5) |
| Hydronephrosis | | 1 (20%) | |
| Nephropathy | | | 1 (20%) |
| Urethra | (2) | | (1) |
| Calculus, microscopic observation only | 2 (100%) | | 1 (100%) |
| Urinary bladder | (5) | (5) | (5) |
| Calculus, microscopic observation only | 1 (20%) | | |
| ***Systems Examined With No Lesions Observed*** | | | |
| **Cardiovascular System** | | | |
| **General Body System** | | | |
| **Nervous System** | | | |
| **Special Senses System** | | | |

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Gallbladder | (57) | (50) | (54) |
| Epithelium, hyperplasia | | 1 (2%) | |
| Intestine large, cecum | (57) | (54) | (55) |
| Lymphoid tissue, hyperplasia | | 1 (2%) | |
| Lymphoid tissue, hyperplasia, lymphoid | 1 (2%) | | 3 (5%) |
| Intestine small, ileum | (55) | (51) | (55) |
| Peyer's patch, hyperplasia, lymphoid | | | 3 (5%) |
| Liver | (61) | (59) | (59) |
| Angiectasis | 2 (3%) | 3 (5%) | 1 (2%) |
| Atrophy | 1 (2%) | 1 (2%) | 2 (3%) |
| Basophilic focus | 2 (3%) | 1 (2%) | 1 (2%) |
| Degeneration | 1 (2%) | 1 (2%) | |
| Eosinophilic focus | 2 (3%) | 2 (3%) | |
| Hepatodiaphragmatic nodule | | 2 (3%) | |
| Infarct | 2 (3%) | 2 (3%) | 2 (3%) |
| Infiltration cellular, lymphocyte | 1 (2%) | | |
| Inflammation | 2 (3%) | | |
| Mixed cell focus | 1 (2%) | | 1 (2%) |
| Necrosis | 7 (11%) | 9 (15%) | 6 (10%) |
| Pigmentation, hemosiderin | | 1 (2%) | 1 (2%) |
| Regeneration | | 1 (2%) | |
| Bile duct, hyperplasia | | 1 (2%) | |
| Sinusoid, cyst | | | 1 (2%) |
| Pancreas | (61) | (59) | (58) |
| Infiltration cellular, lymphocyte | | 1 (2%) | |
| Acinus, atrophy | 1 (2%) | 1 (2%) | |
| Acinus, hyperplasia | 1 (2%) | | |
| Stomach, forestomach | (61) | (59) | (57) |
| Inflammation | | 1 (2%) | |
| Stomach, glandular | (61) | (59) | (57) |
| Degeneration | | | 1 (2%) |
| Inflammation | 1 (2%) | 2 (3%) | |
| Tooth | (4) | (1) | (4) |
| Developmental malformation | 1 (25%) | | 2 (50%) |
| Inflammation | 3 (75%) | 1 (100%) | 1 (25%) |
| **Cardiovascular System** | | | |
| Heart | (61) | (59) | (60) |
| Angiectasis | | | 1 (2%) |
| Cardiomyopathy | 1 (2%) | 2 (3%) | |

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Endocrine System** | | | |
| Adrenal cortex | (61) | (59) | (58) |
| Cyst | 1 (2%) | | |
| Degeneration | | 1 (2%) | |
| Hyperplasia | | 1 (2%) | |
| Hyperplasia, focal | 1 (2%) | 2 (3%) | 4 (7%) |
| Hypertrophy, focal | | 1 (2%) | |
| Necrosis | | 1 (2%) | |
| Islets, pancreatic | (61) | (59) | (58) |
| Hyperplasia | | 1 (2%) | |
| Pituitary gland | (58) | (58) | (55) |
| Pars distalis, hyperplasia | 1 (2%) | | 1 (2%) |
| Thyroid gland | (61) | (59) | (59) |
| Follicular cell, hyperplasia | 27 (44%) | 25 (42%) | 24 (41%) |
| **General Body System** | | | |
| None | | | |
| **Genital System** | | | |
| Penis | (12) | (9) | (8) |
| Concretion | 4 (33%) | 2 (22%) | 1 (13%) |
| Inflammation | 5 (42%) | 6 (67%) | 6 (75%) |
| Preputial gland | (61) | (58) | (60) |
| Atrophy | 3 (5%) | 1 (2%) | 1 (2%) |
| Ectasia | 28 (46%) | 31 (53%) | 42 (70%) |
| Hyperplasia | 2 (3%) | | |
| Inflammation, chronic | 24 (39%) | 14 (24%) | 7 (12%) |
| Prostate | (61) | (59) | (59) |
| Inflammation | | 1 (2%) | 2 (3%) |
| Seminal vesicle | (61) | (59) | (59) |
| Hyperplasia | 2 (3%) | | |
| Testes | (61) | (59) | (59) |
| Atrophy | 1 (2%) | | 2 (3%) |
| Germinal epithelium, atrophy | | 2 (3%) | |
| **Hematopoietic System** | | | |
| Bone marrow | (61) | (59) | (59) |
| Thrombosis | | | 1 (2%) |
| Erythroid cell, hyperplasia | 2 (3%) | 3 (5%) | 1 (2%) |
| Myeloid cell, hyperplasia | 23 (38%) | 11 (19%) | 15 (25%) |

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Hematopoietic System** (continued) | | | |
| Lymph node | (18) | (11) | (11) |
| Iliac, hyperplasia, lymphoid | 3 (17%) | | 3 (27%) |
| Iliac, hyperplasia, plasma cell | 7 (39%) | 1 (9%) | 3 (27%) |
| Iliac, inflammation | 1 (6%) | 1 (9%) | |
| Iliac, pigmentation | 2 (11%) | 1 (9%) | 1 (9%) |
| Inguinal, hyperplasia, lymphoid | 6 (33%) | 5 (45%) | 6 (55%) |
| Inguinal, hyperplasia, plasma cell | 2 (11%) | 3 (27%) | |
| Inguinal, inflammation | | 1 (9%) | |
| Inguinal, pigmentation | 1 (6%) | | 1 (9%) |
| Lumbar, hyperplasia, plasma cell | 1 (6%) | | |
| Lumbar, pigmentation | 1 (6%) | 1 (9%) | |
| Pancreatic, hyperplasia, lymphoid | | 1 (9%) | |
| Renal, hyperplasia, lymphoid | 1 (6%) | | |
| Renal, hyperplasia, plasma cell | 1 (6%) | | |
| Lymph node, bronchial | (40) | (53) | (54) |
| Hyperplasia, lymphoid | 4 (10%) | 40 (75%) | 49 (91%) |
| Hyperplasia, macrophage | 1 (3%) | 47 (89%) | 50 (93%) |
| Hyperplasia, plasma cell | 1 (3%) | | |
| Lymph node, mandibular | (52) | (52) | (56) |
| Hyperplasia, lymphoid | 3 (6%) | | 1 (2%) |
| Hyperplasia, plasma cell | 1 (2%) | | |
| Lymph node, mesenteric | (58) | (57) | (55) |
| Hyperplasia, lymphoid | 2 (3%) | 5 (9%) | 6 (11%) |
| Hyperplasia, macrophage | 1 (2%) | | |
| Inflammation | 3 (5%) | 1 (2%) | |
| Lymph node, mediastinal | (12) | (18) | (17) |
| Hyperplasia, lymphoid | 2 (17%) | 1 (6%) | 1 (6%) |
| Hyperplasia, macrophage | 1 (8%) | 1 (6%) | 1 (6%) |
| Hyperplasia, plasma cell | | 1 (6%) | |
| Spleen | (61) | (58) | (57) |
| Atrophy | 1 (2%) | 1 (2%) | 1 (2%) |
| Hematopoietic cell proliferation | 8 (13%) | 11 (19%) | 5 (9%) |
| Hyperplasia, lymphoid | 16 (26%) | 8 (14%) | 8 (14%) |
| Inflammation | | | 1 (2%) |
| Thymus | (48) | (51) | (41) |
| Atrophy | | 1 (2%) | |
| Degeneration | 12 (25%) | 13 (25%) | 16 (39%) |

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Integumentary System** | | | |
| Skin | (61) | (57) | (59) |
| Alopecia | 1 (2%) | | 1 (2%) |
| Fibrosis | 1 (2%) | | |
| Inflammation | 2 (3%) | | 2 (3%) |
| Necrosis | 1 (2%) | | |
| Parakeratosis | | 1 (2%) | |
| Pinna, hyperkeratosis | 1 (2%) | | |
| Prepuce, hyperkeratosis | | | 1 (2%) |
| Prepuce, inflammation | 16 (26%) | 9 (16%) | 13 (22%) |
| Tail, hyperkeratosis | | 1 (2%) | |
| Tail, inflammation | 1 (2%) | 1 (2%) | 1 (2%) |
| Tail, necrosis | | 1 (2%) | |
| **Musculoskeletal System** | | | |
| Bone | (61) | (59) | (59) |
| Developmental malformation | | 1 (2%) | |
| Hyperostosis | | 1 (2%) | |
| **Nervous System** | | | |
| Brain | (61) | (59) | (59) |
| Cerebellum, white matter, degeneration, focal | | 1 (2%) | |
| Medulla, degeneration, focal | 1 (2%) | | 1 (2%) |
| Medulla, demyelination | 1 (2%) | | |
| Spinal cord | | (1) | (1) |
| Degeneration, secondary Wallerian | | 1 (100%) | |
| **Respiratory System** | | | |
| Lung | (61) | (59) | (58) |
| Autolysis | | | 1 (2%) |
| Fibrosis | | 3 (5%) | 16 (28%) |
| Infiltration cellular | | 1 (2%) | |
| Inflammation, acute | | | 2 (3%) |
| Inflammation, chronic active | 1 (2%) | 52 (88%) | 53 (91%) |
| Bronchialization | 3 (5%) | 53 (90%) | 54 (93%) |
| Alveolar epithelium, metaplasia, squamous | | | 1 (2%) |
| Alveolus, hyperplasia | | | 1 (2%) |
| Alveolus, hyperplasia, macrophage | 6 (10%) | 57 (97%) | 58 (100%) |
| Alveolus, proteinosis | | 57 (97%) | 57 (98%) |
| Bronchus, hyperplasia, lymphoid | 22 (36%) | 29 (49%) | 14 (24%) |
| Interstitium, infiltration cellular | 10 (16%) | 55 (93%) | 55 (95%) |
| Nose | (61) | (59) | (59) |
| Foreign body | | | 1 (2%) |
| Inflammation, acute | | | 3 (5%) |
| Olfactory epithelium, atrophy | 1 (2%) | 27 (46%) | 55 (93%) |
| Olfactory epithelium, degeneration | 3 (5%) | 8 (14%) | 6 (10%) |

TABLE C5
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Special Senses System** | | | |
| None | | | |
| **Urinary System** | | | |
| Kidney | (61) | (59) | (59) |
| Hydronephrosis | 8 (13%) | 5 (8%) | 5 (8%) |
| Infiltration cellular, lymphocyte | 7 (11%) | 3 (5%) | 2 (3%) |
| Inflammation | 5 (8%) | 1 (2%) | 2 (3%) |
| Nephropathy | 9 (15%) | 10 (17%) | 6 (10%) |
| Cortex, atrophy | | 2 (3%) | |
| Cortex, fibrosis | | | 1 (2%) |
| Pelvis, inflammation | 5 (8%) | 1 (2%) | 2 (3%) |
| Renal tubule, atrophy | | | 1 (2%) |
| Renal tubule, degeneration | 1 (2%) | | |
| Renal tubule, necrosis | | | 1 (2%) |
| Ureter | (2) | | |
| Inflammation | 2 (100%) | | |
| Urethra | (6) | (8) | (11) |
| Calculus, microscopic observation only | | | 2 (18%) |
| Concretion | 5 (83%) | 7 (88%) | 8 (73%) |
| Inflammation | 1 (17%) | | 1 (9%) |
| Urinary bladder | (61) | (59) | (58) |
| Calculus, gross observation | 1 (2%) | 2 (3%) | 1 (2%) |
| Calculus, microscopic observation only | 1 (2%) | 1 (2%) | 2 (3%) |
| Crystals | 1 (2%) | | |
| Hyperplasia | | 1 (2%) | |
| Inflammation | 11 (18%) | 2 (3%) | 4 (7%) |

# APPENDIX D
# SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF NICKEL SUBSULFIDE

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 80 | 80 | 80 |
| *7-Month interim evaluation*[b] | 10 | 10 | 10 |
| *15-Month interim evaluation*[b] | 10 | 10 | 10 |
| Early deaths | | | |
| Moribund | 14 | 15 | 13 |
| Natural deaths | 8 | 11 | 9 |
| Survivors | | | |
| Terminal sacrifice | 36 | 34 | 38 |
| Missexed | 2 | | |
| Animals examined microscopically | 68 | 70 | 70 |
| ***7-Month Interim Evaluation*** | | | |
| **Genital System** | | | |
| Uterus | | | (1) |
| Polyp stromal | | | 1 (100%) |
| ***Systems Examined With No Neoplasms Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Hematopoietic System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Respiratory System** | | | |
| **Special Senses System** | | | |
| **Urinary System** | | | |
| ***15-Month Interim Evaluation*** | | | |
| **Alimentary System** | | | |
| Liver | (5) | (5) | (5) |
| Hemangioma | 1 (20%) | | |
| Hemangiosarcoma | | | 1 (20%) |
| Hepatocellular adenoma | 1 (20%) | | |
| ***Systems Examined With No Neoplasms Observed*** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Genital System** | | | |
| **Hematopoietic System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |

TABLE D1
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | |
| ***Systems Examined With No Neoplasms Observed*** (continued) | | | |
| **Nervous System** | | | |
| **Respiratory System** | | | |
| **Special Senses System** | | | |
| **Urinary System** | | | |
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Gallbladder | (53) | (51) | (53) |
| Intestine large, colon | (56) | (55) | (54) |
| Intestine large, cecum | (54) | (54) | (55) |
| Intestine small, duodenum | (53) | (53) | (53) |
| Polyp adenomatous | 1 (2%) | | |
| Intestine small, jejunum | (54) | (53) | (53) |
| Adenoma | | | 1 (2%) |
| Liver | (58) | (60) | (60) |
| Hemangiosarcoma | 2 (3%) | 1 (2%) | 1 (2%) |
| Hepatocellular carcinoma | 11 (19%) | 8 (13%) | 4 (7%) |
| Hepatocellular carcinoma, multiple | | 1 (2%) | |
| Hepatocellular adenoma | 9 (16%) | 8 (13%) | 9 (15%) |
| Hepatocellular adenoma, multiple | 4 (7%) | 2 (3%) | 1 (2%) |
| Histiocytic sarcoma | | 2 (3%) | 2 (3%) |
| Histiocytic sarcoma, metastatic, uterus | 1 (2%) | | |
| Sarcoma, metastatic, skeletal muscle | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (2%) | |
| Mesentery | (3) | (4) | (1) |
| Carcinoma, metastatic, islets, pancreatic | 1 (33%) | | |
| Histiocytic sarcoma | | | 1 (100%) |
| Sarcoma, metastatic, skeletal muscle | | 1 (25%) | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (25%) | |
| Oral mucosa | | | (1) |
| Buccal, squamous cell papilloma | | | 1 (100%) |
| Pancreas | (58) | (56) | (59) |
| Sarcoma, metastatic, skeletal muscle | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (2%) | |
| Salivary glands | (58) | (60) | (60) |
| Stomach, forestomach | (57) | (60) | (58) |
| Squamous cell carcinoma | | 1 (2%) | |
| Squamous cell papilloma | 1 (2%) | | |
| Stomach, glandular | (57) | (58) | (58) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (2%) | |

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Cardiovascular System** | | | |
| Heart | (58) | (60) | (59) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (2%) | |
| Hemangiosarcoma, metastatic, liver | 1 (2%) | | |
| Sarcoma, metastatic, skeletal muscle | | 1 (2%) | |
| **Endocrine System** | | | |
| Adrenal cortex | (58) | (58) | (60) |
| Adenoma | 1 (2%) | | |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) |
| Sarcoma, metastatic, skeletal muscle | | 1 (2%) | 1 (2%) |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (2%) | |
| Adrenal medulla | (58) | (58) | (60) |
| Pheochromocytoma benign | 1 (2%) | | 1 (2%) |
| Islets, pancreatic | (58) | (56) | (59) |
| Adenoma | | 1 (2%) | |
| Carcinoma | 1 (2%) | | |
| Pituitary gland | (58) | (57) | (60) |
| Pars distalis, adenoma | 8 (14%) | 5 (9%) | 3 (5%) |
| Thyroid gland | (58) | (60) | (60) |
| Follicular cell, adenoma | 2 (3%) | 4 (7%) | 3 (5%) |
| Follicular cell, carcinoma | 1 (2%) | | |
| **General Body System** | | | |
| Tissue NOS | | (4) | (1) |
| Histiocytic sarcoma | | 1 (25%) | |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (25%) | |
| Mediastinum, hemangiosarcoma | | 1 (25%) | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (25%) | |
| **Genital System** | | | |
| Ovary | (58) | (58) | (60) |
| Cystadenoma | 2 (3%) | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) |
| Histiocytic sarcoma, metastatic, uterus | 1 (2%) | | |
| Luteoma | | 1 (2%) | |
| Sarcoma, metastatic, skeletal muscle | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (2%) | |
| Teratoma benign | | 1 (2%) | |
| Teratoma malignant | | 1 (2%) | |

TABLE D1
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Genital System** (continued) | | | |
| Uterus | (58) | (60) | (60) |
| Fibroma | | | 1 (2%) |
| Hemangioma | 1 (2%) | | |
| Histiocytic sarcoma | 2 (3%) | 1 (2%) | 1 (2%) |
| Polyp stromal | 1 (2%) | 1 (2%) | 1 (2%) |
| Endometrium, adenocarcinoma | | | 1 (2%) |
| **Hematopoietic System** | | | |
| Bone marrow | (57) | (60) | (59) |
| Hemangiosarcoma, metastatic, tissue NOS | | 1 (2%) | |
| Histiocytic sarcoma | | | 1 (2%) |
| Histiocytic sarcoma, metastatic, uterus | 1 (2%) | | |
| Lymph node | (9) | (12) | (11) |
| Iliac, hemangiosarcoma | 1 (11%) | | |
| Iliac, sarcoma, metastatic, skeletal muscle | | | 1 (9%) |
| Pancreatic, histiocytic sarcoma | | 1 (8%) | |
| Pancreatic, sarcoma, metastatic, skeletal muscle | | | 1 (9%) |
| Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (8%) | |
| Renal, histiocytic sarcoma, metastatic, uterus | 1 (11%) | | |
| Renal, sarcoma, metastatic, skeletal muscle | | | 1 (9%) |
| Lymph node, bronchial | (50) | (57) | (59) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | |
| Histiocytic sarcoma, metastatic, uterus | 1 (2%) | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (2%) | |
| Lymph node, mandibular | (57) | (59) | (60) |
| Lymph node, mesenteric | (55) | (54) | (57) |
| Hemangiosarcoma, metastatic, spleen | | 1 (2%) | |
| Histiocytic sarcoma, metastatic, uterus | 1 (2%) | | |
| Sarcoma, metastatic, skeletal muscle | | | 1 (2%) |
| Lymph node, mediastinal | (15) | (28) | (30) |
| Histiocytic sarcoma, metastatic, uterus | 1 (7%) | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (4%) | |
| Spleen | (58) | (60) | (60) |
| Fibrosarcoma | 1 (2%) | | |
| Hemangiosarcoma | | 1 (2%) | 1 (2%) |
| Hemangiosarcoma, metastatic, tissue NOS | | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | 1 (2%) |
| Histiocytic sarcoma, metastatic, uterus | 1 (2%) | | |
| Teratoma malignant, metastatic, ovary | | 1 (2%) | |
| Thymus | (58) | (57) | (54) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | |

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Integumentary System** | | | |
| Mammary gland | (57) | (59) | (60) |
| Adenocarcinoma | 1 (2%) | 3 (5%) | |
| Skin | (58) | (60) | (60) |
| Fibroma | | | 1 (2%) |
| Fibrosarcoma | | | 1 (2%) |
| Keratoacanthoma | | 1 (2%) | |
| Pinna, fibrosarcoma | 2 (3%) | | 1 (2%) |
| Pinna, squamous cell carcinoma | | | 1 (2%) |
| Sebaceous gland, squamous cell carcinoma | | | 1 (2%) |
| **Musculoskeletal System** | | | |
| Bone | (57) | (60) | (59) |
| Hemangiosarcoma | | | 1 (2%) |
| Skeletal muscle | (1) | (3) | (1) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | 1 (100%) | | |
| Hemangiosarcoma | | 1 (33%) | |
| Hemangiosarcoma, metastatic, spleen | | 1 (33%) | |
| Sarcoma | | 1 (33%) | 1 (100%) |
| **Nervous System** | | | |
| Brain | (58) | (60) | (60) |
| **Respiratory System** | | | |
| Larynx | (54) | (55) | (53) |
| Epithelium, squamous cell carcinoma | | 1 (2%) | |
| Lung | (58) | (59) | (60) |
| Adenocarcinoma, metastatic, mammary gland | 1 (2%) | | |
| Alveolar/bronchiolar adenoma | 3 (5%) | 1 (2%) | 1 (2%) |
| Alveolar/bronchiolar carcinoma | 7 (12%) | 1 (2%) | 2 (3%) |
| Hepatocellular carcinoma, metastatic | 1 (2%) | | |
| Hepatocellular carcinoma, metastatic, liver | 2 (3%) | 6 (10%) | 1 (2%) |
| Histiocytic sarcoma | | 1 (2%) | 1 (2%) |
| Sarcoma, metastatic, skeletal muscle | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (2%) | |
| Nose | (58) | (59) | (60) |
| Hemangioma | | | 1 (2%) |
| Trachea | (57) | (57) | (58) |
| **Special Senses System** | | | |
| Harderian gland | (1) | | (1) |
| Adenoma | 1 (100%) | | 1 (100%) |

TABLE D1
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Urinary System** | | | |
| Kidney | (58) | (60) | (60) |
| Adenocarcinoma, metastatic, mammary gland | 1 (2%) | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | 1 (2%) | 1 (2%) | |
| Histiocytic sarcoma | | | 1 (2%) |
| Histiocytic sarcoma, metastatic, uterus | 1 (2%) | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | 1 (2%) | |
| Teratoma malignant, metastatic, ovary | | 1 (2%) | |
| Urinary bladder | (56) | (55) | (59) |
| **Systemic Lesions** | | | |
| Multiple organs[c] | (58) | (60) | (60) |
| Histiocytic sarcoma | 2 (3%) | 2 (3%) | 2 (3%) |
| Lymphoma malignant | 5 (9%) | 7 (12%) | 6 (10%) |
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[d] | | | |
| 7-Month interim evaluation | | | 1 |
| 15-Month interim evaluation | 2 | | 1 |
| 2-Year study | 42 | 39 | 37 |
| Total primary neoplasms | | | |
| 7-Month interim evaluation | | | 1 |
| 15-Month interim evaluation | 2 | | 1 |
| 2-Year study | 69 | 55 | 49 |
| Total animals with benign neoplasms | | | |
| 7-Month interim evaluation | | | 1 |
| 15-Month interim evaluation | 2 | | |
| 2-Year study | 27 | 22 | 20 |
| Total benign neoplasms | | | |
| 7-Month interim evaluation | | | 1 |
| 15-Month interim evaluation | 2 | | |
| 2-Year study | 35 | 25 | 26 |
| Total animals with malignant neoplasms | | | |
| 15-Month interim evaluation | | | 1 |
| 2-Year study | 26 | 27 | 22 |
| Total malignant neoplasms | | | |
| 15-Month interim evaluation | | | 1 |
| 2-Year study | 34 | 30 | 23 |
| Total animals with metastatic neoplasms | | | |
| 2-Year study | 7 | 12 | 2 |
| Total metastatic neoplasms | | | |
| 2-Year study | 18 | 37 | 7 |

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Five animals in each exposure group were histopathologically examined at the interim evaluations.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**

| Number of Days on Study | 2 8 8 | 3 0 0 | 3 8 5 | 4 1 9 | 5 0 8 | 5 3 6 | 5 5 2 | 5 6 3 | 5 9 8 | 6 0 0 | 6 0 3 | 6 4 5 | 6 4 9 | 6 7 4 | 6 7 9 | 6 8 0 | 6 8 3 | 6 9 1 | 6 9 4 | 6 9 6 | 7 2 3 | 7 2 7 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 4 | 1 4 2 | 1 5 5 | 1 0 8 | 1 4 6 | 1 4 7 | 1 4 4 | 1 4 9 | 1 0 8 1 | 1 5 3 | 1 2 0 | 0 8 5 | 1 0 2 | 1 2 8 | 1 1 4 | 1 3 5 | 1 0 9 | 0 8 9 | 0 8 7 | 1 1 2 | 1 1 8 | 0 9 3 | 0 8 4 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | A | + | + | + | A | + | + | + | + | + | + | A | + | + | + | A | + | + | + | + | + | + | + |
| *Intestine large, colon* | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | A | + | + | + | M | + | M | + | + | + | + | A | + | + | + | + | + | + | + |
| Intestine large, cecum | A | + | + | A | A | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + |
| Intestine small, duodenum | A | + | + | A | A | + | + | + | + | + | + | A | + | + | + | A | + | + | + | + | + | + | + |
| Polyp adenomatous | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | A | + | + | A | A | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + |
| Intestine small, ileum | A | + | + | A | A | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| *Hemangiosarcoma* | | | | | | | | | | | | | | | | X | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | | X | X | | | | | X | X | X | X | X | | |
| Hepatocellular adenoma | | | | | X | | | | | | | | | | | | X | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | X | | | X | | |
| Histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | + | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, islets, pancreatic | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| *Salivary glands* | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| *Pars distalis, adenoma* | | | | | | X | | | | | | | | | | | | | | | | | X |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | X | | | | | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | |

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

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| 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 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 9 6 | 1 0 0 | 1 0 5 | 1 2 1 | 1 3 0 | 1 3 2 | 1 5 1 | 1 5 2 | 1 5 4 | 0 8 6 | 0 9 9 | 0 1 4 | 1 1 0 | 1 1 5 | 1 1 7 | 1 2 7 | 1 3 7 | 1 4 1 | 0 8 8 | 0 9 7 | 0 9 8 | 1 1 6 | 1 1 9 | 1 3 1 | 1 3 8 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | M | M | M | + | + | M | + | + | M | + | + | + | + | + | + | + | + | + | M |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp adenomatous | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | X | | | | | | | | | | | | | | X | | | | | | | | | |
| Hepatocellular adenoma | | X | | | X | | | X | X | | | | | | | | | X | | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | X | | | X | | | | | | | | | | | |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | + | | | | | | |
| Carcinoma, metastatic, islets, pancreatic | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | + | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | M |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | X | | | | X | | X | | | X | | | | | | | | | X | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Follicular cell, carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 5 9 | 1 6 0 | 0 8 3 | 0 9 1 | 1 0 1 | 1 0 6 | 1 2 9 | 1 3 6 | 1 4 8 | 1 5 8 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | 57 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | 56 |
| Intestine large, rectum | M | + | + | + | + | + | + | + | + | + | 47 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | 53 |
| Polyp adenomatous | | | | | | | | X | | | 1 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | 54 |
| Liver | + | + | + | + | + | + | + | + | + | + | 58 |
| Hemangiosarcoma | | | | | | | | X | | | 2 |
| Hepatocellular carcinoma | | | | | X | X | | | | | 11 |
| Hepatocellular adenoma | | | | | | | X | X | | | 9 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | 4 |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | + | | | 3 |
| Carcinoma, metastatic, islets, pancreatic | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | 58 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | 58 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | 57 |
| Squamous cell papilloma | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | 57 |
| Tooth | | | | + | | | | | | | 2 |
| **Cardiovascular System** | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | 58 |
| Hemangiosarcoma, metastatic, liver | | | | | | | | X | | | 1 |
| **Endocrine System** | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | 58 |
| Adenoma | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | 58 |
| Pheochromocytoma benign | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | 58 |
| Carcinoma | | | | | | | | | | | 1 |
| Parathyroid gland | + | M | + | + | + | + | + | + | + | + | 52 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | 58 |
| Pars distalis, adenoma | | | | X | | | | | | | 8 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | 58 |
| Follicular cell, adenoma | | | | | | | | | | | 2 |
| Follicular cell, carcinoma | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | |
| None | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 2 8 8 | 3 0 0 | 3 8 5 | 4 1 9 | 5 0 8 | 5 3 6 | 5 5 2 | 5 6 3 | 5 9 8 | 6 0 0 | 6 0 3 | 6 4 5 | 6 4 9 | 6 7 4 | 6 7 9 | 6 8 0 | 6 8 3 | 6 9 1 | 6 9 4 | 6 9 6 | 7 2 3 | 7 2 7 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 4 | 1 4 2 | 1 5 5 | 1 0 8 | 1 4 6 | 1 4 7 | 1 4 4 | 1 4 9 | 0 8 1 | 1 5 3 | 1 2 0 | 0 8 5 | 1 0 2 | 1 2 8 | 1 1 4 | 1 3 5 | 1 0 9 | 0 8 9 | 0 8 7 | 1 1 2 | 1 1 8 | 0 9 3 | 0 8 4 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | | | | | | | X | | |
| Histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node | | | + | + | | | | | | | | | | | + | | | | | | + | | |
| Iliac, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Renal, histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, bronchial | I | I | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | M |
| Histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | M | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, mediastinal | M | M | M | + | M | M | + | M | M | M | M | + | + | M | + | M | M | M | + | + | M | M | M |
| Histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrosarcoma | | | | | | | | | | | | | | | | X | | | | | | | |
| Histiocytic sarcoma, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pinna, fibrosarcoma | | | | | | | | | X | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | | + | | | | | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | | | | | + | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| 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 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 9 6 | 1 0 0 | 1 0 5 | 1 2 1 | 1 3 0 | 1 3 2 | 1 5 1 | 1 5 2 | 1 5 4 | 0 8 6 | 0 9 9 | 0 1 4 | 1 1 0 | 1 1 5 | 1 1 7 | 1 2 7 | 1 3 7 | 1 4 1 | 0 8 8 | 0 9 7 | 0 9 8 | 1 1 6 | 1 1 9 | 1 3 1 | 1 3 8 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | | | | | | | | | | | | | | | + | | | | | | | | | + | |
| Iliac, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Renal, histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | I | + | I | M | + | + | + | + | + | I | + | + | + |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mediastinal | I | M | I | M | M | + | M | M | M | M | + | + | M | I | M | + | + | M | M | M | M | M | M | + | + |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pinna, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year alation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 5 9 | 1 6 0 | 0 8 3 | 0 9 1 | 1 0 1 | 1 0 6 | 1 2 9 | 1 3 6 | 1 4 8 | 1 5 8 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | M | + | + | + | + | 55 |
| Ovary | + | + | + | + | + | + | + | + | + | + | 58 |
| Cystadenoma | | | | | | | | | | | 2 |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | 58 |
| Hemangioma | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | X | | | | | | 2 |
| Polyp stromal | | | | | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | M | + | + | 57 |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Lymph node | | + | | | | + | + | | | | 9 |
| Iliac, hemangiosarcoma | | | | | | X | | | | | 1 |
| Renal, histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | 57 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | 55 |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Lymph node, mediastinal | M | M | M | M | M | + | M | M | M | M | 15 |
| Histiocytic sarcoma, metastatic, uterus | | • | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | 58 |
| Fibrosarcoma | | | | | | | | | | | 1 |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | 58 |
| **Integumentary System** | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | 57 |
| Adenocarcinoma | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | 58 |
| Pinna, fibrosarcoma | | | | | | | X | | | | 2 |
| **Musculoskeletal System** | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | M | + | + | 57 |
| Skeletal muscle | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | 58 |
| Spinal cord | | | | | | | | | | | 1 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 2 8 8 | 3 0 0 | 3 8 5 | 4 1 9 | 5 0 8 | 5 3 6 | 5 5 2 | 5 6 3 | 5 9 8 | 6 0 0 | 6 0 3 | 6 4 5 | 6 4 9 | 6 7 4 | 6 7 9 | 6 8 0 | 6 8 3 | 6 9 1 | 6 9 4 | 6 9 6 | 7 2 3 | 7 2 7 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 4 | 1 4 2 | 1 5 5 | 1 0 8 | 1 4 6 | 1 4 7 | 1 4 4 | 1 4 9 | 0 8 1 | 1 5 3 | 1 2 0 | 0 8 5 | 1 0 2 | 1 1 8 | 1 2 4 | 1 3 5 | 1 0 9 | 0 8 9 | 0 8 7 | 1 1 2 | 1 1 8 | 0 9 3 | 0 8 4 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | X | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | X | | | | | | |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | X | X | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | + | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | + | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | + | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | X | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | X | | | | | | |
| Histiocytic sarcoma, metastatic, uterus | | | | X | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | | | | | | | | X | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| 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 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 9 6 | 1 0 0 | 1 0 5 | 1 2 1 | 1 3 0 | 1 3 2 | 1 5 1 | 1 5 2 | 1 5 4 | 0 8 6 | 0 9 9 | 1 0 4 | 1 1 0 | 1 1 5 | 1 1 7 | 1 2 7 | 1 3 7 | 1 4 1 | 0 8 8 | 0 9 7 | 0 9 8 | 1 1 6 | 1 1 9 | 1 3 1 | 1 3 8 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | I | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Alveolar/bronchiolar adenoma | | | X | | | | | | X | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | X | | | | | X | | | | | X | | | X | | X | | | | | | | | |
| Hepatocellular carcinoma, metastatic | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | + | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | | | | X | | | | X | | | | | | | | | X | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 5 9 | 1 6 0 | 0 8 3 | 0 9 1 | 1 0 1 | 1 0 6 | 1 2 9 | 1 3 6 | 1 4 8 | 1 5 8 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | |
| Larynx | + | M | + | + | + | + | + | + | + | + | 54 |
| Lung | + | + | + | + | + | + | + | + | + | + | 58 |
| Adenocarcinoma, metastatic, mammary gland | | | | | | | | | | | 1 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | 3 |
| Alveolar/bronchiolar carcinoma | X | | | | | | | | | | 7 |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | 2 |
| Nose | + | + | + | + | + | + | + | + | + | + | 58 |
| Trachea | + | + | + | + | + | + | + | + | + | + | 57 |
| **Special Senses System** | | | | | | | | | | | |
| Ear | | | | | | | | | | | 2 |
| Eye | + | | | | | | | | | | 2 |
| Harderian gland | | | | | | | | | | | 1 |
| Adenoma | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | 58 |
| Adenocarcinoma, metastatic, mammary gland | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| Histiocytic sarcoma, metastatic, uterus | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | 56 |
| **Systemic Lesions** | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | 58 |
| Histiocytic sarcoma | | | | | X | | | | | | 2 |
| Lymphoma malignant | | X | | | | | | | | | 5 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**

