NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 454

TOXICOLOGY AND CARCINOGENESIS STUDIES OF NICKEL SULFATE HEXAHYDRATE

(CAS NO. 10101-97-0)

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.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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July 1996

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

J.K. Dunnick, Ph.D., Study Scientist
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
R.E. Chapin, Ph.D.
M.P. Dieter, Ph.D.
M.R. Elwell, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
A. Radovsky, D.V.M., Ph.D.
G.N. Rao, D.V.M., Ph.D.
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

Experimental Pathology Laboratories, Inc.

Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
S. Botts, D.V.M., Ph.D.
E.T. Gaillard, D.V.M., Ph.D.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

Lovelace Inhalation Toxicology Research Institute

Conducted 16-day studies, evaluated pathology findings

R.O. McClellan, D.V.M., Director
C.H. Hobbs, D.V.M., Principal Investigator
J.M. Benson, Ph.D., Study Director
D.G. Burt, D.V.M.
R.L. Carpenter, Ph.D.
F.F. Hahn, D.V.M., Ph.D.
P.J. Haley, D.V.M.
J.A. Pickrell, D.V.M., Ph.D.

Conducted 13-week studies, evaluated pathology findings

R.O. McClellan, D.V.M., Director
C.H. Hobbs, D.V.M., Principal Investigator
J.M. Benson, Ph.D., Study Director
D.E. Bice, Ph.D.
D.G. Burt, D.V.M.
Y.S. Cheng, Ph.D.
F.F. Hahn, D.V.M., Ph.D.
J.A. Pickrell, D.V.M., Ph.D.
G.M. Shopp, Jr., Ph.D.

Conducted 2-year studies, evaluated pathology findings

C.H. Hobbs, D.V.M., Principal Investigator
J.M. Benson, Ph.D., Study Director
E.B. Barr, M.S.
D.G. Burt, D.V.M.
Y.S. Cheng, Ph.D.
G.L. Finch, Ph.D.
F.F. Hahn, D.V.M., Ph.D.
P.J. Haley, D.V.M., Ph.D.
K.R. Maples, Ph.D.
K.J. Nikula, D.V.M., Ph.D.

NTP Pathology Working Group

Evaluated slides, prepared pathology report on rats (2 June 1994)

M.P. Jokinen, D.V.M., Chair
Pathology Associates, Inc.
J. Cullen, V.M.D., Ph.D., Observer
NiPERA, Inc.
D. Dixon, D.V.M., Ph.D.
National Toxicology Program
E.T. Gaillard, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
K.T. Morgan, B.V.Sc., Ph.D.
Chemical Industry Institute of Toxicology
A. Radovsky, D.V.M., Ph.D.
National Toxicology Program

Analytical Sciences, Inc.

Provided statistical analyses

R.W. Morris, M.S., Principal Investigator
N.G. Mintz, B.S.
S. Rosenblum, M.S.

Evaluated slides, prepared pathology report on mice (4 Month 1993)

R.A. Herbert, D.V.M., Ph.D., Chair
National Toxicology Program
S. Botts, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
D. Dixon, D.V.M., Ph.D.
National Toxicology Program
S.L. Eustis, D.V.M., Ph.D.
National Toxicology Program
J. Everitt, D.V.M.
Chemical Industry Institute of Toxicology
J.R. Hailey, D.V.M.
National Toxicology Program
J. Swenberg, D.V.M., Ph.D., Observer
NiPERA, Inc.
K. Takahashi, D.V.M., M.Sc., Ph.D.
National Toxicology Program

Biotechnical Services, Inc.

Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
C.M. Bailey, B.S. Pharm.
J.R. Carlton, B.A.
S.R. Gunnels, M.A.
T.A. King-Hunter, B.S.
S.M. Swift, B.S.

CONTENTS

ABSTRACT

$NiSO_4 \cdot 6H_2O$

NICKEL SULFATE HEXAHYDRATE

CAS No. 10101-97-0

Chemical Formula: $NiSO_4 \cdot 6H_2O$ Molecular Weight: 262.86

Synonyms: Blue salt; hexahydrate, nickel (2+) salt; nickel monosulfate hexahydrate; nickel (2+) sulfate hexahydrate; nickel (II) sulfate hexahydrate; nickel sulphate hexahydrate; nickelous sulfate hexahydrate; nickelous sulphate hexahydrate; single nickel salt, sulfuric acid

Nickel sulfate hexahydrate is used in nickel plating, as a mordant in dyeing and printing textiles, as a blackening agent for zinc and brass, and in the manufacture of organic nickel salts. Nickel sulfate hexahydrate was nominated by the National Cancer Institute to the NTP 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 sulfate hexahydrate (greater than 98% pure) by inhalation for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in L5178Y mouse lymphoma cells.

16-Day Study in Rats

Groups of five male and five female F344/N rats were exposed to 0, 3.5, 7, 15, 30, or 60 mg nickel sulfate hexahydrate/m^3 (equivalent to 0, 0.7, 1.4, 3.1, 6.1, or 12.2 mg nickel/m^3). Rats were exposed on weekdays only, for a total of 12 exposure days during a 16-day period. Additional groups of four or five male and female F344/N rats were exposed to 0, 3.5, 15, or 30 mg nickel sulfate hexahydrate/m^3 for tissue burden studies. In the core study, two 60 mg/m^3 males, one 30 mg/m^3 female, and all 60 mg/m^3 females died before the end of the study. Final mean body weights of all exposed groups of males and females were significantly lower than those of the controls, as were mean body weight gains of male rats. Clinical findings included increased rates of respiration and reduced activity levels in rats in all exposure groups, except those exposed to 3.5 mg/m^3. Absolute lung weights of 60 mg/m^3 males and of all exposed groups of females were significantly greater than those of the controls, as were the relative lung weights of all exposed groups of males and females. Inflammation (including degeneration and necrosis of the bronchiolar epithelium) occurred in the lungs of all exposed groups of males and females. Atrophy of the olfactory epithelium occurred in the nasal passages of all exposed groups of males (except 60 mg/m^3) and in 15, 30, and 60 mg/m^3 females. Lymphoid hyperplasia in the bronchial or mediastinal lymph nodes was observed in 30 mg/m^3 males and in 60 mg/m^3 males and females. The concentration of nickel in the lungs of all exposed groups of males and females was greater than in control animals.

16-Day Study in Mice

Groups of five male and five female $B6C3F_1$ mice were exposed to 0, 3.5, 7, 15, 30, or 60 mg nickel sulfate hexahydrate/m^3. Mice were exposed on weekdays only, for a total of 12 exposure days during a 16-day period. Additional groups of

five male and five female B6C3F$_1$ mice were exposed to 0 or 3.5 mg nickel sulfate hexahydrate/m^3 for tissue burden studies. All core study mice exposed to 7 mg/m^3 or greater died before the end of the study; all control and 3.5 mg/m^3 mice survived to the end of the study. Final mean body weights and weight gains of 7, 15, 30, and 60 mg/m^3 males and females were significantly less than those of the controls, and clinical findings in these groups included emaciation, lethargy, and rapid respiration rates. Absolute and relative lung weights of male and female mice exposed to 7 mg/m^3 or greater were significantly greater than those of the controls. Only tissues from mice exposed to 0, 3.5, or 7 mg/m^3 were examined histopathologically. Inflammation occurred in the lungs of 3.5 and 7 mg/m^3 males and females; necrosis of the alveolar and bronchiolar epithelium was a component of the inflammation in 7 mg/m^3 males and females. In addition, atrophy of the olfactory epithelium of the nasal passages was observed in 3.5 mg/m^3 males and females. Nickel concentrations in the lungs of mice exposed to 3.5 mg/m^3 were greater than those in the controls.

13-Week Study in Rats

Groups of ten male and ten female F344/N rats were exposed to 0, 0.12, 0.25, 0.5, 1, or 2 mg nickel sulfate hexahydrate (equivalent to 0, 0.03, 0.06, 0.11, 0.22, or 0.44 mg nickel/m^3), 5 days per week for 13 weeks. Additional groups of six male and six female F344/N rats were exposed to 0, 0.12, 0.5, or 2 mg nickel sulfate hexahydrate/m^3 for tissue burden studies. In the core study, one 2 mg/m^3 male rat died before the end of the study; all other males and all females survived until the end of the study. Final mean body weights and body weight gains of all exposed groups were similar to those of the controls. There were no significant clinical findings noted during the study. Exposure-related increases in neutrophil and lymphocyte numbers occurred and were most pronounced in female rats. With the exception of 0.12 mg/m^3 rats, absolute and relative lung weights of all exposed groups were generally significantly greater than those of the controls. Exposure-related increases in the incidence and severity of inflammatory lesions (alveolar macrophages, chronic inflammation, and interstitial infiltration) occurred in the lungs of all exposed groups of males and females. Lymphoid hyperplasia of the bronchial and/or mediastinal lymph nodes occurred in males exposed to 0.5 mg/m^3 or greater. Atrophy of the olfactory epithelium occurred in males and females exposed to 0.5, 1, and 2 mg/m^3 and in 0.25 mg/m^3 females. The concentration of nickel in the lungs of 0.5 and 2 mg/m^3 rats was greater than that in the lungs of control animals at 4, 9, and 13 weeks for males and at 13 weeks for females.

13-Week Study in Mice

Groups of ten male and ten female B6C3F$_1$ mice were exposed to 0, 0.12, 0.25, 0.5, 1, or 2 mg nickel sulfate hexahydrate, 5 days per week for 13 weeks. Additional groups of up to five or six male and female B6C3F$_1$ mice were exposed to 0, 0.12, 0.5, or 2 mg nickel sulfate hexahydrate/m^3 for tissue burden studies. In the core study, four control males, three control females, and one 0.12 mg/m^3 male died before the end of the study; the deaths were not considered to be chemical related, and all other mice survived to the end of the study. The final mean body weights and body weight gains of all exposed groups were similar to those of the controls. There were no chemical-related clinical findings. Hematology changes similar to those reported in female rats occurred in female mice, but the mice were minimally affected. The absolute and relative lung weights of 1 mg/m^3 males and 2 mg/m^3 males and females were significantly greater than those of the controls. Increased numbers of alveolar macrophages occurred in all males and females exposed to 0.5 mg/m^3 or greater. Chronic active inflammation and fibrosis occurred in 1 and 2 mg/m^3 males and females. Lymphoid hyperplasia of the bronchial lymph node and atrophy of the olfactory epithelium in the nasal passages were observed in 2 mg/m^3 males and females. Nickel concentration in the lung of 2 mg/m^3 females was significantly greater than in control animals.

2-YEAR STUDY IN RATS

Groups of 63 to 65 male and 63 to 64 female rats were exposed to nickel sulfate hexahydrate by inhalation at concentrations of 0, 0.12, 0.25, or 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, or 0.11 mg nickel/m^3). Animals were exposed for 6 hours plus T_{90} (8 minutes) 5 days per week for 104 weeks. Five male and five female rats from each group were evaluated at 7 months for histopathology; an additional seven males and seven females from each group were evaluated at 7 months for nickel tissue burden in the lung and kidney; and five males and five females from each group were evaluated at 15 months for alterations in hematology, nickel tissue burden in the lung and kidney, and histopathology.

Survival, Body Weights, Clinical Findings, and Hematology

The survival rates of all exposed groups of males and females were similar to those of the controls. Mean body weights of 0.5 mg/m^3 female rats were slightly lower (6% to 9%) than those of the controls throughout the second year of the study; final mean body weights of all exposed groups of males and 0.12 and 0.25 mg/m^3 females were similar to those of the controls. There were no clinical findings or hematology differences that were considered to be related to nickel sulfate hexahydrate administration.

Pathology Findings

No exposure-related neoplasms occurred in male or female rats exposed by inhalation to nickel sulfate hexahydrate for 2 years. Increased incidences of inflammatory lung lesions were generally observed in all exposed groups of male and female rats at the end of the study. The incidences of chronic active inflammation, macrophage hyperplasia, alveolar proteinosis, and fibrosis were markedly increased in male and female rats exposed to 0.25 or 0.5 mg/m^3. Increased incidences of lymphoid hyperplasia in the bronchial lymph nodes occurred in 0.5 mg/m^3 male and female rats at the end of the 2-year study. The incidences of atrophy of the olfactory epithelium in 0.5 mg/m^3 males and females were significantly greater than those in controls at the end of the study.

Tissue Burden Analyses

Lung nickel burdens in exposed male and female rats were greater than those in the controls at the 7- and 15-month interim evaluations, and lung nickel burdens values increased with increasing exposure concentration.

2-YEAR STUDY IN MICE

Groups of 80 male and 80 female mice were exposed to nickel sulfate hexahydrate by inhalation at concentrations of 0, 0.25, 0.5, or 1 mg/m^3 (equivalent to 0, 0.06, 0.11, or 0.22 mg nickel/m^3). Animals were exposed for 6 hours plus T_{90} (8 minutes) 5 days per week for 104 weeks. Five male and five female mice from each group were evaluated at 7 months for histopathology; five males and five females from each group were evaluated at 7 months for nickel tissue burden in the lung and kidney; five males and five females from each group were evaluated at 15 months for alterations in hematology and histopathology; and five males and five females from each group were evaluated at 15 months for nickel tissue burden in the lung and kidney.

Survival, Body Weights, Clinical Findings, and Hematology

The survival rates of all exposed groups of males and females were similar to those of the controls. The mean body weights of 1 mg/m^3 males and of all exposed groups of females were lower than those of the controls during the second year of the study. There were no clinical findings or hematology differences considered to be related to chemical exposure.

Pathology Findings

Inflammatory lesions of the lung generally occurred in all exposed groups of male and female mice at the end of the 2-year study. These lesions included macrophage hyperplasia, chronic active inflammation, bronchialization (alveolar epithelial hyperplasia), alveolar proteinosis, and infiltrating cells in the interstitium. Incidences of macrophage hyperplasia and/or lymphoid hyperplasia occurred in the bronchial lymph nodes of most of the 1 mg/m^3 males and females and in some 0.5 mg/m^3 females at the end of the 2-year study. Atrophy of the olfactory epithelium was observed in 0.5 and 1 mg/m^3 males and in all exposed groups of females at the end of the 2-year study.

Tissue Burden Analyses

At the 7- and 15-month interim evaluations, lung nickel burden parameters measured in control and exposed groups were below the limit of detection. Absolute lung weights of 0.5 and 1 mg/m^3 lung burden study females were significantly greater than those of the controls at 15 months.

GENETIC TOXICOLOGY

Nickel sulfate hexahydrate (500 to 800 μg/mL) was tested for induction of trifluorothymidine resistance in L5178Y mouse lymphoma cells. A positive response was observed in the absence of S9. The test was not performed with S9.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of nickel sulfate hexahydrate in male or female F344/N rats exposed to 0.12, 0.25, or 0.5 mg/m^3 (0.03, 0.06, or 0.11 mg nickel/m^3). There was *no evidence of carcinogenic activity* of nickel sulfate hexahydrate in male or female B6C3F$_1$ mice exposed to 0.25, 0.5, or 1 mg/m^3 (0.06, 0.11, or 0.22 mg nickel/m^3).

Exposure of rats to nickel sulfate hexahydrate by inhalation for 2 years resulted in increased incidences of chronic active inflammation, macrophage hyperplasia, alveolar proteinosis, and fibrosis of the lung; lymphoid hyperplasia of the bronchial lymph node; and atrophy of the olfactory epithelium. Exposure of mice to nickel sulfate hexahydrate by inhalation for 2 years resulted in increased incidences of chronic active inflammation, bronchialization (alveolar epithelial hyperplasia), macrophage hyperplasia, interstitial infiltration, and alveolar proteinosis of the lung; lymphoid and macrophage hyperplasia of the bronchial lymph node; and atrophy of the olfactory epithelium.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Nickel Sulfate Hexahydrate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure concentrations	0, 0.12, 0.25, or 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, or 0.11 mg nickel/m^3)	0, 0.12, 0.25, or 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, or 0.11 mg nickel/m^3)	0, 0.25, 0.5, or 1 mg/m^3 (equivalent to 0, 0.06, 0.11, or 0.22 mg nickel/m^3)	0, 0.25, 0.5, or 1 mg/m^3 (equivalent to 0, 0.06, 0.11, or 0.22 mg nickel/m^3)
Body weights	Exposed groups similar to controls	0.5 mg/m^3 group lower than controls	1 mg/m^3 group lower than controls	Exposed groups lower than controls
2-Year survival rates	16/54, 16/53, 18/53, 21/53	22/53, 17/53, 28/54, 29/55	26/61, 23/61, 24/62, 25/62	34/61, 39/60, 45/60, 37/60
Nonneoplastic effects	Lung: chronic active inflammation (14/54, 11/53, 42/53, 46/53); macrophage hyperplasia (7/54, 9/53, 35/53, 48/53); alveolar proteinosis (0/54, 0/53, 12/53, 41/53); fibrosis (3/54, 6/53, 35/53, 43/53) Bronchial lymph node: lymphoid hyperplasia (0/51, 0/49, 3/47, 10/52) Nose (olfactory epithelium): atrophy (0/54, 0/52, 3/53, 7/53)	Lung: chronic active inflammation (14/52, 13/53, 49/53, 52/54); macrophage hyperplasia (9/52, 10/53, 32/53, 45/54); alveolar proteinosis (1/52, 0/53, 22/53, 49/54); fibrosis (8/52, 7/53, 45/53, 49/54) Bronchial lymph node: lymphoid hyperplasia (2/50, 1/52, 0/51, 11/49) Nose (olfactory epithelium): atrophy (0/51, 1/52, 1/53, 7/54)	Lung: chronic active inflammation (1/61, 2/61, 8/62, 29/61); bronchialization (1/61, 4/61, 19/62, 39/61); macrophage hyperplasia (6/61, 9/61, 35/62, 59/61); interstitial infiltration (1/61, 0/61, 3/62, 17/61); alveolar proteinosis (0/61, 0/61, 0/62, 42/61) Bronchial lymph node: lymphoid hyperplasia (2/46, 4/49, 2/45, 17/54); macrophage hyperplasia (0/46, 0/49, 8/45, 39/54) Nose (olfactory epithelium): atrophy (0/61, 0/61, 12/61, 37/60)	Lung: chronic active inflammation (1/61, 7/60, 14/60, 40/60); bronchialization (0/61, 9/60, 32/60, 45/60); macrophage hyperplasia (7/61, 24/60, 53/60, 59/60); interstitial infiltration (0/61, 4/60, 16/60, 39/60); alveolar proteinosis (0/61, 0/60, 11/60, 45/60) Bronchial lymph node: lymphoid hyperplasia (15/50, 9/54, 16/58, 26/56); macrophage hyperplasia (2/50, 0/54, 14/58, 37/56) Nose (olfactory epithelium): atrophy (3/61, 2/59, 1/60, 17/60)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
L5178Y mouse lymphoma cells gene mutations:	Positive without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on nickel sulfate hexahydrate 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.

Arnold L. Brown, M.D., Chair
University of Wisconsin Medical School
Madison, WI

Thomas L. Goldsworthy, Ph.D., Principal Reviewer
Department of Environmental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Meryl H. Karol, Ph.D.*
Department of Environmental Occupational Health
University of Pittsburgh
Pittsburgh, PA

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

Claudia S. Miller, M.D.
University of Texas Health Sciences Center
San Antonio, TX

Janardan K. Reddy, M.D.*
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D., Principal Reviewer
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D.
Division of Biostatistics
Harvard School of Public Health and
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D., Principal Reviewer
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Mary Jo Vodicnik, Ph.D.*
Lilly MSG Development Center
Belgium

Jerrold M. Ward, D.V.M., Ph.D.
National Cancer Institute
Frederick, MD

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

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

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of nickel sulfate hexahydrate by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in male and female rats and mice. The proposed conclusions were *no evidence of carcinogenic activity* in male and female F344/N rats and *no evidence of carcinogenic activity* in male and female B6C3F$_1$ mice.

Dr. Taylor, a principal reviewer, agreed with the proposed conclusions. He said that the exposure concentrations could have been slightly higher.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions although he also thought the exposure concentrations selected might have been higher, especially in mice. Dr. Goldsworthy observed that exposure concentrations selected for minimal to mild responses at 13 weeks resulted in minimal to mild changes at 2 years, including no target tissue weight changes in some circumstances. Dr. M.R. Elwell, NIEHS, commented that the high dose was based on the morphologic appearance of the lungs being similar to that in high dose animals in the nickel oxide study. Based on body weight decreases, he believed that a higher exposure concentration might have resulted in exceeding the maximum tolerated dose. Dr. Goldsworthy said that target tissue (lung) nickel concentrations were not observed at any exposure concentration in mice, and thus, exposure-response linkages could not be made, limiting extrapolation of data and comparison to other nickel studies. Dr. J.R. Bucher, NIEHS, explained that lung burden information would have been used if in the prechronic studies there had been a non-linear increase, i.e., an overload condition was reached with a particular dose. This did not occur, so in this case all exposure concentrations were selected based on inflammatory changes in the lung and decreases in body weight gain.

Dr. Russo, the third principal reviewer, agreed with the proposed conclusions. She stated that the lymph node hyperplasia should be documented in order to prove that the lesions represented a reactive process, either a reactive hyperplasia or a granulomatous reaction, versus monoclonal proliferation or early lymphoma.

Dr. Klaassen expressed surprise in view of the epidemiological data that the nickel compounds did not provide stronger evidence of carcinogenic activity in the NTP animal studies by the inhalation route. Dr. Dunnick noted the evidence for multiple exposures in the workplace and speculated that this could result in concurrent biologic events that might enhance cancer development. Dr. Goldsworthy commented again that since toxicity did not predict or relate to carcinogenicity, future studies with metals and inhaled toxicants should be more concerned with pulmonary function. Dr. G.W. Lucier, NIEHS, said that the discussions regarding dose selection and how one compares studies across a class of chemicals illustrate why the NTP in its more recent study designs is incorporating mechanistic markers or toxicokinetic profiles to enable better comparisons across organs and species.

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

INTRODUCTION

$NiSO_4 \cdot 6H_2O$

NICKEL SULFATE HEXAHYDRATE

CAS No. 10101-97-0

Chemical Formula: $NiSO_4 \cdot 6H_2O$ Molecular Weight: 262.86

Synonyms: Blue salt; hexahydrate, nickel (2+) salt; nickel monosulfate hexahydrate; nickel (2+) sulfate hexahydrate; nickel (II) sulfate hexahydrate; nickel sulphate hexahydrate; nickelous sulfate hexahydrate; nickelous sulphate hexahydrate; single nickel salt, sulfuric acid

CHEMICAL AND PHYSICAL PROPERTIES

Nickel sulfate hexahydrate (a blue-green crystalline powder) is a water-soluble nickel compound with a melting point of 53.3° C and a density of 2.07 g/cm^3 (*Merck Index*, 1989). The mean value for the mass median aerodynamic diameter at each exposure concentration of nickel sulfate hexahydrate used in these 2-year studies ranged from 2.2 to 2.5 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 (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

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 disposal 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 μm, geometric standard deviation [σ_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 μm, σ_g of 2.5) for 6 to 7 hours per day for 1 to 2 months, the lung clearance was estimated to be 100 μg 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 μm, 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 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.

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)

(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 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)
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.

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 reduced body weight, reduced leukocyte count, increased 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, or nickel chloride, there were increases in the following parameters in lung lavage fluid: lactate dehydrogenase, β-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 β-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 each of 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).

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).

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)

(continued)

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

Nickel Compound	Species/Route	Treatment	Response	Reference
Humoral Immunity (continued)				
Nickel chloride (continued)	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)
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 μmol/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)

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 or 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 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 or 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.

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 μm in diameter; 25% of particles were between 1 and 1.5 μm) 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 μm; 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).

Information on the hazards associated with exposure to nickel came from studies on occupational exposure in nickel refineries 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).

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 8 mg/m^3: 1/8 lung lesion	Horie *et al.* (1985)
Nickel monoxide	Rat/inhalation	0.06 mg/m^3: 0/40 lesion 0.2 mg/m^3: 0/20 lesion	Glaser *et al.* (1986)
	Rat/intrapleural	Controls: 0/32 local lesions 31/32 local lesions	Skaug *et al.* (1985)
	Rat/intratracheal	Controls: 0/40 lesions 10 × 5 mg: 10/37 lung lesions 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 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 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 Crystalline: 3/20 local lesions 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 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 15/208 benign lung lesions	Ottolenghi *et al.* (1975)
	Rat/intratracheal	0.94 mg: 7/47 lung lesions 1.88 mg: 13/45 lung lesions 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 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: 1/19 local lesion 10 mg powder: 19/20 local lesions 10 mg diffusion chamber: 14/17 local lesions 500 mg fragments: 5/7 local lesions 500 mg discs: 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 Removal of disc after 128 days: 7/10 local lesions Removal of disc after 206 days: 10/10 local lesions	Herchen and Gilman (1964)
Nickel subsulfide	Rat/intramuscular	NIH black: 28/28 local lesions Hooded: 14/23 local lesions	Daniel (1966)
	Rat/intramuscular	3.3 mg: 38/39 local lesions 10 mg: 34/40 local lesions	Mason (1972)
	Rat/intramuscular	5 mg: 8/20 local lesions 20 mg: 9/9 local lesions	Sunderman and Maenza (1976)
	Rat/intramuscular	Fischer: 59/63 local lesions Hooded: 11/20 local lesions	Yamashiro *et al.* (1980)
	Rat/intramuscular	0.6 mg: 7/30 local lesions 1.2 mg: 23/30 local lesions 2.5 mg: 28/30 local lesions 5 mg: 29/30 local lesions	Sunderman *et al.* (1976)
	Rat/intramuscular	0.63 mg: 7/29 local lesions 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 12 mg: 25/35 local lesions 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 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 NIH black: 6/12 local lesions Fischer 344: 9/32 local lesions 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 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 10 mg: 7/8 local lesions	Oskarsson *et al.* (1979)
	Mouse/intramuscular	Swiss: 27/45 local lesions C3H: 9/18 local lesions	Gilman (1962)
	Mouse/intramuscular	5 mg: 4/8 local lesions 10 mg: 4/8 local lesions	Oskarsson *et al.* (1979)
	Mouse/intramuscular	C57B16: 5/10 local lesions 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 5 mg: 4/15 local lesions 10 mg: 12/17 local lesions	Sunderman (1983b)
α-Nickel subsulfide	Hamster/topical	54 mg total: 0/6 local lesions 108 mg total: 0/7 local lesions 540 mg total: 0/15 local lesions 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 25 mg: 1/35 lung lesions 50 mg: 3/33 lung lesions	Pott *et al.* (1989, 1992)
Nickel acetate	Mouse/intraperitoneal	72 mg: 8/18 lung lesions 180 mg: 7/14 lung lesions 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 1.5 lung lesions/animal	Poirier *et al.* (1984)
	Rat/intraperitoneal	Controls: 1/33 lung lesions 25 mg: 3/35 lung lesions 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 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 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 60 mg/m^3 for 32 weeks: 1/32 pulmonary lesions 250 mg/m^3 once: 1/80 pulmonary lesion	Sunderman *et al.* (1957, 1959)
	Rat/inhalation	Controls: 0/32 lung lesions 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

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 day 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 an 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/10$T_{1/2}$ 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 (NTP, 1996b), and nickel sulfate hexahydrate were performed to provide comparative toxicology and carcinogenicity information on these nickel compounds. The results of the nickel sulfate hexahydrate studies are presented in this Technical Report.

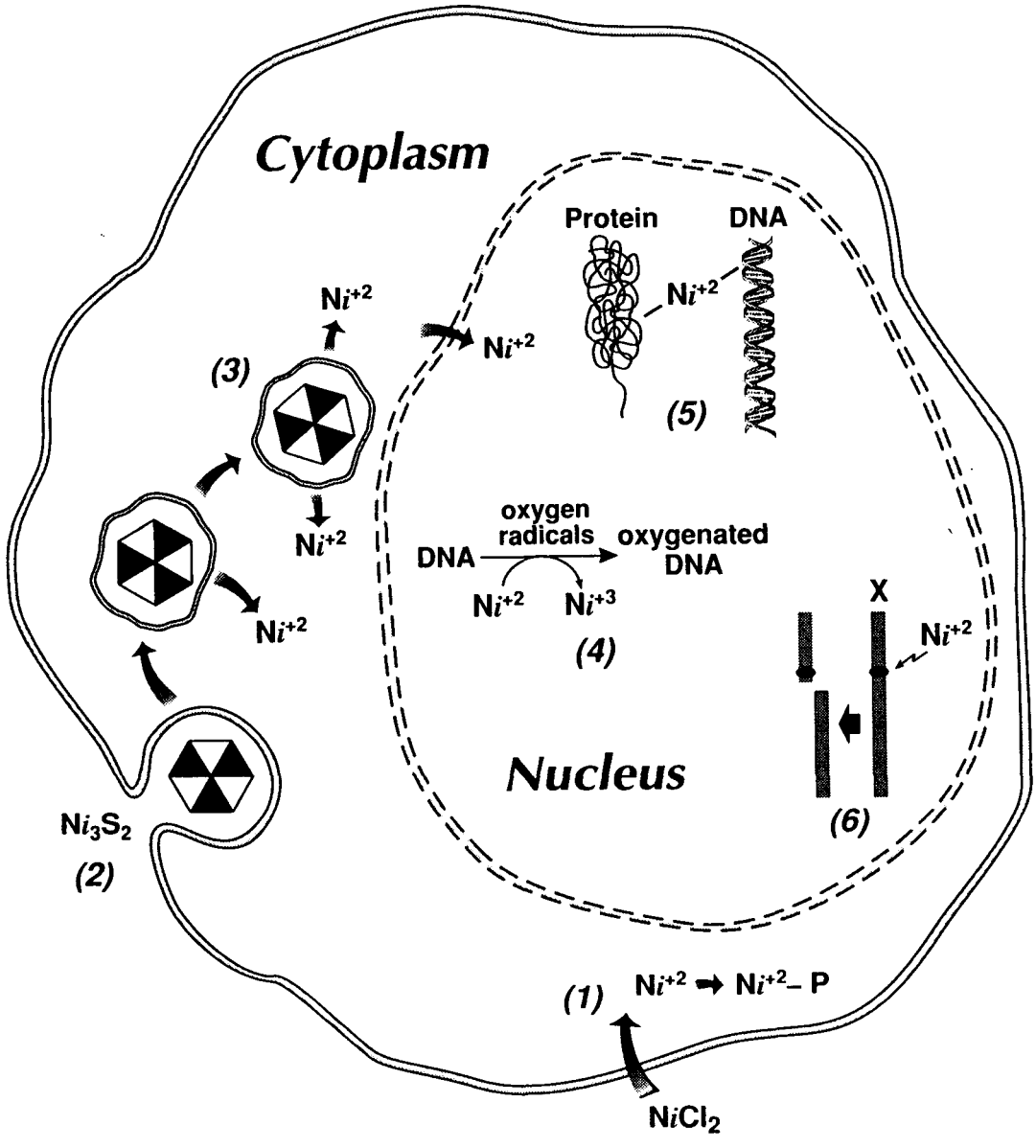

FIGURE 1
Possible Mechanisms of Nickel-Induced Genotoxicity

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 SULFATE HEXAHYDRATE

Nickel sulfate hexahydrate was obtained from Aldrich Chemical Co. (Milwaukee, WI) in one lot (M062883), which was used during the 16-day, 13-week, and 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 sulfate hexahydrate studies are on file at the National Institute of Environmental Health Sciences (NIEHS). The methods and results of these studies are detailed in Appendix K. The chemical, a blue-green crystalline powder, was identified as nickel sulfate hexahydrate by infrared and ultraviolet/visible spectroscopy. The purity of lot M062883 was determined by elemental analyses, Karl Fischer water analysis, spark source mass spectrometry, and chelometric titration. Elemental analyses for nickel and hydrogen were in agreement with the theoretical values for nickel sulfate hexahydrate. Karl Fischer water analysis indicated 41.3% ± 0.7% water, confirming that the chemical was the hexahydrate. Spark source mass spectrometry indicated the major inorganic impurities were cobalt (approximately 1,500 ppm), silicon (470 ppm), and magnesium (120 ppm). Chelometric titration indicated a purity of 98.8% ± 0.8% nickel sulfate hexahydrate. The overall purity was determined to be greater than 98%. No accelerated chemical stability studies were performed for nickel sulfate hexahydrate based on literature information about the physical and chemical properties of the compound (Ostroff and Sanderson, 1959; *Merck Index*, 1989).

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) using elemental analyses for nickel, hydrogen, and sulfur prior to and after all studies and every 4 months during the 2-year studies. No change in the purity of the bulk chemical was observed during the studies.

AEROSOL GENERATION AND EXPOSURE SYSTEM

Nickel sulfate hexahydrate aerosol was generated from aqueous solution (62.1 g/L in distilled and deionized water). The solution was atomized with a Retec nebulizer (In Tox Products, Albuquerque, NM) (Figure K2). The generation system, which included a solution reservoir and manifold for up to four nebulizers, is shown in Figure K3. One generator was used for each chamber and only one nebulizer was required for each generator system in the 2-year study. The aerosol was then mixed with additional dilution air to achieve the proper concentration and air flow rate. Water then evaporated from the aerosol droplets, leaving the nickel sulfate hexahydrate aerosol. All dilutions took place in a radial dilutor for uniform mixing, and the diluting air was filtered and conditioned to achieve a relative humidity of about 40%. The aerosol particle size was determined monthly during the 13-week and 2-year studies using a cascade impactor. The particle size as expressed as mass median aerodynamic diameter (MMAD) was similar for all exposure concentrations and ranged from 1.8 to 3.1 μm with a geometric standard deviation ranging from 1.6 to 2.9 (Tables K1 to K3). Stainless steel, multitiered, whole-body exposure chambers (H1000 and H2000, Hazleton Systems, Aberdeen, MD) were used to expose the rats and mice in these studies (Figure K4). A small boxer fan (model W52107FL-1002, Newark Electronics, Chicago, IL) was placed below the chamber inlet to further mix the aerosol as it entered the chamber.

AEROSOL CONCENTRATION MONITORING

In the 13-week studies in rats and mice and the 2-year study in rats, the aerosol concentrations were determined gravimetrically from two 3-hour samples

(4.5 L/min flow rate) for the 0.12 and 0.25 mg/m^3 exposure chambers and from three 2-hour filter samples (3 L/min flow rate) for the higher concentration exposure chambers during each 6-hour exposure day. In the 2-year study in mice, the aerosol concentrations were monitored by collecting three 2-hour filter samples (3 L/min flow rate) from each exposure chamber. 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. 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. 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 2 minutes at the beginning, middle, and end of each filter sampling period.

CHAMBER ATMOSPHERE CHARACTERIZATION

A Kr-85 discharger was installed in the line to reduce particle charge. The aerosol was analyzed for extent of hydration by thermogravimetric analysis (Perkin Elmer TGS-2 Thermogravimetric Analysis Unit) and for nickel content by electrothermal atomic absorption spectroscopy prior to exposure and once during the first week of exposure to ensure that the aerosol generated was nickel subsulfate hexahydrate. 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 in the chambers during the first week of exposure, and was checked quarterly during the 2-year studies. The spatial variation ranged from 0% to 9.29% 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 12 minutes during the 16-day and 13-week studies and 8 minutes during the 2-year studies. The daily exposure time was set at 6 hours plus T_{90}.

16-DAY 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 approximately 4 weeks old. Animals were quarantined for 19 to 22 days 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 and gross observation for evidence of disease.

Groups of five male and five female rats and mice were exposed to nickel sulfate hexahydrate by inhalation at concentrations of 0, 3.5, 7, 15, 30, or 60 mg/m^3 (equivalent to 0, 0.7, 1.4, 3.1, 6.1, or 12.2 mg nickel/m^3). Animals were in the chambers for 12 minutes before T_{90} was reached; thus, animals were exposed 6 hours and 12 minutes per day (excluding weekends) for 12 exposure days during a 16-day period. Feed was available *ad libitum*, except during exposure periods, and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded prior to the start of the studies, on day 5, and at the end of the studies for rats and mice. The animals were weighed prior to the start of the study, on day 5, 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 performed on four or five male and female rats and mice exposed to 0, 3.5, 15, or 30 mg nickel sulfate hexahydrate/m^3. Samples of lung (rats and mice) and kidney (rats only) from these animals were analyzed for nickel content. For determination of nickel concentration, rats and mice were killed using carbon monoxide and exsanguination on 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 diluted with deionized water (Millipore Co., Bedford, MA), and the nickel content was determined 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). Tissues analyzed are listed in Table 4 and results of the tissue burden studies are found in Appendixes H and I.

A necropsy was performed on all rats and mice. The brain, heart, right kidney, liver, lung, right testis, and thymus were weighed. Complete histopathologic examinations were performed on all 0, 30, and 60 mg/m^3 rats, on all 0, 3.5, and 7 mg/m^3 mice, and on target organs from rats in all other exposure groups. 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 sulfate hexahydrate 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 Simonsen Laboratories (Gilroy, CA). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 19 or 20 days 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 from the core study and on five male and female control mice from the core or tissue burden studies 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 sulfate hexahydrate by inhalation at concentrations of 0, 0.12, 0.25, 0.5, 1, or 2 mg/m^3 (equivalent to 0, 0.03, 0.06. 0.11, 0.22, or 0.44 mg nickel/m^3). Animals were in the chambers for 12 minutes before T_{90} was reached; thus, animals were exposed 6 hours and 12 minutes per day, five days per week during a 13-week period. Feed was available *ad libitum*, except during exposure periods, and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded prior to the start of the study and then weekly for rats and mice. The animals were weighed initially, weekly, 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 performed on five or six male and female rats and mice exposed to 0, 0.12, 0.5, or 2 mg nickel sulfate hexahydrate/m^3. Lung (rats and mice) and kidney (rats only) tissues from these animals were analyzed for nickel content. Tissue burden methodologies used were those described for the 16-day studies. Tissues analyzed are listed in Table 4, and results of the studies are found in Appendixes H and I.

At the end of the 13-week studies, samples were collected from 0, 0.5, 1, and 2 mg/m^3 rats and mice for sperm morphology and vaginal cytology evaluations. 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 scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male rats and mice were evaluated for sperm morphology, count, and motility. The 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 for hematology from all surviving animals by cardiac puncture. Blood for hematology determinations was placed in tubes containing potassium EDTA as the anticoagulant. The hematology parameters measured are listed in Table 4. Hematology determinations were performed on an Ortho ELT-8/ds hematology analyzer (Ortho Instruments, Westwood, MA). Leukocyte differential counts and morphologic evaluation of blood cells were determined by light microscopic examination of blood films stained with Wright-Giemsa. 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.

A necropsy was performed on all animals and organ weights were taken from all animals that survived to the end of the studies; organs weighed were brain, heart, right kidney, liver, lung, right testis, and thymus. 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 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all 0 and 2 mg/m^3 rats and mice, and on target organs from rats and mice in all other exposure groups. The organs and tissues examined are listed in Table 4.

2-YEAR STUDIES

Study Design

Groups of 63 to 65 male and 63 to 64 female rats were exposed to nickel sulfate hexahydrate by inhalation at concentrations of 0, 0.12, 0.25, or 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, or 0.11 mg nickel/m^3). Animals were exposed for 6 hours plus T_{90} (8 minutes) five days per week for 104 weeks. Five male and five female rats from each group were evaluated at 7 months for histopathology; as many as seven males and seven females from each group were evaluated at 7 months for nickel tissue burden in the lung; and five males and five females from each group were evaluated at 15 months for alterations in hematology, nickel tissue burden in the lung, and histopathology.

Groups of 80 male and 80 female mice were exposed to nickel sulfate hexahydrate by inhalation at concentrations of 0, 0.25, 0.5, or 1 mg/m^3 (equivalent to 0, 0.06, 0.11, or 0.22 mg nickel/m^3). Animals were exposed for 6 hours plus T_{90} (8 minutes) five days per week for 104 weeks. Five male and five female mice from each group were evaluated at 7 months for histopathology; five males and five females from each group were evaluated at 7 months for nickel tissue burden in the lung and kidney; five males and five females from each group were evaluated at 15 months for alterations in hematology and histopathology; and five males and five females from each group were evaluated at 15 months for nickel tissue burden in the lung and kidney.

Source and Specification of Animals

Male and female F344/N rats were obtained from Taconic Farms (Germantown, NY) and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. On receipt, animals were approximately 4 weeks old. Animals were quarantined for 10 (rats) or 11 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 for viral screening. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Rats and mice were housed individually. Feed was available *ad libitum*, except during exposure periods, and water was available *ad libitum*. Cages and racks were rotated weekly. 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

All animals were observed twice daily for signs of toxicity, mortality, and moribundity. Clinical findings and body weights were recorded prior to the

start of the study, weekly for 13 weeks, monthly thereafter, and at the end of the studies.

A complete necropsy and microscopic examination were performed on all rats and mice. At the 7- and 15-month interim evaluations, the brain, right kidney, liver, lung, spleen, right testis (rats at 7 months only), and thymus of rats and mice were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, 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.

As many as five male and five female rats and mice were evaluated for hematology alterations at 15 months, using the methods described for the 13-week study, except blood was drawn from the retro-orbital sinus. The parameters evaluated are listed in Table 4. In addition, a tissue burden study was performed on rats and mice evaluated at 7 and 15 months. Concentrations of nickel in the lung (rats and mice) and kidney (mice only) were determined. Methods used were those described for the 16-day studies, and results of the studies are found in Appendixes H and I.

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 lymph node, and nose of rats and mice.

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 dose groups or previously rendered diagnoses. 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 missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions 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 incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when

macroscopic examination was required to detect neoplasms in certain tissues (e.g., 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 incidences 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 incidences (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 assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for

simultaneous equality of measurements across exposure 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 incidences 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 sulfate hexahydrate was assessed by testing the ability of the chemical to induce mutations in L5178Y mouse lymphoma cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of nickel sulfate hexahydrate 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 Sulfate Hexahydrate

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 Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories (Gilroy, CA)	Rats: Taconic Farms (Germantown, NY) Mice: Simonsen Laboratories (Gilroy, CA)
Time Held Before Studies		
Rats: 19 days (males) or 20 days (females) Mice: 21 days (males) or 22 days (females)	19 days (males) or 20 days (females)	Rats: 10 days Mice: 11 days
Average Age When Studies Began		
7 weeks	7 weeks	6 weeks
Date of First Dose		
Rats: 23 September (males) or 24 September (females) 1985 Mice: 16 September (males) or 17 September (females) 1985	Rats: 2 June (males) or 3 June (females) 1986 Mice: 9 June (males) or 10 June (females) 1986	Rats: 20 June 1988 Mice: 30 May 1988
Duration of Dosing		
6 hours per day, 5 days per week for 16 days	6 hours per day, 5 days per week for 13 weeks	6 hours per day, 5 days per week for 104 weeks
Date of Last Dose		
Rats: 8 October (males) or 9 October (females) 1985 Mice: 1 October (males) or 2 October (females) 1985	Rats: 2-3 September (males) or 4-5 September (females) 1986 Mice: 9-10 September (males) or 11-12 September (females) 1986	Rats 7-Month interim evaluation: 3-4 January 1989 15-Month interim evaluation: 19-20 September 1989 Terminal sacrifice: 15 June 1990 Mice 7-Month interim evaluation: 20-21 December 1988 15-Month interim evaluation: 29-30 August 1989 Terminal sacrifice: 25 May 1990

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

16-Day Studies	13-Week Studies	2-Year Studies
Necropsy Dates		
Rats: 9 October (males) or 10 October (females) 1985 Mice: 2 October (males) or 3 October (females) 1985	Rats: 3-4 September (males) or 5-6 September (females) 1986 Mice: 10-11 September (males) or 12-13 September (females) 1986	Rats 7-Month interim evaluation: 4-5 January 1989 15-Month interim evaluation: 20-21 September 1989 Terminal sacrifice: 22, 25-26 June 1990 (males) 18-21 June 1990 (females) Mice 7-Month interim evaluation: 21-22 December 1988 15-Month interim evaluation: 30-31 August 1989 Terminal sacrifice: 5-7 June 1990 (males) 29 May-4 June 1990 (females)
Average Age at Necropsy		
9 weeks	20 weeks	7-Month interim evaluation: 35 weeks 15-Month interim evaluation: 72 weeks Terminal sacrifice: 110-111 weeks
Size of Study Groups		
Core studies: 5 male and 5 female rats and mice Tissue burden studies: 4 or 5 male and female rats and mice	Core studies: 10 male and 10 female rats and mice Tissue burden studies: 5 or 6 male and female rats and mice	Core studies: 7-Month interim evaluation: 5 male and 5 female rats and mice 15-Month interim evaluation: 5 male and 5 female rats and mice 2-Year studies: 53-54 male and 53-55 female rats and 61-62 male and 60-61 female mice Tissue burden studies: 7-Month interim evaluation: 6 or 7 male rats, 5 to 7 female rats, 5 male mice, and 5 female mice 15-Month interim evaluation: 5 male and 5 female rats and mice
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 16-day studies	Same as 16-day studies

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

16-Day Studies	13-Week Studies	2-Year Studies
Animals per Cage		
1	1	1
Method of Animal Identification		
Toe clip, ear tag, and location within chamber unit	Toe clip, ear tag, and location within chamber unit	Tail tattoo (rats and mice) and ear tag (mice)
Diet		
NIH-07 open formula rat and mouse ration (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods; changed at least once weekly	Same as 16-day studies	Same as 16-day studies
Water Distribution		
Tap water (Albuquerque municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*; checked twice daily	Same as 16-day studies	Same as 16-day studies
Cages		
Stainless steel (Hazleton Systems, Inc., Aberdeen, MD), cage units rotated every 4 exposure days; changed weekly	Same as 16-day studies, except cage units were rotated once weekly	Stainless steel wire mesh (Lab Products, Inc., Maywood, N.J.), cage units rotated once weekly
Bedding/Cageboard		
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 Filters		
High-efficiency particulate air filter (Flanders, Washington, DC), changed as needed	Same as 16-day studies	Same as 16-day studies
Chambers		
Stainless steel (Hazleton, Aberdeen, MD), changed weekly	Same as 16-day studies	Same as 16-day studies
Chamber Environment		
Temperature: 17.0° to 28.2° C Relative humidity: 13% to 82% Fluorescent light: 12 hours/day	Temperature: 19.1° to 27.6° C Relative humidity: 43% to 76% Fluorescent light: 12 hours/day	Temperature: 17.2° to 29.6°C Relative humidity: 8% to 99% Fluorescent light: 12 hours/day Chamber air changes: 9–21/hour

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

16-Day Studies	13-Week Studies	2-Year Studies
Doses		
Core studies: 0, 3.5, 7, 15, 30, or 60 mg nickel sulfate hexahydrate/m^3 (0, 0.7, 1.4, 3.1, 6.1, or 12.2 mg nickel/m^3) Tissue burden studies: 0, 3.5, 15, or 30 mg/m^3	Core studies: 0, 0.12, 0.25, 0.50, 1, or 2 mg nickel sulfate hexahydrate/m^3 (0, 0.03, 0.06, 0.11, 0.22, or 0.44 mg nickel/m^3) Tissue burden studies: 0, 0.12, 0.5, or 2 mg/m^3	Rats: 0, 0.12, 0.25, or 0.5 mg nickel sulfate hexahydrate/m^3 (0, 0.03, 0.06, 0.11 mg nickel/m^3) (core and tissue burden studies) Mice: 0, 0.25, 0.5, or 1 mg nickel sulfate hexahydrate/m^3 (0, 0.06, 0.11, or 0.22 mg Ni/m^3) (core and tissue burden studies)
Type and Frequency of Observation		
Observed twice daily; clinical observations were recorded and animals were weighed initially, on day 5, and at the end of the studies.	Observed twice daily; clinical observations were recorded and animals were weighed initially, weekly, 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		
Exsanguination under halothane anesthesia	Same as 16-day studies	Exsanguination under carbon dioxide anesthesia
Necropsy		
Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. Organs weighed were 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, right testis (rats at 7 months only), and thymus.
Clinical Pathology		
None	Blood was collected from all animals by cardiac puncture for hematology. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin concentration, reticulocytes, total leukocytes and differential, and nucleated erythrocytes.	Blood was collected from the retroorbital sinus of as many as five male and five female rats and mice at the 15-month interim evaluation. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, reticulocytes, total leukocytes and differential, and nucleated erythrocytes.

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

16-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Complete histopathology was performed on 0, 30, and 60 mg/m^3 rats and on 0, 3.5, and 7 mg/m^3 mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone, brain, clitoral gland (rats only), epididymis or oviduct, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidneys, larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, nose, ovary, pancreas, pancreatic islets (rats only), parathyroid gland, pituitary gland, preputial gland (rats only), prostate, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the following target organs were examined from 3.5, 7, and 15 mg/m^3 rats: liver, lung, respiratory tract lymph nodes (bronchial and mediastinal), nose, spleen (15 mg/m^3 only), testis, and thymus.	Complete histopathology was performed on 0 and 2 mg/m^3 rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone, brain, clitoral gland (rats only), epididymis or oviduct, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidneys, larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, nose, ovary, pancreas, pancreatic islets (rats only), parathyroid gland, pituitary gland, preputial gland (rats only), prostate, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the following organs were examined from selected exposure groups of rats and mice: lung, nose, and respiratory tract lymph nodes (bronchial and mediastinal).	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone, brain, clitoral gland, epididymis or oviduct, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidneys, larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, nose, ovary, pancreas, pancreatic islets (rats only), parathyroid gland, pituitary gland, preputial gland (except 0 mg\m^3 male mice), prostate, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Tissue Burden Analyses		
Lung (rats and mice) and kidney (rats only) (see Appendixes H and I)	Lung (rats and mice) and kidney (rats only) (see Appendixes H and I)	Lung (rats and mice) and kidney (mice only) (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, 0.5, 1 and 2 mg/m^3 exposure groups for sperm morphology evaluations. The parameters evaluated were sperm density, morphology, and motility. The right epididymis, right caudae, 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, 0.5, 1, and 2 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

Two 60 mg/m^3 males, one 30 mg/m^3 female, and all 60 mg/m^3 females died before the end of the study (Table 5). All exposed groups lost weight during the study, and the final mean body weights of all exposed groups were significantly lower than those of the controls. Rats in all exposure groups became noticeably thin, and red staining of the hair was observed around the noses and chins of the animals. Respiration rates were increased, breathing was labored, and activity levels were reduced.

Absolute and relative lung weights of 60 mg/m^3 males and of all exposed groups of females were significantly greater than those of the controls (Table F1). The absolute and relative thymus weights of all exposed groups of males and females were generally significantly less than those of the controls.

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

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	167 ± 5	225 ± 5	58 ± 3	
3.5	5/5	164 ± 4	162 ± 8**	−2 ± 6**	72
7	5/5	165 ± 5	136 ± 2**	−8 ± 4**	60
15	5/5	160 ± 6	127 ± 2**	−33 ± 4**	56
30	5/5	164 ± 2	123 ± 9**	−41 ± 9**	55
60	3/5[c]	161 ± 3	102 ± 0**	−58 ± 4**	45
Female					
0	5/5	125 ± 1	147 ± 4	22 ± 3	
3.5	5/5	123 ± 3	120 ± 7**	−3 ± 4	82
7	5/5	126 ± 3	105 ± 2**	−21 ± 2	71
15	5/5	122 ± 3	100 ± 5**	−22 ± 2	68
30	4/5[d]	123 ± 3	93 ± 4**	−29 ± 6	63
60	0/5[e]	123 ± 3	—	—	—

** Significantly different ($P \leq 0.01$) 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. Subsequent calculations are based on animals surviving to the end of the study. No final mean body weights or weight changes were calculated for groups with 100% mortality.
[c] Days of death: 5, 6
[d] Day of death: 6
[e] Days of death: four on day 5, one on day 16

At necropsy, the lungs of rats exposed to 7 mg/m^3 or greater did not collapse to the extent normally observed in controls when the thoracic cavity is opened. The majority of the gross lesions observed in male and female rats exposed to nickel sulfate hexahydrate were considered secondary effects typically observed in animals that die early or are killed moribund because of marked body weight loss and generalized toxicity. Such findings include a decrease in thymus size and foci of red or purple discolorations in lung or other organs.

Treatment-related histopathologic lesions were present in the lungs, bronchial and mediastinal lymph nodes, and noses of male and female rats (Table 6). In the lungs of rats exposed to nickel sulfate hexahydrate, there was inflammation with degeneration and necrosis. Inflammation in the lungs consisted of an accumulation of alveolar macrophages and a mixed inflammatory cell infiltrate in the alveolar septae. Necrotic cell debris and fibrin containing inflammatory cells were present in the terminal airways. Degeneration or necrosis of bronchiolar epithelium occurred in all groups of rats exposed to nickel sulfate hexahydrate. In the bronchial and mediastinal lymph nodes associated with the lower respiratory tract, there was hyperplasia characterized by an increased number of lymphocytes in the paracortical regions. Mild to moderate atrophy of the nasal olfactory epithelium was present in all exposed groups of rats. Atrophy consisted of a thinning of the olfactory epithelial layer, primarily in the anterior portion of the dorsal meatus in the nasal passage. Other histopathologic lesions present in a few animals from the higher exposure groups were considered nonspecific and secondary to generalized toxicity and marked body weight loss. These nonspecific lesions included: lymphoid depletion in the spleen, thymus, and lymph nodes; testicular degeneration; and a slight decrease in the size of hepatocytes.

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

	0 mg/m^3	3.5 mg/m^3	7 mg/m^3	15 mg/m^3	30 mg/m^3	60 mg/m^3
Male						
Lung[a]	5	5	5	5	5	5
Inflammation[b]	0	5** (1.2)[c]	5** (2.6)	5** (2.4)	5** (1.8)	4* (2.0)
Degeneration, Bronchiolar Epithelium	0	5** (1.0)	5** (2.8)	5** (2.0)	5** (1.8)	1 (2.0)
Lymph Node, Bronchial	2	5	4	5	3	5
Hyperplasia	0	4 (1.8)	4 (1.5)	5* (1.8)	0	0
Lymph Node, Mediastinal	2	3	3	3	3	3
Hyperplasia	0	2 (1.5)	3 (1.7)	2 (2.0)	0	0
Nose	5	5	5	5	5	5
Atrophy, Olfactory Epithelium	0	5** (2.6)	5** (2.8)	5** (3.0)	5** (3.0)	4* (3.3)
Degeneration, Respiratory Epithelium	0	1 (1.0)	1 (1.0)	5** (2.2)	4* (2.8)	0

(continued)

TABLE 6
Incidences of Selected Nonneoplastic Lesions in Rats in the 16-Day Inhalation Study of Nickel Sulfate Hexahydrate (continued)

	0 mg/m³	3.5 mg/m³	7 mg/m³	15 mg/m³	30 mg/m³	60 mg/m³
Female						
Lung	5	5	5	5	5	5
Inflammation	0	5** (1.8)	5** (1.2)	5** (3.0)	5** (1.8)	5** (1.2)
Degeneration, Bronchial Epithelium	0	5** (1.2)	5** (2.2)	5** (2.4)	4* (2.3)	0
Necrosis, Bronchial Epithelium	0	0	0	0	0	4* (1.8)
Lymph Node, Bronchial	3	4	4	4	2	4
Hyperplasia	0	3 (1.3)	4* (1.8)	4* (2.3)	0	0
Lymph Node, Mediastinal	3	5	4	3	4	2
Hyperplasia	0	3 (1.7)	3 (1.7)	2 (2.5)	0	0
Nose	5	5	5	5	5	5
Atrophy, Olfactory Epithelium	0	5** (2.0)	5** (3.0)	5** (3.0)	5** (2.4)	5** (3.2)
Degeneration, Respiratory Epithelium	0	0	0	5** (1.4)	2 (2.5)	2 (1.5)

* Significantly different ($P \leq 0.05$) from the control 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

The concentrations of nickel in the lungs of males and females exposed to 3.5, 15, or 30 mg/m^3 was significantly greater than those in the lung of control animals (Tables 7 and H1). The concentration of nickel in the kidney of males and females exposed to 30 mg/m^3 was significantly greater than those in the control animals (Table H2).

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

	0 mg/m^3	3.5 mg/m^3	15 mg/m^3	30 mg/m^3
Male				
n	5	5	4	5
Absolute lung wt (g)	0.920 ± 0.034	1.322 ± 0.043**	1.353 ± 0.084**	1.262 ± 0.027**
μg Ni/lung	—[b]	6.700 ± 0.326**	12.575 ± 1.326**	9.700 ± 1.522**
μg Ni/g lung	—	5.100 ± 0.318**	9.425 ± 1.055**	7.700 ± 1.190**
μg Ni/g control lung	—	7.300 ± 0.355**	13.650 ± 1.436**	10.560 ± 1.643**
Female				
n	5	5	5	4
Absolute lung wt (g)	0.762 ± 0.038	1.230 ± 0.039**	1.244 ± 0.026**	1.075 ± 0.032**
μg Ni/lung	—	9.400 ± 0.517**	12.980 ± 1.293**	9.900 ± 2.539**
μg Ni/g lung	—	7.640 ± 0.333**	10.500 ± 1.063**	9.225 ± 2.415**
μg Ni/g control lung	—	10.060 ± 0.434**	17.060 ± 1.694**	13.025 ± 3.355**

** Significantly different ($P \leq 0.01$) from the control group by Dunnett's 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 0.155 μg Ni (the limit of detection), or below the level of quantitation.

13-WEEK STUDY

One 2 mg/m^3 male died during week 3; all other animals survived to the end of the study (Table 8). Final mean body weights and mean body weight gains of all exposed groups of males and females were similar to those of the controls. There were no clinical findings observed.

Hematology data for the rats are presented in Table G1. A mature neutrophilia, evidenced by increased segmented neutrophil numbers, occurred in females exposed to 0.25 mg/m^3 or greater and in males exposed to 1 or 2 mg/m^3; this condition would be consistent with the presence of chronic active pulmonary inflammation in these animals. A lymphocytosis also occurred in the 1 and 2 mg/m^3 female groups and may be a reflection of the bronchial and mediastinal lymph node hyperplasia observed. While elevated peripheral neutrophil and lymphocyte numbers can be related to increased production, increases can also occur as a result of altered cell margination or homing, tissue migration, and recirculation. The occurrence of increased leukocyte numbers in female rats exposed to 0.5 mg/m^3 or greater was a result of the changes in neutrophil and lymphocyte numbers. Minimal increases in hematocrit, hemoglobin concentration, and erythrocyte count in 1 and 2 mg/m^3 females would be consistent with a mild dehydration (relative erythrocytosis). Secondary erythrocytosis, related to tissue hypoxia, has been observed with pulmonary or cardiovascular disease, altered erythrocyte/hemoglobin oxygen transport, and reduced atmospheric oxygen. In the present study, pulmonary lesions were observed microscopically in 1 and 2 mg/m^3 females, and these lesions could account for the observed increases in hematologic parameters. There were slight increases in the mean cell hemoglobin concentration (MCHC) in all exposed groups of males. Increases in MCHC have been related to erythrocyte hemolysis (*in vivo* or *in vitro*) or alterations in the hemoglobin concentration or hematocrit. There are no indications that hemolysis or altered hemoglobin concentrations or hematocrit values occurred. The slightly increased MCHC values are an enigma and probably not biologically significant.

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

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	134 ± 4	328 ± 5	195 ± 4	
0.12	10/10	133 ± 5	325 ± 4	192 ± 5	99
0.25	10/10	135 ± 3	339 ± 6	203 ± 7	103
0.5	10/10	133 ± 4	317 ± 5	184 ± 4	96
1	10/10	135 ± 3	334 ± 5	199 ± 5	102
2	9/10[c]	131 ± 3	311 ± 5	181 ± 4	95
Female					
0	10/10	112 ± 2	197 ± 4	84 ± 4	
0.12	10/10	106 ± 4	189 ± 4	83 ± 3	96
0.25	10/10	110 ± 2	193 ± 3	83 ± 3	98
0.5	10/10	109 ± 3	192 ± 3	83 ± 2	98
1	10/10	110 ± 2	198 ± 3	88 ± 2	101
2	10/10	111 ± 2	187 ± 3	76 ± 2	95

[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group were not significant by Dunnett's test.
[c] Week of death: 3

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

With the exception of 0.12 mg/m^3 rats, the absolute and relative lung weights of all exposed groups of males and females were generally significantly greater than those of the controls (Table F2). At necropsy, treatment-related gross lesions were observed in the lung and bronchial and mediastinal lymph nodes. Numerous white foci (1 to 2 mm) were scattered throughout the lung parenchyma of rats from groups exposed to 0.5 mg/m^3 or greater. Both the incidence and number of these foci increased with exposure concentration. There was enlargement of the bronchial lymph nodes of most rats in the 1 and 2 mg/m^3 exposure groups; enlargement of these nodes was observed in one male and two females from the 0.5 mg/m^3 groups. Mediastinal lymph nodes were also grossly enlarged in most rats exposed to 2 mg/m^3 and in three male and three female 1 mg/m^3 rats.

Treatment-related histopathologic lesions were present in the lungs, bronchial and mediastinal lymph nodes, and noses of male and female rats (Table 9). Minimal increases in the number of macrophages within the pulmonary alveoli were observed in 0.12 and 0.25 mg/m^3 male and female rats. The severity and spectrum of inflammatory changes in the lung increased with increasing exposure concentration. The number of alveolar macrophages also increased with increasing exposure concentration; in 0.25 and 0.5 mg/m^3 groups, there were focal aggregates of these macrophages along with granular, eosinophilic proteinaceous material and a few neutrophils within the alveolar spaces. Minimal focal interstitial infiltrates of lymphocytes and macrophages were present around blood vessels scattered throughout the lung. Chronic active inflammation was characterized by slight thickening of alveolar septae attributed to an increase in mononuclear inflammatory cells, a few neutrophils, and fibroblasts in the interstitium. In focal areas of inflammation, there was often a slight enlargement of Type II cells lining the septae. In the lymph nodes associated with the respiratory tract, there was lymphoid hyperplasia characterized by an increase in lymphocytes, primarily located in the paracortical region. Hyperplasia was observed in rats exposed to 0.5 mg/m^3 or greater; the increasing severity coincided with an increased size of lymph nodes observed at necropsy. Atrophy of the olfactory epithelium was observed in all rats exposed to 1 or 2 mg/m^3 and consisted of a minimal to mild reduction in the normal thickness of this neuroepithelial layer in the nasal passages. Atrophy was attributed to a decrease in the amount of cytoplasm in the apical portion of the cells as well as a slight decrease in the number of cells. The atrophy was present primarily in the region of the dorsal meatus of the nasal passages.