| Number of Days on Study | 1 1 2 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7<br>1 1 0 0 2 2 3 3 5 6 0 2 3 4 5 5 5 5 5 9 9 1 1 1 2<br>2 6 6 3 5 0 0 6 2 3 5 3 6 2 2 3 5 5 5 2 4 1 2 7 0 |
|---|---|
| **Carcass ID Number** | 3 3 3 2 2 2 3 2 2 3 2 3 2 2 2 3 2 2 2 2 3 2 2 3 3<br>1 0 0 4 9 9 0 4 5 1 7 1 5 4 5 0 4 8 8 5 0 7 6 1 1<br>8 8 4 8 1 3 7 6 7 4 7 1 5 7 1 1 4 1 4 8 2 2 9 2 0 |
| **Alimentary System** | |
| Esophagus | + + + + + + + + + + + + + + + + + + + + + + + + |
| Gallbladder | A + A A A + + + + + + + M + + + A + M + + + A M + |
| Intestine large, colon | A + A A + + + + + + + + + + + + + + A + + + A + + |
| Intestine large, rectum | A + A M A + M + + + + + M + + + M + A + + + A M + |
| Intestine large, cecum | A + A A A + + + + + + + + + + + + + A + + + A + + |
| Intestine small, duodenum | A + A A A + + + + + + + + + + + A + A + + + A + + |
| Intestine small, jejunum | A + A A A + + + + + + + + + + + A + A + + + A + + |
| Intestine small, ileum | A + A A A + + + + + + + + + + + A + A + + + A + A |
| Liver | + + + + + + + + + + + + + + + + + + + + + + + + |
| Hemangiosarcoma | |
| Hepatocellular carcinoma | X X X X |
| Hepatocellular carcinoma, multiple | X |
| Hepatocellular adenoma | X X |
| Hepatocellular adenoma, multiple | X |
| Histiocytic sarcoma | X |
| Sarcoma, metastatic, skeletal muscle | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Mesentery | + + + |
| Sarcoma, metastatic, skeletal muscle | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Pancreas | A + A + + + + + + + + + + + + + + + + A + + + + M + |
| Sarcoma, metastatic, skeletal muscle | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Salivary glands | + + + + + + + + + + + + + + + + + + + + + + + + |
| Stomach, forestomach | + + + + + + + + + + + + + + + + + + + + + + + + |
| Squamous cell carcinoma | X |
| Stomach, glandular | A + + A + + + + + + + + + + + + + + + + + + + + + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | X |
| Tooth | |
| **Cardiovascular System** | |
| Heart | + + + + + + + + + + + + + + + + + + + + + + + + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | X |
| Sarcoma, metastatic, skeletal muscle | X |
| **Endocrine System** | |
| Adrenal cortex | + + + + + + + + + + + + + + + + M + + + + + + + |
| Sarcoma, metastatic, skeletal muscle | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Adrenal medulla | + + + + + + + + + + + + + + + + M + + + + + + + |
| Islets, pancreatic | A + A + + + + + + + + + + + + + + + + A + + + + M + |
| Adenoma | X |
| Parathyroid gland | M M + + + M + + M + + + + + + + + + + + + + + + + |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 728 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 734 | 734 | 734 | 734 | 734 | 734 | 734 | 734 | 734 | 734 | 734 | 735 | 735 | 735 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 26101 | 24202 | 26202 | 26606 | 27101 | 27705 | 28000 | 29505 | 29908 | 31303 | 31705 | 32401 | 32405 | 32409 | 32500 | 32603 | 32604 | 32608 | 32704 | 32904 | 33003 | 33009 | 33506 | 33703 | 33706 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Hepatocellular carcinoma | X | | | | | | | | | | | | | X | | | | | | | | | | | |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | X | | | | | | | | | | | | X | | | | | X | X | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | + | | | | | | | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tooth | | | | | | | | | | | | + | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 8 3 | 3 0 5 | 3 2 0 | 2 4 3 | 2 6 7 | 2 7 8 | 2 8 5 | 2 9 6 | 3 0 6 | 3 1 9 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | 60 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | 51 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | 55 |
| Intestine large, rectum | + | + | + | M | + | + | + | + | + | + | 47 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | 52 |
| Liver | + | + | + | + | + | + | + | + | + | + | 60 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | | X | | | X | | | | 8 |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | 1 |
| Hepatocellular adenoma | | X | | | | | | | X | | 8 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | 2 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | 4 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | 56 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | 60 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | 60 |
| Squamous cell carcinoma | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | 58 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| Tooth | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | 60 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| **Endocrine System** | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | 58 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | 58 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | 56 |
| Adenoma | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | M | + | 55 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 1 1 2 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7<br>1 1 0 0 2 2 3 3 5 6 0 2 3 4 5 5 5 5 5 9 9 1 1 1 2<br>2 6 6 3 5 0 0 6 2 3 5 3 6 2 2 3 5 5 5 2 4 1 2 7 0 |
|---|---|
| **Carcass ID Number** | 3 3 3 2 2 2 3 2 2 3 2 3 2 2 2 3 2 2 2 2 3 2 2 3 3<br>1 0 0 4 9 9 0 4 5 1 7 1 5 4 5 0 4 8 8 5 0 7 6 1 1<br>8 8 4 8 1 3 7 6 7 4 7 1 5 7 1 1 4 1 4 8 2 2 9 2 0 |
| **Endocrine System** (continued) | |
| Pituitary gland | + I M + + + + + + + + + + + + + + + + + + M + + + + |
| Pars distalis, adenoma | X X |
| Thyroid gland | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Follicular cell, adenoma | X |
| **General Body System** | |
| Tissue NOS | + + + + |
| Histiocytic sarcoma | X |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | X |
| Mediastinum, hemangiosarcoma | X |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | X |
| **Genital System** | |
| Clitoral gland | + + M + + + + + + + + + + + + + + + + + + + + + + |
| Ovary | A + + + + + + + + + + + + + + + + + + M + + + + + |
| Luteoma | |
| Sarcoma, metastatic, skeletal muscle | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Teratoma benign | X |
| Teratoma malignant | X |
| Uterus | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Histiocytic sarcoma | |
| Polyp stromal | X |
| **Hematopoietic System** | |
| Bone marrow | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Hemangiosarcoma, metastatic, tissue NOS | X |
| Lymph node | + + + + + + + + + + + |
| Pancreatic, histiocytic sarcoma | X |
| Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Lymph node, bronchial | M M + + + + M + + + + + + + + + + + + + + + + + + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | X |
| Histiocytic sarcoma | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Lymph node, mandibular | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Lymph node, mesenteric | A + A A + + + + + + + + M + + + + + + + A + + + + + |
| Hemangiosarcoma, metastatic, spleen | X |
| Lymph node, mediastinal | M M M M + + + + M + + M M + + + + M + + + + + M + |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 7 2 8 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 6 1 | 2 4 2 | 2 6 2 | 2 6 6 | 2 7 1 | 2 7 5 | 2 8 0 | 2 9 5 | 2 9 8 | 3 1 3 | 3 1 5 | 2 4 1 | 2 4 5 | 2 4 9 | 2 5 0 | 2 6 3 | 2 6 4 | 2 6 8 | 2 7 4 | 2 9 9 | 3 0 3 | 3 0 9 | 2 5 6 | 2 7 3 | 2 7 6 |
| **Endocrine System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | X | | | | | | X | | | X | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | X | | | | | | | | | | | | | | | | | | X | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Luteoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Teratoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Teratoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma, metastatic, tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | | | | | | | + | + | | | | | + | | | | | | | | | | | | |
| Pancreatic, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, Metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mediastinal | M | M | + | + | I | + | + | I | M | + | + | M | M | + | I | M | I | + | M | M | I | M | M | M | M |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 8 3 | 3 0 5 | 3 2 0 | 2 4 3 | 2 6 7 | 2 7 8 | 2 8 5 | 2 9 6 | 3 0 6 | 3 1 9 | Total Tissues/ Tumors |
| **Endocrine System** (continued) | | | | | | | | | | | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | 57 |
| Pars distalis, adenoma | | | | | | | | | | | 5 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | 60 |
| Follicular cell, adenoma | | | | | | | | | X | | 4 |
| **General Body System** | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | 4 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| Mediastinum, hemangiosarcoma | | | | | | | | | | | 1 |
| Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| **Genital System** | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | 59 |
| Ovary | + | + | + | + | + | + | + | + | + | + | 58 |
| Luteoma | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Teratoma benign | | | | | | | | | | | 1 |
| Teratoma malignant | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | 60 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Polyp stromal | | | | | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | 60 |
| Hemangiosarcoma, metastatic, tissue NOS | | | | | | | | | | | 1 |
| Lymph node | | | | | | + | | | + | | 12 |
| Pancreatic, histiocytic sarcoma | | | | | | | | | | | 1 |
| Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | 57 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | M | + | + | + | + | 59 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | 54 |
| Hemangiosarcoma, metastatic, spleen | | | | | | | | | | | 1 |
| Lymph node, mediastinal | M | M | + | + | + | + | M | M | M | I | 28 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 1 1 2 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7<br>1 1 0 0 2 2 3 3 5 6 0 2 3 4 5 5 5 5 5 9 9 1 1 1 2<br>2 6 6 3 5 0 0 6 2 3 5 3 6 2 2 3 5 5 5 2 4 1 2 7 0 |
|---|---|
| **Carcass ID Number** | 3 3 3 2 2 2 3 2 2 3 2 3 2 2 2 3 2 2 2 2 3 2 2 3 3<br>1 0 0 4 9 9 0 4 5 1 7 1 5 4 5 0 4 8 8 5 0 7 6 1 1<br>1 8 8 4 8 1 3 7 6 7 4 7 1 5 7 1 1 4 1 4 8 2 2 9 2 0 |
| **Hematopoietic System** (continued) | |
| Spleen | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Hemangiosarcoma | X |
| Hemangiosarcoma, metastatic, tissue NOS | X |
| Histiocytic sarcoma | X |
| Teratoma malignant, metastatic, ovary | X |
| Thymus | A + A + + + + + + + + + + + M + + + + + + + + + + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | X |
| Histiocytic sarcoma | X |
| **Integumentary System** | |
| Mammary gland | M + + + + + + + + + + + + + + + + + + + + + + + + |
| Adenocarcinoma | X |
| Skin | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Keratoacanthoma | X |
| **Musculoskeletal System** | |
| Bone | + + + + + + + + + + + + + + + + + + + + + + + + + |
| Skeletal muscle | + + |
| Hemangiosarcoma | |
| Hemangiosarcoma, metastatic, spleen | X |
| Sarcoma | X |
| **Nervous System** | |
| Brain | + + + + + + + + + + + + + + + + + + + + + + + + + |
| **Respiratory System** | |
| Larynx | + + + + + + + + + + + + + + + M + + + + + + + + + |
| Epithelium, squamous cell carcinoma | X |
| Lung | + + A + + + + + + + + + + + + + + + + + + + + + + |
| Alveolar/bronchiolar adenoma | |
| Alveolar/bronchiolar carcinoma | X |
| Hepatocellular carcinoma, metastatic, liver | X X X X X |
| Histiocytic sarcoma | X |
| Lymphoma malignant lymphocytic, metastatic | X |
| Sarcoma, metastatic, skeletal muscle | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Nose | A + + + + + + + + + + + + + + + + + + + + + + + + |
| Trachea | + + A + + + M + + + + + + + + + M + + + + + + + + |
| **Special Senses System** | |
| Ear | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 7 2 8 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 6 1 | 2 4 2 | 2 6 2 | 2 6 6 | 2 7 1 | 2 7 5 | 2 8 0 | 2 9 5 | 2 9 8 | 3 1 3 | 3 1 5 | 2 4 1 | 2 4 5 | 2 4 9 | 2 5 0 | 2 6 3 | 2 6 4 | 2 6 8 | 2 7 4 | 2 9 9 | 3 0 3 | 3 0 9 | 2 5 6 | 2 7 3 | 2 7 6 |
| **Hematopoietic System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma, metastatic, tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Teratoma malignant, metastatic, ovary | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma | | | | | | X | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | + | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | X | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | I | + | I |
| Epithelium, squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | X | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | X | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant lymphocytic, metastatic | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | + | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 8 3 | 3 0 5 | 3 2 0 | 2 4 3 | 2 6 7 | 2 7 8 | 2 8 5 | 2 9 6 | 3 0 6 | 3 1 9 | Total Tissues/ Tumors |
| **Hematopoietic System** (continued) | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | 60 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Hemangiosarcoma, metastatic, tissue NOS | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Teratoma malignant, metastatic, ovary | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | 57 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | 59 |
| Adenocarcinoma | | | | X | | | | | | | 3 |
| Skin | + | + | + | + | + | + | + | + | + | + | 60 |
| Keratoacanthoma | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | 60 |
| Skeletal muscle | | | | | | | | | | | 3 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Hemangiosarcoma, metastatic, spleen | | | | | | | | | | | 1 |
| Sarcoma | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | 60 |
| **Respiratory System** | | | | | | | | | | | |
| Larynx | + | I | + | + | + | + | + | + | + | + | 55 |
| Epithelium, squamous cell carcinoma | | | | | | | | | | | 1 |
| Lung | + | + | + | + | + | + | + | + | + | + | 59 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | 6 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Lymphoma malignant lymphocytic, metastatic | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | 59 |
| Trachea | + | + | + | + | + | + | + | + | + | + | 57 |
| **Special Senses System** | | | | | | | | | | | |
| Ear | | | | | | | | | | | 1 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 1 1 2 | 1 1 6 | 2 0 6 | 4 0 3 | 4 2 5 | 5 2 0 | 5 3 0 | 5 3 6 | 5 5 2 | 5 6 3 | 6 0 5 | 6 2 3 | 6 3 6 | 6 4 2 | 6 5 2 | 6 5 3 | 6 5 5 | 6 5 5 | 6 5 5 | 6 9 2 | 6 9 4 | 7 1 1 | 7 1 2 | 7 1 7 | 7 2 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 1 8 | 3 0 8 | 3 0 4 | 2 4 8 | 2 9 1 | 2 9 3 | 3 0 7 | 2 4 6 | 2 5 7 | 3 1 4 | 2 7 7 | 3 1 1 | 2 5 5 | 2 4 7 | 2 5 1 | 3 0 1 | 2 4 4 | 2 8 1 | 2 8 4 | 3 5 8 | 2 0 2 | 2 7 2 | 2 6 9 | 3 1 2 | 3 1 0 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Teratoma malignant, metastatic, ovary | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | A | + | A | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | 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 Nickel Subsulfide: 0.6 mg/m³**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 7 2 8 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 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 |
| **Carcass ID Number** | 2 6 1 | 2 4 2 | 2 6 2 | 2 6 6 | 2 7 1 | 2 7 5 | 2 8 0 | 2 9 5 | 2 9 8 | 3 1 3 | 3 1 5 | 2 4 1 | 2 4 5 | 2 4 9 | 2 5 0 | 2 6 3 | 2 6 4 | 2 6 8 | 2 7 4 | 2 9 9 | 3 0 3 | 3 0 9 | 2 5 6 | 2 7 3 | 2 7 6 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | | | | | | | | | | | | | | | |
| Teratoma malignant, metastatic, ovary | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymphoma malignant | | | | | | | X | | | | | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 0.6 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 8 3 | 3 0 5 | 3 2 0 | 2 4 3 | 2 6 7 | 2 7 8 | 2 8 5 | 2 9 6 | 3 0 6 | 3 1 9 | Total Tissues/ Tumors |
| **Urinary System** | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | 60 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | 1 |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | | | | | | | | 1 |
| Teratoma malignant, metastatic, ovary | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | 55 |
| **Systemic Lesions** | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | 60 |
| Histiocytic sarcoma | | | | | | | | | | | 2 |
| Lymphoma malignant | | | | | | X | | | | | 7 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**

| Number of Days on Study | 0 7 4 | 2 3 4 | 3 4 0 | 4 4 5 | 4 9 9 | 5 0 7 | 5 6 3 | 5 8 0 | 5 8 0 | 5 8 0 | 5 8 8 | 6 0 7 | 6 2 8 | 6 3 0 | 6 3 2 | 6 5 3 | 6 7 2 | 6 8 5 | 7 0 3 | 7 2 9 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 2 6 | 4 2 2 | 4 5 2 | 4 7 4 | 4 4 1 | 4 5 9 | 4 7 0 | 4 3 0 | 4 4 0 | 4 7 4 | 4 7 9 | 4 0 6 | 4 1 2 | 4 0 9 | 4 3 3 | 4 2 7 | 4 6 2 | 4 5 6 | 4 1 5 | 4 1 9 | 4 1 4 | 4 3 7 | 4 7 3 | 4 0 2 | 4 3 8 | 4 4 5 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | A | + | + | + | M | + | + | + | + | + | A | M | + | A | + | + | A | A | + | + | + | + | + | + |
| Intestine large, colon | + | A | + | + | + | + | + | + | M | + | + | A | + | + | A | + | + | A | + | A | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | A | + | + | + | + | + | + | + | + | + | A | + | + | A | + | + | A | + | A | + | + | + | + | + |
| Intestine small, duodenum | + | A | + | + | + | + | + | + | + | + | + | A | A | + | A | + | + | A | A | A | + | + | + | + | + |
| Intestine small, jejunum | + | A | + | + | + | + | + | + | + | + | + | A | A | + | A | + | + | A | A | A | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Intestine small, ileum | + | A | + | + | + | + | + | + | + | + | + | A | + | + | A | + | + | A | A | A | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | X | | | | | | X | X | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | X | | | | | | | | | | | | X | | | X | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Histiocytic sarcoma | | | | X | | | | X | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | + | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | |
| Buccal, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | A | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | A | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | + | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | M | + | + | M | + | + | + | + | + | + | + | + | M | I | + | + | + | + | + | M | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | X | | | | | | | | | X | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | + | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| 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 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 4 6 | 4 4 7 | 4 5 1 | 4 6 6 | 4 7 1 | 4 7 8 | 4 0 8 | 4 2 0 | 4 2 9 | 4 3 4 | 4 3 9 | 4 5 7 | 4 6 4 | 4 0 1 | 4 0 7 | 4 1 3 | 4 1 8 | 4 3 2 | 4 4 2 | 4 4 3 | 4 4 8 | 4 5 3 | 4 5 4 | 4 5 8 | 4 6 0 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | M | + | M | + | M | M | + | + | + | + | + | + | M | + | M | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | X | X | X | X | | | X | | | | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | |
| Buccal, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | X | | | | | | | | | | | | X | | | | | | | | | | | | X |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 6 8 | 4 7 5 | 4 0 3 | 4 2 1 | 4 2 5 | 4 3 6 | 4 5 0 | 4 5 5 | 4 6 3 | 4 6 5 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | 60 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | 54 |
| Intestine large, rectum | + | M | M | + | M | + | + | M | + | + | 48 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | 55 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | 53 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | 53 |
| Adenoma | | | | | | | | | | | 1 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | 54 |
| Liver | + | + | + | + | + | + | + | + | + | + | 60 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | | | | | | | | | 4 |
| Hepatocellular adenoma | | | X | | | | | | | | 9 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 2 |
| Mesentery | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Oral mucosa | + | | | | | | | | | | 1 |
| Buccal, squamous cell papilloma | X | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | 59 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | 60 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | 58 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | 58 |
| Tooth | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | | + | + | 59 |
| **Endocrine System** | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | 60 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | 60 |
| Pheochromocytoma benign | | X | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | 59 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | 55 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | 60 |
| Pars distalis, adenoma | | | | | | | | | | | 3 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | 60 |
| Follicular cell, adenoma | | | | | | | | | | | 3 |
| **General Body System** | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | 1 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 0 7 4 | 2 3 9 | 3 4 0 | 4 4 5 | 4 9 9 | 5 0 7 | 5 6 3 | 5 8 0 | 5 8 0 | 5 8 0 | 5 8 8 | 6 0 7 | 6 2 8 | 6 3 0 | 6 3 2 | 6 5 3 | 6 7 2 | 6 8 5 | 7 0 3 | 7 2 9 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 2 6 | 4 2 2 | 4 5 2 | 4 7 4 | 4 4 1 | 4 5 9 | 4 7 0 | 4 3 0 | 4 4 4 | 4 7 9 | 4 0 6 | 4 1 2 | 4 0 9 | 4 3 3 | 4 3 7 | 4 6 2 | 4 5 6 | 4 1 5 | 4 1 9 | 4 1 4 | 4 3 7 | 4 7 3 | 4 0 2 | 4 3 8 | 4 4 5 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | M | A | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | M | + | M | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Endometrium, adenocarcinoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Lymph node | | | | | | | | | | | | | | | | + | | + | + | + | + | | | | |
| Iliac, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Pancreatic, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Renal, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Lymph node, bronchial | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | A | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Lymph node, mediastinal | M | + | M | + | M | M | + | M | + | M | + | + | M | M | + | M | + | + | + | M | + | + | M | I | M |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | M | + | + | + | + | + | + | + | M | + | M | M | M | M | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Fibrosarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Pinna, fibrosarcoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Pinna, squamous cell carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Sebaceous gland, squamous cell carcinoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | + | | | | | |
| Sarcoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | + | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| 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 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 4 6 | 4 4 7 | 4 5 1 | 4 6 6 | 4 7 1 | 4 7 8 | 4 0 8 | 4 2 0 | 4 2 9 | 4 3 4 | 4 3 9 | 4 5 7 | 4 6 4 | 4 0 1 | 4 0 7 | 4 1 3 | 4 1 8 | 4 3 2 | 4 4 2 | 4 4 3 | 4 4 8 | 4 5 3 | 4 5 4 | 4 5 8 | 4 6 0 |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endometrium, adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood | | | | | | | | | | | + | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | | + | | | | + | | | | | | | | | | | | | | | + | | | | |
| Iliac, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreatic, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Renal, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mediastinal | I | + | + | + | M | + | M | + | I | M | M | M | M | + | I | + | + | + | I | + | + | M | M | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pinna, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pinna, squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sebaceous gland, squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 6 8 | 4 7 5 | 4 0 3 | 4 2 1 | 4 2 5 | 4 3 6 | 4 5 0 | 4 5 5 | 4 6 3 | 4 6 5 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | M | + | + | + | + | + | 52 |
| Ovary | + | + | + | + | + | + | + | + | + | + | 60 |
| Cystadenoma | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | 60 |
| Fibroma | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Polyp stromal | | | | | | | | | | | 1 |
| Endometrium, adenocarcinoma | | | | | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | |
| Blood | | | | | | | | | | | 1 |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | 59 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Lymph node | | + | + | | | | + | | | | 11 |
| Iliac, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Pancreatic, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Renal, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Lymph node, bronchial | + | + | + | + | + | + | + | + | + | + | 59 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | 60 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | 57 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | 1 |
| Lymph node, mediastinal | + | + | M | M | M | M | + | M | + | + | 30 |
| Spleen | + | + | + | + | + | + | + | + | + | + | 60 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | 54 |
| **Integumentary System** | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | 60 |
| Skin | + | + | + | + | + | + | + | + | + | + | 60 |
| Fibroma | | | | | | | | | | | 1 |
| Fibrosarcoma | | | | | | | | | | | 1 |
| Pinna, fibrosarcoma | | | | | | | | | | | 1 |
| Pinna, squamous cell carcinoma | | | | | | | | | | | 1 |
| Sebaceous gland, squamous cell carcinoma | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | 59 |
| Hemangiosarcoma | | | | | | | | | | | 1 |
| Skeletal muscle | | | | | | | | | | | 1 |
| Sarcoma | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | 60 |
| Spinal cord | | | | | | | | | | | 1 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 0 7 4 | 2 3 9 | 3 4 0 | 4 4 5 | 4 9 9 | 5 0 7 | 5 6 3 | 5 8 0 | 5 8 0 | 5 8 0 | 5 8 8 | 6 0 7 | 6 2 8 | 6 3 0 | 6 3 2 | 6 5 3 | 6 7 2 | 6 8 5 | 7 0 3 | 7 2 9 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 2 6 | 4 2 2 | 4 5 2 | 4 7 4 | 4 4 1 | 4 5 9 | 4 7 0 | 4 3 0 | 4 4 4 | 4 7 9 | 4 0 6 | 4 1 2 | 4 0 9 | 4 3 3 | 4 2 7 | 4 6 2 | 4 5 6 | 4 1 5 | 4 1 9 | 4 1 4 | 4 3 7 | 4 7 3 | 4 0 2 | 4 3 8 | 4 4 5 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | X | | | | | | | | | | |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | M | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | + | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | + | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | X | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | | |
| Urethra | | | | | | | | | | | | | | | | | | | + | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| **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 Nickel Subsulfide: 1.2 mg/m³**
(continued)

| 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 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 4 6 | 4 4 7 | 4 5 1 | 4 6 6 | 4 7 1 | 4 7 8 | 4 0 8 | 4 2 0 | 4 2 9 | 4 3 4 | 4 3 9 | 4 5 7 | 4 6 4 | 4 0 1 | 4 0 7 | 4 1 3 | 4 1 8 | 4 3 2 | 4 4 2 | 4 4 3 | 4 4 8 | 4 5 3 | 4 5 4 | 4 5 8 | 4 6 0 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Larynx | + | I | + | + | + | I | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | M | I | + |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | X | | X | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | + | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urethra | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant | | X | | | | | | | | | | | | | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide: 1.2 mg/m³**
(continued)

| Number of Days on Study | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 6 8 | 4 7 5 | 4 0 3 | 4 2 1 | 4 2 5 | 4 3 6 | 4 5 0 | 4 5 5 | 4 6 3 | 4 6 5 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | |
| Larynx | I | + | + | + | + | + | + | + | + | + | 53 |
| Lung | + | + | + | + | + | + | + | + | + | + | 60 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | 2 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | 60 |
| Hemangioma | | | | | | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | 58 |
| **Special Senses System** | | | | | | | | | | | |
| Ear | | | | | | | | | | | 2 |
| Harderian gland | | | | | | | | | | | 1 |
| Adenoma | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | 60 |
| Histiocytic sarcoma | | | | | | | | | | | 1 |
| Urethra | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | 59 |
| **Systemic Lesions** | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | 60 |
| Histiocytic sarcoma | | | | | | | | | | | 2 |
| Lymphoma malignant | | | X | | | | X | X | | | 6 |