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Male						
Lung[a]	10	10	10	10	10	9
Alveolar Macrophage Hyperplasia[b]	0	10** (1.0)[c]	10** (1.0)	10** (1.0)	10** (2.4)	9** (3.6)
Interstitial Infiltrate	1 (1.0)	0	1 (1.0)	5 (1.0)	10** (1.0)	9** (1.1)
Inflammation, Chronic Active	0	0	0	2 (1.0)	10** (1.5)	8** (1.3)
Lymph Node, Bronchial	5	—[d]	8	10	10	9
Hyperplasia	0		0	4 (1.0)	8** (1.6)	9** (2.4)
Lymph Node, Mediastinal	5	—	—	10	10	9
Hyperplasia	0			0	9** (1.3)	7* (2.6)
Nose	10	10	10	10	10	9
Olfactory Epithelium, Atrophy	0	0	0	1 (1.0)	10** (1.0)	9** (1.7)
Female						
Lung	10	10	10	10	10	10
Alveolar Macrophage Hyperplasia	0	8** (1.0)	10** (1.0)	10** (1.1)	10** (2.2)	10** (3.6)
Interstitial Infiltrate	0	0	0	6** (1.0)	10** (1.0)	10** (1.0)
Inflammation, Chronic Active	0	0	0	4* (1.0)	10** (1.3)	10** (1.0)
Lymph Node, Bronchial	7	—	10	10	9	10
Hyperplasia	0		0	4 (1.0)	9** (1.4)	10** (2.3)
Lymph Node, Mediastinal	9	—	—	8	10	10
Hyperplasia	0			0	8** (1.5)	9** (1.6)
Nose	10	10	10	10	10	10
Olfactory Epithelium, Atrophy	0	0	1 (1.0)	2 (1.0)	10** (1.0)	10** (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
[d] Organ not examined at this exposure concentration

The concentrations of nickel in the lung of rats exposed to 0.5 or 2 mg/m^3 were significantly greater than those in the controls at 4, 9, and 13 weeks for males and at 13 weeks for females (Tables 10 and H3). The concentrations of nickel in the kidney of males and females exposed to 0.5 or 2 mg/m^3 were similar to those in the controls (Table H4).

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

	0 mg/m^3	0.12 mg/m^3	0.5 mg/m^3	2 mg/m^3
n	6	6	6	6
Male				
4 weeks				
μg Ni/g lung	—[b]	—	1.357 ± 0.135**	2.696 ± 0.124**[c]
μg Ni/g control lung	—	—	1.693 ± 0.200**	4.562 ± 0.240**[c]
9 weeks				
μg Ni/g lung	—	—	2.153 ± 0.086**	4.770 ± 0.207**
μg Ni/g control lung	—	—	2.695 ± 0.065**	8.348 ± 0.446**
13 weeks				
Absolute lung wt (g)	1.03 ± 0.01	1.09 ± 0.06	1.39 ± 0.07**	1.96 ± 0.06**
μg Ni/lung	—	0.145 ± 0.145	1.490 ± 0.163**	6.557 ± 0.166**
μg Ni/g lung	—	0.120 ± 0.120	1.055 ± 0.075**	3.348 ± 0.067**
μg Ni/g control lung	—	0.140 ± 0.140	1.450 ± 0.158**	6.368 ± 0.161**
Female				
13 weeks				
Absolute lung wt (g)	0.791 ± 0.031	0.835 ± 0.033	1.201 ± 0.034**	1.469 ± 0.040**
μg Ni/lung	—	—	1.395 ± 0.083**	5.460 ± 0.384**
μg Ni/g lung	—	—	1.157 ± 0.050**	3.725 ± 0.270**
μg Ni/g control lung	—	—	1.765 ± 0.104**	6.897 ± 0.486**

** 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 0.216 μg Ni (the limit of detection), or below the level of quantitation.
[c] n=5

Dose Selection Rationale: Based on lung weight increases and increased incidence and severity of lung lesions in 1 and 2 mg/m^3 males and females, nickel sulfate hexahydrate exposure concentrations selected for the 2-year inhalation study in rats were 0.12, 0.25, and 0.5 mg/m^3.

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 (Figure 2). No significant differences in survival were observed.

Body Weights and Clinical Findings

Mean body weights of exposed groups of male rats were similar to those of the controls throughout the study; mean body weights of 0.5 mg/m^3 female rats were slightly lower (6% to 9%) than those of the controls throughout the second year of the study (Figure 3 and Tables 12 and 13). Rats exhibited no clinical findings considered related to chemical administration.

Hematology

No biologically significant hematology differences occurred in male or female rats (Table G2).

TABLE 11
Survival of Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
Male				
Animals initially in study	64	63	63	63
7-Month interim evaluation[a]	5	5	5	5
15-Month interim evaluation[a]	5	5	5	5
Accidental death[a]	0	0	1	0
Moribund kills	34	30	31	28
Natural deaths	4	7	3	4
Animals surviving to study termination	16	16	18	21[e]
Percent probability of survival at end of study[b]	30	30	36	40
Mean survival (days)[c]	641	663	654	654
Survival analysis[d]	P=0.373N	P=0.730N	P=0.597N	P=0.418N
Female				
Animals initially in study	63	63	64	65
7-Month interim evaluation[a]	5	5	5	5
15-Month interim evaluation[a]	5	5	5	5
Accidental death[a]	0	0	0	1
Missexed[a]	0	0	1	0
Missing[a]	0	0	0	1
Moribund kills	27	32	22	21
Natural deaths	4	4	3	3
Animals surviving to study termination	22	17	28	29
Percent probability of survival at end of study	42	32	53	55
Mean survival (days)	676	651	690	624
Survival analysis	P=0.156N	P=0.160	P=0.299N	P=0.510N

[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 dosed columns. A negative trend or a lower mortality in a dose group is indicated by N.
[e] Includes one animal that died during the last week of the study.

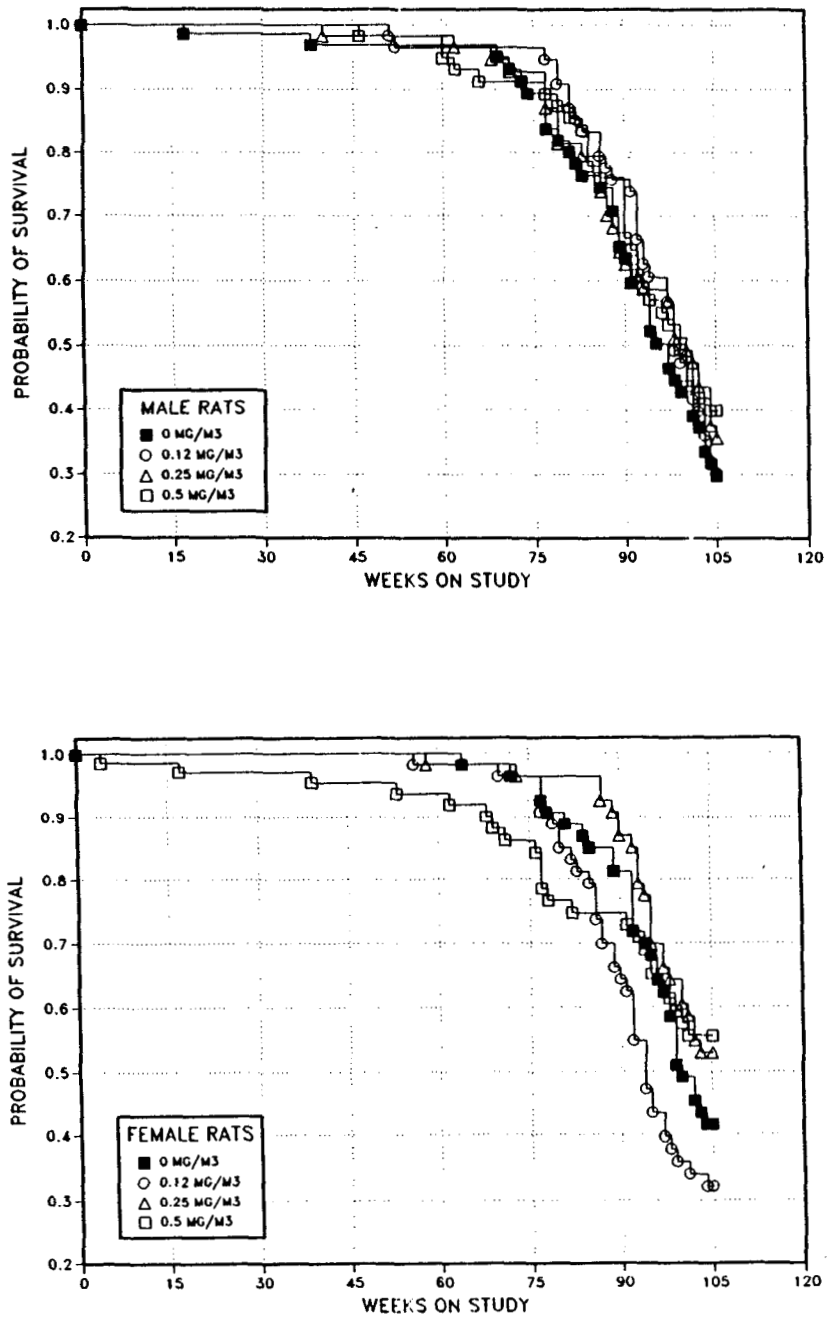

FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Nickel Sulfate Hexahydrate by Inhalation for 2 Years

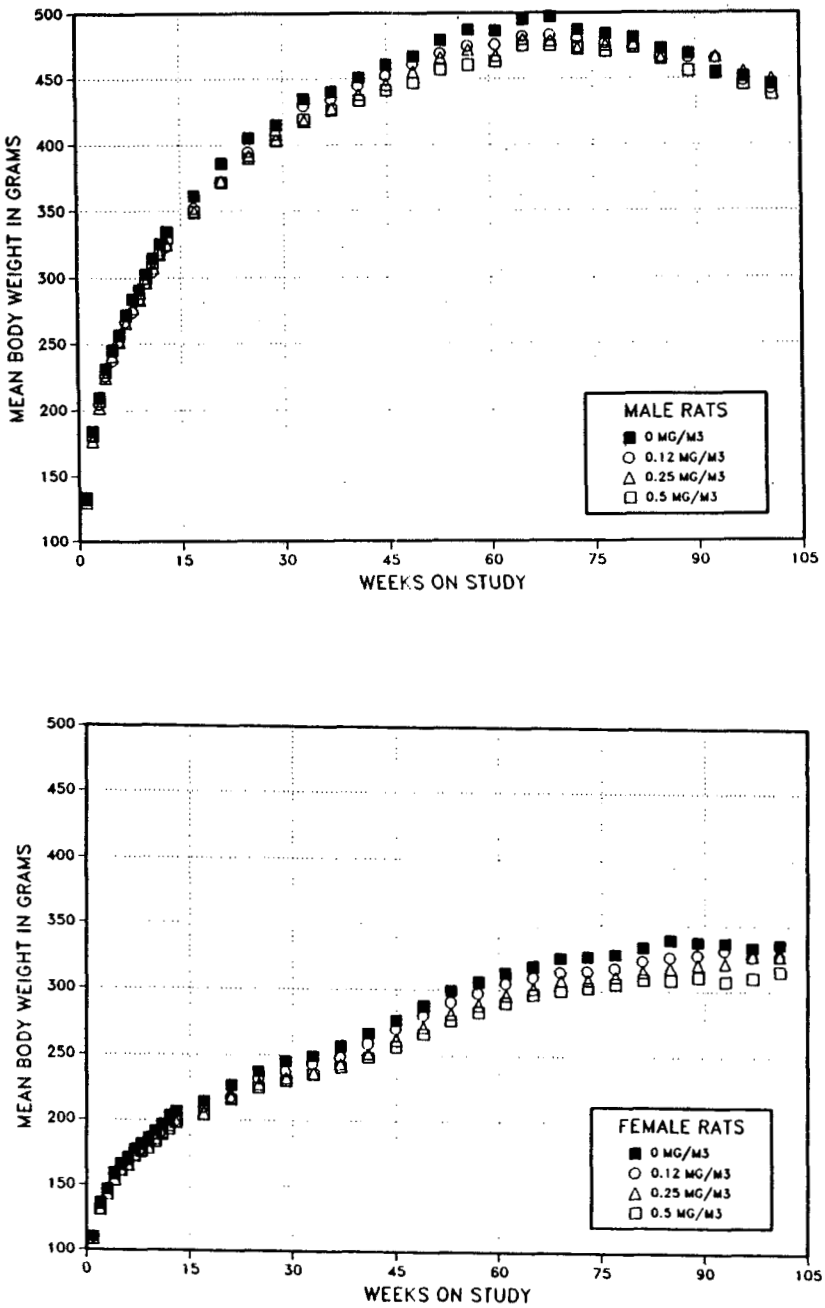

FIGURE 3
Growth Curves for Male and Female Rats Administered Nickel Sulfate Hexahydrate by Inhalation for 2 Years

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

Weeks on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ No. of Survivors	0.12 mg/m³ Av. Wt. (g)	0.12 mg/m³ Wt. (% of controls)	0.12 mg/m³ No. of Survivors	0.25 mg/m³ Av. Wt. (g)	0.25 mg/m³ Wt. (% of controls)	0.25 mg/m³ No. of Survivors	0.5 mg/m³ Av. Wt. (g)	0.5 mg/m³ Wt. (% of controls)	0.5 mg/m³ No. of Survivors
1	133	64	132	99	63	130	98	63	132	100	63
2	183	64	181	99	63	177	97	63	182	99	63
3	209	64	205	98	63	203	97	63	208	100	63
4	230	64	226	98	63	225	98	63	230	100	63
5	245	64	238	97	63	241	99	63	247	101	63
6	256	64	252	98	63	252	98	63	257	100	63
7	272	64	268	98	63	266	98	63	273	100	63
8	284	64	275	97	63	277	98	63	285	101	63
9	291	64	284	98	63	283	98	63	289	100	63
10	303	64	296	98	63	297	98	63	301	99	63
11	314	64	305	97	63	308	98	63	313	100	63
12	325	64	319	98	63	318	98	63	323	99	63
13	334	64	324	97	63	326	98	63	331	99	63
17	361	63	353	98	63	350	97	63	350	97	63
21	386	63	373	97	63	373	97	63	373	97	63
25	405	63	396	98	63	393	97	63	390	96	63
29[a]	415	58	408	98	58	404	97	58	403	97	58
33	435	58	430	99	58	418	96	58	419	96	58
37	440	58	435	99	58	428	97	58	426	97	58
41	451	57	445	99	58	438	97	57	434	96	58
45	461	57	453	98	58	446	97	57	441	96	58
49	467	57	461	99	58	456	98	57	447	96	57
53	479	57	469	98	56	466	97	57	457	95	57
57	487	57	475	97	56	472	97	57	461	95	57
61	487	57	476	98	56	467	96	57	463	95	55
65	495	57	482	97	56	480	97	56	475	96	54
69[a]	497	51	483	97	51	479	96	50	475	96	48
73	487	49	480	99	51	473	97	49	474	97	48
77	485	47	477	98	51	476	98	46	471	97	48
81	481	43	474	98	46	476	99	43	473	98	45
85	473	41	466	99	44	465	98	42	465	98	41
89	469	35	466	99	40	470	100	34	456	97	40
93	454	32	465	103	33	467	103	32	455	100	32
97	452	25	448	99	30	455	101	30	445	99	28
101	446	21	442	99	22	450	101	25	438	98	23
Mean for weeks											
1-13	260		254	98		254	98		259	100	
14-52	425		417	98		412	97		409	96	
53-101	476		469	99		469	99		462	97	

[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 Sulfate Hexahydrate

Weeks on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ No. of Survivors	0.12 mg/m³ Av. Wt. (g)	0.12 mg/m³ Wt. (% of controls)	0.12 mg/m³ No. of Survivors	0.25 mg/m³ Av. Wt. (g)	0.25 mg/m³ Wt. (% of controls)	0.25 mg/m³ No. of Survivors	0.5 mg/m³ Av. Wt. (g)	0.5 mg/m³ Wt. (% of controls)	0.5 mg/m³ No. of Survivors
1	110	63	109	99	63	109	99	63	108	98	65
2	136	63	135	99	63	131	96	63	131	96	65
3	147	63	146	100	63	143	98	63	143	97	65
4	159	63	157	99	63	154	97	63	153	96	65
5	166	63	160	97	63	162	97	63	161	97	64
6	171	63	168	98	63	165	97	63	165	97	64
7	178	63	177	99	63	172	97	63	172	97	64
8	182	63	176	97	63	176	97	63	176	97	64
9	186	63	182	98	63	178	96	63	178	95	64
10	191	63	188	98	63	185	97	63	183	95	64
11	196	63	190	97	63	190	97	63	188	96	64
12	203	63	198	98	63	195	96	63	192	95	64
13	206	63	199	96	63	198	96	63	198	96	64
17	214	63	208	97	63	204	95	63	204	95	64
21	227	63	216	95	63	216	95	63	215	95	63
25	237	63	230	97	63	227	96	63	224	94	63
29[a]	245	58	237	97	58	232	95	58	230	94	57
33	249	58	243	98	58	236	95	58	235	94	57
37	257	58	249	97	58	243	95	58	241	94	57
41	267	58	259	97	58	251	94	58	249	93	56
45	277	58	270	98	58	262	95	58	257	93	56
49	288	58	281	98	58	271	94	58	266	93	55
53	300	58	291	97	58	282	94	58	277	92	54
57	306	58	297	97	57	289	94	58	283	93	54
61	313	58	305	98	57	296	95	57	290	93	54
65	318	57	310	97	57	301	95	57	297	93	53
69[a]	324	52	314	97	52	307	95	52	299	92	46
73	326	51	315	97	51	308	95	51	302	93	45
77	328	49	317	97	49	311	95	51	306	93	43
81	333	47	323	97	45	315	95	51	309	93	40
85	339	45	326	96	42	318	94	51	308	91	39
89	338	43	327	97	35	321	95	48	311	92	39
93	337	38	331	98	29	321	95	42	308	91	37
97	334	33	326	98	21	327	98	35	310	93	34
101	336	26	327	97	18	327	97	31	315	94	29
Mean for weeks											
1-13	172		168	98		166	97		165	96	
14-52	251		244	97		238	95		236	94	
53-101	326		316	97		309	95		301	92	

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

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the lung, bronchial lymph node, and nose. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats.

Lung: Absolute and relative lung weights of 0.5 mg/m^3 males and females were generally significantly greater than those of the controls at 7 (Table F3) and 15 months (Table F4). There were no exposure-related neoplasms observed in the lung of male or female rats (Tables 14, A3, and B3). Increased incidences of inflammatory lung lesions were generally observed in 0.25 and 0.5 mg/m^3 male and female rats at 7 and 15 months and at the end of the study (Tables 14, A5, and B5). The incidences of chronic active inflammation, macrophage hyperplasia, alveolar proteinosis, and fibrosis were markedly increased in male and female rats exposed to 0.25 or 0.5 mg/m^3. Chronic active inflammation consisted of multifocal, minimal to mild accumulations of macrophages, neutrophils and cell debris within alveolar spaces, frequently subjacent to pleural surfaces (Plate 1). Macrophage hyperplasia was of minimal to mild severity and consisted of macrophages (usually with abundant pale vacuolated cytoplasm) within alveolar spaces. The source of these macrophages was probably the intravascular pool of circulating monocytes. Proteinosis consisted of minimal to mild amounts of eosinophilic granular or globular homogeneous pale, acellular, proteinaceous material within alveolar spaces (Plate 2). Fibrosis included increased connective tissue and collagen involving alveolar septae within the parenchyma and subjacent to the pleura and focal solid sclerotic areas either subjacent to the pleura or at the tips of the lung lobes. Focal alveolar epithelial hyperplasia was slightly increased in 0.5 mg/m^3 female rats. Focal alveolar epithelial hyperplasia was a discrete cluster of alveoli lined by low cuboidal or low columnar cells. Squamous metaplasia (4/54) and squamous cysts (2/54) occurred in the lungs of 0.5 mg/m^3 female rats. Squamous metaplasia was characterized by replacement of pneumocytes by well-differentiated squamous epithelium. Squamous cysts had outer walls of well-differentiated, stratified squamous epithelium without cellular atypia, and central lumens containing keratin.

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Male				
7-Month Interim Evaluation				
Lung[a]	5	5	5	5
Inflammation, Chronic Active[b]	0	4* (1.0)[c]	4* (1.3)	5** (1.8)
Macrophage Hyperplasia	0	1 (1.0)	5** (1.0)	5** (2.0)
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic Active	0	1 (1.0)	1 (1.0)	5** (1.0)
Macrophage Hyperplasia	0	0	2 (1.0)	5** (2.0)
Alveolar Proteinosis	0	0	1 (1.0)	4* (1.8)
Fibrosis	0	0	0	2 (1.0)
Hyperplasia, Focal	0	0	1	0
2-Year Study				
Lung	54	53	53	53
Inflammation, Chronic Active	14 (1.1)	11 (1.2)	42** (1.9)	46** (2.2)
Macrophage Hyperplasia	7 (1.3)	9 (1.2)	35** (1.6)	48** (2.2)
Alveolar Proteinosis	0	0	12** (1.4)	41** (1.9)
Fibrosis	3 (1.0)	6 (1.2)	35** (1.7)	43** (1.8)
Hyperplasia, Focal	3	2	3	2
Alveolar/bronchiolar Adenoma or Carcinoma	1	0	1	3
Squamous Cell Carcinoma or Alveolar/bronchiolar Adenoma or Carcinoma[d]				
Overall rate[e]	2/54 (4%)	0/53 (0%)	1/53 (2%)	3/53 (6%)
Adjusted rate[f]	12.5%	0.0%	4.0%	11.8%
Terminal rate[g]	2/16 (13%)	0/16 (0%)	0/18 (0%)	2/21 (10%)
First incidence (days)	733 (T)	—[i]	711	628
Logistic regression test[h]	P=0.249	P=0.236N	P=0.456N	P=0.532

(continued)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Female				
7-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic Active	0	2 (1.0)	4* (1.3)	5** (2.0)
Macrophage Hyperplasia	0	2 (1.0)	4* (1.0)	5** (2.0)
Alveolar Proteinosis	0	0	0	2 (1.0)
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic Active	2 (1.0)	0	4 (1.0)	5 (1.2)
Macrophage Hyperplasia	1 (1.0)	1 (1.0)	3 (1.3)	5* (1.8)
Alveolar Proteinosis	0	0	3 (1.3)	5** (1.4)
Fibrosis	0	0	1 (1.0)	3 (1.3)
Hyperplasia, Focal	1	0	0	1
2-Year Study				
Lung	52	53	53	54
Inflammation, Chronic Active	14 (1.4)	13 (1.2)	49** (2.1)	52** (2.3)
Macrophage Hyperplasia	9 (1.6)	10 (1.1)	32** (1.5)	45** (1.8)
Alveolar Proteinosis	1 (1.0)	0	22** (1.5)	49** (2.6)
Fibrosis	8 (1.4)	7 (1.3)	45** (1.7)	49** (1.9)
Hyperplasia, Focal	5	3	7	10
Squamous Metaplasia	0	0	0	4
Alveolar/bronchiolar Adenoma	0	0	0	1

(T)Terminal sacrifice
* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)
[a] Number of animals with lung examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Historical incidence for 2-year inhalation studies with control groups (mean ± standard deviation): 27/703 (3.8% ± 3.8%); range 0% to 10%
[e] Number of animals with neoplasm per number of animals 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 exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by N.
[i] Not applicable; no neoplasms in animal group

Bronchial Lymph Node: Increased incidences of lymphoid hyperplasia in the bronchial lymph nodes occurred in 0.5 mg/m^3 male and female rats at the end of the 2-year study (Tables 15, A5, and B5). Lymphoid hyperplasia consisted of a relative increase in the number of lymphocytes, primarily in the paracortex, accompanied by an increase in the size of the lymph node. The lymphocytes were at different stages of differentiation, and overall architecture of the lymph node was maintained.

TABLE 15
Incidences of Nonneoplastic Lesions of the Bronchial Lymph Node of Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
Male				
7-Month Interim Evaluation				
Bronchial Lymph Node[a]	5	5	5	5
Lymphoid Hyperplasia[b]	0	5** (1.6)[c]	2 (1.0)	5** (1.6)
15-Month Interim Evaluation				
Bronchial Lymph Node	5	5	5	4
Lymphoid Hyperplasia	0	0	1 (1.0)	1 (1.0)
2-Year Study				
Bronchial Lymph Node	51	49	47	52
Lymphoid Hyperplasia	0	0	3 (2.3)	10** (1.4)
Female				
7-Month Interim Evaluation				
Bronchial Lymph Node	5	5	4	5
Lymphoid Hyperplasia	1 (1.0)	4 (1.5)	4 (1.0)	4 (1.3)
15-Month Interim Evaluation				
Bronchial Lymph Node	4	5	3	5
Lymphoid Hyperplasia	0	0	0	1 (1.0)
2-Year Study				
Bronchial Lymph Node	50	52	51	49
Lymphoid Hyperplasia	2 (1.5)	1 (2.0)	0	11** (1.8)

** 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 bronchial lymph node examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Nose: The incidences of atrophy of the olfactory epithelium in 0.5 mg/m^3 males and females were significantly greater than those in controls at the end of the study (Tables 16, A5, and B5). This lesion was typically a minimal unilateral focal decrease in the number of cell layers of olfactory epithelial cells.

Other Organs: Incidences of thyroid gland C-cell adenoma and C-cell adenoma or carcinoma (combined) occurred with statistically significant negative trends in all exposed groups of male rats [adenoma: 0 mg/m^3, 8/53; 0.12 mg/m^3, 1/53; 0.25 mg/m^3, 2/51; 0.5 mg/m^3, 1/52; adenoma or carcinoma (combined): 8/53, 2/53, 2/51, 3/52; Table A3]. However, incidences of thyroid gland C-cell hyperplasia were slightly increased in all exposed groups (5/53, 7/53, 8/51, 6/52; Table A5).

Incidences of mammary gland fibroadenoma, adenoma, or carcinoma (combined) in female rats also occurred with statistically significant negative trends (22/53, 21/53, 11/53, 10/54; Table B3). However, the incidences were within the 16% to 46% range of historical controls in 2-year NTP inhalation studies.

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
Male				
7-Month Interim Evaluation				
Nose[a]	5	5	5	5
Atrophy, Olfactory Epithelium[b]	0	0	1 (1.0)[c]	1 (1.0)
2-Year Study				
Nose	54	52	53	53
Atrophy, Olfactory Epithelium	0	0	3 (1.0)	7** (1.0)
Female				
7-Month Interim Evaluation				
Nose	5	5	5	5
Atrophy, Olfactory Epithelium	0	0	0	1 (1.0)
15-Month Interim Evaluation				
Nose	5	5	5	5
Atrophy, Olfactory Epithelium	0	0	0	1 (1.0)
2-Year Study				
Nose	51	52	53	54
Atrophy, Olfactory Epithelium	0	1 (1.0)	1 (1.0)	7** (1.6)

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
[a] Number of animals with nose examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Tissue Burden Analyses

Lung nickel burdens in exposed male and female rats were greater than those in the controls at the 7- and 15-month interim evaluations (Tables 17 and H5), and lung nickel burden values increased with increasing exposure concentration. Additionally, the absolute lung weight of 0.5 mg/m^3 lung burden study females was significantly greater than that of the control at 7 months, as were the absolute lung weights of 0.5 mg/m^3 lung burden study males and females at 15 months.

TABLE 17
Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
Male				
n	6	7	7	7
7-Month Interim Evaluation				
Absolute lung wt (g)	1.64 ± 0.09	1.64 ± 0.06	1.61 ± 0.05	1.77 ± 0.07
μg Ni/lung	—[b]	—	—	1.426 ± 0.084**
μg Ni/g lung	—	—	—	0.804 ± 0.031**
μg Ni/g control lung	—	—	—	0.868 ± 0.051**
n	4	5	5	4
15-Month Interim Evaluation				
Absolute lung wt (g)	2.12 ± 0.10[c]	2.48 ± 0.10	2.50 ± 0.11	3.00 ± 0.26**[c]
μg Ni/lung	—	0.374 ± 0.038*	1.117 ± 0.128**	3.575 ± 0.545**
μg Ni/g lung	—	0.151 ± 0.015*	0.448 ± 0.049**	1.268 ± 0.205**
μg Ni/g control lung	—	0.177 ± 0.018*	0.528 ± 0.061**	1.688 ± 0.257**
Female				
n	7	7	6	5
7-Month Interim Evaluation				
Absolute lung wt (g)	1.13 ± 0.04	1.21 ± 0.04	1.10 ± 0.03	1.33 ± 0.04**
μg Ni/lung	—	—	—	1.326 ± 0.095**
μg Ni/g lung	—	—	—	0.996 ± 0.071**
μg Ni/g control lung	—	—	—	1.176 ± 0.084**
n	5	5	5	5
15-Month Interim Evaluation				
Absolute lung wt (g)	1.37 ± 0.07	1.58 ± 0.13	1.49 ± 0.04	1.82 ± 0.08**
μg Ni/lung	—	0.257 ± 0.017**	0.739 ± 0.057**	3.034 ± 0.586**
μg Ni/g lung	—	0.166 ± 0.012**	0.493 ± 0.031**	1.657 ± 0.285**
μg Ni/g control lung	—	0.188 ± 0.013**	0.538 ± 0.042**	2.212 ± 0.427**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's 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 0.282 (7 months) or 0.044 (15 months) (the limits of detection), or below the level of quantitation.
[c] n=5

MICE

16-DAY STUDY

All mice exposed to 7 mg/m^3 or greater died before the end of the study; all control and 3.5 mg/m^3 mice survived to the end of the study (Table 18). Mice exposed to 7, 15, 30, or 60 mg/m^3 appeared emaciated and lethargic and had rapid respiration rates.

TABLE 18
Survival and Body Weights of Mice in the 16-Day Inhalation Study of Nickel Sulfate Hexahydrate

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b](g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	22.6 ± 0.4	24.0 ± 0.4	1.4 ± 0.2	
3.5	5/5	22.2 ± 0.3	22.9 ± 0.2	0.7 ± 0.2	95
7	0/5[c]	22.7 ± 0.4	—	—	—
15	0/5[c]	21.9 ± 0.3	—	—	—
30	0/5[c]	22.3 ± 0.4	—	—	—
60	0/5[d]	22.2 ± 0.3	—	—	—
Female					
0	5/5	19.1 ± 0.3	20.2 ± 0.3	1.1 ± 0.2	
3.5	5/5	18.8 ± 0.2	19.5 ± 0.7	0.7 ± 0.5	96
7	0/5[e]	18.7 ± 0.2	—	—	—
15	0/5[f]	18.7 ± 0.6	—	—	—
30	0/5[d]	18.6 ± 0.5	—	—	—
60	0/5[g]	18.4 ± 0.3	—	—	—

[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Days of death: 2 on day 4, 3 on day 5
[d] Days of death: 1 on day 4, 4 on day 5
[e] Days of death: 1 on day 5, 4 on day 6
[f] Days of death: 3 on day 5, 2 on day 6
[g] Days of death: 5 on day 5

Absolute and relative lung weights of male and female mice exposed to 7 mg/m^3 or greater were significantly greater than those of the controls (Table F5). The absolute and relative thymus weights of mice in all but the 3.5 mg/m^3 groups were significantly less than those of the controls. At necropsy, treatment-related gross lesions were limited to the observation of diffusely reddened lungs in all male and female mice from the 7, 15, 30, and 60 mg/m^3 exposure groups. Because of the high mortality in the first week of the study, histopathology evaluations were limited to the 0, 3.5, and 7 mg/m^3 exposure groups. Treatment-related histopathologic lesions were present in the lung and nose of male and female mice (Table 19). Inflammation occurred in the lungs of all exposed mice. Diffuse, necrotizing inflammatory lesions with edema, vascular congestion, and cellular infiltrate of neutrophils and macrophages occurred in the lungs of 7 mg/m^3 mice. Inflammation in the lungs of 3.5 mg/m^3 mice was a mild lesion that consisted of an accumulation of a few macrophages and neutrophils in the alveolar

TABLE 19
Incidences of Selected Nonneoplastic Lesions in Mice in the 16-Day Inhalation Study of Nickel Sulfate Hexahydrate

	0 mg/m^3	3.5 mg/m^3	7 mg/m^3
Male			
Lung[a]	5	5	5
Inflammation[b]	0	4* (2.3)[c]	5** (2.8)
Lymph Node, Bronchial	4	3	4
Hyperplasia	0	0	0
Nose	5	5	5
Olfactory Epithelium, Atrophy	0	5** (2.2)	0
Female			
Lung	5	5	5
Inflammation	0	5** (1.4)	5** (2.6)
Lymph Node, Bronchial	2	4	4
Hyperplasia	0	1 (1.0)	0
Nose	5	5	3
Olfactory Epithelium, Atrophy	0	5** (1.6)	0

* Significantly different ($P \leq 0.05$) from the control 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

spaces and alveolar septae. A moderate lymphoid hyperplasia was present in the bronchial lymph node of one 3.5 mg/m^3 male mouse. Atrophy of the olfactory epithelium was present in all 3.5 mg/m^3 mice. Other microscopic lesions observed in 3.5 mg/m^3 males and females included lymphoid depletion in the spleen, thymus, and lymph nodes and were considered to be nonspecific findings typically observed in mice that die early or are sacrificed because of a moribund condition.

Nickel concentrations in the lung of mice exposed to 3.5 mg/m^3 were significantly greater than those in the lung of controls (Tables 20 and I1).

TABLE 20
Lung Weight and Lung Burden in Mice in the 16-Day Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m^3	3.5 mg/m^3
n	5	5
Male		
Absolute lung wt (g)	0.144 ± 0.006	0.221 ± 0.012**
μg Ni/lung	—[b]	0.664 ± 0.090**
μg Ni/g lung	—	3.020 ± 0.437**
μg Ni/g control lung	—	4.620 ± 0.609**
Female		
Absolute lung wt (g)	0.143 ± 0.007	0.206 ± 0.015**
μg Ni/lung	—	0.712 ± 0.080**
μg Ni/g lung	—	3.540 ± 0.493**
μg Ni/g control lung	—	4.980 ± 1.324**

** 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 0.170 μg Ni (the limit of detection), or below the level of quantitation.

13-WEEK STUDY

Four male and three female control mice and one 0.12 mg/m^3 male died before week 10; all other mice survived to the end of the study (Table 21). Final mean body weights and body weight gains of all exposed groups of mice were similar to those of the controls. There were no clinical findings attributed to chemical exposure.

In general, hematology changes similar to those reported for female rats occurred in female mice (Table G3), although the changes in mice were not as numerous or severe. Increased segmented neutrophil counts occurred in females exposed to 0.5 mg/m^3 or greater. This change could be consistent with the presence of chronic active pulmonary inflammation. However, little or no inflammation was observed in the 0.5 or 1 mg/m^3 female groups. Increased lymphocyte counts occurred in the 0.5 or 1 mg/m^3 groups. This could be related to the lymph node hyperplasia observed, but the lesion only occurred in 2 mg/m^3 females. While elevated peripheral neutrophil and lymphocyte counts can be related to increased cellular production, increases can also occur as a result of altered cell margination or homing, tissue migration, and recirculation. Mild increases in leukocyte counts in females exposed to 1 or 2 mg/m^3 were a reflection of the increased neutrophil and lymphocyte counts. A minimal increase in hemoglobin concentration occurred in 1 and 2 mg/m^3 females. No significant hematology changes occurred in the exposed groups of males.

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

The absolute and relative lung weights of 1 mg/m^3 males and 2 mg/m^3 males and females were significantly greater than those of the controls (Table F6).

TABLE 21
Survival and Body Weights of Mice in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	6/10[c]	24.1 ± 0.5	30.7 ± 0.5	7.2 ± 0.5	
0.12	8/9[d]	23.4 ± 1.0	32.1 ± 0.9	8.9 ± 1.0	105
0.25	10/10	24.9 ± 0.3	30.6 ± 0.5	5.7 ± 0.6	100
0.5	10/10	23.2 ± 0.6	31.9 ± 0.6	8.7 ± 0.6	104
1	10/10	24.1 ± 0.3	31.9 ± 0.7	7.8 ± 0.8	104
2	10/10	23.0 ± 0.8	31.4 ± 0.5	8.4 ± 0.9	102
Female					
0	7/10[e]	17.8 ± 0.7	25.9 ± 0.8	7.1 ± 0.8	
0.12	10/10	19.2 ± 0.3	27.2 ± 0.5	8.0 ± 0.3	105
0.25	10/10	19.1 ± 0.6	27.0 ± 0.6	7.9 ± 0.9	104
0.5	10/10	19.1 ± 0.2	27.3 ± 0.4	8.2 ± 0.3	105
1	10/10	18.9 ± 0.4	26.6 ± 0.5	7.7 ± 0.6	103
2	10/10	18.5 ± 0.4	25.2 ± 0.6	6.7 ± 0.4	97

[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group were not significant by Dunnett's test.
[c] Week of death: 5
[d] Week of death: 10
[e] Weeks of death: 1, 3, 5

There were no other significant differences in absolute or relative organ weights. At necropsy, treatment-related gross lesions were observed in the lungs and bronchial lymph nodes of 2 mg/m^3 mice. In five 2 mg/m^2 female mice, there were numerous white foci, approximately 1 mm in diameter, scattered throughout the lung parenchyma. In addition, the bronchial lymph nodes were enlarged in all female and seven male 2 mg/m^3 mice.

Treatment-related histopathologic lesions were present in the lung, bronchial lymph nodes, and nose of male and female mice (Table 22). There was an exposure-related increase in the incidence and severity of inflammatory lesions in the lung. There was a minimal increase in the number of macrophages within the alveoli of 0.25 mg/m^3 male and female mice. The number of alveolar macrophages observed in the lungs of 1 and 2 mg/m^3 mice was greater than the number observed in 0.5 mg/m^3 mice; however, the lesions were of minimal severity. Fibrosis was present in most 2 mg/m^3 male and female mice, and the lesion was characterized by a focal thickening of the alveolar septae, resulting from a chronic inflammatory cell infiltrate and an increase in the number of fibroblasts. Scattered foci of chronic alveolar inflammation without fibrosis and interstitial infiltrates of lymphocytes and macrophages around blood vessels were also present in male and female mice. Microscopically, there was hyperplasia in the bronchial lymph nodes, which corresponded to the gross enlargement of these lymph nodes. This consisted of an increase in lymphocytes, primarily in the paracortical region of the lymph nodes. A minimal atrophy of the olfactory epithelium was present only in the highest exposure groups of male and female mice and consisted of a slight thinning of this neuroepithelial layer. The olfactory lesion was most evident in the dorsal meatus of the nasal passages. No treatment-related histopathologic changes were observed in mice exposed to 0.12 or 0.25 mg/m^3 nickel sulfate hexahydrate.

TABLE 22
Incidences of Selected Nonneoplastic Lesions in Mice in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Male						
Lung[a]	6	9	10	10	10	10
Alveolar Macrophage, Hyperplasia[b]	0	0	0	10** (1.0)[c]	10** (1.0)	10** (1.0)
Interstitial Infiltrate	0	0	0	0	2 (1.0)	8** (1.0)
Inflammation, Chronic Active	0	0	0	0	2 (1.0)	2 (1.5)
Fibrosis	0	0	0	0	2 (1.5)	10** (2.0)
Lymph Node, Bronchial	2	—[d]	—	—	6	8
Hyperplasia	0				0	5 (1.0)
Nose	6	9	10	10	10	10
Olfactory Epithelium, Atrophy	0	0	0	0	0	10** (1.0)
Female						
Lung	7	10	10	10	10	10
Alveolar Macrophage, Hyperplasia	0	0	0	10** (1.0)	10** (1.0)	10** (1.0)
Interstitial Infiltrate	1 (1.0)	0	0	1 (1.0)	1 (1.0)	8* (1.3)
Inflammation, Chronic Active	0	0	0	0	1 (1.0)	9** (1.9)
Fibrosis	0	0	0	0	1 (1.0)	8** (1.5)
Lymph Node, Bronchial	4	—	—	—	7	10
Hyperplasia	0				0	8* (1.1)
Nose	7	10	10	10	10	10
Olfactory Epithelium, Atrophy	0	0	0	0	0	5* (1.0)

* 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
[d] Organ not examined at this exposure concentration.

The nickel concentration in the lung of feamles exposed to 2 mg/m^3 was significantly greater than that in the lung of control animals (Tables 23 and I2).

TABLE 23
Lung Weight and Lung Burden in Mice in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m^3	0.12 mg/m^3	0.5 mg/m^3	2 mg/m^3
Male				
n	5	6	6	6
Absolute lung wt (g)	0.183 ± 0.008	0.166 ± 0.011	0.175 ± 0.002	0.300 ± 0.014**
μg Ni/lung	—[b]	—	—	0.234 ± 0.148
μg Ni/g lung	—	—	—	0.790 ± 0.503
μg Ni/g control lung	—	—	—	1.275 ± 0.807
Female				
n	5	6	5	6
Absolute lung wt (g)	0.157 ± 0.009	0.149 ± 0.007	0.156 ± 0.008	0.279 ± 0.008**
μg Ni/lung	—	—	—	0.630 ± 0.126**
μg Ni/g lung	—	—	—	2.205 ± 0.444**
μg Ni/g control lung	—	—	—	4.008 ± 0.804**

** 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 0.228 μg Ni (the limit of detection) or below the level of quantitation.

Dose Selection Rationale: Based on the lung weight increases and increased incidences of lung lesions in 2 mg/m^3 males and females, nickel sulfate hexahydrate exposure concentrations selected for the 2-year inhalation study in mice were 0.25, 0.5, and 1 mg/m^3.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 24 and in the Kaplan-Meier survival curves (Figure 4). The survival rates of all exposed groups of males and females were similar to those of the controls.

Body Weights and Clinical Findings

The mean body weights of 1 mg/m^3 males and of all exposed groups of females were lower than those of the controls during the second year of the study (Figure 5 and Tables 25 and 26). Mice exhibited no clinical findings considered related to chemical administration.

TABLE 24
Survival of Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
Male				
Animals initially in study	71	71	72	72
7-Month interim evaluation[a]	5	5	5	5
15-Month interim evaluation[a]	5	5	5	5
Moribund kills	30	29	29	27
Natural deaths	5	9	9	10
Animals surviving to study termination	26	23	24	25
Percent probability of survival at end of study[b]	43	38	40	42
Mean survival (days)[c]	647	634	637	650
Survival analysis[d]	P=0.890N	P=0.657	P=0.877	P=1.000N
Female				
Animals initially in study	71	70	70	70
7-Month interim evaluation[a]	5	5	5	5
15-Month interim evaluation[a]	5	5	5	5
Moribund kills	20	11	11	17
Natural deaths	7	10	4	6
Animals surviving to study termination	34[e]	39[a]	45	37
Percent probability of survival at end of study	57	65	75	62
Mean survival (days)	673	674	697	662
Survival analysis	P=0.791N	P=0.494N	P=0.062N	P=0.843N

[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 dosed columns. A negative trend or a lower mortality in a dose group is indicated by N.
[e] Includes one animal that died during the last week of the study.

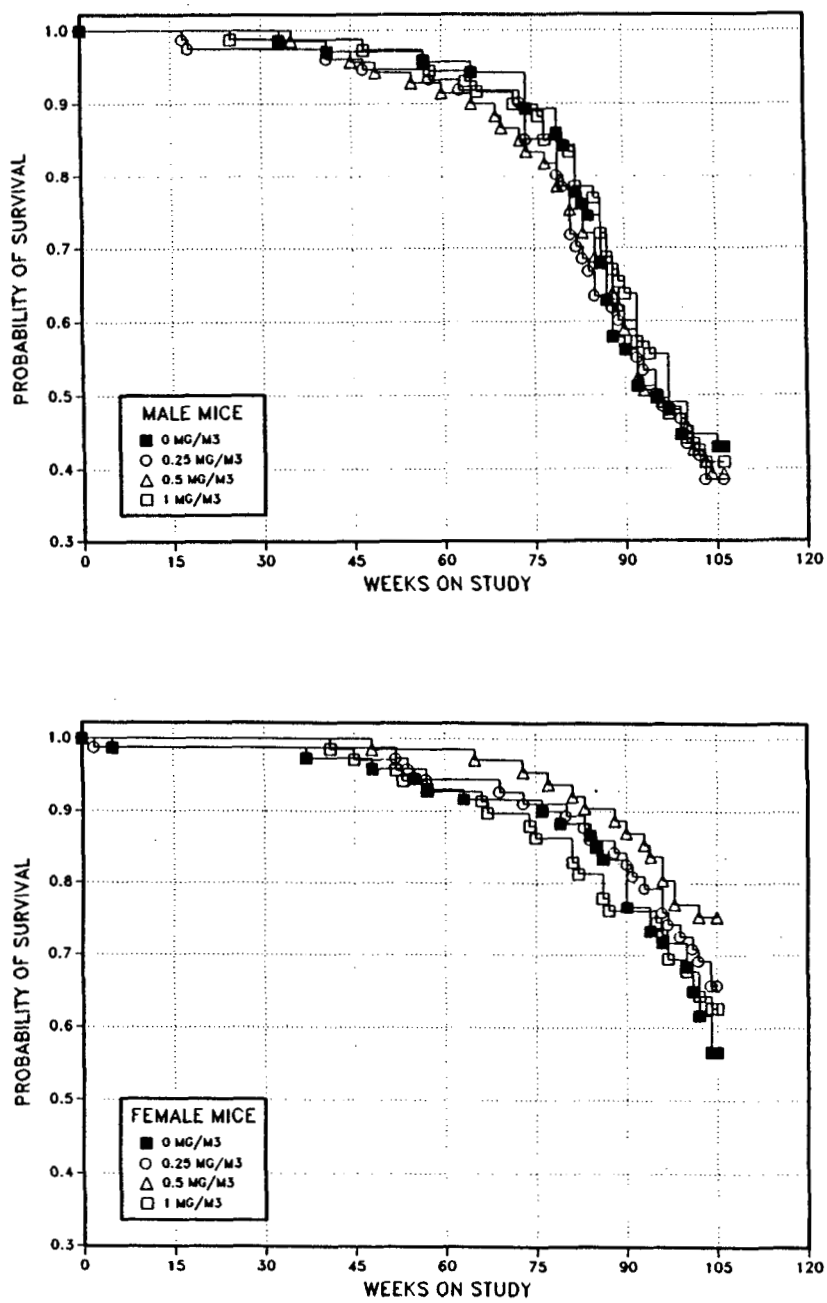

FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Nickel Sulfate Hexahydrate by Inhalation for 2 Years

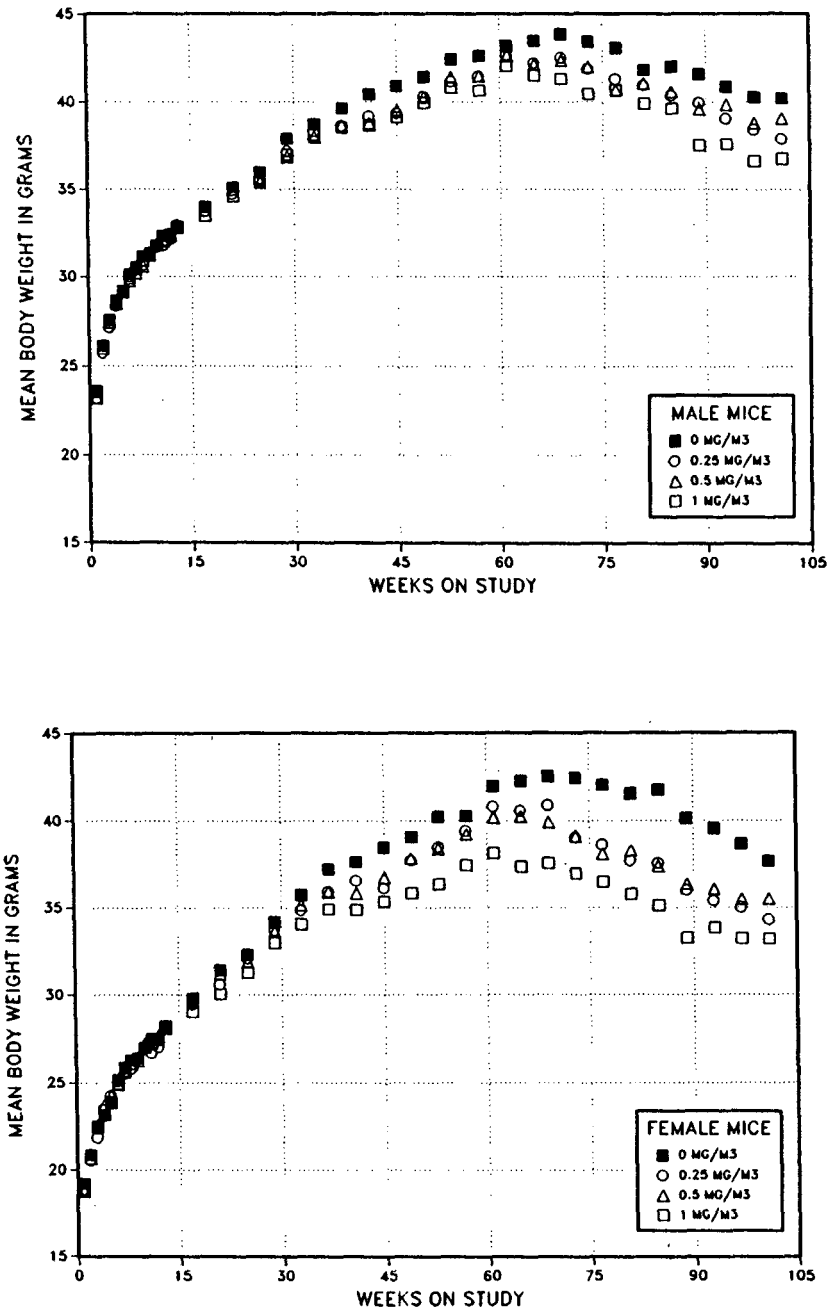

FIGURE 5
Growth Curves for Male and Female Mice Administered Nickel Sulfate Hexahydrate by Inhalation for 2 Years

TABLE 25
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

Weeks on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ No. of Survivors	0.25 mg/m³ Av. Wt. (g)	0.25 mg/m³ Wt. (% of controls)	0.25 mg/m³ No. of Survivors	0.5 mg/m³ Av. Wt. (g)	0.5 mg/m³ Wt. (% of controls)	0.5 mg/m³ No. of Survivors	1 mg/m³ Av. Wt. (g)	1 mg/m³ Wt. (% of controls)	1 mg/m³ No. of Survivors
1	23.5	80	23.2	99	80	23.2	99	80	23.1	98	80
2	26.1	80	25.7	99	80	26.2	100	80	25.9	99	80
3	27.6	80	27.2	99	80	27.4	99	80	27.4	99	80
4	28.6	80	28.4	99	80	28.5	100	80	28.5	100	80
5	29.2	80	29.2	100	80	29.1	100	80	29.2	100	80
6	30.1	80	30.0	100	80	29.8	99	80	29.9	99	80
7	30.5	80	30.5	100	80	30.2	99	80	30.4	100	80
8	31.2	80	30.6	98	80	30.6	98	80	30.9	99	80
9	31.4	80	31.2	99	80	31.3	100	80	31.2	99	80
10	31.8	80	31.7	100	80	31.8	100	80	31.8	100	80
11	32.4	80	31.8	98	80	32.2	99	80	32.0	99	80
12	32.4	80	32.2	99	80	32.4	100	80	32.3	100	80
13	32.8	80	33.0	101	80	32.8	100	80	32.8	100	80
17	34.0	80	33.7	99	80	33.8	99	80	33.5	99	80
21	35.1	80	34.7	99	78	35.0	100	80	34.6	99	80
25	36.0	80	35.6	99	78	35.4	98	80	35.5	99	79
29	37.9	80	37.2	98	78	36.9	97	80	36.9	97	79
33[a]	38.7	70	38.3	99	69	38.0	98	70	38.1	98	69
37	39.6	69	38.6	98	69	38.7	98	69	38.5	97	69
41	40.5	69	39.2	97	69	38.8	96	68	38.7	96	69
45	40.9	68	39.4	96	68	39.5	97	67	39.1	96	69
49	41.4	68	40.3	97	67	40.3	97	66	39.9	96	68
53	42.4	68	41.2	97	67	41.4	98	66	40.8	96	68
57	42.6	67	41.5	97	67	41.5	97	65	40.6	95	67
61	43.2	67	42.7	99	66	42.6	99	64	42.1	98	66
65	43.5	66	42.2	97	65	42.1	97	64	41.5	95	65
69[a]	43.9	57	42.5	97	55	42.4	97	55	41.3	94	56
73	43.4	57	41.9	97	54	42.0	97	53	40.5	93	55
77	43.1	54	41.3	96	51	40.7	94	50	40.7	94	52
81	41.8	51	41.0	98	45	41.1	98	46	39.9	96	51
85	42.0	45	40.4	96	38	40.6	97	42	39.6	94	47
89	41.6	35	40.0	96	36	39.6	95	38	37.5	90	40
93	40.9	31	39.0	95	32	39.8	97	31	37.6	92	35
97	40.3	29	38.4	95	29	38.8	96	30	36.6	91	30
101	40.2	27	37.9	94	26	39.1	97	26	36.7	91	27
Mean for weeks											
1-13	29.8		29.6	99		29.7	100		29.7	100	
14-52	38.2		37.4	98		37.4	98		37.2	97	
53-101	42.2		40.8	97		40.9	97		39.7	94	

[a] Interim evaluations occurred during weeks 30 and 66.

TABLE 26
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

Weeks on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ No. of Survivors	0.25 mg/m³ Av. Wt. (g)	0.25 mg/m³ Wt. (% of controls)	0.25 mg/m³ No. of Survivors	0.5 mg/m³ Av. Wt. (g)	0.5 mg/m³ Wt. (% of controls)	0.5 mg/m³ No. of Survivors	1 mg/m³ Av. Wt. (g)	1 mg/m³ Wt. (% of controls)	1 mg/m³ No. of Survivors
1	19.2	80	18.9	98	80	18.8	98	80	18.9	98	80
2	20.9	80	20.6	99	80	20.9	100	80	20.7	99	80
3	22.5	80	21.9	97	79	22.6	100	80	22.4	100	80
4	23.1	80	23.1	100	79	23.7	103	80	23.4	101	80
5	23.8	80	24.2	102	79	24.2	102	80	23.9	100	80
6	25.2	79	25.1	100	79	24.9	99	80	24.9	99	80
7	25.8	79	25.5	99	79	25.6	99	80	25.7	100	80
8	26.3	79	25.8	98	79	26.1	99	80	26.1	99	80
9	26.5	79	26.3	99	79	26.5	100	80	26.2	99	80
10	27.0	79	27.0	100	79	27.3	101	80	27.0	100	80
11	27.5	79	26.7	97	79	27.4	100	80	27.2	99	80
12	27.5	79	27.1	99	79	27.7	101	80	27.5	100	80
13	28.3	79	28.3	100	79	28.2	100	80	28.1	99	80
17	29.8	79	29.5	99	79	29.6	99	80	29.1	98	80
21	31.4	79	30.6	98	79	31.2	99	80	30.1	96	80
25	32.3	79	32.1	99	79	31.9	99	80	31.3	97	80
29	34.2	79	33.7	99	79	33.6	98	80	33.0	97	80
33[a]	35.7	70	34.9	98	69	35.2	99	70	34.0	95	70
37	37.2	69	35.9	97	69	35.9	97	70	34.9	94	70
41	37.7	69	36.6	97	69	35.8	95	70	34.9	93	69
45	38.5	69	36.1	94	69	36.8	96	70	35.4	92	68
49	39.1	68	37.8	97	69	37.9	97	69	35.8	92	68
53	40.3	68	38.5	96	68	38.4	95	69	36.4	90	67
57	40.3	67	39.4	98	66	39.3	98	69	37.5	93	65
61	42.0	66	40.8	97	66	40.2	96	69	38.1	91	65
65	42.3	65	40.6	96	66	40.3	95	69	37.4	88	65
69[a]	42.6	55	40.9	96	56	39.9	94	58	37.6	88	53
73	42.5	55	39.1	92	55	39.1	92	57	37.0	87	53
77	42.1	54	38.6	92	54	38.1	91	57	36.5	87	51
81	41.6	53	37.7	91	53	38.3	92	56	35.8	86	49
85	41.8	52	37.6	90	51	37.4	90	54	35.1	84	48
89	40.2	50	36.0	90	50	36.4	91	53	33.3	83	45
93	39.6	46	35.4	89	47	36.1	91	51	33.8	85	45
97	38.7	43	35.0	90	45	35.5	92	48	33.2	86	42
101	37.7	40	34.3	91	42	35.5	94	46	33.2	88	40
Mean for weeks											
1-13	24.9		24.7	99		24.9	100		24.8	99	
14-52	35.1		34.1	97		34.2	97		33.2	95	
53-101	40.9		38.0	93		38.0	93		35.8	88	

[a] Interim evaluations occurred during weeks 30 and 66.

Hematology

No biologically significant hematology differences occurred in male or female mice (Table G4).

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the lung, bronchial lymph node, and nose. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and 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: The absolute lung weights of 1 mg/m^3 males and females were significantly greater than those of the controls at the 15-month interim evaluation (Table F8). There was no increase in focal hyperplasia or in the incidence of neoplasms in exposed groups of mice. Treatment-related inflammatory lesions of the lung occurred in all exposed groups of female mice and in the 0.5 and 1 mg/m^3 males at the end of the 2-year study (Tables 27, C5, and D5). These lesions included macrophage hyperplasia, chronic active inflammation, bronchialization (alveolar epithelial hyperplasia), alveolar proteinosis, and infiltrating cells in the interstitium. Macrophage hyperplasia was the most commonly diagnosed lesion in the lungs and consisted of scattered enlarged macrophages within alveolar spaces. The source of these macrophages was probably the intravascular pool of circulating monocytes. Chronic active inflammation consisted of intra-alveolar accumulations of macrophages, neutrophils, and lymphocytes sometimes mixed with cell debris and/or brightly eosinophilic crystalline material (Plate 3). There often was minimal to mild septal fibrosis in alveolar septae adjacent to these inflammatory cell accumulations. In the present study, bronchialization was defined as hyperplastic and/or hypertrophic cuboidal epithelial cells extended from the terminal bronchiole into the alveolar ducts and proximal alveoli, because it appeared as though the epithelial lining of the bronchiole extends farther into the peripheral lung than normal. 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. Alveolar proteinosis was an eosinophilic, acellular, granular or hyaline material within a variable number of alveolar spaces. Infiltrating cells in the interstitium were primarily lymphocytes with fewer macrophages primarily in the perivascular and peribronchiolar connective tissue.

TABLE 27
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung of Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
Male				
7-Month Interim Evaluation				
Lung[a]	5	5	5	5
Inflammation, Chronic Active[b]	0	0	0	0
Macrophage Hyperplasia	0	0	1 (1.0)[c]	5** (1.0)
Interstitial Infiltration	0	0	0	1 (1.0)
Alveolar Proteinosis	0	0	0	0
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic Active	0	0	0	4* (1.3)
Bronchialization	0	1 (1.0)	0	5** (1.0)
Macrophage Hyperplasia	0	1 (1.0)	4* (1.0)	5** (1.0)
Interstitial Infiltration	0	0	0	5** (1.0)
Alveolar Proteinosis	0	0	0	3 (1.0)
2-Year Study				
Lung	61	61	62	61
Inflammation, Chronic Active	1 (2.0)	2 (1.0)	8* (1.5)	29** (1.9)
Bronchialization	1 (1.0)	4 (1.5)	19** (1.1)	39** (1.1)
Macrophage Hyperplasia	6 (2.8)	9 (1.4)	35** (1.5)	59** (2.1)
Interstitial Infiltration	1 (3.0)	0	3 (1.3)	17** (1.2)
Alveolar Proteinosis	0	0	0	42** (2.0)
Alveolar Epithelial Hyperplasia, Focal	0	0	0	0
Alveolar/bronchiolar Adenoma	5	5	3	5
Alveolar/bronchiolar Carcinoma	9	13	4	3
Alveolar/bronchiolar Adenoma or Carcinoma[d]				
Overall rate[e]	13/61 (21%)	18/61 (30%)	7/62 (11%)	8/61 (13%)
Adjusted rate[f]	43.6%	65.4%	21.2%	26.2%
Terminal rate[g]	10/26 (38%)	14/23 (61%)	3/24 (13%)	5/25 (20%)
First incidence (days)	516	552	552	561
Logistic regression test[h]	P=0.029N	P=0.144	P=0.111N	P=0.142N

(continued)

TABLE 27
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung of Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate (continued)

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Female				
7-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic Active	0	0	0	2 (1.0)
Macrophage Hyperplasia	0	0	1 (1.0)	5** (1.0)
Interstitial Infiltration	0	0	0	1 (2.0)
Alveolar Proteinosis	0	0	0	0
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic Active	0	0	0	5** (1.2)
Bronchialization	0	0	1 (1.0)	5** (1.0)
Macrophage Hyperplasia	0	1 (1.0)	2 (1.0)	5** (1.2)
Interstitial Infiltration	1 (1.0)	0	0	5* (1.2)
Alveolar Proteinosis	0	0	0	5** (1.2)
2-Year Study				
Lung	61	60	60	60
Inflammation, Chronic Active	1 (1.0)	7* (1.3)	14** (1.1)	40** (1.6)
Bronchialization	0	9** (1.0)	32** (1.0)	45** (1.1)
Macrophage Hyperplasia	7 (1.6)	24** (1.3)	53** (1.5)	59** (2.4)
Interstitial Infiltration	0	4 (2.0)	16** (1.1)	39** (1.4)
Alveolar Proteinosis	0	0	11** (1.4)	45** (1.9)
Alveolar Epithelial Hyperplasia, Focal	0	1 (2.0)	1 (2.0)	0
Alveolar/bronchiolar Adenoma	3	3	2	0
Alveolar/bronchiolar Carcinoma	4	3	9	2
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	7/61 (11%)	6/60 (10%)	10/60 (17%)	2/60 (3%)
Adjusted rate	19.3%	13.9%	21.1%	4.3%
Terminal rate	6/34 (18%)	3/39 (8%)	8/45 (18%)	0/37 (0%)
First incidence (days)	627	649	656	562
Logistic regression test	P=0.111N	P=0.481N	P=0.371	P=0.088N

* 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 lung examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Historical incidence for 2-year inhalation studies with control groups (mean ± standard deviation): 205/952 (21.5% ± 8.0%); range 10% to 42%
[e] Number of animals with neoplasm per number of animals 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 exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[i] Historical incidence: 97/944 (10.3% ± 3.7%); range, 0% to 16%

Bronchial Lymph Node: Incidences of macrophage hyperplasia and/or lymphoid hyperplasia occurred in the bronchial lymph nodes of most of the 1 mg/m^3 males and females and in some 0.5 mg/m^3 females at the end of the 2-year study (Tables 28, C5, and D5). Macrophage hyperplasia consisted of scattered clusters of a few to several hypertrophic macrophages within the lymph node. The increased numbers of macrophages within the bronchial lymph node are consistent with the inflammatory alterations in the lungs. Lymphoid hyperplasia was an increased number of cortical and/or paracortical lymphocytes in various stages of differentiation that resulted in variable enlargement of the lymph node without distortion of its architecture.