**TABLE D3**
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Liver: Hepatocellular Adenoma** | | | |
| Overall rate[a] | 13/58 (22%) | 10/60 (17%) | 10/60 (17%) |
| Adjusted rate[b] | 31.7% | 25.7% | 23.8% |
| Terminal rate[c] | 9/36 (25%) | 7/34 (21%) | 7/38 (18%) |
| First incidence (days) | 508 | 520 | 563 |
| Life table test[d] | P=0.242N | P=0.365N | P=0.277N |
| Logistic regression test[d] | P=0.252N | P=0.315N | P=0.293N |
| Cochran-Armitage test[d] | P=0.248N | | |
| Fisher exact test[d] | | P=0.289N | P=0.289N |
| **Liver: Hepatocellular Carcinoma** | | | |
| Overall rate | 11/58 (19%) | 9/60 (15%) | 4/60 (7%) |
| Adjusted rate | 25.0% | 21.2% | 8.4% |
| Terminal rate | 4/36 (11%) | 3/34 (9%) | 1/38 (3%) |
| First incidence (days) | 603 | 552 | 563 |
| Life table test | P=0.043N | P=0.434N | P=0.051N |
| Logistic regression test | P=0.032N | P=0.345N | P=0.042N |
| Cochran-Armitage test | P=0.034N | | |
| Fisher exact test | | P=0.371N | P=0.041N |
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | |
| Overall rate | 20/58 (34%) | 18/60 (30%) | 13/60 (22%) |
| Adjusted rate | 44.8% | 41.6% | 29.3% |
| Terminal rate | 12/36 (33%) | 10/34 (29%) | 8/38 (21%) |
| First incidence (days) | 508 | 520 | 563 |
| Life table test | P=0.087N | P=0.477N | P=0.099N |
| Logistic regression test | P=0.077N | P=0.409N | P=0.091N |
| Cochran-Armitage test | P=0.075N | | |
| Fisher exact test | | P=0.373N | P=0.089N |
| **Lung: Alveolar/bronchiolar Adenoma** | | | |
| Overall rate | 3/58 (5%) | 1/59 (2%) | 1/60 (2%) |
| Adjusted rate | 7.8% | 2.9% | 2.6% |
| Terminal rate | 2/36 (6%) | 1/34 (3%) | 1/38 (3%) |
| First incidence (days) | 683 | 733 (T) | 733 (T) |
| Life table test | P=0.193N | P=0.324N | P=0.290N |
| Logistic regression test | P=0.194N | P=0.308N | P=0.294N |
| Cochran-Armitage test | P=0.194N | | |
| Fisher exact test | | P=0.303N | P=0.297N |
| **Lung: Alveolar/bronchiolar Carcinoma** | | | |
| Overall rate | 7/58 (12%) | 1/59 (2%) | 2/60 (3%) |
| Adjusted rate | 18.7% | 1.9% | 5.3% |
| Terminal rate | 6/36 (17%) | 0/34 (0%) | 2/38 (5%) |
| First incidence (days) | 683 | 552 | 733 (T) |
| Life table test | P=0.033N | P=0.040N | P=0.070N |
| Logistic regression test | P=0.033N | P=0.033N | P=0.071N |
| Cochran-Armitage test | P=0.033N | | |
| Fisher exact test | | P=0.029N | P=0.074N |

TABLE D3
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | |
| Overall rate | 9/58 (16%) | 2/59 (3%) | 3/60 (5%) |
| Adjusted rate | 24.1% | 4.8% | 7.9% |
| Terminal rate | 8/36 (22%) | 1/34 (3%) | 3/38 (8%) |
| First incidence (days) | 683 | 552 | 733 (T) |
| Life table test | P=0.026N | P=0.035N | P=0.051N |
| Logistic regression test | P=0.027N | P=0.028N | P=0.050N |
| Cochran-Armitage test | P=0.027N | | |
| Fisher exact test | | P=0.025N | P=0.055N |
| **Mammary Gland: Carcinoma** | | | |
| Overall rate | 1/58 (2%) | 3/60 (5%) | 0/60 (0%) |
| Adjusted rate | 2.8% | 8.3% | 0.0% |
| Terminal rate | 1/36 (3%) | 2/34 (6%) | 0/38 (0%) |
| First incidence (days) | 733 (T) | 711 | —[e] |
| Life table test | P=0.361N | P=0.294 | P=0.489N |
| Logistic regression test | P=0.365N | P=0.297 | P=0.489N |
| Cochran-Armitage test | P=0.367N | | |
| Fisher exact test | | P=0.322 | P=0.492N |
| **Pituitary Gland (Pars Distalis): Adenoma** | | | |
| Overall rate | 8/58 (14%) | 5/57 (9%) | 3/60 (5%) |
| Adjusted rate | 21.0% | 13.6% | 7.0% |
| Terminal rate | 7/36 (19%) | 3/34 (9%) | 1/38 (3%) |
| First incidence (days) | 536 | 712 | 607 |
| Life table test | P=0.066N | P=0.309N | P=0.089N |
| Logistic regression test | P=0.068N | P=0.290N | P=0.094N |
| Cochran-Armitage test | P=0.067N | | |
| Fisher exact test | | P=0.290N | P=0.092N |
| **Thyroid Gland (Follicular Cell): Adenoma** | | | |
| Overall rate | 2/58 (3%) | 4/60 (7%) | 3/60 (5%) |
| Adjusted rate | 5.1% | 11.2% | 7.9% |
| Terminal rate | 1/36 (3%) | 3/34 (9%) | 3/38 (8%) |
| First incidence (days) | 691 | 711 | 733 (T) |
| Life table test | P=0.445 | P=0.324 | P=0.522 |
| Logistic regression test | P=0.436 | P=0.331 | P=0.516 |
| Cochran-Armitage test | P=0.433 | | |
| Fisher exact test | | P=0.356 | P=0.516 |
| **Thyroid Gland (Follicular Cell): Adenoma or Carcinoma** | | | |
| Overall rate | 3/58 (5%) | 4/60 (7%) | 3/60 (5%) |
| Adjusted rate | 7.9% | 11.2% | 7.9% |
| Terminal rate | 2/36 (6%) | 3/34 (9%) | 3/38 (8%) |
| First incidence (days) | 691 | 711 | 733 (T) |
| Life table test | P=0.550N | P=0.480 | P=0.639N |
| Logistic regression test | P=0.558N | P=0.492 | P=0.646N |
| Cochran-Armitage test | P=0.562N | | |
| Fisher exact test | | P=0.519 | P=0.644N |

TABLE D3
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **All Organs: Hemangiosarcoma** | | | |
| Overall rate | 3/58 (5%) | 4/60 (7%) | 3/60 (5%) |
| Adjusted rate | 7.8% | 10.1% | 7.9% |
| Terminal rate | 2/36 (6%) | 2/34 (6%) | 3/38 (8%) |
| First incidence (days) | 680 | 623 | 733 (T) |
| Life table test | P=0.554N | P=0.482 | P=0.641N |
| Logistic regression test | P=0.564N | P=0.502 | P=0.647N |
| Cochran-Armitage test | P=0.562N | | |
| Fisher exact test | | P=0.519 | P=0.644N |
| **All Organs: Hemangioma or Hemangiosarcoma** | | | |
| Overall rate | 4/58 (7%) | 4/60 (7%) | 4/60 (7%) |
| Adjusted rate | 10.5% | 10.1% | 10.5% |
| Terminal rate | 3/36 (8%) | 2/34 (6%) | 4/38 (11%) |
| First incidence (days) | 680 | 623 | 733 (T) |
| Life table test | P=0.544N | P=0.621 | P=0.617N |
| Logistic regression test | P=0.556N | P=0.642N | P=0.623N |
| Cochran-Armitage test | P=0.553N | | |
| Fisher exact test | | P=0.622N | P=0.622N |
| **All Organs: Malignant Lymphoma** | | | |
| Overall rate | 5/58 (9%) | 7/60 (12%) | 6/60 (10%) |
| Adjusted rate | 13.1% | 15.8% | 14.6% |
| Terminal rate | 4/36 (11%) | 2/34 (6%) | 4/38 (11%) |
| First incidence (days) | 679 | 425 | 653 |
| Life table test | P=0.474 | P=0.365 | P=0.532 |
| Logistic regression test | P=0.460 | P=0.400 | P=0.521 |
| Cochran-Armitage test | P=0.464 | | |
| Fisher exact test | | P=0.405 | P=0.524 |
| **All Organs: Benign Neoplasms** | | | |
| Overall rate | 29/58 (50%) | 22/60 (37%) | 21/60 (35%) |
| Adjusted rate | 65.3% | 49.6% | 47.1% |
| Terminal rate | 21/36 (58%) | 13/34 (38%) | 15/38 (39%) |
| First incidence (days) | 508 | 116 | 563 |
| Life table test | P=0.066N | P=0.196N | P=0.073N |
| Logistic regression test | P=0.061N | P=0.117N | P=0.070N |
| Cochran-Armitage test | P=0.060N | | |
| Fisher exact test | | P=0.101N | P=0.072N |
| **All Organs: Malignant Neoplasms** | | | |
| Overall rate | 26/58 (45%) | 27/60 (45%) | 23/60 (38%) |
| Adjusted rate | 54.8% | 51.3% | 44.8% |
| Terminal rate | 15/36 (42%) | 9/34 (26%) | 11/38 (29%) |
| First incidence (days) | 419 | 206 | 445 |
| Life table test | P=0.293N | P=0.455 | P=0.314N |
| Logistic regression test | P=0.286N | P=0.558 | P=0.296N |
| Cochran-Armitage test | P=0.266N | | |
| Fisher exact test | | P=0.566 | P=0.299N |

TABLE D3
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ |
|---|---|---|---|
| **All Organs: Benign or Malignant Neoplasms** | | | |
| Overall rate | 43/58 (74%) | 39/60 (65%) | 39/60 (65%) |
| Adjusted rate | 85.8% | 70.5% | 73.4% |
| Terminal rate | 29/36 (81%) | 18/34 (53%) | 24/38 (63%) |
| First incidence (days) | 419 | 116 | 445 |
| Life table test | P=0.223N | P=0.408N | P=0.228N |
| Logistic regression test | P=0.176N | P=0.205N | P=0.200N |
| Cochran-Armitage test | P=0.169N | | |
| Fisher exact test | | P=0.190N | P=0.190N |

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4
**Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Female B6C3F$_1$ Mice**[a]

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| **Historical Incidence at Lovelace Inhalation Toxicology Research Institute** | | | |
| Nickel Oxide | 2/64 | 4/64 | 6/64 |
| Nickel Subsulfide | 3/58 | 7/58 | 9/58 |
| Nickel Sulfate Hexahydrate | 3/61 | 4/61 | 7/61 |
| Talc | 3/46 | 2/46 | 5/46 |
| **Overall Historical Incidence in Inhalation Studies** | | | |
| Total | 6/944 (6.5%) | 38/944 (4.0%) | 97/944 (10.3%) |
| Standard deviation | 3/1% | 3.2% | 3.7% |
| Range | 0%-14% | 0%-12% | 0%-16% |
| **Overall Historical Incidence in Feed Studies** | | | |
| Total | 78/1,319 (5.9%) | 26/1,319 (2.0%) | 102/1,319 (7.7%) |
| Standard deviation | 5.0% | 2.3% | 5.3% |
| Range | 0%-24% | 0%-8% | 2%-26% |

[a] Data as of 17 June 1994

TABLE D5
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 80 | 80 | 80 |
| *7-Month interim evaluation*[b] | 10 | 10 | 10 |
| *15-Month interim evaluation*[b] | 10 | 10 | 10 |
| Early deaths | | | |
| Moribund | 14 | 15 | 13 |
| Natural deaths | 8 | 11 | 9 |
| Survivors | | | |
| Terminal sacrifice | 36 | 34 | 38 |
| Missexed | 2 | | |
| Animals examined microscopically | 68 | 70 | 70 |
| ***7-Month Interim Evaluation*** | | | |
| **Hematopoietic System** | | | |
| Lymph node | | (1) | |
| Pigmentation | | 1 (100%) | |
| Lymph node, bronchial | (5) | (4) | (5) |
| Hyperplasia, lymphoid | | 1 (25%) | |
| Hyperplasia, macrophage | | 1 (25%) | 1 (20%) |
| Lymph node, mandibular | (3) | (2) | (3) |
| Hyperplasia | | | 1 (33%) |
| Hyperplasia, lymphoid | 2 (67%) | 1 (50%) | 1 (33%) |
| **Respiratory System** | | | |
| Lung | (5) | (5) | (5) |
| Inflammation, chronic active | | 2 (40%) | 5 (100%) |
| Alveolus, hyperplasia, macrophage | 1 (20%) | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 4 (80%) | 5 (100%) |
| Interstitium, infiltration cellular | 1 (20%) | 5 (100%) | 4 (80%) |
| Nose | (5) | (5) | (5) |
| Olfactory epithelium, atrophy | | | 1 (20%) |
| Olfactory epithelium, degeneration | 4 (80%) | | |
| ***Systems Examined With No Lesions Observed*** | | | |
| **Alimentary System** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Genital System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Special Senses System** | | | |
| **Urinary System** | | | |

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Five animals in each exposure group were histopathologically examined at the interim evaluations.

TABLE D5
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** | | | |
| **Alimentary System** | | | |
| Intestine large, cecum | (5) | (5) | (5) |
| Hyperplasia, lymphoid | 1 (20%) | 2 (40%) | 2 (40%) |
| Intestine small, ileum | (5) | (5) | (5) |
| Hyperplasia | 1 (20%) | | |
| Hyperplasia, lymphoid | 1 (20%) | | |
| Liver | (5) | (5) | (5) |
| Basophilic focus | 1 (20%) | | |
| **Genital System** | | | |
| Clitoral gland | (5) | (5) | (4) |
| Ectasia | 1 (20%) | | |
| Uterus | (5) | (5) | (5) |
| Endometrium, hyperplasia | 3 (60%) | 2 (40%) | 3 (60%) |
| **Hematopoietic System** | | | |
| Lymph node, bronchial | (5) | (5) | (5) |
| Hyperplasia, lymphoid | | 5 (100%) | 5 (100%) |
| Hyperplasia, macrophage | | 5 (100%) | 5 (100%) |
| Lymph node, mandibular | (4) | (5) | (5) |
| Hyperplasia, lymphoid | 2 (50%) | 1 (20%) | 2 (40%) |
| Lymph node, mesenteric | (5) | (5) | (5) |
| Hyperplasia, lymphoid | | | 1 (20%) |
| Spleen | (5) | (5) | (5) |
| Hematopoietic cell proliferation | 2 (40%) | | |
| **Respiratory System** | | | |
| Larynx | (4) | (4) | (4) |
| Inflammation, chronic | | 1 (25%) | |
| Lung | (5) | (5) | (5) |
| Inflammation, chronic active | | 4 (80%) | 5 (100%) |
| Bronchialization | | 2 (40%) | 5 (100%) |
| Alveolus, hyperplasia, macrophage | | 5 (100%) | 5 (100%) |
| Alveolus, proteinosis | | 5 (100%) | 5 (100%) |
| Bronchus, hyperplasia, lymphoid | 4 (80%) | 4 (80%) | 4 (80%) |
| Interstitium, infiltration cellular | 1 (20%) | 5 (100%) | 5 (100%) |
| Nose | (5) | (5) | (5) |
| Olfactory epithelium, degeneration | 1 (20%) | | |
| **Special Senses System** | | | |
| Ear | (1) | | |
| External ear, ulcer | 1 (100%) | | |

TABLE D5
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | |
| ***Systems Examined With No Lesions Observed*** | | | |
| **Cardiovascular System** | | | |
| **Endocrine System** | | | |
| **General Body System** | | | |
| **Integumentary System** | | | |
| **Musculoskeletal System** | | | |
| **Nervous System** | | | |
| **Urinary System** | | | |
| ***2-Year Study*** | | | |
| **Alimentary System** | | | |
| Gallbladder | (53) | (51) | (53) |
| Epithelium, hyperplasia | 1 (2%) | | |
| Intestine large, cecum | (54) | (54) | (55) |
| Lymphoid tissue, hyperplasia, lymphoid | 1 (2%) | 2 (4%) | |
| Intestine small, duodenum | (53) | (53) | (53) |
| Atrophy | 1 (2%) | | |
| Inflammation | | 2 (4%) | |
| Intestine small, jejunum | (54) | (53) | (53) |
| Atrophy | 1 (2%) | | |
| Intestine small, ileum | (54) | (52) | (54) |
| Atrophy | 1 (2%) | | |
| Peyer's patch, hyperplasia, lymphoid | | 1 (2%) | |
| Liver | (58) | (60) | (60) |
| Angiectasis | 3 (5%) | 1 (2%) | 3 (5%) |
| Atrophy | | 4 (7%) | 2 (3%) |
| Basophilic focus | | 1 (2%) | 1 (2%) |
| Cyst | 1 (2%) | | |
| Degeneration | 1 (2%) | 1 (2%) | 3 (5%) |
| Eosinophilic focus | | 1 (2%) | 3 (5%) |
| Fibrosis | 1 (2%) | | |
| Infarct | 1 (2%) | 2 (3%) | 2 (3%) |
| Infiltration cellular, lymphocyte | 2 (3%) | 2 (3%) | 3 (5%) |
| Inflammation | 4 (7%) | 3 (5%) | 1 (2%) |
| Mixed cell focus | | 1 (2%) | 1 (2%) |
| Necrosis | 2 (3%) | 3 (5%) | 1 (2%) |
| Pigmentation, hemosiderin | | 1 (2%) | |
| Mesentery | (3) | (4) | (1) |
| Inflammation | | 1 (25%) | |
| Necrosis | 1 (33%) | | |
| Artery, inflammation | 1 (33%) | | |
| Pancreas | (58) | (56) | (59) |
| Atrophy, focal | 2 (3%) | | |
| Cyst | | 1 (2%) | |
| Infiltration cellular, lymphocyte | 1 (2%) | 3 (5%) | |
| Inflammation | | 1 (2%) | 1 (2%) |
| Acinus, atrophy | 2 (3%) | 1 (2%) | 1 (2%) |

**TABLE D5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Alimentary System** (continued) | | | |
| Stomach, forestomach | (57) | (60) | (58) |
| Hyperplasia, focal, squamous | | | 1 (2%) |
| Hyperplasia, squamous | 2 (4%) | | |
| Inflammation | | | 1 (2%) |
| Stomach, glandular | (57) | (58) | (58) |
| Inflammation | 2 (4%) | 5 (9%) | 4 (7%) |
| Tooth | (2) | (1) | (1) |
| Developmental malformation | | 1 (100%) | 1 (100%) |
| Inflammation | 2 (100%) | | |
| **Cardiovascular System** | | | |
| Heart | (58) | (60) | (59) |
| Cardiomyopathy | | 1 (2%) | 1 (2%) |
| Inflammation | 1 (2%) | | |
| Artery, inflammation | 1 (2%) | | |
| Atrium, thrombosis | 2 (3%) | | |
| **Endocrine System** | | | |
| Adrenal cortex | (58) | (58) | (60) |
| Angiectasis | 1 (2%) | 1 (2%) | 2 (3%) |
| Atrophy | | 1 (2%) | 1 (2%) |
| Degeneration | | | 3 (5%) |
| Hematopoietic cell proliferation | | | 1 (2%) |
| Hyperplasia | | | 1 (2%) |
| Hyperplasia, focal | | 1 (2%) | |
| Adrenal medulla | (58) | (58) | (60) |
| Angiectasis | 1 (2%) | 2 (3%) | 1 (2%) |
| Hyperplasia | | | 1 (2%) |
| Pituitary gland | (58) | (57) | (60) |
| Angiectasis | 2 (3%) | 6 (11%) | 1 (2%) |
| Cyst | 1 (2%) | | |
| Pars distalis, hyperplasia | 7 (12%) | 10 (18%) | 11 (18%) |
| Thyroid gland | (58) | (60) | (60) |
| Inflammation | | | 1 (2%) |
| Artery, inflammation | 1 (2%) | | |
| Follicle, atrophy | 1 (2%) | | |
| Follicular cell, hyperplasia | 20 (34%) | 28 (47%) | 37 (62%) |
| **General Body System** | | | |
| Tissue NOS | | (4) | (1) |
| Thoracic, inflammation | | | 1 (100%) |

TABLE D5
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Genital System** | | | |
| Clitoral gland | (55) | (59) | (52) |
| Atrophy | | 1 (2%) | 8 (15%) |
| Ectasia | 2 (4%) | 1 (2%) | 1 (2%) |
| Inflammation | | 2 (3%) | |
| Ovary | (58) | (58) | (60) |
| Abscess | | 1 (2%) | 1 (2%) |
| Cyst | 6 (10%) | 8 (14%) | 11 (18%) |
| Hemorrhage | | | 1 (2%) |
| Periovarian tissue, cyst | | | 1 (2%) |
| Uterus | (58) | (60) | (60) |
| Abscess | 1 (2%) | 1 (2%) | |
| Angiectasis | 1 (2%) | | |
| Cyst | 5 (9%) | 3 (5%) | 3 (5%) |
| Cyst, multiple | | 2 (3%) | |
| Inflammation | | 1 (2%) | 3 (5%) |
| Endometrium, hyperplasia | 14 (24%) | 19 (32%) | 19 (32%) |
| **Hematopoietic System** | | | |
| Bone marrow | (57) | (60) | (59) |
| Inflammation | 1 (2%) | | |
| Erythroid cell, hyperplasia | | 3 (5%) | 1 (2%) |
| Myeloid cell, atrophy | | 1 (2%) | |
| Myeloid cell, hyperplasia | 7 (12%) | 7 (12%) | 5 (8%) |
| Lymph node | (9) | (12) | (11) |
| Iliac, hyperplasia, lymphoid | | 1 (8%) | 2 (18%) |
| Inguinal, hyperplasia, lymphoid | 1 (11%) | | |
| Inguinal, inflammation | 1 (11%) | | |
| Pancreatic, hyperplasia | | | 1 (9%) |
| Pancreatic, inflammation | 1 (11%) | 1 (8%) | 1 (9%) |
| Renal, hyperplasia, lymphoid | | 2 (17%) | 3 (27%) |
| Renal, inflammation | | 1 (8%) | |
| Renal, inflammation, granulomatous | | 1 (8%) | |
| Lymph node, bronchial | (50) | (57) | (59) |
| Hyperplasia, lymphoid | 10 (20%) | 46 (81%) | 52 (88%) |
| Hyperplasia, macrophage | | 44 (77%) | 47 (80%) |
| Inflammation | 1 (2%) | 1 (2%) | |
| Inflammation, granulomatous | | 1 (2%) | |
| Lymph node, mandibular | (57) | (59) | (60) |
| Hyperplasia, lymphoid | 18 (32%) | 7 (12%) | 4 (7%) |
| Hyperplasia, plasma cell | 2 (4%) | 1 (2%) | |
| Inflammation | 1 (2%) | | |
| Lymph node, mesenteric | (55) | (54) | (57) |
| Ectasia | 1 (2%) | | |
| Hyperplasia, lymphoid | 4 (7%) | 4 (7%) | 6 (11%) |
| Inflammation | 3 (5%) | 1 (2%) | 2 (4%) |
| Lymph node, mediastinal | (15) | (28) | (30) |
| Hyperplasia, lymphoid | 1 (7%) | | 5 (17%) |
| Inflammation | | | 1 (3%) |

TABLE D5
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Hematopoietic System** (continued) | | | |
| Spleen | (58) | (60) | (60) |
| Atrophy | | 1 (2%) | 1 (2%) |
| Hematopoietic cell proliferation | 14 (24%) | 15 (25%) | 9 (15%) |
| Hyperplasia, lymphoid | 17 (29%) | 27 (45%) | 19 (32%) |
| Inflammation | 1 (2%) | | |
| Lymphoid follicle, atrophy | 2 (3%) | | |
| Red pulp, atrophy | 1 (2%) | 1 (2%) | |
| Thymus | (58) | (57) | (54) |
| Degeneration | 8 (14%) | 5 (9%) | 8 (15%) |
| Hyperplasia | 2 (3%) | | |
| Hyperplasia, lymphoid | | 2 (4%) | |
| **Integumentary System** | | | |
| *Mammary gland* | (57) | (59) | (60) |
| Hyperplasia | 8 (14%) | 11 (19%) | 7 (12%) |
| Hyperplasia, cystic | 1 (2%) | | |
| Inflammation | | | 1 (2%) |
| Skin | (58) | (60) | (60) |
| Fibrosis | 1 (2%) | | |
| Hemorrhage | | | 1 (2%) |
| Inflammation | 3 (5%) | | 1 (2%) |
| Pinna, cyst epithelial inclusion | | | 1 (2%) |
| Pinna, hyperkeratosis | | | 1 (2%) |
| Pinna, inflammation | 2 (3%) | | |
| **Musculoskeletal System** | | | |
| Bone | (57) | (60) | (59) |
| Hyperostosis | 1 (2%) | | 1 (2%) |
| Inflammation | 1 (2%) | | 1 (2%) |
| Femur, hyperostosis | 10 (18%) | 9 (15%) | 10 (17%) |
| Maxilla, hyperostosis | | | 1 (2%) |
| Tibia, fracture | | 1 (2%) | |
| **Nervous System** | | | |
| Brain | (58) | (60) | (60) |
| Thalamus, degeneration, focal | | | 1 (2%) |
| Spinal cord | (1) | | (1) |
| Abscess | | | 1 (100%) |
| Degeneration | 1 (100%) | | |
| **Respiratory System** | | | |
| Larynx | (54) | (55) | (53) |
| Inflammation | | 1 (2%) | |
| Epithelium, hyperplasia | | 1 (2%) | |

TABLE D5
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| ***2-Year Study*** (continued) | | | |
| **Respiratory System** (continued) | | | |
| Lung | (58) | (59) | (60) |
| Bronchiectasis | | 1 (2%) | |
| Fibrosis | | 7 (12%) | 17 (28%) |
| Inflammation, acute | | 1 (2%) | |
| Inflammation, chronic active | 1 (2%) | 46 (78%) | 58 (97%) |
| Bronchializtion | 3 (5%) | 53 (90%) | 58 (97%) |
| Alveolus, hyperplasia, macrophage | 5 (9%) | 57 (97%) | 60 (100%) |
| Alveolus, proteinosis | | 54 (92%) | 59 (98%) |
| Bronchus, hyperplasia, lymphoid | 34 (59%) | 26 (44%) | 34 (57%) |
| Interstitium, infiltration cellular | 19 (33%) | 53 (90%) | 58 (97%) |
| Interstitium, inflammation | 1 (2%) | | |
| Nose | (58) | (59) | (60) |
| Inflammation, acute | | 11 (19%) | 14 (23%) |
| Olfactory epithelium, atrophy | 1 (2%) | 11 (19%) | 41 (68%) |
| Olfactory epithelium, degeneration | 26 (45%) | 3 (5%) | 12 (20%) |
| Respiratory epithelium, degeneration | 1 (2%) | | |
| **Special Senses System** | | | |
| Ear | (2) | (1) | (2) |
| Inflammation | 1 (50%) | 1 (100%) | |
| External ear, inflammation | 1 (50%) | | |
| Eye | (2) | | |
| Cataract | 1 (50%) | | |
| **Urinary System** | | | |
| Kidney | (58) | (60) | (60) |
| Hydronephrosis | | 1 (2%) | 1 (2%) |
| Infarct | 1 (2%) | | |
| Infiltration cellular, lymphocyte | 9 (16%) | 12 (20%) | 1 (2%) |
| Inflammation | 1 (2%) | | |
| Metaplasia, osseous | | | 1 (2%) |
| Nephropathy | 5 (9%) | 2 (3%) | 2 (3%) |
| Glomerulus, inflammation | | | 1 (2%) |
| Pelvis, inflammation | | | 1 (2%) |
| Renal tubule, pigmentation, hemosiderin | | | 1 (2%) |
| Urinary bladder | (56) | (55) | (59) |
| Infiltration cellular, lymphocyte | 1 (2%) | 3 (5%) | |

# APPENDIX E
# GENETIC TOXICOLOGY

# GENETIC TOXICOLOGY

## *SALMONELLA TYPHIMURIUM* MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). Nickel subsulfide was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA102, and TA1535, either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following 2 days incubation at 37° C. All tests were repeated using either the same or different S9 concentrations.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of nickel subsulfide. In the absence of toxicity, 10,000 μg/plate was selected as the high dose.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

## MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). At the end of the 13-week toxicity study, peripheral blood samples were obtained from male and female B6C3F$_1$ mice and smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. From 6,400 to 7,400 normochromatic erythrocytes (NCEs) were scored in up to 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei.

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 was analyzed by a statistical software package that tested for increasing trend over exposure groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (Margolin *et al.*, 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 1) the trend test P value is less than or equal to 0.025 or 2) the P value for any single exposure group is less than or equal to 0.025/N where N equals the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, reproducibility of any effects observed, and the magnitudes of those effects.

## RESULTS

Nickel subsulfide was tested for induction of gene mutations in five strains of *Salmonella typhimurium* (Table E1). Results of these tests were considered to be equivocal overall due to the response seen in strain TA100. Varied indications of mutagenic activity were observed with and without S9 in TA100, with the most consistent demonstration of mutagenicity noted in the presence of 10% rat liver S9. No mutagenic responses were observed in strains TA97, TA98, TA102, or TA1535, with or without S9. Nickel subsulfide was also tested for induction of micronuclei in NCEs of male and female mice exposed by inhalation for 13 weeks. Nickel subsulfide did not induce an increase in the frequency of micronucleated NCEs in peripheral blood samples (Table E2).