TABLE 28
Incidences of Nonneoplastic Lesions of the Bronchial Lymph Node of Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

	0 mg/m^3		0.25 mg/m^3		0.5 mg/m^3		1 mg/m^3	
Male								
7-Month Interim Evaluation								
Bronchial Lymph Node[a]	5		3		2		5	
Lymphoid Hyperplasia[b]	1	(1.0)[c]	1	(1.0)	1	(1.0)	0	
Macrophage Hyperplasia	0		0		0		0	
15-Month Interim Evaluation								
Bronchial Lymph Node	4		5		5		5	
Lymphoid Hyperplasia	1	(1.0)	3	(1.3)	1	(1.0)	0	
Macrophage Hyperplasia	1	(1.0)	0		0		4	(1.0)
2-Year Study								
Bronchial Lymph Node	46		49		45		54	
Lymphoid Hyperplasia	2	(1.5)	4	(1.5)	2	(2.0)	17**	(1.6)
Macrophage Hyperplasia	0		0		8**	(1.1)	39**	(1.4)
Female								
7-Month Interim Evaluation								
Bronchial Lymph Node	5		4		4		4	
Lymphoid Hyperplasia	2	(1.0)	2	(1.0)	1	(1.0)	3	(1.7)
Macrophage Hyperplasia	0		0		0		0	
15-Month Interim Evaluation								
Bronchial Lymph Node	2		5		5		4	
Lymphoid Hyperplasia	0		1	(1.0)	2	(1.0)	4	(1.5)
Macrophage Hyperplasia	0		0		0		4	(1.0)
2-Year Study								
Bronchial Lymph Node	50		54		58		56	
Lymphoid Hyperplasia	15	(1.8)	9	(1.8)	16	(1.6)	26*	(2.0)
Macrophage Hyperplasia	2	(1.0)	0		14*	(1.1)	37**	(1.5)

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
[a] Number of animals with bronchial lymph node examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Nose: Atrophy of the olfactory epithelium was observed in 0.5 and 1 mg/m^3 males and in all groups of females at the end of the 2-year study (Tables 29, C5, and D5). The incidences of this lesion in 1 mg/m^3 males and females and in 0.5 mg/m^3 males were significantly greater than those in the controls at the end of the study. Typically, this lesion was a minimal focal decrease in the number of olfactory cells resulting in a thinning of the affected portion of the epithelium (Plate 4).

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

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
Male				
7-Month Interim Evaluation				
Nose[a]	5	5	5	5
Atrophy, Olfactory Epithelium[b]	0	0	0	2 (1.0)[c]
15-Month Interim Evaluation				
Nose	5	5	5	5
Atrophy, Olfactory Epithelium	0	0	1 (1.0)	3 (1.0)
2-Year Study				
Nose	61	61	61	60
Atrophy, Olfactory Epithelium	0	0	12** (1.0)	37** (1.0)
Female				
7-Month Interim Evaluation				
Nose	5	5	5	5
Atrophy, Olfactory Epithelium	0	0	0	0
15-Month Interim Evaluation				
Nose	5	5	5	5
Atrophy, Olfactory Epithelium	0	0	0	1 (1.0)
2-Year Study				
Nose	61	59	60	60
Atrophy, Olfactory Epithelium	3 (1.3)	2 (1.0)	1 (1.0)	17** (1.0)

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
[a] Number of animals with nose examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Liver: Statistically significant increases in the incidence of hepatocellular adenoma or carcinoma (combined) occurred at the end of 2 years in 0.25 mg/m^3 female mice (0 mg/m^3, 18/61; 0.25 mg/m^3, 28/59; 0.5 mg/m^3, 15/60; 1 mg/m^3, 19/60; Table D3). However, these incidences did not exceed the range of historical control data for the combined incidence of this neoplasm in 2-year NTP inhalation studies [148/759 (19.5% ± 12.4%); range, 3% to 54%].

Tissue Burden Analyses

At the 7- and 15-month interim evaluations, lung nickel burden parameters measured in control and exposed groups were below the limit of detection (Tables 30 and I3). Absolute lung weights of 0.5 and 1 mg/m^3 lung burden study females were significantly greater than those of the controls at 15 months. Also at the 15-month interim evaluation, the concentration of nickel in the kidney of male and female mice exposed to 0.25, 0.5 or 1 mg/m^3 was similar to that in the controls (Table I4).

TABLE 30.
Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
Male				
n	5	4	5	5
7-Month Interim Evaluation				
Absolute lung wt (g)	0.230 ± 0.013	0.239 ± 0.023	0.294 ± 0.024	0.251 ± 0.028
μg Ni/lung	—[b]	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—
n	4	5	3	3
15-Month Interim Evaluation				
Absolute lung wt (g)	0.208 ± 0.009	0.223 ± 0.028	0.204 ± 0.017	0.251 ± 0.006
μg Ni/lung	—	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—
Female				
n	4	5	5	5
7-Month Interim Evaluation				
Absolute lung wt (g)	0.221 ± 0.020	0.218 ± 0.015	0.212 ± 0.009	0.257 ± 0.009
μg Ni/lung	—	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—
n	5	5	5	5
15-Month Interim Evaluation				
Absolute lung wt (g)	0.205 ± 0.005	0.214 ± 0.007	0.225 ± 0.006*	0.275 ± 0.004**
μg Ni/lung	—	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.323 μg Ni (7 months) or 0.256 μg Ni (15 months) (the limits of detection), or below the level of quantitation.

GENETIC TOXICOLOGY

Nickel sulfate hexahydrate (500 to 800 μg/mL) was tested for induction of trifluorothymidine resistance in L5178Y mouse lymphoma cells (Table E1; McGregor *et al.*, 1988). A positive response was observed in the absence of S9. The test was not performed with S9.

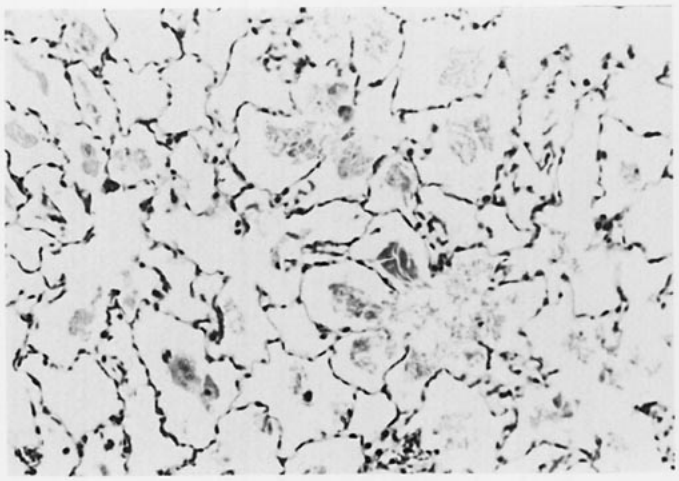

PLATE 1
Chronic active inflammation subjacent to the pleura in the lung of a male F344/N rat exposed to 0.5 mg/m^3 nickel sulfate hexahydrate by inhalation for 2 years. Macrophages and cellular debris are within alveolar spaces; connective tissue and reactive alveolar epithelial hyperplasia thicken alveolar septae. H&E, 215×

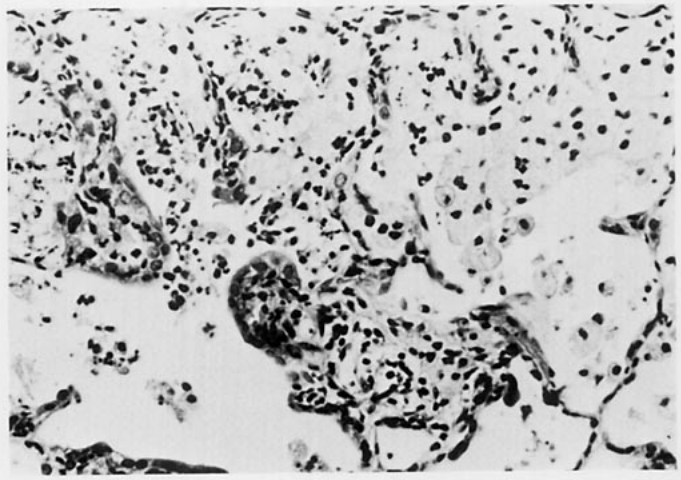

PLATE 2
Proteinaceous material within alveolar spaces in the lung of a male F344/N rat exposed to 0.5 mg/m^3 nickel sulfate hexahydrate by inhalation for 2 years. H&E, 135×

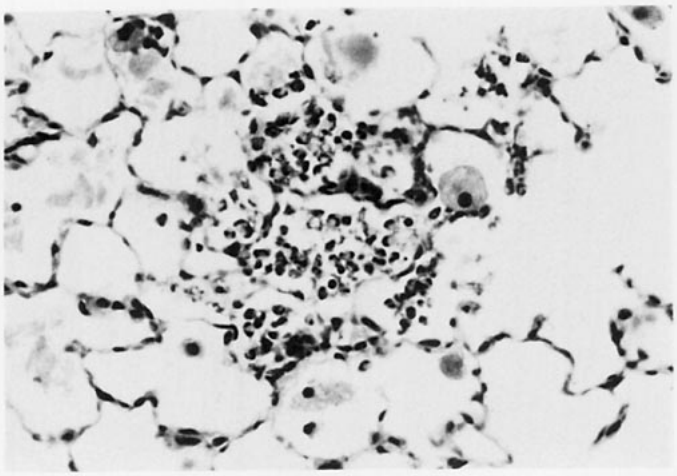

PLATE 3
Chronic active inflammation in the lung of a male B6C3F$_1$ mouse exposed to 1 mg/m^3 nickel sulfate hexahydrate by inhalation for 2 years. Note aggregates of neutrophils and cell debris within central alveolar spaces; other alveoli contain proteinaceous material or macrophages. H&E, 270×

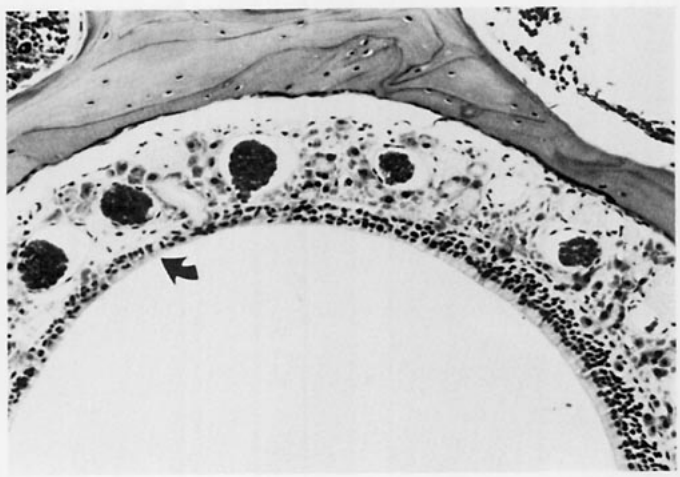

PLATE 4
Atrophy of the olfactory epithelium in the nose of a male B6C3F$_1$ mouse exposed to 1 mg/m^3 nickel sulfate hexahydrate for 2 years. Note thinning (arrow) of the layers of this pseudostratified epithelium. H&E, 135×

DISCUSSION AND CONCLUSIONS

Nickel sulfate hexahydrate is a water-soluble nickel compound used in electroplating, and exposure may also occur during other mining and refinery operations (Doll *et al.*, 1990). There have been no studies of nickel sulfate reported in which inhalation exposure concentration and toxic response relationships have been established or where toxic effects in organs other than the lung have been examined. In these inhalation studies of nickel sulfate hexahydrate in rats and mice, the major toxicity was to the respiratory system.

In the 16-day studies, rats and mice were exposed to nickel sulfate hexahydrate at concentrations of 3.5 to 60 mg/m^3 (equivalent to 0.7 to 12.2 mg nickel/m^3) (Table 31). Mice were more susceptible than rats to the lethal effects of exposure; two male rats and all female rats exposed to 60 mg/m^3 died before the end of the study, as did all male and female mice exposed to 7 mg/m^3 or greater. Respiratory toxicity, evidenced by labored respiration, occurred in all exposed groups of rats and mice. Histopathologic findings that corresponded to the respiratory toxicity in the lungs of rats and mice included inflammation, degeneration, and necrosis of the respiratory epithelium. The severity of the lung lesions increased with exposure concentration. Deaths were considered due to pulmonary inflammation and necrosis.

At the end of the 16-day studies, quantities of nickel were measured in the lungs of rats and mice from special study groups exposed to selected concentrations of nickel sulfate hexahydrate (Table 32). The nickel concentrations in the lungs of rats did not increase with exposure concentration. Lung burdens in mice exposed to 3.5 mg/m^3 were approximately 50% of those in the 3.5 mg/m^3 rats. Early deaths in the 16-day mouse study prevented an evaluation of dose-response effects in that species.

These data indicate that nickel sulfate hexahydrate is rapidly cleared from the rat lung, a finding supported by toxicokinetic studies of nickel sulfate hexahydrate in which the reported lung half-life is 1 to 3 days (Medinsky *et al.*, 1987). The data also indicate that toxic effects are related to exposure concentration and not nickel lung burden. The relatively constant amount of nickel within the lung over a range of increasing exposure concentrations implies that a small fraction of the delivered nickel may be bound to macromolecules within the lung. Evidence for nickel-binding constituents in the lung has been presented by Oskarsson and Tjalve (1979).

The distribution of nickel to other tissues was indicated by the presence of nickel in the kidney of exposed rats. The quantity of nickel in the kidney increased in proportion to exposure concentration, and these results are consistent with the finding that the major route of elimination of soluble nickel is through the urine (Medinsky *et al.*, 1987). Although quantifiable amounts of nickel were found in the kidneys of rats at all exposure concentrations, there were no treatment-related gross or histopathologic lesions present in the kidney.

In the 16-day studies, nickel sulfate hexahydrate was more toxic to rats and mice than either nickel subsulfide or nickel oxide (Table 33). Lung inflammatory lesions were observed with all three nickel compounds, but these lesions occurred at lower exposure concentrations in the nickel sulfate hexahydrate 16-day studies. Atrophy of the nasal olfactory epithelium was observed in the nickel sulfate hexahydrate and nickel subsulfide studies, but not in the nickel oxide study.

In the 13-week studies, there were no treatment-related deaths and only minimal effects on body weight changes in rats and mice (Table 34). However, exposure concentrations of 0.25 to 2 mg nickel sulfate hexahydrate/m^3 in rats and 0.5 to 2 mg/m^3 in mice caused treatment-related respiratory toxicity evidenced by increases in lung weights and inflammatory changes in the lung, nose, and bronchial lymph nodes. The nasal toxicity reported in these studies is characteristic of inhalation exposure to other metal compounds (cadmium oxide; NTP, 1995), and is

most likely due to direct exposure of the olfactory epithelium to the metal compound, not to systemic exposure. Nickel sulfate hexahydrate had no significant effects on sperm morphology or vaginal cytology in rats or mice.

After 13 weeks of exposure, the amount of nickel present in the lungs of rats and mice reached a steady state (Table 32). The amount of nickel in the lungs of male and female rats was similar, although the amount of nickel in the lungs of female mice was greater than in male mice. Nickel concentrations in the lungs of male rats following 13 weeks of exposure to approximately 0.4 mg nickel/m^3 were 6, 7, and 80 μg nickel/g lung for nickel sulfate hexahydrate, nickel subsulfide, and nickel oxide, respectively (Table 32). The very low retention of nickel in the lungs of rats exposed to nickel sulfate hexahydrate and very high retention in those exposed to nickel oxide are consistent with previous studies of nickel sulfate hexahydrate (Medinsky *et al.*, 1987) and nickel oxide in rats (Benson *et al.*, 1994). The retention of nickel subsulfide is low because of a relatively rapid clearance of this soluble nickel compound from the lung (Valentine and Fisher, 1984; Benson *et al.*, 1994).

The most significant effect of nickel sulfate hexahydrate exposure observed in the immunologic assays was an increase in the number of cells in the lung-associated lymph nodes, but this did not affect the ability of the animals to respond to intratracheally deposited antigen. There were no major changes in alveolar macrophage phagocytosis or spleen natural killer cell activity. Systemic immunity was not altered by exposure to nickel sulfate hexahydrate. There were no alterations in the antibody-forming cell response following intraperitoneal immunization in female mice exposed to nickel sulfate hexahydrate. In addition, negative results were obtained in the natural killer cell assay, the mixed lymphocyte assay, and the lymphocytic proliferative assay in these female mice (Haley *et al.*, 1990).

At 13 weeks, biochemical changes monitored in the lung lavage fluid were generally similar between male and female rats and mice (Benson *et al.*, 1989). Increased numbers of total nucleated cells indicated that some pulmonary inflammation was in progress, and that there had been an influx of inflammatory cells into the pulmonary tissue. Most of these cells were macrophages; however, modestly increased numbers of polymorphonuclear leukocytes were also present. The changes noted in these assays generally paralleled histopathologic findings.

In the present 13-week studies, the no-effect level for lung alveolar hyperplasia and inflammation and olfactory epithelial atrophy was 0.25 mg/m^3 (equivalent to 0.06 mg nickel/m^3) in rats and 0.5 mg/m^3 (equivalent to 0.11 mg nickel/m^3) in mice (Table 34). The no-effect level for nasal toxicity was approximately 0.25 mg/m^3 for rats and 1.0 mg/m^3 for mice. Respiratory toxicity produced by nickel sulfate hexahydrate in rats and mice occurs at or below the present threshold limit value levels of water-soluble nickel salts (0.1 mg nickel/m^3) (ACGIH, 1993).

Chronic active inflammation of the lung was considered to be potentially life threatening because of the possibility of reduced lung function. The highest exposure concentrations used in the 2-year studies were just below concentrations at which mild chronic active inflammation was observed in the 13-week studies.

Results of the three 13-week studies demonstrate that nickel sulfate hexahydrate was the most toxic and nickel oxide the least toxic (Table 34). The lung and nasal toxicity reflects the relative solubility of the nickel compounds in water and biological fluids, with the most soluble nickel (nickel sulfate hexahydrate) being the most toxic. The soluble nickel compounds are thought to be more toxic than the insoluble nickel compounds because the availability of relatively higher concentrations of free nickel ions for diffusion across the cell membrane and interaction with cytoplasmic proteins, thereby causing toxicity. In contrast, it is thought that the water-insoluble nickel compounds are phagocytized and do not cause extensive damage to cytoplasmic components of the alveolar/bronchiolar epithelium (Lee *et al.*, 1993; Costa *et al.*, 1994).

In the 2-year studies of nickel sulfate hexahydrate, there were no treatment-related effects on survival (Table 35). Mean body weights of exposed male rats were similar to those of the controls. However, mean body weights of female rats, male mice, and female mice exposed to 0.5 mg/m^3 and those of

0.25 mg/m^3 female rats and female mice were slightly less than those of the controls during most of the last year of the study.

Toxic responses in the lungs of rats and mice exposed for 2 years by inhalation to nickel sulfate hexahydrate were less severe than those observed in the lungs of rats and mice exposed similarly to nickel oxide or nickel subsulfide (Table 35). The exposure concentrations used in the nickel sulfate hexahydrate 2-year studies were lower than those used in studies of the other nickel compounds (Table 31), primarily because nickel sulfate hexahydrate has a steeper toxic response curve. For example, the highest exposure concentration used in the nickel oxide 2-year studies delivered 2 mg nickel/m^3 to rats and 4 mg nickel/m^3 to mice, and these nickel exposure concentrations were fatal to rats and mice in the 16-day nickel sulfate hexahydrate studies. The highest exposure concentration used in the nickel subsulfide 2-year studies delivered 0.73 mg nickel/m^3 to rats and 0.88 mg nickel/m^3 to mice, and similar concentrations of nickel caused lung toxicity in rats and mice after 12 days of exposure to nickel sulfate hexahydrate.

No exposure-related lung neoplasms occurred in rats or mice exposed to nickel sulfate hexahydrate for 2 years (Table 35). This is consistent with previous studies which have examined the carcinogenic potential of nickel sulfate hexahydrate administered via local injection (Payne, 1964; Gilman, 1962, 1966; Kasprzak *et al.*, 1983; Pott *et al.*, 1989, 1992). In these studies, no treatment-related carcinogenic responses were observed.

Female rats exposed to 0.25 or 0.5 mg/m^3 nickel sulfate hexahydrate during the 2-year study had decreased incidences of spontaneous mammary gland neoplasms. Rao *et al.* (1987) reported that decreases in mammary gland neoplasms in rats are associated with decreased body weights; the mean body weights of 0.25 mg/m^3 female rats were decreased approximately 2% to 6% and those of 0.5 mg/m^3 female rats were decreased approximately 7% to 10% during the last year of the study. Decreases in body weights may affect the development of spontaneous mammary gland neoplasms by decreasing cell proliferation and the development/progression of endogenous mutagenic events.

Although no exposure-related neoplasms were observed in male or female rats or mice in the present studies, the lung, bronchial lymph node, and olfactory epithelium of exposed animals did have significant alterations compared with controls. Both rats and mice exposed to nickel sulfate hexahydrate had a spectrum of inflammatory changes in the lung similar to those in the nickel oxide and nickel subsulfide studies, but the severity and progression of lesions over exposure time were less in animals exposed to nickel sulfate hexahydrate.

Respiratory toxicity in the lung of rats exposed to nickel sulfate hexahydrate occurred for the most part in 0.25 and 0.5 mg/m^3 rats and was characterized by fibrosis, hyperplasia, and alveolar proteinosis; these lesions were considered to be the various components of chronic active inflammation. In mice, treatment-related lung lesions were diagnosed as inflammation, hyperplasia, proteinosis, and cellular infiltration; these lung lesions were observed primarily in 0.5 and 1 mg/m^3 mice.

Some generalities can be made about the comparative lung pathology in rats and mice after 2 years of exposure to nickel sulfate hexahydrate, nickel oxide, or nickel subsulfide. There was similar incidence, appearance, and severity of spontaneous lesions in the lung of the rats in the control groups for all three compounds; lung lesions in the control groups of mice for all three compounds were also similar. Alveolar/bronchiolar neoplasms in rats and mice exposed to nickel sulfate hexahydrate and in mice exposed to nickel oxide or nickel subsulfide were typical of spontaneously occurring neoplasms. In all three nickel studies, mice were less susceptible to proliferative and fibrotic lung lesions than were 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. Similar squamous differentiation was present in 2 of 21 alveolar/bronchiolar adenomas and in 4 of 14 alveolar/bronchiolar carcinomas in rats exposed to nickel subsulfide. Such proliferative squamous differentiation is not characteristic of spontaneous alveolar/bronchiolar neoplasms in rats, but it has been observed in studies of other inhaled particulates in rats. In the present inhalation studies

with soluble (rather than particulate) nickel sulfate hexahydrate, there were no increased incidences of lung neoplasms in exposed groups of rats or mice, but some exposed animals had squamous metaplasia or squamous cysts in the lungs. This suggests that nickel in any form may stimulate rodent lung tissue to form squamous epithelium.

Incidences of lung neoplasms observed in the three nickel compound studies are not a direct function of the amount of nickel deposited in the lung as measured by atomic absorption spectroscopy at various time points during the course of exposures (Table 32). At the 15-month interim evaluation, less than 30 μg nickel/g of lung was measured in rats and mice in all exposure groups in the nickel sulfate hexahydrate and nickel subsulfide studies, and while nickel subsulfide caused a clear carcinogenic response in the rat lung, nickel sulfate hexahydrate did not. In nickel oxide rats at 15 months, amounts of nickel deposited in the lung were much greater (approximately 300 to 1,100 μg nickel/g lung). However, rats exposed to nickel oxide developed fewer lung neoplasms than did rats exposed to nickel subsulfide.

The results of the present studies with the three nickel compounds showed that water-insoluble nickel compounds (nickel oxide and nickel subsulfide) were carcinogenic to the rat lung, whereas the water-soluble nickel compound (nickel sulfate hexahydrate) was not. Costa *et al.* (1994) has suggested that water-insoluble nickel compounds are capable of causing more critical cancer damage because they are delivered at higher concentrations to the nucleus than are water-soluble nickel compounds such as nickel sulfate hexahydrate.

The incidences of inflammatory lung lesions observed in rats exposed to nickel sulfate hexahydrate occurred with significant positive trends. However, the differences between severities of lung inflammatory lesions observed in exposed and control rats in the nickel oxide and nickel subsulfide studies were greater than the differences observed between severities of exposed and control nickel sulfate hexahydrate rats. Additionally, rats exposed to nickel oxide or nickel subsulfide had significant parenchymal damage secondary to inflammation. In rats exposed to 1 mg/m^3 nickel subsulfide or 2.5 mg/m^3 nickel oxide, protein accumulations with variable numbers of foamy macrophages were widespread in alveolar spaces. Fibrosis, consolidation, and cellular proliferation apparently secondary to inflammation were multifocally extensive in both nickel subsulfide- and nickel oxide-exposed rats. Foci of necrotic cellular debris, regenerative alveolar epithelial proliferation, and foci of collapse or consolidation were somewhat more prominent in nickel subsulfide-exposed rats. Exposure-related pigment and the condensed appearance of the intra-alveolar protein were noteworthy in the nickel oxide-exposed rats. Pigment occurred in the lungs and bronchial lymph nodes of rats and mice exposed to nickel oxide, but was not observed in the nickel subsulfide- or nickel sulfate hexahydrate-exposed animals.

With the exception of the pigment observed in nickel oxide-exposed mice, nonneoplastic lesions in the lungs of exposed mice were similar in all three nickel studies and were composed of various inflammatory reactions, including: intra-alveolar protein and macrophages; mononuclear inflammatory cells around vessels; and multifocal intra-alveolar aggregates of various combinations of lymphocytes, macrophages, and neutrophils. 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 or nickel subsulfide were predominantly mononuclear cells with little evidence of necrotic cell debris.

In areas where epidemiology studies were available, Doll *et al.* (1990) estimated exposures to individual nickel compounds at various refineries or nickel operations throughout the world. In most cases, nickel sulfate hexahydrate, nickel oxide, and nickel subsulfide exposures occurred simultaneously, and workers tended to work in several departments with different nickel exposures throughout their careers. Therefore, it was not possible from the human studies to obtain a risk from exposure to nickel sulfate hexahydrate alone. However, in certain subpopulations such as in the electrolysis departments in the Kristiansand refinery workers (Norway) or the

hydrometallury departments at the Clydach refinery (Canada), nickel sulfate hexahydrate exposures were particularly high (1 to 5 mg/m^3), and there was evidence that exposure to soluble nickel increased the risk of lung cancer in workers also exposed to oxidic, sulfidic, and/or metallic nickel. Soluble nickel was thought to have a synergistic role with oxidic or other forms of nickel in causing lung and nasal neoplasms (Doll *et al.*, 1990). No exposure-related neoplasms were observed in the nasal cavities of rats or mice exposed to nickel sulfate hexahydrate, nickel subsulfide, or nickel oxide.

Experimental studies have provided evidence to suggest that water-soluble nickel salts may enhance the carcinogenic response from exposures to other environmental agents. In *in vitro* studies, water-soluble nickel salts (i.e. nickel chloride) have been shown to enhance the cytotoxicity and mutagenicity of DNA-damaging agents by inhibiting nucleotide excision repair in mammalian cells and repair of ultraviolet-induced photoproducts (Hartwig *et al.*, 1994). These studies suggest that exposure to water-soluble nickel salts may be a factor in the eventual development of cancer when there is concomitant exposure to other agents.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of nickel sulfate hexahydrate in male or female F344/N rats exposed to 0.12, 0.25, or 0.5 mg/m^3 (0.03, 0.06, or 0.11 mg nickel/m^3). There was *no evidence of carcinogenic activity* of nickel sulfate hexahydrate in male or female B6C3F$_1$ mice exposed to 0.25, 0.5, or 1 mg/m^3 (0.06, 0.11, or 0.22 mg nickel/m^3).

Exposure of rats to nickel sulfate hexahydrate by inhalation for 2 years resulted in increased incidences of chronic active inflammation, macrophage hyperplasia, alveolar proteinosis, and fibrosis of the lung; lymphoid hyperplasia of the bronchial lymph node; and atrophy of the olfactory epithelium. Exposure of mice to nickel sulfate hexahydrate by inhalation for 2 years resulted in increased incidences of chronic active inflammation, bronchialization (alveolar epithelial hyperplasia), macrophage hyperplasia, interstitial infiltration, and alveolar proteinosis of the lung; lymphoid and macrophage hyperplasia of the bronchial lymph node; and atrophy of the olfactory epithelium.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

TABLE 31
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 32
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 32
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.

TABLE 33
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 33
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 34
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 (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 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 34
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 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 34
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)
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 34
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 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 (mg Ni/m³)	0	0.12 (0.03)	0.25 (0.06)	0.5 (0.11)	0	0.15 (0.11)	1 (0.73)	0	0.62 (0.5)	1.25 (1.0)	2.5 (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 (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)**
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)

Dose mg/m³ (mg Ni/m³)	Nickel Sulfate Hexahydrate (22.3% Ni) 0	0.25 (0.06)	0.5 (0.11)	1 (0.22)	Nickel Subsulfide (73.3% Ni) 0	0.6 (0.44)	1.2 (0.88)	Nickel Oxide (78.6% Ni) 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%)]

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF NICKEL SULFATE HEXAHYDRATE

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/mg^3	0.5 mg/m^3
Disposition Summary				
Animals initially in study	64	63	63	63
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death			1	
Moribund	34	30	31	28
Natural deaths	4	7	3	4
Survivors				
Died last week of study				1
Terminal sacrifice	16	16	18	20
Animals examined microscopically	64	63	63	63
7-Month Interim Evaluation				
Nervous System				
Brain			(1)	
Oligodendroglioma NOS			1 (100%)	
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Endocrine System				
Islets, pancreatic	(5)	(5)	(5)	(5)
Adenoma		1 (20%)		
Pituitary gland	(5)	(5)	(5)	(5)
Pars distalis, adenoma	2 (40%)			1 (20%)
Genital System				
Testes	(5)	(5)	(5)	(5)
Bilateral, interstitial cell, adenoma	5 (100%)	5 (100%)	5 (100%)	4 (80%)

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/mg^3	0.5 mg/m^3
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, bronchial	(5)	(5)	(5)	(4)
Spleen	(5)	(5)	(5)	(5)
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Keratoacanthoma	1 (20%)			
Systemic Lesions				
Multiple organs[b]	(5)	(5)	(5)	(5)
Leukemia mononuclear			1 (20%)	
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(54)*	(53)	(53)	(52)
Intestine large, cecum	(54)	(53)	(53)	(52)
Sarcoma		1 (2%)		
Intestine small, duodenum	(54)	(53)	(51)	(53)
Intestine small, jejunum	(54)	(52)	(50)	(53)
Intestine small, ileum	(54)	(51)	(48)	(53)
Liver	(54)	(53)	(53)	(53)
Cholangiocarcinoma	1 (2%)			
Hepatocellular carcinoma	1 (2%)	1 (2%)		
Hepatocellular adenoma	1 (2%)		2 (4%)	2 (4%)
Mesentery	(2)	(4)		(1)
Lipoma		2 (50%)		
Schwannoma benign	1 (50%)			
Oral mucosa	(3)	(2)	(4)	
Squamous cell carcinoma			3 (75%)	
Squamous cell papilloma	2 (67%)	1 (50%)	1 (25%)	
Pancreas	(53)	(52)	(53)	(53)
Salivary glands	(54)	(53)	(53)	(53)
Stomach, forestomach	(54)	(53)	(52)	(52)
Stomach, glandular	(54)	(53)	(53)	(53)
Tongue		(1)		
Squamous cell carcinoma		1 (100%)		

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/mg^3	0.5 mg/m^3
2-Year Study (continued)				
Cardiovascular System				
Heart	(54)	(53)	(53)	(53)
Endocrine System				
Adrenal cortex	(54)	(53)	(53)	(53)
Adenoma		1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)			
Adrenal medulla	(54)	(53)	(53)	(53)
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant		3 (6%)	2 (4%)	1 (2%)
Pheochromocytoma benign	11 (20%)	10 (19%)	12 (23%)	9 (17%)
Bilateral, pheochromocytoma benign	5 (9%)	6 (11%)		2 (4%)
Islets, pancreatic	(52)	(51)	(52)	(53)
Adenoma	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Carcinoma			1 (2%)	1 (2%)
Parathyroid gland	(49)	(51)	(51)	(48)
Adenoma				1 (2%)
Pituitary gland	(54)	(51)	(53)	(53)
Pars distalis, adenoma	13 (24%)	12 (24%)	18 (34%)	13 (25%)
Thyroid gland	(53)	(53)	(51)	(52)
Bilateral, C-cell, adenoma	1 (2%)			
C-cell, adenoma	7 (13%)	1 (2%)	2 (4%)	1 (2%)
C-cell, carcinoma		1 (2%)		2 (4%)
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma				1 (2%)
General Body System				
Tissue NOS	(4)	(1)	(5)	(4)
Cholangiocarcinoma, metastatic, liver	1 (25%)			
Fibroma			1 (20%)	
Paraganglioma	1 (25%)			1 (25%)
Abdominal, chondrosarcoma				1 (25%)
Thoracic, chordoma				1 (25%)
Genital System				
Epididymis	(54)	(53)	(53)	(53)
Preputial gland	(54)	(53)	(52)	(53)
Adenoma	2 (4%)		3 (6%)	3 (6%)
Carcinoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Prostate	(54)	(53)	(53)	(53)
Seminal vesicle	(54)	(53)	(53)	(53)
Testes	(54)	(53)	(53)	(53)
Bilateral, interstitial cell, adenoma	32 (59%)	38 (72%)	38 (72%)	39 (74%)
Interstitial cell, adenoma	13 (24%)	8 (15%)	7 (13%)	11 (21%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/mg³	0.5 mg/m³
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(54)	(52)	(52)	(53)
Osteosarcoma, metastatic, bone	1 (2%)			
Lymph node	(11)	(14)	(11)	(12)
Lymph node, bronchial	(51)	(49)	(47)	(52)
Carcinoma, metastatic, preputial gland		1 (2%)		
Lymph node, mandibular	(52)	(53)	(52)	(53)
Squamous cell carcinoma, metastatic, oral mucosa			2 (4%)	
Lymph node, mesenteric	(54)	(53)	(53)	(53)
Hemangioma			1 (2%)	
Lymph node, mediastinal	(51)	(49)	(46)	(50)
Spleen	(54)	(53)	(51)	(53)
Hemangiosarcoma		1 (2%)		
Thymus	(49)	(48)	(48)	(46)
Integumentary System				
Mammary gland	(43)	(48)	(49)	(44)
Adenocarcinoma	1 (2%)	1 (2%)		
Fibroadenoma			1 (2%)	1 (2%)
Fibroadenoma, multiple		1 (2%)		
Skin	(53)	(53)	(53)	(53)
Basal cell adenoma				1 (2%)
Basal cell carcinoma				1 (2%)
Fibroma		1 (2%)		3 (6%)
Keratoacanthoma	4 (8%)	1 (2%)	1 (2%)	
Lipoma		1 (2%)	1 (2%)	
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma			2 (4%)	2 (4%)
Lip, trichoepithelioma		1 (2%)		
Subcutaneous tissue, osteosarcoma				1 (2%)
Subcutaneous tissue, sarcoma			1 (2%)	
Musculoskeletal System				
Bone	(54)	(53)	(53)	(53)
Humerus, osteosarcoma	1 (2%)			
Nervous System				
Brain	(54)	(53)	(53)	(53)
Glioma NOS	1 (2%)			

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/mg^3	0.5 mg/m^3
2-Year Study (continued)				
Respiratory System				
Larynx	(54)	(52)	(53)	(53)
Lung	(54)	(53)	(53)	(53)
Alveolar/bronchiolar adenoma				2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)	1 (2%)
Chordoma, metastatic, tissue NOS				1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Squamous cell carcinoma	1 (2%)			
Nose	(54)	(52)	(53)	(53)
Special Senses System				
Zymbal's gland	(1)		(2)	
Carcinoma	1 (100%)		2 (100%)	
Urinary System				
Kidney	(54)	(52)	(52)	(53)
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)		
Renal tubule, adenoma	1 (2%)			1 (2%)
Urinary bladder	(54)	(53)	(53)	(53)
Systemic Lesions				
Multiple organs	(54)	(53)	(53)	(53)
Leukemia mononuclear	31 (57%)	36 (68%)	38 (72%)	38 (72%)
Lymphoma malignant			1 (2%)	
Mesothelioma malignant		1 (2%)		
Mesothelioma NOS		1 (2%)		

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/mg^3	0.5 mg/m^3
Neoplasm Summary				
Total animals with primary neoplasms[c]				
7-Month interim evaluation			1	
15-Month interim evaluation	5	5	5	4
2-Year study	53	52	51	51
Total primary neoplasms				
7-Month interim evaluation			1	
15-Month interim evaluation	8	6	6	5
2-Year study	136	136	142	145
Total animals with benign neoplasms				
15-Month interim evaluation	5	5	5	4
2-Year study	49	50	50	51
Total benign neoplasms				
15-Month interim evaluation	8	6	5	5
2-Year study	96	85	92	96
Total animals with malignant neoplasms				
15-Month interim evaluation			1	
2-Year study	37	43	41	41
Total malignant neoplasms				
15-Month interim evaluation			1	
2-Year study	39	50	50	49
Total animals with metastatic neoplasms				
2-Year study	2	3	3	1
Total metastatic neoplasms				
2-Year study	6	3	3	1
Total animals with uncertain neoplasms - benign or malignant				
7-Month interim evaluation			1	
2-Year study	1	1		
Total uncertain neoplasms				
7-Month interim evaluation			1	
2-Year study	1	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 Sulfate Hexahydrate: 0 mg/m³

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

+: 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 Sulfate Hexahydrate: 0 mg/m³ (continued)

Number of Days on Study	6 5 8	6 6 2	6 7 9	6 7 9	6 8 6	6 9 3	7 0 3	7 0 3	7 0 8	7 2 0	7 2 1	7 2 6	7 3 1	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 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 6	0 0 2	0 1 2	0 6 5	0 5 0	0 6 0	0 5 6	0 6 1	0 4 2	0 1 3	0 2 8	0 3 5	0 1 9	0 2 5	0 4 1	0 5 4	0 5 5	0 5 7	0 0 1	0 0 9	0 1 4	0 2 4	0 3 3	0 6 7	0 0 6	0 1 7	0 3 7	0 4 4	0 5 3	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Cholangiocarcinoma						X																							1
Hepatocellular carcinoma																													1
Hepatocellular adenoma																													1
Mesentery							+																						2
Schwannoma benign																													1
Oral mucosa										+															+				3
Squamous cell papilloma										X																			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Tooth	+						+			+																			9
Cardiovascular System																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Osteosarcoma, metastatic, bone																													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Osteosarcoma, metastatic, bone																													1
Pheochromocytoma benign							X	X			X			X	X					X		X			X				11
Bilateral, pheochromocytoma benign			X			X				X											X		X						5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma				X																									2
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Pars distalis, adenoma				X				X		X	X									X			X	X					13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Bilateral, C-cell, adenoma																			X										1
C-cell, adenoma									X		X	X				X					X							X	7
General Body System																													
Tissue NOS				+	+	+									+														4
Cholangiocarcinoma, metastatic, liver						X																							1
Paraganglioma				X																									1

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

Number of Days on Study	1 1 7	2 6 2	4 8 2	4 9 6	5 0 5	5 1 8	5 3 6	5 3 9	5 3 9	5 5 0	5 6 5	5 6 9	5 7 7	5 9 7	6 1 0	6 1 4	6 1 8	6 2 2	6 2 2	6 2 6	6 3 4	6 3 7	6 5 5	6 5 7	6 5 7
Carcass ID Number	0 3 9	0 4 3	0 1 6	0 4 0	0 6 3	0 1 1	0 0 8	0 3 6	0 6 9	0 5 1	0 0 3	0 2 7	0 2 0	0 4 9	0 6 8	0 0 7	0 1 5	0 2 1	0 5 9	0 0 4	0 5 8	0 4 7	0 3 2	0 2 3	0 4 5
Genital System																									
Coagulating gland							+																		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								+	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma			X																						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X					X	X			X	X			X	X	X
Interstitial cell, adenoma			X					X	X			X	X	X			X	X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Lymph node						+									+	+								+	+
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Adenocarcinoma																									
Skin	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma NOS																							X		
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic, bone		X																							
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	6 5 8	6 6 2	6 7 9	6 7 9	6 8 6	6 9 3	7 0 3	7 0 3	7 0 8	7 2 0	7 2 1	7 2 6	7 3 1	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 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 6	0 0 2	0 1 2	0 6 5	0 5 0	0 6 0	0 5 6	0 6 1	0 4 2	0 1 3	0 2 8	0 3 5	0 1 9	0 2 5	0 4 1	0 5 4	0 5 5	0 5 7	0 0 1	0 0 9	0 1 4	0 2 4	0 3 3	0 6 7	0 0 6	0 1 7	0 3 7	0 4 4	0 5 3	Total Tissues/ Tumors
Genital System																														
Coagulating gland																														1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Penis																														1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adenoma											X																			2
Carcinoma																														1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
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	X	X	X	32
Interstitial cell, adenoma			X							X										X			X		X					13
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Osteosarcoma, metastatic, bone																														1
Lymph node	+	+	+										+	+											+					11
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	51
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node, mediastinal	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	49
Integumentary System																														
Mammary gland	+	M	M	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	43
Adenocarcinoma																							X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Keratoacanthoma			X			X		X								X														4
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Humerus, osteosarcoma																														1
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Glioma NOS																														1
Respiratory System																														
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Alveolar/bronchiolar carcinoma																	X													1
Osteosarcoma, metastatic, bone																														1
Squamous cell carcinoma																												X		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54

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

Number of Days on Study	1 1 7	2 6 2	4 8 2	4 9 6	5 0 5	5 1 8	5 3 6	5 3 9	5 3 9	5 5 0	5 6 5	5 6 9	5 7 7	5 9 7	6 1 0	6 1 4	6 1 8	6 2 2	6 2 2	6 2 6	6 3 4	6 3 7	6 5 5	6 5 7	6 5 7
Carcass ID Number	0 3 9	0 4 3	0 1 6	0 4 0	0 6 3	0 1 1	0 0 3	0 3 6	0 6 9	0 5 1	0 0 3	0 2 7	0 2 0	0 4 9	0 6 8	0 0 7	0 1 5	0 2 1	0 5 9	0 0 4	0 5 8	0 4 7	0 3 2	0 2 3	0 4 5
Special Senses System																									
Eye																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Renal tubule, adenoma																									
Urethra	+																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				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 Sulfate Hexahydrate: 0 mg/m³ (continued)

Number of Days on Study	6 5 8	6 6 2	6 7 9	6 7 9	6 8 6	6 9 3	7 0 3	7 0 3	7 0 8	7 2 0	7 2 1	7 2 6	7 3 1	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 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 6	0 0 2	0 1 2	0 6 5	0 5 0	0 6 0	0 5 6	0 6 1	0 4 2	0 1 3	0 2 8	0 3 5	0 1 9	0 2 5	0 4 1	0 5 4	0 5 5	0 5 7	0 0 1	0 0 9	0 1 4	0 2 4	0 3 3	0 6 7	0 0 6	0 1 7	0 3 7	0 4 4	0 5 3	Total Tissues/ Tumors
Special Senses System																													
Eye																		+											1
Zymbal's gland				+																									1
Carcinoma				X																									1
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Osteosarcoma, metastatic, bone																													1
Renal tubule, adenoma													X																1
Urethra																													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Leukemia mononuclear	X	X	X		X	X		X		X		X	X	X	X		X	X	X	X	X	X			X	X				31

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (continued)

Number of Days on Study	6 8 3	6 8 5	6 9 2	7 0 2	7 0 3	7 0 4	7 0 8	7 2 0	7 2 0	7 2 6	7 2 6	7 3 2	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	7 3 7	7 3 7		
Carcass ID Number	2 0 9	1 0 3	1 0 5	1 0 7	1 0 6	1 0 7	1 0 8	1 0 8	1 0 9	1 0 8	1 2 0	1 0 9	1 0 4	1 0 6	1 0 9	1 0 4	1 0 7	1 0 8	1 0 8	1 0 9	1 0 5	2 0 6	2 0 1	1 0 4	1 0 8	1 0 6	1 0 5	1 0 6	1 0 3	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Sarcoma								X																					1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular carcinoma																						X							1
Mesentery		+	+																										4
Lipoma		X																											2
Oral mucosa																													2
Squamous cell papilloma																													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue																													1
Squamous cell carcinoma																													1
Tooth								+																				+	3
Cardiovascular System																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant						X																							3
Pheochromocytoma benign	X			X					X						X			X								X		X		10
Bilateral, pheochromocytoma benign							X						X								X	X				X			6
Islets, pancreatic	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma						X																							1
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma					X	X				X	X		X	X														X	12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma																				X									1
C-cell, carcinoma																													1
General Body System																													
Tissue NOS			+																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (continued)

Number of Days on Study	3 5 2	3 6 3	5 3 9	5 4 7	5 5 1	5 6 6	5 6 6	5 7 0	5 8 0	5 9 8	6 0 0	6 0 7	6 1 5	6 3 2	6 4 0	6 4 0	6 4 3	6 4 4	6 4 6	6 5 0	6 5 8	6 7 5	6 7 9	6 8 2	6 8 3
Carcass ID Number	1 9 6	1 4 4	1 7 3	1 5 5	1 4 5	2 0 8	2 1 0	1 5 2	1 4 2	1 7 6	1 5 0	1 5 4	1 5 9	1 5 8	1 4 9	1 8 5	1 7 2	1 6 0	1 4 7	1 8 6	1 9 0	1 7 1	1 5 1	2 0 2	1 8 7
Genital System																									
Coagulating gland			+	+						+															
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes								X																	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X						X			X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X					X	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	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+					+					+					+			
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	I	+	+	+	+
Carcinoma, metastatic, preputial gland																		X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma, multiple																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Keratoacanthoma																									
Lipoma																									
Squamous cell carcinoma																									
Lip, trichoepithelioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (continued)

Number of Days on Study	6 8 3	6 8 5	6 9 2	7 0 2	7 0 3	7 0 4	7 0 8	7 2 0	7 2 0	7 2 6	7 2 6	7 3 2	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	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 0 9	1 0 3	1 0 5	1 0 7	1 0 6 4	1 0 6 4	1 0 7 4	1 0 8 4	1 0 8 2	1 0 9 8	1 0 8 1	1 1 0 1	1 1 0 9 5	1 1 4 6	1 1 6 9	1 1 9 4	1 2 0 4	1 1 0 7	1 1 8 3	1 1 8 8	1 1 9 7	1 2 0 5	2 0 0 6	1 1 4 1	1 1 4 8	1 1 5 6	1 1 5 7	1 1 6 5	1 1 9 3	Total Tissues/ Tumors
Genital System																													
Coagulating gland																													3
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesothelioma malignant, metastatic, testes																													1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																													3
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	X	X	X	X	X	X	X		X	38
Interstitial cell, adenoma					X	X										X											X		8
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node	+		+			+	+	+	+								+		+			+							14
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	49
Carcinoma, metastatic, preputial gland																													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	I	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hemangiosarcoma				X																									1
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																													
Mammary gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	48
Adenocarcinoma													X																1
Fibroadenoma, multiple																													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibroma						X																							1
Keratoacanthoma						X																							1
Lipoma																						X							1
Squamous cell carcinoma																											X		1
Lip, trichoepithelioma	X																												1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Respiratory System																													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (continued)

Number of Days on Study	3	3	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	5	6	3	4	5	6	6	7	8	9	0	0	1	3	4	4	4	4	4	5	5	7	7	8	8
	2	3	9	7	1	6	6	0	0	8	0	7	5	2	0	0	3	4	6	0	8	5	9	2	3
Carcass ID Number	1	1	1	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1
	9	4	7	5	4	0	1	5	4	7	5	5	5	5	4	8	7	6	4	8	9	7	5	0	8
	6	4	3	5	5	8	0	2	2	6	0	4	9	8	9	5	2	0	7	6	0	1	1	2	7
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla														X											
Urethra	+	+																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X	X	X	X	X		X		X			X	X			X		X		X	X
Mesothelioma malignant								X																	
Mesothelioma NOS		X																							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (continued)

Number of Days on Study	6 8 3	6 8 5	6 9 2	7 0 2	7 0 3	7 0 4	7 0 8	7 2 0	7 2 0	7 2 6	7 2 6	7 3 2	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	7 3 7	7 3 7	
Carcass ID Number	2 0 9	1 0 3	1 0 5	1 0 7	1 0 6	1 0 7	1 0 4	1 0 4	1 0 2	1 0 8	1 1 1	1 1 1	1 1 5	1 1 6	1 1 9	1 2 4	1 0 4	1 0 7	1 1 3	1 1 8	1 2 7	1 2 5	1 2 6	1 1 1	1 1 8	1 1 5	1 1 6	1 1 7	1 1 5	1 1 3	Total Tissues/ Tumors
Special Senses System																													
None																													
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma malignant, metastatic, adrenal medulla																													1
Urethra									+																				3
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	36
Mesothelioma malignant																													1
Mesothelioma NOS																													1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³

Number of Days on Study	2	4	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6
	7	3	7	9	3	3	3	5	5	5	7	9	9	0	0	0	1	1	2	2	4	5	7	8	8
	9	2	1	2	5	5	8	0	1	1	6	7	7	1	6	7	4	7	1	8	3	1	9	3	4
Carcass ID Number	3	2	3	3	2	3	3	3	2	2	3	2	2	3	3	2	2	3	2	3	2	3	3	3	3
	0	9	2	4	9	0	1	3	8	9	1	8	9	3	0	8	8	4	9	3	9	4	2	2	4
	2	0	1	2	7	6	8	7	4	4	5	6	1	6	7	9	3	1	5	9	8	4	4	6	8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X																						
Oral mucosa																		+							
Squamous cell carcinoma																									
Squamous cell papilloma																		X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+	+	+																			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																						X			
Pheochromocytoma benign			X																X			X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																	X								
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X							X						X	X				X	X		
Thyroid gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X																		
Follicular cell, adenoma																									
General Body System																									
Tissue NOS									+			+				+				+					
Fibroma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	6 8 5	6 9 7	7 0 6	7 1 1	7 1 3	7 1 7	7 2 5	7 2 6	7 2 7	7 3 2	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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 5 0	3 1 9	2 8 7	3 0 8	3 2 2	3 1 3	3 3 1	3 4 9	3 0 3	3 0 9	2 8 1	2 8 2	3 0 0	3 0 4	3 1 0	3 1 6	3 4 6	3 2 0	3 3 3	3 3 4	3 4 5	3 0 1	3 0 5	3 1 2	3 2 5	3 2 8	3 4 3	3 4 7	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular adenoma					X																								2
Oral mucosa		+						+															+						4
Squamous cell carcinoma		X						X															X						3
Squamous cell papilloma																													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		52
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth																													3
Cardiovascular System																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant																		X											2
Pheochromocytoma benign		X			X					X			X			X									X	X	X	X	12
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma												X																	1
Carcinoma																													1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma	X		X					X					X	X	X	X		X	X		X						X		18
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma								X																					2
Follicular cell, adenoma							X																						1
General Body System																													
Tissue NOS			+																										5
Fibroma			X																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	2 7 9	4 3 2	4 7 1	4 9 2	5 3 5	5 3 5	5 3 8	5 5 0	5 5 1	5 7 1	5 9 6	5 7 7	5 9 7	6 0 1	6 0 6	6 0 7	6 1 4	6 1 7	6 2 1	6 2 8	6 4 3	6 5 1	6 7 9	6 8 3	6 8 4
Carcass ID Number	3 0 2	2 9 0	3 2 1	3 4 2	2 9 7	3 0 6	3 1 8	3 3 7	2 8 4	2 9 4	3 1 5	2 8 6	2 9 1	3 3 6	3 0 7	2 8 9	2 8 3	3 4 1	2 9 5	3 3 9	2 9 8	3 4 4	3 2 4	3 2 6	3 4 8
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X		X																
Carcinoma																							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	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymph node, mediastinal	M	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	A	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Lipoma																									
Squamous cell papilloma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma malignant, metastatic, adrenal medulla																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	6 8 5	6 9 7	7 0 6	7 1 1	7 1 3	7 1 7	7 2 5	7 2 6	7 2 7	7 3 2	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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 5 0	3 1 9	2 8 7	3 0 8	3 2 2	3 1 3	3 3 1	3 4 9	3 0 3	3 0 9	2 8 1	2 8 2	3 0 0	3 0 4	3 1 0	3 1 6	3 4 6	3 2 0	3 3 3	3 3 4	4 0 5	0 0 1	0 1 5	1 2 2	2 2 5	3 3 8	4 4 3	4 4 7	Total Tissues/ Tumors
Genital System																													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+		52
Adenoma																											X		3
Carcinoma																													1
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	X	X		X	X	X	X	X	X	X	38
Interstitial cell, adenoma			X	X																	X								7
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node		+		+	+					+											+								11
Lymph node, bronchial	I	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	I	+	+	47
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma, metastatic, oral mucosa		X						X																					2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hemangioma					X																								1
Lymph node, mediastinal	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	48
Integumentary System																													
Mammary gland	+	+	+		+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																							X						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Keratoacanthoma	X																												1
Lipoma															X														1
Squamous cell papilloma																		X	X										2
Subcutaneous tissue, sarcoma				X																									1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Respiratory System																													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar carcinoma				X																									1
Pheochromocytoma malignant, metastatic, adrenal medulla																													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	2 7 9	4 3 2	4 7 1	4 9 2	5 3 5	5 3 5	5 3 8	5 5 0	5 5 1	5 5 1	5 7 6	5 9 7	5 9 7	6 0 1	6 0 6	6 0 7	6 1 4	6 1 7	6 2 1	6 2 8	6 4 3	6 5 1	6 7 9	6 8 3	6 8 4
Carcass ID Number	3 0 2	2 9 0	3 2 1	3 4 2	2 9 7	3 0 6	3 1 8	3 3 7	2 8 4	2 9 4	3 1 5	2 8 6	2 9 1	3 3 6	3 0 7	2 8 9	2 8 3	3 4 1	2 9 5	3 3 9	2 9 8	3 4 4	3 4 4	3 2 6	3 2 8	3 4 8
Special Senses System																										
Ear																				+						
Eye																										
Zymbal's gland	+																			+						
Carcinoma	X																			X						
Urinary System																										
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	
Lymphoma malignant								X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m^3 (continued)

Number of Days on Study	6 8 5	6 9 7	7 0 6	7 1 1	7 1 3	7 1 7	7 2 5	7 2 6	7 2 7	7 3 2	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 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 5 0	3 1 9	2 8 7	3 0 8	3 2 2	3 1 3	3 3 1	3 4 9	3 0 3	3 0 9	2 8 1	2 8 2	3 0 0	3 0 4	3 1 0	3 1 6	3 4 6	3 2 0	3 3 3	3 3 4	3 4 5	3 0 1	3 0 5	3 1 2	3 2 5	3 2 8	3 4 3	3 4 7	Total Tissues/ Tumors
Special Senses System																											
Ear																											1
Eye															+												1
Zymbal's gland																											2
Carcinoma																											2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	38
Lymphoma malignant																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³

Number of Days on Study	3 2 0	4 1 9	4 2 0	4 3 3	4 6 0	5 3 9	5 5 2	5 6 3	5 7 6	5 8 3	5 8 4	5 8 4	6 0 2	6 2 8	6 2 8	6 2 8	6 2 9	6 3 0	6 3 4	6 3 8	6 4 0	6 5 1	6 5 4	6 7 1	6 7 6
Carcass ID Number	4 6 6 8	4 6 6	4 4 3	4 4 2	4 7 1	4 8 5	4 7 2	4 3 7	4 8 1	4 6 2	4 4 7	4 7 9	4 2 5	4 3 4	4 7 3	4 7 5	4 7 7	4 5 6	4 4 0	4 3 8	4 2 2	4 5 1	4 2 6	4 2 4	4 6 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	M
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X											X				
Mesentery																		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X					X		
Carcinoma																				X					
Parathyroid gland	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																	X			X				X	
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																								X	
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS													+						+						
Paraganglioma																			X						
Abdominal, chondrosarcoma																									
Thoracic, chordoma																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X							X													
Carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	6 8 8	6 8 8	6 9 7	6 9 7	6 9 9	7 1 3	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 3 5	4 7 8	4 2 3	4 8 3	4 2 9	4 4 8	4 8 2	4 2 7	4 2 8	4 4 9	4 6 0	4 6 3	4 7 0	4 7 4	4 8 4	4 9 0	4 2 1	4 3 1	4 4 4	4 4 6	4 5 9	4 4 5	4 5 0	4 5 5	4 5 7	4 6 1	4 6 7	4 8 0	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular adenoma																													2
Mesentery																													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth				+										+															3
Cardiovascular System																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant																												X	1
Pheochromocytoma benign		X			X	X		X			X							X			X			X				9
Bilateral, pheochromocytoma benign				X													X									X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma								X																				X	4
Carcinoma																													1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma															X														1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma			X		X	X	X	X					X				X	X			X					X			13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma																			X										1
C-cell, carcinoma																									X				2
Follicular cell, carcinoma												X																	1
General Body System																													
Tissue NOS							+																					+	4
Paraganglioma																													1
Abdominal, chondrosarcoma																												X	1
Thoracic, chordoma																												X	1
Genital System																													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma									X																				3
Carcinoma																													1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	3	4	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6
	2	1	2	3	6	3	5	6	7	8	8	8	0	2	2	2	2	3	3	3	4	5	5	7	7
	0	9	0	3	0	9	2	3	6	3	4	4	2	8	8	8	9	0	4	8	0	1	4	1	6
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	6	6	4	4	7	8	7	3	8	6	4	7	2	3	7	7	7	5	4	3	2	5	2	2	6
	8	6	3	2	1	5	2	7	1	2	7	9	5	4	3	5	7	6	0	8	2	1	6	4	9
Genital System (continued)																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X	X		X	X						X			X	X	X		X	X	X	X	X	X	X	X
Interstitial cell, adenoma						X	X	X		X		X	X				X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+		+			+		+				+		+		+			
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	I	M	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Fibroadenoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma		X																							
Basal cell carcinoma																									
Fibroma																X									
Squamous cell papilloma																									
Subcutaneous tissue, osteosarcoma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X									
Chordoma, metastatic, tissue NOS																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
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	X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	6 8 8	6 8 8	6 9 7	6 9 7	6 9 9	7 1 3	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 3 5	4 7 8	4 2 3	4 8 3	4 2 9	4 4 8	4 8 2	4 2 7	4 2 8	4 4 9	4 6 0	4 6 3	4 7 0	4 7 4	4 8 4	4 9 0	4 2 1	4 3 1	4 4 4	4 4 6	4 5 9	4 4 5	4 5 0	4 5 5	4 5 7	4 6 1	4 6 7	4 8 0	Total Tissues/ Tumors
Genital System (continued)																													
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	X	X	39
Interstitial cell, adenoma	X	X			X												X												11
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node						+	+				+		+																12
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																													
Mammary gland	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Fibroadenoma																													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Basal cell adenoma																													1
Basal cell carcinoma						X																							1
Fibroma	X								X																				3
Squamous cell papilloma									X																	X			2
Subcutaneous tissue, osteosarcoma																													1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Respiratory System																													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma											X									X									2
Alveolar/bronchiolar carcinoma																													1
Chordoma, metastatic, tissue NOS																												X	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																													
Eye											+																		1
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Renal tubule, adenoma	X																												1
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						X		X	X	X		38

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	16/54 (30%)	16/53 (30%)	12/53 (23%)	11/53 (21%)
Adjusted rate[b]	61.2%	62.3%	46.2%	43.3%
Terminal rate[c]	7/16 (44%)	8/16 (50%)	6/18 (33%)	7/21 (33%)
First incidence (days)	622	580	471	688
Life table test[d]	P=0.045N	P=0.523N	P=0.185N	P=0.088N
Logistic regression test[d]	P=0.085N	P=0.477N	P=0.204N	P=0.142N
Cochran-Armitage test[d]	P=0.126N			
Fisher exact test[d]		P=0.559	P=0.274N	P=0.202N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	0/54 (0%)	3/53 (6%)	2/53 (4%)	1/53 (2%)
Adjusted rate	0.0%	9.7%	8.5%	4.8%
Terminal rate	0/16 (0%)	0/16 (0%)	1/18 (6%)	1/21 (5%)
First incidence (days)	—[e]	632	651	733 (T)
Life table test	P=0.601	P=0.150	P=0.253	P=0.554
Logistic regression test	P=0.566	P=0.123	P=0.244	P=0.554
Cochran-Armitage test	P=0.557			
Fisher exact test		P=0.118	P=0.243	P=0.495
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	16/54 (30%)	19/53 (36%)	13/53 (25%)	12/53 (23%)
Adjusted rate	61.2%	66.0%	50.7%	47.4%
Terminal rate	7/16 (44%)	8/16 (50%)	7/18 (39%)	8/21 (38%)
First incidence (days)	622	580	471	688
Life table test	P=0.049N	P=0.419	P=0.243N	P=0.122N
Logistic regression test	P=0.092N	P=0.439	P=0.274N	P=0.168N
Cochran-Armitage test	P=0.137N			
Fisher exact test		P=0.316	P=0.354N	P=0.274N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/54 (2%)	0/53 (0%)	1/53 (2%)	3/53 (6%)
Adjusted rate	6.3%	0.0%	4.0%	11.8%
Terminal rate	1/16 (6%)	0/16 (0%)	0/18 (0%)	2/21 (10%)
First incidence (days)	733 (T)	—	711	628
Life table test	P=0.137	P=0.500N	P=0.722N	P=0.396
Logistic regression test	P=0.098	P=0.500N	P=0.740N	P=0.325
Cochran-Armitage test	P=0.093			
Fisher exact test		P=0.505N	P=0.748	P=0.302
Lung: Squamous Cell Carcinoma, Alveolar/bronchiolar Adenoma, or Alveolar/bronchiolar Carcinoma				
Overall rate	2/54 (4%)	0/53 (0%)	1/53 (2%)	3/53 (6%)
Adjusted rate	12.5%	0.0%	4.0%	11.8%
Terminal rate	2/16 (13%)	0/16 (0%)	0/18 (0%)	2/21 (10%)
First incidence (days)	733 (T)	—	711	628
Life table test	P=0.315	P=0.236N	P=0.447N	P=0.614
Logistic regression test	P=0.249	P=0.236N	P=0.456N	P=0.532
Cochran-Armitage test	P=0.234			
Fisher exact test		P=0.252N	P=0.507N	P=0.491

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Carcinoma				
Overall rate	0/54 (0%)	1/53 (2%)	3/53 (6%)	0/53 (0%)
Adjusted rate	0.0%	2.9%	13.4%	0.0%
Terminal rate	0/16 (0%)	0/16 (0%)	1/18 (6%)	0/21 (0%)
First incidence (days)	—	646	697	—
Life table test	P=0.590N	P=0.518	P=0.151	—
Logistic regression test	P=0.627N	P=0.494	P=0.135	—
Cochran-Armitage test	P=0.629			
Fisher exact test		P=0.495	P=0.118	—
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	2/54 (4%)	2/53 (4%)	4/53 (8%)	0/53 (0%)
Adjusted rate	7.3%	5.3%	15.8%	0.0%
Terminal rate	0/16 (0%)	0/16 (0%)	1/18 (6%)	0/21 (0%)
First incidence (days)	577	640	617	—
Life table test	P=0.211N	P=0.655N	P=0.377	P=0.224N
Logistic regression test	P=0.234N	P=0.685	P=0.343	P=0.241N
Cochran-Armitage test	P=0.238N			
Fisher exact test		P=0.684	P=0.330	P=0.252N
Oral Mucosa: Squamous Cell Carcinoma				
Overall rate	0/54 (0%)	0/53 (0%)	3/53 (6%)	0/53 (0%)
Adjusted rate	0.0%	0.0%	13.4%	0.0%
Terminal rate	0/16 (0%)	0/16 (0%)	1/18 (6%)	0/21 (0%)
First incidence (days)	—	—	697	—
Life table test	P=0.586	—	P=0.151	—
Logistic regression test	P=0.553	—	P=0.135	—
Cochran-Armitage test	P=0.530			
Fisher exact test		—	P=0.118	—
Pancreatic Islets: Adenoma				
Overall rate	2/52 (4%)	1/51 (2%)	1/52 (2%)	4/53 (8%)
Adjusted rate	6.8%	4.3%	5.9%	14.9%
Terminal rate	0/16 (0%)	0/16 (0%)	1/17 (6%)	2/21 (10%)
First incidence (days)	657	704	733 (T)	630
Life table test	P=0.198	P=0.466N	P=0.477N	P=0.384
Logistic regression test	P=0.171	P=0.491N	P=0.494N	P=0.353
Cochran-Armitage test	P=0.171			
Fisher exact test		P=0.507N	P=0.500N	P=0.348
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	2/52 (4%)	1/51 (2%)	2/52 (4%)	5/53 (9%)
Adjusted rate	6.8%	4.3%	8.4%	17.4%
Terminal rate	0/16 (0%)	0/16 (0%)	1/17 (6%)	2/21 (10%)
First incidence (days)	657	704	614	630
Life table test	P=0.097	P=0.466N	P=0.679N	P=0.261
Logistic regression test	P=0.080	P=0.491N	P=0.693N	P=0.228
Cochran-Armitage test	P=0.082			
Fisher exact test		P=0.507N	P=0.691N	P=0.226

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	13/54 (24%)	12/51 (24%)	18/53 (34%)	13/53 (25%)
Adjusted rate	42.5%	42.4%	59.2%	45.1%
Terminal rate	3/16 (19%)	3/15 (20%)	8/18 (44%)	6/21 (29%)
First incidence (days)	505	547	432	629
Life table test	P=0.450N	P=0.452N	P=0.292	P=0.439N
Logistic regression test	P=0.472	P=0.526N	P=0.196	P=0.571N
Cochran-Armitage test	P=0.453			
Fisher exact test		P=0.565N	P=0.180	P=0.567
Preputial Gland: Adenoma				
Overall rate	2/54 (4%)	0/53 (0%)	3/52 (6%)	3/53 (6%)
Adjusted rate	7.8%	0.0%	9.9%	8.9%
Terminal rate	0/16 (0%)	0/16 (0%)	1/17 (6%)	1/21 (5%)
First incidence (days)	622	—	538	460
Life table test	P=0.266	P=0.231N	P=0.513	P=0.543
Logistic regression test	P=0.212	P=0.232N	P=0.476	P=0.479
Cochran-Armitage test	P=0.222			
Fisher exact test		P=0.252N	P=0.482	P=0.491
Preputial Gland: Carcinoma				
Overall rate	1/54 (2%)	3/53 (6%)	1/52 (2%)	1/53 (2%)
Adjusted rate	1.9%	8.0%	3.2%	2.2%
Terminal rate	0/16 (0%)	0/16 (0%)	0/17 (0%)	0/21 (0%)
First incidence (days)	482	607	679	563
Life table test	P=0.446N	P=0.333	P=0.750N	P=0.756
Logistic regression test	P=0.462N	P=0.250	P=0.736	P=0.717
Cochran-Armitage test	P=0.444N			
Fisher exact test		P=0.302	P=0.743	P=0.748
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/54 (6%)	3/53 (6%)	4/52 (8%)	4/53 (8%)
Adjusted rate	9.6%	8.0%	12.8%	10.9%
Terminal rate	0/16 (0%)	0/16 (0%)	1/17 (6%)	1/21 (5%)
First incidence (days)	482	607	538	460
Life table test	P=0.418	P=0.632N	P=0.518	P=0.534
Logistic regression test	P=0.359	P=0.625	P=0.461	P=0.452
Cochran-Armitage test	P=0.379			
Fisher exact test		P=0.652	P=0.479	P=0.489
Skin: Fibroma				
Overall rate	0/54 (0%)	1/53 (2%)	0/53 (0%)	3/53 (6%)
Adjusted rate	0.0%	4.3%	0.0%	10.5%
Terminal rate	0/16 (0%)	0/16 (0%)	0/18 (0%)	1/21 (5%)
First incidence (days)	—	704	—	628
Life table test	P=0.060	P=0.518	—	P=0.161
Logistic regression test	P=0.044	P=0.515	—	P=0.124
Cochran-Armitage test	P=0.044			
Fisher exact test		P=0.495	—	P=0.118

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Skin: Fibroma or Sarcoma				
Overall rate	0/54 (0%)	1/53 (2%)	1/53 (2%)	3/53 (6%)
Adjusted rate	0.0%	4.3%	4.0%	10.5%
Terminal rate	0/16 (0%)	0/16 (0%)	0/18 (0%)	1/21 (5%)
First incidence (days)	—	704	711	628
Life table test	P=0.073	P=0.518	P=0.545	P=0.161
Logistic regression test	P=0.055	P=0.515	P=0.514	P=0.124
Cochran-Armitage test	P=0.053			
Fisher exact test		P=0.495	P=0.495	P=0.118
Skin: Keratoacanthoma				
Overall rate	4/54 (7%)	1/53 (2%)	1/53 (2%)	0/53 (0%)
Adjusted rate	17.2%	4.3%	3.6%	0.0%
Terminal rate	1/16 (6%)	0/16 (0%)	0/18 (0%)	0/21 (0%)
First incidence (days)	679	704	685	—
Life table test	P=0.030N	P=0.167N	P=0.151N	P=0.055N
Logistic regression test	P=0.031N	P=0.084N	P=0.150N	P=0.056N
Cochran-Armitage test	P=0.036N			
Fisher exact test		P=0.187N	P=0.187N	P=0.061N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma or Carcinoma, or Squamous Cell Carcinoma				
Overall rate	4/54 (7%)	3/53 (6%)	3/53 (6%)	4/53 (8%)
Adjusted rate	17.2%	13.4%	14.3%	15.1%
Terminal rate	1/16 (6%)	1/16 (6%)	2/18 (11%)	2/21 (10%)
First incidence (days)	679	683	685	419
Life table test	P=0.518N	P=0.465N	P=0.436N	P=0.566N
Logistic regression test	P=0.544	P=0.343N	P=0.465N	P=0.638N
Cochran-Armitage test	P=0.527			
Fisher exact test		P=0.511N	P=0.511N	P=0.632
Testes: Adenoma				
Overall rate	45/54 (83%)	46/53 (87%)	45/53 (85%)	50/53 (94%)
Adjusted rate	100.0%	97.8%	97.8%	98.0%
Terminal rate	16/16 (100%)	15/16 (94%)	17/18 (94%)	20/21 (95%)
First incidence (days)	482	539	538	320
Life table test	P=0.432N	P=0.474N	P=0.367N	P=0.468N
Logistic regression test	P=0.032	P=0.535N	P=0.624	P=0.063
Cochran-Armitage test	P=0.063			
Fisher exact test		P=0.409	P=0.517	P=0.066
Thyroid Gland (C-cell): Adenoma				
Overall rate	8/53 (15%)	1/53 (2%)	2/51 (4%)	1/52 (2%)
Adjusted rate	37.6%	6.3%	6.8%	4.8%
Terminal rate	4/16 (25%)	1/16 (6%)	0/18 (0%)	1/21 (5%)
First incidence (days)	577	733 (T)	538	733 (T)
Life table test	P=0.008N	P=0.018N	P=0.036N	P=0.008N
Logistic regression test	P=0.013N	P=0.012N	P=0.046N	P=0.012N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.016N	P=0.053N	P=0.017N

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/53 (15%)	2/53 (4%)	2/51 (4%)	3/52 (6%)
Adjusted rate	37.6%	8.8%	6.8%	12.5%
Terminal rate	4/16 (25%)	1/16 (6%)	0/18 (0%)	2/21 (10%)
First incidence (days)	577	643	538	671
Life table test	P=0.062N	P=0.046N	P=0.036N	P=0.054N
Logistic regression test	P=0.092N	P=0.034N	P=0.046N	P=0.077N
Cochran-Armitage test	P=0.104N			
Fisher exact test		P=0.046N	P=0.053N	P=0.107N
All Organs: Mononuclear Cell Leukemia				
Overall rate	31/54 (57%)	36/53 (68%)	38/53 (72%)	38/53 (72%)
Adjusted rate	81.4%	89.0%	90.1%	82.2%
Terminal rate	10/16 (63%)	12/16 (75%)	14/18 (78%)	13/21 (62%)
First incidence (days)	496	539	551	539
Life table test	P=0.450	P=0.383	P=0.329	P=0.424
Logistic regression test	P=0.048	P=0.243	P=0.108	P=0.052
Cochran-Armitage test	P=0.086			
Fisher exact test		P=0.178	P=0.090	P=0.090
All Organs: Benign Neoplasms				
Overall rate	50/54 (93%)	50/53 (94%)	50/53 (94%)	51/53 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	16/16 (100%)	16/16 (100%)	18/18 (100%)	21/21 (100%)
First incidence (days)	482	539	432	320
Life table test	P=0.249N	P=0.410N	P=0.376N	P=0.275N
Logistic regression test	P=0.215	P=0.618N	P=0.647	P=0.423
Cochran-Armitage test	P=0.281			
Fisher exact test		P=0.511	P=0.511	P=0.348
All Organs: Malignant Neoplasms				
Overall rate	37/54 (69%)	43/53 (81%)	41/53 (77%)	41/53 (77%)
Adjusted rate	88.8%	93.1%	90.8%	86.9%
Terminal rate	12/16 (75%)	13/16 (81%)	14/18 (78%)	15/21 (71%)
First incidence (days)	262	539	279	320
Life table test	P=0.383N	P=0.361	P=0.447	P=0.494N
Logistic regression test	P=0.276	P=0.136	P=0.169	P=0.232
Cochran-Armitage test	P=0.257			
Fisher exact test		P=0.100	P=0.149	P=0.209

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	53/54 (98%)	52/53 (98%)	51/53 (96%)	51/53 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	16/16 (100%)	16/16 (100%)	18/18 (100%)	21/21 (100%)
First incidence (days)	262	363	279	320
Life table test	P=0.149N	P=0.363N	P=0.294N	P=0.171N
Logistic regression test	P=0.196N	P=0.394N	P=0.306N	P=0.283N
Cochran-Armitage test	P=0.331N			
Fisher exact test		P=0.748N	P=0.493N	P=0.493N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] 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 A4
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 A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Disposition Summary				
Animals initially in study	64	63	63	63
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death			1	
Moribund	34	30	31	28
Natural deaths	4	7	3	4
Survivors				
Died last week of study				1
Terminal sacrifice	16	16	18	20
Animals examined microscopically	64	63	63	63
7-Month Interim Evaluation				
Hematopoietic System				
Lymph node, bronchial	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid		5 (100%)	2 (40%)	5 (100%)
Lymph node, mediastinal	(3)	(5)	(4)	(4)
Hyperplasia, lymphoid		4 (80%)	2 (50%)	2 (50%)
Thymus			(1)	
Congestion			1 (100%)	
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Hyperplasia, macrophage		1 (20%)	5 (100%)	5 (100%)
Inflammation, chronic active		4 (80%)	4 (80%)	5 (100%)
Alveolar epithelium, hyperplasia, focal				1 (20%)
Bronchus, hyperplasia, lymphoid				2 (40%)
Interstitium, infiltration cellular	2 (40%)	5 (100%)	5 (100%)	5 (100%)
Nose	(5)	(5)	(5)	(5)
Olfactory epithelium, atrophy			1 (20%)	1 (20%)
Olfactory epithelium, degeneration				1 (20%)
Respiratory epithelium, degeneration			1 (20%)	
Respiratory epithelium, hyperplasia		1 (20%)		1 (20%)
Respiratory epithelium, metaplasia, squamous			1 (20%)	1 (20%)
Urinary System				
Kidney	(5)	(5)	(5)	(5)
Nephropathy		1 (20%)		
Urinary bladder		(3)	(1)	(2)
Calculus, microscopic observation only		3 (100%)	1 (100%)	2 (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 Sulfate Hexahydrate (continued)

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 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, colon	(5)	(5)	(5)	(5)
Parasite metazoan	1 (20%)			2 (40%)
Intestine large, rectum	(5)	(5)	(5)	(5)
Parasite metazoan	1 (20%)	1 (20%)	1 (20%)	
Intestine large, cecum	(5)	(5)	(5)	(5)
Parasite metazoan		1 (20%)	1 (20%)	2 (40%)
Liver	(5)	(5)	(5)	(5)
Basophilic focus	2 (40%)	4 (80%)	5 (100%)	5 (100%)
Degeneration, cystic		1 (20%)		
Hepatodiaphragmatic nodule	1 (20%)		1 (20%)	1 (20%)
Pancreas	(5)	(5)	(5)	(5)
Inflammation, focal				1 (20%)
Acinus, atrophy	1 (20%)			
Endocrine System				
Adrenal cortex	(5)	(5)	(5)	(5)
Cyst		1 (20%)		
Hyperplasia		1 (20%)		
Pituitary gland	(5)	(5)	(5)	(5)
Pars distalis, hyperplasia, focal	2 (40%)	1 (20%)	1 (20%)	3 (60%)
Genital System				
Prostate	(5)	(4)	(5)	(5)
Inflammation	1 (20%)	1 (25%)	2 (40%)	1 (20%)
Testes	(5)	(5)	(5)	(5)
Germinal epithelium, degeneration			1 (20%)	
Hematopoietic System				
Bone marrow	(5)	(5)	(5)	(5)
Hyperplasia			1 (20%)	
Lymph node, bronchial	(5)	(5)	(5)	(4)
Hyperplasia, lymphoid			1 (20%)	1 (25%)
Thymus	(5)	(5)	(5)	(4)
Cyst	1 (20%)			

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Fibrosis				2 (40%)
Hyperplasia, macrophage			2 (40%)	5 (100%)
Inflammation, chronic active		1 (20%)	1 (20%)	5 (100%)
Alveolar epithelium, hyperplasia, focal			1 (20%)	
Alveolus, proteinosis			1 (20%)	4 (80%)
Interstitium, infiltration cellular	1 (20%)			
Nose	(5)	(5)	(5)	(5)
Olfactory epithelium, degeneration	4 (80%)	3 (60%)	1 (20%)	
Olfactory epithelium, inflammation				1 (20%)
Respiratory epithelium, degeneration		1 (20%)		
Respiratory epithelium, inflammation		1 (20%)	1 (20%)	1 (20%)
Urinary System				
Kidney	(5)	(5)	(5)	(5)
Nephropathy	5 (100%)	5 (100%)	4 (80%)	5 (100%)
Urinary bladder	(5)	(5)	(5)	(5)
Calculus, microscopic observation only	2 (40%)	4 (80%)	2 (40%)	1 (20%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(54)	(53)	(53)	(52)
Autolysis		1 (2%)	1 (2%)	
Parasite metazoan		2 (4%)		
Intestine large, rectum	(54)	(53)	(52)	(50)
Autolysis		1 (2%)	1 (2%)	
Intestine large, cecum	(54)	(53)	(53)	(52)
Autolysis		1 (2%)	1 (2%)	
Intestine small, duodenum	(54)	(53)	(51)	(53)
Autolysis		1 (2%)		
Ulcer	1 (2%)			
Intestine small, jejunum	(54)	(52)	(50)	(53)
Autolysis		1 (2%)		
Peyer's patch, hyperplasia	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Intestine small, ileum	(54)	(51)	(48)	(53)
Autolysis		1 (2%)		

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(54)	(53)	(53)	(53)
Angiectasis	6 (11%)	11 (21%)	4 (8%)	10 (19%)
Autolysis		1 (2%)	2 (4%)	
Basophilic focus	32 (59%)	28 (53%)	41 (77%)	35 (66%)
Clear cell focus	2 (4%)	5 (9%)	2 (4%)	4 (8%)
Congestion	2 (4%)		2 (4%)	
Cyst	1 (2%)			
Degeneration, cystic	11 (20%)	12 (23%)	7 (13%)	8 (15%)
Degeneration, fatty	6 (11%)	5 (9%)	12 (23%)	8 (15%)
Eosinophilic focus	5 (9%)	7 (13%)	5 (9%)	5 (9%)
Fatty change			1 (2%)	
Hematopoietic cell proliferation				1 (2%)
Hepatodiaphragmatic nodule	4 (7%)	2 (4%)	5 (9%)	7 (13%)
Infarct	1 (2%)			
Mixed cell focus	2 (4%)	3 (6%)		1 (2%)
Thrombosis	4 (7%)	1 (2%)		1 (2%)
Bile duct, hyperplasia	36 (67%)	33 (62%)	37 (70%)	35 (66%)
Centrilobular, atrophy	6 (11%)	4 (8%)	5 (9%)	7 (13%)
Hepatocyte, hyperplasia	1 (2%)	2 (4%)	1 (2%)	
Hepatocyte, necrosis	16 (30%)	18 (34%)	12 (23%)	16 (30%)
Mesentery	(2)	(4)		(1)
Cyst		1 (25%)		
Fat, necrosis	1 (50%)			
Oral mucosa	(3)	(2)	(4)	
Hyperplasia, squamous	1 (33%)	1 (50%)		
Pancreas	(53)	(52)	(53)	(53)
Atrophy, focal				1 (2%)
Autolysis			2 (4%)	
Cytoplasmic alteration	1 (2%)			
Infarct	1 (2%)			
Polyarteritis				1 (2%)
Thrombosis				1 (2%)
Acinus, atrophy	5 (9%)	6 (12%)	9 (17%)	6 (11%)
Acinus, hyperplasia		1 (2%)	1 (2%)	
Stomach, forestomach	(54)	(53)	(52)	(52)
Diverticulum		1 (2%)		
Edema				1 (2%)
Hyperplasia, squamous	1 (2%)			
Inflammation	1 (2%)			
Perforation	1 (2%)			
Ulcer	4 (7%)	1 (2%)	2 (4%)	1 (2%)
Stomach, glandular	(54)	(53)	(53)	(53)
Autolysis		1 (2%)		
Erosion	1 (2%)			
Inflammation		2 (4%)		
Necrosis	1 (2%)		1 (2%)	
Ulcer			1 (2%)	1 (2%)
Tooth	(9)	(3)	(3)	(3)
Developmental malformation			2 (67%)	
Peridontal tissue, hyperplasia			1 (33%)	
Peridontal tissue, inflammation	9 (100%)	3 (100%)	1 (33%)	3 (100%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Cardiovascular System				
Heart	(54)	(53)	(53)	(53)
Autolysis			1 (2%)	
Cardiomyopathy	31 (57%)	31 (58%)	29 (55%)	32 (60%)
Fibrosis				1 (2%)
Infarct				1 (2%)
Inflammation		1 (2%)		
Proliferation connective tissue			1 (2%)	
Thrombosis	8 (15%)	5 (9%)	5 (9%)	2 (4%)
Atrium, thrombosis				1 (2%)
Epicardium, inflammation	1 (2%)			
Endocrine System				
Adrenal cortex	(54)	(53)	(53)	(53)
Atrophy	1 (2%)	3 (6%)		1 (2%)
Autolysis			1 (2%)	
Cytoplasmic alteration		1 (2%)		
Degeneration, cystic				1 (2%)
Hyperplasia	3 (6%)	6 (11%)	4 (8%)	4 (8%)
Hypertrophy	1 (2%)			
Vacuolization cytoplasmic	11 (20%)	10 (19%)	17 (32%)	16 (30%)
Capsule, fibrosis			1 (2%)	
Adrenal medulla	(54)	(53)	(53)	(53)
Autolysis			1 (2%)	
Cyst	1 (2%)			
Hemorrhage		1 (2%)		
Hyperplasia	28 (52%)	20 (38%)	18 (34%)	26 (49%)
Islets, pancreatic	(52)	(51)	(52)	(53)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	4 (8%)
Parathyroid gland	(49)	(51)	(51)	(48)
Hyperplasia	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Bilateral, hyperplasia				1 (2%)
Pituitary gland	(54)	(51)	(53)	(53)
Angiectasis	3 (6%)	7 (14%)	3 (6%)	2 (4%)
Cyst				1 (2%)
Hemorrhage	1 (2%)			
Pigmentation, ceroid				1 (2%)
Pars distalis, hyperplasia, diffuse		2 (4%)		
Pars distalis, hyperplasia, focal	14 (26%)	15 (29%)	15 (28%)	16 (30%)
Thyroid gland	(53)	(53)	(51)	(52)
Autolysis		1 (2%)	1 (2%)	1 (2%)
C-cell, hyperplasia	5 (9%)	7 (13%)	8 (16%)	6 (12%)
Follicular cell, hyperplasia, cystic	1 (2%)			
General Body System				
Tissue NOS	(4)	(1)	(5)	(4)
Hemorrhage				1 (25%)
Mediastinum, polyarteritis	1 (25%)			
Oral, inflammation	1 (25%)			
Pelvic, ectopic tissue			1 (20%)	

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Genital System				
Coagulating gland	(1)	(3)		
Inflammation	1 (100%)	3 (100%)		
Epididymis	(54)	(53)	(53)	(53)
Granuloma sperm				1 (2%)
Spermatocele				1 (2%)
Penis	(1)			
Inflammation	1 (100%)			
Preputial gland	(54)	(53)	(52)	(53)
Atrophy	1 (2%)	2 (4%)	2 (4%)	
Autolysis			1 (2%)	
Ectasia	2 (4%)	5 (9%)	5 (10%)	5 (9%)
Hyperplasia	3 (6%)		1 (2%)	
Infiltration cellular	1 (2%)			
Inflammation	2 (4%)	5 (9%)	1 (2%)	2 (4%)
Prostate	(54)	(53)	(53)	(53)
Inflammation		3 (6%)	2 (4%)	2 (4%)
Seminal vesicle	(54)	(53)	(53)	(53)
Atrophy	2 (4%)	3 (6%)	7 (13%)	2 (4%)
Autolysis			1 (2%)	
Ectasia	1 (2%)			
Hyperplasia		1 (2%)		1 (2%)
Hyperplasia, cystic		1 (2%)		
Inflammation			1 (2%)	
Testes	(54)	(53)	(53)	(53)
Atrophy	7 (13%)	3 (6%)	10 (19%)	4 (8%)
Cyst	1 (2%)	1 (2%)		
Infarct				1 (2%)
Interstitial cell, hyperplasia, focal	11 (20%)	7 (13%)	6 (11%)	5 (9%)
Hematopoietic System				
Bone marrow	(54)	(52)	(52)	(53)
Atrophy	1 (2%)	1 (2%)	1 (2%)	
Atrophy, focal	1 (2%)		2 (4%)	1 (2%)
Erythroid cell, hyperplasia	2 (4%)	1 (2%)		
Myeloid cell, hyperplasia	17 (31%)	11 (21%)	18 (35%)	18 (34%)
Lymph node	(11)	(14)	(11)	(12)
Iliac, hyperplasia, plasma cell				1 (8%)
Iliac, pigmentation			1 (9%)	
Inguinal, hyperplasia, histiocytic				1 (8%)
Inguinal, hyperplasia, lymphoid			1 (9%)	
Inguinal, inflammation, granulomatous		1 (7%)		
Pancreatic, inflammation			1 (9%)	
Pancreatic, pigmentation, hemosiderin				1 (8%)
Renal, inflammation	1 (9%)			
Renal, pigmentation, hemosiderin	1 (9%)			1 (8%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, bronchial	(51)	(49)	(47)	(52)
Autolysis		1 (2%)		
Congestion		1 (2%)		1 (2%)
Edema				2 (4%)
Hyperplasia, lymphoid			3 (6%)	10 (19%)
Hyperplasia, plasma cell			2 (4%)	1 (2%)
Inflammation	2 (4%)			
Lymph node, mandibular	(52)	(53)	(52)	(53)
Hyperplasia, lymphoid	5 (10%)	3 (6%)	9 (17%)	6 (11%)
Hyperplasia, plasma cell	1 (2%)	2 (4%)	6 (12%)	1 (2%)
Inflammation			1 (2%)	1 (2%)
Lymph node, mesenteric	(54)	(53)	(53)	(53)
Autolysis		1 (2%)		
Congestion	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)	
Pigmentation, hemosiderin	1 (2%)			
Lymph node, mediastinal	(51)	(49)	(46)	(50)
Autolysis	1 (2%)	2 (4%)		
Congestion		2 (4%)	3 (7%)	1 (2%)
Edema				2 (4%)
Hyperplasia, lymphoid	3 (6%)	3 (6%)	5 (11%)	7 (14%)
Hyperplasia, macrophage	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, plasma cell		1 (2%)		2 (4%)
Pigmentation				4 (8%)
Pigmentation, hemosiderin		1 (2%)		
Spleen	(54)	(53)	(51)	(53)
Angiectasis		2 (4%)		
Atrophy	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Autolysis	1 (2%)	1 (2%)		
Congestion	5 (9%)	2 (4%)	1 (2%)	1 (2%)
Fibrosis	13 (24%)	16 (30%)	14 (27%)	14 (26%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Hemorrhage				1 (2%)
Hyperplasia, lymphoid				1 (2%)
Infarct		1 (2%)	1 (2%)	2 (4%)
Pigmentation, hemosiderin		2 (4%)		
Thymus	(49)	(48)	(48)	(46)
Atrophy	16 (33%)	13 (27%)	10 (21%)	17 (37%)
Autolysis		1 (2%)		
Congestion	1 (2%)	1 (2%)		
Cyst				1 (2%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Integumentary System				
Mammary gland	(43)	(48)	(49)	(44)
Hemorrhage			1 (2%)	
Skin	(53)	(53)	(53)	(53)
Angiectasis	1 (2%)			
Cyst epithelial inclusion		3 (6%)	1 (2%)	2 (4%)
Edema				1 (2%)
Hyperkeratosis				1 (2%)
Inflammation	2 (4%)			
Necrosis				1 (2%)
Prepuce, fibrosis			1 (2%)	
Sebaceous gland, inflammation			1 (2%)	
Musculoskeletal System				
Bone	(54)	(53)	(53)	(53)
Fibrous osteodystrophy	1 (2%)			
Hyperostosis	2 (4%)	1 (2%)		1 (2%)
Nervous System				
Brain	(54)	(53)	(53)	(53)
Compression	5 (9%)	5 (9%)	5 (9%)	5 (9%)
Degeneration		2 (4%)		1 (2%)
Hemorrhage	3 (6%)	2 (4%)	1 (2%)	
Hydrocephalus		1 (2%)		
Infarct		1 (2%)		
Infiltration cellular, histiocyte		1 (2%)		1 (2%)
Necrosis		1 (2%)		1 (2%)
Ventricle, hydrocephalus	1 (2%)			
Respiratory System				
Larynx	(54)	(52)	(53)	(53)
Hyperplasia			3 (6%)	
Inflammation	8 (15%)	9 (17%)	13 (25%)	8 (15%)
Metaplasia, squamous			1 (2%)	
Necrosis				1 (2%)
Lung	(54)	(53)	(53)	(53)
Autolysis		1 (2%)		
Congestion	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Emphysema		1 (2%)		
Fibrosis	3 (6%)	6 (11%)	35 (66%)	43 (81%)
Hemorrhage	2 (4%)	5 (9%)	1 (2%)	1 (2%)
Hyperplasia, macrophage	7 (13%)	9 (17%)	35 (66%)	48 (91%)
Inflammation, chronic active	14 (26%)	11 (21%)	42 (79%)	46 (87%)
Inflammation, suppurative				1 (2%)
Metaplasia, osseous	1 (2%)			
Alveolar epithelium, hyperplasia, focal	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Alveolus, proteinosis			12 (23%)	41 (77%)
Interstitium, infiltration cellular	11 (20%)	2 (4%)	3 (6%)	11 (21%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(54)	(52)	(53)	(53)
Thrombosis		6 (12%)	4 (8%)	1 (2%)
Thrombosis, multiple	8 (15%)	1 (2%)	4 (8%)	8 (15%)
Glands, inflammation			1 (2%)	
Nasolacrimal duct, hyperplasia				1 (2%)
Nasolacrimal duct, inflammation	4 (7%)	4 (8%)	4 (8%)	3 (6%)
Nasopharyngeal duct, hyperplasia		2 (4%)		
Nasopharyngeal duct, hyperplasia, lymphoid		1 (2%)		1 (2%)
Nasopharyngeal duct, inflammation	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Olfactory epithelium, atrophy			3 (6%)	7 (13%)
Olfactory epithelium, degeneration	35 (65%)	16 (31%)	13 (25%)	14 (26%)
Olfactory epithelium, inflammation			1 (2%)	
Olfactory epithelium, metaplasia, squamous			1 (2%)	
Olfactory epithelium, necrosis		1 (2%)		
Respiratory epithelium, degeneration	2 (4%)		1 (2%)	
Respiratory epithelium, hyperplasia	18 (33%)	16 (31%)	27 (51%)	34 (64%)
Respiratory epithelium, inflammation	14 (26%)	12 (23%)	17 (32%)	24 (45%)
Respiratory epithelium, metaplasia, squamous	2 (4%)	2 (4%)	2 (4%)	6 (11%)
Vomeronasal organ, inflammation	1 (2%)		1 (2%)	
Special Senses System				
Eye	(1)		(1)	(1)
Cataract	1 (100%)		1 (100%)	
Retinal detachment	1 (100%)			
Synechia	1 (100%)			1 (100%)
Urinary System				
Kidney	(54)	(52)	(52)	(53)
Autolysis			2 (4%)	
Cyst	2 (4%)	1 (2%)		1 (2%)
Infarct	1 (2%)	2 (4%)	2 (4%)	
Inflammation		1 (2%)	1 (2%)	
Nephropathy	50 (93%)	45 (87%)	45 (87%)	39 (74%)
Renal tubule, pigmentation	7 (13%)	7 (13%)	8 (15%)	8 (15%)
Urethra	(1)	(3)		(1)
Calculus, microscopic observation only	1 (100%)	3 (100%)		1 (100%)
Urinary bladder	(54)	(53)	(53)	(53)
Autolysis		1 (2%)		
Calculus, microscopic observation only	1 (2%)		4 (8%)	2 (4%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF NICKEL SULFATE HEXAHYDRATE

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Disposition Summary				
Animals initially in study	63	63	64	65
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death				1
Moribund	27	32	22	21
Natural deaths	4	4	3	3
Survivors				
Terminal sacrifice	22	17	28	29
Missing				1
Missexed			1	
Animals examined microscopically	63	63	63	64
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				
Genital System				
Uterus	(5)	(5)	(5)	(5)
Polyp stromal	1 (20%)		1 (20%)	
Systemic Lesions				
Multiple organs[b]	(5)	(5)	(5)	(5)
Leukemia mononuclear		1 (20%)	1 (20%)	

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
15-Month Interim Evaluation (continued)				
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				
2-Year Study				
Alimentary System				
Intestine large, colon	(52)	(50)	(53)	(54)
Carcinoma, metastatic, pancreas	1 (2%)			
Intestine large, cecum	(51)	(53)	(53)	(53)
Lipoma		1 (2%)		
Intestine small, duodenum	(51)	(53)	(52)	(53)
Carcinoma, metastatic, pancreas	1 (2%)			
Intestine small, jejunum	(52)	(53)	(53)	(54)
Carcinoma, metastatic, pancreas	1 (2%)			
Intestine small, ileum	(49)	(51)	(52)	(53)
Fibrosarcoma		1 (2%)		
Liver	(52)	(53)	(53)	(54)
Carcinoma, metastatic, pancreas	1 (2%)			
Mesentery	(1)	(2)	(2)	(1)
Lipoma			1 (50%)	
Oral mucosa	(3)	(2)	(2)	(1)
Squamous cell carcinoma	3 (100%)	1 (50%)	2 (100%)	1 (100%)
Squamous cell papilloma		1 (50%)		
Pancreas	(52)	(53)	(53)	(54)
Carcinoma	1 (2%)			
Salivary glands	(52)	(53)	(53)	(54)
Stomach, forestomach	(52)	(53)	(53)	(53)
Carcinoma, metastatic, pancreas	1 (2%)			
Stomach, glandular	(52)	(53)	(53)	(54)
Carcinoma, metastatic, pancreas	1 (2%)			
Cardiovascular System				
Heart	(53)	(53)	(53)	(54)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(52)	(53)	(53)	(54)
Adrenal medulla	(51)	(53)	(53)	(54)
Pheochromocytoma complex			1 (2%)	
Pheochromocytoma benign	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Islets, pancreatic	(52)	(53)	(53)	(54)
Parathyroid gland	(49)	(52)	(51)	(49)
Pituitary gland	(52)	(53)	(53)	(54)
Pars distalis, adenoma	22 (42%)	24 (45%)	24 (45%)	22 (41%)
Thyroid gland	(52)	(53)	(53)	(52)
C-cell, adenoma	1 (2%)	2 (4%)	4 (8%)	2 (4%)
C-cell, carcinoma	1 (2%)		2 (4%)	3 (6%)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma		1 (2%)		
General Body System				
Tissue NOS	(6)	(4)	(2)	(5)
Pericardial, carcinoma, metastatic, pancreas	1 (17%)			
Genital System				
Clitoral gland	(51)	(52)	(52)	(54)
Adenoma	4 (8%)	4 (8%)	3 (6%)	2 (4%)
Carcinoma		1 (2%)		1 (2%)
Bilateral, adenoma				1 (2%)
Ovary	(52)	(53)	(53)	(54)
Granulosa cell tumor malignant		1 (2%)		1 (2%)
Granulosa cell tumor benign	1 (2%)			
Granulosa-theca tumor benign				1 (2%)
Uterus	(52)	(53)	(53)	(54)
Carcinoma, metastatic, pancreas	1 (2%)			
Polyp stromal	4 (8%)	3 (6%)	3 (6%)	7 (13%)
Sarcoma stromal				1 (2%)
Schwannoma malignant		1 (2%)		1 (2%)
Vagina	(1)	(1)	(1)	
Carcinoma, metastatic, pancreas	1 (100%)			
Fibroma			1 (100%)	
Schwannoma malignant		1 (100%)		
Hematopoietic System				
Bone marrow	(52)	(53)	(53)	(54)
Lymph node	(8)	(7)	(11)	(3)
Iliac, carcinoma, metastatic, pancreas	1 (13%)			
Pancreatic, carcinoma, metastatic, pancreas	1 (13%)			
Lymph node, bronchial	(50)	(52)	(51)	(49)
Carcinoma, metastatic, pancreas	1 (2%)			
Lymph node, mandibular	(52)	(52)	(52)	(50)
Squamous cell carcinoma, metastatic, oral mucosa	1 (2%)			

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(52)	(53)	(53)	(54)
Lymph node, mediastinal	(48)	(50)	(44)	(50)
Carcinoma, metastatic, pancreas	1 (2%)			
Spleen	(52)	(52)	(53)	(54)
Carcinoma, metastatic, pancreas	1 (2%)			
Thymus	(48)	(49)	(51)	(52)
Integumentary System				
Mammary gland	(52)	(53)	(53)	(54)
Adenocarcinoma	4 (8%)	4 (8%)	1 (2%)	1 (2%)
Adenoma	1 (2%)			
Fibroadenoma	14 (27%)	16 (30%)	8 (15%)	7 (13%)
Fibroadenoma, multiple	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Skin	(53)	(53)	(52)	(53)
Fibroma			1 (2%)	1 (2%)
Plasma cell tumor malignant		1 (2%)		
Squamous cell carcinoma	1 (2%)			
Pinna, fibroma				1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(53)	(53)	(53)	(54)
Osteosarcoma			1 (2%)	
Nervous System				
Brain	(52)	(53)	(53)	(54)
Astrocytoma NOS			1 (2%)	
Cerebrum, astrocytoma NOS		1 (2%)		
Respiratory System				
Lung	(52)	(53)	(53)	(54)
Alveolar/bronchiolar adenoma				1 (2%)
Squamous cell carcinoma, metastatic, uncertain primary site			1 (2%)	
Nose	(51)	(52)	(53)	(54)
Special Senses System				
Eye	(1)	(4)	(1)	(6)
Retrobulbar, carcinoma		1 (25%)		
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 Sulfate Hexahydrate
(continued)

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Urinary System				
Kidney	(52)	(53)	(53)	(54)
Carcinoma, metastatic, pancreas	1 (2%)			
Urinary bladder	(53)	(53)	(53)	(54)
Papilloma		1 (2%)		
Systemic Lesions				
Multiple organs	(53)	(53)	(53)	(54)
Leukemia mononuclear	25 (47%)	25 (47%)	33 (62%)	23 (43%)
Lymphoma malignant				1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	1	2	
2-Year study	49	52	50	48
Total primary neoplasms				
15-Month interim evaluation	1	1	2	
2-Year study	88	98	91	83
Total animals with benign neoplasms				
15-Month interim evaluation	1		1	
2-Year study	35	42	35	36
Total benign neoplasms				
15-Month interim evaluation	1		1	
2-Year study	52	59	49	50
Total animals with malignant neoplasms				
15-Month interim evaluation		1	1	
2-Year study	35	33	37	29
Total malignant neoplasms				
15-Month interim evaluation		1	1	
2-Year study	36	38	41	33
Total animals with metastatic neoplasms				
2-Year study	2		1	1
Total metastatic neoplasms				
2-Year study	16		1	3
Total animals with malignant neoplasms of uncertain primary site				
2-Year study			1	
Total animals with uncertain neoplasms - benign or malignant				
2-Year study		1	1	
Total uncertain neoplasms				
2-Year study		1	1	

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0 mg/m³

Number of Days on Study	4 4 6	5 0 3	5 3 6	5 3 8	5 4 2	5 6 6	5 8 4	5 8 9	6 2 1	6 2 2	6 4 0	6 4 3	6 4 3	6 4 3	6 4 3	6 5 8	6 6 3	6 6 6	6 7 9	6 7 7	6 8 3	6 8 6	6 8 8	6 9 0	6 9 1
Carcass ID Number	1 3 2	0 9 0	1 2 7	0 9 3	1 3 3	1 3 8	1 2 6	0 8 6	1 2 2	0 7 9	0 9 5	1 0 9	1 1 1	1 1 4	1 1 8	0 8 4	0 9 8	0 9 6	1 1 5	0 7 6	1 2 9	1 2 1	1 3 0	0 9 9	0 8 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Intestine small, ileum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Mesentery																									
Oral mucosa			+					+							+										
Squamous cell carcinoma			X					X							X										
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									X
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Tooth					+																				+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X																		
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X	X		X			X	X	X			X	X		X		
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X																
C-cell, carcinoma																									
General Body System																									
Tissue NOS				+							+														+
Pericardial, carcinoma, metastatic, pancreas																									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 Sulfate Hexahydrate: 0 mg/m³ (continued)

Number of Days on Study	6 9 2	6 9 6	7 1 3	7 1 4	7 2 1	7 2 7	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 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	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 5	1 0 0	1 0 4	1 0 8	1 0 5	1 1 3	1 7 4	1 1 6	1 3 6	1 4 0	1 8 8	1 0 1	1 2 8	1 3 9	0 8 2	0 9 2	0 9 7	1 0 4	1 3 1	0 8 1	0 8 7	1 0 3	1 0 7	1 2 0	1 2 3	1 2 4	1 3 5	1 3 7	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																												1
Intestine large, rectum	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, pancreas																												1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																												1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																												1
Mesentery								+																				1
Oral mucosa																												3
Squamous cell carcinoma																												3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma																												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																												1
Tooth																										+		3
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign																									X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma	X		X							X		X	X		X	X		X	X	X			X	X		X		22
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma																												1
C-cell, carcinoma							X																					1
General Body System																												
Tissue NOS		+						+									+											6
Pericardial, carcinoma, metastatic, pancreas																												1

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

Number of Days on Study	4 4 6	5 0 3	5 3 6	5 3 8	5 4 2	5 6 6	5 8 4	5 8 9	6 2 1	6 2 2	6 4 0	6 4 3	6 4 3	6 4 3	6 4 3	6 5 8	6 6 3	6 6 6	6 6 9	6 7 7	6 8 3	6 8 6	6 8 8	6 9 0	6 9 1
Carcass ID Number	1 3 2	0 9 0	1 2 7	0 9 3	1 3 3	1 3 8	1 2 6	0 8 6	1 2 2	0 7 9	0 9 5	1 0 9	1 1 1	1 1 4	1 1 8	0 8 4	0 9 8	0 9 6	1 1 5	0 7 6	1 2 9	1 2 1	1 3 0	0 9 9	0 8 0
Genital System																									
Clitoral gland	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X		X		
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Polyp stromal							X													X			X	
Vagina																									+
Carcinoma, metastatic, pancreas																									X
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+						+			+											+
Iliac, carcinoma, metastatic, pancreas																									X
Pancreatic, carcinoma, metastatic, pancreas																									X
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Lymph node, mandibular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa			X																						
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Thymus	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X								X					
Adenoma																		X							
Fibroadenoma					X			X		X			X		X				X						X
Fibroadenoma, multiple																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma						X																			
Subcutaneous tissue, sarcoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	6 9 2	6 9 6	7 1 3	7 1 4	7 2 1	7 2 7	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 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	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 5	1 0 0	1 3 4	1 0 8	1 0 5	1 1 3	0 7 4	1 1 6	1 3 6	1 4 0	0 8 8	1 0 1	1 2 8	1 3 9	0 8 2	0 9 2	0 9 7	1 0 4	1 3 1	0 8 1	0 8 7	1 0 3	1 0 7	1 2 0	1 2 3	1 2 4	1 3 5	1 3 7	Total Tissues/ Tumors
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma			X																									X	4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Granulosa cell tumor benign																X													1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																													1
Polyp stromal							X																						4
Vagina																													1
Carcinoma, metastatic, pancreas																													1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node		+				+		+																					8
Iliac, carcinoma, metastatic, pancreas																													1
Pancreatic, carcinoma, metastatic, pancreas																													1
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma, metastatic, oral mucosa																													1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	I	+	M	+	+	+	48
Carcinoma, metastatic, pancreas																													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																													1
Thymus	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenocarcinoma																								X		X			4
Adenoma																													1
Fibroadenoma	X				X						X			X		X		X							X				14
Fibroadenoma, multiple												X							X										3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Squamous cell carcinoma																													1
Subcutaneous tissue, sarcoma																													1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52

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

Number of Days on Study	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	4	0	3	3	4	6	8	8	2	2	4	4	4	4	4	5	6	6	6	7	8	8	8	9	9
	6	3	6	8	2	6	4	9	1	2	0	3	3	3	3	8	3	6	9	7	3	6	8	0	1
Carcass ID Number	1	0	1	0	1	1	1	0	1	0	0	1	1	1	1	0	0	0	1	0	1	1	1	0	0
	3	9	2	9	3	3	2	8	2	7	9	0	1	1	1	8	9	9	1	7	2	2	3	9	8
	2	0	7	3	3	8	6	6	2	9	5	9	1	4	8	4	8	6	5	6	9	1	0	9	0
Respiratory System																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+																					
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		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 Sulfate Hexahydrate: 0 mg/m³ (continued)

Number of Days on Study	6 9 2	6 9 6	7 1 3	7 1 4	7 2 1	7 2 7	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 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	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 5	1 0 0	1 0 4	1 0 8	1 0 5	1 1 3	0 7 4	1 1 6	1 3 6	1 4 0	0 8 8	1 0 1	1 2 8	1 3 9	0 8 2	0 9 2	0 9 7	1 0 4	1 3 1	0 8 1	0 8 7	1 0 3	1 0 7	1 2 0	1 2 3	1 2 4	1 3 5	1 3 7	Total Tissues/ Tumors
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	51
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																												
Eye																												1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, pancreas																												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X	X		X	X	X		X			X						X	X	X		X		X			X		25

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³

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
	9	8	3	3	3	5	5	5	7	8	9	9	9	0	0	0	1	2	2	3	4	4	4	5
	2	9	7	7	9	0	9	9	3	0	2	6	6	0	5	7	9	0	7	6	3	4	4	3
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
	7	5	5	5	7	7	3	6	5	3	2	6	7	6	4	4	7	7	1	2	1	1	6	7	8
	2	3	7	9	6	9	1	8	6	9	0	4	8	1	7	8	0	4	6	9	7	1	2	3	0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Fibrosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery									+	+															
Oral mucosa								+																	
Squamous cell carcinoma								X																	
Squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue								+																	
Tooth					+													+					+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X	X			X			X			X				X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
Follicular cell, adenoma																			X						
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS																		+				+	+		
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Schwannoma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (continued)

Number of Days on Study	6 5 6	6 5 7	6 5 8	6 6 4	6 6 4	6 7 6	6 7 8	6 8 2	6 9 1	7 0 6	7 2 5	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 1	7 3 1	7 3 1	7 3 2	7 3 2	
Carcass ID Number	2 2 1	2 3 5	2 4 0	2 4 3	2 5 1	2 2 2	2 1 3	2 6 9	2 6 3	2 4 1	2 3 6	2 1 5	2 2 3	2 2 8	2 4 2	2 4 9	2 5 4	2 6 5	2 3 8	2 5 0	2 7 5	2 7 7	2 2 6	2 3 3	2 6 7	2 1 8	2 2 7	2 3 0	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lipoma														X														1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrosarcoma														X														1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesentery																												2
Oral mucosa															+													2
Squamous cell carcinoma																												1
Squamous cell papilloma															X													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue																												1
Tooth					+													+										5
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign	X		X																					X				4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma	X					X		X	X	X	X			X	X		X		X	X		X	X	X			X		24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma																X												2
Follicular cell, adenoma																												1
Follicular cell, carcinoma									X																			1
General Body System																												
Tissue NOS																					+							4
Genital System																												
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma														X											X	X		4
Carcinoma																												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Granulosa cell tumor malignant																											X	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Polyp stromal	X							X														X						3
Schwannoma malignant			X																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (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
	9	8	3	3	3	5	5	5	7	8	9	9	9	0	0	0	1	2	2	3	4	4	4	5
	2	9	7	7	9	0	9	9	3	0	2	6	6	0	5	7	9	0	7	6	3	4	4	3
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
	7	5	5	5	7	7	3	6	5	3	2	6	7	6	4	4	7	7	1	2	1	1	6	7	8
	2	3	7	9	6	9	1	8	6	9	0	4	8	1	7	8	0	4	6	9	7	1	2	3	0
Genital System (continued)																									
Vagina													+												
Schwannoma malignant													X												
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+			+									+						+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma	X	X	X	X	X			X	X			X				X							X	X	
Fibroadenoma, multiple																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, astrocytoma NOS																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+																							
Retrobulbar, carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X	X		X	X					X		X	X	X	X		X	X		X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.12 mg/m³ (continued)

Number of Days on Study	6 5 6	6 5 7	6 5 8	6 6 4	6 6 4	6 7 6	6 7 8	6 8 2	6 9 1	7 0 6	7 2 5	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 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 2 1	2 3 5	2 4 0	2 4 3	2 5 1	2 2 2	2 1 3	2 6 9	2 6 3	2 4 1	2 3 6	2 1 5	2 2 3	2 2 8	2 4 2	2 4 9	2 5 4	2 6 5	2 3 8	2 5 0	2 7 5	2 7 7	2 2 6	2 3 3	3 6 7	1 8 8	2 7 7	2 3 0	Total Tissues/ Tumors
Genital System (continued)																												
Vagina																												1
Schwannoma malignant																												1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node		+							+									+										7
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenocarcinoma										X	X				X												X	4
Fibroadenoma				X	X		X	X			X																	16
Fibroadenoma, multiple																										X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Plasma cell tumor malignant																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cerebrum, astrocytoma NOS																	X											1
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																												
Eye	+												+					+										4
Retrobulbar, carcinoma													X															1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Papilloma																					X							1
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X	X						X	X	X			X				X	X			X		X		X			25

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³

Number of Days on Study	4 0 3	5 1 0	6 0 5	6 0 8	6 1 7	6 2 9	6 2 9	6 4 2	6 4 7	6 4 8	6 4 8	6 5 5	6 6 1	6 6 2	6 6 2	6 6 2	6 7 5	6 7 5	6 8 3	6 9 7	7 0 0	7 0 6	7 1 0	7 1 1
Carcass ID Number	3 5 6	4 0 0	3 5 1	3 7 4	3 6 0	3 6 6	3 9 3	3 5 9	3 5 4	3 7 8	3 9 0	3 7 7	3 7 9	3 6 9	3 8 1	3 8 7	3 6 1	3 8 8	3 8 6	4 1 6	3 7 0	3 5 2	3 6 4	3 8 4
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery												+												
Lipoma																								
Oral mucosa													+				+							
Squamous cell carcinoma													X				X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex																				X				
Pheochromocytoma benign																								X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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							X					
C-cell, carcinoma																								
General Body System																								
Tissue NOS																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma									X															
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																		X						
Vagina																								
Fibroma																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	7 1 5	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 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	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 8 5	3 7 1	3 7 3	3 9 6	3 9 7	4 1 5	3 6 8	3 7 2	3 9 9	4 0 6	4 1 4	4 1 7	3 5 8	3 6 2	3 6 5	3 9 4	3 9 5	4 0 1	4 0 7	4 0 8	4 1 1	4 1 2	3 7 5	3 8 2	3 8 3	4 0 2	4 1 3	4 1 8	4 2 0	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesentery																				+										2
Lipoma																				X										1
Oral mucosa																														2
Squamous cell carcinoma																														2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cardiovascular System																														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma complex																														1
Pheochromocytoma benign											X																			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	51
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma					X	X	X		X	X	X		X		X				X	X		X		X	X	X				24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma																				X										4
C-cell, carcinoma																	X		X											2
General Body System																														
Tissue NOS							+														+									2
Genital System																														
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma														X								X								3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Polyp stromal								X																				X		3
Vagina				+																										1
Fibroma				X																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	4	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7
	0	1	0	0	1	2	2	4	4	4	4	5	6	6	6	6	7	7	8	9	0	0	1	1
	3	0	5	8	7	9	9	2	7	8	8	5	1	2	2	2	5	5	3	7	0	6	0	1
Carcass ID Number	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	3	3	3	3
	5	0	5	7	6	6	9	5	5	7	9	7	7	6	8	8	6	8	8	1	7	5	6	8
	6	0	1	4	0	6	3	9	4	8	0	7	9	9	1	7	1	8	6	6	0	2	4	4
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+		+			+			+		+		+		+	+	+						
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma														X										
Fibroadenoma					X														X					
Fibroadenoma, multiple												X			X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma					X																			
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS			X																					
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, uncertain primary site																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye		+																						
Zymbal's gland		+																						
Carcinoma		X																						
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	X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	7 1 5	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 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 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 8 5	3 7 1	3 7 3	3 9 6	3 9 7	4 1 5	3 6 8	3 7 2	3 9 9	4 0 6	4 1 4	4 1 7	3 5 8	3 6 2	3 6 5	3 9 4	3 9 5	4 0 1	4 0 7	4 0 8	4 1 1	4 1 2	4 3 5	3 7 2	3 8 3	4 0 2	4 1 3	4 1 8	4 2 0	Total Tissues/ Tumors
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node							+																						11
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal	+	I	+	M	I	+	+	M	+	+	+	M	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenocarcinoma																													1
Fibroadenoma		X			X									X					X							X		X	8
Fibroadenoma, multiple																													2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	52
Fibroma											X																		1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma																													1
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma NOS																													1
Respiratory System																													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	52
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Squamous cell carcinoma, metastatic, uncertain primary site																										X			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																													
Eye																													1
Zymbal's gland																													1
Carcinoma																													1
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		33

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³

Number of Days on Study	0 2 8	1 1 9	2 7 2	3 2 3	3 7 0	4 3 2	4 7 5	4 8 0	4 9 7	5 2 7	5 3 8	5 3 8	5 3 8	5 4 1	5 6 8	6 3 7	6 4 8	6 5 4	6 6 1	6 6 2	6 8 1	6 8 5	6 8 8	6 9 7
Carcass ID Number	5 4 4	5 2 7	4 9 9	4 9 7	5 5 3	4 9 2	5 0 2	5 0 0	5 4 9	5 3 4	5 0 6	5 1 5	5 2 0	5 0 9	5 5 4	5 0 5	4 9 1	5 4 7	4 9 4	5 4 3	5 1 4	5 0 3	4 9 5	5 4 0
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																		+						
Oral mucosa								+																
Squamous cell carcinoma								X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant, metastatic, thymus			X																					
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X				X					X	X			X
Thyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								
C-cell, carcinoma																			X					
General Body System																								
Tissue NOS				+													+		+					
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma																								
Bilateral, adenoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																								
Granulosa-theca tumor benign																							X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal													X	X								X		
Sarcoma stromal																								X
Schwannoma malignant																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	7 0 2	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 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	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 2 5	5 1 9	5 2 9	5 4 2	5 5 0	5 5 1	5 5 5	5 5 6	5 0 4	5 1 6	5 1 7	5 2 4	5 2 6	5 2 8	5 3 0	5 3 3	5 3 8	5 5 8	5 0 7	5 1 1	5 1 8	5 3 2	5 3 6	5 4 8	4 9 8	5 1 2	5 2 3	5 3 5	5 3 9	5 5 2	Total Tissues/ Tumors
Alimentary System																															
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	I	I	+	+	+	I	+	+	+	+	I	I	+	+	+	+	+	+	I	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Mesentery																															1
Oral mucosa																															1
Squamous cell carcinoma																															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Tooth													+																		1
Cardiovascular System																															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymphoma malignant, metastatic, thymus																															1
Endocrine System																															
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Pheochromocytoma benign							X							X								X									3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Pars distalis, adenoma	X		X	X			X		X	X	X						X			X	X		X	X	X	X	X	X	X		22
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma								X																		X					2
C-cell, carcinoma																								X	X						3
General Body System																															
Tissue NOS														+						+											5
Genital System																															
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adenoma										X								X													2
Carcinoma																													X		1
Bilateral, adenoma																										X					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Granulosa cell tumor malignant																											X				1
Granulosa-theca tumor benign																															1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Polyp stromal							X								X					X										X	7
Sarcoma stromal																															1
Schwannoma malignant					X																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	0 2 8	1 1 9	2 7 2	3 2 3	3 7 0	4 3 2	4 7 5	4 8 0	4 9 7	5 2 7	5 3 8	5 3 8	5 3 8	5 4 1	5 6 8	6 3 7	6 4 8	6 5 4	6 6 1	6 6 2	6 8 1	6 8 5	6 8 8	6 9 7
Carcass ID Number	5 4 4	5 2 7	4 9 9	4 9 7	5 5 3	4 9 2	5 0 2	5 0 0	5 4 9	5 3 4	5 0 6	5 1 5	5 2 0	5 0 9	5 5 4	5 0 5	4 9 1	5 4 7	4 9 4	5 4 3	5 1 4	5 0 3	4 9 5	5 4 0
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+		+	+						
Lymph node, bronchial	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant, metastatic, thymus			X																					
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Fibroadenoma											X	X												
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma								X																
Pinna, fibroma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																				
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord				+																				
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Lymphoma malignant, metastatic, thymus			X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear														+										
Eye								+					+	+										+
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X		X	X					X	X	X	X		X	X	X	X	X
Lymphoma malignant			X																					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	7 0 2	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 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	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 2 5	5 1 9	5 2 9	5 4 2	5 5 0	5 5 1	5 5 5	5 5 6	5 5 4	5 1 6	5 1 7	5 2 4	5 2 6	5 2 8	5 3 0	5 3 3	5 3 8	5 5 8	5 0 7	5 1 1	5 1 8	5 3 2	5 3 6	5 4 8	4 9 8	5 1 2	5 2 3	5 3 5	5 3 9	5 5 2	Total Tissues/ Tumors
Hematopoietic System																															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node																															3
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Lymphoma malignant, metastatic, thymus																															1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Integumentary System																															
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adenocarcinoma																											X				1
Fibroadenoma	X		X					X		X														X							7
Fibroadenoma, multiple												X				X															2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	53
Fibroma																															1
Pinna, fibroma																														X	1
Musculoskeletal System																															
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Skeletal muscle					.																										1
Nervous System																															
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Spinal cord																															1
Respiratory System																															
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Alveolar/bronchiolar adenoma																							X								1
Lymphoma malignant, metastatic, thymus																															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Special Senses System																															
Ear																															1
Eye		+									+																				6
Urinary System																															
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Systemic Lesions																															
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Leukemia mononuclear	X	X					X		X		X		X	X					X	X						X			X		23
Lymphoma malignant																															1

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/51 (4%)	4/53 (8%)	2/53 (4%)	3/54 (6%)
Adjusted rate[b]	6.6%	15.5%	6.8%	10.3%
Terminal rate[c]	1/22 (5%)	1/17 (6%)	1/28 (4%)	3/29 (10%)
First incidence (days)	584	644	711	729 (T)
Life table test[d]	P=0.516N	P=0.238	P=0.628N	P=0.583
Logistic regression test[d]	P=0.528	P=0.349	P=0.679N	P=0.484
Cochran-Armitage test[d]	P=0.550			
Fisher exact test[d]		P=0.358	P=0.676N	P=0.527
Adrenal Medulla: Benign or Complex Pheochromocytoma				
Overall rate	2/51 (4%)	4/53 (8%)	3/53 (6%)	3/54 (6%)
Adjusted rate	6.6%	15.5%	9.6%	10.3%
Terminal rate	1/22 (5%)	1/17 (6%)	1/28 (4%)	3/29 (10%)
First incidence (days)	584	644	700	729 (T)
Life table test	P=0.524N	P=0.238	P=0.584	P=0.583
Logistic regression test	P=0.506	P=0.349	P=0.523	P=0.484
Cochran-Armitage test	P=0.529			
Fisher exact test		P=0.358	P=0.518	P=0.527
Clitoral Gland: Adenoma				
Overall rate	4/51 (8%)	4/52 (8%)	3/52 (6%)	3/54 (6%)
Adjusted rate	13.9%	19.7%	9.2%	10.3%
Terminal rate	1/22 (5%)	3/17 (18%)	2/28 (7%)	3/29 (10%)
First incidence (days)	683	596	647	729 (T)
Life table test	P=0.242N	P=0.471	P=0.413N	P=0.405N
Logistic regression test	P=0.359N	P=0.539	P=0.465N	P=0.500N
Cochran-Armitage test	P=0.360N			
Fisher exact test		P=0.631N	P=0.489N	P=0.468N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	4/51 (8%)	5/52 (10%)	3/52 (6%)	4/54 (7%)
Adjusted rate	13.9%	22.4%	9.2%	13.8%
Terminal rate	1/22 (5%)	3/17 (18%)	2/28 (7%)	4/29 (14%)
First incidence (days)	683	596	647	729 (T)
Life table test	P=0.327N	P=0.323	P=0.413N	P=0.535N
Logistic regression test	P=0.472N	P=0.403	P=0.465N	P=0.640N
Cochran-Armitage test	P=0.464N			
Fisher exact test		P=0.512	P=0.489N	P=0.610N
Mammary Gland: Fibroadenoma				
Overall rate	17/53 (32%)	18/53 (34%)	10/53 (19%)	9/54 (17%)
Adjusted rate	49.0%	44.1%	28.8%	26.8%
Terminal rate	7/22 (32%)	1/17 (6%)	6/28 (21%)	6/29 (21%)
First incidence (days)	542	392	617	538
Life table test	P=0.010N	P=0.262	P=0.045N	P=0.036N
Logistic regression test	P=0.014N	P=0.527N	P=0.080N	P=0.074N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.500	P=0.090N	P=0.051N