TABLE E1
**Mutagenicity of Nickel Subsulfide in *Salmonella typhimurium*[a]**

| Strain | Dose (μg/plate) | Revertants/plate[b] -S9 Trial 1 | -S9 Trial 2 | +hamster S9 10% | +hamster S9 30% | +rat S9 10% | +rat S9 30% |
|---|---|---|---|---|---|---|---|
| TA102 | 0 | 227 ± 4.2 | 161 ± 13.6 | 211 ± 8.7 | 249 ± 2.5 | 207 ± 12.7 | 312 ± 30.0 |
| | 100 | 230 ± 14.3 | 148 ± 3.2 | 224 ± 11.2 | 234 ± 11.2 | 212 ± 5.9 | 351 ± 15.4 |
| | 333 | 236 ± 19.8 | 160 ± 18.4 | 220 ± 12.5 | 276 ± 14.6 | 197 ± 13.8 | 338 ± 5.5 |
| | 1,000 | 210 ± 10.7 | 154 ± 3.1 | 209 ± 13.8 | 281 ± 16.7 | 196 ± 8.2 | 352 ± 12.2 |
| | 3,333 | 151 ± 4.7[c] | 163 ± 2.6[c] | 210 ± 2.1[c] | 279 ± 15.8 | 198 ± 16.7[c] | 321 ± 15.5[c] |
| | 10,000 | 154 ± 3.8[c] | 151 ± 2.6[c] | 233 ± 5.0[c] | 300 ± 5.8 | 250 ± 8.1[c] | 350 ± 17.9[c] |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control[d] | | 813 ± 13.5 | 737 ± 7.8 | 534 ± 59.0 | 926 ± 74.0 | 1,110 ± 17.2 | 1,236 ± 18.7 |

| | | Revertants/plate -S9 Trial 1 | -S9 Trial 2 | -S9 Trial 3 | +5% hamster S9 Trial 1 | +5% hamster S9 Trial 2 | +5% hamster S9 Trial 3 |
|---|---|---|---|---|---|---|---|
| TA100 | 0 | 131 ± 3.2 | 111 ± 2.8 | 143 ± 17.3 | 100 ± 5.7 | 109 ± 15.4 | 145 ± 13.9 |
| | 100 | 110 ± 7.5 | 111 ± 12.5 | | 105 ± 17.0 | | 111 ± 11.2 |
| | 333 | 132 ± 11.6 | 131 ± 8.6 | 132 ± 9.5 | 110 ± 2.7 | 120 ± 13.4 | 120 ± 10.7 |
| | 1,000 | 127 ± 6.1 | 145 ± 8.8 | 162 ± 3.5 | 122 ± 14.0 | 138 ± 7.3 | 128 ± 6.1 |
| | 1,666 | | | | 152 ± 6.0 | | |
| | 3,333 | 98 ± 5.5[c] | 156 ± 9.0[c] | 184 ± 11.7 | 155 ± 7.9[c] | 136 ± 4.4[c] | 131 ± 10.0[c] |
| | 6,666 | | | 199 ± 4.4 | 129 ± 5.5[c] | | |
| | 10,000 | 126 ± 6.9[c] | 183 ± 9.1[c] | 178 ± 5.8 | 147 ± 5.2[c] | | 133 ± 2.0[c] |
| Trial summary | | Negative | Weak positive | Equivocal | Equivocal | Equivocal | Negative |
| Positive control | | 429 ± 7.8 | 390 ± 20.3 | 295 ± 7.5 | 922 ± 44.3 | 897 ± 57.6 | 1,270 ± 30.7 |

| | | Revertants/plate 10% +hamster S9 Trial 1 | 10% +hamster S9 Trial 2 | 10% +hamster S9 Trial 3 | 30% +hamster S9 Trial 1 | 30% +hamster S9 Trial 2 | 30% +hamster S9 Trial 3 |
|---|---|---|---|---|---|---|---|
| TA100 (continued) | 0 | 102 ± 7.2 | 147 ± 6.4 | 137 ± 13.1 | 124 ± 4.7 | 127 ± 12.8 | 126 ± 15.3 |
| | 100 | 128 ± 8.6 | 129 ± 8.2 | 134 ± 9.3 | 125 ± 5.3 | 130 ± 3.9 | 146 ± 5.1 |
| | 333 | 121 ± 2.7 | 130 ± 3.5 | 147 ± 3.1 | 137 ± 5.8 | 132 ± 2.5 | 141 ± 3.2 |
| | 1,000 | 129 ± 6.9 | 136 ± 7.3 | 160 ± 4.6 | 164 ± 7.2 | 146 ± 7.9 | 129 ± 21.5 |
| | 1,666 | | | | | | 157 ± 2.7 |
| | 3,333 | 140 ± 3.5[c] | 126 ± 13.7[c] | 171 ± 5.8[c] | 142 ± 2.3[c] | 147 ± 10.2[c] | 141 ± 11.9[c] |
| | 6,666 | | | | | | 137 ± 7.2[c] |
| | 10,000 | 144 ± 1.9[c] | 146 ± 1.5[c] | 154 ± 7.5[c] | 160 ± 10.6[c] | 131 ± 6.7[c] | 151 ± 4.4[c] |
| Trial summary | | Equivocal | Negative | Negative | Equivocal | Negative | Negative |
| Positive control | | 577 ± 10.9 | 760 ± 22.6 | 764 ± 17.2 | 462 ± 31.2 | 457 ± 22.2 | 703 ± 13.1 |

TABLE E1
Mutagenicity of Nickel Subsulfide in *Salmonella typhimurium* (continued)

| Strain | Dose (μg/plate) | Revertants/plate +5% rat S9 Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|---|
| TA100 | 0 | 104 ± 3.8 | 119 ± 11.1 | 154 ± 5.8 |
| (continued) | 100 | 125 ± 16.5 | | 138 ± 2.4 |
| | 333 | 132 ± 4.7 | 131 ± 9.3 | 144 ± 5.7 |
| | 1,000 | 133 ± 2.1 | 153 ± 8.2 | 156 ± 2.8 |
| | 3,333 | 141 ± 8.9[c] | 151 ± 13.0[c] | 152 ± 5.2[c] |
| | 10,000 | 125 ± 5.8[c] | | 145 ± 8.4[c] |
| Trial summary | | Negative | Equivocal | Negative |
| Positive control | | 909 ± 16.2 | 1,011 ± 25.0 | 940 ± 11.2 |

| Strain | Dose (μg/plate) | Revertants/plate +10% rat S9 Trial 1 | Trial 2 | Trial 3 | Trial 4 |
|---|---|---|---|---|---|
| TA100 | 0 | 124 ± 11.0 | 140 ± 15.4 | 122 ± 14.4 | 132 ± 9.3 |
| (continued) | 100 | 110 ± 6.8 | 136 ± 2.6 | 130 ± 12.8 | |
| | 333 | 129 ± 4.3 | 139 ± 4.8 | 149 ± 1.5 | 143 ± 4.7 |
| | 1,000 | 134 ± 9.8 | 152 ± 6.1 | 163 ± 8.2 | 151 ± 6.6 |
| | 3,333 | 145 ± 2.1[c] | 154± 5.3[c] | 162 ± 7.2[c] | 185 ± 3.4 |
| | 6,666 | | | 187 ± 10.0 | |
| | 10,000 | 147 ± 8.5[c] | 146 ± 12.1[c] | 187 ± 11.4[c] | 188 ± 7.3 |
| Trial summary | | Negative | Negative | Weak positive | Weak positive |
| Positive control | | 556 ± 32.4 | 589 ± 41.9 | 441 ± 9.8 | 585 ± 32.7 |

| Strain | Dose (μg/plate) | Revertants/plate +30% rat S9 Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|---|
| TA100 | 0 | 140 ± 9.9 | 141 ± 9.1 | 133 ± 13.9 |
| (continued) | 100 | 131 ± 19.6 | 131 ± 11.1 | 112 ± 6.7 |
| | 333 | 161 ± 4.6 | 141 ± 12.3 | 140 ± 16.0 |
| | 1,000 | 202 ± 19.0 | 152 ± 4.9 | 122 ± 3.8 |
| | 3,333 | 196 ± 9.0[c] | 159 ± 3.7[c] | 146 ± 8.4[c] |
| | 10,000 | 180 ± 6.1[c] | 164 ± 20.4[c] | 168 ± 9.2[c] |
| Trial summary | | Equivocal | Negative | Negative |
| Positive control | | 244 ± 6.7 | 521 ± 412 | 626 ± 17.3 |

TABLE E1
**Mutagenicity of Nickel Subsulfide in *Salmonella typhimurium*** (continued)

| Strain | Dose (μg/plate) | Revertants/plate -S9 Trial 1 | +hamster S9 5% | +hamster S9 10% | +hamster S9 30% |
|---|---|---|---|---|---|
| TA1535 | 0 | 21 ± 1.2 | 8 ± 1.9 | 9 ± 1.8 | 9 ± 2.0 |
| | 100 | 16 ± 0.6 | 8 ± 1.2 | 10 ± 0.6 | 6 ± 1.2 |
| | 333 | 16 ± 2.0 | 7 ± 0.7 | 10 ± 0.9 | 7 ± 1.5 |
| | 1,000 | 17 ± 0.9 | 6 ± 0.3 | 11 ± 1.5 | 11 ± 1.5 |
| | 3,333 | 14 ± 2.5 | 8 ± 0.9[c] | 8 ± 0.3[c] | 10 ± 0.9[c] |
| | 10,000 | 7 ± 1.9 | 9 ± 1.9[c] | 11 ± 1.8[c] | 14 ± 2.0[c] |
| Trial summary | | Negative | Negative | Negative | Negative |
| Positive control | | 719 ± 54.9 | 131 ± 4.8 | 119 ± 4.8 | 296 ± 10.5 |

| Strain | Dose (μg/plate) | Revertants/plate +30% rat S9 Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|---|
| TA1535 (continued) | 0 | 13 ± 1.9 | 14 ± 2.5 | 14 ± 0.3 |
| | 100 | 11 ± 1.3 | 9 ± 0.6 | 21 ± 3.7 |
| | 333 | 7 ± 0.3 | 9 ± 2.2 | 11 ± 1.9 |
| | 1,000 | 10 ± 1.5 | 11 ± 3.2 | 15 ± 0.7 |
| | 3,333 | 12 ± 2.5[c] | 10 ± 0.6[c] | 14 ± 1.8[c] |
| | 10,000 | 9 ± 2.6[c] | 7 ± 1.2[c] | 14 ± 1.5[c] |
| Trial summary | | Negative | Negative | Negative |
| Positive control | | 181 ± 18.8 | 163 ± 7.8 | 144 ± 3.5 |

| Strain | Dose (μg/plate) | Revertants/plate -S9 Trial 1 | -S9 Trial 2 | +10% hamster S9 Trial 1 | +10% hamster S9 Trial 2 | +10% rat S9 Trial 1 | +10% rat S9 Trial 2 |
|---|---|---|---|---|---|---|---|
| TA97 | 0 | 153 ± 7.1 | 158 ± 6.6 | 147 ± 6.0 | 152 ± 4.5 | 164 ± 6.4 | 188 ± 6.1 |
| | 100 | 150 ± 5.8 | 163 ± 8.7 | 153 ± 9.5 | 145 ± 10.2 | 169 ± 4.4 | 182 ± 15.1 |
| | 333 | 169 ± 11.1 | 161 ± 5.5 | 153 ± 7.8 | 164 ± 8.4 | 171 ± 7.8 | 159 ± 17.9 |
| | 1,000 | 173 ± 5.5 | 171 ± 2.3 | 158 ± 2.0 | 154 ± 9.0 | 153 ± 7.5 | 188 ± 12.1 |
| | 3,333 | 176 ± 3.3 | 182 ± 9.1[c] | 165 ± 13.8[c] | 164 ± 8.7[c] | 174 ± 0.9[c] | 165 ± 19.1[c] |
| | 10,000 | 162 ± 5.0 | 174 ± 6.0 | 157 ± 10.7 | 149 ± 15.6 | 176 ± 5.3 | 172 ± 9.2 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 497 ± 34.3 | 374 ± 4.7 | 541 ± 23.7 | 554 ± 16.8 | 324 ± 10.1 | 343 ± 13.5 |

**TABLE E1**
**Mutagenicity of Nickel Subsulfide in *Salmonella typhimurium*** (continued)

| Strain | Dose (μg/plate) | Revertants/plate -S9 Trial 1 | -S9 Trial 2 | +hamster S9 10% | +hamster S9 30% | +rat S9 10% | +rat S9 30% |
|---|---|---|---|---|---|---|---|
| TA98 | 0 | 24 ± 3.5 | 16 ± 1.5 | 24 ± 2.6 | 40 ± 1.5 | 31 ± 1.3 | 32 ± 0.6 |
| | 100 | 22 ± 3.9 | 15 ± 0.3 | 22 ± 1.0 | 28 ± 2.7 | 26 ± 1.2 | 30 ± 1.8 |
| | 333 | 22 ± 1.5 | 28 ± 1.8 | 20 ± 0.9 | 32 ± 3.3 | 25 ± 3.5 | 31 ± 2.9 |
| | 1,000 | 20 ± 1.7 | 29 ± 4.4 | 23 ± 2.6 | 42 ± 7.9 | 30 ± 1.2 | 21 ± 2.1 |
| | 3,333 | 15 ± 1.8[c] | 20 ± 2.3[c] | 29 ± 1.9[c] | 32 ± 3.1[c] | 23 ± 1.8[c] | 27 ± 0.7[c] |
| | 10,000 | 8 ± 3.5 | 15 ± 0.7[c] | 27 ± 3.5[c] | 27 ± 4.5[c] | 24 ± 2.7[c] | 23 ± 4.7[c] |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 372 ± 12.5 | 521 ± 13.1 | 614 ± 29.2 | 495 ± 21.7 | 286 ± 10.7 | 104 ± 5.9 |

[a] Study performed at SRI, International. The detailed protocol and these data are presented in Zeiger *et al.* (1992); 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± standard error from three plates.

[c] Precipitate on plate

[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), 4-nitro-*o*-phenylenediamine (TA98), mitomycin C (TA102). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
**Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with Nickel Subsulfide by Inhalation for 13 Weeks[a]**

| | Dose ($mg/m^3$) | Micronucleated Normochromatic Erythrocytes/1,000 Cells[b] | Number of Mice |
|---|---|---|---|
| **Male** | | | |
| | 0 | 1.14 ± 0.15 | 10 |
| | 0.6 | 1.11 ± 0.18 | 10 |
| | 1.2 | 1.07 ± 0.13 | 10 |
| Trend test | | P=0.634[c] | |
| **Female** | | | |
| | 0 | 0.66 ± 0.14 | 8 |
| | 0.6 | 0.81 ± 0.14 | 10 |
| | 1.2 | 0.66 ± 0.14 | 10 |
| Trend test | | P=0.522 | |
| Urethane[d] | 0.2 | 16.76 ± 0.73 | 3 |
| Trend test | | P=0.000* | |

* P<0.001
[a] Slides scored at SRI, International. The detailed protocol is presented in MacGregor *et al.*. (1990); a minimum of 6,400 NCEs were scored per animal.
[b] Data presented as mean ± standard error. NCE = normochromatic erythrocyte.
[c] Significance of percent micronucleated NCE determined by a one-tailed trend test.
[d] Urethane was used as the positive control and is presented as parts per million.

# APPENDIX F
# ORGAN WEIGHTS
# AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ | 5 mg/m³ | 10 mg/m³ |
|---|---|---|---|---|---|---|
| n | 5 | 5 | 5 | 5 | 5 | 5 |
| **Male** | | | | | | |
| Necropsy body wt | 216 ± 13 | 236 ± 4 | 226 ± 6 | 198 ± 6 | 155 ± 8** | 113 ± 5** |
| Brain | | | | | | |
| Absolute | 1.767 ± 0.027 | 1.755 ± 0.021 | 1.802 ± 0.013 | 1.731 ± 0.024 | 1.679 ± 0.054*[b] | 1.657 ± 0.016** |
| Relative | 8.33 ± 0.59 | 7.45 ± 0.13 | 8.01 ± 0.22 | 8.78 ± 0.23 | 11.14 ± 0.85**[b] | 14.76 ± 0.51** |
| Heart | | | | | | |
| Absolute | 0.753 ± 0.028 | 0.802 ± 0.040 | 0.842 ± 0.044 | 0.750 ± 0.022 | 0.770 ± 0.035 | 0.644 ± 0.036 |
| Relative | 3.52 ± 0.11 | 3.41 ± 0.20 | 3.73 ± 0.18 | 3.80 ± 0.08 | 5.03 ± 0.40** | 5.75 ± 0.43** |
| R. Kidney | | | | | | |
| Absolute | 0.831 ± 0.107 | 0.929 ± 0.033 | 0.923 ± 0.040 | 0.849 ± 0.030 | 0.708 ± 0.052 | 0.611 ± 0.026* |
| Relative | 3.90 ± 0.51 | 3.94 ± 0.15 | 4.09 ± 0.14 | 4.30 ± 0.10 | 4.56 ± 0.18 | 5.46 ± 0.38** |
| Liver | | | | | | |
| Absolute | 11.711 ± 1.401 | 12.304 ± 0.722 | 12.872 ± 0.414[b] | 10.796 ± 0.312 | 7.699 ± 0.552** | 4.916 ± 0.472** |
| Relative | 53.45 ± 4.10 | 52.29 ± 3.48 | 56.28 ± 1.44[b] | 54.80 ± 2.23 | 49.49 ± 1.17 | 43.32 ± 3.11* |
| Lung | | | | | | |
| Absolute | 1.130 ± 0.052 | 1.406 ± 0.067 | 1.602 ± 0.244* | 1.593 ± 0.054* | 1.820 ± 0.120** | 1.536 ± 0.033** |
| Relative | 5.32 ± 0.42 | 5.97 ± 0.31 | 7.11 ± 1.05 | 8.06 ± 0.11** | 11.84 ± 0.86** | 13.68 ± 0.49** |
| Testes | | | | | | |
| Absolute | 1.253 ± 0.048[b] | 1.253 ± 0.017 | 1.323 ± 0.019 | 1.208 ± 0.032 | 1.166 ± 0.048 | 0.813 ± 0.029** |
| Relative | 6.05 ± 0.58[b] | 5.32 ± 0.12 | 5.88 ± 0.14 | 6.11 ± 0.05 | 7.54 ± 0.12** | 7.21 ± 0.13** |
| Thymus | | | | | | |
| Absolute | 0.315 ± 0.044 | 0.358 ± 0.023 | 0.383 ± 0.045 | 0.318 ± 0.023 | 0.184 ± 0.045* | 0.056 ± 0.007** |
| Relative | 1.43 ± 0.16 | 1.52 ± 0.11 | 1.69 ± 0.17 | 1.61 ± 0.12 | 1.15 ± 0.25 | 0.49 ± 0.04** |
| **Female** | | | | | | |
| Necropsy body wt | 151 ± 4 | 149 ± 4 | 147 ± 5 | 138 ± 1* | 117 ± 6** | 86 ± 1** |
| Brain | | | | | | |
| Absolute | 1.580 ± 0.042 | 1.659 ± 0.017 | 1.669 ± 0.040 | 1.625 ± 0.008 | 1.603 ± 0.016 | 1.546 ± 0.027 |
| Relative | 10.49 ± 0.29 | 11.14 ± 0.24 | 11.39 ± 0.26 | 11.82 ± 0.11* | 13.80 ± 0.59** | 18.08 ± 0.35** |
| Heart | | | | | | |
| Absolute | 0.549 ± 0.030 | 0.558 ± 0.009 | 0.555 ± 0.040 | 0.530 ± 0.012 | 0.569 ± 0.023 | 0.473 ± 0.014 |
| Relative | 3.63 ± 0.12 | 3.75 ± 0.12 | 3.77 ± 0.21 | 3.85 ± 0.06 | 4.87 ± 0.07** | 5.53 ± 0.17** |
| R. Kidney | | | | | | |
| Absolute | 0.573 ± 0.019 | 0.610 ± 0.015 | 0.614 ± 0.029 | 0.576 ± 0.014 | 0.511 ± 0.030 | 0.458 ± 0.019** |
| Relative | 3.80 ± 0.10 | 4.09 ± 0.06 | 4.18 ± 0.12* | 4.19 ± 0.09* | 4.37 ± 0.17** | 5.35 ± 0.17** |
| Liver | | | | | | |
| Absolute | 7.399 ± 0.508 | 7.005 ± 0.427 | 6.636 ± 0.408 | 6.587 ± 0.192 | 5.661 ± 0.585** | 3.682 ± 0.140** |
| Relative | 48.96 ± 2.82 | 46.76 ± 1.69 | 45.01 ± 1.27 | 47.92 ± 1.54 | 47.87 ± 2.51 | 42.99 ± 1.31 |
| Lung | | | | | | |
| Absolute | 0.821 ± 0.060 | 1.124 ± 0.056** | 1.115 ± 0.044** | 1.356 ± 0.047** | 1.422 ± 0.049** | 1.253 ± 0.050** |
| Relative | 5.43 ± 0.31 | 7.58 ± 0.54** | 7.62 ± 0.41** | 9.86 ± 0.33** | 12.26 ± 0.74** | 14.64 ± 0.54** |
| Thymus | | | | | | |
| Absolute | 0.272 ± 0.015[b] | 0.330 ± 0.024 | 0.290 ± 0.019 | 0.320 ± 0.036 | 0.243 ± 0.047 | 0.100 ± 0.013** |
| Relative | 1.80 ± 0.15[b] | 2.20 ± 0.11 | 1.97 ± 0.09 | 2.33 ± 0.26 | 2.02 ± 0.30 | 1.17 ± 0.15 |

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

TABLE F2
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 0.3 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 10 | 10 | 10 | 9 | 10 | 10 |
| Necropsy body wt | 352 ± 4 | 354 ± 5 | 339 ± 4 | 328 ± 6 | 344 ± 4 | 335 ± 11 |
| Brain | | | | | | |
| Absolute | 1.933 ± 0.008 | 1.909 ± 0.014 | 1.917 ± 0.016 | 1.906 ± 0.025 | 1.934 ± 0.016 | 1.958 ± 0.034 |
| Relative | 5.49 ± 0.06 | 5.40 ± 0.07 | 5.66 ± 0.08 | 5.82 ± 0.12 | 5.63 ± 0.03 | 5.90 ± 0.20* |
| Heart | | | | | | |
| Absolute | 1.040 ± 0.040 | 1.010 ± 0.051 | 1.030 ± 0.033 | 0.998 ± 0.034 | 0.949 ± 0.028 | 1.051 ± 0.044 |
| Relative | 2.95 ± 0.11 | 2.84 ± 0.11 | 3.04 ± 0.11 | 3.07 ± 0.13 | 2.76 ± 0.07 | 3.15 ± 0.11 |
| R. Kidney | | | | | | |
| Absolute | 1.156 ± 0.024 | 1.153 ± 0.023 | 1.110 ± 0.024 | 1.112 ± 0.019 | 1.122 ± 0.019 | 1.132 ± 0.036 |
| Relative | 3.28 ± 0.05 | 3.26 ± 0.06 | 3.28 ± 0.06 | 3.37 ± 0.07 | 3.27 ± 0.04 | 3.39 ± 0.06 |
| Liver | | | | | | |
| Absolute | 12.670 ± 0.240 | 12.830 ± 0.213 | 12.040 ± 0.225 | 11.430 ± 0.277** | 11.890 ± 0.159** | 11.580 ± 0.387** |
| Relative | 35.95 ± 0.41 | 36.27 ± 0.45 | 35.52 ± 0.43 | 35.01 ± 0.52 | 34.62 ± 0.41 | 34.69 ± 0.82 |
| Lung | | | | | | |
| Absolute | 1.330 ± 0.015 | 1.740 ± 0.052** | 1.830 ± 0.037** | 2.300 ± 0.067** | 2.630 ± 0.030** | 2.420 ± 0.068** |
| Relative | 3.78 ± 0.06 | 4.92 ± 0.12** | 5.40 ± 0.07** | 7.01 ± 0.29** | 7.66 ± 0.10** | 7.25 ± 0.11** |
| R. Testis | | | | | | |
| Absolute | 1.438 ± 0.035 | 1.478 ± 0.032 | 1.470 ± 0.023 | 1.385 ± 0.020 | 1.507 ± 0.018 | 1.477 ± 0.026 |
| Relative | 4.09 ± 0.11 | 4.18 ± 0.05 | 4.34 ± 0.07 | 4.22 ± 0.08 | 4.39 ± 0.04* | 4.45 ± 0.13** |
| Thymus | | | | | | |
| Absolute | 0.251 ± 0.013 | 0.225 ± 0.011 | 0.244 ± 0.013 | 0.232 ± 0.010 | 0.246 ± 0.015 | 0.215 ± 0.007 |
| Relative | 0.71 ± 0.03 | 0.64 ± 0.03 | 0.72 ± 0.04 | 0.71 ± 0.03 | 0.71 ± 0.04 | 0.64 ± 0.02 |
| **Female** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 202 ± 3 | 204 ± 4 | 205 ± 4 | 199 ± 2 | 196 ± 4 | 194 ± 2 |
| Brain | | | | | | |
| Absolute | 1.786 ± 0.020 | 1.785 ± 0.019 | 1.795 ± 0.018 | 1.797 ± 0.015 | 1.810 ± 0.014 | 1.817 ± 0.014 |
| Relative | 8.85 ± 0.09 | 8.76 ± 0.14 | 8.80 ± 0.20 | 9.02 ± 0.09 | 9.25 ± 0.14 | 9.41 ± 0.17* |
| Heart | | | | | | |
| Absolute | 0.673 ± 0.029 | 0.681 ± 0.023 | 0.662 ± 0.023 | 0.655 ± 0.021 | 0.650 ± 0.019 | 0.657 ± 0.016 |
| Relative | 3.33 ± 0.14 | 3.34 ± 0.11 | 3.24 ± 0.10 | 3.28 ± 0.09 | 3.32 ± 0.08 | 3.40 ± 0.08 |
| R. Kidney | | | | | | |
| Absolute | 0.678 ± 0.019 | 0.680 ± 0.015 | 0.704 ± 0.012 | 0.693 ± 0.019 | 0.683 ± 0.013 | 0.688 ± 0.012 |
| Relative | 3.36 ± 0.07 | 3.33 ± 0.06 | 3.44 ± 0.05 | 3.48 ± 0.09 | 3.48 ± 0.04 | 3.56 ± 0.06 |
| Liver | | | | | | |
| Absolute | 6.860 ± 0.189 | 7.020 ± 0.170 | 6.790 ± 0.188 | 6.610 ± 0.177 | 6.550 ± 0.177 | 6.300 ± 0.167* |
| Relative | 33.95 ± 0.67 | 34.41 ± 0.63 | 33.14 ± 0.58 | 33.12 ± 0.66 | 33.40 ± 0.73 | 32.57 ± 0.82 |
| Lung | | | | | | |
| Absolute | 1.010 ± 0.028 | 1.290 ± 0.023** | 1.390 ± 0.035** | 1.820 ± 0.044** | 1.850 ± 0.037** | 1.810 ± 0.038** |
| Relative | 5.01 ± 0.16 | 6.33 ± 0.12** | 6.80 ± 0.19** | 9.13 ± 0.22** | 9.44 ± 0.14** | 9.36 ± 0.20** |
| Thymus | | | | | | |
| Absolute | 0.218 ± 0.015 | 0.201 ± 0.010 | 0.199 ± 0.007 | 0.200 ± 0.008 | 0.192 ± 0.007 | 0.195 ± 0.009 |
| Relative | 1.08 ± 0.06 | 0.99 ± 0.06 | 0.97 ± 0.03 | 1.00 ± 0.04 | 0.98 ± 0.04 | 1.01 ± 0.05 |

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

TABLE F3
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 7-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Subsulfide**[a]

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| n | 5 | 5 | 5 |
| **Male** | | | |
| Necropsy body wt | 391 ± 9 | 397 ± 12 | 365 ± 6 |
| Brain | | | |
| Absolute | 2.066 ± 0.026 | 1.988 ± 0.032 | 1.994 ± 0.034 |
| Relative | 5.29 ± 0.09 | 5.02 ± 0.11 | 5.47 ± 0.07 |
| R. Kidney | | | |
| Absolute | 1.382 ± 0.032 | 1.298 ± 0.041 | 1.274 ± 0.029 |
| Relative | 3.54 ± 0.11 | 3.27 ± 0.02* | 3.49 ± 0.05 |
| Liver | | | |
| Absolute | 12.920 ± 0.454 | 13.584 ± 0.426 | 13.372 ± 0.692 |
| Relative | 33.00 ± 0.63 | 34.24 ± 0.32 | 36.60 ± 1.33* |
| Lung | | | |
| Absolute | 1.874 ± 0.078 | 2.376 ± 0.108** | 3.478 ± 0.050** |
| Relative | 4.79 ± 0.14 | 5.98 ± 0.18** | 9.55 ± 0.22** |
| Spleen | | | |
| Absolute | 0.776 ± 0.010 | 0.774 ± 0.018 | 0.776 ± 0.025 |
| Relative | 1.99 ± 0.03 | 1.96 ± 0.06 | 2.13 ± 0.05 |
| Thymus | | | |
| Absolute | 0.227 ± 0.006 | 0.257 ± 0.017 | 0.257 ± 0.008 |
| Relative | 0.58 ± 0.02 | 0.65 ± 0.04 | 0.71 ± 0.03* |
| **Female** | | | |
| Necropsy body wt | 221 ± 3 | 219 ± 11 | 218 ± 4 |
| Brain | | | |
| Absolute | 1.830 ± 0.011 | 1.854 ± 0.062 | 1.804 ± 0.043 |
| Relative | 8.28 ± 0.10 | 8.51 ± 0.33 | 8.27 ± 0.19 |
| R. Kidney | | | |
| Absolute | 0.788 ± 0.026 | 0.830 ± 0.032 | 0.830 ± 0.021 |
| Relative | 3.56 ± 0.10 | 3.81 ± 0.13 | 3.81 ± 0.14 |
| Liver | | | |
| Absolute | 8.004 ± 0.568 | 7.758 ± 0.338 | 7.544 ± 0.415 |
| Relative | 36.34 ± 3.11 | 35.47 ± 0.60 | 34.61 ± 2.00 |
| Lung | | | |
| Absolute | 1.314 ± 0.039 | 1.746 ± 0.078** | 2.586 ± 0.114** |
| Relative | 5.94 ± 0.16 | 8.01 ± 0.38** | 11.87 ± 0.59** |
| Spleen | | | |
| Absolute | 0.546 ± 0.036 | 0.494 ± 0.019 | 0.506 ± 0.033 |
| Relative | 2.48 ± 0.20 | 2.26 ± 0.07 | 2.32 ± 0.15 |
| Thymus | | | |
| Absolute | 0.199 ± 0.012 | 0.199 ± 0.024 | 0.184 ± 0.014 |
| Relative | 0.90 ± 0.04 | 0.91 ± 0.09 | 0.84 ± 0.05 |