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	18/53 (34%)	18/53 (34%)	10/53 (19%)	9/54 (17%)
Adjusted rate	50.5%	44.1%	28.8%	26.8%
Terminal rate	7/22 (32%)	1/17 (6%)	6/28 (21%)	6/29 (21%)
First incidence (days)	542	392	617	538
Life table test	P=0.007N	P=0.311	P=0.031N	P=0.025N
Logistic regression test	P=0.009N	P=0.442N	P=0.055N	P=0.050N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.581N	P=0.061N	P=0.033N
Mammary Gland: Carcinoma				
Overall rate	4/53 (8%)	4/53 (8%)	1/53 (2%)	1/54 (2%)
Adjusted rate	13.9%	21.1%	2.5%	3.4%
Terminal rate	2/22 (9%)	2/17 (12%)	0/28 (0%)	1/29 (3%)
First incidence (days)	643	706	662	729 (T)
Life table test	P=0.044N	P=0.482	P=0.147N	P=0.141N
Logistic regression test	P=0.066N	P=0.501	P=0.173N	P=0.194N
Cochran-Armitage test	P=0.073N			
Fisher exact test		P=0.642N	P=0.181N	P=0.176N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	5/53 (9%)	4/53 (8%)	1/53 (2%)	1/54 (2%)
Adjusted rate	16.3%	21.1%	2.5%	3.4%
Terminal rate	2/22 (9%)	2/17 (12%)	0/28 (0%)	1/29 (3%)
First incidence (days)	643	706	662	729 (T)
Life table test	P=0.023N	P=0.589	P=0.085N	P=0.084N
Logistic regression test	P=0.037N	P=0.639N	P=0.101N	P=0.116N
Cochran-Armitage test	P=0.040N			
Fisher exact test		P=0.500N	P=0.103N	P=0.098N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	22/53 (42%)	21/53 (40%)	11/53 (21%)	10/54 (19%)
Adjusted rate	59.4%	53.7%	30.7%	30.0%
Terminal rate	9/22 (41%)	3/17 (18%)	6/28 (21%)	7/29 (24%)
First incidence (days)	542	392	617	538
Life table test	P=0.001N	P=0.322	P=0.009N	P=0.006N
Logistic regression test	P=0.002N	P=0.419N	P=0.015N	P=0.015N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.500N	P=0.018N	P=0.008N
Oral Mucosa: Squamous Cell Carcinoma				
Overall rate	3/53 (6%)	1/53 (2%)	2/53 (4%)	1/54 (2%)
Adjusted rate	6.4%	2.1%	5.1%	2.1%
Terminal rate	0/22 (0%)	0/17 (0%)	0/28 (0%)	0/29 (0%)
First incidence (days)	536	559	661	480
Life table test	P=0.298N	P=0.338N	P=0.468N	P=0.355N
Logistic regression test	P=0.159N	P=0.197N	P=0.568N	P=0.178N
Cochran-Armitage test	P=0.277N			
Fisher exact test		P=0.309N	P=0.500N	P=0.302N

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Oral Mucosa: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/53 (6%)	2/53 (4%)	2/53 (4%)	1/54 (2%)
Adjusted rate	6.4%	7.9%	5.1%	2.1%
Terminal rate	0/22 (0%)	1/17 (6%)	0/28 (0%)	0/29 (0%)
First incidence (days)	536	559	661	480
Life table test	P=0.232N	P=0.552N	P=0.468N	P=0.355N
Logistic regression test	P=0.145N	P=0.404N	P=0.568N	P=0.178N
Cochran-Armitage test	P=0.228N			
Fisher exact test		P=0.500N	P=0.500N	P=0.302N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	22/52 (42%)	24/53 (45%)	24/53 (45%)	22/54 (41%)
Adjusted rate	63.6%	72.3%	62.1%	62.3%
Terminal rate	11/22 (50%)	9/17 (53%)	14/28 (50%)	16/29 (55%)
First incidence (days)	621	537	629	538
Life table test	P=0.142N	P=0.118	P=0.430N	P=0.321N
Logistic regression test	P=0.536	P=0.268	P=0.549	P=0.463
Cochran-Armitage test	P=0.434N			
Fisher exact test		P=0.456	P=0.456	P=0.513N
Thyroid Gland (C-cell): Adenoma				
Overall rate	1/52 (2%)	2/53 (4%)	4/53 (8%)	2/52 (4%)
Adjusted rate	2.2%	8.4%	10.6%	6.9%
Terminal rate	0/22 (0%)	1/17 (6%)	1/28 (4%)	2/29 (7%)
First incidence (days)	621	619	648	729 (T)
Life table test	P=0.476	P=0.419	P=0.224	P=0.547
Logistic regression test	P=0.376	P=0.526	P=0.174	P=0.482
Cochran-Armitage test	P=0.384			
Fisher exact test		P=0.507	P=0.187	P=0.500
Thyroid Gland (C-cell): Carcinoma				
Overall rate	1/52 (2%)	0/53 (0%)	2/53 (4%)	3/52 (6%)
Adjusted rate	4.5%	0.0%	7.1%	9.5%
Terminal rate	1/22 (5%)	0/17 (0%)	2/28 (7%)	2/29 (7%)
First incidence (days)	729 (T)	—[e]	729 (T)	661
Life table test	P=0.176	P=0.551N	P=0.585	P=0.379
Logistic regression test	P=0.127	P=0.551N	P=0.585	P=0.297
Cochran-Armitage test	P=0.100			
Fisher exact test		P=0.495N	P=0.507	P=0.309
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	2/52 (4%)	2/53 (4%)	6/53 (11%)	5/52 (10%)
Adjusted rate	6.7%	8.4%	17.3%	16.2%
Terminal rate	1/22 (5%)	1/17 (6%)	3/28 (11%)	4/29 (14%)
First incidence (days)	621	619	648	661
Life table test	P=0.206	P=0.604	P=0.200	P=0.292
Logistic regression test	P=0.106	P=0.686	P=0.145	P=0.197
Cochran-Armitage test	P=0.107			
Fisher exact test		P=0.684N	P=0.141	P=0.218

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Uterus: Stromal Polyp				
Overall rate	4/53 (8%)	3/53 (6%)	3/53 (6%)	7/54 (13%)
Adjusted rate	12.3%	13.6%	9.7%	20.3%
Terminal rate	1/22 (5%)	1/17 (6%)	2/28 (7%)	4/29 (14%)
First incidence (days)	584	656	675	538
Life table test	P=0.240	P=0.637	P=0.421N	P=0.319
Logistic regression test	P=0.132	P=0.540N	P=0.492N	P=0.248
Cochran-Armitage test	P=0.149			
Fisher exact test		P=0.500N	P=0.500N	P=0.274
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	4/53 (8%)	3/53 (6%)	3/53 (6%)	8/54 (15%)
Adjusted rate	12.3%	13.6%	9.7%	22.9%
Terminal rate	1/22 (5%)	1/17 (6%)	2/28 (7%)	4/29 (14%)
First incidence (days)	584	656	675	538
Life table test	P=0.154	P=0.637	P=0.421N	P=0.236
Logistic regression test	P=0.071	P=0.540N	P=0.492N	P=0.164
Cochran-Armitage test	P=0.083			
Fisher exact test		P=0.500N	P=0.500N	P=0.189
All Organs: Mononuclear Cell Leukemia				
Overall rate	25/53 (47%)	25/53 (47%)	33/53 (62%)	23/54 (43%)
Adjusted rate	62.0%	66.9%	66.6%	54.2%
Terminal rate	8/22 (36%)	7/17 (41%)	12/28 (43%)	10/29 (34%)
First incidence (days)	503	537	403	475
Life table test	P=0.198N	P=0.218	P=0.362	P=0.308N
Logistic regression test	P=0.273	P=0.553	P=0.066	P=0.404
Cochran-Armitage test	P=0.407N			
Fisher exact test		P=0.577N	P=0.086	P=0.389N
All Organs: Benign Neoplasms				
Overall rate	35/53 (66%)	42/53 (79%)	35/53 (66%)	36/54 (67%)
Adjusted rate	82.1%	90.9%	82.7%	87.6%
Terminal rate	15/22 (68%)	13/17 (76%)	21/28 (75%)	24/29 (83%)
First incidence (days)	542	392	617	480
Life table test	P=0.077N	P=0.020	P=0.225N	P=0.336N
Logistic regression test	P=0.519	P=0.070	P=0.460N	P=0.268
Cochran-Armitage test	P=0.353N			
Fisher exact test		P=0.095	P=0.581N	P=0.554
All Organs: Malignant Neoplasms				
Overall rate	35/53 (66%)	34/53 (64%)	37/53 (70%)	29/54 (54%)
Adjusted rate	73.5%	80.8%	72.1%	64.0%
Terminal rate	10/22 (45%)	10/17 (59%)	14/28 (50%)	13/29 (45%)
First incidence (days)	503	392	403	272
Life table test	P=0.063N	P=0.211	P=0.381N	P=0.152N
Logistic regression test	P=0.348N	P=0.445N	P=0.251	P=0.172N
Cochran-Armitage test	P=0.113N			
Fisher exact test		P=0.500N	P=0.418	P=0.135N

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/53 (92%)	52/53 (98%)	50/53 (94%)	48/54 (89%)
Adjusted rate	96.1%	98.1%	96.1%	98.0%
Terminal rate	20/22 (91%)	16/17 (94%)	26/28 (93%)	28/29 (97%)
First incidence (days)	503	392	403	272
Life table test	P=0.052N	P=0.043	P=0.203N	P=0.217N
Logistic regression test	P=0.571N	P=0.140	P=0.551	P=0.334
Cochran-Armitage test	P=0.156N			
Fisher exact test		P=0.181	P=0.500	P=0.383N

(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, 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 B4
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 B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Disposition Summary				
Animals initially in study	63	63	64	65
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death				1
Moribund	27	32	22	21
Natural deaths	4	4	3	3
Survivors				
Terminal sacrifice	22	17	28	29
Missing				1
Missexed			1	
Animals examined microscopically	63	63	63	64
7-Month Interim Evaluation				
Hematopoietic System				
Lymph node, bronchial	(5)	(5)	(4)	(5)
Hyperplasia, lymphoid	1 (20%)	4 (80%)	4 (100%)	4 (80%)
Lymph node, mediastinal	(3)	(5)	(5)	(5)
Hyperplasia, lymphoid		2 (40%)	2 (40%)	2 (40%)
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Hyperplasia, macrophage		2 (40%)	4 (80%)	5 (100%)
Inflammation, chronic active		2 (40%)	4 (80%)	5 (100%)
Alveolus, proteinosis				2 (40%)
Interstitium, infiltration cellular	1 (20%)	4 (80%)	5 (100%)	3 (60%)
Nose	(5)	(5)	(5)	(5)
Olfactory epithelium, atrophy				1 (20%)
Olfactory epithelium, degeneration	2 (40%)	1 (20%)		
Respiratory epithelium, degeneration	1 (20%)			
Respiratory epithelium, inflammation	1 (20%)			3 (60%)
Special Senses System				
Eye				(1)
Cataract				1 (100%)
Systems Examined With No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous 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 Sulfate Hexahydrate (continued)

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
15-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(5)	(5)	(4)	(5)
Parasite metazoan	1 (20%)			
Liver	(5)	(5)	(5)	(5)
Angiectasis			1 (20%)	
Basophilic focus	4 (80%)	3 (60%)	4 (80%)	4 (80%)
Endocrine System				
Pituitary gland	(5)	(5)	(5)	(5)
Cyst		1 (20%)		
Pars distalis, hyperplasia, focal	1 (20%)	1 (20%)	1 (20%)	1 (20%)
Hematopoietic System				
Bone marrow	(5)	(5)	(5)	(5)
Hyperplasia		1 (20%)	1 (20%)	
Lymph node, bronchial	(4)	(5)	(3)	(5)
Hyperplasia, lymphoid				1 (20%)
Lymph node, mesenteric	(5)	(5)	(5)	(5)
Pigmentation, hemosiderin		1 (20%)		
Respiratory System				
Larynx	(5)	(4)	(5)	(5)
Inflammation		1 (25%)		
Lung	(5)	(5)	(5)	(5)
Fibrosis			1 (20%)	3 (60%)
Hyperplasia, macrophage	1 (20%)	1 (20%)	3 (60%)	5 (100%)
Inflammation, chronic active	2 (40%)		4 (80%)	5 (100%)
Alveolar epithelium, hyperplasia, focal	1 (20%)			1 (20%)
Alveolus, proteinosis			3 (60%)	5 (100%)
Interstitium, infiltration cellular	1 (20%)	1 (20%)		1 (20%)
Nose	(5)	(5)	(5)	(5)
Olfactory epithelium, atrophy				1 (20%)
Olfactory epithelium, degeneration	4 (80%)	2 (40%)		
Olfactory epithelium, inflammation			3 (60%)	
Respiratory epithelium, degeneration	3 (60%)	3 (60%)		2 (40%)
Respiratory epithelium, inflammation			2 (40%)	
Trachea	(5)	(5)	(5)	(5)
Epithelium, hyperplasia		1 (20%)		
Special Senses System				
Eye	(1)	(1)		(1)
Anterior chamber, inflammation	1 (100%)	1 (100%)		1 (100%)
Urinary System				
Kidney	(5)	(5)	(5)	(5)
Nephropathy	3 (60%)	2 (40%)	2 (40%)	5 (100%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
15-Month Interim Evaluation (continued)				
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	(52)	(50)	(53)	(54)
Hyperplasia, lymphoid	1 (2%)			
Parasite metazoan				1 (2%)
Intestine large, rectum	(51)	(51)	(49)	(45)
Parasite metazoan	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Intestine large, cecum	(51)	(53)	(53)	(53)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, granulomatous	1 (2%)			
Parasite metazoan				1 (2%)
Ulcer		1 (2%)		
Intestine small, duodenum	(51)	(53)	(52)	(53)
Ulcer	1 (2%)			
Intestine small, jejunum	(52)	(53)	(53)	(54)
Autolysis			1 (2%)	
Peyer's patch, hyperplasia	2 (4%)	1 (2%)	3 (6%)	3 (6%)
Intestine small, ileum	(49)	(51)	(52)	(53)
Autolysis			1 (2%)	
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Liver	(52)	(53)	(53)	(54)
Angiectasis	3 (6%)	4 (8%)	1 (2%)	
Basophilic focus	45 (87%)	43 (81%)	41 (77%)	41 (76%)
Clear cell focus	4 (8%)	1 (2%)	2 (4%)	4 (7%)
Congestion				1 (2%)
Degeneration, cystic	4 (8%)	5 (9%)	5 (9%)	4 (7%)
Degeneration, fatty	15 (29%)	13 (25%)	14 (26%)	7 (13%)
Eosinophilic focus	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Granuloma			2 (4%)	
Hepatodiaphragmatic nodule	5 (10%)	5 (9%)	6 (11%)	8 (15%)
Inflammation	4 (8%)			
Mixed cell focus	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Thrombosis, multiple	1 (2%)			
Bile duct, hyperplasia	10 (19%)	11 (21%)	16 (30%)	12 (22%)
Centrilobular, atrophy	2 (4%)	5 (9%)	7 (13%)	2 (4%)
Hepatocyte, necrosis	13 (25%)	11 (21%)	3 (6%)	8 (15%)
Mesentery	(1)	(2)	(2)	(1)
Hemorrhage		1 (50%)		
Pancreas	(52)	(53)	(53)	(54)
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, granulomatous	1 (2%)			
Necrosis				1 (2%)
Acinus, atrophy		1 (2%)	4 (8%)	1 (2%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Salivary glands	(52)	(53)	(53)	(54)
Duct, submandibular gland, hyperplasia		1 (2%)		
Stomach, forestomach	(52)	(53)	(53)	(53)
Edema		1 (2%)		
Hyperkeratosis	1 (2%)			
Hyperplasia			1 (2%)	
Inflammation		1 (2%)	1 (2%)	1 (2%)
Ulcer			1 (2%)	2 (4%)
Stomach, glandular	(52)	(53)	(53)	(54)
Erosion	1 (2%)	1 (2%)		
Hyperplasia	1 (2%)			
Inflammation	1 (2%)		1 (2%)	
Tongue		(1)		
Inflammation		1 (100%)		
Tooth	(3)	(5)		(1)
Epithelium alveolus, hyperplasia, squamous		1 (20%)		
Peridontal tissue, inflammation	3 (100%)	5 (100%)		1 (100%)
Cardiovascular System				
Heart	(53)	(53)	(53)	(54)
Cardiomyopathy	12 (23%)	9 (17%)	8 (15%)	13 (24%)
Thrombosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(52)	(53)	(53)	(54)
Autolysis	1 (2%)			
Congestion	2 (4%)			
Cyst	2 (4%)			
Cytoplasmic alteration				1 (2%)
Degeneration	1 (2%)			
Hemorrhage			1 (2%)	
Hyperplasia	7 (13%)	6 (11%)	5 (9%)	8 (15%)
Hypertrophy			1 (2%)	
Necrosis				1 (2%)
Pigmentation, hemosiderin	1 (2%)			
Vacuolization cytoplasmic	8 (15%)	8 (15%)	7 (13%)	16 (30%)
Adrenal medulla	(51)	(53)	(53)	(54)
Angiectasis	1 (2%)			
Cyst		1 (2%)		
Hyperplasia	6 (12%)	4 (8%)	8 (15%)	8 (15%)
Islets, pancreatic	(52)	(53)	(53)	(54)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Parathyroid gland	(49)	(52)	(51)	(49)
Hyperplasia		2 (4%)	1 (2%)	
Hyperplasia, focal				1 (2%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(52)	(53)	(53)	(54)
Angiectasis	4 (8%)	5 (9%)	5 (9%)	2 (4%)
Autolysis				1 (2%)
Cyst	5 (10%)	3 (6%)	1 (2%)	4 (7%)
Hemorrhage			2 (4%)	1 (2%)
Pars distalis, hyperplasia, diffuse	4 (8%)	1 (2%)	3 (6%)	1 (2%)
Pars distalis, hyperplasia, focal	12 (23%)	15 (28%)	11 (21%)	12 (22%)
Thyroid gland	(52)	(53)	(53)	(52)
Autolysis			1 (2%)	1 (2%)
Fibrosis	1 (2%)			
C-cell, hyperplasia	9 (17%)	7 (13%)	7 (13%)	8 (15%)
Follicular cell, hyperplasia			1 (2%)	1 (2%)
General Body System				
Tissue NOS	(6)	(4)	(2)	(5)
Hemorrhage				1 (20%)
Inflammation, granulomatous	1 (17%)			
Abdominal, polyarteritis		1 (25%)		
Mediastinum, inflammation		1 (25%)		
Oral, inflammation, granulomatous				1 (20%)
Genital System				
Clitoral gland	(51)	(52)	(52)	(54)
Ectasia	4 (8%)	7 (13%)	2 (4%)	3 (6%)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hyperplasia, squamous	1 (2%)			1 (2%)
Inflammation	1 (2%)		2 (4%)	1 (2%)
Ovary	(52)	(53)	(53)	(54)
Atrophy		2 (4%)		1 (2%)
Congestion				1 (2%)
Cyst	7 (13%)	5 (9%)	4 (8%)	5 (9%)
Bilateral, cyst				1 (2%)
Uterus	(52)	(53)	(53)	(54)
Fibrosis				1 (2%)
Hemorrhage		1 (2%)	1 (2%)	
Inflammation				1 (2%)
Endometrium, fibrosis	2 (4%)			
Endometrium, hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Hematopoietic System				
Bone marrow	(52)	(53)	(53)	(54)
Atrophy	2 (4%)			
Atrophy, diffuse		1 (2%)		
Atrophy, focal			1 (2%)	
Autolysis		1 (2%)		
Hyperplasia, reticulum cell		1 (2%)		
Necrosis				1 (2%)
Myeloid cell, hyperplasia	8 (15%)	10 (19%)	10 (19%)	9 (17%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(8)	(7)	(11)	(3)
Iliac, hyperplasia, lymphoid		1 (14%)		
Lymph node, bronchial	(50)	(52)	(51)	(49)
Congestion		4 (8%)	2 (4%)	
Hyperplasia, lymphoid	2 (4%)	1 (2%)		11 (22%)
Hyperplasia, plasma cell			1 (2%)	
Lymph node, mandibular	(52)	(52)	(52)	(50)
Autolysis		1 (2%)		
Hyperplasia, lymphoid	5 (10%)	3 (6%)	5 (10%)	3 (6%)
Hyperplasia, plasma cell		2 (4%)		1 (2%)
Inflammation, granulomatous	1 (2%)			
Lymph node, mesenteric	(52)	(53)	(53)	(54)
Autolysis		1 (2%)	1 (2%)	
Congestion	2 (4%)	2 (4%)	2 (4%)	
Edema		1 (2%)		
Hyperplasia, histiocytic		1 (2%)		
Hyperplasia, lymphoid				1 (2%)
Hyperplasia, macrophage				1 (2%)
Infarct	1 (2%)			
Inflammation		1 (2%)		
Inflammation, granulomatous	1 (2%)			
Pigmentation, hemosiderin	1 (2%)		3 (6%)	2 (4%)
Lymph node, mediastinal	(48)	(50)	(44)	(50)
Autolysis	1 (2%)	2 (4%)		
Congestion	3 (6%)	6 (12%)	1 (2%)	1 (2%)
Hemorrhage				1 (2%)
Hyperplasia, histiocytic		1 (2%)		1 (2%)
Hyperplasia, lymphoid	2 (4%)	4 (8%)	2 (5%)	7 (14%)
Inflammation, granulomatous	1 (2%)			
Pigmentation				4 (8%)
Spleen	(52)	(52)	(53)	(54)
Angiectasis			1 (2%)	
Atrophy	1 (2%)			1 (2%)
Autolysis				1 (2%)
Fibrosis	3 (6%)	2 (4%)	6 (11%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		3 (6%)
Hemorrhage		1 (2%)		
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, RE cell			1 (2%)	
Infarct	1 (2%)			
Inflammation, focal				1 (2%)
Metaplasia, osseous	1 (2%)			
Necrosis	1 (2%)			
Thymus	(48)	(49)	(51)	(52)
Atrophy	14 (29%)	19 (39%)	13 (25%)	13 (25%)
Autolysis		1 (2%)		1 (2%)

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Integumentary System				
Mammary gland	(52)	(53)	(53)	(54)
Hyperplasia		1 (2%)	1 (2%)	
Hyperplasia, focal		1 (2%)		
Duct, ectasia		2 (4%)		1 (2%)
Duct, hyperplasia				1 (2%)
Epithelium, hyperplasia		1 (2%)		
Skin	(53)	(53)	(52)	(53)
Cyst epithelial inclusion	1 (2%)	1 (2%)		
Inflammation	1 (2%)			1 (2%)
Dermis, edema	1 (2%)			
Musculoskeletal System				
Bone	(53)	(53)	(53)	(54)
Fracture			1 (2%)	
Hyperostosis	4 (8%)	1 (2%)	2 (4%)	3 (6%)
Ligament, intervertebral disc, degeneration	1 (2%)			
Tibia, fracture			1 (2%)	
Skeletal muscle				(1)
Hemorrhage				1 (100%)
Nervous System				
Brain	(52)	(53)	(53)	(54)
Autolysis			1 (2%)	
Compression	9 (17%)	14 (26%)	5 (9%)	5 (9%)
Degeneration			1 (2%)	1 (2%)
Hemorrhage		2 (4%)		1 (2%)
Hydrocephalus				1 (2%)
Necrosis			1 (2%)	1 (2%)
Meninges, inflammation	1 (2%)			
Ventricle, hydrocephalus		1 (2%)		
Spinal cord				(1)
Meninges, hemorrhage				1 (100%)
Respiratory System				
Larynx	(51)	(53)	(52)	(53)
Hyperplasia		1 (2%)	1 (2%)	2 (4%)
Inflammation	9 (18%)	12 (23%)	21 (40%)	15 (28%)
Metaplasia, squamous		1 (2%)		1 (2%)
Lung	(52)	(53)	(53)	(54)
Congestion	1 (2%)	1 (2%)	1 (2%)	
Cyst, squamous				2 (4%)
Fibrosis	8 (15%)	7 (13%)	45 (85%)	49 (91%)
Hemorrhage		1 (2%)		
Hyperplasia, macrophage	9 (17%)	10 (19%)	32 (60%)	45 (83%)
Inflammation, chronic active	14 (27%)	13 (25%)	49 (92%)	52 (96%)
Inflammation, granulomatous	1 (2%)			
Inflammation, suppurative	1 (2%)			

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Respiratory System (continued)				
Lung (continued)	(52)	(53)	(53)	(54)
Alveolar epithelium, hyperplasia				1 (2%)
Alveolar epithelium, hyperplasia, focal	5 (10%)	3 (6%)	7 (13%)	9 (17%)
Alveolar epithelium, metaplasia, squamous				4 (7%)
Alveolus, proteinosis	1 (2%)		22 (42%)	49 (91%)
Interstitium, infiltration cellular	13 (25%)	9 (17%)	4 (8%)	10 (19%)
Nose	(51)	(52)	(53)	(54)
Congestion				1 (2%)
Hemorrhage				1 (2%)
Thrombosis	4 (8%)	4 (8%)	5 (9%)	3 (6%)
Thrombosis, multiple	1 (2%)			1 (2%)
Nasolacrimal duct, ectasia	1 (2%)			
Nasolacrimal duct, hyperplasia				1 (2%)
Nasolacrimal duct, inflammation	5 (10%)	4 (8%)	1 (2%)	8 (15%)
Nasopharyngeal duct, hyperplasia		1 (2%)	1 (2%)	1 (2%)
Nasopharyngeal duct, inflammation		1 (2%)	1 (2%)	1 (2%)
Olfactory epithelium, atrophy		1 (2%)	1 (2%)	7 (13%)
Olfactory epithelium, degeneration	41 (80%)	18 (35%)	11 (21%)	12 (22%)
Olfactory epithelium, erosion			1 (2%)	
Olfactory epithelium, inflammation	1 (2%)			
Olfactory epithelium, metaplasia	1 (2%)		1 (2%)	
Olfactory epithelium, metaplasia, squamous	1 (2%)			
Respiratory epithelium, degeneration	11 (22%)	14 (27%)	5 (9%)	2 (4%)
Respiratory epithelium, erosion			1 (2%)	
Respiratory epithelium, hyperplasia	9 (18%)	17 (33%)	17 (32%)	17 (31%)
Respiratory epithelium, inflammation	13 (25%)	8 (15%)	10 (19%)	13 (24%)
Respiratory epithelium, metaplasia, squamous	1 (2%)			
Vomeronasal organ, inflammation	1 (2%)			
Trachea	(52)	(53)	(53)	(54)
Autolysis				1 (2%)
Hyperplasia			1 (2%)	
Inflammation		1 (2%)	1 (2%)	
Metaplasia, squamous			1 (2%)	
Special Senses System				
Eye	(1)	(4)	(1)	(6)
Cataract				1 (17%)
Hemorrhage				1 (17%)
Inflammation		1 (25%)		
Phthisis bulbi		1 (25%)		3 (50%)
Synechia		1 (25%)		2 (33%)
Cornea, fibrosis			1 (100%)	
Posterior chamber, inflammation	1 (100%)			

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
2-Year Study (continued)				
Urinary System				
Kidney	(52)	(53)	(53)	(54)
Autolysis	2 (4%)	1 (2%)		2 (4%)
Congestion	1 (2%)			
Cyst		1 (2%)		
Degeneration, fatty			1 (2%)	
Infarct			1 (2%)	
Inflammation, granulomatous	1 (2%)			
Nephropathy	40 (77%)	39 (74%)	39 (74%)	39 (72%)
Pigmentation				1 (2%)
Pelvis, dilatation	1 (2%)	1 (2%)	2 (4%)	
Renal tubule, degeneration			1 (2%)	1 (2%)
Renal tubule, necrosis	1 (2%)		1 (2%)	
Renal tubule, necrosis, acute				1 (2%)
Renal tubule, pigmentation	3 (6%)	8 (15%)	8 (15%)	6 (11%)
Urinary bladder	(53)	(53)	(53)	(54)
Inflammation		1 (2%)		
Inflammation, granulomatous	1 (2%)			

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF NICKEL SULFATE HEXAHYDRATE

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Disposition Summary				
Animals initially in study	71	71	72	72
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	30	29	29	27
Natural deaths	5	9	9	10
Survivors				
Terminal sacrifice	26	23	24	25
Animals examined microscopically	71	71	72	72
7-Month Interim Evaluation				
Integumentary System				
Skin		(1)		
Subcutaneous tissue, mast cell tumor NOS		1 (100%)		
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(5)	(5)	(5)	(5)
Hepatocellular adenoma	2 (40%)	1 (20%)	1 (20%)	
Endocrine System				
Adrenal cortex	(5)	(5)	(5)	(5)
Capsule, adenoma		1 (20%)		

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(56)	(59)	(56)	(54)
Carcinoma, metastatic, liver	1 (2%)			
Intestine large, colon	(60)	(61)	(60)	(59)
Liver	(61)	(61)	(62)	(60)
Carcinoma	1 (2%)			
Hemangiosarcoma	1 (2%)		2 (3%)	
Hepatocellular carcinoma	10 (16%)	8 (13%)	12 (19%)	8 (13%)
Hepatocellular carcinoma, multiple		3 (5%)	3 (5%)	2 (3%)
Hepatocellular adenoma	17 (28%)	6 (10%)	18 (29%)	10 (17%)
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)	
Mesentery	(1)	(2)	(1)	(1)
Carcinoma, metastatic, liver	1 (100%)			
Histiocytic sarcoma		1 (50%)		
Pancreas	(61)	(60)	(60)	(59)
Carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Salivary glands	(61)	(61)	(62)	(61)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(61)	(60)	(61)	(60)
Capsule, adenoma	1 (2%)	1 (2%)	3 (5%)	1 (2%)
Extra adrenal tissue, histiocytic sarcoma		1 (2%)		
Islets, pancreatic	(61)	(60)	(57)	(58)
Adenoma			1 (2%)	
Thyroid gland	(61)	(61)	(61)	(62)
Follicular cell, adenoma		2 (3%)	1 (2%)	1 (2%)
General Body System				
Tissue NOS	(1)	(2)	(1)	
Hemangiosarcoma, metastatic, bone	1 (100%)			

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Genital System				
Epididymis	(61)	(61)	(62)	(61)
Carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)		2 (3%)	
Testes	(61)	(61)	(62)	(61)
Histiocytic sarcoma			1 (2%)	
Hematopoietic System				
Bone marrow	(61)	(61)	(61)	(61)
Hemangiosarcoma, metastatic, bone	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Lymph node	(24)	(21)	(20)	(26)
Iliac, histiocytic sarcoma		1 (5%)		
Pancreatic, carcinoma, metastatic, liver	1 (4%)			
Renal, carcinoma, metastatic, liver	1 (4%)			
Renal, histiocytic sarcoma		1 (5%)		
Lymph node, bronchial	(46)	(49)	(45)	(54)
Carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Lymph node, mandibular	(56)	(50)	(57)	(45)
Lymph node, mesenteric	(56)	(53)	(57)	(54)
Lymph node, mediastinal	(18)	(24)	(20)	(23)
Spleen	(61)	(61)	(61)	(60)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Thymus	(55)	(49)	(53)	(45)
Integumentary System				
Skin	(61)	(61)	(62)	(61)
Musculoskeletal System				
Bone	(61)	(61)	(62)	(62)
Hemangiosarcoma	1 (2%)			
Nervous System				
None				
Respiratory System				
Larynx	(59)	(59)	(58)	(62)
Lung	(61)	(61)	(62)	(61)
Alveolar/bronchiolar adenoma	3 (5%)	4 (7%)	3 (5%)	4 (7%)
Alveolar/bronchiolar adenoma, multiple	2 (3%)	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma	9 (15%)	10 (16%)	3 (5%)	3 (5%)
Alveolar/bronchiolar carcinoma, multiple		3 (5%)	1 (2%)	
Carcinoma, metastatic, liver	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	1 (2%)	2 (3%)	3 (5%)	2 (3%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Special Senses System				
Ear	(2)			
Fibrosarcoma	1 (50%)			
Harderian gland		(2)	(2)	(1)
Adenoma		2 (100%)	2 (100%)	1 (100%)
Urinary System				
Kidney	(61)	(61)	(61)	(61)
Histiocytic sarcoma		1 (2%)		
Urinary bladder	(60)	(60)	(60)	(59)
Histiocytic sarcoma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(61)	(61)	(62)	(62)
Histiocytic sarcoma	1 (2%)	1 (2%)	2 (3%)	
Lymphoma malignant	2 (3%)	1 (2%)	3 (5%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
7-Month interim evaluation		1		
15-Month interim evaluation	2	2	1	
2-Year study	38	35	41	27
Total primary neoplasms				
7-Month interim evaluation		1		
15-Month interim evaluation	2	2	1	
2-Year study	50	44	54	31
Total animals with benign neoplasms				
15-Month interim evaluation	2	2	1	
2-Year study	22	16	24	16
Total benign neoplasms				
15-Month interim evaluation	2	2	1	
2-Year study	24	17	28	18
Total animals with malignant neoplasms				
2-Year study	20	22	25	13
Total malignant neoplasms				
2-Year study	26	27	26	13
Total animals with metastatic neoplasms				
2-Year study	3	2	3	2
Total metastatic neoplasms				
2-Year study	11	2	3	2
Total animals with uncertain neoplasms - benign or malignant				
7-Month interim evaluation		1		
Total uncertain neoplasms				
7-Month interim evaluation		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 C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0 mg/m³

Number of Days on Study	2 3 0	2 8 7	3 9 5	4 5 2	5 1 4	5 1 6	5 1 6	5 5 2	5 5 3	5 5 5	5 6 8	5 7 0	5 7 0	5 7 3	5 8 0	5 8 5	5 9 7	5 9 7	5 9 8	6 0 1	6 0 7	6 0 8	6 0 9	6 1 4	6 1 4
Carcass ID Number	0 7 2	0 3 2	0 2 7	0 5 1	0 0 9	0 6 3	0 7 6	0 4 9	0 4 0	0 1 2	0 6 0	0 0 7	0 2 4	0 1 5	0 1 1	0 3 8	0 5 7	0 5 9	0 0 3	0 3 0	0 0 8	0 4 5	0 7 1	0 5 4	0 5 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																X									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, rectum	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Hemangiosarcoma																									
Hepatocellular carcinoma				X			X	X			X			X			X						X		
Hepatocellular adenoma			X					X				X		X	X				X	X					
Hepatocellular adenoma, multiple																									
Mesentery																+									
Carcinoma, metastatic, liver																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																X									
Pharynx			+																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	I	+	+	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	I	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																									
Hemangiosarcoma, metastatic, bone																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																X									
Histiocytic sarcoma																									
Penis															+		+								+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: 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 Sulfate Hexahydrate: 0 mg/m³ (continued)

Number of Days on Study	6 1 6	6 2 7	6 4 0	6 4 2	6 4 2	6 6 5	6 7 6	6 8 7	6 8 8	7 3 4	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	0 7 8	0 2 1	0 4 7	0 2 2	0 7 5	0 7 0	0 1 6	0 0 2	0 0 1	0 4 8	0 0 4	0 1 0	0 3 4	0 3 5	0 3 6	0 6 1	0 6 7	0 6 8	0 6 9	0 6 5	0 1 4	0 1 7	0 2 9	0 4 1	0 5 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Hemangiosarcoma								X																	
Hepatocellular carcinoma							X									X									
Hepatocellular adenoma			X							X		X							X	X	X			X	X
Hepatocellular adenoma, multiple															X										
Mesentery																									
Carcinoma, metastatic, liver																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																									
Pharynx																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	M	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS									+																
Hemangiosarcoma, metastatic, bone									X																
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																									
Histiocytic sarcoma											X														
Penis						+																			
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 0 6	0 1 8	0 2 0	0 2 6	0 2 8	0 3 9	0 4 2	0 4 4	0 4 6	0 5 5	0 7 3	Total Tissues/ Tumors
Alimentary System												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	56
Carcinoma, metastatic, liver												1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	I	+	+	+	+	+	+	+	M	55
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	61
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	61
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	M	59
Liver	+	+	+	+	+	+	+	+	+	+	+	61
Carcinoma												1
Hemangiosarcoma												1
Hepatocellular carcinoma								X				10
Hepatocellular adenoma					X		X					17
Hepatocellular adenoma, multiple												1
Mesentery												1
Carcinoma, metastatic, liver												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	61
Carcinoma, metastatic, liver												1
Pharynx												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	61
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	61
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	61
Cardiovascular System												
Heart	+	+	+	+	+	+	+	+	+	+	+	61
Endocrine System												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	61
Capsule, adenoma										X		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	61
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	61
Parathyroid gland	I	+	+	+	+	+	+	M	+	+	+	49
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	53
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	61
General Body System												
Tissue NOS												1
Hemangiosarcoma, metastatic, bone												1
Genital System												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	61
Carcinoma, metastatic, liver												1
Histiocytic sarcoma												1
Penis												4
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	59
Prostate	+	+	+	+	+	+	+	+	+	+	+	60

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

Number of Days on Study	2 3 0	2 3 7	3 9 5	4 5 2	5 1 4	5 1 6	5 1 6	5 5 2	5 5 3	5 5 5	5 6 8	5 7 0	5 7 0	5 7 3	5 8 0	5 8 5	5 9 7	5 9 7	5 9 8	6 0 1	6 0 7	6 0 8	6 0 9	6 1 4	6 1 4
Carcass ID Number	0 7 2	0 3 2	0 2 7	0 5 1	0 0 9	0 6 3	0 7 6	0 4 9	0 4 0	0 1 2	0 6 0	0 0 7	0 2 4	0 1 5	0 1 1	0 3 8	0 5 7	0 5 9	0 0 3	0 3 0	0 4 8	0 4 5	0 7 1	0 5 4	0 5 8
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, bone																									
Lymph node		+	+				+	+		+	+	+	+	+		+	+	+			+			
Pancreatic, carcinoma, metastatic, liver																X									
Renal, carcinoma, metastatic, liver																X									
Lymph node, bronchial	+	+	M	I	+	+	+	M	I	+	+	+	I	+	M	+	+	+	+	+	+	+	M	+	+
Carcinoma, metastatic, liver																X									
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	M	M	M	M	+	+	M	M	+	+	+	M	M	M	M	M	+	M	M	M	I	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma							X																		
Carcinoma, metastatic, liver																X									
Hepatocellular carcinoma, metastatic, liver							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear					+																				
Fibrosarcoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter								+																	
Urethra				+		+							+	+						+					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant																									

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

Number of Days on Study	6 1 6	6 2 7	6 4 0	6 4 2	6 4 2	6 6 5	6 7 6	6 8 7	6 8 8	7 3 4	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	0 7 8	0 2 1	0 4 7	0 2 2	0 7 5	0 7 0	0 1 6	0 0 2	0 0 1	0 4 8	0 0 4	0 1 0	0 3 4	0 3 5	0 3 6	0 6 1	0 6 7	0 6 8	0 6 9	0 0 5	0 1 4	0 1 7	0 2 9	0 4 1	0 5 6
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, bone									X																
Lymph node	+	+		+	+	+				+				+		+									
Pancreatic, carcinoma, metastatic, liver																									
Renal, carcinoma, metastatic, liver																									
Lymph node, bronchial	+	+	+	+	I	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+
Lymph node, mediastinal	+	M	M	M	+	+	M	M	M	M	M	+	I	+	+	M	M	+	M	I	+	M	M	M	I
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar adenoma, multiple									X											X					
Alveolar/bronchiolar carcinoma						X			X		X					X									
Carcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																						+			
Fibrosarcoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter	+																								
Urethra						+				+															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Lymphoma malignant														X											

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

Number of Days on Study	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 0 6 6	0 1 8	0 2 0	0 2 6	0 2 8	0 3 9	0 4 2	0 4 4	0 4 6	0 5 5	0 7 3	Total Tissues/ Tumors
Genital System (continued)												
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	61
Testes	+	+	+	+	+	+	+	+	+	+	+	61
Hematopoietic System												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	61
Hemangiosarcoma, metastatic, bone												1
Lymph node			+			+	+					24
Pancreatic, carcinoma, metastatic, liver												1
Renal, carcinoma, metastatic, liver												1
Lymph node, bronchial	+	I	I	M	+	+	+	+	+	+	+	46
Carcinoma, metastatic, liver												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	56
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	56
Lymph node, mediastinal	I	M	+	I	M	+	M	+	M	M	M	18
Spleen	+	+	+	+	+	+	+	+	+	+	+	61
Thymus	+	+	+	+	+	+	+	+	M	M	+	55
Integumentary System												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	61
Skin	+	+	+	+	+	+	+	+	+	+	+	61
Musculoskeletal System												
Bone	+	+	+	+	+	+	+	+	+	+	+	61
Hemangiosarcoma												1
Nervous System												
Brain	+	+	+	+	+	+	+	+	+	+	+	61
Respiratory System												
Larynx	+	+	+	+	+	+	+	+	+	+	+	59
Lung	+	+	+	+	+	+	+	+	+	+	+	61
Alveolar/bronchiolar adenoma		X							X			3
Alveolar/bronchiolar adenoma, multiple												2
Alveolar/bronchiolar carcinoma						X	X	X			X	9
Carcinoma, metastatic, liver												1
Hepatocellular carcinoma, metastatic, liver												1
Nose	+	+	+	+	+	+	+	+	+	+	+	61
Trachea	+	+	+	+	+	+	+	+	+	+	+	61
Special Senses System												
Ear												2
Fibrosarcoma												1
Urinary System												
Kidney	+	+	+	+	+	+	+	+	+	+	+	61
Ureter												2
Urethra	+									+	+	10
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	61
Histiocytic sarcoma												1
Lymphoma malignant							X					2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³

Number of Days on Study	1 1 2 3 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 1 2 8 2 0 3 1 1 1 1 4 5 5 5 6 6 6 6 6 8 8 9 9 1 2 8 2 6 5 0 8 0 6 6 7 9 2 2 9 2 4 7 7 9 1 4 4 4 4 1
Carcass ID Number	2 2 2 1 2 1 1 1 1 1 2 2 2 1 1 1 2 2 1 1 2 1 2 2 1 0 1 0 9 1 7 8 6 8 6 2 0 3 9 6 9 0 1 9 8 2 6 3 0 8 2 3 8 5 4 8 8 1 6 2 8 5 2 1 6 7 0 7 6 0 6 5 6 1 2
Alimentary System	
Esophagus	+ +
Gallbladder	+ +
Intestine large, colon	+ +
Intestine large, rectum	+ M + M
Intestine large, cecum	+ +
Intestine small, duodenum	+ + + + + + + + + + + + + + + A + + + + + + + + +
Intestine small, jejunum	+ +
Intestine small, ileum	+ + + + + + + + + + + + + + + A + + + + + + + + +
Liver	+ +
Hepatocellular carcinoma	X X X
Hepatocellular carcinoma, multiple	
Hepatocellular adenoma	X X X
Hepatocellular adenoma, multiple	
Histiocytic sarcoma	X
Mesentery	+
Histiocytic sarcoma	X
Pancreas	+ +
Histiocytic sarcoma	X
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ I + + +
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Capsule, adenoma	X
Extra adrenal tissue, histiocytic sarcoma	X
Adrenal medulla	M I I +
Islets, pancreatic	+ +
Parathyroid gland	M M M M + M M M + + + + + + M + M + + + M M M + +
Pituitary gland	M + + + + + + + M + + + + + + + + + M + + + + M + +
Thyroid gland	+ +
Follicular cell, adenoma	X
General Body System	
Tissue NOS	
Genital System	
Epididymis	+ +
Penis	+ + +
Preputial gland	I +
Prostate	M +
Seminal vesicle	+ +
Testes	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	6 4 0	6 4 1	6 4 4	6 4 9	6 6 3	6 6 3	6 7 1	6 8 7	6 9 4	6 9 9	7 1 4	7 2 0	7 2 1	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	1 1 6 8	2 1 9	1 6 7	1 6 9	2 2 0	2 3 0	2 0 7	1 8 3	1 8 4	2 2 3	2 2 4	1 8 5	1 7 4	1 6 3	1 6 4	1 7 2	1 7 3	1 9 3	1 9 4	1 9 9	2 3 8	1 7 5	1 7 6	1 7 9	1 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma													X								X		X		
Hepatocellular carcinoma, multiple								X		X	X														
Hepatocellular adenoma			X	X		X																			
Hepatocellular adenoma, multiple		X																							
Histiocytic sarcoma																									
Mesentery								+																	
Histiocytic sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Capsule, adenoma																									
Extra adrenal tissue, histiocytic sarcoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	I	M	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	M	+	+
Pituitary gland	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																			X						
General Body System																									
Tissue NOS								+														+			
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis				+																					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	1 9 0	1 9 8	2 0 9	2 2 5	1 7 7	1 9 2	2 1 2	2 1 6	2 1 8	2 2 2	2 3 4	Total Tissues/ Tumors
Alimentary System												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	61
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	59
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	61
Intestine large, rectum	I	+	+	+	+	+	+	+	+	+	+	57
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	61
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	60
Liver	+	+	+	+	+	+	+	+	+	+	+	61
Hepatocellular carcinoma								X				8
Hepatocellular carcinoma, multiple												3
Hepatocellular adenoma												6
Hepatocellular adenoma, multiple												1
Histiocytic sarcoma												1
Mesentery												2
Histiocytic sarcoma												1
Pancreas	+	+	+	+	+	I	+	+	+	+	+	60
Histiocytic sarcoma												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	61
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	60
Cardiovascular System												
Heart	+	+	+	+	+	+	+	+	+	+	+	61
Endocrine System												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	60
Capsule, adenoma												1
Extra adrenal tissue, histiocytic sarcoma												1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	57
Islets, pancreatic	+	+	+	+	+	M	+	+	+	+	+	60
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	54
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	61
Follicular cell, adenoma												2
General Body System												
Tissue NOS												2
Genital System												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	61
Penis				+			+	+				7
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	59
Prostate	+	+	+	+	+	+	+	+	+	+	+	60
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	61
Testes	+	+	+	+	+	+	+	+	+	+	+	61

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	1 1 2 3 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 1 2 8 2 0 3 1 1 1 1 4 5 5 5 6 6 6 6 6 8 8 9 9 1 2 8 2 6 5 0 8 0 6 6 7 9 2 2 9 2 4 7 7 9 1 4 4 4 4 1
Carcass ID Number	2 2 2 1 2 1 1 1 1 1 2 2 2 1 1 1 2 2 1 1 2 1 2 2 1 0 1 0 9 1 7 8 6 8 6 2 0 3 9 6 9 0 1 9 8 2 6 3 0 8 2 3 8 5 4 8 8 1 6 2 8 5 2 1 6 7 0 7 6 0 6 5 6 1 2
Hematopoietic System	
Bone marrow	+ +
Histiocytic sarcoma	X
Lymph node	+ + + + + + + + + + + + + + + + +
Iliac, histiocytic sarcoma	X
Renal, histiocytic sarcoma	X
Lymph node, bronchial	M + + M + + + + M + + + + + M + + + + + + I + + + +
Lymph node, mandibular	+ + + + + + M M + + M + + + + + + + + + + + + M +
Lymph node, mesenteric	+ M + I + + + M + + + M + + + + + + + + + + + + +
Lymph node, mediastinal	M M M M M + M M M + M + I + M + + M + + M + M + +
Spleen	+ +
Hemangiosarcoma	
Histiocytic sarcoma	X
Thymus	+ + + + + A + + + + + + + + + + + + + + + + + M +
Integumentary System	
Mammary gland	+ +
Skin	+ +
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Larynx	+ + + + I +
Lung	+ +
Alveolar/bronchiolar adenoma	X
Alveolar/bronchiolar adenoma, multiple	
Alveolar/bronchiolar carcinoma	
Alveolar/bronchiolar carcinoma, multiple	
Hepatocellular carcinoma, metastatic, liver	
Nose	+ +
Trachea	+ +
Special Senses System	
Harderian gland	
Adenoma	
Zymbal's gland	+
Urinary System	
Kidney	+ +
Histiocytic sarcoma	X
Urethra	+ + + + + + + + +
Urinary bladder	+ + + + + + + + + + + + + + + A + + + + + + + + +
Histiocytic sarcoma	X
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	X
Lymphoma malignant	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	6 4 0	6 4 1	6 4 4	6 4 9	6 6 3	6 6 3	6 7 1	6 8 7	6 9 4	6 9 9	7 1 4	7 2 0	7 2 1	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	1 6 8	2 1 9	1 6 7	1 6 9	2 2 0	2 3 0	2 0 7	1 8 3	1 8 4	2 2 3	2 2 4	1 8 5	1 7 4	1 6 3	1 6 4	1 7 2	1 7 3	1 9 3	1 9 4	1 9 9	2 3 8	1 7 5	1 7 6	1 7 9	1 8 1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymph node	+	+	+	+		+		+	+	+		+												
Iliac, histiocytic sarcoma																								
Renal, histiocytic sarcoma																								
Lymph node, bronchial	M	+	+	M	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+
Lymph node, mandibular	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Lymph node, mesenteric	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mediastinal	M	+	M	I	+	M	M	+	M	M	+	M	+	M	+	+	+	+	M	I	+	+	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X						
Histiocytic sarcoma																								
Thymus	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	I	M	M	+	+	+	+	I	M	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X													X									
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma								X			X						X			X	X	X		X
Alveolar/bronchiolar carcinoma, multiple																		X					X	
Hepatocellular carcinoma, metastatic, liver										X			X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland											+													
Adenoma											X													
Zymbal's gland																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Urethra					+	+		+	+															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymphoma malignant								X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m^3 (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	1 9 0	1 9 8	2 0 9	2 2 5	1 7 7	1 9 2	2 1 2	2 1 6	2 1 8	2 2 2	2 3 4	Total Tissues/ Tumors
Hematopoietic System												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	61
Histiocytic sarcoma												1
Lymph node												21
Iliac, histiocytic sarcoma												1
Renal, histiocytic sarcoma												1
Lymph node, bronchial	+	I	I	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	I	M	M	+	M	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	53
Lymph node, mediastinal	M	M	I	I	+	I	+	M	I	M	M	24
Spleen	+	+	+	+	+	+	+	+	+	+	+	61
Hemangiosarcoma												1
Histiocytic sarcoma												1
Thymus	+	+	+	M	+	+	+	+	M	+	+	49
Integumentary System												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	61
Skin	+	+	+	+	+	+	+	+	+	+	+	61
Musculoskeletal System												
Bone	+	+	+	+	+	+	+	+	+	+	+	61
Nervous System												
Brain	+	+	+	+	+	+	+	+	+	+	+	61
Respiratory System												
Larynx	+	+	+	+	+	+	+	+	+	+	+	59
Lung	+	+	+	+	+	+	+	+	+	+	+	61
Alveolar/bronchiolar adenoma						X						4
Alveolar/bronchiolar adenoma, multiple										X		1
Alveolar/bronchiolar carcinoma	X								X		X	10
Alveolar/bronchiolar carcinoma, multiple					X							3
Hepatocellular carcinoma, metastatic, liver												2
Nose	+	+	+	+	+	+	+	+	+	+	+	61
Trachea	+	+	+	+	+	+	+	+	+	+	+	61
Special Senses System												
Harderian gland	+											2
Adenoma	X											2
Zymbal's gland												1
Urinary System												
Kidney	+	+	+	+	+	+	+	+	+	+	+	61
Histiocytic sarcoma												1
Urethra							+	+				13
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma												1
Systemic Lesions												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	61
Histiocytic sarcoma												1
Lymphoma malignant												1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³

Number of Days on Study	2 4 5	2 8 4	3 1 0	3 3 7	3 8 4	4 1 9	4 5 5	4 8 2	4 8 5	5 1 1	5 1 3	5 3 8	5 5 2	5 5 3	5 6 4	5 6 4	5 7 8	5 8 1	5 9 1	5 9 4	6 1 3	6 1 3	6 1 4	6 2 1	6 2 7
Carcass ID Number	3 8 5	3 8 3	3 2 3	3 7 5	3 5 1	3 2 8	3 9 9	3 8 9	3 5 8	3 6 4	3 6 1	3 9 1	3 5 2	3 2 5	3 3 7	3 4 9	3 5 6	3 7 0	4 4 6	3 3 3	3 4 3	3 9 8	3 5 7	3 2 7	3 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	M	+	+	A	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma								X			X			X	X										
Hepatocellular carcinoma, multiple																	X		X						
Hepatocellular adenoma		X			X								X		X			X				X			
Histiocytic sarcoma									X																
Mesentery																									
Pancreas	I	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Tooth																								+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																								X	
Adrenal medulla	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Islets, pancreatic	M	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Thyroid gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									X
General Body System																									
Tissue NOS																								+	
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Penis																				+		+	+	+	+
Preputial gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m^3 (continued)

Number of Days on Study	6 2 9	6 3 9	6 4 0	6 4 2	6 4 2	6 4 8	6 7 2	6 9 6	6 9 9	7 0 2	7 0 5	7 1 7	7 2 8	7 3 7	7 3 7	7 3 7	7 4 5	7 5 7	7 7 7	7 8 8	7 3 9	7 4 7	7 4 8	7 5 0	7 3 6
Carcass ID Number	3 9 3	3 8 0	3 4 2	3 2 4	3 7 6	3 7 4	3 8 8	3 2 6	3 9 6	3 9 5	3 3 0	3 9 4	3 5 3	3 2 1	3 3 4	3 3 8	3 4 4	3 5 5	3 7 2	3 8 4	3 3 9	3 4 7	3 4 8	3 5 0	3 6 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	I	+	+	M
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	I	I	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Hepatocellular carcinoma			X	X					X					X					X						
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma							X		X	X		X				X							X		X
Histiocytic sarcoma																									
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+													+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma							X																		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Penis	+	+			+						+	I													
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	3 6 7	3 6 9	3 7 3	3 8 7	3 2 2	3 3 1	3 4 0	3 4 1	3 5 9	3 6 5	3 7 7	3 8 6	Total Tissues/ Tumors
Alimentary System													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	61
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	56
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	I	+	+	+	+	+	I	I	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	M	+	+	+	57
Liver	+	+	+	+	+	+	+	+	+	+	+	+	62
Hemangiosarcoma				X									2
Hepatocellular carcinoma						X			X		X		12
Hepatocellular carcinoma, multiple							X						3
Hepatocellular adenoma				X	X		X		X			X	18
Histiocytic sarcoma													1
Mesentery												+	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	62
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	62
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	60
Tooth										+			4
Cardiovascular System													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	62
Endocrine System													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	61
Capsule, adenoma								X					3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	59
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	57
Adenoma													1
Parathyroid gland	M	+	+	+	+	+	+	+	+	I	+	+	51
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	58
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	61
Follicular cell, adenoma													1
General Body System													
Tissue NOS													1
Genital System													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	62
Histiocytic sarcoma													2
Penis													9
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	60
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	61
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	61
Testes	+	+	+	+	+	+	+	+	+	+	+	+	62
Histiocytic sarcoma													1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	2 4 5	2 8 4	3 1 0	3 3 7	3 8 4	4 1 9	4 5 5	4 8 2	4 8 5	5 1 1	5 1 3	5 3 8	5 5 2	5 5 3	5 6 4	5 6 4	5 7 8	5 8 1	5 9 1	5 9 4	6 1 3	6 1 3	6 2 4	6 2 1	6 2 7
Carcass ID Number	3 8 5	3 8 3	3 2 3	3 7 5	3 5 1	3 2 8	3 9 9	3 8 9	3 5 8	3 6 4	3 6 1	3 9 1	3 5 2	3 2 5	3 3 7	3 4 9	3 5 6	3 7 0	3 4 6	3 3 3	3 4 3	3 9 8	3 5 7	3 2 7	3 8 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+								+			+	+					+	+		+			
Lymph node, bronchial	M	I	M	+	M	A	+	M	+	+	I	+	+	M	+	I	+	+	+	I	+	M	+	+	+
Histiocytic sarcoma									X																
Lymph node, mandibular	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	M	M	M	A	M	+	M	I	+	+	M	M	I	+	M	+	+	M	+	M	M	I	M
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	A	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	A	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Alveolar/bronchiolar carcinoma																				X					
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver											X						X								
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland												+													
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter			+																						
Urethra			+																+	+		+			+
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	6 2 9	6 3 9	6 4 0	6 4 2	6 4 2	6 4 8	6 7 2	6 9 6	6 9 9	7 0 2	7 0 5	7 1 7	7 2 8	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	3 9 3	3 8 0	3 4 2	3 2 4	3 7 6	3 7 4	3 8 8	3 2 6	3 9 6	3 9 5	3 3 0	3 9 4	3 5 3	3 2 1	3 3 4	3 3 8	3 4 4	3 5 5	3 7 2	3 8 4	3 3 9	3 4 7	3 4 8	3 5 0	3 6 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+			+		+		+			+											+	
Lymph node, bronchial	+	M	+	I	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	M	+	M	M	M	+	M	M	M	+	I	+	M	+	M	M	M	+	M	+	+	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Alveolar/bronchiolar carcinoma		X																				X			
Alveolar/bronchiolar carcinoma, multiple																			X						
Hepatocellular carcinoma, metastatic, liver														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Urethra					+			+		+	+	+	+		+	+					+				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymphoma malignant													X												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	3 6 7	3 6 9	3 7 3	3 8 7	3 2 2	3 3 1	3 4 0	3 4 1	3 5 9	3 6 5	3 7 7	3 8 6	Total Tissues/ Tumors
Hematopoietic System													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	61
Lymph node		+		+			+			+			20
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	+	45
Histiocytic sarcoma													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	57
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	57
Lymph node, mediastinal	M	M	+	+	M	M	M	I	M	M	M	+	20
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	61
Thymus	+	+	+	M	+	+	+	+	+	M	+	+	53
Integumentary System													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	61
Skin	+	+	+	+	+	+	+	+	+	+	+	+	62
Musculoskeletal System													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	62
Nervous System													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	62
Respiratory System													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	58
Lung	+	+	+	+	+	+	+	+	+	+	+	+	62
Alveolar/bronchiolar adenoma									X				3
Alveolar/bronchiolar carcinoma													3
Alveolar/bronchiolar carcinoma, multiple													1
Hepatocellular carcinoma, metastatic, liver													3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	61
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	61
Special Senses System													
Eye						+							1
Harderian gland						+							2
Adenoma						X							2
Urinary System													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	61
Ureter													1
Urethra												+	15
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	60
Systemic Lesions													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	62
Histiocytic sarcoma													2
Lymphoma malignant		X										X	3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	5 0 4	5 1 3	5 2 1	5 2 4	5 5 8	5 2 9	5 3 9	5 4 5	5 4 7	5 5 1	5 5 3	5 5 9	Total Tissues/ Tumors
Alimentary System													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	61
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	I	I	+	+	I	+	+	I	I	+	I	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	58
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	56
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	56
Liver	+	+	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma				X									8
Hepatocellular carcinoma, multiple												X	2
Hepatocellular adenoma					X								10
Mesentery													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	59
Pharynx				+									2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	61
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	60
Tooth			+										2
Cardiovascular System													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	61
Endocrine System													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	60
Capsule, adenoma													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	58
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	58
Parathyroid gland	+	+	M	+	+	+	+	+	M	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	58
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	62
Follicular cell, adenoma													1
General Body System													
None													
Genital System													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	61
Penis													13
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	60
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	61
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	61
Testes	+	+	+	+	+	+	+	+	+	+	+	+	61

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	1 6 9	3 2 8	3 9 4	4 0 4	4 4 7	4 5 8	5 0 3	5 2 9	5 3 3	5 3 3	5 6 1	5 6 8	5 7 0	5 7 2	5 9 4	5 9 7	5 9 7	6 0 1	6 0 3	6 0 4	6 1 0	6 2 1	6 3 0	6 3 8	6 4 5
Carcass ID Number	4 9 2	5 6 0	5 5 6	5 4 2	5 3 8	5 1 1	5 3 1	5 3 7	5 4 9	5 5 4	5 0 3	5 0 8	5 1 2	5 0 1	5 3 2	5 8 3	5 4 3	5 8 1	5 2 5	5 3 0	5 2 6	5 2 0	5 5 0	5 1 4	5 8 5
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+			+	+	+		+		+	+	+	+	+	+		+		+	+		+	+
Lymph node, bronchial	+	I	+	+	A	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Lymph node, mandibular	M	M	M	+	A	+	+	+	M	+	M	+	+	I	+	+	+	M	+	M	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	A	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	M	M	M	M	M	M	+	+	M	I	+	M	M	+	M	I	+	M	M	M	+	M
Spleen	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	I	+	+	A	+	+	+	+	M	A	M	+	+	+	+	+	+	+	+	+	+	M	+	M
Integumentary System																									
Mammary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma											X														
Hepatocellular carcinoma, metastatic, liver										X															
Nose	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter	+					+																			
Urethra	+	+						+				+			+		+					+		+	+
Urinary bladder	+	+	+	+	A	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	6 4 1	6 4 1	6 5 7	6 7 5	6 7 5	6 7 6	6 7 6	6 7 9	6 9 9	6 9 9	7 0 9	7 2 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8
Carcass ID Number	5 2 3	5 4 6	5 3 3	5 3 4	5 3 5	4 9 5	5 1 5	5 1 0	5 1 9	5 4 4	4 9 0	5 2 7	4 8 4	4 8 8	4 9 6	5 0 0	5 0 6	5 0 7	5 0 9	5 1 6	5 1 7	5 2 8	4 9 4	4 9 7	4 9 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+			+		+														+	
Lymph node, bronchial	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Lymph node, mandibular	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+
Lymph node, mesenteric	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	M	M	+	I	+	+	M	M	I	+	M	+	+	+	+	+	M	M	M	I	M	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar adenoma, multiple												X													
Alveolar/bronchiolar carcinoma																X			X						
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland												+													
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Urethra				+	+	+	+				+							+						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	5 0 4	5 1 3	5 2 1	5 2 4	5 5 8	5 2 9	5 3 9	5 4 5	5 4 7	5 5 1	5 5 3	5 5 9	Total Tissues/ Tumors
Hematopoietic System													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	61
Lymph node											+	+	26
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node, mandibular	+	+	+	M	+	+	+	M	+	M	+	+	45
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	54
Lymph node, mediastinal	M	M	M	M	M	+	M	+	+	+	I	M	23
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	60
Thymus	I	+	+	+	+	M	+	+	+	M	M	+	45
Integumentary System													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	61
Skin	+	+	+	+	+	+	+	+	+	+	+	+	61
Musculoskeletal System													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	62
Nervous System													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	62
Respiratory System													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	62
Lung	+	+	+	+	+	+	+	+	+	+	+	+	61
Alveolar/bronchiolar adenoma									X		X		4
Alveolar/bronchiolar adenoma, multiple													1
Alveolar/bronchiolar carcinoma													3
Hepatocellular carcinoma, metastatic, liver												X	2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	61
Special Senses System													
Harderian gland													1
Adenoma													1
Urinary System													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	61
Ureter													2
Urethra					+								16
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	59
Systemic Lesions													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	62

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Adrenal Cortex: Adenoma				
Overall rate[a]	1/61 (2%)	1/60 (2%)	3/61 (5%)	1/60 (2%)
Adjusted rate[b]	3.8%	2.0%	9.6%	2.2%
Terminal rate[c]	1/26 (4%)	0/22 (0%)	1/24 (4%)	0/25 (0%)
First incidence (days)	737 (T)	552	621	601
Life table test[d]	P=0.577	P=0.733	P=0.306	P=0.757N
Logistic regression test[d]	P=0.556	P=0.756	P=0.299	P=0.761
Cochran-Armitage test[d]	P=0.552			
Fisher exact test[d]		P=0.748	P=0.309	P=0.748
Liver: Hepatocellular Adenoma				
Overall rate	18/61 (30%)	7/61 (11%)	18/62 (29%)	10/60 (17%)
Adjusted rate	47.2%	17.4%	48.9%	25.3%
Terminal rate	9/26 (35%)	0/23 (0%)	8/24 (33%)	3/25 (12%)
First incidence (days)	395	517	284	404
Life table test	P=0.176N	P=0.030N	P=0.510	P=0.079N
Logistic regression test	P=0.186N	P=0.014N	P=0.577N	P=0.072N
Cochran-Armitage test	P=0.190N			
Fisher exact test		P=0.012N	P=0.556N	P=0.072N
Liver: Hepatocellular Carcinoma				
Overall rate	11/61 (18%)	11/61 (18%)	15/62 (24%)	10/60 (17%)
Adjusted rate	24.4%	31.8%	39.7%	26.9%
Terminal rate	2/26 (8%)	3/23 (13%)	6/24 (25%)	3/25 (12%)
First incidence (days)	452	552	482	533
Life table test	P=0.461N	P=0.498	P=0.235	P=0.478N
Logistic regression test	P=0.538N	P=0.590N	P=0.211	P=0.522N
Cochran-Armitage test	P=0.506N			
Fisher exact test		P=0.593N	P=0.269	P=0.517N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	27/61 (44%)	18/61 (30%)	29/62 (47%)	19/60 (32%)
Adjusted rate	60.3%	43.6%	67.4%	44.7%
Terminal rate	11/26 (42%)	3/23 (13%)	12/24 (50%)	6/25 (24%)
First incidence (days)	395	517	284	404
Life table test	P=0.201N	P=0.168N	P=0.365	P=0.125N
Logistic regression test	P=0.220N	P=0.071N	P=0.451	P=0.108N
Cochran-Armitage test	P=0.210N			
Fisher exact test		P=0.066N	P=0.461	P=0.107N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	5/61 (8%)	5/61 (8%)	3/62 (5%)	5/61 (8%)
Adjusted rate	18.4%	17.2%	9.1%	17.2%
Terminal rate	4/26 (15%)	3/23 (13%)	1/24 (4%)	3/25 (12%)
First incidence (days)	688	552	552	597
Life table test	P=0.525N	P=0.574	P=0.384N	P=0.615
Logistic regression test	P=0.509N	P=0.606	P=0.363N	P=0.614N
Cochran-Armitage test	P=0.532N			
Fisher exact test		P=0.628N	P=0.350N	P=0.628N

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	9/61 (15%)	13/61 (21%)	4/62 (6%)	3/61 (5%)
Adjusted rate	29.5%	51.6%	13.0%	9.8%
Terminal rate	6/26 (23%)	11/23 (48%)	2/24 (8%)	2/25 (8%)
First incidence (days)	516	687	613	561
Life table test	P=0.012N	P=0.155	P=0.138N	P=0.068N
Logistic regression test	P=0.009N	P=0.191	P=0.122N	P=0.057N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.240	P=0.114N	P=0.063N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/61 (21%)	18/61 (30%)	7/62 (11%)	8/61 (13%)
Adjusted rate	43.6%	65.4%	21.2%	26.2%
Terminal rate	10/26 (38%)	14/23 (61%)	3/24 (13%)	5/25 (20%)
First incidence (days)	516	552	552	561
Life table test	P=0.040N	P=0.105	P=0.135N	P=0.179N
Logistic regression test	P=0.029N	P=0.144	P=0.111N	P=0.142N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=0.203	P=0.103N	P=0.169N
All Organs: Malignant Lymphoma				
Overall rate	2/61 (3%)	1/61 (2%)	3/62 (5%)	0/62 (0%)
Adjusted rate	7.7%	3.4%	12.0%	0.0%
Terminal rate	2/26 (8%)	0/23 (0%)	2/24 (8%)	0/25 (0%)
First incidence (days)	737 (T)	687	728	—[e]
Life table test	P=0.248N	P=0.528N	P=0.464	P=0.246N
Logistic regression test	P=0.233N	P=0.516N	P=0.480	P=0.246N
Cochran-Armitage test	P=0.237N			
Fisher exact test		P=0.500N	P=0.508	P=0.244N
All Organs: Benign Neoplasms				
Overall rate	24/61 (39%)	16/61 (26%)	25/62 (40%)	16/62 (26%)
Adjusted rate	59.9%	41.8%	60.5%	42.5%
Terminal rate	12/26 (46%)	5/23 (22%)	10/24 (42%)	7/25 (28%)
First incidence (days)	395	517	284	404
Life table test	P=0.165N	P=0.177N	P=0.445	P=0.111N
Logistic regression test	P=0.138N	P=0.101N	P=0.503	P=0.078N
Cochran-Armitage test	P=0.144N			
Fisher exact test		P=0.088N	P=0.529	P=0.079N
All Organs: Malignant Neoplasms				
Overall rate	20/61 (33%)	22/61 (36%)	25/62 (40%)	13/62 (21%)
Adjusted rate	48.9%	66.8%	64.1%	34.8%
Terminal rate	8/26 (31%)	13/23 (57%)	12/24 (50%)	5/25 (20%)
First incidence (days)	452	552	482	533
Life table test	P=0.095N	P=0.302	P=0.205	P=0.129N
Logistic regression test	P=0.065N	P=0.368	P=0.222	P=0.100N
Cochran-Armitage test	P=0.073N			
Fisher exact test		P=0.425	P=0.248	P=0.101N

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

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	39/61 (64%)	35/61 (57%)	42/62 (68%)	27/62 (44%)
Adjusted rate	83.8%	84.3%	82.9%	62.4%
Terminal rate	19/26 (73%)	17/23 (74%)	16/24 (67%)	11/25 (44%)
First incidence (days)	395	517	284	404
Life table test	P=0.053N	P=0.515N	P=0.318	P=0.054N
Logistic regression test	P=0.015N	P=0.368N	P=0.349	P=0.017N
Cochran-Armitage test	P=0.019N			
Fisher exact test		P=0.289N	P=0.399	P=0.018N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; 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 C4a
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 March 1994

TABLE C4b
Historical Incidence of Hepatocellular 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	8/57	6/57	12/57
Nickel Subsulfide	13/61	11/61	24/61
Nickel Sulfate Hexahydrate	18/61	11/61	27/61
Talc	3/45	6/45	9/45
Overall Historical Incidence in Inhalation Studies			
Total	201/952 (21.1%)	185/952 (19.4%)	360/952 (37.8%)
Standard deviation	11.7%	5.8%	12.6%
Range	4%-46%	9%-29%	11%-60%
Overall Historical Incidence in Feed Studies			
Total	344/1,316 (26.1%)	220/1,316 (16.7%)	509/1,316 (38.7%)
Standard deviation	13.2%	7.2%	13.9%
Range	4%-60%	3%-29%	10%-68%

[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 Sulfate Hexahydrate[a]

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Disposition Summary				
Animals initially in study	71	71	72	72
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	30	29	29	27
Natural deaths	5	9	9	10
Survivors				
Terminal sacrifice	26	23	24	25
Animals examined microscopically	71	71	72	72
7-Month Interim Evaluation				
Alimentary System				
Liver		(1)	(1)	
Hepatocyte, hyperplasia		1 (100%)	1 (100%)	
Genital System				
Preputial gland	(2)		(2)	(1)
Ectasia	2 (100%)		2 (100%)	1 (100%)
Hematopoietic System				
Lymph node, bronchial	(5)	(3)	(2)	(5)
Hyperplasia, lymphoid	1 (20%)	1 (33%)	1 (50%)	
Lymph node, mediastinal		(3)		
Hyperplasia, lymphoid		1 (33%)		
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Hyperplasia, macrophage			1 (20%)	5 (100%)
Inflammation, acute	1 (20%)			
Interstitium, infiltration cellular				1 (20%)
Nose	(5)	(5)	(5)	(5)
Inflammation, acute	1 (20%)	2 (40%)	1 (20%)	2 (40%)
Olfactory epithelium, atrophy				2 (40%)
Systems Examined With No Lesions Observed				
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 C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate (continued)

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
15-Month Interim Evaluation				
Alimentary System				
Liver	(5)	(5)	(5)	(5)
Infarct, focal		1 (20%)		
Hepatocyte, hyperplasia	1 (20%)			
Endocrine System				
Thyroid gland	(5)	(5)	(5)	(5)
Follicular cell, hyperplasia, focal				1 (20%)
Genital System				
Preputial gland	(5)	(5)	(5)	(5)
Ectasia	5 (100%)	5 (100%)	5 (100%)	5 (100%)
Inflammation	2 (40%)	2 (40%)		3 (60%)
Hematopoietic System				
Lymph node		(1)	(2)	(2)
Iliac, hyperplasia, lymphoid		1 (100%)	2 (100%)	2 (100%)
Iliac, inflammation				1 (50%)
Inguinal, hyperplasia, lymphoid		1 (100%)		1 (50%)
Inguinal, thrombosis				1 (50%)
Lumbar, hyperplasia, lymphoid			1 (50%)	
Renal, hyperplasia, lymphoid				1 (50%)
Lymph node, bronchial	(4)	(5)	(5)	(5)
Hyperplasia, lymphoid	1 (25%)	3 (60%)	1 (20%)	
Hyperplasia, macrophage	1 (25%)			4 (80%)
Lymph node, mandibular	(4)	(5)	(5)	(4)
Inflammation		1 (20%)		
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Ulcer, chronic active				1 (20%)
Dermis, inflammation, chronic active			1 (20%)	
Subcutaneous tissue, inflammation	1 (20%)			
Respiratory System				
Larynx	(5)	(5)	(4)	(3)
Inflammation	1 (20%)			
Lung	(5)	(5)	(5)	(5)
Hyperplasia, macrophage		1 (20%)	4 (80%)	5 (100%)
Inflammation, chronic active				4 (80%)
Bronchialization		1 (20%)		5 (100%)
Alveolar epithelial hyperplasia, focal	1 (20%)			
Alveolus, proteinosis				3 (60%)
Interstitium, infiltration cellular				5 (100%)
Interstitium, inflammation, focal	1 (20%)			

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
15-Month Interim Evaluation (continued)				
Respiratory System (continued)				
Nose	(5)	(5)	(5)	(5)
Developmental malformation		1 (20%)		
Inflammation, acute	1 (20%)			
Glands, inflammation	1 (20%)			1 (20%)
Olfactory epithelium, atrophy			1 (20%)	3 (60%)
Olfactory epithelium, degeneration	2 (40%)			
Respiratory epithelium, degeneration	2 (40%)			
Vomeronasal organ, infiltration cellular, polymorphonuclear	1 (20%)	1 (20%)		
Trachea	(5)	(5)	(5)	(5)
Inflammation			1 (20%)	1 (20%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(60)	(61)	(61)	(61)
Hyperkeratosis	2 (3%)		1 (2%)	1 (2%)
Gallbladder	(56)	(59)	(56)	(54)
Autolysis		3 (5%)	1 (2%)	1 (2%)
Intestine large, colon	(60)	(61)	(60)	(59)
Autolysis		1 (2%)		
Hemorrhage	1 (2%)			
Intestine large, rectum	(55)	(57)	(50)	(50)
Autolysis		1 (2%)		1 (2%)
Anus, inflammation		1 (2%)		1 (2%)
Intestine large, cecum	(59)	(60)	(60)	(58)
Autolysis		1 (2%)	2 (3%)	4 (7%)
Hyperplasia, lymphoid	1 (2%)			
Intestine small, duodenum	(61)	(60)	(59)	(56)
Autolysis		1 (2%)		2 (4%)
Intestine small, jejunum	(61)	(61)	(59)	(59)
Autolysis		1 (2%)		3 (5%)
Peyer's patch, hyperplasia	1 (2%)		1 (2%)	
Peyer's patch, inflammation		1 (2%)		
Intestine small, ileum	(59)	(60)	(57)	(56)
Autolysis		1 (2%)		3 (5%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(61)	(61)	(62)	(60)
Angiectasis, focal			1 (2%)	
Autolysis			2 (3%)	
Basophilic focus	2 (3%)	4 (7%)	1 (2%)	
Clear cell focus	1 (2%)			1 (2%)
Congestion	1 (2%)		1 (2%)	
Cyst		1 (2%)		
Eosinophilic focus			1 (2%)	
Fatty change		1 (2%)		
Hepatodiaphragmatic nodule				1 (2%)
Infarct	5 (8%)	1 (2%)	1 (2%)	3 (5%)
Inflammation		1 (2%)	1 (2%)	1 (2%)
Necrosis		1 (2%)	1 (2%)	2 (3%)
Necrosis, diffuse	7 (11%)	5 (8%)	7 (11%)	6 (10%)
Pigmentation			1 (2%)	
Bile duct, cyst				2 (3%)
Centrilobular, degeneration	1 (2%)	1 (2%)		
Mesentery	(1)	(2)	(1)	(1)
Inflammation			1 (100%)	1 (100%)
Pancreas	(61)	(60)	(60)	(59)
Atrophy		1 (2%)		
Autolysis		1 (2%)		
Cyst			1 (2%)	
Inflammation		1 (2%)		
Acinus, hyperplasia		1 (2%)		
Pharynx	(1)			(2)
Hyperkeratosis	1 (100%)			
Hyperplasia, squamous				2 (100%)
Salivary glands	(61)	(61)	(62)	(61)
Autolysis			1 (2%)	1 (2%)
Stomach, forestomach	(61)	(60)	(62)	(60)
Autolysis	1 (2%)			
Hyperplasia, squamous			1 (2%)	
Stomach, glandular	(61)	(60)	(60)	(60)
Autolysis		1 (2%)	2 (3%)	2 (3%)
Inflammation			1 (2%)	
Tooth			(4)	(2)
Peridontal tissue, inflammation			4 (100%)	2 (100%)
Cardiovascular System				
Heart	(61)	(61)	(62)	(61)
Cardiomyopathy	5 (8%)	2 (3%)	3 (5%)	2 (3%)
Inflammation	1 (2%)	1 (2%)		2 (3%)
Thrombosis				1 (2%)
Atrium, thrombosis	2 (3%)			

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(61)	(60)	(61)	(60)
Accessory adrenal cortical nodule		1 (2%)		
Cyst multilocular		1 (2%)		
Hyperplasia	2 (3%)		3 (5%)	1 (2%)
Hypertrophy		1 (2%)	1 (2%)	
Infarct			1 (2%)	
Capsule, hyperplasia		1 (2%)		
Adrenal medulla	(61)	(57)	(59)	(58)
Infarct			1 (2%)	
Islets, pancreatic	(61)	(60)	(57)	(58)
Hyperplasia			2 (4%)	
Parathyroid gland	(49)	(41)	(51)	(45)
Autolysis			1 (2%)	2 (4%)
Pituitary gland	(53)	(54)	(58)	(58)
Autolysis			1 (2%)	
Cyst			1 (2%)	
Pars distalis, hyperplasia	1 (2%)	2 (4%)		
Thyroid gland	(61)	(61)	(61)	(62)
Autolysis			1 (2%)	1 (2%)
Follicular cell, hyperplasia			1 (2%)	
Follicular cell, hyperplasia, cystic	26 (43%)	26 (43%)	25 (41%)	25 (40%)
General Body System				
Tissue NOS	(1)	(2)	(1)	
Abdominal, abscess		1 (50%)		
Genital System				
Epididymis	(61)	(61)	(62)	(61)
Autolysis			1 (2%)	1 (2%)
Penis	(4)	(7)	(9)	(13)
Bacterium				1 (8%)
Hyperplasia, squamous	4 (100%)	2 (29%)	6 (67%)	3 (23%)
Inflammation		2 (29%)	3 (33%)	8 (62%)
Preputial gland	(59)	(59)	(60)	(60)
Atrophy	1 (2%)		2 (3%)	1 (2%)
Autolysis				1 (2%)
Cyst		1 (2%)		
Ectasia	45 (76%)	31 (53%)	32 (53%)	37 (62%)
Inflammation	23 (39%)	35 (59%)	34 (57%)	35 (58%)
Duct, hyperplasia		1 (2%)		1 (2%)
Prostate	(60)	(60)	(61)	(61)
Autolysis		1 (2%)		1 (2%)
Congestion		1 (2%)		
Hyperplasia			1 (2%)	
Inflammation	3 (5%)	3 (5%)	3 (5%)	2 (3%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Genital System (continued)				
Seminal vesicle	(61)	(61)	(61)	(61)
Autolysis				1 (2%)
Ectasia	1 (2%)	1 (2%)	1 (2%)	2 (3%)
Hemorrhage	1 (2%)			
Hyperplasia			1 (2%)	
Inflammation				1 (2%)
Testes	(61)	(61)	(62)	(61)
Atrophy		1 (2%)	1 (2%)	
Autolysis			1 (2%)	2 (3%)
Granuloma sperm	1 (2%)			
Tunic, inflammation				2 (3%)
Hematopoietic System				
Bone marrow	(61)	(61)	(61)	(61)
Autolysis				1 (2%)
Erythroid cell, hyperplasia	1 (2%)			
Myeloid cell, hyperplasia	18 (30%)	15 (25%)	12 (20%)	12 (20%)
Lymph node	(24)	(21)	(20)	(26)
Iliac, hyperplasia, histiocytic	1 (4%)			1 (4%)
Iliac, hyperplasia, lymphoid	4 (17%)	1 (5%)	4 (20%)	
Iliac, hyperplasia, plasma cell	12 (50%)	10 (48%)	7 (35%)	12 (46%)
Iliac, inflammation		1 (5%)		
Iliac, pigmentation	1 (4%)			
Inguinal, hyperplasia, histiocytic			2 (10%)	2 (8%)
Inguinal, hyperplasia, lymphoid	8 (33%)	11 (52%)	7 (35%)	11 (42%)
Inguinal, hyperplasia, plasma cell	6 (25%)	5 (24%)	4 (20%)	3 (12%)
Inguinal, inflammation	1 (4%)	2 (10%)	1 (5%)	1 (4%)
Inguinal, pigmentation	2 (8%)	1 (5%)		2 (8%)
Lumbar, hyperplasia, plasma cell	1 (4%)		1 (5%)	2 (8%)
Pancreatic, hyperplasia, lymphoid				1 (4%)
Pancreatic, thrombosis			1 (5%)	
Popliteal, hyperplasia, plasma cell	1 (4%)			
Renal, congestion			1 (5%)	
Renal, hyperplasia, histiocytic			1 (5%)	
Renal, hyperplasia, lymphoid	1 (4%)			2 (8%)
Renal, hyperplasia, plasma cell	5 (21%)	1 (5%)	1 (5%)	
Renal, inflammation	2 (8%)		1 (5%)	
Lymph node, bronchial	(46)	(49)	(45)	(54)
Congestion		1 (2%)	1 (2%)	1 (2%)
Edema	1 (2%)			
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, histiocytic		2 (4%)		
Hyperplasia, lymphoid	2 (4%)	4 (8%)	2 (4%)	17 (31%)
Hyperplasia, macrophage			8 (18%)	39 (72%)
Hyperplasia, plasma cell	1 (2%)	2 (4%)		
Inflammation				1 (2%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(56)	(50)	(57)	(45)
Ectasia			1 (2%)	
Hyperplasia, lymphoid	2 (4%)	2 (4%)	4 (7%)	1 (2%)
Hyperplasia, plasma cell	1 (2%)	3 (6%)		1 (2%)
Inflammation		1 (2%)		1 (2%)
Lymph node, mesenteric	(56)	(53)	(57)	(54)
Angiectasis			2 (4%)	
Atrophy				1 (2%)
Congestion	2 (4%)	4 (8%)	1 (2%)	4 (7%)
Edema				1 (2%)
Hematopoietic cell proliferation		2 (4%)		1 (2%)
Hyperplasia, histiocytic		2 (4%)	2 (4%)	
Hyperplasia, lymphoid		4 (8%)	2 (4%)	3 (6%)
Inflammation	5 (9%)	5 (9%)		2 (4%)
Lymph node, mediastinal	(18)	(24)	(20)	(23)
Autolysis				1 (4%)
Congestion				1 (4%)
Hyperplasia, histiocytic		2 (8%)		1 (4%)
Hyperplasia, lymphoid	1 (6%)			1 (4%)
Hyperplasia, plasma cell	1 (6%)			1 (4%)
Pigmentation		1 (4%)		
Spleen	(61)	(61)	(61)	(60)
Angiectasis		1 (2%)		
Autolysis			1 (2%)	
Hematopoietic cell proliferation	9 (15%)	12 (20%)	11 (18%)	11 (18%)
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	3 (5%)	1 (2%)	5 (8%)
Inflammation		2 (3%)		
Thymus	(55)	(49)	(53)	(45)
Atrophy	28 (51%)	15 (31%)	19 (36%)	13 (29%)
Integumentary System				
Skin	(61)	(61)	(62)	(61)
Hyperkeratosis	1 (2%)			
Hyperplasia, squamous			1 (2%)	
Inflammation	5 (8%)	1 (2%)	4 (6%)	1 (2%)
Inflammation, chronic			1 (2%)	
Necrosis		1 (2%)		1 (2%)
Foot, inflammation	1 (2%)	1 (2%)	3 (5%)	1 (2%)
Foot, necrosis	1 (2%)			
Pinna, inflammation		1 (2%)		
Prepuce, edema		1 (2%)		
Prepuce, hyperplasia, squamous	1 (2%)			
Prepuce, inflammation	8 (13%)	15 (25%)	19 (31%)	13 (21%)
Subcutaneous tissue, edema				1 (2%)
Subcutaneous tissue, inflammation	1 (2%)			
Tail, hyperkeratosis	1 (2%)		1 (2%)	
Tail, inflammation	5 (8%)	2 (3%)	2 (3%)	2 (3%)
Tail, necrosis	11 (18%)	4 (7%)	6 (10%)	6 (10%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Musculoskeletal System				
Bone	(61)	(61)	(62)	(62)
Femur, hyperostosis	2 (3%)	1 (2%)	2 (3%)	
Femur, osteoporosis		1 (2%)		
Nervous System				
Brain	(61)	(61)	(62)	(62)
Autolysis				1 (2%)
Congestion				1 (2%)
Cerebrum, degeneration			1 (2%)	
Hippocampus, degeneration			1 (2%)	
Meninges, inflammation		1 (2%)		
Thalamus, degeneration			1 (2%)	
Respiratory System				
Larynx	(59)	(59)	(58)	(62)
Autolysis			1 (2%)	1 (2%)
Hyperplasia, squamous			1 (2%)	1 (2%)
Lung	(61)	(61)	(62)	(61)
Autolysis			1 (2%)	
Congestion	2 (3%)			
Fibrosis	1 (2%)		1 (2%)	
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia, macrophage	6 (10%)	9 (15%)	35 (56%)	59 (97%)
Infarct		1 (2%)		
Inflammation	1 (2%)	2 (3%)		
Inflammation, chronic active	1 (2%)	2 (3%)	8 (13%)	29 (48%)
Thrombosis, multiple				1 (2%)
Bronchialization	1 (2%)	4 (7%)	19 (31%)	39 (64%)
Alveolus, proteinosis				42 (69%)
Bronchiole, hyperplasia	1 (2%)			
Interstitium, infiltration cellular	1 (2%)		3 (5%)	17 (28%)
Nose	(61)	(61)	(61)	(60)
Autolysis				1 (2%)
Olfactory epithelium, atrophy			12 (20%)	37 (62%)
Olfactory epithelium, degeneration		1 (2%)		
Olfactory epithelium, inflammation	1 (2%)			1 (2%)
Respiratory epithelium, degeneration	2 (3%)	2 (3%)		2 (3%)
Respiratory epithelium, inflammation	2 (3%)	2 (3%)	5 (8%)	5 (8%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)		
Trachea	(61)	(61)	(61)	(61)
Autolysis			1 (2%)	1 (2%)
Epithelium, hyperplasia			1 (2%)	
Special Senses System				
Eye			(1)	
Phthisis bulbi			1 (100%)	

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Urinary System				
Kidney	(61)	(61)	(61)	(61)
Autolysis				1 (2%)
Congestion		1 (2%)		
Dilatation		1 (2%)		
Fibrosis		1 (2%)		
Hydronephrosis			2 (3%)	
Inflammation	8 (13%)	7 (11%)	8 (13%)	7 (11%)
Metaplasia, osseous				1 (2%)
Mineralization		1 (2%)		2 (3%)
Nephropathy	9 (15%)	8 (13%)	9 (15%)	8 (13%)
Cortex, cyst		2 (3%)	1 (2%)	
Pelvis, dilatation	16 (26%)	19 (31%)	10 (16%)	10 (16%)
Renal tubule, pigmentation	1 (2%)			
Ureter	(2)		(1)	(2)
Dilatation	1 (50%)			
Inflammation	1 (50%)		1 (100%)	2 (100%)
Urethra	(10)	(13)	(15)	(16)
Calculus, microscopic observation only	10 (100%)	8 (62%)	15 (100%)	14 (88%)
Inflammation	1 (10%)	4 (31%)	3 (20%)	5 (31%)
Transitional epithelium, hyperplasia		2 (15%)		
Urinary bladder	(60)	(60)	(60)	(59)
Autolysis		1 (2%)		3 (5%)
Calculus, microscopic observation only	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Congestion			1 (2%)	
Dilatation	1 (2%)		1 (2%)	2 (3%)
Hemorrhage			1 (2%)	1 (2%)
Inflammation	7 (12%)	6 (10%)	9 (15%)	6 (10%)
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Transitional epithelium, metaplasia, squamous		1 (2%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF NICKEL SULFATE HEXAHYDRATE

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Disposition Summary				
Animals initially in study	71	70	70	70
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	20	11	11	17
Natural deaths	7	10	4	6
Survivors				
Died last week of study	1	1		
Terminal sacrifice	33	38	45	37
Animals examined microscopically	71	70	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)	(5)
Hepatocellular adenoma			2 (40%)	1 (20%)
Genital System				
Ovary	(5)	(5)	(5)	(5)
Luteoma		1 (20%)		
Special Senses System				
Harderian gland				(1)
Adenoma				1 (100%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(60)	(55)	(57)	(54)
Wall, cholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine large, colon	(61)	(57)	(58)	(60)
Intestine large, rectum	(57)	(57)	(55)	(47)
Anus, squamous cell papilloma		1 (2%)		
Intestine large, cecum	(61)	(57)	(60)	(59)
Lymphatic, cholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, duodenum	(58)	(57)	(59)	(58)
Adenocarcinoma			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Serosa, cholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, jejunum	(61)	(58)	(59)	(59)
Histiocytic sarcoma		1 (2%)		
Intestine small, ileum	(61)	(58)	(58)	(59)
Liver	(61)	(59)	(60)	(60)
Carcinoma, metastatic, lung				1 (2%)
Cholangiocarcinoma		1 (2%)		
Hemangiosarcoma				1 (2%)
Hepatocellular carcinoma	7 (11%)	9 (15%)	5 (8%)	10 (17%)
Hepatocellular carcinoma, multiple		5 (8%)		1 (2%)
Hepatocellular adenoma	11 (18%)	13 (22%)	10 (17%)	8 (13%)
Hepatocellular adenoma, multiple	2 (3%)	1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (3%)	2 (3%)	3 (5%)
Osteosarcoma, metastatic, bone				1 (2%)
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)		
Mesentery	(7)	(4)	(4)	(5)
Carcinoma, metastatic, lung			1 (25%)	
Cholangiocarcinoma, metastatic, liver		1 (25%)		
Fibrosarcoma, metastatic, skin	1 (14%)			
Fibrosarcoma, metastatic, skeletal muscle				1 (20%)
Histiocytic sarcoma	1 (14%)		1 (25%)	1 (20%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(60)	(58)	(60)	(60)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibrosarcoma, metastatic, skin	1 (2%)			
Histiocytic sarcoma	1 (2%)		1 (2%)	
Salivary glands	(61)	(59)	(60)	(60)
Stomach, forestomach	(61)	(58)	(60)	(60)
Histiocytic sarcoma		1 (2%)		
Squamous cell papilloma		1 (2%)		
Serosa, cholangiocarcinoma, metastatic, liver		1 (2%)		
Stomach, glandular	(60)	(58)	(59)	(59)
Carcinoma, metastatic, lung			1 (2%)	
Cardiovascular System				
Heart	(61)	(59)	(60)	(60)
Carcinoma, metastatic, lung			1 (2%)	
Fibrosarcoma, metastatic, skin	1 (2%)			
Neoplasm NOS, metastatic, uncertain primary site		1 (2%)		
Epicardium, cholangiocarcinoma, metastatic, liver		1 (2%)		
Endocrine System				
Adrenal cortex	(60)	(58)	(60)	(60)
Capsule, adenoma	1 (2%)			
Extra adrenal tissue, carcinoma, metastatic, lung			1 (2%)	
Extra adrenal tissue, cholangiocarcinoma, metastatic, liver		1 (2%)		
Extra adrenal tissue, histiocytic sarcoma			1 (2%)	
Adrenal medulla	(60)	(57)	(60)	(60)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign	1 (2%)	1 (2%)		
Islets, pancreatic	(60)	(56)	(59)	(60)
Adenoma	2 (3%)	1 (2%)	1 (2%)	1 (2%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Parathyroid gland	(40)	(44)	(50)	(49)
Pituitary gland	(59)	(56)	(59)	(57)
Pars distalis, adenoma	8 (14%)	9 (16%)	5 (8%)	4 (7%)
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(60)	(59)	(60)	(60)
Carcinoma, metastatic, lung				1 (2%)
Follicular cell, adenoma	1 (2%)		2 (3%)	1 (2%)
Follicular cell, adenoma, multiple		1 (2%)		

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
General Body System				
Tissue NOS	(5)	(8)	(4)	(3)
Fibrosarcoma, metastatic, skin			1 (25%)	
Mediastinum, carcinoma, metastatic, lung			1 (25%)	
Mediastinum, cholangiocarcinoma, metastatic, liver		1 (13%)		
Mediastinum, fibrosarcoma, metastatic, skin	1 (20%)			
Thoracic, carcinoma, metastatic, lung			1 (25%)	
Thoracic, neoplasm NOS, metastatic, uncertain primary site		1 (13%)		
Genital System				
Ovary	(59)	(58)	(60)	(59)
Cystadenoma	2 (3%)	1 (2%)		
Granulosa cell tumor malignant		1 (2%)		
Granulosa cell tumor benign	1 (2%)			1 (2%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Tubulostromal adenoma				1 (2%)
Bilateral, cholangiocarcinoma, metastatic, liver		1 (2%)		
Periovarian tissue, histiocytic sarcoma				1 (2%)
Uterus	(61)	(60)	(60)	(60)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibroma		1 (2%)		
Hemangioma			1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	2 (3%)
Leiomyoma	1 (2%)			
Leiomyosarcoma			1 (2%)	
Polyp stromal	2 (3%)	2 (3%)		1 (2%)
Polyp stromal, multiple		1 (2%)		
Vagina			(1)	
Fibroma			1 (100%)	
Hematopoietic System				
Bone marrow	(61)	(59)	(60)	(60)
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymph node	(11)	(11)	(13)	(13)
Axillary, carcinoma, metastatic, lung			1 (8%)	
Axillary, fibrosarcoma, metastatic, skin	1 (9%)			
Axillary, histiocytic sarcoma				1 (8%)
Iliac, fibrosarcoma, metastatic, skin	1 (9%)			
Iliac, histiocytic sarcoma	1 (9%)	1 (9%)	1 (8%)	1 (8%)
Inguinal, carcinoma, metastatic, lung			1 (8%)	
Inguinal, histiocytic sarcoma	1 (9%)	1 (9%)		
Pancreatic, carcinoma, metastatic, lung			1 (8%)	
Pancreatic, histiocytic sarcoma	1 (9%)		1 (8%)	3 (23%)
Pancreatic, neoplasm NOS			1 (8%)	
Renal, histiocytic sarcoma	1 (9%)	1 (9%)	2 (15%)	1 (8%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, bronchial	(50)	(54)	(58)	(56)
Carcinoma, metastatic, lung			1 (2%)	1 (2%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibrosarcoma, metastatic, skin	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Neoplasm NOS, metastatic, lung				1 (2%)
Neoplasm NOS, metastatic, uncertain primary site		1 (2%)		
Lymph node, mandibular	(56)	(56)	(60)	(55)
Carcinoma, metastatic				1 (2%)
Histiocytic sarcoma		1 (2%)	2 (3%)	2 (4%)
Mast cell tumor benign				1 (2%)
Lymph node, mesenteric	(57)	(52)	(56)	(51)
Carcinoma, metastatic, lung			1 (2%)	
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Lymph node, mediastinal	(30)	(28)	(33)	(22)
Carcinoma, metastatic, lung			1 (3%)	1 (5%)
Cholangiocarcinoma, metastatic, liver		1 (4%)		
Fibrosarcoma, metastatic, skin	1 (3%)			
Histiocytic sarcoma		1 (4%)	1 (3%)	1 (5%)
Neoplasm NOS, metastatic, uncertain primary site		1 (4%)		
Spleen	(61)	(58)	(60)	(60)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Capsule, cholangiocarcinoma, metastatic, liver		1 (2%)		
Thymus	(58)	(54)	(54)	(56)
Carcinoma, metastatic, lung				1 (2%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibrosarcoma, metastatic, skin	1 (2%)			
Histiocytic sarcoma	1 (2%)			2 (4%)
Neoplasm NOS, metastatic, uncertain primary site		1 (2%)		
Integumentary System				
Mammary gland	(61)	(58)	(60)	(60)
Carcinoma	2 (3%)	1 (2%)		1 (2%)
Fibroadenoma		1 (2%)		
Skin	(61)	(59)	(59)	(60)
Basosquamous tumor malignant	1 (2%)			
Squamous cell papilloma		1 (2%)		
Subcutaneous tissue, carcinoma, metastatic, lung			1 (2%)	
Subcutaneous tissue, fibrosarcoma	5 (8%)		1 (2%)	2 (3%)
Subcutaneous tissue, hemangioma		1 (2%)		1 (2%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Musculoskeletal System				
Bone	(61)	(60)	(60)	(60)
Maxilla, fibrosarcoma, metastatic, skin	1 (2%)			
Maxilla, histiocytic sarcoma			1 (2%)	
Vertebra, osteosarcoma				1 (2%)
Skeletal muscle	(4)	(3)	(3)	
Fibrosarcoma, metastatic, skin	1 (25%)			
Neoplasm NOS, metastatic, uncertain primary site		1 (33%)		
Abdominal, carcinoma, metastatic, lung			1 (33%)	
Abdominal, cholangiocarcinoma, metastatic, liver		1 (33%)		
Diaphragm, cholangiocarcinoma, metastatic, liver		1 (33%)		
Nervous System				
Brain	(61)	(59)	(59)	(60)
Respiratory System				
Larynx	(58)	(56)	(58)	(56)
Carcinoma, metastatic, lung				1 (2%)
Lung	(61)	(60)	(60)	(60)
Alveolar/bronchiolar adenoma	3 (5%)	3 (5%)	2 (3%)	
Alveolar/bronchiolar carcinoma	4 (7%)	3 (5%)	8 (13%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	
Carcinoma				1 (2%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibrosarcoma, metastatic, skin	1 (2%)			1 (2%)
Hepatocellular carcinoma, metastatic		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)	2 (3%)		1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Neoplasm NOS				1 (2%)
Neoplasm NOS, metastatic, uncertain primary site		1 (2%)		
Trachea	(61)	(60)	(60)	(59)
Special Senses System				
Harderian gland		(2)	(4)	
Adenoma		2 (100%)	4 (100%)	
Zymbal's gland			(1)	
Carcinoma			1 (100%)	

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

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
2-Year Study (continued)				
Urinary System				
Kidney	(61)	(60)	(60)	(60)
Carcinoma, metastatic, lung				1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)			
Histiocytic sarcoma		1 (2%)	2 (3%)	1 (2%)
Perirenal tissue, cholangiocarcinoma, metastatic, liver		1 (2%)		
Urinary bladder	(59)	(60)	(58)	(58)
Serosa, cholangiocarcinoma, metastatic, liver		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(61)	(60)	(60)	(60)
Histiocytic sarcoma	1 (2%)	4 (7%)	2 (3%)	4 (7%)
Lymphoma malignant	7 (11%)	12 (20%)	9 (15%)	6 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation		1	2	2
2-Year study	41	45	40	36
Total primary neoplasms				
15-Month interim evaluation		1	2	2
2-Year study	63	78	58	49
Total animals with benign neoplasms				
15-Month interim evaluation		1	2	2
2-Year study	27	34	22	16
Total benign neoplasms				
15-Month interim evaluation		1	2	2
2-Year study	35	41	28	20
Total animals with malignant neoplasms				
2-Year study	26	27	26	25
Total malignant neoplasms				
2-Year study	28	37	29	28
Total animals with metastatic neoplasms				
2-Year study	3	5	2	6
Total metastatic neoplasms				
2-Year study	14	33	15	13
Total animals with malignant neoplasms uncertain primary site				
2-Year study		1		
Total animals with uncertain neoplasms - benign or malignant				
2-Year study			1	1
Total uncertain neoplasms				
2-Year study			1	1

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

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

Number of Days on Study	0 3 5	2 5 8	3 3 5	3 8 4	3 9 8	4 4 0	5 3 0	5 4 7	5 8 5	5 9 5	5 9 8	6 2 6	6 2 7	6 2 7	6 2 9	6 5 4	6 5 5	6 7 0	6 9 6	7 0 0	7 0 5	7 0 7	7 1 4	7 1 4	7 2 3
Carçass ID Number	1 1 7	1 1 8	1 0 4	1 2 0	0 8 8	1 3 0	1 2 4	1 2 9	1 5 6	1 5 3	0 8 9	1 0 1	1 1 2	1 2 5	1 4 0	1 3 8	1 5 2	1 1 6	1 1 1	0 9 3	1 4 3	0 9 8	0 9 4	0 9 7	1 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	I	+	M
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X									X						X			
Hepatocellular adenoma								X								X									
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																		X							
Mesentery									+			+						+					+	+	
Fibrosarcoma, metastatic, skin																								X	
Histiocytic sarcoma																		X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibrosarcoma, metastatic, skin							X																		
Histiocytic sarcoma																		X							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Capsule, adenoma																			X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Parathyroid gland	M	M	M	+	+	+	+	+	M	M	M	I	M	+	+	+	+	M	+	+	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																			X		X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Follicular cell, adenoma																									
General Body System																									
Tissue NOS			+				+		+														+		
Mediastinum, fibrosarcoma, metastatic, skin							X																		

+: 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 Sulfate Hexahydrate: 0 mg/m³ (continued)

Number of Days on Study	7 2 5	7 2 8	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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3
Carcass ID Number	1 0 8	0 8 1	0 8 5	0 9 5	1 0 2	1 0 3	1 1 5	1 3 3	1 3 4	1 3 9	1 8 2	0 9 0	0 9 2	0 1 1	1 2 7	1 2 2	1 3 2	1 4 1	1 4 5	1 0 0	1 2 6	1 2 8	1 3 1	1 6 0	0 8 7	1 4 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X															X			X			
Hepatocellular adenoma						X					X								X						
Hepatocellular adenoma, multiple													X											X	
Histiocytic sarcoma																									
Mesentery	+						+																		
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	M	+	M	M	+	I	I	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X			X					X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS							+																		
Mediastinum, fibrosarcoma, metastatic, skin																									

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

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	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 4 6	1 5 1	1 5 4	1 2 3	0 8 6	0 9 1	0 9 6	1 0 5	1 3 7	1 5 0	1 5 7	Total Tissues/ Tumors
Alimentary System												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	61
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	61
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	57
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	61
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	58
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	61
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	61
Liver	+	+	+	+	+	+	+	+	+	+	+	61
Hepatocellular carcinoma										X		7
Hepatocellular adenoma	X	X			X	X		X			X	11
Hepatocellular adenoma, multiple												2
Histiocytic sarcoma												1
Mesentery												7
Fibrosarcoma, metastatic, skin												1
Histiocytic sarcoma												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma, metastatic, skin												1
Histiocytic sarcoma												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	61
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	61
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	60
Cardiovascular System												
Heart	+	+	+	+	+	+	+	+	+	+	+	61
Fibrosarcoma, metastatic, skin												1
Endocrine System												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	60
Capsule, adenoma												1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma benign												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	60
Adenoma				X								2
Parathyroid gland	+	+	+	I	+	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	59
Pars distalis, adenoma											X	8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma						X						1
General Body System												
Tissue NOS												5
Mediastinum, fibrosarcoma, metastatic, skin												1

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

Number of Days on Study	0 3 5	2 5 8	3 3 5	3 8 4	3 9 8	4 4 0	5 3 0	5 4 7	5 8 5	5 9 5	5 9 8	6 2 6	6 2 7	6 2 7	6 2 9	6 5 4	6 5 5	6 7 0	7 0 6	7 0 0	7 0 5	7 1 7	7 1 4	7 2 3
Carcass ID Number	1 1 7	1 1 8	1 0 4	1 2 0	0 8 8	1 3 0	1 2 4	1 2 9	1 5 6	1 5 3	0 8 9	1 0 1	1 1 2	1 2 5	1 4 0	1 3 8	1 5 2	1 1 6	1 1 3	1 9 3	0 4 3	1 9 8	0 9 4	1 9 7	1 1 3
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																									
Histiocytic sarcoma																		X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Leiomyoma																						X			
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+			+		+			+						+					+		+
Axillary, fibrosarcoma, metastatic, skin							X																		
Iliac, fibrosarcoma, metastatic, skin							X																		
Iliac, histiocytic sarcoma																		X							
Inguinal, histiocytic sarcoma																		X							
Pancreatic, histiocytic sarcoma																		X							
Renal, histiocytic sarcoma																		X							
Lymph node, bronchial	M	M	+	+	I	+	+	M	+	I	I	+	+	+	+	I	+	+	+	+	+	M	+	+	+
Fibrosarcoma, metastatic, skin							X																		
Histiocytic sarcoma																		X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymph node, mediastinal	M	+	M	M	M	+	+	+	M	M	+	+	+	+	M	M	+	+	M	M	+	M	M	M	M
Fibrosarcoma, metastatic, skin							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																		X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin							X																		
Histiocytic sarcoma																		X							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant																									
Subcutaneous tissue, fibrosarcoma				X		X	X						X											X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, fibrosarcoma, metastatic, skin							X																		
Skeletal muscle							+																+		
Fibrosarcoma, metastatic, skin							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 5	7 2 8	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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3
Carcass ID Number	1 0 8	0 8 1	0 8 5	0 9 5	1 0 2	1 0 3	1 1 5	1 3 3	1 3 4	1 3 9	0 8 2	0 9 0	0 9 2	1 2 1	1 2 7	1 3 2	1 4 1	1 4 5	1 0 0	1 2 6	1 2 8	1 3 1	1 6 0	0 8 7	1 4 2
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Ovary	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma		X																							
Granulosa cell tumor benign	X																								
Histiocytic sarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyoma																									
Polyp stromal									X						X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+						+				+														
Axillary, fibrosarcoma, metastatic, skin																									
Iliac, fibrosarcoma, metastatic, skin																									
Iliac, histiocytic sarcoma																									
Inguinal, histiocytic sarcoma																									
Pancreatic, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mediastinal	+	M	M	M	+	I	+	+	+	+	+	+	+	+	M	+	I	M	M	M	M	+	I	M	I
Fibrosarcoma, metastatic, skin																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant		X																							
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, fibrosarcoma, metastatic, skin																									
Skeletal muscle	+																								
Fibrosarcoma, metastatic, skin																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	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 4 6	1 5 1	1 5 4	1 2 3	0 8 6	0 9 1	0 9 6	1 0 5	1 3 7	1 5 0	1 5 7	Total Tissues/ Tumors
Genital System												
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	58
Ovary	+	+	+	+	+	+	+	+	+	+	+	59
Cystadenoma				X								2
Granulosa ceil tumor benign												1
Histiocytic sarcoma												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	61
Histiocytic sarcoma												1
Leiomyoma												1
Polyp stromal												2
Hematopoietic System												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	61
Lymph node				+								11
Axillary, fibrosarcoma, metastatic, skin												1
Iliac, fibrosarcoma, metastatic, skin												1
Iliac, histiocytic sarcoma												1
Inguinal, histiocytic sarcoma												1
Pancreatic, histiocytic sarcoma												1
Renal, histiocytic sarcoma												1
Lymph node, bronchial	+	+	I	+	I	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin												1
Histiocytic sarcoma												1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	56
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	57
Histiocytic sarcoma												1
Lymph node, mediastinal	+	M	M	+	+	I	M	+	+	+	+	30
Fibrosarcoma, metastatic, skin												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	61
Hemangiosarcoma				X								1
Histiocytic sarcoma												1
Thymus	M	+	+	+	M	+	+	+	+	+	+	58
Fibrosarcoma, metastatic, skin												1
Histiocytic sarcoma												1
Integumentary System												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	61
Carcinoma										X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	61
Basosquamous tumor malignant												1
Subcutaneous tissue, fibrosarcoma												5
Musculoskeletal System												
Bone	+	+	+	+	+	+	+	+	+	+	+	61
Maxilla, fibrosarcoma, metastatic, skin												1
Skeletal muscle				+								4
Fibrosarcoma, metastatic, skin												1
Nervous System												
Brain	+	+	+	+	+	+	+	+	+	+	+	61

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

Number of Days on Study	0 3 5	2 5 8	3 3 5	3 8 4	3 9 8	4 4 0	5 3 0	5 4 7	5 8 5	5 9 5	5 9 8	6 2 6	6 2 7	6 2 7	6 2 9	6 5 4	6 5 5	6 7 0	6 9 6	7 0 0	7 0 5	7 0 7	7 1 4	7 1 4	7 2 3
Carcass ID Number	1 1 7	1 1 8	1 0 4	1 2 0	0 8 8	1 3 0	1 2 4	1 2 9	1 5 6	1 5 3	0 8 9	1 0 1	1 1 2	1 2 5	1 4 0	1 3 8	1 5 2	1 1 6	1 1 1	0 9 3	1 4 3	0 9 8	0 9 4	0 9 7	1 1 3
Respiratory System																									
Larynx	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma														X											
Fibrosarcoma, metastatic, skin							X																		
Hepatocellular carcinoma, metastatic, liver																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin							X																		
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymphoma malignant												X											X		X

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

Number of Days on Study	7 2 5	7 2 8	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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3
Carcass ID Number	1 0 8	0 8 1	0 8 5	0 9 5	1 0 2	1 0 3	1 1 5	1 3 3	1 3 4	1 3 9	1 0 2	1 0 9	1 0 2	1 1 1	1 2 7	1 2 2	1 3 2	1 4 1	1 4 5	1 0 0	1 2 6	1 2 8	1 3 1	1 6 0	1 8 7	1 4 2
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X																						
Alveolar/bronchiolar carcinoma									X	X			X												
Fibrosarcoma, metastatic, skin																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant	X						X				X								X						

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

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	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 4 6	1 5 1	1 5 4	1 2 3	0 8 6	0 9 1	0 9 6	1 0 5	1 3 7	1 5 0	1 5 7	Total Tissues/ Tumors
Respiratory System												
Larynx	+	+	+	+	+	+	+	+	+	+	+	58
Lung	+	+	+	+	+	+	+	+	+	+	+	61
Alveolar/bronchiolar adenoma				X		X						3
Alveolar/bronchiolar carcinoma												4
Fibrosarcoma, metastatic, skin												1
Hepatocellular carcinoma, metastatic, liver												1
Nose	+	+	+	+	+	+	+	+	+	+	+	61
Trachea	+	+	+	+	+	+	+	+	+	+	+	61
Special Senses System												
None												
Urinary System												
Kidney	+	+	+	+	+	+	+	+	+	+	+	61
Fibrosarcoma, metastatic, skin												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	59
Systemic Lesions												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	61
Histiocytic sarcoma												1
Lymphoma malignant												7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³

Number of Days on Study	0 1 4	3 6 1	3 7 5	3 9 8	4 8 3	5 1 1	5 5 9	5 7 8	5 8 8	6 1 4	6 2 4	6 3 5	6 4 9	6 6 6	6 7 2	6 7 9	6 8 7	7 0 3	7 1 1	7 2 5	7 2 8	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 6 2	2 5 7	3 0 9	3 0 5	3 0 7	2 7 7	2 8 8	2 8 1	3 0 6	2 5 6	2 9 3	2 7 3	2 6 7	2 6 6	3 2 0	2 6 0	2 4 3	2 8 2	3 1 6	2 4 1	2 4 8	2 4 7	2 5 0	2 6 3	2 8 0
Alimentary System																									
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	+	+	+	M	+	+	+	+	A	M	+	+	+	+	+	A	+	+	+	+
Wall, cholangiocarcinoma, metastatic, liver								X																	
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Anus, squamous cell papilloma																X									
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Lymphatic, cholangiocarcinoma, metastatic, liver								X																	
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Serosa, cholangiocarcinoma, metastatic, liver								X																	
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma								X																	
Hepatocellular carcinoma								X	X		X		X				X			X					
Hepatocellular carcinoma, multiple						X									X	X					X				
Hepatocellular adenoma												X											X		
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma				X																					
Pheochromocytoma malignant, metastatic, adrenal medulla															X										
Mesentery								+									+	+			+				
Cholangiocarcinoma, metastatic, liver								X																	
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Squamous cell papilloma																									
Serosa, cholangiocarcinoma, metastatic, liver								X																	
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm NOS, metastatic, uncertain primary site									X																
Epicardium, cholangiocarcinoma, metastatic, liver								X																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m^3 (continued)

Number of Days on Study	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 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 8 9	2 9 2	2 9 4	3 0 2	3 1 5	3 1 8	2 4 4	2 4 6	2 5 3	2 6 1	2 6 4	2 7 0	2 7 1	2 8 5	2 9 7	3 0 1	2 5 2	2 7 5	2 9 0	3 0 4	2 4 5	2 4 9	2 5 8	2 6 8	2 7 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Wall, cholangiocarcinoma, metastatic, liver																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anus, squamous cell papilloma																									
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphatic, cholangiocarcinoma, metastatic, liver																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Serosa, cholangiocarcinoma, metastatic, liver																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hepatocellular carcinoma											X	X							X						
Hepatocellular carcinoma, multiple		X																							
Hepatocellular adenoma			X			X		X						X				X		X			X	X	
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma		X																							
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Mesentery																									
Cholangiocarcinoma, metastatic, liver																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Squamous cell papilloma										X															
Serosa, cholangiocarcinoma, metastatic, liver																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																					+		+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm NOS, metastatic, uncertain primary site																									
Epicardium, cholangiocarcinoma, metastatic, liver																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 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 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 7 9	2 9 1	2 9 8	3 1 2	3 1 9	2 5 9	2 8 7	2 9 9	3 1 4	3 1 7	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	59
Gallbladder	+	+	+	+	+	+	+	+	+	+	55
Wall, cholangiocarcinoma, metastatic, liver											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	57
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	57
Anus, squamous cell papilloma											1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	57
Lymphatic, cholangiocarcinoma, metastatic, liver											1
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	57
Histiocytic sarcoma											1
Serosa, cholangiocarcinoma, metastatic, liver											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	58
Histiocytic sarcoma											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	58
Liver	+	+	+	+	+	+	+	+	+	+	59
Cholangiocarcinoma											1
Hepatocellular carcinoma											9
Hepatocellular carcinoma, multiple											5
Hepatocellular adenoma	X	X						X			13
Hepatocellular adenoma, multiple						X					1
Histiocytic sarcoma											2
Pheochromocytoma malignant, metastatic, adrenal medulla											1
Mesentery											4
Cholangiocarcinoma, metastatic, liver											1
Pancreas	+	+	+	+	+	+	+	+	+	+	58
Cholangiocarcinoma, metastatic, liver											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	58
Histiocytic sarcoma											1
Squamous cell papilloma											1
Serosa, cholangiocarcinoma, metastatic, liver											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	58
Tooth											2
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	59
Neoplasm NOS, metastatic, uncertain primary site											1
Epicardium, cholangiocarcinoma, metastatic, liver											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	0 1 4	3 6 1	3 7 5	3 9 8	4 8 3	5 1 1	5 5 9	5 7 8	5 8 8	6 1 4	6 2 4	6 3 5	6 4 9	6 6 6	6 7 2	6 7 9	6 8 7	7 0 3	7 1 1	7 2 5	7 2 8	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 6 2	2 5 7	3 0 9	3 0 5	3 0 7	2 7 7	2 8 8	2 8 1	3 0 6	2 5 6	2 9 3	2 7 3	2 6 7	2 6 6	3 2 0	2 6 0	2 4 3	2 8 2	3 1 6	2 4 1	2 4 8	2 4 7	2 5 0	2 6 3	2 8 0
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, cholangiocarcinoma, metastatic, liver								X																	
Adrenal medulla	+	+	+	+	+	I	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant															X										
Pheochromocytoma benign															X										
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Cholangiocarcinoma, metastatic, liver								X																	
Parathyroid gland	+	+	+	M	M	+	+	+	M	+	M	M	M	M	M	+	I	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	I	+	+	+	+
Pars distalis, adenoma							X										X								X
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma, multiple																									
General Body System																									
Tissue NOS								+	+												+				
Mediastinum, cholangiocarcinoma, metastatic, liver								X																	
Thoracic, neoplasm NOS, metastatic, uncertain primary site									X																
Genital System																									
Clitoral gland	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor malignant																									
Bilateral, cholangiocarcinoma, metastatic, liver								X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver								X																	
Fibroma																									
Histiocytic sarcoma																					X				
Polyp stromal														X											
Polyp stromal, multiple										X															
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node				+						+								+		+					+
Iliac, histiocytic sarcoma				X																					
Inguinal, histiocytic sarcoma				X																					
Renal, histiocytic sarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	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 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 8 9	2 9 2	2 9 4	3 0 2	3 1 5	3 1 8	2 4 4	2 4 6	2 5 3	2 6 1	2 6 4	2 7 0	2 7 1	2 8 5	2 9 7	3 0 1	2 5 1	2 7 2	2 9 5	3 0 0	2 4 4	2 4 5	2 5 9	2 6 8	2 7 6
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, cholangiocarcinoma, metastatic, liver																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Adenoma																									
Cholangiocarcinoma, metastatic, liver																									
Parathyroid gland	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X			X			X					X			X	X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma, multiple																				X					
General Body System																									
Tissue NOS						+							+			+									
Mediastinum, cholangiocarcinoma, metastatic, liver																									
Thoracic, neoplasm NOS, metastatic, uncertain primary site																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor malignant																									
Bilateral, cholangiocarcinoma, metastatic, liver																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																									
Fibroma																	X								
Histiocytic sarcoma																									
Polyp stromal											X														
Polyp stromal, multiple																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node						+		+			+					+				+				
Iliac, histiocytic sarcoma																									
Inguinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																				X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 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 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 7 9	2 9 1	2 9 8	3 1 2	3 1 9	2 5 9	2 8 7	2 9 9	3 1 4	3 1 7	Total Tissues/ Tumors
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	58
Extra adrenal tissue, cholangiocarcinoma, metastatic, liver											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	57
Pheochromocytoma malignant											1
Pheochromocytoma benign											1
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	56
Adenoma				X							1
Cholangiocarcinoma, metastatic, liver											1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	56
Pars distalis, adenoma											9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
Follicular cell, adenoma, multiple											1
General Body System											
Tissue NOS		+						+			8
Mediastinum, cholangiocarcinoma, metastatic, liver											1
Thoracic, neoplasm NOS, metastatic, uncertain primary site											1
Genital System											
Clitoral gland	+	M	+	+	+	+	+	+	+	+	56
Ovary	+	+	+	+	+	+	+	+	+	+	58
Cystadenoma			X								1
Granulosa cell tumor malignant								X			1
Bilateral, cholangiocarcinoma, metastatic, liver											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Cholangiocarcinoma, metastatic, liver											1
Fibroma											1
Histiocytic sarcoma											1
Polyp stromal											2
Polyp stromal, multiple											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma											1
Lymph node				+							11
Iliac, histiocytic sarcoma											1
Inguinal, histiocytic sarcoma											1
Renal, histiocytic sarcoma											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	0 1 4	3 6 1	3 7 5	3 9 8	4 8 3	5 1 1	5 5 9	5 7 8	5 8 8	6 1 4	6 2 4	6 3 5	6 4 9	6 6 6	6 7 2	6 7 9	6 8 7	7 0 3	7 1 1	7 2 5	7 2 8	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 6 2	2 5 7	3 0 9	3 0 5	3 0 7	2 7 7	2 8 8	2 8 1	3 0 6	2 5 6	2 9 3	2 7 3	2 6 7	2 6 6	2 6 0	2 6 0	2 4 3	2 8 2	3 1 6	2 4 1	2 4 8	2 4 7	2 5 0	2 6 3	2 8 0
Hematopoietic System (continued)																									
Lymph node, bronchial	M	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver								X																	
Histiocytic sarcoma				X																					
Neoplasm NOS, metastatic, uncertain primary site									X																
Lymph node, mandibular	+	+	+	+	M	+	+	I	+	+	+	+	+	A	+	I	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	A	+	+	A	I	+	+	+	+	+	A	+	+	+	+
Cholangiocarcinoma, metastatic, liver								X																	
Histiocytic sarcoma				X																					
Lymph node, mediastinal	M	M	M	+	M	M	+	+	+	M	+	M	M	M	M	M	+	+	+	+	+	M	+	M	M
Cholangiocarcinoma, metastatic, liver								X																	
Histiocytic sarcoma				X																					
Neoplasm NOS, metastatic, uncertain primary site									X																
Spleen	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Capsule, cholangiocarcinoma, metastatic, liver								X																	
Thymus	+	I	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver								X																	
Neoplasm NOS, metastatic, uncertain primary site									X																
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, hemangioma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+	+										+						
Neoplasm NOS, metastatic, uncertain primary site									X																
Abdominal, cholangiocarcinoma, metastatic, liver								X																	
Diaphragm, cholangiocarcinoma, metastatic, liver								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	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 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 8 9	2 9 2	2 9 4	3 0 2	3 1 5	3 1 8	2 4 4	2 4 6	2 5 3	2 6 1	2 6 4	2 7 0	2 7 1	2 8 5	2 9 7	3 0 1	2 5 2	2 7 5	2 9 0	3 0 4	2 4 5	2 4 9	2 5 8	2 6 8	2 7 6
Hematopoietic System (continued)																									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+
Cholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Neoplasm NOS, metastatic, uncertain primary site																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+	I	+	+
Cholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Lymph node, mediastinal	M	+	+	M	M	+	+	+	+	+	+	M	+	+	M	M	I	+	M	M	M	+	M	M	M
Cholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Neoplasm NOS, metastatic, uncertain primary site																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Capsule, cholangiocarcinoma, metastatic, liver																									
Thymus	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																									
Neoplasm NOS, metastatic, uncertain primary site																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Subcutaneous tissue, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Neoplasm NOS, metastatic, uncertain primary site																									
Abdominal, cholangiocarcinoma, metastatic, liver																									
Diaphragm, cholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 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 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 7 9	2 9 1	2 9 8	3 1 2	3 1 9	2 5 9	2 8 7	2 9 9	3 1 4	3 1 7	Total Tissues/ Tumors
Hematopoietic System (continued)											
Lymph node, bronchial	+	+	I	+	+	+	+	+	+	+	54
Cholangiocarcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Neoplasm NOS, metastatic, uncertain primary site											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	56
Histiocytic sarcoma											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	52
Cholangiocarcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Lymph node, mediastinal	+	+	M	M	+	+	M	M	+	M	28
Cholangiocarcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Neoplasm NOS, metastatic, uncertain primary site											1
Spleen	+	+	+	+	+	+	+	+	+	+	58
Histiocytic sarcoma											2
Capsule, cholangiocarcinoma, metastatic, liver											1
Thymus	M	+	+	+	+	+	+	+	+	+	54
Cholangiocarcinoma, metastatic, liver											1
Neoplasm NOS, metastatic, uncertain primary site											1
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	58
Carcinoma											1
Fibroadenoma											1
Skin	+	+	+	+	+	+	+	+	I	+	59
Squamous cell papilloma											1
Subcutaneous tissue, hemangioma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											3
Neoplasm NOS, metastatic, uncertain primary site											1
Abdominal, cholangiocarcinoma, metastatic, liver											1
Diaphragm, cholangiocarcinoma, metastatic, liver											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	59