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

TABLE F4
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| n | 5 | 5 | 5 |
| **Male** | | | |
| Necropsy body wt | 469 ± 15 | 462 ± 8 | 443 ± 9 |
| Brain | | | |
| Absolute | 2.076 ± 0.030 | 2.092 ± 0.018 | 2.074 ± 0.020 |
| Relative | 4.45 ± 0.12 | 4.53 ± 0.07 | 4.69 ± 0.11 |
| R. Kidney | | | |
| Absolute | 1.634 ± 0.075 | 1.634 ± 0.071 | 1.590 ± 0.081 |
| Relative | 3.49 ± 0.14 | 3.53 ± 0.12 | 3.59 ± 0.18 |
| Liver | | | |
| Absolute | 18.116 ± 1.674 | 17.036 ± 1.289 | 16.300 ± 0.501 |
| Relative | 38.58 ± 3.12 | 36.75 ± 2.33 | 36.83 ± 1.15 |
| Lung | | | |
| Absolute | 2.268 ± 0.090 | 3.308 ± 0.219** | 6.838 ± 0.697** |
| Relative | 4.84 ± 0.13 | 7.14 ± 0.39 | 15.47 ± 1.65** |
| Spleen | | | |
| Absolute | 0.992 ± 0.059 | 0.892 ± 0.024 | 1.284 ± 0.409 |
| Relative | 2.12 ± 0.09 | 1.93 ± 0.05 | 2.92 ± 0.95 |
| Thymus | | | |
| Absolute | 0.266 ± 0.027 | 0.259 ± 0.037 | 0.246 ± 0.024 |
| Relative | 0.57 ± 0.07 | 0.56 ± 0.09 | 0.56 ± 0.06 |
| **Female** | | | |
| Necropsy body wt | 300 ± 4 | 299 ± 12 | 268 ± 11 |
| Brain | | | |
| Absolute | 1.890 ± 0.017 | 1.842 ± 0.033 | 1.860 ± 0.040 |
| Relative | 6.30 ± 0.04 | 6.20 ± 0.20 | 6.99 ± 0.32 |
| R. Kidney | | | |
| Absolute | 0.946 ± 0.034 | 1.018 ± 0.069 | 1.022 ± 0.043 |
| Relative | 3.15 ± 0.11 | 3.41 ± 0.15 | 3.84 ± 0.19* |
| Liver | | | |
| Absolute | 9.496 ± 0.288 | 10.212 ± 0.813 | 9.172 ± 0.435 |
| Relative | 31.60 ± 0.59 | 34.04 ± 1.43 | 34.27 ± 0.96 |
| Lung | | | |
| Absolute | 1.524 ± 0.106 | 2.516 ± 0.252** | 4.140 ± 0.105** |
| Relative | 5.06 ± 0.28 | 8.43 ± 0.80** | 15.54 ± 0.30** |
| Spleen | | | |
| Absolute | 0.596 ± 0.023 | 0.592 ± 0.037 | 0.572 ± 0.034 |
| Relative | 1.98 ± 0.06 | 1.99 ± 0.13 | 2.16 ± 0.18 |
| Thymus | | | |
| Absolute | 0.243 ± 0.026 | 0.250 ± 0.047 | 0.218 ± 0.018 |
| Relative | 0.81 ± 0.09 | 0.84 ± 0.15 | 0.82 ± 0.08 |

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

**TABLE F5**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ | 5 mg/m³ | 10 mg/m³ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 5 | 5 | 5 | 5 | 5 | 5 |
| Necropsy body wt | 23.6 ± 1.7 | 25.0 ± 0.4 | 22.8 ± 1.8 | 23.4 ± 0.5 | 21.8 ± 0.5 | 16.7 ± 0.4**[b] |
| Brain | | | | | | |
| Absolute | 0.435 ± 0.023 | 0.442 ± 0.004 | 0.454 ± 0.009 | 0.431 ± 0.010 | 0.424 ± 0.007 | 0.385 ± 0.023* |
| Relative | 18.60 ± 0.55 | 17.72 ± 0.36 | 20.35 ± 1.55 | 18.47 ± 0.34 | 19.47 ± 0.66 | 23.17 ± 1.86* |
| Heart | | | | | | |
| Absolute | 0.129 ± 0.006 | 0.150 ± 0.013 | 0.147 ± 0.022 | 0.159 ± 0.011 | 0.135 ± 0.011 | 0.162 ± 0.013 |
| Relative | 5.56 ± 0.41 | 6.00 ± 0.46 | 6.54 ± 0.92 | 6.83 ± 0.54 | 6.15 ± 0.44 | 9.70 ± 0.92** |
| R. Kidney | | | | | | |
| Absolute | 0.224 ± 0.016 | 0.233 ± 0.007 | 0.207 ± 0.020 | 0.227 ± 0.007 | 0.193 ± 0.004 | 0.169 ± 0.014** |
| Relative | 9.56 ± 0.33 | 9.33 ± 0.24 | 9.00 ± 0.23 | 9.72 ± 0.25 | 8.85 ± 0.06 | 10.12 ± 0.80 |
| Liver | | | | | | |
| Absolute | 1.478 ± 0.186 | 1.624 ± 0.017 | 1.346 ± 0.201 | 1.485 ± 0.041 | 1.246 ± 0.036 | 0.886 ± 0.100** |
| Relative | 61.42 ± 4.48 | 65.02 ± 0.64 | 57.33 ± 5.73 | 63.54 ± 0.80 | 57.11 ± 0.82 | 53.03 ± 6.03 |
| Lung | | | | | | |
| Absolute | 0.215 ± 0.015 | 0.202 ± 0.016 | 0.22 ± 0.151 | 0.278 ± 0.013 | 0.305 ± 0.022** | 0.380 ± 0.036** |
| Relative | 9.40 ± 1.11 | 8.09 ± 0.56 | 15.90 ± 6.12 | 11.96 ± 0.70 | 13.94 ± 0.80 | 22.78 ± 2.29** |
| Testes | | | | | | |
| Absolute | 0.096 ± 0.008 | 0.095 ± 0.006 | 0.099 ± 0.009 | 0.103 ± 0.002 | 0.100 ± 0.003 | 0.079 ± 0.025 |
| Relative | 4.04 ± 0.09 | 3.80 ± 0.21 | 4.33 ± 0.22 | 4.42 ± 0.11 | 4.61 ± 0.17 | 4.63 ± 1.37 |
| Thymus | | | | | | |
| Absolute | 0.042 ± 0.008 | 0.048 ± 0.004 | 0.045 ± 0.009 | 0.046 ± 0.005 | 0.033 ± 0.002 | 0.013 ± 0.005** |
| Relative | 1.71 ± 0.29 | 1.91 ± 0.18 | 1.89 ± 0.32 | 1.97 ± 0.23 | 1.52 ± 0.08 | 0.76 ± 0.29* |
| **Female** | | | | | | |
| n | 5 | 5 | 5 | 5 | 5 | 4 |
| Necropsy body wt | 20.3 ± 2.0 | 21.6 ± 0.2 | 21.1 ± 0.4 | 20.6 ± 0.3 | 20.1 ± 0.6 | 13.5 ± 0.8**[b] |
| Brain | | | | | | |
| Absolute | 0.433 ± 0.014 | 0.438 ± 0.004 | 0.450 ± 0.006 | 0.437 ± 0.007 | 0.434 ± 0.001 | 0.408 ± 0.014 |
| Relative | 22.05 ± 2.07 | 20.31 ± 0.18 | 21.36 ± 0.43 | 21.22 ± 0.60 | 21.62 ± 0.58 | 30.55 ± 1.44** |
| Heart | | | | | | |
| Absolute | 0.117 ± 0.015 | 0.140 ± 0.014 | 0.122 ± 0.007 | 0.118 ± 0.005 | 0.117 ± 0.005 | 0.124 ± 0.014 |
| Relative | 5.81 ± 0.50 | 6.47 ± 0.67 | 5.80 ± 0.34 | 5.71 ± 0.23 | 5.84 ± 0.28 | 9.32 ± 1.26** |
| R. Kidney | | | | | | |
| Absolute | 0.160 ± 0.011 | 0.165 ± 0.004 | 0.159 ± 0.005 | 0.156 ± 0.006 | 0.154 ± 0.008 | 0.114 ± 0.003** |
| Relative | 8.00 ± 0.33 | 7.66 ± 0.19 | 7.55 ± 0.14 | 7.56 ± 0.21 | 7.65 ± 0.35 | 8.57 ± 0.48 |
| Liver | | | | | | |
| Absolute | 1.322 ± 0.212 | 1.473 ± 0.027 | 1.429 ± 0.073 | 1.334 ± 0.040 | 1.201 ± 0.048 | 0.732 ± 0.075** |
| Relative | 62.81 ± 5.88 | 68.26 ± 1.41 | 67.54 ± 2.12 | 64.67 ± 1.05 | 59.72 ± 1.79 | 54.03 ± 2.67 |
| Lung | | | | | | |
| Absolute | 0.203 ± 0.014 | 0.206 ± 0.009 | 0.215 ± 0.008 | 0.271 ± 0.010 | 0.356 ± 0.048* | 0.252 ± 0.045 |
| Relative | 10.18 ± 0.62 | 9.52 ± 0.42 | 10.17 ± 0.30 | 13.14 ± 0.50 | 17.60 ± 2.02** | 18.77 ± 3.32** |
| Thymus | | | | | | |
| Absolute | 0.045 ± 0.011 | 0.062 ± 0.005 | 0.065 ± 0.003 | 0.063 ± 0.003 | 0.058 ± 0.006 | 0.012 ± 0.003** |
| Relative | 2.13 ± 0.43 | 2.86 ± 0.22 | 3.10 ± 0.16 | 3.07 ± 0.13 | 2.87 ± 0.29 | 0.86 ± 0.15* |

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] All animals in this exposure group died early.

TABLE F6
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 0.3 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 8 | 10 | 10 | 8 | 9 | 10 |
| Necropsy body wt | 28.8 ± 0.8 | 29.6 ± 0.5 | 31.0 ± 0.7 | 28.9 ± 0.4 | 28.8 ± 0.8 | 27.1 ± 0.4 |
| Brain | | | | | | |
| Absolute | 0.451 ± 0.007 | 0.450 ± 0.004 | 0.455 ± 0.006 | 0.465 ± 0.005 | 0.462 ± 0.004 | 0.455 ± 0.007 |
| Relative | 15.80 ± 0.59 | 15.26 ± 0.22 | 14.72 ± 0.28 | 16.13 ± 0.25 | 16.15 ± 0.49 | 16.85 ± 0.49 |
| Heart | | | | | | |
| Absolute | 0.158 ± 0.009 | 0.151 ± 0.006 | 0.168 ± 0.006 | 0.155 ± 0.007 | 0.159 ± 0.007 | 0.146 ± 0.006 |
| Relative | 5.48 ± 0.28 | 5.11 ± 0.17 | 5.42 ± 0.17 | 5.36 ± 0.22 | 5.52 ± 0.18 | 5.40 ± 0.23 |
| R. Kidney | | | | | | |
| Absolute | 0.286 ± 0.008 | 0.275 ± 0.011 | 0.303 ± 0.011 | 0.273 ± 0.009 | 0.270 ± 0.014 | 0.256 ± 0.007 |
| Relative | 9.97 ± 0.21 | 9.28 ± 0.25 | 9.75 ± 0.17 | 9.44 ± 0.27 | 9.33 ± 0.27 | 9.45 ± 0.25 |
| Liver | | | | | | |
| Absolute | 1.525 ± 0.080 | 1.570 ± 0.058 | 1.780 ± 0.077* | 1.600 ± 0.038 | 1.567 ± 0.055 | 1.300 ± 0.033* |
| Relative | 52.85 ± 1.72 | 53.11 ± 1.65 | 57.19 ± 1.49 | 55.40 ± 0.68 | 54.33 ± 0.82 | 48.06 ± 1.37 |
| Lung | | | | | | |
| Absolute | 0.188 ± 0.013 | 0.200 ± 0.000 | 0.220 ± 0.020 | 0.213 ± 0.013 | 0.233 ± 0.017* | 0.280 ± 0.013** |
| Relative | 6.53 ± 0.44 | 6.78 ± 0.11 | 7.10 ± 0.61 | 7.37 ± 0.45 | 8.20 ± 0.72* | 10.39 ± 0.58** |
| R. Testis | | | | | | |
| Absolute | 0.110 ± 0.003 | 0.107 ± 0.005 | 0.121 ± 0.002 | 0.113 ± 0.006 | 0.120 ± 0.003 | 0.121 ± 0.008 |
| Relative | 3.83 ± 0.08 | 3.62 ± 0.18 | 3.93 ± 0.14 | 3.90 ± 0.20 | 4.19 ± 0.15 | 4.50 ± 0.34* |
| Thymus | | | | | | |
| Absolute | 0.031 ± 0.002 | 0.034 ± 0.004 | 0.037 ± 0.001 | 0.042 ± 0.004 | 0.043 ± 0.005 | 0.035 ± 0.003 |
| Relative | 1.08 ± 0.05 | 1.17 ± 0.14 | 1.21 ± 0.06 | 1.45 ± 0.13 | 1.52 ± 0.22 | 1.28 ± 0.11 |

**TABLE F6**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 0.3 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|---|---|
| **Female** | | | | | | |
| n | 9 | 8 | 10 | 9 | 10 | 8 |
| Necropsy body wt | 24.1 ± 0.8 | 24.5 ± 0.4 | 25.0 ± 0.7 | 23.9 ± 0.4 | 24.1 ± 0.3 | 22.7 ± 0.5 |
| Brain | | | | | | |
| Absolute | 0.455 ± 0.007 | 0.465 ± 0.005 | 0.465 ± 0.005 | 0.463 ± 0.008 | 0.456 ± 0.005[b] | 0.455 ± 0.005 |
| Relative | 19.05 ± 0.89 | 19.01 ± 0.25 | 18.73 ± 0.54 | 19.39 ± 0.45 | 19.00 ± 0.17[b] | 20.08 ± 0.54 |
| Heart | | | | | | |
| Absolute | 0.128 ± 0.003 | 0.135 ± 0.007 | 0.137 ± 0.007 | 0.136 ± 0.009 | 0.134 ± 0.010 | 0.134 ± 0.007 |
| Relative | 5.38 ± 0.15 | 5.52 ± 0.27 | 5.50 ± 0.27 | 5.70 ± 0.44 | 5.53 ± 0.33 | 5.90 ± 0.32 |
| R. Kidney | | | | | | |
| Absolute | 0.187 ± 0.008 | 0.194 ± 0.007 | 0.185 ± 0.005 | 0.180 ± 0.005 | 0.176 ± 0.005 | 0.176 ± 0.005 |
| Relative | 7.66 ± 0.20 | 7.90 ± 0.19 | 7.45 ± 0.31 | 7.52 ± 0.15 | 7.30 ± 0.18 | 7.75 ± 0.17 |
| Liver | | | | | | |
| Absolute | 1.360 ± 0.070 | 1.350 ± 0.019 | 1.580 ± 0.096 | 1.289 ± 0.045 | 1.280 ± 0.039 | 1.213 ± 0.055 |
| Relative | 56.02 ± 1.94 | 55.22 ± 1.11 | 63.67 ± 4.21 | 53.82 ± 1.54 | 53.10 ± 1.29 | 53.18 ± 1.63 |
| Lung | | | | | | |
| Absolute | 0.190 ± 0.010 | 0.175 ± 0.016 | 0.200 ± 0.000 | 0.211 ± 0.011 | 0.260 ± 0.022** | 0.288 ± 0.013** |
| Relative | 7.98 ± 0.63 | 7.14 ± 0.66 | 8.06 ± 0.23 | 8.84 ± 0.48 | 10.74 ± 0.87** | 12.62 ± 0.43** |
| Thymus | | | | | | |
| Absolute | 0.039 ± 0.004 | 0.042 ± 0.004 | 0.044 ± 0.003 | 0.038 ± 0.002 | 0.038 ± 0.003 | 0.038 ± 0.003 |
| Relative | 1.59 ± 0.15 | 1.70 ± 0.14 | 1.77 ± 0.11 | 1.59 ± 0.10 | 1.58 ± 0.11 | 1.66 ± 0.14 |

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F7
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 7-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| n | 5 | 5 | 5 |
| **Male** | | | |
| Necropsy body wt | 36.6 ± 0.6 | 35.6 ± 1.0 | 34.4 ± 0.5 |
| Brain | | | |
| Absolute | 0.478 ± 0.004 | 0.472 ± 0.002 | 0.472 ± 0.002 |
| Relative | 13.08 ± 0.26 | 13.31 ± 0.35 | 13.72 ± 0.20 |
| R. Kidney | | | |
| Absolute | 0.386 ± 0.009 | 0.366 ± 0.016 | 0.388 ± 0.012 |
| Relative | 10.56 ± 0.31 | 10.30 ± 0.40 | 11.28 ± 0.44 |
| Liver | | | |
| Absolute | 1.786 ± 0.111 | 1.798 ± 0.040 | 1.650 ± 0.045 |
| Relative | 48.78 ± 2.88 | 50.60 ± 0.66 | 47.98 ± 1.77 |
| Lung | | | |
| Absolute | 0.240 ± 0.022 | 0.274 ± 0.013 | 0.342 ± 0.022** |
| Relative | 6.57 ± 0.62 | 7.71 ± 0.33 | 9.92 ± 0.57** |
| Spleen | | | |
| Absolute | 0.086 ± 0.002 | 0.082 ± 0.004 | 0.078 ± 0.004 |
| Relative | 2.35 ± 0.06 | 2.30 ± 0.07 | 2.27 ± 0.12 |
| Thymus | | | |
| Absolute | 0.034 ± 0.003 | 0.034 ± 0.003 | 0.037 ± 0.003 |
| Relative | 0.92 ± 0.09 | 0.97 ± 0.12 | 1.08 ± 0.09 |
| **Female** | | | |
| Necropsy body wt | 29.8 ± 1.2 | 30.8 ± 1.5 | 29.9 ± 0.6 |
| Brain | | | |
| Absolute | 0.486 ± 0.008 | 0.480 ± 0.007 | 0.476 ± 0.002 |
| Relative | 16.43 ± 0.63 | 15.75 ± 0.81 | 15.96 ± 0.35 |
| R. Kidney | | | |
| Absolute | 0.224 ± 0.009 | 0.248 ± 0.013 | 0.236 ± 0.011 |
| Relative | 7.55 ± 0.27 | 8.16 ± 0.70 | 7.90 ± 0.34 |
| Liver | | | |
| Absolute | 1.456 ± 0.067 | 1.478 ± 0.009 | 1.500 ± 0.053 |
| Relative | 48.95 ± 1.28 | 48.42 ± 2.17 | 50.16 ± 1.15 |
| Lung | | | |
| Absolute | 0.186 ± 0.011 | 0.256 ± 0.011* | 0.288 ± 0.025** |
| Relative | 6.25 ± 0.23 | 8.37 ± 0.44* | 9.62 ± 0.74** |
| Spleen | | | |
| Absolute | 0.102 ± 0.007 | 0.100 ± 0.003 | 0.100 ± 0.008 |
| Relative | 3.43 ± 0.18 | 3.27 ± 0.14 | 3.33 ± 0.23 |
| Thymus | | | |
| Absolute | 0.040 ± 0.005 | 0.036 ± 0.006 | 0.036 ± 0.004 |
| Relative | 1.31 ± 0.14 | 1.16 ± 0.17 | 1.20 ± 0.10 |

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

TABLE F8
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| n | 5 | 5 | 5 |
| **Male** | | | |
| Necropsy body wt | 39.5 ± 0.7 | 39.2 ± 0.7 | 39.1 ± 1.9 |
| Brain | | | |
| Absolute | 0.474 ± 0.010 | 0.468 ± 0.006 | 0.458 ± 0.005 |
| Relative | 12.02 ± 0.31 | 11.95 ± 0.25 | 11.84 ± 0.69 |
| R. Kidney | | | |
| Absolute | 0.398 ± 0.021 | 0.410 ± 0.009 | 0.410 ± 0.009 |
| Relative | 10.10 ± 0.57 | 10.48 ± 0.38 | 10.58 ± 0.56 |
| Liver | | | |
| Absolute | 1.892 ± 0.087 | 1.948 ± 0.051 | 2.198 ± 0.273 |
| Relative | 48.10 ± 2.90 | 49.82 ± 2.02 | 56.07 ± 5.65 |
| Lung | | | |
| Absolute | 0.232 ± 0.009 | 0.402 ± 0.020** | 0.408 ± 0.048** |
| Relative | 5.90 ± 0.31 | 10.27 ± 0.58** | 10.39 ± 1.13** |
| Spleen | | | |
| Absolute | 0.074 ± 0.004 | 0.084 ± 0.005 | 0.084 ± 0.007 |
| Relative | 1.88 ± 0.10 | 2.15 ± 0.17 | 2.14 ± 0.12 |
| Thymus | | | |
| Absolute | 0.037 ± 0.004 | 0.040 ± 0.005 | 0.041 ± 0.005 |
| Relative | 0.93 ± 0.11 | 1.00 ± 0.12 | 1.03 ± 0.09 |
| **Female** | | | |
| Necropsy body wt | 37.4 ± 2.1 | 34.7 ± 1.8 | 33.5 ± 1.5 |
| Brain | | | |
| Absolute | 0.490 ± 0.004 | 0.500 ± 0.009 | 0.494 ± 0.005 |
| Relative | 13.25 ± 0.77 | 14.50 ± 0.52 | 14.86 ± 0.55 |
| R. Kidney | | | |
| Absolute | 0.252 ± 0.007 | 0.260 ± 0.008 | 0.248 ± 0.013 |
| Relative | 6.81 ± 0.42 | 7.53 ± 0.23 | 7.41 ± 0.21 |
| Liver | | | |
| Absolute | 1.906 ± 0.070 | 1.836 ± 0.140 | 1.644 ± 0.106 |
| Relative | 51.42 ± 2.92 | 52.73 ± 2.21 | 49.02 ± 1.71 |
| Lung | | | |
| Absolute | 0.256 ± 0.021 | 0.390 ± 0.025** | 0.496 ± 0.023** |
| Relative | 6.94 ± 0.69 | 11.49 ± 1.33** | 14.85 ± 0.55** |
| Spleen | | | |
| Absolute | 0.136 ± 0.012 | 0.114 ± 0.006 | 0.118 ± 0.006 |
| Relative | 3.66 ± 0.35 | 3.28 ± 0.06 | 3.54 ± 0.16 |
| Thymus | | | |
| Absolute | 0.053 ± 0.006 | 0.047 ± 0.002 | 0.045 ± 0.004 |
| Relative | 1.41 ± 0.14 | 1.35 ± 0.05 | 1.33 ± 0.10 |

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

# APPENDIX G
# HEMATOLOGY RESULTS

TABLE G1
**Hematology Data for Rats in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 0.3 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ | 2.5 mg/m$^3$ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 10 | 10 | 9 | 10 | 10 | 8 |
| Hematocrit (%) | 42.9 ± 0.3 | 43.4 ± 0.6 | 43.2 ± 0.6 | 43.7 ± 0.7 | 43.7 ± 0.3 | 45.1 ± 0.4** |
| Hemoglobin (g/dL) | 15.5 ± 0.2 | 15.7 ± 0.2 | 15.6 ± 0.2 | 15.9 ± 0.4 | 16.2 ± 0.1** | 16.7 ± 0.2** |
| Erythrocytes ($10^6/\mu L$) | 8.20 ± 0.07 | 8.34 ± 0.11 | 8.24 ± 0.09 | 8.34 ± 0.22 | 8.55 ± 0.05** | 8.73 ± 0.14** |
| Mean cell volume (fL) | 51.7 ± 0.3 | 51.4 ± 0.3 | 51.9 ± 0.4 | 52.1 ± 1.0 | 50.6 ± 0.2** | 51.1 ± 0.9* |
| Mean cell hemoglobin concentration (g/dL) | 36.1 ± 0.3 | 36.2 ± 0.2 | 36.2 ± 0.3 | 36.4 ± 0.4 | 37.0 ± 0.2* | 37.1 ± 0.2** |
| Reticulocytes ($10^6/\mu L$) | 0.7 ± 0.1 | 0.7 ± 0.1 | 0.6 ± 0.1 | 0.8 ± 0.2 | 0.8 ± 0.1 | 0.7 ± 0.1 |
| Leukocytes ($10^3/\mu L$) | 2.19 ± 0.18 | 2.85 ± 0.26 | 2.79 ± 0.23 | 3.04 ± 0.37 | 2.93 ± 0.41 | 3.58 ± 0.47* |
| Segmented neutrophils ($10^3/\mu L$) | 0.63 ± 0.06 | 1.16 ± 0.10** | 1.06 ± 0.09** | 1.19 ± 0.14** | 1.08 ± 0.14** | 1.82 ± 0.33** |
| Lymphocytes ($10^3/\mu L$) | 1.50 ± 0.15 | 1.62 ± 0.19 | 1.63 ± 0.15 | 1.82 ± 0.26 | 1.80 ± 0.26 | 1.69 ± 0.17 |
| Monocytes ($10^3/\mu L$) | 0.03 ± 0.01 | 0.05 ± 0.02 | 0.05 ± 0.01 | 0.02 ± 0.01 | 0.04 ± 0.02 | 0.05 ± 0.02 |
| Eosinophils ($10^3/\mu L$) | 0.03 ± 0.01 | 0.02 ± 0.01 | 0.03 ± 0.01 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.02 ± 0.01 |
| Nucleated erythrocytes ($10^3/\mu L$) | 0.06 ± 0.02 | 0.10 ± 0.03 | 0.08 ± 0.02 | 0.09 ± 0.03 | 0.11 ± 0.03 | 0.15 ± 0.06 |

TABLE G1
**Hematology Data for Rats in the 13-Week Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m³ | 0.15 mg/m³ | 0.3 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|---|---|
| **Female** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Hematocrit (%) | 40.8 ± 0.5 | 41.0 ± 0.3 | 41.4 ± 0.5 | 41.3 ± 0.5 | 41.7 ± 0.4 | 42.3 ± 0.4* |
| Hemoglobin (g/dL) | 14.8 ± 0.2 | 14.9 ± 0.1 | 15.2 ± 0.2 | 15.1 ± 0.2 | 15.4 ± 0.2* | 15.8 ± 0.1** |
| Erythrocytes ($10^6/\mu L$) | 7.27 ± 0.08 | 7.38 ± 0.06 | 7.51 ± 0.10** | 7.49 ± 0.12** | 7.63 ± 0.06** | 7.79 ± 0.06** |
| Mean cell volume (fL) | 55.6 ± 0.2 | 55.0 ± 0.2 | 54.6 ± 0.2** | 54.7 ± 0.4* | 54.2 ± 0.3** | 53.8 ± 0.3** |
| Mean cell hemoglobin concentration (g/dL) | 36.3 ± 0.2 | 36.3 ± 0.2 | 36.6 ± 0.2 | 36.5 ± 0.3 | 37.0 ± 0.3* | 37.2 ± 0.3* |
| Reticulocytes ($10^6/\mu L$) | 0.6 ± 0.1 | 0.5 ± 0.1 | 0.7 ± 0.1 | 0.7 ± 0.1 | 0.5 ± 0.0 | 0.6 ± 0.1 |
| Leukocytes ($10^3/\mu L$) | 2.06 ± 0.22 | 2.72 ± 0.33 | 2.30 ± 0.21 | 2.21 ± 0.10 | 2.24 ± 0.18 | 2.66 ± 0.32 |
| Segmented neutrophils ($10^3/\mu L$) | 0.44 ± 0.11 | 0.82 ± 0.12** | 0.62 ± 0.09* | 0.67 ± 0.06* | 0.84 ± 0.08** | 1.01 ± 0.11** |
| Lymphocytes ($10^3/\mu L$) | 1.55 ± 0.17 | 1.85 ± 0.23 | 1.63 ± 0.14 | 1.48 ± 0.06 | 1.35 ± 0.11 | 1.59 ± 0.23 |
| Monocytes ($10^3/\mu L$) | 0.03 ± 0.01 | 0.02 ± 0.01 | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.02 ± 0.01 | 0.04 ± 0.01 |
| Eosinophils ($10^3/\mu L$) | 0.04 ± 0.01 | 0.03 ± 0.01 | 0.02 ± 0.01 | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.03 ± 0.01 |
| Nucleated erythrocytes ($10^3/\mu L$) | 0.05 ± 0.01 | 0.09 ± 0.02 | 0.13 ± 0.04 | 0.07 ± 0.03 | 0.19 ± 0.03** | 0.14 ± 0.03** |

* Significantly different ($P \leq 0.05$) from the 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 G2
**Hematology Data for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Subsulfide**[a]

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|
| n | 5 | 5 | 5 |
| **Male** | | | |
| Hematocrit (%) | 51.3 ± 0.7 | 52.8 ± 0.6 | 56.1 ± 0.8** |
| Hemoglobin (g/dL) | 15.9 ± 0.1 | 16.5 ± 0.2 | 17.5 ± 0.4** |
| Erythrocytes ($10^6/\mu L$) | 10.06 ± 0.18 | 10.42 ± 0.08 | 10.80 ± 0.19** |
| Mean cell volume (fL) | 53.6 ± 0.5 | 53.2 ± 0.4 | 54.6 ± 0.5 |
| Mean cell hemoglobin (pg) | 15.9 ± 0.2 | 15.8 ± 0.1 | 16.2 ± 0.1 |
| Mean cell hemoglobin concentration (g/dL) | 31.1 ± 0.3 | 31.2 ± 0.2 | 31.1 ± 0.4 |
| Reticulocytes ($10^6/\mu L$) | 0.3 ± 0.0 | 0.2 ± 0.0 | 0.3 ± 0.1 |
| Leukocytes ($10^3/\mu L$) | 5.68 ± 0.15 | 6.40 ± 0.46 | 7.60 ± 1.53 |
| Segmented neutrophils ($10^3/\mu L$) | 1.10 ± 0.13 | 1.86 ± 0.29 | 1.58 ± 0.27 |
| Lymphocytes ($10^3/\mu L$) | 4.32 ± 0.26 | 4.32 ± 0.38 | 5.30 ± 0.85 |
| Monocytes ($10^3/\mu L$) | 0.24 ± 0.05 | 0.18 ± 0.05 | 0.64 ± 0.49 |
| Eosinophils ($10^3/\mu L$) | 0.06 ± 0.02 | 0.06 ± 0.02 | 0.08 ± 0.04 |
| **Female** | | | |
| Hematocrit (%) | 48.9 ± 0.5 | 48.6 ± 0.8 | 51.8 ± 0.7* |
| Hemoglobin (g/dL) | 15.6 ± 0.1 | 15.4 ± 0.2 | 16.4 ± 0.2* |
| Erythrocytes ($10^6/\mu L$) | 8.86 ± 0.10 | 8.84 ± 0.14 | 9.20 ± 0.10 |
| Mean cell volume (fL) | 57.8 ± 0.4 | 57.4 ± 0.4 | 59.0 ± 0.6 |
| Mean cell hemoglobin (pg) | 17.6 ± 0.2 | 17.5 ± 0.1 | 17.9 ± 0.2 |
| Mean cell hemoglobin concentration (g/dL) | 31.9 ± 0.2 | 31.8 ± 0.1 | 31.8 ± 0.1 |
| Reticulocytes ($10^6/\mu L$) | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.1 ± 0.0 |
| Leukocytes ($10^3/\mu L$) | 5.44 ± 0.73 | 5.24 ± 0.58 | 4.64 ± 0.53 |
| Segmented neutrophils ($10^3/\mu L$) | 1.04 ± 0.19 | 1.80 ± 0.64 | 1.14 ± 0.19 |
| Lymphocytes ($10^3/\mu L$) | 4.18 ± 0.53 | 3.16 ± 0.16 | 3.32 ± 0.37 |
| Monocytes ($10^3/\mu L$) | 0.16 ± 0.05 | 0.22 ± 0.05 | 0.12 ± 0.02 |
| Eosinophils ($10^3/\mu L$) | 0.04 ± 0.02 | 0.06 ± 0.04 | 0.04 ± 0.02 |

* Significantly different ($P \leq 0.05$) from the 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 G3
**Hematology Data for Mice in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 0.3 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 4 | 4 | 5 | 3 | 5 | 5 |
| Hematocrit (%) | 39.5 ± 1.7 | 35.5 ± 7.4 | 40.6 ± 1.4 | 41.2 ± 0.4 | 41.4 ± 1.0 | 42.2 ± 1.9 |
| Hemoglobin (g/dL) | 13.7 ± 0.7 | 12.3 ± 2.5 | 14.3 ± 0.4 | 14.3 ± 0.1 | 14.5 ± 0.4 | 14.3 ± 0.5 |
| Erythrocytes ($10^6/\mu L$) | 7.79 ± 0.35 | 6.92 ± 1.41 | 8.09 ± 0.34 | 8.17 ± 0.08 | 8.18 ± 0.17 | 8.50 ± 0.38 |
| Mean cell volume (fL) | 50.0 ± 0.4 | 50.0 ± 0.8 | 49.6 ± 0.7 | 49.7 ± 0.3 | 50.0 ± 0.3 | 49.0 ± 0.0 |
| Mean cell hemoglobin concentration (g/dL) | 34.6 ± 0.5 | 34.7 ± 0.4 | 35.2 ± 0.4 | 34.8 ± 0.3 | 35.1 ± 0.1 | 34.1 ± 1.2 |
| Reticulocytes ($10^6/\mu L$) | 0.5 ± 0.1 | 0.4 ± 0.1 | 0.7 ± 0.2 | 0.6 ± 0.0 | 0.6 ± 0.1 | 0.7 ± 0.1 |
| Leukocytes ($10^3/\mu L$) | 0.50 ± 0.11 | 0.43 ± 0.23 | 1.18 ± 0.18 | 0.77 ± 0.17 | 1.66 ± 0.22 | 1.02 ± 0.22 |
| Segmented neutrophils ($10^3/\mu L$) | 0.15 ± 0.02 | 0.19 ± 0.13 | 0.59 ± 0.14 | 0.48 ± 0.18 | 0.55 ± 0.09 | 0.29 ± 0.05 |
| Lymphocytes ($10^3/\mu L$) | 0.34 ± 0.12 | 0.23 ± 0.11 | 0.57 ± 0.08 | 0.27 ± 0.01 | 1.14 ± 0.20* | 0.73 ± 0.19* |
| Monocytes ($10^3/\mu L$) | 0.01 ± 0.01 | 0.00 ± 0.00 | 0.03 ± 0.02 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.00 ± 0.00 |
| Eosinophils ($10^3/\mu L$) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.00 ± 0.00 |
| Nucleated erythrocytes ($10^3/\mu L$) | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.03 ± 0.00[b] | 0.01 ± 0.01 | 0.10 ± 0.02 | 0.04 ± 0.02 |

TABLE G3
**Hematology Data for Mice in the 13-Week Inhalation Study of Nickel Subsulfide** (continued)

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 0.3 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ | 2.5 mg/m$^3$ |
|---|---|---|---|---|---|---|
| **Female** | | | | | | |
| n | 5 | 3 | 5 | 5 | 5 | 5 |
| Hematocrit (%) | 38.3 ± 1.1 | 40.9 ± 0.8 | 41.1 ± 0.3 | 40.8 ± 0.5 | 41.6 ± 0.7 | 42.1 ± 1.1 |
| Hemoglobin (g/dL) | 13.6 ± 0.3 | 14.5 ± 0.2 | 14.7 ± 0.1** | 14.6 ± 0.2* | 14.8 ± 0.1** | 15.0 ± 0.4** |
| Erythrocytes ($10^6/\mu L$) | 7.65 ± 0.16 | 8.11 ± 0.14 | 8.27 ± 0.09** | 8.18 ± 0.12* | 8.40 ± 0.13** | 8.66 ± 0.20** |
| Mean cell volume (fL) | 49.4 ± 0.5 | 49.7 ± 0.3 | 49.2 ± 0.2 | 49.3 ± 0.2 | 48.8 ± 0.4 | 48.2 ± 0.4 |
| Mean cell hemoglobin concentration (g/dL) | 35.6 ± 0.5 | 35.5 ± 0.9 | 35.8 ± 0.2 | 35.8 ± 0.2 | 35.5 ± 0.4 | 35.7 ± 0.1 |
| Reticulocytes ($10^6/\mu L$) | 0.6 ± 0.1 | 0.4 ± 0.1 | 0.6 ± 0.2 | 0.8 ± 0.4 | 2.1 ± 1.2 | 1.3 ± 0.5 |
| Leukocytes ($10^3/\mu L$) | 1.00 ± 0.24 | 0.77 ± 0.03 | 0.82 ± 0.20 | 1.66 ± 0.51 | 1.66 ± 0.44 | 1.30 ± 0.34 |
| Segmented neutrophils ($10^3/\mu L$) | 0.23 ± 0.09 | 0.14 ± 0.01 | 0.27 ± 0.06 | 0.47 ± 0.22 | 0.71 ± 0.20 | 0.34 ± 0.05 |
| Lymphocytes ($10^3/\mu L$) | 0.75 ± 0.19 | 0.58 ± 0.04 | 0.53 ± 0.15 | 1.12 ± 0.38 | 0.95 ± 0.28 | 0.82 ± 0.21 |
| Monocytes ($10^3/\mu L$) | 0.03 ± 0.01 | 0.02 ± 0.01 | 0.00 ± 0.00 | 0.02 ± 0.01 | 0.00 ± 0.00 | 0.03 ± 0.02 |
| Eosinophils ($10^3/\mu L$) | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.02 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 |

* Significantly different ($P \leq 0.05$) from the 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] $n=3$

TABLE G4
**Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 1.2 mg/m$^3$ |
|---|---|---|---|
| **Male** | | | |
| n | 5 | 5 | 5 |
| Hematocrit (%) | 50.2 ± 0.5 | 52.1 ± 1.5 | 51.5 ± 1.5 |
| Hemoglobin (g/dL) | 15.5 ± 0.1 | 16.0 ± 0.3 | 15.9 ± 0.6 |
| Erythrocytes ($10^6/\mu L$) | 10.56 ± 0.15 | 10.69 ± 0.24 | 10.93 ± 0.43 |
| Mean cell volume (fL) | 49.8 ± 0.4 | 51.0 ± 0.7 | 49.2 ± 0.7 |
| Mean cell hemoglobin (pg) | 14.7 ± 0.1 | 15.0 ± 0.2 | 14.5 ± 0.2 |
| Mean cell hemoglobin concentration (g/dL) | 30.9 ± 0.3 | 30.8 ± 0.4 | 30.8 ± 0.2 |
| Reticulocytes ($10^6/\mu L$) | 0.2 ± 0.0[b] | 0.2 ± 0.0 | 0.2 ± 0.0 |
| Leukocytes ($10^3/\mu L$) | 3.88 ± 0.58 | 3.48 ± 0.36 | 3.92 ± 0.59 |
| Segmented neutrophils ($10^3/\mu L$) | 1.28 ± 0.20 | 1.12 ± 0.22 | 1.16 ± 0.21 |
| Lymphocytes ($10^3/\mu L$) | 2.42 ± 0.44 | 2.28 ± 0.20 | 2.56 ± 0.32 |
| Monocytes ($10^3/\mu L$) | 0.10 ± 0.00 | 0.02 ± 0.02 | 0.12 ± 0.07 |
| Eosinophils ($10^3/\mu L$) | 0.08 ± 0.02 | 0.04 ± 0.02 | 0.06 ± 0.04 |
| **Female** | | | |
| n | 5 | 4 | 5 |
| Hematocrit (%) | 49.4 ± 1.8 | 50.8 ± 0.5 | 52.6 ± 0.5* |
| Hemoglobin (g/dL) | 15.5 ± 0.5 | 15.9 ± 0.1 | 16.3 ± 0.1 |
| Erythrocytes ($10^6/\mu L$) | 10.69 ± 0.43 | 10.91 ± 0.18 | 11.17 ± 0.07 |
| Mean cell volume (fL) | 48.6 ± 0.2 | 48.8 ± 0.6 | 49.2 ± 0.6 |
| Mean cell hemoglobin (pg) | 14.5 ± 0.2 | 14.6 ± 0.3 | 14.6 ± 0.1 |
| Mean cell hemoglobin concentration (g/dL) | 31.4 ± 0.2 | 31.3 ± 0.3 | 31.0 ± 0.3 |
| Reticulocytes ($10^6/\mu L$) | 0.2 ± 0.0 | 0.1 ± 0.0 | 0.2 ± 0.1 |
| Leukocytes ($10^3/\mu L$) | 3.04 ± 0.40 | 4.45 ± 0.51 | 4.88 ± 0.16* |
| Segmented neutrophils ($10^3/\mu L$) | 1.04 ± 0.13 | 1.28 ± 0.15 | 1.56 ± 0.07** |
| Lymphocytes ($10^3/\mu L$) | 1.92 ± 0.32 | 2.90 ± 0.35 | 3.02 ± 0.16* |
| Monocytes ($10^3/\mu L$) | 0.04 ± 0.02 | 0.15 ± 0.05 | 0.18 ± 0.06* |
| Eosinophils ($10^3/\mu L$) | 0.04 ± 0.02 | 0.13 ± 0.03 | 0.14 ± 0.05 |

* Significantly different ($P \leq 0.05$) from the 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=4

# APPENDIX H
# TISSUE BURDEN IN RATS

TABLE H1
**Lung Weight and Lung Burden in Rats in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 2.5 mg/m³ | 10 mg/m³ |
|---|---|---|---|---|
| n | 3 | 3 | 3 | 3 |
| **Male** | | | | |
| Absolute lung wt (g) | 0.827 ± 0.009 | 1.000 ± 0.000 | 1.370 ± 0.012** | 1.577 ± 0.150** |
| μg Ni/lung | —[b] | 7 ± 0.9* | 25 ± 0.6** | 103 ± 2.9** |
| μg Ni/g lung | — | 7 ± 0.9* | 18 ± 0.3** | 67 ± 8.7** |
| μg Ni/g control lung | — | 9 ± 1.0* | 30 ± 0.6** | 127 ± 3.3** |
| **Female** | | | | |
| Absolute lung wt (g) | 0.810 ± 0.169 | 0.883 ± 0.041 | 1.263 ± 0.078* | 1.167 ± 0.087 |
| μg Ni/lung | — | 8 ± 1.3* | 24 ± 1.9** | 87 ± 9.3** |
| μg Ni/g lung | — | 9 ± 1.3* | 19 ± 1.6** | 77 ± 12.1** |
| μg Ni/g control lung | — | 12 ± 2.0* | 36 ± 3.0** | 133 ± 13.3** |

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's or Williams' test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.093 μg Ni (the limit of detection).

TABLE H2
**Kidney Weight and Kidney Burden in Rats in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 2.5 mg/m³ | 10 mg/m³ |
|---|---|---|---|
| n | 3 | 3 | 3 |
| **Male** | | | |
| Absolute kidney wt (g) | 1.96 ± 0.12 | 1.75 ± 0.07 | 1.27 ± 0.12** |
| μg Ni/kidney | —[b] | 0.362 ± 0.028* | 2.658 ± 1.473** |
| μg Ni/g kidney | — | 0.209 ± 0.022* | 1.993 ± 0.964** |
| **Female** | | | |
| Absolute kidney wt (g) | 1.33 ± 0.11 | 1.42 ± 0.10 | 1.01± 0.05 |
| μg Ni/kidney | 0.115 ± 0.058 | 0.263 ± 0.012* | 1.242 ± 0.273** |
| μg Ni/g kidney | — | 0.187 ± 0.017* | 1.269 ± 0.327** |

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's or Williams' test (kidney weight) or Shirley's test (kidney burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.093 μg Ni (the limit of detection).

TABLE H3
**Lung Weight and Lung Burden in Rats in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 0.6 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 6 | 6 | 6 | 6 |
| 4 weeks | | | | |
| μg Ni/g lung | —[b] | 3 ± 0.2** | 6 ± 0.7** | 15 ± 1.4** |
| μg Ni/g control lung | — | 3 ± 0.2** | 8 ± 0.9** | 23 ± 2.2** |
| 9 weeks | | | | |
| μg Ni/g lung | — | 5 ± 0.2** | 7 ± 0.6** | 16 ± 1.0** |
| μg Ni/g control lung | — | 6 ± 0.2** | 12 ± 1.2** | 31 ± 1.7** |
| 13 weeks | | | | |
| Absolute lung wt (g) | 1.15 ± 0.03 | 1.56 ± 0.01** | 2.23 ± 0.08** | 2.38 ± 0.03** |
| μg Ni/lung | — | 8 ± 0.3** | 17 ± 1.0** | 42 ± 1.3** |
| μg Ni/g lung | — | 5 ± 0.2** | 7 ± 0.4** | 18 ± 0.5** |
| μg Ni/g control lung | — | 7 ± 0.3** | 14 ± 0.9** | 36 ± 1.2** |
| **Female** | | | | |
| n | 6 | 6 | 6 | 5 |
| 13 weeks | | | | |
| Absolute lung wt (g) | 0.849 ± 0.026 | 1.234 ± 0.053** | 1.570 ± 0.034** | 1.607 ± 0.045** |
| μg Ni/lung | — | 6 ± 0.2** | 11 ± 0.3** | 28 ± 1.4** |
| μg Ni/g lung | — | 5 ± 0.1** | 7 ± 0.1** | 17 ± 0.7** |
| μg Ni/g control lung | — | 7 ± 0.3** | 13 ± 0.4** | 33 ± 1.7** |

** Significantly different ($P \leq 0.01$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.218 μg Ni (the limit of detection).

**TABLE H4**
**Kidney and Testes Burden in Male Rats in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.6 mg/m$^3$ | 2.5 mg/m$^3$ |
|---|---|---|---|
| n | 6 | 6 | 6 |
| Kidney | | | |
| 13 weeks | | | |
| $\mu$g Ni/g kidney | —[b] | — | 0.140 ± 0.063* |
| Testes | | | |
| 13 weeks | | | |
| $\mu$g Ni/g testes | 0.480 ± 0.041 | 0.048 ± 0.048** | 0.465 ± 0.007 |

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.218 $\mu$g Ni (the limit of detection).

TABLE H5
**Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| n | 7 | 7 | 7 |
| 7-Month interim evaluation | | | |
| Absolute lung wt (g) | 1.53 ± 0.13 | 1.97 ± 0.09** | 3.21 ± 0.08** |
| μg Ni/lung | —[b] | 12 ± 0.5** | 28 ± 1.8** |
| μg Ni/g lung | — | 6 ± 0.2** | 9 ± 0.5** |
| μg Ni/g control lung | — | 8 ± 0.3** | 18 ± 1.2** |
| n | 5 | 5 | 5 |
| 15-Month interim evaluation | | | |
| Absolute lung wt (g) | 2.27 ± 0.09 | 3.31 ± 0.22** | 6.84 ± 0.70** |
| μg Ni/lung | — | 14 ± 0.6** | 21 ± 1.5** |
| μg Ni/g lung | — | 4 ± 0.2** | 3 ± 0.1 |
| μg Ni/g control lung | — | 6 ± 0.3** | 9 ± 0.7** |
| **Female** | | | |
| n | 7 | 7 | 7 |
| 7-Month interim evaluation | | | |
| Absolute lung wt (g) | 1.10 ± 0.03 | 1.48 ± 0.04** | 2.44 ± 0.07** |
| μg Ni/lung | — | 9 ± 0.4** | 23 ± 0.7** |
| μg Ni/g lung | — | 6 ± 0.2** | 9 ± 0.4** |
| μg Ni/g control lung | — | 8 ± 0.4** | 21 ± 0.6** |
| n | 5 | 5 | 5 |
| 15-Month interim evaluation | | | |
| Absolute lung wt (g) | 1.52 ± 0.11 | 2.52 ± 0.25** | 4.15 ± 0.10** |
| μg Ni/lung | — | 9 ± 0.8** | 29 ± 1.0** |
| μg Ni/g lung | — | 4 ± 0.5** | 7 ± 0.2** |
| μg Ni/g control lung | — | 6 ± 0.5** | 19 ± 0.6** |

** Significantly different ($P \leq 0.01$) from the control group by Williams' test (lung weight) or Dunn's or Shirley's test (lung burden parameters)

[a] Mean ± standard error; statistical tests were performed on unrounded data.

[b] Results were below 0.035 μg Ni (the limit of detection) for the 7-month interim evaluation and below 0.119 μg Ni for the 15-month interim evaluation.

**TABLE H6**
**Kidney Burden in Rats in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 1 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| n | 7 | 7 | 7 |
| 7-Month interim evaluation | | | |
| μg Ni/g kidney | —[b] | 0.044 ± 0.005** | 0.224 ± 0.023** |
| n | 5 | 5 | 5 |
| 15-Month interim evaluation | | | |
| μg Ni/g kidney | — | 0.307 ± 0.101 | 0.312 ± 0.091 |
| **Female** | | | |
| n | 7 | 7 | 7 |
| 7-Month interim evaluation | | | |
| μg Ni/g kidney | — | 0.036 ± 0.003** | 0.217 ± 0.011** |
| n | 5 | 5 | 5 |
| 15-Month interim evaluation | | | |
| μg Ni/g kidney | — | 0.522 ± 0.123* | 0.757 ± 0.094** |

* Significantly different ($P \leq 0.05$) from the 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] Results were below 0.033 μg Ni (the limit of detection) for the 7-month interim evaluation and below 0.113 μg Ni for the 15-month interim evaluation.

# APPENDIX I
# TISSUE BURDEN IN MICE

TABLE I1
**Lung Weight and Lung Burden in Mice in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 2.5 mg/m³ | 10 mg/m³ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 3 | 3 | 3 | 2 |
| Absolute lung wt (g) | 0.138 ± 0.004 | 0.145 ± 0.006 | 0.200 ± 0.014** | 0.335 ± 0.005** |
| μg Ni/lung | —[b] | 1 ± 0.2* | 4 ± 0.9** | 4 ± 0.9* |
| μg Ni/g lung | — | 10 ± 0.7* | 20 ± 3.2** | 13 ± 2.5* |
| μg Ni/g control lung | — | 10 ± 1.0* | 30 ± 6.8** | 31 ± 6.0* |
| **Female** | | | | |
| n | 3 | 3 | 3 | 3 |
| Absolute lung wt (g) | 0.125 ± 0.002 | 0.153 ± 0.011 | 0.197 ± 0.006* | 0.380 ± 0.040** |
| μg Ni/lung | — | 1 ± 0.1* | 4 ± 0.5** | 3 ± 0.5* |
| μg Ni/g lung | — | 8 ± 0.4 | 20 ± 2.6** | 8 ± 1.9 |
| μg Ni/g control lung | — | 10 ± 1.0* | 31 ± 4.1** | 22 ± 3.9* |

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Dunn's or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.155 μg Ni (the limit of detection).

TABLE I2
**Kidney Weight and Kidney Burden in Mice in the 16-Day Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 2.5 mg/m³ | 10 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| n | 3 | 3 | 2 |
| Absolute kidney wt (g) | 0.472 ± 0.019 | 0.442 ± 0.010 | 0.265 ± 0.015** |
| μg Ni/kidney | —[b] | 0.054 ± 0.054 | 1.142 ± 0.648* |
| μg Ni/g kidney | — | 0.122 ± 0.122 | 4.440 ± 2.680* |
| **Female** | | | |
| n | 3 | 3 | 3 |
| Absolute kidney wt (g) | 0.328 ± 0.017 | 0.332 ± 0.021 | 0.213 ± 0.024* |
| μg Ni/kidney | — | 0.146 ± 0.080 | 0.276 ± 0.040* |
| μg Ni/g kidney | — | 0.457 ± 0.269 | 1.283 ± 0.041* |

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test (kidney weight) or Dunn's or Shirley's test (kidney burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.155 μg Ni (the limit of detection).

TABLE I3
**Lung Weight and Lung Burden in Mice in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 0.6 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 6 | 5 | 6 | 6 |
| Absolute lung wt (g) | 0.158 ± 0.005 | 0.178 ± 0.010 | 0.195 ± 0.010* | 0.258 ± 0.013** |
| μg Ni/lung | —[b] | 1 ± 0.2* | 2 ± 0.1** | 4 ± 0.5** |
| μg Ni/g lung | — | 3 ± 0.9* | 11 ± 0.8** | 17 ± 1.6** |
| μg Ni/g control lung | — | 4 ± 1.0* | 14 ± 0.8** | 28 ± 3.2** |
| **Female** | | | | |
| n | 6 | 5 | 5 | 6 |
| Absolute lung wt (g) | 0.163 ± 0.004 | 0.139 ± 0.007 | 0.170 ± 0.011 | 0.298 ± 0.012** |
| μg Ni/lung | — | 1 ± 0.1** | 2 ± 0.1** | 7 ± 0.5** |
| μg Ni/g lung | — | 6 ± 0.4** | 13 ± 1.0** | 23 ± 1.4** |
| μg Ni/g control lung | — | 5 ± 0.4** | 14 ± 0.8** | 41 ± 2.9** |

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.255 μg Ni (the limit of detection).

TABLE I4
**Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| n | 5 | 5 | 5 |
| **Male** | | | |
| 7-Month interim evaluation | | | |
| Absolute lung wt (g) | 0.219 ± 0.015[b] | 0.311 ± 0.016** | 0.406 ± 0.018** |
| μg Ni/lung | —[c] | 3 ± 0.1** | 4 ± 0.3** |
| μg Ni/g lung | — | 10 ± 0.2** | 11 ± 1.2* |
| μg Ni/g control lung | — | 15 ± 0.5** | 20 ± 1.6** |
| 15-Month interim evaluation | | | |
| Absolute lung wt (g) | 0.184 ± 0.009 | 0.354 ± 0.017** | 0.410 ± 0.017** |
| μg Ni/lung | — | 4 ± 0.3** | 8 ± 0.7** |
| μg Ni/g lung | — | 12 ± 0.7** | 20 ± 0.9** |
| μg Ni/g control lung | — | 24 ± 1.9** | 44 ± 4.0** |
| **Female** | | | |
| 7-Month interim evaluation | | | |
| Absolute lung wt (g) | 0.247 ± 0.026 | 0.325 ± 0.020* | 0.358 ± 0.012** |
| μg Ni/lung | — | 3 ± 0.1** | 5 ± 0.2** |
| μg Ni/g lung | — | 10 ± 0.6** | 14 ± 1.0** |
| μg Ni/g control lung | — | 13 ± 0.4** | 19 ± 1.0** |
| 15-Month interim evaluation | | | |
| Absolute lung wt (g) | 0.178 ± 0.011 | 0.346 ± 0.019** | 0.414 ± 0.020** |
| μg Ni/lung | — | 5 ± 0.9** | 11 ± 1.3** |
| μg Ni/g lung | — | 15 ± 0.7** | 26 ± 2.2** |
| μg Ni/g control lung | — | 30 ± 4.9** | 61 ± 7.4** |

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Dunn's or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] n=4
[c] Results were below 0.0037 μg Ni (the limit of detection) for the 7-month interim evaluation and below 0.0034 μg Ni for the 15-month interim evaluation.

TABLE I5
**Kidney Burden in Mice in the 2-Year Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.6 mg/m³ | 1.2 mg/m³ |
|---|---|---|---|
| **Male** | | | |
| n | 4 | 5 | 5 |
| 7-Month interim evaluation | | | |
| μg Ni/g kidney | 0.025 ± 0.018 | 0.065 ± 0.014 | 0.082 ± 0.014 |
| n | 5 | 5 | 5 |
| 15-Month interim evaluation | | | |
| μg Ni/g kidney | 0.015 ± 0.012 | 0.061 ± 0.014* | 0.076 ± 0.006** |
| **Female** | | | |
| n | 5 | 5 | 5 |
| 7-Month interim evaluation | | | |
| μg Ni/g kidney | 0.874 ± 0.632 | 0.130 ± 0.061 | 0.364 ± 0.107 |
| n | 5 | 5 | 5 |
| 15-Month interim evaluation | | | |
| μg Ni/g kidney | 0.097 ± 0.028 | 0.097 ± 0.024 | 0.258 ± 0.054* |

* Significantly different ($P \leq 0.05$) from the 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 J
# REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

**TABLE J1**
**Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m$^3$ | 0.15 mg/m$^3$ | 0.6 mg/m$^3$ | 2.5 mg/m$^3$ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 10 | 10 | 10 | 10 |
| Weights (g) | | | | |
| R. cauda | 0.126 ± 0.005 | 0.122 ± 0.006 | 0.137 ± 0.008 | 0.126 ± 0.007 |
| R. epididymis | 0.513 ± 0.015 | 0.519 ± 0.011 | 0.490 ± 0.021 | 0.533 ± 0.010[b] |
| R. testis | 1.438 ± 0.035 | 1.478 ± 0.032 | 1.385 ± 0.020[b] | 1.477 ± 0.026 |
| Epididymal spermatozoal parameters | | | | |
| Motility (%) | 94.87 ± 0.73 | 93.83 ± 0.98 | 94.16 ± 1.03 | 93.72 ± 0.53 |
| Abnormal (%) | 0.640 ± 0.154 | 0.500 ± 0.091 | 0.500 ± 0.061 | 0.500 ± 0.080 |
| Concentration ($10^6$/g cauda epididymal tissue) | 713 ± 39 | 696 ± 53 | 736 ± 50 | 742 ± 33 |
| **Female** | | | | |
| n | 9 | 9 | 10 | 10 |
| Estrous cycle length (days)[c] | 5.00 ± 0.29[d] | 4.89 ± 0.26[d] | 5.20 ± 0.20 | 5.00 ± 0.21 |
| Estrous stages (% of cycle) | | | | |
| Diestrus | 35.7 | 31.4 | 35.7 | 32.9 |
| Proestrus | 21.4 | 12.9 | 18.6 | 18.6 |
| Estrus | 30.0 | 38.6 | 24.3 | 30.0 |
| Metestrus | 12.9 | 17.1 | 21.4 | 18.6 |

[a] Data are presented as mean ± standard error. Differences from the control group for all study parameters are not significant by Dunn's or Dunnett's test.
[b] n=9
[c] There is no evidence of any differences between the exposed and control groups in cycle length or in relative length of time spent in estrous stages.
[d] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

TABLE J2
**Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Inhalation Study of Nickel Subsulfide[a]**

| | 0 mg/m³ | 0.15 mg/m³ | 0.6 mg/m³ | 2.5 mg/m³ |
|---|---|---|---|---|
| **Male** | | | | |
| n | 8 | 10 | 8 | 10 |
| Weights (g) | | | | |
| R. cauda | 0.013 ± 0.001 | 0.012 ± 0.001[b] | 0.012 ± 0.000[c] | 0.011 ± 0.000 |
| R. epididymis | 0.048 ± 0.002 | 0.046 ± 0.003 | 0.046 ± 0.002[c] | 0.044 ± 0.001 |
| R. testis | 0.110 ± 0.003 | 0.107 ± 0.005 | 0.113 ± 0.006 | 0.121 ± 0.008 |
| Epididymal spermatozoal parameters | | | | |
| Motility (%) | 90.70 ± 0.38 | 91.93 ± 0.73 | 91.75 ± 0.94 | 91.55 ± 0.84 |
| Abnormal (%) | 1.53 ± 0.16 | 1.02 ± 0.10 | 1.30 ± 0.23 | 1.26 ± 0.14 |
| Concentration ($10^6$/g cauda epididymal tissue) | 1,228 ± 173 | 1,244 ± 140 | 1,396 ± 111 | 1,406 ± 48 |
| **Female** | | | | |
| n | 10 | 6 | 9 | 6 |
| Estrous cycle length (days)[d] | 4.50 ± 0.31 | 4.00 ± 0.26[e] | 4.22 ± 0.15 | 4.50 ± 0.22[f] |
| Estrous stages (% of cycle) | | | | |
| Diestrus | 25.7 | 37.5 | 20.6 | 16.3 |
| Proestrus | 12.9 | 14.3 | 12.7 | 14.3 |
| Estrus | 37.1 | 26.8 | 42.9 | 51.0 |
| Metestrus | 24.3 | 21.4 | 23.8 | 18.4 |

[a] Data are presented as mean ± standard error. Differences from the control group for all study parameters are not significant by Dunn's or Dunnett's test.
[b] n=9
[c] n=7
[d] There is no evidence of any differences between the exposed and control groups in cycle length or in relative length of time spent in estrous stages.
[e] Estrous cycle was longer than 7 days or was unclear in 2 of 8 animals.
[f] Estrous cycle was longer than 7 days or was unclear in 1 of 7 animals.