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	0 1 4	3 6 1	3 7 5	3 9 8	4 8 3	5 1 1	5 5 9	5 7 8	5 8 8	6 1 4	6 2 4	6 3 5	6 4 9	6 6 6	6 7 2	6 7 9	6 8 7	7 0 3	7 1 1	7 2 5	7 2 8	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 6 2	2 5 7	3 0 9	3 0 5	3 0 7	2 7 7	2 8 8	2 8 1	3 0 6	2 5 6	2 9 3	2 7 3	2 6 7	2 6 6	2 6 0	2 6 0	2 4 3	2 8 2	3 1 6	2 4 1	2 4 8	2 4 7	2 5 0	2 6 3	2 8 0
Respiratory System																									
Larynx	+	+	+	I	M	+	+	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X	X					
Alveolar/bronchiolar carcinoma													X												
Cholangiocarcinoma, metastatic, liver								X																	
Hepatocellular carcinoma, metastatic											X														
Hepatocellular carcinoma, metastatic, liver						X									X										
Histiocytic sarcoma				X																					
Neoplasm NOS, metastatic, uncertain primary site									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear		+																							
Harderian gland												+													
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Perirenal tissue, cholangiocarcinoma, metastatic, liver								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, cholangiocarcinoma, metastatic, liver								X																	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																	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 Sulfate Hexahydrate: 0.25 mg/m³ (continued)

Number of Days on Study	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 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 8 9	2 9 2	2 9 4	3 0 2	3 1 5	3 1 8	2 4 4	2 4 6	2 5 3	2 6 1	2 6 4	2 7 0	2 7 1	2 8 5	2 9 7	3 0 1	2 5 2	2 7 5	2 9 0	3 0 4	2 4 5	2 4 9	2 5 8	2 6 8	2 7 6
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma										X													X		
Cholangiocarcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Neoplasm NOS, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland	+																								
Adenoma	X																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Perirenal tissue, cholangiocarcinoma, metastatic, liver																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, cholangiocarcinoma, metastatic, liver																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																		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 Sulfate Hexahydrate: 0.25 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 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 7 9	2 9 1	2 9 8	3 1 2	3 1 9	2 5 9	2 8 7	2 9 9	3 1 4	3 1 7	Total Tissues/ Tumors
Respiratory System											
Larynx	+	+	+	+	+	+	+	+	+	+	56
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma		X									3
Alveolar/bronchiolar carcinoma											3
Cholangiocarcinoma, metastatic, liver											1
Hepatocellular carcinoma, metastatic											1
Hepatocellular carcinoma, metastatic, liver											2
Histiocytic sarcoma											1
Neoplasm NOS, metastatic, uncertain primary site											1
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear											1
Harderian gland											2
Adenoma											2
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Perirenal tissue, cholangiocarcinoma, metastatic, liver											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Serosa, cholangiocarcinoma, metastatic, liver											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											4
Lymphoma malignant		X						X			12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³

Number of Days on Study	3 3 4	4 5 4	5 1 0	5 3 9	5 6 7	5 7 7	6 1 4	6 2 9	6 4 9	6 5 6	6 7 2	6 7 2	6 8 1	6 8 1	7 1 4	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
Carcass ID Number	4 1 8	4 5 4	4 1 7	4 3 1	4 5 8	4 2 4	4 7 9	4 7 8	4 5 2	4 3 9	4 1 9	4 2 9	4 6 8	4 6 9	4 5 7	4 0 5	4 0 6	4 1 0	4 1 1	4 1 2	4 1 5	4 2 5	4 2 8	4 4 2	4 7 4
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X				X				X		
Hepatocellular adenoma														X		X	X				X			X
Hepatocellular adenoma, multiple																								
Histiocytic sarcoma						X																		
Mesentery					+	+				+					+									
Carcinoma, metastatic, lung										X														
Histiocytic sarcoma						X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung										X														
Tooth																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung										X														
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, carcinoma, metastatic, lung										X														
Extra adrenal tissue, histiocytic sarcoma						X																		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	M	+	+	+	+	+	+	M	+	M	+	M	+	M	M	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																						X		
Pars intermedia, adenoma																	X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																					X			
General Body System																								
Tissue NOS			+							+					+									
Fibrosarcoma, metastatic, skin			X																					
Mediastinum, carcinoma, metastatic, lung										X														
Thoracic, carcinoma, metastatic, lung										X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m^3 (continued)

Number of Days on Study	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	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6
Carcass ID Number	4 0 3	4 0 7	4 3 5	4 4 0	4 4 9	4 5 6	4 7 5	4 0 1	4 0 8	4 1 3	4 1 4	4 2 3	4 3 2	4 4 3	4 7 3	4 8 0	4 0 4	4 2 6	4 2 7	4 4 1	4 4 5	4 5 3	4 7 7	4 0 2	4 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma															X			X							
Hepatocellular adenoma								X					X						X		X				
Hepatocellular adenoma, multiple		X																							
Histiocytic sarcoma	X																								
Mesentery																									
Carcinoma, metastatic, lung																									
Histiocytic sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																									
Tooth		+																							
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, carcinoma, metastatic, lung																									
Extra adrenal tissue, histiocytic sarcoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X		X				X				
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
General Body System																									
Tissue NOS																									
Fibrosarcoma, metastatic, skin																									
Mediastinum, carcinoma, metastatic, lung																									
Thoracic, carcinoma, metastatic, lung																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 2 2	4 3 0	4 4 7	4 4 8	4 5 0	4 5 5	4 6 0	4 6 7	4 7 2	4 7 6	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	59
Gallbladder	+	+	+	+	+	+	+	+	+	+	57
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Intestine large, rectum	M	+	+	+	+	+	+	+	+	I	55
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma		X									1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	M	+	+	+	58
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma											5
Hepatocellular adenoma										X	10
Hepatocellular adenoma, multiple											1
Histiocytic sarcoma											2
Mesentery											4
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Carcinoma, metastatic, lung											1
Tooth											1
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, lung											1
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Extra adrenal tissue, carcinoma, metastatic, lung											1
Extra adrenal tissue, histiocytic sarcoma											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	59
Pars distalis, adenoma								X			5
Pars intermedia, adenoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma											2
General Body System											
Tissue NOS		+									4
Fibrosarcoma, metastatic, skin											1
Mediastinum, carcinoma, metastatic, lung											1
Thoracic, carcinoma, metastatic, lung											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	3 3 4	4 5 4	5 1 0	5 3 9	5 6 7	5 7 7	6 1 4	6 2 9	6 4 9	6 5 6	6 7 2	6 7 2	6 8 1	6 8 1	7 1 4	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
Carcass ID Number	4 1 8	4 5 4	4 1 7	4 3 1	4 5 8	4 2 4	4 7 9	4 7 8	4 5 2	4 3 9	4 1 9	4 2 9	4 6 8	4 6 9	4 5 7	4 0 5	4 0 6	4 1 0	4 1 1	4 1 2	4 1 5	4 2 5	4 2 5	4 4 8	4 7 4
Genital System																								
Clitoral gland	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma						X																			
Leiomyosarcoma													X												
Vagina																									
Fibroma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+	+			+					+							+			
Axillary, carcinoma, metastatic, lung										X															
Iliac, histiocytic sarcoma																									
Inguinal, carcinoma, metastatic, lung										X															
Pancreatic, carcinoma, metastatic, lung										X															
Pancreatic, histiocytic sarcoma																									
Pancreatic, neoplasm NOS																									
Renal, histiocytic sarcoma						X																			
Lymph node, bronchial	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung										X															
Histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung										X															
Histiocytic sarcoma						X																			
Lymph node, mediastinal	+	M	M	+	+	+	+	M	I	+	M	M	+	M	+	+	+	M	M	M	+	+	+	+	+
Carcinoma, metastatic, lung										X															
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Subcutaneous tissue, carcinoma, metastatic, lung										X															
Subcutaneous tissue, fibrosarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, histiocytic sarcoma						X																			
Skeletal muscle					+					+					+										
Abdominal, carcinoma, metastatic, lung										X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	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	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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
Carcass ID Number	4 0 3	4 0 7	4 3 5	4 4 0	4 4 9	4 5 6	4 7 5	4 0 1	4 0 8	4 1 3	4 1 4	4 2 3	4 3 2	4 4 3	4 7 3	4 8 0	4 0 4	4 2 6	4 2 7	4 4 1	4 4 5	4 5 3	4 7 7	4 0 2	4 2 1
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																									
Leiomyosarcoma																									
Vagina																									
Fibroma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+								+		+		+					+				
Axillary, carcinoma, metastatic, lung																									
Iliac, histiocytic sarcoma	X																								
Inguinal, carcinoma, metastatic, lung																									
Pancreatic, carcinoma, metastatic, lung																									
Pancreatic, histiocytic sarcoma	X																								
Pancreatic, neoplasm NOS																X									
Renal, histiocytic sarcoma	X																								
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																									
Histiocytic sarcoma	X																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Lymph node, mesenteric	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																									
Histiocytic sarcoma	X																								
Lymph node, mediastinal	+	+	M	+	+	M	I	+	+	M	+	+	+	+	M	+	I	+	M	M	+	M	M	M	M
Carcinoma, metastatic, lung																									
Histiocytic sarcoma	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Thymus	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, carcinoma, metastatic, lung																									
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, histiocytic sarcoma																									
Skeletal muscle																									
Abdominal, carcinoma, metastatic, lung																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 2 2	4 3 0	4 4 7	4 4 8	4 5 0	4 5 5	4 6 0	4 6 7	4 7 2	4 7 6	Total Tissues/ Tumors
Genital System											
Clitoral gland	+	+	M	+	+	+	+	+	+	+	52
Ovary	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Hemangioma					X						1
Histiocytic sarcoma											1
Leiomyosarcoma											1
Vagina	+										1
Fibroma	X										1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node				+							13
Axillary, carcinoma, metastatic, lung											1
Iliac, histiocytic sarcoma											1
Inguinal, carcinoma, metastatic, lung											1
Pancreatic, carcinoma, metastatic, lung											1
Pancreatic, histiocytic sarcoma											1
Pancreatic, neoplasm NOS											1
Renal, histiocytic sarcoma											2
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	58
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	56
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											2
Lymph node, mediastinal	+	+	M	+	+	M	M	+	M	M	33
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											1
Spleen	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Thymus	+	+	M	+	+	M	+	M	+	+	54
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Skin	+	+	+	+	+	+	+	+	+	+	59
Subcutaneous tissue, carcinoma, metastatic, lung											1
Subcutaneous tissue, fibrosarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Maxilla, histiocytic sarcoma											1
Skeletal muscle											3
Abdominal, carcinoma, metastatic, lung											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	3	4	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	3	5	1	3	6	7	1	2	4	5	7	7	8	8	1	3	3	3	3	3	3	3	3	3	3
	4	4	0	9	7	7	4	9	9	6	2	2	1	1	4	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	1	5	1	3	5	2	7	7	5	3	1	2	6	6	5	0	0	1	1	1	1	2	2	4	7
	8	4	7	1	8	4	9	8	2	9	9	9	8	9	7	5	6	0	1	2	5	5	8	2	4
Nervous System																									
Brain	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma										X			X												
Alveolar/bronchiolar carcinoma, multiple																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland											+	+													
Adenoma											X	X													
Lacrimal gland				+																					
Zymbal's gland				+																					
Carcinoma				X																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymphoma malignant					X		X								X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 0.5 mg/m^3 (continued)

Number of Days on Study	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	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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
Carcass ID Number	4 0 3	4 0 7	4 3 5	4 4 0	4 4 9	4 5 6	4 7 5	4 0 1	4 0 8	4 1 3	4 1 4	4 2 3	4 3 2	4 4 3	4 7 3	4 8 0	4 0 4	4 2 6	4 2 7	4 4 1	4 4 5	4 5 3	4 7 7	4 0 2	4 2 1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma				X							X						X								
Alveolar/bronchiolar carcinoma, multiple																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear	+																								
Harderian gland																		+					+		
Adenoma																		X					X		
Lacrimal gland																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Sulfate Hexahydrate: 0.5 mg/m³ (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 2 2	4 3 0	4 4 7	4 4 8	4 5 0	4 5 5	4 6 0	4 6 7	4 7 2	4 7 6	Total Tissues/ Tumors
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	59
Respiratory System											
Larynx	+	+	I	+	+	+	+	+	+	+	58
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma	X										2
Alveolar/bronchiolar carcinoma		X						X		X	8
Alveolar/bronchiolar carcinoma, multiple											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear	+										2
Harderian gland											4
Adenoma											4
Lacrimal gland											1
Zymbal's gland											1
Carcinoma											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	58
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Lymphoma malignant				X							9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³

Number of Days on Study	2 8 1	3 1 0	3 6 1	3 7 0	3 9 3	4 5 7	4 6 3	5 1 6	5 2 1	5 6 2	5 6 2	5 7 1	5 9 6	6 0 1	6 0 4	6 5 9	6 6 9	6 7 5	6 7 9	6 9 8	7 1 3	7 1 4	7 2 8	7 3 0	7 3 0
Carcass ID Number	5 8 4	6 1 2	5 8 1	6 0 4	5 9 3	5 7 5	6 3 3	6 0 7	6 0 8	5 9 1	6 0 6	6 1 5	6 1 8	6 0 5	6 1 6	6 3 1	6 9 6	6 2 7	6 6 6	6 0 9	6 7 4	6 6 8	6 9 0	5 8 3	5 9 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	M	+	A	M	+	A	+	+	+	+	+	M	+	+	+	I	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	I	M	M	+	+	I	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung											X														
Hemangiosarcoma																		X							
Hepatocellular carcinoma								X	X		X	X				X	X								
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																					X	X		X	
Hepatocellular adenoma, multiple																	X								
Histiocytic sarcoma												X			X	X									
Osteosarcoma, metastatic, bone						X																			
Mesentery																+							+		
Fibrosarcoma, metastatic, skeletal muscle																									
Histiocytic sarcoma																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																			+						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	M	M	M	M	M	M	+	+	+	M	+	+	+	+	M	+	+	M	+	+
Pituitary gland	+	+	I	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X						X	X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung											X														
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 Sulfate Hexahydrate: 1 mg/m³ (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	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	
Carcass ID Number	6 2 3	6 3 5	6 3 6	5 6 7	5 7 7	5 7 8	5 9 2	6 0 0	6 1 7	6 2 9	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	I	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	59
Liver	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, lung											1
Hemangiosarcoma											1
Hepatocellular carcinoma									X		10
Hepatocellular carcinoma, multiple											1
Hepatocellular adenoma			X							X	8
Hepatocellular adenoma, multiple											1
Histiocytic sarcoma											3
Osteosarcoma, metastatic, bone											1
Mesentery				+							5
Fibrosarcoma, metastatic, skeletal muscle											1
Histiocytic sarcoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	M	+	+	+	+	+	+	+	+	59
Tooth											1
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	57
Pars distalis, adenoma											4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, lung											1
Follicular cell, adenoma											1
General Body System											
Tissue NOS											3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	2 8 1	3 1 0	3 6 1	3 7 0	3 9 3	4 5 7	4 6 3	5 1 6	5 2 1	5 6 2	5 6 2	5 7 1	5 9 6	6 0 1	6 0 4	6 5 9	6 6 9	6 7 5	6 7 9	6 9 8	7 1 3	7 1 4	7 2 8	7 3 0	7 3 0
Carcass ID Number	5 8 4	6 1 2	5 8 1	6 0 4	5 9 3	5 7 5	6 3 3	6 0 7	6 0 8	5 9 1	6 0 6	6 1 5	6 1 8	6 1 5	6 1 6	6 3 1	6 9 6	5 2 7	6 6 9	5 0 9	5 7 4	5 6 8	5 9 0	5 8 3	5 9 4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Tubulostromal adenoma																									
Periovarian tissue, histiocytic sarcoma																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Lymph node												+	+		+	+		+			+	+	+		
Axillary, histiocytic sarcoma															X										
Iliac, histiocytic sarcoma															X										
Pancreatic, histiocytic sarcoma												X			X	X									
Renal, histiocytic sarcoma															X										
Lymph node, bronchial	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung											X														
Histiocytic sarcoma												X			X										
Neoplasm NOS, metastatic, lung									X																
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Carcinoma, metastatic																						X			
Histiocytic sarcoma												X			X										
Mast cell tumor benign																									
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M		+	+	+	+	M	+	+	+
Histiocytic sarcoma															X										
Lymph node, mediastinal	M	M	M	M	M	M	M	M	I	M	+	+	+	M	M	M	+	+	I	M	M	+	+	M	M
Carcinoma, metastatic, lung											X														
Histiocytic sarcoma												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Carcinoma, metastatic, lung											X														
Histiocytic sarcoma												X			X										
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma					X																				
Subcutaneous tissue, hemangioma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	730	730	730	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733
Carcass ID Number	59898	62806	62699	58939	59913	61134	61144	63347	63347	63643	66404	67700	67711	67712	67723	67730	68806	68816	68821	62201	62320	63605	68757	69051
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign									X															
Tubulostromal adenoma									X															
Periovarian tissue, histiocytic sarcoma																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Polyp stromal			X																					
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymph node						+				+										+	+		+	
Axillary, histiocytic sarcoma																								
Iliac, histiocytic sarcoma																								
Pancreatic, histiocytic sarcoma																								
Renal, histiocytic sarcoma																								
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																								
Histiocytic sarcoma																								
Neoplasm NOS, metastatic, lung																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Carcinoma, metastatic																								
Histiocytic sarcoma																								
Mast cell tumor benign																X								
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma																								
Lymph node, mediastinal	I	+	I	I	M	M	+	+	M	+	+	I	+	+	+	I	M	+	M	M	+	I	+	+	M
Carcinoma, metastatic, lung																								
Histiocytic sarcoma																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Carcinoma, metastatic, lung																								
Histiocytic sarcoma																								
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X																
Subcutaneous tissue, hemangioma																								X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	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	
Carcass ID Number	6 2 3	6 3 5	6 3 6	5 6 7	5 7 7	5 7 8	5 9 2	6 0 0	6 1 7	6 2 9	Total Tissues/ Tumors
Genital System											
Clitoral gland	+	+	M	+	+	+	+	+	+	+	58
Ovary	+	+	+	+	+	+	+	+	+	+	59
Granulosa cell tumor benign											1
Tubulostromal adenoma											1
Periovarian tissue, histiocytic sarcoma											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma								X			2
Polyp stromal											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Lymph node											13
Axillary, histiocytic sarcoma											1
Iliac, histiocytic sarcoma											1
Pancreatic, histiocytic sarcoma											3
Renal, histiocytic sarcoma											1
Lymph node, bronchial	+	+	+	+	+	M	+	+	+	+	56
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											2
Neoplasm NOS, metastatic, lung											1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	55
Carcinoma, metastatic											1
Histiocytic sarcoma											2
Mast cell tumor benign											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma								X			2
Lymph node, mediastinal	M	M	+	M	+	I	M	+	M	M	22
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											1
Spleen	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Thymus	+	+	+	+	+	M	+	+	+	+	56
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											2
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Carcinoma					X						1
Skin	+	+	+	+	+	+	+	+	+	+	60
Subcutaneous tissue, fibrosarcoma											2
Subcutaneous tissue, hemangioma											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m^3 (continued)

Number of Days on Study	2 8 1	3 1 0	3 6 1	3 7 0	3 9 3	4 5 7	4 6 3	5 1 6	5 2 1	5 6 2	5 6 2	5 7 1	5 9 6	6 0 1	6 0 4	6 5 9	6 6 9	6 7 5	6 7 9	6 9 8	7 1 3	7 1 4	7 2 8	7 3 0	7 3 0
Carcass ID Number	5 8 4	6 1 2	5 8 1	6 0 4	5 9 3	5 7 5	6 3 3	6 0 7	6 0 8	5 9 1	6 0 6	6 1 5	6 1 8	5 0 5	6 1 6	6 3 1	5 9 6	6 2 7	5 6 6	6 0 9	5 7 4	5 6 8	5 9 0	5 8 3	5 9 4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung											X														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																			X						
Carcinoma											X														
Fibrosarcoma, metastatic, skin					X																				
Hepatocellular carcinoma, metastatic, liver											X														
Histiocytic sarcoma												X													
Neoplasm NOS									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung											X														
Histiocytic sarcoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X			X	X									
Lymphoma malignant													X										X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m^3 (continued)

Number of Days on Study	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	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	5 9 8	6 2 0	6 2 6	5 8 9	5 9 9	6 1 3	6 1 4	6 3 4	6 3 7	5 6 3	5 6 4	5 7 0	5 7 1	5 7 2	5 7 3	5 8 0	5 8 6	5 8 8	6 2 1	6 2 2	6 3 0	5 6 5	5 8 7	5 9 5	6 0 1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	I	+	I	+	+	+	+	+	+	+	I	+	+	+	I	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma																									
Fibrosarcoma, metastatic, skin																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Neoplasm NOS																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																									
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant						X	X													X			X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate: 1 mg/m³ (continued)

Number of Days on Study	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	
Carcass ID Number	6 2 3	6 3 5	6 3 6	5 6 7	5 7 7	5 7 8	5 9 2	6 0 0	6 1 7	6 2 9	Total Tissues/ Tumors
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Vertebra, osteosarcoma											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Larynx	+	+	+	+	+	+	+	+	+	+	56
Carcinoma, metastatic, lung											1
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar carcinoma											1
Carcinoma											1
Fibrosarcoma, metastatic, skin											1
Hepatocellular carcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Neoplasm NOS											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	59
Special Senses System											
None											
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, lung											1
Histiocytic sarcoma											1
Urinary bladder	+	+	+	+	+	+	+	M	+	+	58
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma								X			4
Lymphoma malignant											6

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Harderian Gland: Adenoma				
Overall rate[a]	0/61 (0%)	2/60 (3%)	4/60 (7%)	0/60 (0%)
Adjusted rate[b]	0.0%	4.6%	8.3%	0.0%
Terminal rate[c]	0/34 (0%)	1/39 (3%)	2/45 (4%)	0/37 (0%)
First incidence (days)	—[e]	635	672	—
Life table test[d]	P=0.547N	P=0.262	P=0.097	—
Logistic regression test[d]	P=0.563N	P=0.236	P=0.068	—
Cochran-Armitage test[d]	P=0.560N			
Fisher exact test[d]		P=0.244	P=0.057	—
Liver: Hepatocellular Adenoma				
Overall rate	13/61 (21%)	14/59 (24%)	11/60 (18%)	9/60 (15%)
Adjusted rate	35.0%	34.7%	23.8%	22.2%
Terminal rate	11/34 (32%)	13/39 (33%)	10/45 (22%)	6/37 (16%)
First incidence (days)	547	635	681	669
Life table test	P=0.110N	P=0.529N	P=0.172N	P=0.193N
Logistic regression test	P=0.161N	P=0.519	P=0.314N	P=0.261N
Cochran-Armitage test	P=0.160N			
Fisher exact test		P=0.461	P=0.428N	P=0.254N
Liver: Hepatocellular Carcinoma				
Overall rate	7/61 (11%)	14/59 (24%)	5/60 (8%)	11/60 (18%)
Adjusted rate	17.4%	27.7%	10.8%	23.6%
Terminal rate	4/34 (12%)	4/39 (10%)	4/45 (9%)	5/37 (14%)
First incidence (days)	530	511	681	516
Life table test	P=0.410	P=0.123	P=0.245N	P=0.251
Logistic regression test	P=0.353	P=0.042	P=0.350N	P=0.188
Cochran-Armitage test	P=0.386			
Fisher exact test		P=0.063	P=0.393N	P=0.211
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	18/61 (30%)	28/59 (47%)	15/60 (25%)	19/60 (32%)
Adjusted rate	45.9%	55.5%	32.5%	41.0%
Terminal rate	14/34 (41%)	17/39 (44%)	14/45 (31%)	11/37 (30%)
First incidence (days)	530	511	681	516
Life table test	P=0.273N	P=0.125	P=0.101N	P=0.567
Logistic regression test	P=0.344N	P=0.039	P=0.245N	P=0.464
Cochran-Armitage test	P=0.333N			
Fisher exact test		P=0.033	P=0.362N	P=0.476
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/61 (5%)	3/60 (5%)	2/60 (3%)	0/60 (0%)
Adjusted rate	8.8%	7.2%	4.4%	0.0%
Terminal rate	3/34 (9%)	1/39 (3%)	2/45 (4%)	0/37 (0%)
First incidence (days)	730 (T)	711	730 (T)	—
Life table test	P=0.059N	P=0.602N	P=0.373N	P=0.106N
Logistic regression test	P=0.067N	P=0.638N	P=0.373N	P=0.106N
Cochran-Armitage test	P=0.074N			
Fisher exact test		P=0.652	P=0.508N	P=0.125N

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/61 (7%)	3/60 (5%)	9/60 (15%)	2/60 (3%)
Adjusted rate	10.7%	7.1%	18.9%	4.3%
Terminal rate	3/34 (9%)	2/39 (5%)	7/45 (16%)	0/37 (0%)
First incidence (days)	627	649	656	562
Life table test	P=0.378N	P=0.444N	P=0.238	P=0.332N
Logistic regression test	P=0.415N	P=0.493N	P=0.149	P=0.346N
Cochran-Armitage test	P=0.410N			
Fisher exact test		P=0.509N	P=0.114	P=0.348N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	7/61 (11%)	6/60 (10%)	10/60 (17%)	2/60 (3%)
Adjusted rate	19.3%	13.9%	21.1%	4.3%
Terminal rate	6/34 (18%)	3/39 (8%)	8/45 (18%)	0/37 (0%)
First incidence (days)	627	649	656	562
Life table test	P=0.089N	P=0.415N	P=0.512	P=0.077N
Logistic regression test	P=0.111N	P=0.481N	P=0.371	P=0.088N
Cochran-Armitage test	P=0.111N			
Fisher exact test		P=0.513N	P=0.288	P=0.086N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	8/59 (14%)	9/56 (16%)	5/59 (8%)	4/57 (7%)
Adjusted rate	20.6%	21.8%	11.1%	9.4%
Terminal rate	4/33 (12%)	7/38 (18%)	5/45 (11%)	1/37 (3%)
First incidence (days)	696	559	730 (T)	601
Life table test	P=0.072N	P=0.589	P=0.144N	P=0.172N
Logistic regression test	P=0.086N	P=0.491	P=0.190N	P=0.186N
Cochran-Armitage test	P=0.096N			
Fisher exact test		P=0.453	P=0.279N	P=0.198N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	5/61 (8%)	0/60 (0%)	1/60 (2%)	2/60 (3%)
Adjusted rate	9.5%	0.0%	1.7%	4.4%
Terminal rate	0/34 (0%)	0/39 (0%)	0/45 (0%)	1/37 (3%)
First incidence (days)	384	—	510	393
Life table test	P=0.239N	P=0.037N	P=0.095N	P=0.233N
Logistic regression test	P=0.276N	P=0.037N	P=0.151N	P=0.239N
Cochran-Armitage test	P=0.237N			
Fisher exact test		P=0.030N	P=0.107N	P=0.226N
Uterus: Stromal Polyp				
Overall rate	2/61 (3%)	3/60 (5%)	0/60 (0%)	1/60 (2%)
Adjusted rate	5.9%	6.5%	0.0%	2.7%
Terminal rate	2/34 (6%)	1/39 (3%)	0/45 (0%)	1/37 (3%)
First incidence (days)	730 (T)	614	—	730 (T)
Life table test	P=0.229N	P=0.545	P=0.179N	P=0.470N
Logistic regression test	P=0.246N	P=0.502	P=0.179N	P=0.470N
Cochran-Armitage test	P=0.246N			
Fisher exact test		P=0.492	P=0.252N	P=0.506N

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
All Organs: Malignant Lymphoma				
Overall rate	7/61 (11%)	12/60 (20%)	9/60 (15%)	6/60 (10%)
Adjusted rate	17.6%	28.4%	18.3%	15.0%
Terminal rate	3/34 (9%)	9/39 (23%)	6/45 (13%)	4/37 (11%)
First incidence (days)	626	687	567	596
Life table test	P=0.258N	P=0.238	P=0.574	P=0.467N
Logistic regression test	P=0.305N	P=0.174	P=0.435	P=0.523N
Cochran-Armitage test	P=0.297N			
Fisher exact test		P=0.149	P=0.381	P=0.513N
All Organs: Histiocytic Sarcoma				
Overall rate	1/61 (2%)	4/60 (7%)	2/60 (3%)	4/60 (7%)
Adjusted rate	2.3%	9.1%	4.0%	8.8%
Terminal rate	0/34 (0%)	2/39 (5%)	1/45 (2%)	1/37 (3%)
First incidence (days)	670	398	577	571
Life table test	P=0.217	P=0.213	P=0.551	P=0.181
Logistic regression test	P=0.212	P=0.172	P=0.474	P=0.089
Cochran-Armitage test	P=0.212			
Fisher exact test		P=0.177	P=0.494	P=0.177
All Organs: Benign Neoplasms				
Overall rate	27/61 (44%)	34/60 (57%)	23/60 (38%)	16/60 (27%)
Adjusted rate	60.9%	70.5%	47.8%	37.7%
Terminal rate	17/34 (50%)	25/39 (64%)	20/45 (44%)	11/37 (30%)
First incidence (days)	547	559	672	601
Life table test	P=0.003N	P=0.333	P=0.056N	P=0.025N
Logistic regression test	P=0.004N	P=0.145	P=0.155N	P=0.032N
Cochran-Armitage test	P=0.005N			
Fisher exact test		P=0.118	P=0.317N	P=0.033N
All Organs: Malignant Neoplasms				
Overall rate	26/61 (43%)	27/60 (45%)	26/60 (43%)	26/60 (43%)
Adjusted rate	53.2%	52.4%	47.7%	50.1%
Terminal rate	12/34 (35%)	15/39 (38%)	17/45 (38%)	12/37 (32%)
First incidence (days)	384	398	510	393
Life table test	P=0.467N	P=0.478N	P=0.252N	P=0.516N
Logistic regression test	P=0.534	P=0.486	P=0.567	P=0.546
Cochran-Armitage test	P=0.535			
Fisher exact test		P=0.468	P=0.542	P=0.542

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

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	41/61 (67%)	45/60 (75%)	41/60 (68%)	36/60 (60%)
Adjusted rate	80.1%	80.4%	73.1%	66.6%
Terminal rate	24/34 (71%)	28/39 (72%)	30/45 (67%)	19/37 (51%)
First incidence (days)	384	398	510	393
Life table test	P=0.129N	P=0.545N	P=0.115N	P=0.223N
Logistic regression test	P=0.128N	P=0.264	P=0.480N	P=0.263N
Cochran-Armitage test	P=0.131N			
Fisher exact test		P=0.229	P=0.525	P=0.263N

(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 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 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 Sulfate Hexahydrate[a]

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Disposition Summary				
Animals initially in study	71	70	70	70
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	20	11	11	17
Natural deaths	7	10	4	6
Survivors				
Died last week of study	1	1		
Terminal sacrifice	33	38	45	37
Animals examined microscopically	71	70	70	70
7-Month Interim Evaluation				
Alimentary System				
Stomach, forestomach				(1)
Diverticulum				1 (100%)
Genital System				
Uterus	(1)	(2)	(1)	(1)
Endometrium, hyperplasia	1 (100%)	1 (50%)	1 (100%)	1 (100%)
Hematopoietic System				
Lymph node, bronchial	(5)	(4)	(4)	(4)
Hyperplasia, lymphoid	2 (40%)	2 (50%)	1 (25%)	3 (75%)
Lymph node, mandibular	(3)	(2)	(1)	(1)
Hyperplasia, lymphoid	3 (100%)	1 (50%)	1 (100%)	
Hyperplasia, plasma cell				1 (100%)
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Hyperplasia, macrophage			1 (20%)	5 (100%)
Inflammation, chronic active				2 (40%)
Interstitium, infiltration cellular				1 (20%)
Nose	(5)	(5)	(5)	(5)
Inflammation, acute	3 (60%)	4 (80%)	1 (20%)	4 (80%)
Olfactory epithelium, respiratory epithelium, degeneration	1 (20%)		1 (20%)	
Systems Examined With No Lesions Observed				
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 D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate (continued)

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
15-Month Interim Evaluation				
Endocrine System				
Parathyroid gland	(4)	(3)	(5)	(3)
Cyst		1 (33%)		
Pituitary gland	(5)	(5)	(5)	(4)
Pars distalis, hyperplasia, focal			1 (20%)	2 (50%)
Thyroid gland	(5)	(5)	(5)	(5)
Cyst	1 (20%)			
Follicular cell, hyperplasia, focal		1 (20%)		
Genital System				
Clitoral gland	(5)	(5)	(5)	(5)
Ectasia				1 (20%)
Inflammation	1 (20%)			
Ovary	(5)	(5)	(5)	(5)
Cyst			1 (20%)	1 (20%)
Periovarian tissue, cyst			1 (20%)	
Uterus	(5)	(5)	(5)	(5)
Endometrium, hyperplasia	4 (80%)	5 (100%)	4 (80%)	4 (80%)
Hematopoietic System				
Lymph node, bronchial	(2)	(5)	(5)	(4)
Hyperplasia, lymphoid		1 (20%)	2 (40%)	4 (100%)
Hyperplasia, macrophage				4 (100%)
Lymph node, mandibular	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid	3 (60%)	1 (20%)	1 (20%)	1 (20%)
Spleen	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid			1 (20%)	
Thymus	(5)	(3)	(5)	(5)
Cyst	1 (20%)		1 (20%)	
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Subcutaneous tissue, inflammation		1 (20%)		
Respiratory System				
Larynx	(4)	(4)	(2)	(4)
Inflammation		1 (25%)		
Lung	(5)	(5)	(5)	(5)
Hyperplasia, macrophage		1 (20%)	2 (40%)	5 (100%)
Inflammation, chronic active				5 (100%)
Bronchialization			1 (20%)	5 (100%)
Alveolar epithelial hyperplasia, focal		1 (20%)		
Alveolus, proteinosis				5 (100%)
Interstitium, infiltration cellular	1 (20%)			5 (100%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
15-Month Interim Evaluation (continued)				
Respiratory System (continued)				
Nose	(5)	(5)	(5)	(5)
Inflammation, acute	1 (20%)			1 (20%)
Olfactory epithelium, atrophy				1 (20%)
Olfactory epithelium, degeneration	1 (20%)		1 (20%)	
Respiratory epithelium, degeneration	1 (20%)	2 (40%)	2 (40%)	2 (40%)
Vomeronasal organ, infiltration cellular, polymorphonuclear	1 (20%)			
Systems Examined With No Lesions Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(60)	(55)	(57)	(54)
Concretion		1 (2%)		
Dilatation	1 (2%)			
Intestine large, rectum	(57)	(57)	(55)	(47)
Autolysis		1 (2%)		
Intestine large, cecum	(61)	(57)	(60)	(59)
Autolysis		1 (2%)		
Intestine small, duodenum	(58)	(57)	(59)	(58)
Autolysis		1 (2%)		
Inflammation			1 (2%)	
Intussusception	1 (2%)			
Intestine small, jejunum	(61)	(58)	(59)	(59)
Autolysis		1 (2%)		
Peyer's patch, hyperplasia, lymphoid		1 (2%)	1 (2%)	
Intestine small, ileum	(61)	(58)	(58)	(59)
Autolysis		1 (2%)		
Liver	(61)	(59)	(60)	(60)
Autolysis		1 (2%)		
Basophilic focus	2 (3%)		2 (3%)	
Congestion	1 (2%)			
Eosinophilic focus				1 (2%)
Fatty change	1 (2%)			
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule		1 (2%)		
Infarct	2 (3%)		1 (2%)	1 (2%)
Inflammation	1 (2%)	1 (2%)		
Necrosis	2 (3%)	1 (2%)	2 (3%)	2 (3%)
Necrosis, diffuse	4 (7%)	4 (7%)	1 (2%)	6 (10%)
Bile duct, degeneration				1 (2%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(7)	(4)	(4)	(5)
Infiltration cellular, lymphocyte				1 (20%)
Inflammation	1 (14%)	1 (25%)		1 (20%)
Inflammation, chronic			1 (25%)	
Necrosis				1 (20%)
Pancreas	(60)	(58)	(60)	(60)
Amyloid deposition		1 (2%)		
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation			1 (2%)	1 (2%)
Acinus, hyperplasia, focal	1 (2%)			
Duct, cyst, multiple			1 (2%)	
Duct, ectasia				1 (2%)
Salivary glands	(61)	(59)	(60)	(60)
Angiectasis	1 (2%)			
Stomach, forestomach	(61)	(58)	(60)	(60)
Hyperplasia, squamous		1 (2%)	2 (3%)	
Inflammation	1 (2%)	2 (3%)		
Stomach, glandular	(60)	(58)	(59)	(59)
Hyperplasia			1 (2%)	
Tooth		(2)	(1)	(1)
Peridontal tissue, inflammation		2 (100%)	1 (100%)	1 (100%)
Cardiovascular System				
Heart	(61)	(59)	(60)	(60)
Cardiomyopathy	1 (2%)			
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation		1 (2%)	2 (3%)	1 (2%)
Endocrine System				
Adrenal cortex	(60)	(58)	(60)	(60)
Cyst	1 (2%)			1 (2%)
Hyperplasia				1 (2%)
Hypertrophy				1 (2%)
Capsule, hyperplasia		1 (2%)		
Extra adrenal tissue, inflammation	1 (2%)			1 (2%)
Adrenal medulla	(60)	(57)	(60)	(60)
Hyperplasia				1 (2%)
Mineralization	1 (2%)			
Parathyroid gland	(40)	(44)	(50)	(49)
Cyst			1 (2%)	
Hyperplasia				1 (2%)
Bilateral, hyperplasia	1 (3%)			
Pituitary gland	(59)	(56)	(59)	(57)
Angiectasis	1 (2%)		1 (2%)	
Congestion				1 (2%)
Cyst			1 (2%)	
Pars distalis, angiectasis	3 (5%)	2 (4%)	8 (14%)	1 (2%)
Pars distalis, hyperplasia	12 (20%)	8 (14%)	15 (25%)	11 (19%)
Thyroid gland	(60)	(59)	(60)	(60)
Inflammation				2 (3%)
Follicular cell, hyperplasia, cystic	22 (37%)	20 (34%)	27 (45%)	27 (45%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
General Body System				
Tissue NOS	(5)	(8)	(4)	(3)
Thrombosis	1 (20%)			
Abdominal, cyst			1 (25%)	
Abdominal, inflammation		1 (13%)		1 (33%)
Mediastinum, infiltration cellular, lymphocyte		1 (13%)		
Mediastinum, inflammation	1 (20%)	1 (13%)		
Genital System				
Clitoral gland	(58)	(56)	(52)	(58)
Atrophy			1 (2%)	
Ectasia	4 (7%)	4 (7%)	5 (10%)	2 (3%)
Hyperplasia, squamous		1 (2%)		
Inflammation	2 (3%)	4 (7%)	3 (6%)	1 (2%)
Pigmentation	3 (5%)		2 (4%)	
Ovary	(59)	(58)	(60)	(59)
Angiectasis				1 (2%)
Atrophy	1 (2%)			1 (2%)
Cyst	6 (10%)	8 (14%)	17 (28%)	8 (14%)
Hemorrhage		1 (2%)		2 (3%)
Inflammation	1 (2%)			1 (2%)
Pigmentation, hemosiderin				1 (2%)
Bilateral, cyst		1 (2%)	1 (2%)	
Uterus	(61)	(60)	(60)	(60)
Congestion	1 (2%)			
Dilatation			1 (2%)	
Hemorrhage	1 (2%)			1 (2%)
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation		1 (2%)		1 (2%)
Prolapse				1 (2%)
Thrombosis		1 (2%)		
Endometrium, hyperplasia	30 (49%)	25 (42%)	39 (65%)	41 (68%)
Hematopoietic System				
Bone marrow	(61)	(59)	(60)	(60)
Hyperplasia, histiocytic	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, megakaryocyte	1 (2%)			
Hyperplasia, plasma cell	1 (2%)			
Myelofibrosis	39 (64%)	43 (73%)	52 (87%)	41 (68%)
Erythroid cell, hyperplasia	1 (2%)			
Myeloid cell, hyperplasia	6 (10%)	4 (7%)	2 (3%)	3 (5%)
Lymph node	(11)	(11)	(13)	(13)
Iliac, hyperplasia, lymphoid	1 (9%)	3 (27%)	1 (8%)	1 (8%)
Iliac, hyperplasia, plasma cell	1 (9%)			2 (15%)
Inguinal, hyperplasia, histiocytic				1 (8%)
Inguinal, hyperplasia, lymphoid	2 (18%)		2 (15%)	1 (8%)
Inguinal, pigmentation				1 (8%)
Pancreatic, hematopoietic cell proliferation				1 (8%)
Pancreatic, hyperplasia, lymphoid		1 (9%)	1 (8%)	
Pancreatic, inflammation	1 (9%)			1 (8%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node (continued)	(11)	(11)	(13)	(13)
Renal, fibrosis				1 (8%)
Renal, hyperplasia, histiocytic				1 (8%)
Renal, hyperplasia, lymphoid	1 (9%)	2 (18%)		2 (15%)
Renal, hyperplasia, plasma cell	1 (9%)			
Lymph node, bronchial	(50)	(54)	(58)	(56)
Amyloid deposition		1 (2%)		
Congestion	1 (2%)	1 (2%)		
Edema	1 (2%)			
Hemorrhage				1 (2%)
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid	15 (30%)	9 (17%)	16 (28%)	26 (46%)
Hyperplasia, macrophage	2 (4%)		14 (24%)	37 (66%)
Hyperplasia, plasma cell	2 (4%)			
Inflammation	1 (2%)			
Lymph node, mandibular	(56)	(56)	(60)	(55)
Congestion	1 (2%)			
Cyst	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, histiocytic		2 (4%)		1 (2%)
Hyperplasia, lymphoid	15 (27%)	6 (11%)	5 (8%)	5 (9%)
Hyperplasia, mast cell			1 (2%)	
Hyperplasia, plasma cell	5 (9%)	5 (9%)	5 (8%)	4 (7%)
Inflammation				1 (2%)
Lymph node, mesenteric	(57)	(52)	(56)	(51)
Congestion	4 (7%)	3 (6%)	1 (2%)	
Edema	1 (2%)			
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage				1 (2%)
Hyperplasia, histiocytic		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)	4 (7%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)			
Inflammation	1 (2%)			2 (4%)
Lymph node, mediastinal	(30)	(28)	(33)	(22)
Hyperplasia, histiocytic			2 (6%)	
Hyperplasia, lymphoid	3 (10%)		1 (3%)	3 (14%)
Hyperplasia, plasma cell		1 (4%)		
Inflammation	1 (3%)	1 (4%)		
Spleen	(61)	(58)	(60)	(60)
Angiectasis			1 (2%)	
Congestion	3 (5%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	11 (18%)	9 (16%)	8 (13%)	9 (15%)
Hyperplasia, lymphoid	10 (16%)	4 (7%)	9 (15%)	10 (17%)
Hyperplasia, plasma cell				1 (2%)
Necrosis	1 (2%)			
Thymus	(58)	(54)	(54)	(56)
Atrophy	15 (26%)	11 (20%)	8 (15%)	12 (21%)
Autolysis				1 (2%)
Hyperplasia, lymphoid				1 (2%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Integumentary System				
Mammary gland	(61)	(58)	(60)	(60)
Ectasia	1 (2%)	2 (3%)		
Hyperplasia		1 (2%)		1 (2%)
Skin	(61)	(59)	(59)	(60)
Inflammation	2 (3%)	1 (2%)	1 (2%)	3 (5%)
Ulcer	1 (2%)			
Dermis, fibrosis		1 (2%)	1 (2%)	
Dermis, inflammation, granulomatous			1 (2%)	
Hindlimb, hemorrhage	1 (2%)			
Neck, inflammation			1 (2%)	
Pinna, inflammation	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, edema	1 (2%)			1 (2%)
Tail, inflammation	1 (2%)			
Musculoskeletal System				
Bone	(61)	(60)	(60)	(60)
Femur, hyperostosis	1 (2%)	1 (2%)		
Fibula, fracture			1 (2%)	
Periosteum, femur, inflammation	1 (2%)			
Tibia, fracture	1 (2%)			
Skeletal muscle	(4)	(3)	(3)	
Inflammation	1 (25%)	1 (33%)		
Nervous System				
Brain	(61)	(59)	(59)	(60)
Compression	2 (3%)	5 (8%)	3 (5%)	2 (3%)
Cerebrum, degeneration			3 (5%)	
Meninges, inflammation	1 (2%)			
Pons, degeneration		1 (2%)		
Respiratory System				
Larynx	(58)	(56)	(58)	(56)
Degeneration				1 (2%)
Hyperplasia			2 (3%)	1 (2%)
Inflammation	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Lung	(61)	(60)	(60)	(60)
Congestion	1 (2%)		1 (2%)	1 (2%)
Emphysema		1 (2%)		
Hemorrhage	4 (7%)	1 (2%)	3 (5%)	
Hyperplasia, macrophage	7 (11%)	24 (40%)	53 (88%)	59 (98%)
Inflammation		1 (2%)		
Inflammation, chronic active	1 (2%)	7 (12%)	14 (23%)	40 (67%)
Mineralization		1 (2%)		
Bronchialization		9 (15%)	32 (53%)	45 (75%)
Alveolar epithelial hyperplasia, focal		1 (2%)	1 (2%)	
Alveolar epithelium, metaplasia, squamous				1 (2%)
Alveolus, proteinosis			11 (18%)	45 (75%)

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

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
2-Year Study (continued)				
Respiratory System (continued)				
Lung (continued)	(61)	(60)	(60)	(60)
Bronchiole, degeneration				2 (3%)
Interstitium, infiltration cellular		4 (7%)	16 (27%)	39 (65%)
Pleura, inflammation	1 (2%)			
Nose	(61)	(59)	(60)	(60)
Hemorrhage	1 (2%)			
Olfactory epithelium, atrophy	3 (5%)	2 (3%)	1 (2%)	17 (28%)
Olfactory epithelium, degeneration	12 (20%)	8 (14%)	1 (2%)	8 (13%)
Olfactory epithelium, inflammation		1 (2%)		2 (3%)
Respiratory epithelium, degeneration	11 (18%)	14 (24%)	4 (7%)	7 (12%)
Respiratory epithelium, inflammation	5 (8%)	7 (12%)	11 (18%)	11 (18%)
Respiratory epithelium, metaplasia, squamous	1 (2%)		3 (5%)	2 (3%)
Squamous epithelium, hyperplasia				1 (2%)
Squamous epithelium, inflammation			1 (2%)	1 (2%)
Trachea	(61)	(60)	(60)	(59)
Degeneration				1 (2%)
Special Senses System				
Ear		(1)	(2)	
Hemorrhage		1 (100%)		
External ear, inflammation			2 (100%)	
Lacrimal gland			(1)	
Extraorbital, hyperplasia, plasma cell			1 (100%)	
Urinary System				
Kidney	(61)	(60)	(60)	(60)
Fibrosis				1 (2%)
Inflammation		1 (2%)	1 (2%)	
Metaplasia, osseous	1 (2%)		1 (2%)	
Mineralization		2 (3%)		
Nephropathy	3 (5%)	1 (2%)	1 (2%)	3 (5%)
Glomerulus, inflammation		1 (2%)		
Medulla, cyst	1 (2%)			
Pelvis, dilatation				2 (3%)
Perirenal tissue, inflammation	1 (2%)			1 (2%)
Renal tubule, necrosis, acute		1 (2%)		
Urinary bladder	(59)	(60)	(58)	(58)
Angiectasis	1 (2%)			
Autolysis		1 (2%)		
Calculus, microscopic observation only		1 (2%)		
Hemorrhage		1 (2%)		
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation	1 (2%)			
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1988). Nickel sulfate hexahydrate was supplied as a coded aliquot by Radian Corporation (Austin, TX). The high dose was determined by toxicity. L5178Y mouse lymphoma $TK^{+/-}$ cells were maintained at 37° C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT)-resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for 1 day, to THG for 1 day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added. All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated.

Treated cultures contained 6×10^6 cells in 10 mL of medium. Incubation with nickel sulfate hexahydrate continued for 4 hours at which time the medium plus nickel sulfate hexahydrate was removed, and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of TFT-resistant cells ($TK^{-/-}$), and in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. This assay is initially performed without S9; because a clearly positive response was obtained, the experiment was not performed with S9.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary *et al.* (1988). All data were evaluated statistically for both trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for nickel sulfate hexahydrate to be considered capable of inducing TFT-resistance; a single significant response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

RESULTS

Nickel sulfate hexahydrate (effective dose range, 500-800 μg/mL) was positive in the mouse lymphoma mutation assay in L5178Y cells without S9 activation (Table E1); the test was not performed with S9.

TABLE E1
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Nickel Sulfate Hexahydrate[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Medium		70	117	94	45	
		59	76	112	63	
		51	107	117	76	61
Methyl methanesulfonate		45	50	312	234	
	15	30	47	266	297	265*
Nickel sulfate hexahydrate	300	89	148	120	45	
	400[d]	75	132	117	52	
		81	118	120	49	51
	500	71	105	178	83	
		72	90	131	61	72
	600	65	19	235	120	
		76	33	180	79	99*
	700	47	8	274	194	
		45	6	312	233	241*
	800	lethal				
		lethal				

TABLE E1
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Nickel Sulfate Hexahydrate (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9 (continued)						
Trial 2						
Medium		110	101	168	51	
		94	98	154	55	
		111	103	129	39	
		87	98	145	56	50
Methyl methanesulfonate		55	30	317	193	
	15	61	32	227	125	159*
Nickel sulfate hexahydrate	400[d]	95	40	190	67	
		71	37	165	78	72
	500	61	25	205	112	
		86	39	173	67	90*
	600	65	16	279	143	
		47	12	262	187	165*
	700	30	5	365	408	
		73	8	362	166	287*
	800	43	5	293	226	
		51	5	292	192	209*
	900	lethal				
		lethal				

* Significant positive response ($P \leq 0.05$)
[a] Study performed at Inveresk Research International. The experimental protocol and these data are presented in McGregor *et al.* (1988).
[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/1 $\times 10^6$ cells treated); MF = mutant fraction.
[c] Mean standard of error from three replicate plates of approximately 1/3 (3×10^6) cells each
[d] Acidic pH shift at 400 μg/mL

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 Sulfate Hexahydrate[a]

	0 mg/m³	3.5 mg/m³	7 mg/m³	15 mg/m³	30 mg/m³	60 mg/m³
n	5	5	5	5	5	5
Male						
Necropsy body wt	225 ± 5	162 ± 8**	136 ± 2**	127 ± 2**	123 ± 9**	112 ± 7**
Brain						
Absolute	1.764 ± 0.025	1.690 ± 0.022*	1.654 ± 0.020**	1.640 ± 0.025**	1.654 ± 0.009**	1.652 ± 0.027**
Relative	7.85 ± 0.23	10.54 ± 0.46**	12.15 ± 0.12**	12.93 ± 0.23**	13.73 ± 0.93**	14.98 ± 0.93**
Heart						
Absolute	0.718 ± 0.019	0.646 ± 0.017	0.632 ± 0.009	0.618 ± 0.019	0.626 ± 0.046	0.630 ± 0.038
Relative	3.19 ± 0.06	4.02 ± 0.14*	4.64 ± 0.06**	4.87 ± 0.13**	5.14 ± 0.37**	5.71 ± 0.50**
R. Kidney						
Absolute	0.840 ± 0.023	0.688 ± 0.033**	0.611 ± 0.012**	0.613 ± 0.007**	0.566 ± 0.017**	0.612 ± 0.068**
Relative	3.73 ± 0.05	4.26 ± 0.04	4.49 ± 0.05*	4.84 ± 0.07**	4.70 ± 0.36**	5.41 ± 0.29**
Liver						
Absolute	9.200 ± 0.302	7.080 ± 0.340**	6.000 ± 0.202**	5.280 ± 0.341**	4.580 ± 0.287**	4.600 ± 0.356**
Relative	40.83 ± 0.53	43.84 ± 1.07	44.04 ± 1.09	41.71 ± 2.97	37.71 ± 2.38	41.09 ± 1.70
Lung						
Absolute	0.980 ± 0.020	1.440 ± 0.087**	1.450 ± 0.029**	1.400 ± 0.032*	1.400 ± 0.071*	1.620 ± 0.269**
Relative	4.36 ± 0.07	8.90 ± 0.28**	10.63 ± 0.36**	11.03 ± 0.25**	11.57 ± 0.83**	14.12 ± 1.35**
R. Testis						
Absolute	1.294 ± 0.018	1.090 ± 0.046	0.796 ± 0.081**	0.818 ± 0.105**	0.462 ± 0.029**	0.618 ± 0.128**
Relative	5.76 ± 0.19	6.82 ± 0.46	5.87 ± 0.65	6.43 ± 0.77	3.81 ± 0.26	5.36 ± 0.84
Thymus						
Absolute	0.348 ± 0.025	0.170 ± 0.027**	0.093 ± 0.016**	0.106 ± 0.012**	0.064 ± 0.015**	0.053 ± 0.023**
Relative	1.55 ± 0.12	1.03 ± 0.13**	0.69 ± 0.12**	0.84 ± 0.10**	0.52 ± 0.12**	0.43 ± 0.17**
Female						
Necropsy body wt	147 ± 4	120 ± 7**	105 ± 2**	100 ± 5**	93 ± 3**	90 ± 6**[b]
Brain						
Absolute	1.674 ± 0.011	1.590 ± 0.025**	1.606 ± 0.010*	1.606 ± 0.011*	1.564 ± 0.025**	1.594 ± 0.015*
Relative	11.42 ± 0.28	13.36 ± 0.61	15.36 ± 0.31**	16.19 ± 0.76**	16.84 ± 0.50**	18.19 ± 1.45**
Heart						
Absolute	0.534 ± 0.021	0.542 ± 0.024	0.524 ± 0.014	0.516 ± 0.035	0.478 ± 0.032	0.482 ± 0.032
Relative	3.64 ± 0.16	4.54 ± 0.19**	5.02 ± 0.19**	5.15 ± 0.22**	5.11 ± 0.21**	5.42 ± 0.28**
R. Kidney						
Absolute	0.583 ± 0.019	0.519 ± 0.017	0.535 ± 0.021	0.527 ± 0.021	0.525 ± 0.042	0.548 ± 0.034
Relative	3.97 ± 0.14	4.35 ± 0.14	5.12 ± 0.26**	5.28 ± 0.08**	5.64 ± 0.42**	6.16 ± 0.27**
Liver						
Absolute	5.220 ± 0.211	4.580 ± 0.260	3.900 ± 0.152**	3.760 ± 0.150**	4.160 ± 0.301**	3.280 ± 0.312**
Relative	35.50 ± 0.94	38.14 ± 0.68	37.28 ± 1.54	37.70 ± 1.28	44.49 ± 2.15**	36.58 ± 2.23
Lung						
Absolute	0.760 ± 0.051	1.280 ± 0.086*	1.280 ± 0.058*	1.320 ± 0.080*	1.400 ± 0.279**	1.520 ± 0.166**
Relative	5.19 ± 0.39	10.66 ± 0.43*	12.24 ± 0.63**	13.18 ± 0.47**	14.99 ± 2.90**	17.46 ± 2.47**
Thymus						
Absolute	0.270 ± 0.014	0.196 ± 0.022**	0.119 ± 0.015**	0.101 ± 0.022**	0.051 ± 0.012**	0.061 ± 0.016**
Relative	1.83 ± 0.08	1.62 ± 0.12	1.14 ± 0.14**	0.98 ± 0.18**	0.54 ± 0.12**	0.65 ± 0.17**

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Male						
n	10	10	10	10	10	9
Necropsy body wt	327 ± 5	328 ± 4	334 ± 5	311 ± 5	324 ± 5	310 ± 8
Brain						
Absolute	1.889 ± 0.013	1.888 ± 0.017	1.907 ± 0.019	1.860 ± 0.021	1.916 ± 0.010	1.870 ± 0.024
Relative	5.78 ± 0.07	5.76 ± 0.06	5.71 ± 0.08	6.00 ± 0.07	5.93 ± 0.09	6.06 ± 0.13*
Heart						
Absolute	0.966 ± 0.035	0.930 ± 0.018	0.958 ± 0.026	0.968 ± 0.046	0.960 ± 0.019	0.912 ± 0.028
Relative	2.95 ± 0.09	2.83 ± 0.05	2.87 ± 0.09	3.11 ± 0.13	2.97 ± 0.06	2.96 ± 0.10
R. Kidney						
Absolute	1.108 ± 0.030	1.062 ± 0.026	1.120 ± 0.022	1.079 ± 0.035	1.082 ± 0.018	1.063 ± 0.041
Relative	3.38 ± 0.06	3.24 ± 0.07	3.35 ± 0.04	3.48 ± 0.10	3.35 ± 0.04	3.44 ± 0.14
Liver						
Absolute	11.480 ± 0.241	11.830 ± 0.235	11.690 ± 0.316	10.890 ± 0.294	11.090 ± 0.164	10.644 ± 0.244*
Relative	35.09 ± 0.63	36.04 ± 0.58	34.94 ± 0.66	35.06 ± 0.77	34.30 ± 0.42	34.43 ± 0.55
Lung						
Absolute	1.350 ± 0.043	1.254 ± 0.026	1.509 ± 0.054*	1.641 ± 0.047**	2.137 ± 0.037**	2.217 ± 0.051**
Relative	4.13 ± 0.14	3.82 ± 0.06	4.53 ± 0.19	5.28 ± 0.13**	6.61 ± 0.13**	7.20 ± 0.24**
R. Testis						
Absolute	1.402 ± 0.033	1.376 ± 0.012	1.375 ± 0.052	1.376 ± 0.031	1.443 ± 0.042	1.352 ± 0.035
Relative	4.30 ± 0.14	4.20 ± 0.06	4.11 ± 0.13	4.43 ± 0.07	4.46 ± 0.11	4.38 ± 0.11
Thymus						
Absolute	0.268 ± 0.011	0.248 ± 0.009	0.261 ± 0.014	0.265 ± 0.009	0.273 ± 0.015	0.254 ± 0.017
Relative	0.82 ± 0.03	0.76 ± 0.03	0.78 ± 0.04	0.86 ± 0.03	0.84 ± 0.04	0.83 ± 0.06

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate (continued)

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Female						
n	10	10	10	10	10	10
Necropsy body wt	198 ± 5	195 ± 5	193 ± 4	189 ± 3	193 ± 3	184 ± 4
Brain						
Absolute	1.778 ± 0.016	1.777 ± 0.021	1.763 ± 0.014	1.748 ± 0.015	1.758 ± 0.025	1.738 ± 0.024
Relative	9.03 ± 0.23	9.13 ± 0.15	9.18 ± 0.19	9.25 ± 0.19	9.11 ± 0.16	9.48 ± 0.24
Heart						
Absolute	0.661 ± 0.013	0.673 ± 0.026	0.675 ± 0.015	0.703 ± 0.030	0.669 ± 0.019	0.653 ± 0.016
Relative	3.35 ± 0.06	3.44 ± 0.09	3.51 ± 0.08	3.72 ± 0.16	3.47 ± 0.13	3.55 ± 0.06
R. Kidney						
Absolute	0.713 ± 0.015[b]	0.704 ± 0.026	0.740 ± 0.023[b]	0.697 ± 0.019	0.698 ± 0.013	0.678 ± 0.015
Relative	3.64 ± 0.08[b]	3.60 ± 0.08	3.84 ± 0.12[b]	3.68 ± 0.09	3.62 ± 0.07	3.69 ± 0.08
Liver						
Absolute	7.180 ± 0.149	6.960 ± 0.357	6.850 ± 0.231	6.400 ± 0.193	6.600 ± 0.183	6.270 ± 0.227**
Relative	36.34 ± 0.61	35.46 ± 1.05	35.47 ± 0.63	33.78 ± 0.80	34.15 ± 0.85	33.99 ± 0.73
Lung						
Absolute	1.022 ± 0.021	1.017 ± 0.033	1.162 ± 0.016**	1.335 ± 0.051**	1.715 ± 0.040**	1.722 ± 0.044**[b]
Relative	5.18 ± 0.11	5.20 ± 0.09	6.05 ± 0.17**	7.06 ± 0.29**	8.87 ± 0.14**	9.33 ± 0.15**[b]
Thymus						
Absolute	0.244 ± 0.010	0.227 ± 0.007	0.223 ± 0.007	0.219 ± 0.011	0.245 ± 0.013	0.249 ± 0.017[b]
Relative	1.23 ± 0.04	1.16 ± 0.02	1.16 ± 0.03	1.16 ± 0.05	1.26 ± 0.06	1.34 ± 0.08[b]

* 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 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 Sulfate Hexahydrate[a]

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
n	5	5	5	5
Male				
Necropsy body wt	427 ± 9	390 ± 7	379 ± 25	395 ± 7
Brain				
Absolute	2.040 ± 0.015	1.950 ± 0.043	2.090 ± 0.107	2.000 ± 0.031
Relative	4.79 ± 0.12	5.01 ± 0.13	5.67 ± 0.64	5.06 ± 0.03
R. Kidney				
Absolute	1.498 ± 0.040	1.344 ± 0.055	1.360 ± 0.098	1.368 ± 0.034
Relative	3.52 ± 0.15	3.44 ± 0.09	3.59 ± 0.09	3.46 ± 0.08
Liver				
Absolute	17.034 ± 0.607	15.032 ± 0.449	13.794 ± 1.611	14.742 ± 0.559
Relative	39.88 ± 1.12	38.55 ± 0.71	35.94 ± 2.34	37.32 ± 1.33
Lung				
Absolute	1.674 ± 0.037	1.622 ± 0.080	1.650 ± 0.076	1.886 ± 0.056
Relative	3.93 ± 0.15	4.16 ± 0.18	4.39 ± 0.13*	4.77 ± 0.08**
Spleen				
Absolute	0.792 ± 0.012	0.740 ± 0.028	0.712 ± 0.043	0.772 ± 0.019
Relative	1.86 ± 0.03	1.90 ± 0.04	1.88 ± 0.02	1.96 ± 0.05
R. Testis				
Absolute	1.484 ± 0.150	1.470 ± 0.032	1.534 ± 0.038	1.534 ± 0.019
Relative	3.51 ± 0.40	3.78 ± 0.12	4.11 ± 0.26	3.89 ± 0.10
Thymus				
Absolute	0.309 ± 0.035	0.285 ± 0.016	0.208 ± 0.027*	0.260 ± 0.021
Relative	0.72 ± 0.07	0.73 ± 0.05	0.54 ± 0.04	0.66 ± 0.04
Female				
Necropsy body wt	245 ± 6	230 ± 13	236 ± 8	233 ± 5
Brain				
Absolute	1.856 ± 0.045	1.790 ± 0.024	1.834 ± 0.042	1.804 ± 0.021
Relative	7.60 ± 0.23	7.87 ± 0.39	7.82 ± 0.29	7.75 ± 0.18
R. Kidney				
Absolute	0.960 ± 0.050	0.910 ± 0.019	0.938 ± 0.061	0.896 ± 0.036
Relative	3.92 ± 0.16	3.99 ± 0.14	3.98 ± 0.18	3.84 ± 0.14
Liver				
Absolute	9.582 ± 0.493	8.836 ± 0.428	8.860 ± 0.404	9.094 ± 0.410
Relative	39.08 ± 1.33	38.54 ± 1.06	37.57 ± 0.89	39.05 ± 1.83
Lung				
Absolute	1.250 ± 0.041	1.220 ± 0.041	1.218 ± 0.071	1.454 ± 0.047*
Relative	5.10 ± 0.05	5.35 ± 0.26	5.17 ± 0.22	6.24 ± 0.20**
Spleen				
Absolute	0.560 ± 0.020	0.512 ± 0.021	0.540 ± 0.023	0.542 ± 0.011
Relative	2.29 ± 0.04	2.24 ± 0.07	2.30 ± 0.11	2.33 ± 0.05
Thymus				
Absolute	0.260 ± 0.019	0.208 ± 0.015	0.237 ± 0.016	0.203 ± 0.015
Relative	1.06 ± 0.08	0.91 ± 0.05	1.01 ± 0.06	0.87 ± 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 Sulfate Hexahdyrate[a]