# APPENDIX K
# CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

# CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

## PROCUREMENT AND CHARACTERIZATION OF NICKEL SUBSULFIDE

Nickel subsulfide was obtained from International Nickel Company, Ltd. (Toronto, Ontario), in three lots (HF-1517, I080786 and I072588). Lot HF-1517 was used during the 16-day and 13-week studies, and a blend of the three lots (identified as lot M082288) was used during the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the nickel subsulfide studies are on file at the National Institute of Environmental Health Sciences.

All lots were subjected to particle size reduction with a 4-inch micronizer prior to use (Sturtevant Mills, Inc., Boston, MA). Analyses of lot HF-1517 were performed by elemental analyses and ion chromatography by Galbraith Laboratories, Inc. (Knoxville, TN), and by spark source mass spectrometry by Accu-Labs Research, Inc. (Wheat Ridge, CO), before and after milling of the chemical. Results of elemental analyses before and after milling were in agreement. Results of analysis by ion chromatography before and after milling indicated that there was a higher content of sulfur oxides after milling, but this difference was not considered significant. Spark source mass spectrometry indicated total impurities of 800 ppm before and after milling. These analyses indicated that milling did not significantly alter the purity of the bulk chemical.

The chemical, a gray or black powder with a melting point greater than 300° C, was soluble in nitric acid. The chemical was also identified as nickel subsulfide by infrared and ultraviolet/visible spectroscopy. No absorbance was observed with infrared spectroscopy (Figure K1), and the ultraviolet/visible spectrum was consistent with that expected for the structure. No spectra were found in the literature.

The purity of lot HF-1517 was determined by elemental analyses, Karl Fischer water analysis, ion chromatography, and chelometric titration. For chelometric titration, samples were dissolved in 70% nitric acid for 1 hour, then adjusted to pH 5 with sodium acetate trihydrate and ammonium hydroxide. Ethylenediaminetetraacetate (EDTA) was added, and the samples were back-titrated with aqueous 0.1 N iron (III) chloride. The titration was monitored with a platinum disc indicating electrode and a calomel reference electrode filled with saturated potassium chloride.

Elemental analysis values for nickel in lot HF-1517 were slightly low. Elemental analysis results for sulfur were in agreement with the theoretical values for nickel subsulfide. Karl Fischer water analysis indicated 0.09% ± 0.01% water. Only trace amounts (less than 70 ppm) of sulfate, sulfite, and thiosulfate were detected by ion chromatography. Chelometric titration indicated a purity of 97.0% ± 1.1% nickel subsulfide. The overall purity of lot HF-1517 was determined to be at least 97%.

The purity of the combined lot M082288 was determined by elemental analyses, Karl Fischer water analysis, spark source mass spectrometry, and chelometric titration. The chelometric titration was the same as described for lot HF-1517 except that the samples were adjusted to pH 6. Elemental analysis values were slightly low for nickel and high for sulfur in lot M082288. Karl Fischer water analysis indicated 0.06% ± 0.01% water. Spark source mass spectrometry indicated total impurities of less than or equal to 2,620 ppm; the major inorganic impurities were silicon (1,200 ppm), iron (470 ppm), phosphorus (335 ppm), and chromium (300 ppm). Chelometric titration indicated a purity of 98.0% ± 1.7% nickel subsulfide. The overall purity of lot M082288 was determined to be at least 98%.

An insoluble impurity (~1%) was found in both lots during the ultraviolet/visible spectroscopic analyses. This insoluble material was identified as sulfur by spark source mass spectrometry.

A chemical stability study was not performed for nickel subsulfide because of its inert refractory properties as evidenced by the high melting point and extreme conditions necessary for dissolution. To ensure stability, the analytical chemistry laboratory recommended that the bulk chemical be stored protected from light under an inert gas headspace at room temperature.

The bulk chemical was stored in amber glass bottles at room temperature. Periodic monitoring of the bulk chemical was performed by Huffman Laboratories, Inc. (Golden, CO), prior to and after all studies and every 3 to 4 months during the 2-year studies by elemental analyses for nickel and sulfur. On one occasion out of 10 analyses, values for nickel in the samples fell outside the range recommended by the analytical chemistry laboratory. The result was considered to be an aberration, and it was concluded that there was no degradation of the bulk chemical during the studies.

## AEROSOL GENERATION AND EXPOSURE SYSTEM

Nickel subsulfide aerosol was generated from 2-inch fluid bed generators (FBGs) during all studies. Figure K2 shows the schematic of the FBG with the gravity feed and catch pan collection systems. The FBG contained a bed of stainless steel powder of a diameter too heavy to be carried from the generator in the flow of air. The nickel subsulfide was added to the stainless steel bed, and the motion of the bed when air was passed through the FBG released the much smaller nickel subsulfide particles into the air. A Kr-85 discharger was placed in the generator to reduce the electrical charge on the aerosol. The nickel subsulfide aerosol was mixed with diluting air to achieve the desired concentrations and was delivered to the exposure chambers. Fresh nickel subsulfide-containing bed material was constantly added to the generator from a hopper located above the generator; the nickel subsulfide-depleted stainless steel powder was continually drained from the FBG through an overflow port located at the side of the generator. The depleted stainless steel bed material, collected in an enclosed container at the base of the generator, was loaded into a V-tube mixer and was mixed with a sufficient amount of nickel subsulfide to replenish the bed and maintain a stable aerosol concentration. The amount of nickel subsulfide added to each bed depended on the aerosol concentration desired. The aerosol generation assembly was enclosed in a walk-in hood. Air was circulated through HEPA filters to remove suspended particles in the enclosure. The aerosol delivery system is shown in Figure K3.

Stainless steel, multi-tiered, whole-body exposure chambers (H1000 and H2000, Hazleton Systems, Aberdeen, MD) were used to expose the rats and mice in these studies (Figure K4). In the 16-day studies, the H2000 chambers were used for the 0, 0.6, 2.5, and 10 mg/m$^3$ groups, and the H1000 chambers were used for the 1.2 and 5 mg/m$^3$ groups. During the 13-week studies, the H2000 chambers were used for the 0, 0.15, 0.6, and 2.5 mg/m$^3$ groups, and the H1000 chambers were used for the 0.3 and 1.2 mg/m$^3$ groups. In the 2-year studies, the H2000 chambers were used to expose the rats, and the H1000 chambers were used to expose the mice. The air flow rate in the 16-day studies corresponded to 10 $\pm$ 2 air changes per hour. In the 13-week studies, the air flow rate was 12 $\pm$ 2 ft$^3$/min in the H2000 chambers and 7 $\pm$ 1 ft$^3$/min in the H1000 chambers, corresponding to 12 $\pm$ 2 air changes per hour. In the 2-year studies, the air flow rate was 14.6 $\pm$ 2.0 ft$^3$/min in the rat chambers and 8.7 $\pm$ 1.2 ft$^3$/min in the mouse chambers, corresponding to 5.99 to 21.63 (rats) and 12.02 to 18.06 (mice) air changes per hour. To reduce the spatial variation of aerosol concentration and to increase the uniformity of mixing, the aerosol was diluted in a radial diluter prior to introduction into the chamber, and a small boxer fan (Model WS 2107FL-1002, Newark Electronics, Chicago, IL) with a flow rate of 60 ft$^3$/min was placed below the aerosol entrance to further mix the aerosol as it entered the chamber. During the 2-year studies, a cyclone was placed in the aerosol delivery line to remove coarse aerosol particles. Animal cages were rotated

weekly to reduce the variation of concentrations of aerosols that the animals were being exposed to during the 13-week and 2-year studies. Diagrams of the 13-week and 2-year exposure suites are shown in Figures K5 and K6, respectively.

## AEROSOL CONCENTRATION MONITORING

In the 13-week and 2-year studies, the aerosol concentrations were determined gravimetrically from three 2-hour samples (3 L/min flow rate) from each exposure chamber, except the 0.15 mg/m$^3$ chambers were determined from two 3-hour samples (4.5 L/min flow rate), during each 6-hour exposure day. The background concentrations of total suspended particles in the control chambers were monitored each exposure day of the 2-year studies by collecting one 6-hour filter sample; samples were collected overnight from the control chambers during the 16-day and 13-week studies. The mean concentration of total suspended particles in the control chamber was 0.03 mg particles/m$^3$ in the 16-day studies and was 0.08 mg particles/m$^3$ in the 13-week studies. In the 2-year studies, the mean concentrations of total suspended particles were 0.02 $\pm$ 0.01 mg particle/mg$^3$ in the rat control chamber and 0.01 $\pm$ 0.01 mg particle/m$^3$ in the mouse control chamber.

All samples in the 13-week studies were collected after the initial 15 minutes ($T_{90}$) of aerosol generation at a flow rate of 3 L/min; all samples in the 2-year studies were collected after the initial 8 minutes of aerosol generation. The flow rate was monitored with calibrated rotameters. To determine aerosol concentration, samples were collected with 25 mm fiberglass filters (Type AE, Gelman, Ann Arbor, MI) during the 13-week studies and with 25 mm, Teflon®-coated, fiberglass filters with a pore size of 0.1 $\mu$m (Zefluor, Gelman, Ann Arbor, MI) during the 2-year studies. The quantity of nickel subsulfide collected on the filters was determined gravimetrically by weighing the filters with an electrobalance (Cahn 29, Cahn Instruments, Cerrito, CA) before and after the collection of the samples. The aerosol mass concentrations were calculated by dividing the mass increment (mg) by the volume sampled (m$^3$); the means and standard deviations of each chamber were calculated for each exposure day. Daily mean exposure concentrations for the 13-week studies are presented in Figures K7 and K8. Weekly mean exposure concentrations for the 2-year studies are presented in Figures K9 and K10.

A continuous aerosol monitor (Model RAM-S, GCA, Co., Bedford, MA) was used to monitor the stability of the aerosol concentrations and to determine the need to adjust the aerosol generation system during exposures. The RAM-S was used to monitor each chamber for at least 10 minutes of every exposure hour during the 16-day studies and at least 5 minutes of every exposure hour during the 13-week and 2-year studies. The RAM-S unit has a self-contained sampling system which operates at 2 L/min.

Aerosol concentration was also quantitated with the RAM-S. The RAM-S voltage output was calibrated against the mass concentration obtained gravimetrically. The average of three RAM-S voltage readings taken during a filter-sampling period were plotted versus the aerosol concentration determined gravimetrically. Linear regression analysis was performed monthly on these data, and the RAM-S voltage readings (volts) were converted to mass concentration (mg/m$^3$) based on the slope and intercept of the regression line fitted to the data. The mean and standard deviation of the concentrations were calculated each exposure day for each chamber. The coefficient of variation from the RAM-S measurement was used as an indication of aerosol stability for each exposure day. RAM-S and filter samples were taken at the middle level of the H2000 and H1000 chambers above the animal cage. The probe for the filter sample was at the front of each chamber, and the probe for the RAM-S was at the back of each chamber.

## CHAMBER ATMOSPHERE CHARACTERIZATION

Aerosol size distribution was determined once during the 16-day and 13-week studies and monthly during the 2-year studies for each exposure chamber with a Lovelace multijet cascade impactor operated at a flow rate of 15 L/min. The sampling period ranged from 1 to 6 hours depending on the chamber concentration. Stainless steel shimstock coated with apiezon grease was used as impactor substrate. The amount of nickel subsulfide on each stage was determined by the difference in stage weight before and after the sample was collected. The mass medium aerodynamic diameter and the geometric standard deviation were calculated from the mass data, effective cutoff diameter of each stage, and impactor flow rate. The results are presented in Tables K1 through K4.

The generated aerosol was sampled and compared to the bulk sample by atomic absorption and X-ray diffraction analyses. The nickel contents of both samples were identical and their diffraction patterns conformed to the standard pattern (# 8-126) published by the Joint Committee on Powder Diffraction Standards. The data supports the conclusion that the generation system does not change the crystal structure of the bulk chemical.

Uniformity of aerosol concentration in the exposure chambers was measured prior to the start of the studies without animals in the chambers and with animals during the first week of exposure, and was checked quarterly during the 2-year studies. Three samples were collected with the RAM-S at a specified reference point in each chamber at the start, middle, and end of the procedure. One sample each was collected for the other locations. The total variation of aerosol concentrations is the coefficient of variation of samples collected at different locations, and the temporal variation is the coefficient of variation of the three reference samples. In the 13-week studies, the spatial variations ranged from 1.7% to 8.8%. For rats in the 2-year studies, the mean temporal variations of aerosol concentration during exposure were between 1.63% and 2.31%, and the mean spatial variations were between 1.84% and 3.09%. For mice in the 2-year studies, the mean temporal variations were between 2.91% and 3.17%, and the mean spatial variations were between 2.06% and 2.60%.

The aerosol rise and fall time ($T_{90}$) was determined with a RAM-S, and an exposure day was set at 6 hours plus $T_{90}$. A $T_{90}$ of 10 minutes was used during the 16-day studies, 15 minutes was used during the 13-week studies, and 8 minutes was used during the 2-year studies.

Residual concentration of nickel subsulfide in the chambers during nonexposure hours was evaluated gravimetrically once during the 16-day studies, once during the 13-week studies, and once during the first 2 weeks of exposure and quarterly thereafter during the 2-year studies. The filter samples were collected overnight (about 15 hours) at a flow rate of 3 L/min. Samples were collected from the 2.5 mg/m$^3$ chamber during the 13-week studies. During the 2-year studies, samples were collected from the 1 mg/m$^3$ rat chamber and from the 1.2 mg/m$^3$ mouse chamber. If the weight of the material collected on the filter was greater than 200 $\mu$g, the material collected was analyzed for nickel content by atomic absorption spectroscopy. The mass of the particles collected on the filter during the 16-day and 13-week studies and the 2-year rat study never exceeded 200 $\mu$g. The mass of the particles collected during the 2-year mouse study exceeded 200 $\mu$g four times but was only analyzed for nickel content twice (August 1989 and November 1989). Results of chemical analysis of these filter samples by atomic absorption spectroscopy indicated that the aerosol collected on the filter was not solely nickel subsulfide, but consisted chiefly of non-nickel-containing material.

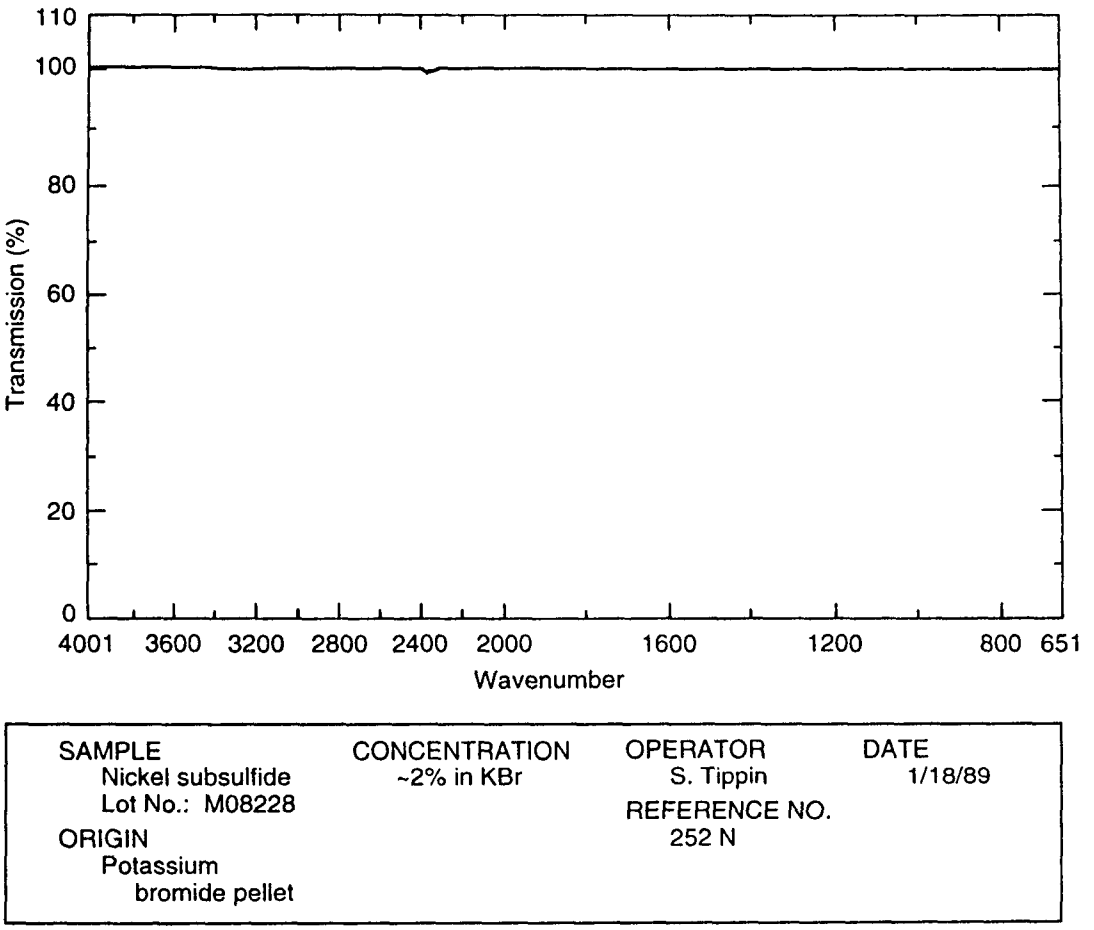


**FIGURE K1**
**Infrared Absorption Spectrum of Nickel Subsulfide**

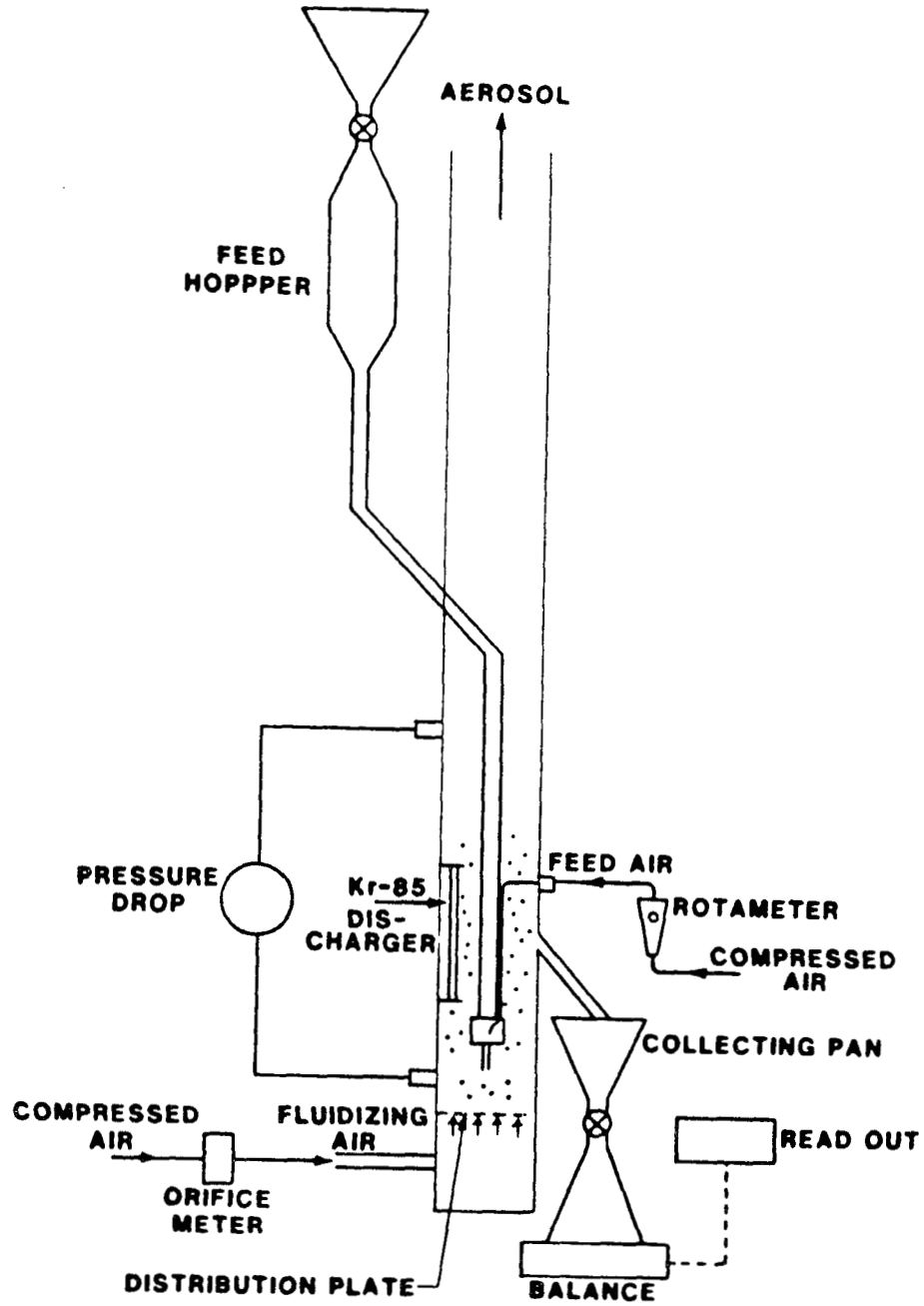


FIGURE K2
Schematic of the Generation System

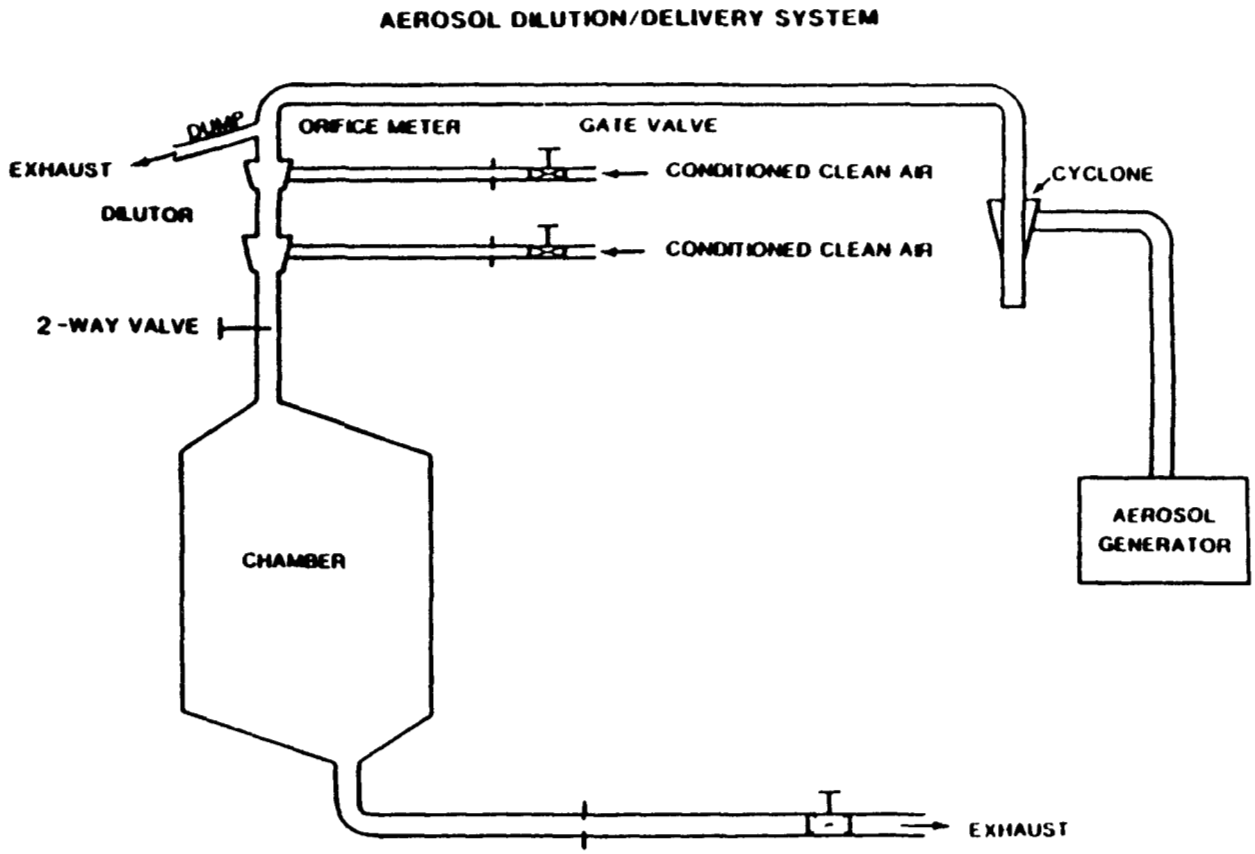


FIGURE K3
Schematic of the Nickel Subsulfide Aerosol Delivery System

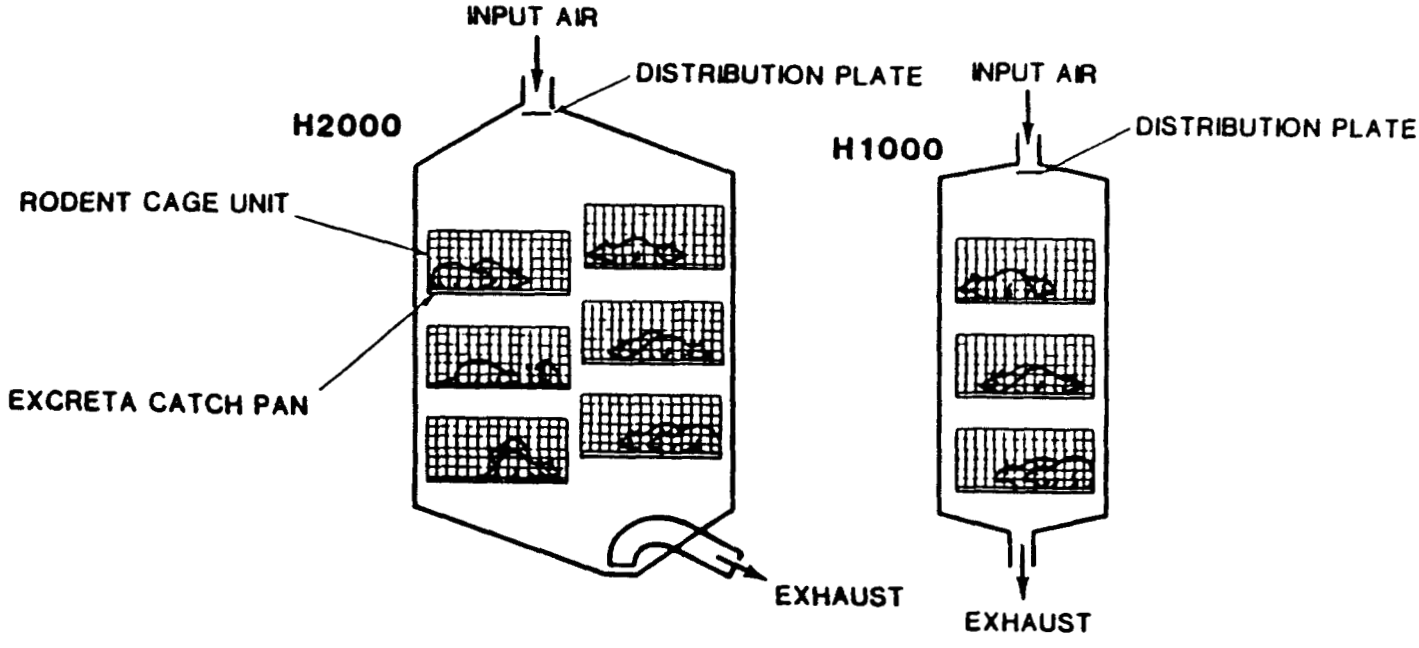


FIGURE K4
Schematic of the H1000 and H2000 Exposure Chambers

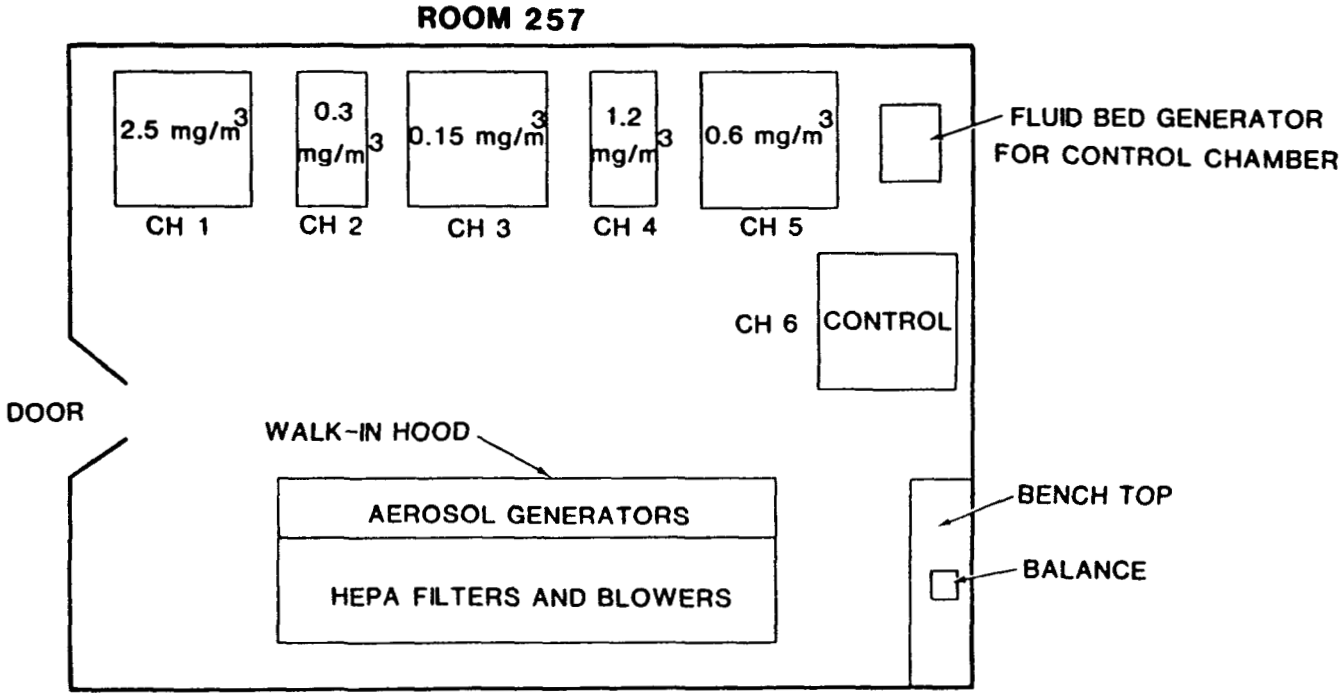


FIGURE K5
13-Week Nickel Subsulfide Inhalation Suite

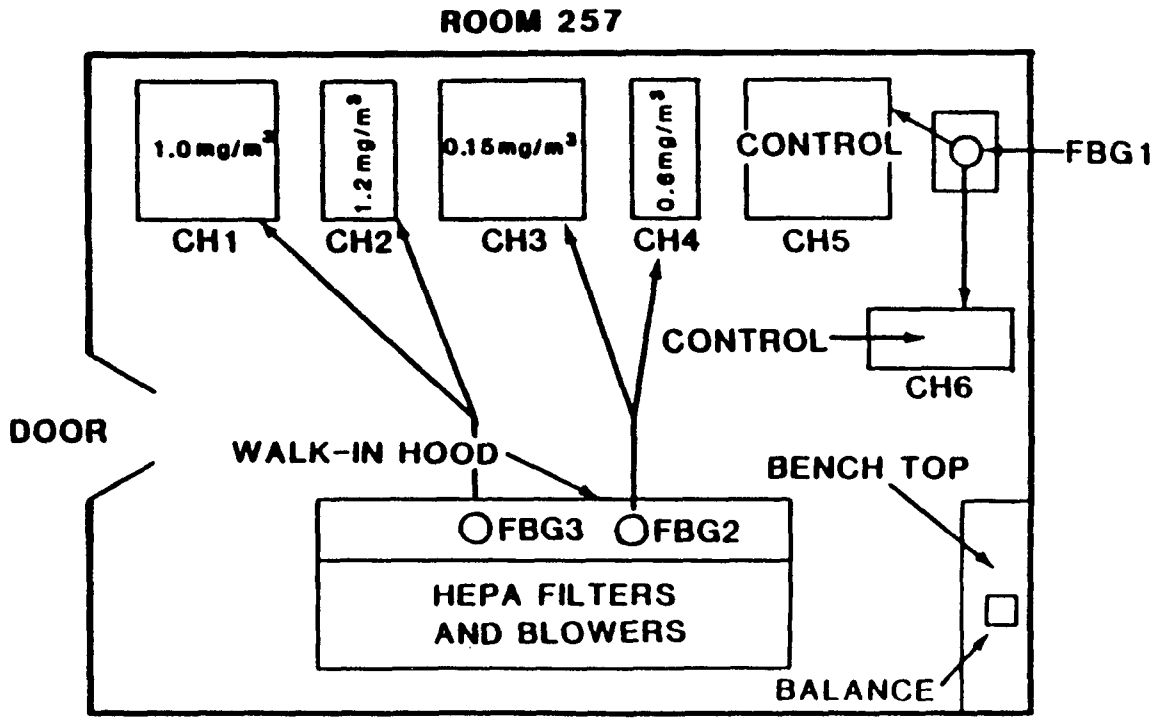


FIGURE K6
2-Year Nickel Subsulfide Inhalation Suite

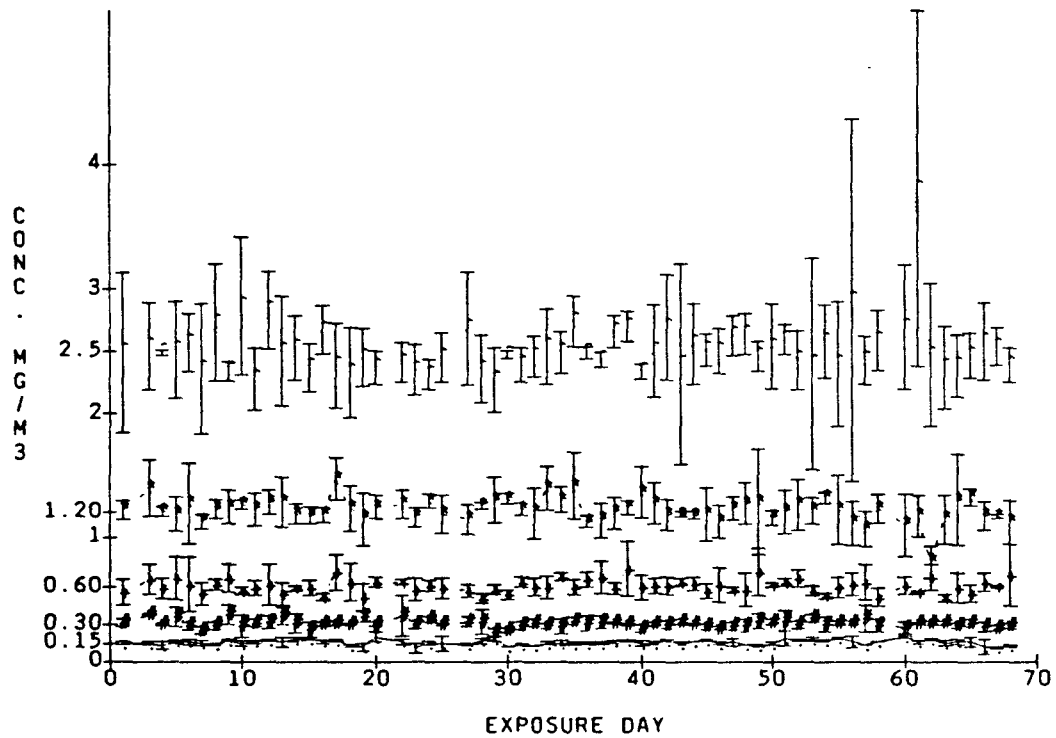


FIGURE K7
Daily Mean Filter Concentrations and Standard Deviations in the 13-Week Inhalation Study in Rats

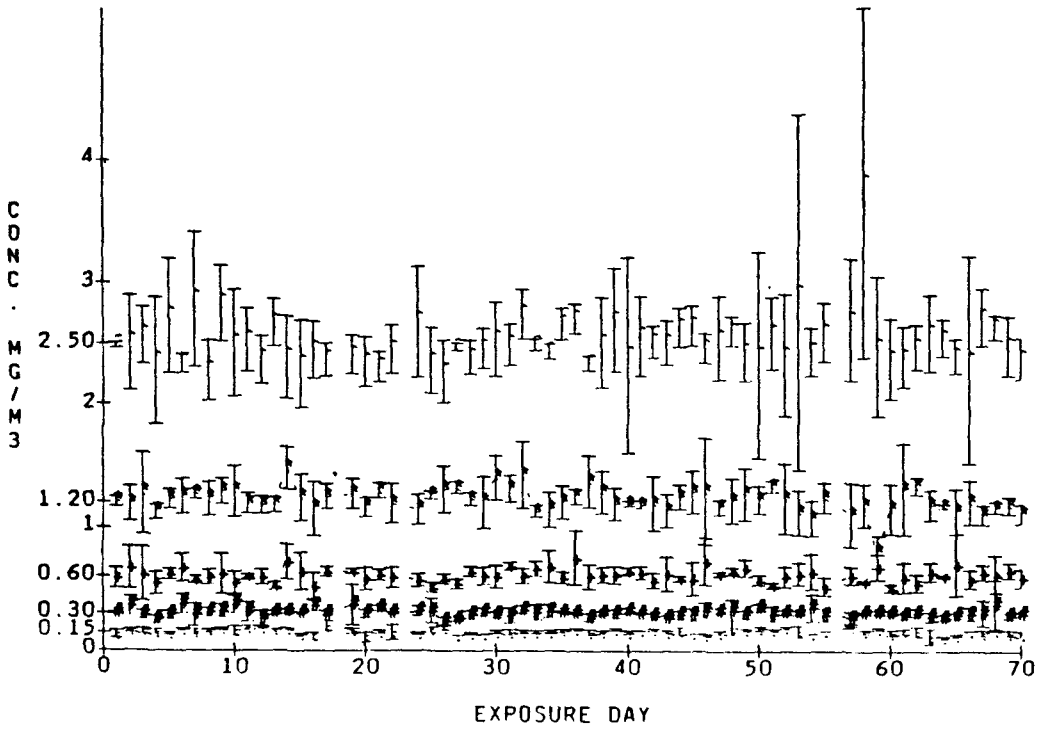


FIGURE K8
Daily Mean Filter Concentrations and Standard Deviations in the 13-Week Inhalation Study in Mice

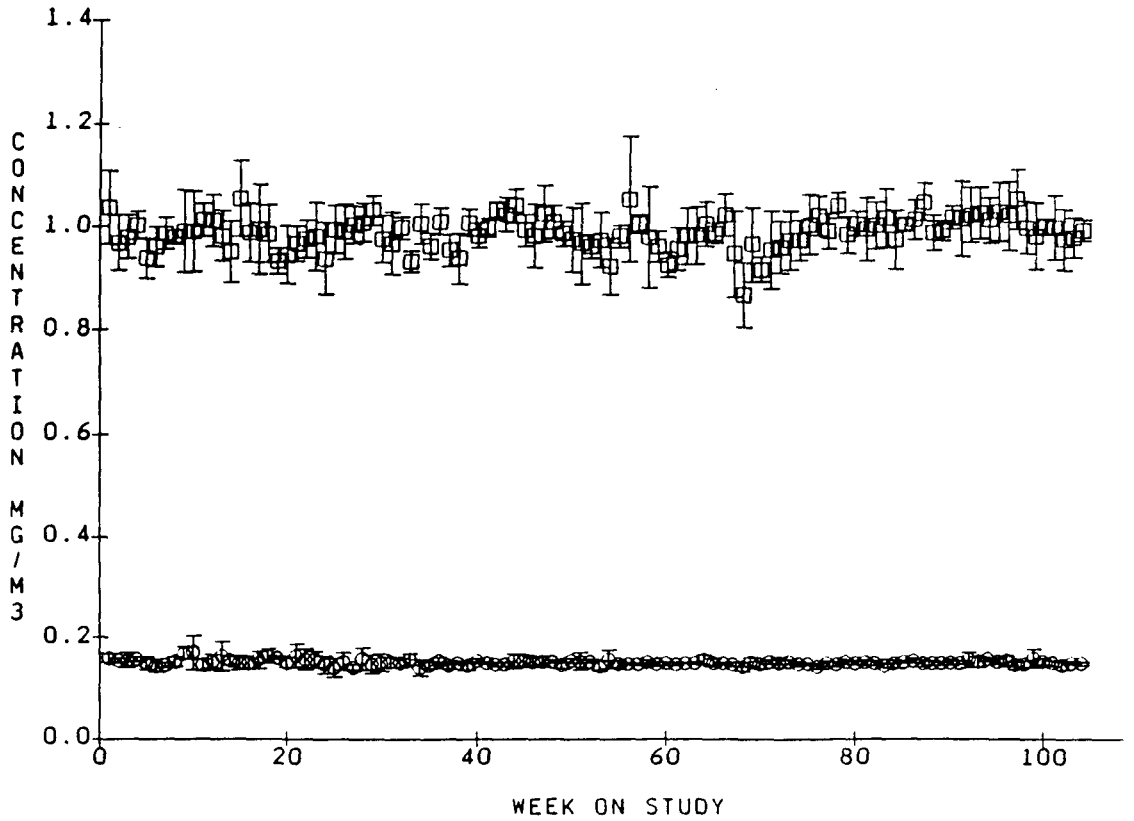


FIGURE K9
Weekly Mean Filter Concentrations and Standard Deviations in the 2-Year Inhalation Study in Rats

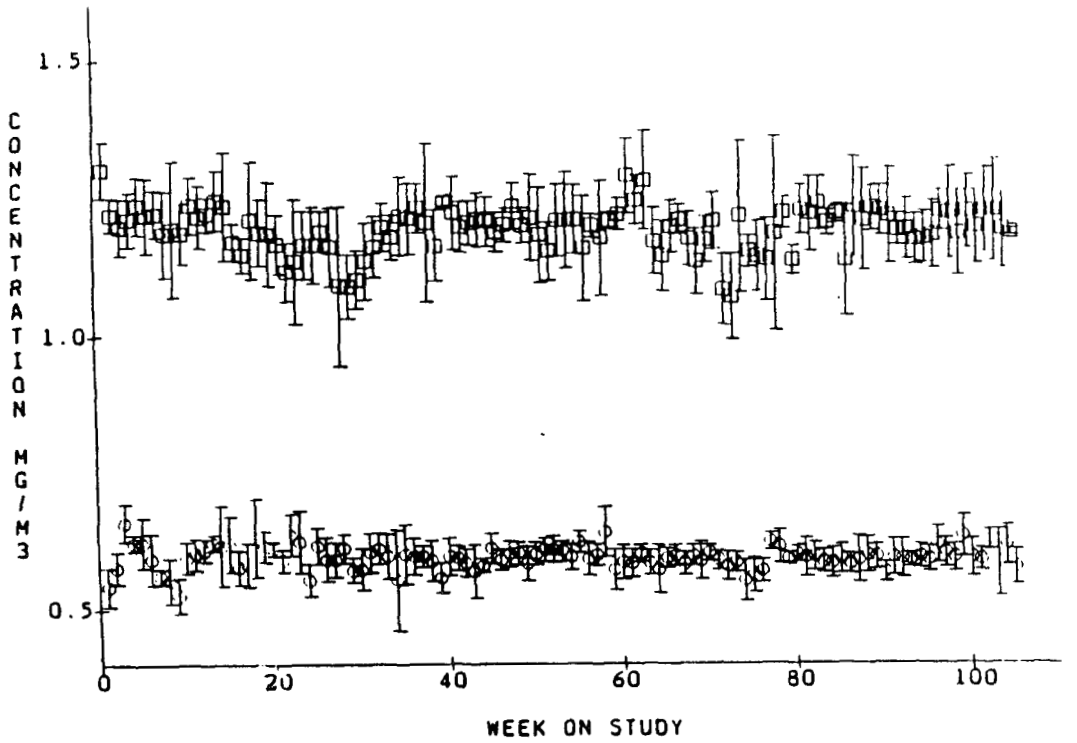


FIGURE K10
Weekly Mean Filter Concentrations and Standard Deviations
in the 2-Year Inhalation Study in Mice

TABLE K1
**Summary of Aerosol Size Measurements for the Rat and Mouse Chambers in the 16-Day Inhalation Studies of Nickel Subsulfide**

| Target Concentration ($mg/m^3$) | Mass Median Aerodynamic Diameter ($\mu m$) | Geometric Standard Deviation |
|---|---|---|
| 0.6 | 2.57 | 1.86 |
| 1.2 | 2.93 | 1.87 |
| 2.5 | 2.91 | 2.09 |
| 5 | 2.65 | 2.12 |
| 10 | 2.79 | 1.95 |

TABLE K2
**Summary of Aerosol Size Measurements for the Rat and Mouse Chambers in the 13-Week Inhalation Studies of Nickel Subsulfide**

| Target Concentration ($mg/m^3$) | Mass Median Aerodynamic Diameter ($\mu m$) | Geometric Standard Deviation |
|---|---|---|
| 0.15 | 2.40 | 2.70 |
| 0.3 | 2.71 | 2.23 |
| 0.6 | 2.16 | 1.99 |
| 1.2 | 2.37 | 2.12 |
| 2.5 | 2.60 | 2.17 |

TABLE K3
**Summary of Aerosol Size Measurements for the 0.15 and 1 mg/m³ Rat Chambers in the 2-Year Inhalation Study of Nickel Subsulfide**

| Date | 0.15 mg/m³ | | 1 mg/m³ | |
|---|---|---|---|---|
| | Mass Median Aerodynamic Diameter (μm) | Geometric Standard Deviation | Mass Median Aerodynamic Diameter (μm) | Geometric Standard Deviation |
| November 1988 | 2.54 | 2.54 | 2.01 | 1.89 |
| December 1988 | 2.21 | 2.18 | 2.06 | 1.69 |
| January 1989 | 2.51 | 2.05 | 2.06 | 2.26 |
| February 1989 | 1.99 | 2.69 | 2.10 | 1.84 |
| March 1989 | 2.99 | 2.02 | 1.80 | 2.03 |
| April 1989 | 2.19 | 2.93 | 1.89 | 2.29 |
| May 1989 | 2.65 | 1.77 | 1.91 | 2.22 |
| June 1989 | 2.11 | 1.82 | 1.93 | 1.81 |
| July 1989 | 2.10 | 2.22 | 1.89 | 1.91 |
| August 1989 | 1.91 | 3.47 | 2.12 | 1.63 |
| September 1989 | 2.38 | 1.85 | 2.17 | 1.97 |
| October 1989 | 2.17 | 2.51 | 2.31 | 1.88 |
| November 1989 | 1.65 | 2.09 | 2.06 | 1.86 |
| December 1989 | 2.58 | 2.51 | 2.60 | 2.15 |
| January 1990 | 1.96 | 2.09 | 2.26 | 2.06 |
| February 1990 | 1.87 | 2.78 | 1.92 | 1.98 |
| March 1990 | 2.19 | 2.23 | 2.15 | 2.02 |
| April 1990 | 2.55 | 2.08 | 2.00 | 1.67 |
| May 1990 | 1.72 | 2.33 | 1.95 | 1.90 |
| June 1990 | 1.76 | 2.76 | 1.94 | 1.87 |
| July 1990 | 2.33 | 2.15 | 1.83 | 1.98 |
| August 1990 | 1.98 | 2.24 | 2.05 | 1.99 |
| September 1990 | 1.79 | 2.38 | 1.97 | 1.95 |
| October 1990 | 1.98 | 2.50 | 1.88 | 1.98 |
| **Mean ± standard deviation** | 2.17 ± 0.34 | 2.34 ± 0.39 | 2.03 ± 0.18 | 1.95 ± 0.17 |

TABLE K4
**Summary of Aerosol Size Measurements for the 0.6 and 1.2 mg/m³ Mouse Chambers in the 2-Year Inhalation Study of Nickel Subsulfide**

| Date | 0.6 mg/m³ | | 1.2 mg/m³ | |
|---|---|---|---|---|
| | Mass Median Aerodynamic Diameter (μm) | Geometric Standard Deviation | Mass Median Aerodynamic Diameter (μm) | Geometric Standard Deviation |
| October 1988 | 2.35 | 1.91 | 2.32 | 1.95 |
| November 1988 | 2.63 | 1.73 | 2.37 | 1.80 |
| December 1988 | 2.39 | 2.00 | 2.45 | 1.85 |
| January 1989 | 2.42 | 2.01 | 2.19 | 1.74 |
| February 1989 | 2.74 | 1.99 | 2.26 | 2.16 |
| March 1989 | 2.77 | 1.79 | 2.38 | 1.99 |
| April 1989 | 2.31 | 2.06 | 1.94 | 2.03 |
| May 1989 | 2.95 | 1.79 | 2.09 | 1.66 |
| June 1989 | 2.27 | 2.03 | 2.54 | 1.84 |
| July 1989 | 1.76 | 1.91 | 1.93 | 2.00 |
| August 1989 | 2.28 | 1.98 | 1.97 | 1.98 |
| September 1989 | 2.09 | 2.26 | 2.05 | 2.05 |
| October 1989 | 1.96 | 1.90 | 2.28 | 1.92 |
| November 1989 | 1.77 | 1.95 | 2.06 | 1.88 |
| December 1989 | 2.31 | 2.32 | 2.72 | 2.01 |
| January 1990 | 1.84 | 2.25 | 2.08 | 2.04 |
| February 1990 | 2.01 | 2.16 | 1.88 | 1.96 |
| March 1990 | 1.99 | 2.08 | 1.98 | 1.99 |
| April 1990 | 2.33 | 1.82 | 2.24 | 1.76 |
| May 1990 | 2.14 | 1.85 | 2.05 | 1.85 |
| June 1990 | 1.90 | 1.93 | 2.14 | 1.82 |
| July 1990 | 2.19 | 1.98 | 1.86 | 2.00 |
| August 1990 | 2.09 | 1.94 | 2.22 | 1.85 |
| September 1990 | 2.24 | 1.79 | 2.34 | 1.76 |
| **Mean ± standard deviation** | 2.24 ± 0.31 | 1.98 ± 0.16 | 2.18 ± 0.22 | 1.91 ± 0.12 |

# APPENDIX L
# INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

## TABLE L1
## Ingredients of NIH-07 Rat and Mouse Ration[a]

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

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

## TABLE L2
## Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE L3
Nutrient Composition of NIH-07 Rat and Mouse Ration

| Nutrient | Mean ± Standard Deviation | Range | Number of Samples |
|---|---|---|---|
| Protein (% by weight) | 23.20 ± 0.70 | 21.80 — 24.20 | 22 |
| Crude fat (% by weight) | 5.30 ± 0.23 | 4.60 — 5.60 | 22 |
| Crude fiber (% by weight) | 3.60 ± 0.43 | 2.80 — 4.30 | 22 |
| Ash (% by weight) | 6.50 ± 0.22 | 6.10 — 6.90 | 22 |
| **Amino Acids (% of total diet)** | | | |
| Arginine | 1.287 ± 0.084 | 1.100 — 1.390 | 10 |
| Cystine | 0.306 ± 0.075 | 0.181 — 0.400 | 10 |
| Glycine | 1.160 ± 0.050 | 1.060 — 1.220 | 10 |
| Histidine | 0.580 ± 0.024 | 0.531 — 0.608 | 10 |
| Isoleucine | 0.917 ± 0.034 | 0.867 — 0.965 | 10 |
| Leucine | 1.972 ± 0.052 | 1.850 — 2.040 | 10 |
| Lysine | 1.273 ± 0.051 | 1.200 — 1.370 | 10 |
| Methionine | 0.437 ± 0.115 | 0.306 — 0.699 | 10 |
| Phenylalanine | 0.994 ± 0.125 | 0.665 — 1.110 | 10 |
| Threonine | 0.896 ± 0.055 | 0.824 — 0.985 | 10 |
| Tryptophan | 0.223 ± 0.160 | 0.107 — 0.671 | 10 |
| Tyrosine | 0.677 ± 0.105 | 0.564 — 0.794 | 10 |
| Valine | 1.089 ± 0.057 | 0.962 — 1.170 | 10 |
| **Essential Fatty Acids (% of total diet)** | | | |
| Linoleic | 2.389 ± 0.233 | 1.830 — 2.570 | 9 |
| Linolenic | 0.277 ± 0.036 | 0.210 — 0.320 | 9 |
| **Vitamins** | | | |
| Vitamin A (IU/kg) | 6,537 ± 2,005 | 4,180 — 12,140 | 22 |
| Vitamin D (IU/kg) | 4,450 ± 1,382 | 3,000 — 6,300 | 4 |
| α-Tocopherol (ppm) | 36.92 ± 9.32 | 22.5 — 48.9 | 9 |
| Thiamine (ppm) | 19.20 ± 2.40 | 16.0 — 28.0 | 22 |
| Riboflavin (ppm) | 7.92 ± 0.93 | 6.10 — 9.00 | 10 |
| Niacin (ppm) | 100.95 ± 25.92 | 65.0 — 150.0 | 9 |
| Pantothenic acid (ppm) | 30.30 ± 3.60 | 23.0 — 34.6 | 10 |
| Pyridoxine (ppm) | 9.25 ± 2.62 | 5.60 — 14.0 | 10 |
| Folic acid (ppm) | 2.51 ± 0.64 | 1.80 — 3.70 | 10 |
| Biotin (ppm) | 0.267 ± 0.049 | 0.19 — 0.35 | 10 |
| Vitamin $B_{12}$ (ppb) | 40.14 ± 20.04 | 10.6 — 65.0 | 10 |
| Choline (ppm) | 3,068 ± 314 | 2,400 — 3,430 | 9 |
| **Minerals** | | | |
| Calcium (%) | 1.21 ± 0.10 | 1.06 — 1.54 | 22 |
| Phosphorus (%) | 0.95 ± 0.03 | 0.89 — 1.00 | 22 |
| Potassium (%) | 0.887 ± 0.067 | 0.772 — 0.971 | 8 |
| Chloride (%) | 0.526 ± 0.092 | 0.380 — 0.635 | 8 |
| Sodium (%) | 0.315 ± 0.034 | 0.258 — 0.370 | 10 |
| Magnesium (%) | 0.168 ± 0.008 | 0.151 — 0.180 | 10 |
| Sulfur (%) | 0.274 ± 0.063 | 0.208 — 0.420 | 10 |
| Iron (ppm) | 356.2 ± 90.0 | 255.0 — 523.0 | 10 |
| Manganese (ppm) | 92.24 ± 5.35 | 81.70 — 99.40 | 10 |
| Zinc (ppm) | 58.14 ± 9.91 | 46.10 — 81.60 | 10 |
| Copper (ppm) | 11.50 ± 2.40 | 8.09 — 15.39 | 10 |
| Iodine (ppm) | 3.70 ± 1.14 | 1.52 — 5.83 | 10 |
| Chromium (ppm) | 1.71 ± 0.45 | 0.85 — 2.09 | 9 |
| Cobalt (ppm) | 0.797 ± 0.23 | 0.49 — 1.15 | 6 |

**TABLE L4**
**Contaminant Levels in NIH-07 Rat and Mouse Ration[a]**

| | Mean ± Standard Deviation[b] | Range | Number of Samples |
|---|---|---|---|
| **Contaminants** | | | |
| Arsenic (ppm) | 0.27 ± 0.18 | 0.06 — 0.60 | 22 |
| Cadmium (ppm) | 0.08 ± 0.02 | 0.05 — 0.10 | 22 |
| Lead (ppm) | 0.23 ± 0.09 | 0.10 — 0.40 | 22 |
| Mercury (ppm)[c] | 0.04 ± 0.02 | 0.02 — 0.11 | 22 |
| Selenium (ppm) | 0.43 ± 0.25 | 0.20 — 1.20 | 22 |
| Aflatoxins (ppb)[c,d] | <5.0 | | 21 |
| Nitrate nitrogen (ppm)[e] | 17.00 ± 4.20 | 8.60 — 24.0 | 22 |
| Nitrite nitrogen (ppm)[e] | 0.26 ± 0.20 | 0.10 — 0.70 | 22 |
| BHA (ppm)[f] | 1.41 ± 0.59 | 1.00 — 3.00 | 22 |
| BHT (ppm)[f] | 1.41 ± 0.59 | 1.00 — 3.00 | 22 |
| Aerobic plate count (CFU/g) | 42,745 ± 26,010 | 6,700 — 120,000 | 22 |
| Coliform (MPN/g) | 4.7 ± 5.6 | 3 — 23 | 22 |
| *Escherichia coli* (MPN/g) | <3.00 | | 22 |
| *Salmonella* (MPN/g) | Negative | | |
| Total nitrosoamines (ppb)[g] | 7.80 ± 3.00 | 3.60 — 16.50 | 22 |
| *N*-Nitrosodimethylamine (ppb)[g] | 6.00 ± 2.74 | 2.60 — 13.00 | 22 |
| *N*-Nitrosopyrrolidine (ppb)[g] | 1.89 ± 0.93 | 1.00 — 3.90 | 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 | <0.1 | | 22 |
| Estimated PCBs | <0.2 | | 22 |
| Ronnel | <0.01 | | 22 |
| Ethion | <0.02 | | 22 |
| Trithion | <0.05 | | 22 |
| Diazinon | <0.1 | | 22 |
| Methyl parathion | <0.02 | | 22 |
| Ethyl parathion | <0.02 | | 22 |
| Malathion | 0.23 ± 0.23 | <0.05 — 1.00 | 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 is hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] All values were less than the detection limit.
[d] No aflatoxin measurement was recorded for the lot milled October 2, 1989.
[e] Sources of contamination: alfalfa, grains, and fish meal.
[f] Sources of contamination: soy oil and fish meal.
[g] All values were corrected for percent recovery.

# APPENDIX M
# 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 13-week and 2-year studies. Blood from each animal was collected, allowed to clot and the serum separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (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** | |
| **13-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 |
| 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 | 7 months, 15 months, study termination |
| RCV/SDA | 7 months, 15 months, study termination |
| Sendai | 7 months, 15 months, study termination |
| Immunofluorescence Assay | |
| RCV/SDA | 7 months |
| Hemagglutination Inhibition | |
| H-1 | 7 months, 15 months, study termination |
| KRV | 7 months, 15 months, study termination |

| Method and Test | Time of Analysis |
|---|---|
| **MICE** | |
| **13-Week Study** | |
| Complement Fixation | |
| LCM (lymphocytic choriomeningitis virus) | Study termination |
| ELISA | |
| Ectromelia virus | Study termination |
| GDVII (mouse encephalomyelitis virus) | Study termination |
| Mouse adenoma virus | 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 | |
| EDIM (epizootic diarrhea of infant mice) | 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 | 7 months, 15 months, study termination |
| EDIM | Study termination |
| GDVII | 7 months, 15 months, study termination |
| LCM | 15 months, study termination |
| MVM | 7 months |
| Mouse adenoma virus | 7 months, study termination |
| MHV | 7 months, 15 months, study termination |
| *M. arthritidis* | Study termination |
| *M. pulmonis* | Study termination |
| PVM | 7 months, 15 months, study termination |
| Reovirus 3 | 7 months, 15 months, study termination |
| Sendai | 7 months, 15 months, study termination |
| Immunofluorescence Assay | |
| EDIM | 7 months, 15 months, study termination |
| LCM | 7 months, 15 months, study termination |
| MVM | 15 months |
| Mouse adenoma virus | 15 months |
| MHV | Study termination |
| Reovirus 3 | 7 months, study termination |
| Sendai | Study termination |

| Method and Test | Time of Analysis |
|---|---|
| **MICE** (continued) | |
| **2-Year Study** (continued) | |
| Hemagglutination Inhibition | |
| K | 7 months, 15 months, study termination |
| MVM | Study termination |
| Polyoma virus | 7 months, 15 months, study termination |

Results of the serology tests are presented in Table M1.

**TABLE M1**
**Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Inhalation Studies of Nickel Subsulfide**

| Interval | Incidence of Antibody in Sentinel Animals | Positive Serologic Reaction for |
|---|---|---|
| **13-Week Studies** | | |
| **Rats** | | |
| Study termination | 0/10 | None positive |
| **Mice** | | |
| Study termination | 0/8 | None positive |
| **2-Year Studies** | | |
| **Rats** | | |
| 7 Months | 0/12 | None positive |
| 15 Months | 0/12 | None positive |
| Study termination | 2/12 | *M. arthritidis*[a] |
| **Mice** | | |
| 7 Months | 2/12 | Reovirus 3 |
| 15 Months | 0/12 | None positive |
| Study termination | 0/12 | None positive |

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to a cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive, and there were no clinical signs or histopathologic changes of *M. arthritidis* infection in rats with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positive.

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