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
n	5	5	5	5
Male				
Necropsy body wt	485 ± 7	486 ± 14	472 ± 10	469 ± 8
Brain				
Absolute	2.064 ± 0.014	2.074 ± 0.020	2.074 ± 0.048	2.056 ± 0.007
Relative	4.26 ± 0.08	4.28 ± 0.12	4.41 ± 0.16	4.39 ± 0.08
R. Kidney				
Absolute	1.582 ± 0.041	1.594 ± 0.056	1.608 ± 0.046	1.610 ± 0.055
Relative	3.26 ± 0.06	3.29 ± 0.13	3.42 ± 0.14	3.44 ± 0.16
Liver				
Absolute	17.788 ± 0.504	17.384 ± 0.827	17.370 ± 0.278	17.614 ± 0.697
Relative	36.69 ± 0.61	35.75 ± 1.20	36.87 ± 0.58	37.55 ± 1.29
Lung				
Absolute	2.118 ± 0.100	2.482 ± 0.102	2.504 ± 0.107	2.996 ± 0.264**
Relative	4.38 ± 0.26	5.12 ± 0.25	5.32 ± 0.27	6.39 ± 0.55**
Spleen				
Absolute	1.050 ± 0.033	0.980 ± 0.034	1.142 ± 0.174	0.994 ± 0.061
Relative	2.17 ± 0.07	2.02 ± 0.05	2.44 ± 0.39	2.12 ± 0.12
Thymus				
Absolute	0.289 ± 0.032	0.291 ± 0.032	0.294 ± 0.034	0.287 ± 0.025
Relative	0.60 ± 0.06	0.59 ± 0.05	0.62 ± 0.06	0.61 ± 0.06
Female				
Necropsy body wt	287 ± 16	290 ± 5	284 ± 6	287 ± 6
Brain				
Absolute	1.848 ± 0.028	1.896 ± 0.017	1.852 ± 0.014	1.894 ± 0.050
Relative	6.53 ± 0.36	6.54 ± 0.12	6.53 ± 0.14	6.60 ± 0.12
R. Kidney				
Absolute	0.944 ± 0.038	1.012 ± 0.056	0.952 ± 0.022	1.054 ± 0.064
Relative	3.33 ± 0.21	3.48 ± 0.16	3.36 ± 0.10	3.67 ± 0.16
Liver				
Absolute	9.282 ± 0.482	9.288 ± 0.445	8.998 ± 0.366	9.196 ± 0.275
Relative	32.51 ± 1.32	31.98 ± 1.24	31.62 ± 0.60	32.07 ± 0.82
Lung				
Absolute	1.372 ± 0.068	1.576 ± 0.128	1.492 ± 0.042	1.818 ± 0.075**
Relative	4.81 ± 0.22	5.41 ± 0.36	5.27 ± 0.20	6.36 ± 0.36**
Spleen				
Absolute	0.562 ± 0.038	0.920 ± 0.433	0.830 ± 0.314	0.544 ± 0.038
Relative	2.00 ± 0.22	3.10 ± 1.40	2.95 ± 1.15	1.90 ± 0.14
Thymus				
Absolute	0.244 ± 0.046	0.208 ± 0.018	0.231 ± 0.025	0.229 ± 0.017
Relative	0.83 ± 0.13	0.72 ± 0.07	0.81 ± 0.08	0.80 ± 0.07

** 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).

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

	0 mg/m³	3.5 mg/m³	7 mg/m³	15 mg/m³	30 mg/m³	60 mg/m³
n	5	5	5	5	5	5
Male						
Necropsy body wt	24.0 ± 0.4	22.9 ± 0.2	17.5 ± 0.4**[b]	17.1 ± 0.4**[b]	17.0 ± 0.5**[b]	16.5 ± 0.4**[b]
Brain						
Absolute	0.440 ± 0.003	0.424 ± 0.004	0.430 ± 0.016	0.416 ± 0.012	0.430 ± 0.013	0.396 ± 0.014
Relative	18.37 ± 0.36	18.52 ± 0.28	24.60 ± 0.91**	24.48 ± 1.13**	25.43 ± 1.34**	24.11 ± 1.01**
Heart						
Absolute	0.114 ± 0.005	0.120 ± 0.003	0.136 ± 0.007	0.134 ± 0.013	0.136 ± 0.009	0.136 ± 0.010
Relative	4.76 ± 0.22	5.24 ± 0.14	7.79 ± 0.44**	7.89 ± 0.84**	8.06 ± 0.67**	8.30 ± 0.69**
R. Kidney						
Absolute	0.210 ± 0.005	0.195 ± 0.010	0.163 ± 0.005**	0.161 ± 0.008**	0.161 ± 0.009**	0.150 ± 0.004**
Relative	8.77 ± 0.28	8.52 ± 0.47	9.30 ± 0.15	9.41 ± 0.25	9.44 ± 0.38	9.12 ± 0.11
Liver						
Absolute	1.300 ± 0.032	1.360 ± 0.051	1.080 ± 0.066*	1.040 ± 0.024**	0.980 ± 0.102**	1.040 ± 0.051**
Relative	54.22 ± 1.10	59.41 ± 2.27	61.55 ± 2.66	61.02 ± 1.20	57.31 ± 5.03	63.16 ± 2.38
Lung						
Absolute	0.200 ± 0.000	0.240 ± 0.024	0.400 ± 0.000**	0.360 ± 0.024**	0.360 ± 0.040**	0.380 ± 0.020**
Relative	8.35 ± 0.14	10.48 ± 1.06	22.91 ± 0.55**	21.10 ± 1.36**	21.10 ± 2.22**	23.20 ± 1.53**
R. Testis						
Absolute	0.100 ± 0.000	0.094 ± 0.002	0.082 ± 0.004**	0.078 ± 0.004**	0.078 ± 0.002**	0.080 ± 0.003**
Relative	4.18 ± 0.07	4.10 ± 0.10	4.71 ± 0.30	4.58 ± 0.23	4.60 ± 0.13	4.86 ± 0.09*
Thymus						
Absolute	0.047 ± 0.004	0.036 ± 0.004	0.013 ± 0.001**	0.015 ± 0.002**	0.018 ± 0.008**	0.014 ± 0.002**
Relative	1.95 ± 0.20	1.55 ± 0.16	0.76 ± 0.06**	0.86 ± 0.14**	1.01 ± 0.41**	0.85 ± 0.10**
Female						
Necropsy body wt	20.2 ± 0.3	19.5 ± 0.7	13.2 ± 0.5**[b]	13.9 ± 0.3**[b]	13.5 ± 0.4**[b]	13.2 ± 0.1**[b]
Brain						
Absolute	0.442 ± 0.007	0.442 ± 0.005	0.378 ± 0.015*	0.386 ± 0.023	0.442 ± 0.025	0.424 ± 0.004
Relative	21.88 ± 0.25	22.80 ± 0.64	28.89 ± 2.10**	27.77 ± 1.58**	32.92 ± 2.21**	32.14 ± 0.50**
Heart						
Absolute	0.108 ± 0.002	0.108 ± 0.007	0.116 ± 0.013	0.122 ± 0.012	0.118 ± 0.015	0.104 ± 0.004
Relative	5.35 ± 0.09	5.55 ± 0.33	8.76 ± 0.92**	8.82 ± 0.92**	8.81 ± 1.14**	7.87 ± 0.26**
R. Kidney						
Absolute	0.152 ± 0.005	0.138 ± 0.006	0.120 ± 0.007**	0.132 ± 0.006**	0.123 ± 0.005**	0.120 ± 0.005**
Relative	7.52 ± 0.20	7.09 ± 0.20	9.03 ± 0.28**	9.47 ± 0.37**	9.15 ± 0.28**	9.12 ± 0.36**
Liver						
Absolute	1.080 ± 0.020	1.120 ± 0.037	0.740 ± 0.081**	0.760 ± 0.051**	0.880 ± 0.037**	0.740 ± 0.068**
Relative	53.48 ± 0.91	57.58 ± 0.62	55.43 ± 4.17	54.56 ± 3.14	65.24 ± 1.55*	55.91 ± 4.67
Lung						
Absolute	0.160 ± 0.024	0.220 ± 0.020	0.360 ± 0.024**	0.360 ± 0.024**	0.380 ± 0.020**	0.400 ± 0.000**
Relative	7.87 ± 1.13	11.50 ± 1.52	27.16 ± 1.26**	25.83 ± 1.40**	28.44 ± 2.13**	30.31 ± 0.28**
Thymus						
Absolute	0.059 ± 0.003	0.055 ± 0.009	0.017 ± 0.003**	0.013 ± 0.001**	0.020 ± 0.003**	0.012 ± 0.001**
Relative	2.93 ± 0.17	2.81 ± 0.40	1.30 ± 0.21**	0.91 ± 0.09**	1.48 ± 0.23**	0.91 ± 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).
[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 Sulfate Hexahydrate[a]

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Male						
n	6	8	10	10	10	10
Necropsy body wt	30.3 ± 0.6	30.8 ± 0.9	30.0 ± 0.4	31.0 ± 0.8	31.8 ± 0.9	30.1 ± 1.1
Brain						
Absolute	0.450 ± 0.007	0.446 ± 0.007	0.445 ± 0.005	0.472 ± 0.008	0.439 ± 0.015	0.460 ± 0.005
Relative	14.89 ± 0.36	14.60 ± 0.46	14.89 ± 0.31	15.28 ± 0.28	13.87 ± 0.52	15.49 ± 0.64
Heart						
Absolute	0.167 ± 0.008	0.161 ± 0.006	0.163 ± 0.004	0.171 ± 0.006	0.178 ± 0.005	0.169 ± 0.006
Relative	5.51 ± 0.27	5.25 ± 0.16	5.45 ± 0.15	5.52 ± 0.14	5.63 ± 0.19	5.66 ± 0.20
R. Kidney						
Absolute	0.292 ± 0.012	0.300 ± 0.013	0.316 ± 0.009	0.329 ± 0.012	0.334 ± 0.012	0.299 ± 0.009
Relative	9.62 ± 0.27	9.76 ± 0.35	10.54 ± 0.24	10.61 ± 0.23	10.54 ± 0.36	10.05 ± 0.45
Liver						
Absolute	1.750 ± 0.062	1.663 ± 0.073	1.600 ± 0.030	1.750 ± 0.073	1.800 ± 0.054	1.610 ± 0.041
Relative	57.79 ± 1.67	54.07 ± 1.84	53.42 ± 0.90	56.35 ± 1.31	56.65 ± 0.73	53.97 ± 1.72
Lung						
Absolute	0.200 ± 0.000	0.200 ± 0.000	0.200 ± 0.000	0.210 ± 0.010	0.250 ± 0.017**	0.310 ± 0.010**
Relative	6.62 ± 0.13	6.54 ± 0.18	6.68 ± 0.08	6.78 ± 0.25	7.87 ± 0.49*	10.43 ± 0.51**
R. Testis						
Absolute	0.113 ± 0.002	0.118 ± 0.003	0.116 ± 0.004	0.129 ± 0.016	0.108 ± 0.009	0.114 ± 0.004
Relative	3.75 ± 0.11	3.83 ± 0.10	3.87 ± 0.13	4.21 ± 0.59	3.47 ± 0.32	3.84 ± 0.20
Thymus						
Absolute	0.034 ± 0.002	0.036 ± 0.004	0.033 ± 0.003	0.033 ± 0.001	0.034 ± 0.002	0.038 ± 0.002
Relative	1.12 ± 0.08	1.16 ± 0.11	1.09 ± 0.09	1.08 ± 0.05	1.06 ± 0.06	1.27 ± 0.10

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

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Female						
n	7	10	10	10	10	10
Necropsy body wt	25.8 ± 0.6	26.3 ± 0.5	27.1 ± 0.6	26.0 ± 0.3	26.3 ± 0.4	24.7 ± 0.5
Brain						
Absolute	0.466 ± 0.004	0.465 ± 0.008	0.467 ± 0.004	0.462 ± 0.005	0.470 ± 0.003	0.463 ± 0.005
Relative	18.12 ± 0.37	17.71 ± 0.29	17.25 ± 0.23	17.78 ± 0.27	17.92 ± 0.33	18.85 ± 0.38
Heart						
Absolute	0.134 ± 0.004	0.131 ± 0.004	0.134 ± 0.004	0.137 ± 0.004	0.131 ± 0.003	0.131 ± 0.003
Relative	5.22 ± 0.18	4.98 ± 0.12	4.93 ± 0.08	5.27 ± 0.15	4.98 ± 0.10	5.34 ± 0.16
R. Kidney						
Absolute	0.204 ± 0.005	0.202 ± 0.006	0.202 ± 0.006	0.209 ± 0.004	0.199 ± 0.005	0.195 ± 0.004
Relative	7.94 ± 0.18	7.67 ± 0.12	7.45 ± 0.13	8.04 ± 0.15	7.57 ± 0.17	7.92 ± 0.13
Liver						
Absolute	1.486 ± 0.040	1.530 ± 0.072	1.490 ± 0.057	1.490 ± 0.028	1.430 ± 0.021	1.350 ± 0.034
Relative	57.64 ± 0.75	57.98 ± 1.77	54.78 ± 1.18	57.27 ± 0.76	54.44 ± 0.65	54.75 ± 0.62
Lung						
Absolute	0.200 ± 0.000	0.200 ± 0.000	0.200 ± 0.000	0.200 ± 0.000	0.220 ± 0.013	0.270 ± 0.015**
Relative	7.78 ± 0.18	7.63 ± 0.16	7.40 ± 0.14	7.70 ± 0.09	8.42 ± 0.59	10.94 ± 0.55**
Thymus						
Absolute	0.042 ± 0.003	0.040 ± 0.002	0.045 ± 0.001	0.045 ± 0.002	0.044 ± 0.003	0.038 ± 0.001
Relative	1.66 ± 0.14	1.52 ± 0.10	1.68 ± 0.06	1.72 ± 0.11	1.66 ± 0.10	1.54 ± 0.07

* 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 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 Sulfate Hexahydrate[a]

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
n	5	5	5	5
Male				
Necropsy body wt	35.6 ± 1.1	36.5 ± 2.5	35.7 ± 0.5	35.8 ± 0.5
Brain				
Absolute	0.478 ± 0.005	0.472 ± 0.007	0.462 ± 0.008	0.454 ± 0.010
Relative	13.47 ± 0.50	13.13 ± 0.77	12.94 ± 0.25	12.69 ± 0.23
R. Kidney				
Absolute	0.406 ± 0.017	0.410 ± 0.016	0.392 ± 0.012	0.382 ± 0.014
Relative	11.39 ± 0.32	11.32 ± 0.43	10.97 ± 0.29	10.68 ± 0.41
Liver				
Absolute	1.752 ± 0.064	1.876 ± 0.053	1.794 ± 0.089	1.660 ± 0.048
Relative	49.23 ± 1.61	52.11 ± 3.05	50.27 ± 2.67	46.41 ± 1.35
Lung				
Absolute	0.212 ± 0.009	0.204 ± 0.013	0.220 ± 0.011	0.232 ± 0.009
Relative	5.94 ± 0.08	5.60 ± 0.18	6.17 ± 0.33	6.48 ± 0.21
Spleen				
Absolute	0.082 ± 0.007	0.084 ± 0.009	0.082 ± 0.004	0.098 ± 0.016
Relative	2.31 ± 0.22	2.35 ± 0.31	2.30 ± 0.11	2.74 ± 0.45
R. Testis				
Absolute	0.124 ± 0.004	0.128 ± 0.006	0.122 ± 0.004	0.124 ± 0.002
Relative	3.49 ± 0.12	3.53 ± 0.12	3.42 ± 0.11	3.47 ± 0.10
Thymus				
Absolute	0.039 ± 0.002	0.034 ± 0.004	0.034 ± 0.004	0.036 ± 0.005
Relative	1.10 ± 0.03	0.94 ± 0.12	0.96 ± 0.11	1.01 ± 0.14
Female				
Necropsy body wt	32.6 ± 1.6	32.5 ± 1.2	30.1 ± 0.8	29.9 ± 0.8
Brain				
Absolute	0.466 ± 0.010	0.464 ± 0.007	0.472 ± 0.006	0.484 ± 0.005
Relative	14.41 ± 0.57	14.40 ± 0.76	15.73 ± 0.48	16.21 ± 0.35
R. Kidney				
Absolute	0.236 ± 0.012	0.270 ± 0.035	0.238 ± 0.010	0.248 ± 0.006
Relative	7.27 ± 0.30	8.31 ± 0.97	7.90 ± 0.25	8.29 ± 0.09
Liver				
Absolute	1.582 ± 0.044	1.544 ± 0.033	1.548 ± 0.038	1.518 ± 0.050
Relative	48.82 ± 1.54	47.70 ± 1.10	51.48 ± 1.01	50.72 ± 0.85
Lung				
Absolute	0.218 ± 0.022	0.212 ± 0.017	0.216 ± 0.012	0.252 ± 0.009
Relative	6.69 ± 0.60	6.54 ± 0.50	7.16 ± 0.24	8.42 ± 0.18*
Spleen				
Absolute	0.108 ± 0.007	0.100 ± 0.007	0.096 ± 0.005	0.108 ± 0.005
Relative	3.34 ± 0.24	3.08 ± 0.16	3.19 ± 0.14	3.61 ± 0.12
Thymus				
Absolute	0.049 ± 0.004	0.040 ± 0.004	0.042 ± 0.002	0.041 ± 0.005
Relative	1.49 ± 0.06	1.22 ± 0.10	1.41 ± 0.07	1.36 ± 0.16

* Significantly different ($P \leq 0.05$) 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).

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 Sulfate Hexahydrate[a]

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
n	5	5	5	5
Male				
Necropsy body wt	39.5 ± 1.3	41.0 ± 0.8	41.1 ± 1.8	42.6 ± 1.9
Brain				
Absolute	0.472 ± 0.012	0.474 ± 0.009	0.482 ± 0.006	0.482 ± 0.007
Relative	12.04 ± 0.65	11.56 ± 0.21	11.82 ± 0.51	11.42 ± 0.61
R. Kidney				
Absolute	0.440 ± 0.024	0.444 ± 0.043	0.456 ± 0.019	0.448 ± 0.034
Relative	11.25 ± 0.90	10.84 ± 1.06	11.19 ± 0.73	10.63 ± 1.03
Liver				
Absolute	2.108 ± 0.156	1.996 ± 0.086	2.132 ± 0.063	2.132 ± 0.115
Relative	53.80 ± 4.90	48.73 ± 2.38	52.28 ± 2.76	50.53 ± 3.78
Lung				
Absolute	0.242 ± 0.020	0.252 ± 0.013	0.260 ± 0.013	0.306 ± 0.012**
Relative	6.19 ± 0.63	6.13 ± 0.22	6.38 ± 0.44	7.23 ± 0.36
Spleen				
Absolute	0.096 ± 0.005[b]	0.076 ± 0.007	0.094 ± 0.011	0.102 ± 0.017
Relative	2.46 ± 0.20[b]	1.85 ± 0.14	2.34 ± 0.35	2.44 ± 0.46
Thymus				
Absolute	0.042 ± 0.006	0.034 ± 0.002	0.035 ± 0.002	0.041 ± 0.007
Relative	1.06 ± 0.14	0.84 ± 0.07	0.85 ± 0.07	0.94 ± 0.13
Female				
Necropsy body wt	39.6 ± 2.5	37.4 ± 1.3	42.6 ± 4.8	34.2 ± 0.9
Brain				
Absolute	0.484 ± 0.010	0.492 ± 0.005	0.478 ± 0.012	0.496 ± 0.007
Relative	12.39 ± 0.71	13.22 ± 0.44	11.71 ± 1.12	14.54 ± 0.51
R. Kidney				
Absolute	0.310 ± 0.017	0.278 ± 0.014	0.292 ± 0.012	0.266 ± 0.009
Relative	7.98 ± 0.74	7.45 ± 0.33	7.04 ± 0.47	7.82 ± 0.44
Liver				
Absolute	1.890 ± 0.102	1.810 ± 0.058	2.040 ± 0.105	1.778 ± 0.040
Relative	48.27 ± 3.33	48.63 ± 2.17	49.45 ± 4.56	52.03 ± 1.46
Lung				
Absolute	0.240 ± 0.014	0.242 ± 0.013	0.276 ± 0.015	0.326 ± 0.016**
Relative	6.17 ± 0.54	6.50 ± 0.39	6.67 ± 0.53	9.57 ± 0.64**
Spleen				
Absolute	0.166 ± 0.028	0.126 ± 0.017	0.130 ± 0.014	0.128 ± 0.010
Relative	4.34 ± 0.89	3.42 ± 0.54	3.19 ± 0.50	3.72 ± 0.23
Thymus				
Absolute	0.048 ± 0.006	0.045 ± 0.004	0.055 ± 0.013	0.044 ± 0.007
Relative	1.21 ± 0.13	1.22 ± 0.14	1.26 ± 0.16	1.28 ± 0.17

** 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).
[b] n=4

APPENDIX G
HEMATOLOGY RESULTS

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3	2 mg/m^3
Male						
n	10	10	10	10	10	9
Hematocrit (%)	44.5 ± 0.5	44.3 ± 0.5	45.1 ± 0.3	44.4 ± 0.5	44.6 ± 0.4	44.2 ± 0.9
Hemoglobin (g/dL)	15.4 ± 0.2	15.6 ± 0.1	16.0 ± 0.1*	15.6 ± 0.1	15.7 ± 0.1	15.8 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.45 ± 0.10	8.55 ± 0.08	8.77 ± 0.08	8.57 ± 0.09	8.55 ± 0.09	8.57 ± 0.16
Mean cell volume (fL)	53.4 ± 0.2	52.6 ± 0.3	52.3 ± 0.2	52.4 ± 0.4	53.1 ± 0.8	52.2 ± 0.2*
Mean cell hemoglobin concentration (g/dL)	34.5 ± 0.1	35.1 ± 0.2*	35.5 ± 0.2**	35.3 ± 0.2**	35.2 ± 0.2**	35.9 ± 0.4**
Reticulocytes ($10^6/\mu L$)	0.6 ± 0.0	0.7 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.6 ± 0.1	0.4 ± 0.1
Leukocytes ($10^3/\mu L$)	2.72 ± 0.20	2.60 ± 0.24	3.44 ± 0.29	2.67 ± 0.32	2.63 ± 0.27	3.49 ± 0.24
Segmented neutrophils ($10^3/\mu L$)	0.69 ± 0.07	0.66 ± 0.07	0.97 ± 0.12	0.90 ± 0.11	1.04 ± 0.12*	1.33 ± 0.09**
Lymphocytes ($10^3/\mu L$)	1.96 ± 0.14	1.85 ± 0.16	2.40 ± 0.23	1.70 ± 0.21	1.52 ± 0.16	2.07 ± 0.17
Monocytes ($10^3/\mu L$)	0.04 ± 0.01	0.05 ± 0.02	0.06 ± 0.02	0.06 ± 0.04	0.05 ± 0.01	0.04 ± 0.01
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.05 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.07 ± 0.01	0.09 ± 0.02	0.06 ± 0.02	0.09 ± 0.02	0.06 ± 0.01	0.12 ± 0.06

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

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3	2 mg/m^3
Female						
n	10	10	10	10	10	10
Hematocrit (%)	40.9 ± 1.0	41.3 ± 0.4	39.3 ± 1.8	41.8 ± 0.3	42.8 ± 0.4*	42.3 ± 0.4
Hemoglobin (g/dL)	14.2 ± 0.3	14.4 ± 0.1	13.7 ± 0.6	14.5 ± 0.1	14.9 ± 0.1**	14.7 ± 0.2*
Erythrocytes ($10^6/\mu L$)	7.31 ± 0.17	7.42 ± 0.07	7.06 ± 0.32	7.43 ± 0.06	7.59 ± 0.05*	7.57 ± 0.07*
Mean cell volume (fL)	56.7 ± 0.2	56.5 ± 0.2	56.4 ± 0.3	57.1 ± 0.2	57.4 ± 0.3	56.5 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.9 ± 0.2	34.8 ± 0.1	34.9 ± 0.1	34.7 ± 0.1	34.8 ± 0.1	34.8 ± 0.1
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.0	0.5 ± 0.0*	0.5 ± 0.1*	0.5 ± 0.1**	0.5 ± 0.1**	0.6 ± 0.1**
Leukocytes ($10^3/\mu L$)	2.45 ± 0.33	2.59 ± 0.33	3.01 ± 0.23	3.68 ± 0.29*	4.42 ± 0.16**	4.31 ± 0.41**
Segmented neutrophils ($10^3/\mu L$)	0.40 ± 0.08	0.42 ± 0.06	0.79 ± 0.11**	1.03 ± 0.09**	1.08 ± 0.05**	1.13 ± 0.14**
Lymphocytes ($10^3/\mu L$)	1.97 ± 0.25	2.11 ± 0.28	2.13 ± 0.14	2.57 ± 0.23	3.26 ± 0.16**	3.07 ± 0.28**
Monocytes ($10^3/\mu L$)	0.03 ± 0.01	0.02 ± 0.01	0.04 ± 0.02	0.06 ± 0.02	0.06 ± 0.01	0.08 ± 0.01*
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.03 ± 0.01	0.05 ± 0.01	0.02 ± 0.01	0.02 ± 0.02	0.03 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.06 ± 0.02	0.07 ± 0.02	0.14 ± 0.03	0.09 ± 0.02	0.18 ± 0.04*	0.09 ± 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 Sulfate Hexahydrate[a]

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3
Male				
n	5	5	4	5
Hematocrit (%)	46.5 ± 0.6	47.7 ± 0.6	48.6 ± 0.5*	48.5 ± 1.2
Hemoglobin (g/dL)	15.4 ± 0.2	15.8 ± 0.1	15.9 ± 0.1	15.8 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.39 ± 0.11	8.66 ± 0.13	8.69 ± 0.15	8.69 ± 0.16
Mean cell volume (fL)	55.0 ± 0.3	54.6 ± 0.2	55.8 ± 0.8	55.6 ± 0.6
Mean cell hemoglobin (pg)	18.4 ± 0.1	18.3 ± 0.2	18.2 ± 0.3	18.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.2 ± 0.2	33.3 ± 0.3	32.6 ± 0.3	32.7 ± 0.6
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.1	0.3 ± 0.0	0.3 ± 0.1	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	5.60 ± 0.27	6.12 ± 0.60	5.45 ± 0.22	5.52 ± 0.20
Segmented neutrophils ($10^3/\mu L$)	1.56 ± 0.12	2.02 ± 0.37	1.58 ± 0.27	1.72 ± 0.12
Lymphocytes ($10^3/\mu L$)	3.72 ± 0.24	3.80 ± 0.36	3.58 ± 0.21	3.50 ± 0.14
Monocytes ($10^3/\mu L$)	0.16 ± 0.05	0.22 ± 0.05	0.23 ± 0.03	0.22 ± 0.04
Eosinophils ($10^3/\mu L$)	0.16 ± 0.04	0.08 ± 0.02	0.08 ± 0.03	0.10 ± 0.00
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.02 ± 0.01	0.09 ± 0.04*	0.04 ± 0.02
Female				
n	5	5	5	3
Hematocrit (%)	50.5 ± 4.7	46.5 ± 1.0	47.3 ± 1.6	47.9 ± 0.1
Hemoglobin (g/dL)	15.4 ± 0.2	15.5 ± 0.2	15.2 ± 0.3	16.1 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.02 ± 0.48	7.86 ± 0.12	7.61 ± 0.17	7.97 ± 0.07
Mean cell volume (fL)	62.2 ± 2.0	60.8 ± 0.9	62.0 ± 2.3	60.0 ± 0.6
Mean cell hemoglobin (pg)	19.4 ± 0.8	20.3 ± 0.3	19.9 ± 0.2	20.3 ± 0.0
Mean cell hemoglobin concentration (g/dL)	31.2 ± 2.0	33.3 ± 0.3	32.1 ± 0.9	33.7 ± 0.5
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.1	0.2 ± 0.0[b]	0.4 ± 0.2	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	4.68 ± 0.19	4.50 ± 0.53[b]	4.72 ± 0.56	4.20 ± 0.64
Segmented neutrophils ($10^3/\mu L$)	0.98 ± 0.08	1.08 ± 0.2[b]	0.98 ± 0.14	1.17 ± 0.29
Lymphocytes ($10^3/\mu L$)	3.42 ± 0.17	3.18 ± 0.30[b]	3.56 ± 0.42	2.87 ± 0.38
Monocytes ($10^3/\mu L$)	0.24 ± 0.07	0.23 ± 0.13[b]	0.18 ± 0.07	0.10 ± 0.06
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.02 ± 0.02	0.02 ± 0.02	0.07 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.04 ± 0.02	0.03 ± 0.03[b]	0.01 ± 0.01	0.04 ± 0.01

* Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] b=4

TABLE G3
Hematology Data for Mice in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3	2 mg/m^3
Male						
n	2	5	4	5	5	5
Hematocrit (%)	40.9 ± 1.0	36.3 ± 2.3	40.2 ± 1.6	42.3 ± 0.9	41.9 ± 1.4	40.4 ± 2.5
Hemoglobin (g/dL)	14.9 ± 0.7	13.1 ± 0.9	14.9 ± 0.7	15.3 ± 0.3	15.1 ± 0.5	14.4 ± 0.6
Erythrocytes ($10^6/\mu L$)	8.22 ± 0.15	6.90 ± 0.63	7.69 ± 0.52	8.36 ± 0.11	8.04 ± 0.43	8.18 ± 0.48
Mean cell volume (fL)	50.5 ± 0.5	54.0 ± 2.2	53.5 ± 2.0	51.2 ± 0.6	53.0 ± 1.6	50.0 ± 0.3
Mean cell hemoglobin concentration (g/dL)	36.3 ± 0.7	35.9 ± 0.6	37.0 ± 0.4	36.3 ± 0.3	36.1 ± 0.2	35.9 ± 1.0
Reticulocytes ($10^6/\mu L$)	0.5 ± 0.2	0.7 ± 0.1	0.7 ± 0.2	0.3 ± 0.1	0.6 ± 0.1	0.7 ± 0.1
Leukocytes ($10^3/\mu L$)	1.30 ± 0.40	1.46 ± 0.26	2.75 ± 0.47	0.86 ± 0.28	1.42 ± 0.73	1.62 ± 0.26
Segmented neutrophils ($10^3/\mu L$)	0.65 ± 0.07	0.66 ± 0.17	0.64 ± 0.08	0.43 ± 0.19	0.48 ± 0.22	0.45 ± 0.09
Lymphocytes ($10^3/\mu L$)	0.64 ± 0.31	0.79 ± 0.14	2.06 ± 0.43	0.42 ± 0.11	0.86 ± 0.45	1.12 ± 0.21
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.02	0.00 ± 0.00	0.06 ± 0.05	0.04 ± 0.02
Eosinophils ($10^3/\mu L$)	0.02 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.00	0.02 ± 0.01	0.08 ± 0.07	0.01 ± 0.00	0.02 ± 0.01	0.06 ± 0.04

TABLE G3
Hematology Data for Mice in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate (continued)

	0 mg/m^3	0.12 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3	2 mg/m^3
Female						
n	7	10	10	10	10	10
Hematocrit (%)	39.9 ± 1.1	38.4 ± 1.3	40.4 ± 0.5	40.9 ± 0.7	40.8 ± 0.5	40.9 ± 0.6
Hemoglobin (g/dL)	14.4 ± 0.3	14.1 ± 0.5	14.6 ± 0.2	14.8 ± 0.2	15.1 ± 0.1**	14.9 ± 0.3*
Erythrocytes ($10^6/\mu L$)	7.89 ± 0.23	7.61 ± 0.27	8.03 ± 0.11	8.09 ± 0.11	8.11 ± 0.11	8.15 ± 0.11
Mean cell volume (fL)	51.1 ± 0.4	51.0 ± 0.3	50.9 ± 0.2	51.2 ± 0.4	51.0 ± 0.3	50.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)	36.2 ± 0.5	36.5 ± 0.2	36.2 ± 0.3	36.1 ± 0.5	37.0 ± 0.3	36.4 ± 0.2
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.0	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	1.66 ± 0.15	1.70 ± 0.10	1.64 ± 0.12	2.15 ± 0.19	2.60 ± 0.24**	2.52 ± 0.13**
Segmented neutrophils ($10^3/\mu L$)	0.28 ± 0.04	0.36 ± 0.09	0.33 ± 0.04	0.54 ± 0.08**	0.59 ± 0.09*	0.49 ± 0.05*
Lymphocytes ($10^3/\mu L$)	1.33 ± 0.13	1.30 ± 0.09	1.27 ± 0.09	1.56 ± 0.17	1.95 ± 0.17*	1.95 ± 0.11*
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.00	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.05 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.04 ± 0.01	0.06 ± 0.02	0.05 ± 0.02	0.07 ± 0.03	0.09 ± 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 G4
Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m^3	0.25 mg/m^3	0.5 mg/m^3	1 mg/m^3
Male				
n	5	4	5	5
Hematocrit (%)	46.2 ± 1.3	44.5 ± 0.5	43.5 ± 2.0	43.0 ± 2.1
Hemoglobin (g/dL)	15.0 ± 0.4	14.8 ± 0.2	14.2 ± 0.7	14.0 ± 0.7
Erythrocytes ($10^6/\mu L$)	9.30 ± 0.32	8.83 ± 0.14	8.50 ± 0.37	8.29 ± 0.42
Mean cell volume (fL)	49.4 ± 0.4	50.0 ± 0.6	50.8 ± 0.4	51.6 ± 0.9
Mean cell hemoglobin (pg)	16.1 ± 0.2	16.8 ± 0.2	16.7 ± 0.2	16.9 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	32.4 ± 0.4	33.3 ± 0.1	32.7 ± 0.3	32.6 ± 0.5
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.1
Leukocytes ($10^3/\mu L$)	4.80 ± 0.83	3.30 ± 0.25	3.64 ± 0.56	4.32 ± 0.68
Segmented neutrophils ($10^3/\mu L$)	1.85 ± 0.39	1.10 ± 0.20	1.18 ± 0.34	1.84 ± 0.47
Lymphocytes ($10^3/\mu L$)	2.83 ± 0.54	2.13 ± 0.14	2.28 ± 0.27	2.26 ± 0.26
Monocytes ($10^3/\mu L$)	0.07 ± 0.02	0.05 ± 0.03	0.06 ± 0.02	0.16 ± 0.11
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.00 ± 0.00	0.08 ± 0.02	0.06 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Female				
n	5	5	5	5
Hematocrit (%)	43.9 ± 1.3	43.9 ± 0.2	47.6 ± 0.9	42.7 ± 2.4
Hemoglobin (g/dL)	14.5 ± 0.6	14.4 ± 0.3	15.4 ± 0.3	14.0 ± 0.9
Erythrocytes ($10^6/\mu L$)	8.94 ± 0.24	8.74 ± 0.14	9.64 ± 0.28	8.56 ± 0.49
Mean cell volume (fL)	48.6 ± 0.2	49.8 ± 0.7	49.4 ± 0.8	49.4 ± 0.2
Mean cell hemoglobin (pg)	16.2 ± 0.3	16.5 ± 0.2	16.1 ± 0.2	16.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.3	32.7 ± 0.4	32.4 ± 0.5	32.7 ± 0.3
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	4.60 ± 1.16	3.12 ± 0.70	2.55 ± 0.05[b]	3.16 ± 0.50
Segmented neutrophils ($10^3/\mu L$)	1.70 ± 0.56	1.28 ± 0.47	0.83 ± 0.10[b]	1.14 ± 0.37
Lymphocytes ($10^3/\mu L$)	2.62 ± 0.76	1.70 ± 0.24	1.65 ± 0.06[b]	1.84 ± 0.38
Monocytes ($10^3/\mu L$)	0.20 ± 0.11	0.08 ± 0.04	0.08 ± 0.03[b]	0.14 ± 0.04
Eosinophils ($10^3/\mu L$)	0.02 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.02 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[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 Sulfate Hexahydrate[a]

	0 mg/m³	3.5 mg/m³	15 mg/m³	30 mg/m³
Male				
n	5	5	4	5
Absolute lung wt (g)	0.920 ± 0.034	1.322 ± 0.043**	1.353 ± 0.084**	1.262 ± 0.027**
μg Ni/lung	—[b]	6.700 ± 0.326**	12.575 ± 1.326**	9.700 ± 1.522**
μg Ni/g lung	—	5.100 ± 0.318**	9.425 ± 1.055**	7.700 ± 1.190**
μg Ni/g control lung	—	7.300 ± 0.355**	13.650 ± 1.436**	10.560 ± 1.643**
Female				
n	5	5	5	4
Absolute lung wt (g)	0.762 ± 0.038	1.230 ± 0.039**	1.244 ± 0.026**	1.075 ± 0.032**
μg Ni/lung	—	9.400 ± 0.517**	12.980 ± 1.293**	9.900 ± 2.539**
μg Ni/g lung	—	7.640 ± 0.333**	10.500 ± 1.063**	9.225 ± 2.415**
μg Ni/g control lung	—	10.060 ± 0.434**	17.060 ± 1.694**	13.025 ± 3.355**

** Significantly different ($P \leq 0.01$) from the control group by Dunnett's 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 0.155 μg Ni (the limit of detection), or below the level of quantitation.

TABLE H2
Kidney Weight and Kidney Burden in Rats in the 16-Day Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	30 mg/m³
Male		
n	5	5
Absolute kidney wt (g)	1.80 ± 0.07	1.11 ± 0.04**
μg Ni/kidney	—[b]	2.080 ± 0.298**
μg Ni/g kidney	—	1.880 ± 0.276**
Female		
n	5	4
Absolute kidney wt (g)	1.32 ± 0.04	0.90 ± 0.03**
μg Ni/kidney	—	1.600 ± 0.193**
μg Ni/g kidney	—	1.783 ± 0.226**

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

TABLE H3
Lung Weight and Lung Burden in Rats in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.12 mg/m³	0.5 mg/m³	2 mg/m³
n	6	6	6	6
Male				
4 weeks				
μg Ni/g lung	—[b]	—	1.357 ± 0.135**	2.696 ± 0.124**[c]
μg Ni/g control lung	—	—	1.693 ± 0.200**	4.562 ± 0.240**[c]
9 weeks				
μg Ni/g lung	—	—	2.153 ± 0.086**	4.770 ± 0.207**
μg Ni/g control lung	—	—	2.695 ± 0.065**	8.348 ± 0.446**
13 weeks				
Absolute lung wt (g)	1.03 ± 0.01	1.09 ± 0.06	1.39 ± 0.07**	1.96 ± 0.06**
μg Ni/lung	—	0.145 ± 0.145	1.490 ± 0.163**	6.557 ± 0.166**
μg Ni/g lung	—	0.120 ± 0.120	1.055 ± 0.075**	3.348 ± 0.067**
μg Ni/g control lung	—	0.140 ± 0.140	1.450 ± 0.158**	6.368 ± 0.161**
Female				
13 weeks				
Absolute lung wt (g)	0.791 ± 0.031	0.835 ± 0.033	1.201 ± 0.034**	1.469 ± 0.040**
μg Ni/lung	—	—	1.395 ± 0.083**	5.460 ± 0.384**
μg Ni/g lung	—	—	1.157 ± 0.050**	3.725 ± 0.270**
μg Ni/g control lung	—	—	1.765 ± 0.104**	6.897 ± 0.486**

** 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 0.216 μg Ni (the limit of detection), or below the level of quantitation.
[c] n=5

TABLE H4
Kidney Burden in Rats in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.5 mg/m³	2 mg/m³
n	6	6	6
Male			
4 weeks			
μg Ni/g kidney	—[b]	0.118 ± 0.118	0.228 ± 0.142[c]
9 weeks			
μg Ni/g kidney	—	0.535 ± 0.377	0.065 ± 0.065
13 weeks			
μg Ni/g kidney	—	0.112 ± 0.112	0.400 ± 0.124
Female			
13 weeks			
μg Ni/g kidney	—	—	0.065 ± 0.065

[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.216 μg Ni (the limit of detection), or below the level of quantitation.
[c] n=5

TABLE H5
Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.12 mg/m³	0.25 mg/m³	0.5 mg/m³
Male				
n	6	7	7	7
7-Month interim evaluation				
Absolute lung wt (g)	1.64 ± 0.09	1.64 ± 0.06	1.61 ± 0.05	1.77 ± 0.07
μg Ni/lung	—[b]	—	—	1.426 ± 0.084**
μg Ni/g lung	—	—	—	0.804 ± 0.031**
μg Ni/g control lung	—	—	—	0.868 ± 0.051**
n	4	5	5	4
15-Month interim evaluation				
Absolute lung wt (g)	2.12 ± 0.10[c]	2.48 ± 0.10	2.50 ± 0.11	3.00 ± 0.26**[c]
μg Ni/lung	—	0.374 ± 0.038*	1.117 ± 0.128**	3.575 ± 0.545**
μg Ni/g lung	—	0.151 ± 0.015*	0.448 ± 0.049**	1.268 ± 0.205**
μg Ni/g control lung	—	0.177 ± 0.018*	0.528 ± 0.061**	1.688 ± 0.257**
Female				
n	7	7	6	5
7-Month interim evaluation				
Absolute lung wt (g)	1.13 ± 0.04	1.21 ± 0.04	1.10 ± 0.03	1.33 ± 0.04**
μg Ni/lung	—	—	—	1.326 ± 0.095**
μg Ni/g lung	—	—	—	0.996 ± 0.071**
μg Ni/g control lung	—	—	—	1.176 ± 0.084**
n	5	5	5	5
15-Month interim evaluation				
Absolute lung wt (g)	1.37 ± 0.07	1.58 ± 0.13	1.49 ± 0.04	1.82 ± 0.08**
μg Ni/lung	—	0.257 ± 0.017**	0.739 ± 0.057**	3.034 ± 0.586**
μg Ni/g lung	—	0.166 ± 0.012**	0.493 ± 0.031**	1.657 ± 0.285**
μg Ni/g control lung	—	0.188 ± 0.013**	0.538 ± 0.042**	2.212 ± 0.427**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's 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 0.282 (7 months) or 0.044 (15 months) (the limits of detection), or below the level of quantitation.
[c] n=5

APPENDIX I
TISSUE BURDEN IN MICE

TABLE I1
Lung Weight and Lung Burden in Mice in the 16-Day Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	3.5 mg/m³
n	5	5
Male		
Absolute lung wt (g)	0.144 ± 0.006	0.221 ± 0.012**
μg Ni/lung	—[b]	0.664 ± 0.090**
μg Ni/g lung	—	3.020 ± 0.437**
μg Ni/g control lung	—	4.620 ± 0.609**
Female		
Absolute lung wt (g)	0.143 ± 0.007	0.206 ± 0.015**
μg Ni/lung	—	0.712 ± 0.080**
μg Ni/g lung	—	3.540 ± 0.493**
μg Ni/g control lung	—	4.980 ± 1.324**

** 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 0.170 μg Ni (the limit of detection), or below the level of quantitation.

TABLE I2
Lung Weight and Lung Burden in Mice in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.12 mg/m³	0.5 mg/m³	2 mg/m³
Male				
n	5	6	6	6
Absolute lung wt (g)	0.183 ± 0.008	0.166 ± 0.011	0.175 ± 0.002	0.300 ± 0.014**
μg Ni/lung	—[b]	—	—	0.234 ± 0.148
μg Ni/g lung	—	—	—	0.790 ± 0.503
μg Ni/g control lung	—	—	—	1.275 ± 0.807
Female				
n	5	6	5	6
Absolute lung wt (g)	0.157 ± 0.009	0.149 ± 0.007	0.156 ± 0.008	0.279 ± 0.008**
μg Ni/lung	—	—	—	0.630 ± 0.126**
μg Ni/g lung	—	—	—	2.205 ± 0.444**
μg Ni/g control lung	—	—	—	4.008 ± 0.804**

** 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 0.228 μg Ni (the limit of detection), or below the level of quantitation.

TABLE I3
Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Male				
n	5	4	5	5
7-Month interim evaluation				
Absolute lung wt (g)	0.230 ± 0.013	0.239 ± 0.023	0.294 ± 0.024	0.251 ± 0.028
μg Ni/lung	—[b]	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—
n	4	5	3	3
15-Month interim evaluation				
Absolute lung wt (g)	0.208 ± 0.009	0.223 ± 0.028	0.204 ± 0.017	0.251 ± 0.006
μg Ni/lung	—	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—
Female				
n	4	5	5	5
7-Month interim evaluation				
Absolute lung wt (g)	0.221 ± 0.020	0.218 ± 0.015	0.212 ± 0.009	0.257 ± 0.009
μg Ni/lung	—	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—
n	5	5	5	5
15-Month interim evaluation				
Absolute lung wt (g)	0.205 ± 0.005	0.214 ± 0.007	0.225 ± 0.006*	0.275 ± 0.004**
μg Ni/lung	—	—	—	—
μg Ni/g lung	—	—	—	—
μg Ni/g control lung	—	—	—	—

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.323 μg Ni (7 months) or 0.256 μg Ni (15 months) (the limits of detection), or below the level of quantitation.

TABLE I4
Kidney Burden in Mice in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.25 mg/m³	0.5 mg/m³	1 mg/m³
Male				
n	5	4	5	5
7-Month interim evaluation μg Ni/g kidney	—[b]	—	—	—
n	4	5	3	3
15-Month interim evaluation μg Ni/g kidney	0.091 ± 0.025	0.076 ± 0.017	0.078 ± 0.004	0.113 ± 0.015
Female				
n	4	5	5	5
7-Month interim evaluation μg Ni/g kidney	—	—	0.395 ± 0.117	—
n	5	5	5	4
15-Month interim evaluation μg Ni/g kidney	0.128 ± 0.034	0.144 ± 0.041	0.217 ± 0.038	0.125 ± 0.030

[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] Results were below 0.305 μg Ni (7 months) or 0.046 μg Ni (15 months) (the limits of detection), or below the level of quantitation.

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 Sulfate Hexahydrate[a]

	0 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Male				
n	10	10	10	9
Weights (g)				
Necropsy body wt	327 ± 5	311 ± 5	324 ± 5	310 ± 8
R. cauda	0.150 ± 0.006	0.139 ± 0.008	0.143 ± 0.004	0.141 ± 0.004
R. epididymis	0.485 ± 0.016	0.478 ± 0.010	0.494 ± 0.006	0.474 ± 0.008
R. testis	1.402 ± 0.033	1.376 ± 0.031	1.443 ± 0.042	1.352 ± 0.035
Epididymal spermatozoal measurements				
Motility (%)	95.48 ± 0.50	95.05 ± 0.53	93.49 ± 0.98	92.68 ± 1.04
Abnormality (%)	0.740 ± 0.103	0.980 ± 0.128	0.760 ± 0.088	0.733 ± 0.088
Concentration (10^6/g cauda epididymal tissue)	855 ± 58	712 ± 25	721 ± 32	707 ± 38
Female				
n	10	10	10	10
Necropsy body wt	198 ± 5	189 ± 3	193 ± 3	184 ± 4
Estrous cycle length (days)	5.14 ± 0.26[c]	4.67 ± 0.24[d]	4.50 ± 0.19[e]	5.25 ± 0.25[e]
Estrous stages[b] (% of cycle)				
Diestrus	38.6	44.3	24.3	34.3
Proestrus	14.3	14.3	17.1	21.4
Estrus	30.0	32.9	38.6	31.4
Metestrus	17.1	8.6	17.1	11.4
Unclear diagnosis	0.0	0.0	2.9	1.4

[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 tests. Statistical tests were performed on unrounded data.
[b] Evidence suggests that females in the 0.5 mg/m³ group differ significantly ($P<0.01$, Wilks' Criterion) from the control females in the relative length of time spent in estrous stages. Females in this exposure group spent more time in diestrus and less time in metestrus than control females.
[c] Estrous cycle was longer than 7 days or was unclear in 3 of 10 animals.
[d] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.
[e] Estrous cycle was longer than 7 days or was unclear in 2 of 10 animals.

TABLE J2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Inhalation Study of Nickel Sulfate Hexahydrate[a]

	0 mg/m³	0.5 mg/m³	1 mg/m³	2 mg/m³
Male				
n	6	10	10	10
Weights (g)				
Necropsy body wt	30.3 ± 0.6	31.0 ± 0.8	31.8 ± 0.9	30.1 ± 1.1
R. cauda	0.014 ± 0.001	0.013 ± 0.001	0.012 ± 0.001	0.014 ± 0.001
R. epididymis	0.051 ± 0.003	0.052 ± 0.001	0.050 ± 0.003	0.050 ± 0.003
R. testis	0.113 ± 0.002	0.129 ± 0.016	0.108 ± 0.009	0.114 ± 0.004
Epididymal spermatozoal measurements				
Motility (%)	94.18 ± 0.56	94.23 ± 0.27	95.00 ± 0.51[b]	95.01 ± 0.30
Abnormality (%)	2.53 ± 0.20	1.76 ± 0.18	2.00 ± 0.20[b]	2.34 ± 0.19
Concentration (10^6/g cauda epididymal tissue)	1,310 ± 212	1,389 ± 74	1,537 ± 138[b]	1,420 ± 101
Female				
n	7	10	10	10
Necropsy body wt	25.8 ± 0.6	26.0 ± 0.3	26.3 ± 0.4	24.7 ± 0.5
Estrous cycle length (days)	4.29 ± 0.36	4.29 ± 0.18[d]	4.40 ± 0.16	4.10 ± 0.18
Estrous stages[c] (% of cycle)				
Diestrus	28.6	24.3	22.9	17.1
Proestrus	16.3	17.1	20.0	20.0
Estrus	36.7	42.9	40.0	44.3
Metestrus	18.4	15.7	17.1	17.1
Unclear diagnosis	0.0	0.0	0.0	1.4

[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 tests. Statistical tests were performed on unrounded data.
[b] n=9
[c] There is no evidence of any difference 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 3 of 10 animals.

APPENDIX K
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF NICKEL SULFATE HEXAHYDRATE

Nickel sulfate hexahydrate was obtained from Aldrich Chemical Co. (Milwaukee, WI) in one lot (M062883), which was used during the 16-day, 13-week, and 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 sulfate hexahydrate studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a blue-green crystalline powder, was identified as nickel sulfate hexahydrate by infrared and ultraviolet/visible spectroscopy. All spectra were consistent with those expected for the structure, and the infrared spectrum was consistent with the literature spectrum (*Sadtler Standard Spectra*) of nickel sulfate hexahydrate (Figure K1). No ultraviolet/visible spectra were found in the literature.

The purity of lot M062883 was determined by elemental analyses, Karl Fischer water analysis, spark source mass spectrometry, and chelometric titration. For chelometric titration, samples were buffered with ammonium/ammonium chloride (NH_3/NH_4Cl) to pH 9, and ascorbic acid and ethylenediaminetetraacetate (EDTA) were added. The samples were back-titrated with a standard manganese (II) chloride solution, and Eriochrome Black T was the indicator.

Elemental analyses for nickel and hydrogen were in agreement with the theoretical values for nickel sulfate hexahydrate. Karl Fischer water analysis indicated 41.3% ± 0.7% water. Spark source mass spectrometry indicated total impurities of less than or equal to 2,320 ppm; the major inorganic impurities were cobalt (approximately 1,500 ppm), silicon (470 ppm), and magnesium (120 ppm). Chelometric titration indicated a purity of 98.8% ± 0.8% nickel sulfate hexahydrate. The overall purity was determined to be greater than 98%.

No accelerated chemical stability studies were performed for nickel sulfate hexahydrate based on literature information about the physical and chemical properties of the compound (Ostroff and Sanderson, 1959; *Merck Index*, 1989). The decomposition temperature of nickel sulfate hexahydrate is given as 675° C. To ensure stability, the analytical chemistry laboratory recommended that the bulk chemical be stored in tightly sealed plastic bags 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 4 months during the 2-year studies. Elemental analyses for nickel, hydrogen, and sulfur were conducted. On two occasions out of the 23 analyses, the values for nickel in the samples fell slightly outside the range recommended by the analytical chemistry laboratory. The values for hydrogen and sulfur consistently fell within the ranges specified by the analytical chemistry laboratory. Because the excursions from specification were sporadic, it was concluded that there was no degradation of the bulk chemical during the studies.

AEROSOL GENERATION AND EXPOSURE SYSTEM

Aerosol Generation System. Nickel sulfate hexahydrate aerosol was generated from aqueous solution (62.1 g/L in distilled and deionized water). The solution was atomized with a Retec nebulizer (In Tox

Products, Albuquerque, NM) (Figure K2). The generation system, which included a solution reservoir and manifold for four nebulizers, is shown in Figure K3. The aerosol generation assembly was enclosed in a walk-in hood. Air was circulated through HEPA filters to remove suspended particles in the enclosure. One generator was used with each exposure chamber, and only one nebulizer was used with each generator because of the low aerosol concentrations. A Kr-85 discharger was installed to reduce the particle charges.

The aerosol left the generator at an air flow rate of about 3 ft^3/min and passed through a dilutor/dump for aerosol concentration adjustment. The aerosol was then mixed with additional dilution air to achieve the proper air flow rate. All dilutions took place in a radial dilutor for uniform mixing, and the diluting air was filtered and conditioned to achieve a relative humidity of about 40%.

Stainless steel, multitiered, 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, 3.5, 15, and 60 mg/m^3 groups, and the H1000 chambers were used for the 7 and 30 mg/m^3 groups. During the 13-week studies, the H2000 chambers were used for the 0, 0.12, 0.5, and 2 mg/m^3 groups, and the H1000 chambers were used for the 0.25 and 1 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 to 12 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 9 to 21 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 dilutor prior to introduction into the chamber, and a small boxer fan (Model WS 2107FL, 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. 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 studies, the aerosol concentrations were determined gravimetrically from two 3-hour samples (4.5 L/min flow rate) for the 0.12 and 0.25 mg/m^3 exposure chambers and from three 2-hour filter samples (3 L/min flow rate) for the 0.5, 1 and 2 mg/m^3 chambers. In the 2-year study in rats, the aerosol concentrations in each exposure chamber were monitored by collecting two 3-hour samples (4.5 L/min flow rate) from the 0.12 and 0.25 mg/m^3 exposure chambers and three 2-hour filter samples (3 L/min flow rate) from the 0.5 mg/m^3 chamber samples during each 6-hour exposure day. In the 2-year study in mice, the aerosol concentrations were monitored by collecting three 2-hour filter samples from the 0.5 and 1 mg/m^3 exposure chambers and two 3-hour filter samples from the 0.25 mg/m^3 exposure chambers. The background concentrations of total suspended particles in the control chambers were monitored each exposure day of the 16-day and 2-year studies by collecting one 6-hour filter sample. No suspended particles were detected during the 16-day 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 12 minutes (T_{90}) of aerosol generation at a flow rate of 3 to 4.5 L/min, and all samples in the 2-year studies were collected after a T_{90} of 8 minutes. The flow rate was monitored with calibrated rotameters. To determine aerosol concentration, samples were collected with 25 mm, Teflon®-coated, fiberglass filters with a pore size of 0.1 μm (Zefluor,

Gelman, Ann Arbor, MI). The quantity of nickel sulfate hexahydrate 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 2 minutes at the beginning, middle, and end of each filter sampling period. 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

The aerosol was analyzed for extent of hydration by thermogravimetric analysis (Perkin Elmer TGS-2 Thermogravimetric Analysis Unit) and for nickel content by electrothermal atomic absorption spectroscopy prior to exposure and once during the first week of exposure to ensure that the aerosol generated was nickel sulfate hexahydrate.

Aerosol size distribution was determined once a month for each exposure chamber with a Lovelace multijet cascade impactor operated at a flow rate of 12 L/min. The sampling period ranged from 2 to 6 hours depending on the chamber concentration. Stainless steel shimstock coated with apiezon grease was used as impactor substrate. The amount of nickel sulfate hexahydrate 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 K3.

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 temporal variations ranged from 1% to 17%, and the spatial variations ranged from 0% to 3%. For rats in the 2-year studies, the mean temporal variations of aerosol concentration during exposure were between 2.42% and 3.03%, and the mean spatial variations were between 1.95% and 3.85%. For mice in the 2-year studies, the mean

temporal variations were between 1.48% and 2.89%, and the mean spatial variations were between 1.56% and 2.81%.

The aerosol rise and fall time (T_{90}) was determined with a RAM-S, and an exposure day was 6 hours plus T_{90}. A T_{90} of 12 minutes was used during the 16-day and 13-week studies, and 8 minutes was used during the 2-year studies.

Residual concentration of nickel sulfate hexahydrate in the chambers during non-exposure hours was evaluated gravimetrically 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 for about 15 hours at a flow rate of 3 L/min. If the weight of the material collected on the filter was greater than 200 μg, the material collected was analyzed for nickel content by atomic absorption spectroscopy. The mass of the particles collected on the filter during the 13-week studies and the 2-year studies in rats never exceeded 200 μg. The mass of the particles collected during the 2-year studies in mice exceeded 200 μg four times (October 1988, and January, April, and October 1989), and were analyzed for nickel content. Results of chemical analysis of these filter samples by atomic absorption spectroscopy indicated that the aerosol collected on the filter was not solely nickel sulfate hexahydrate, but consisted chiefly of non-nickel-containing material.

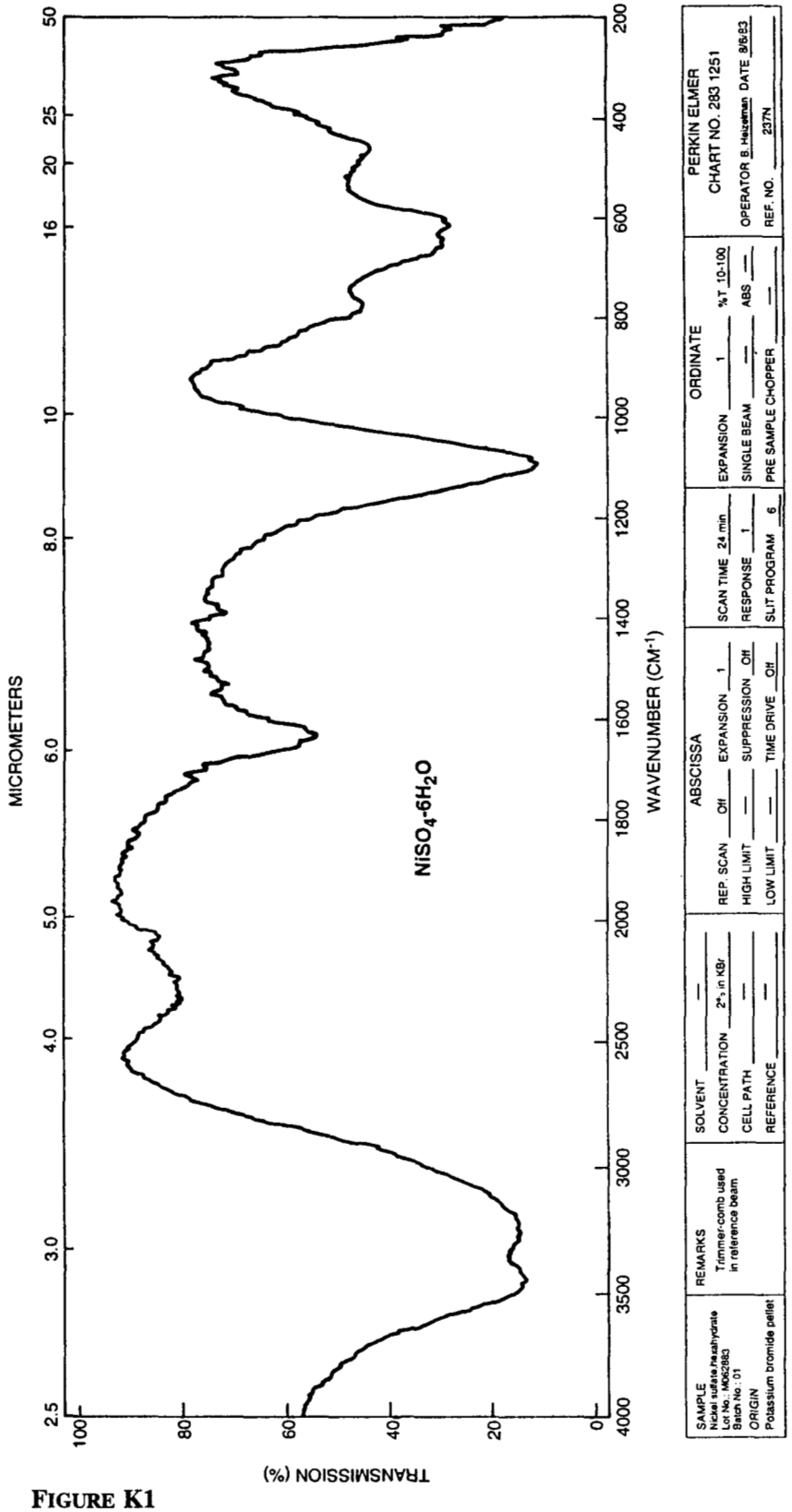

FIGURE K1
Infrared Absorption Spectrum of Nickel Sulfate Hexahydrate

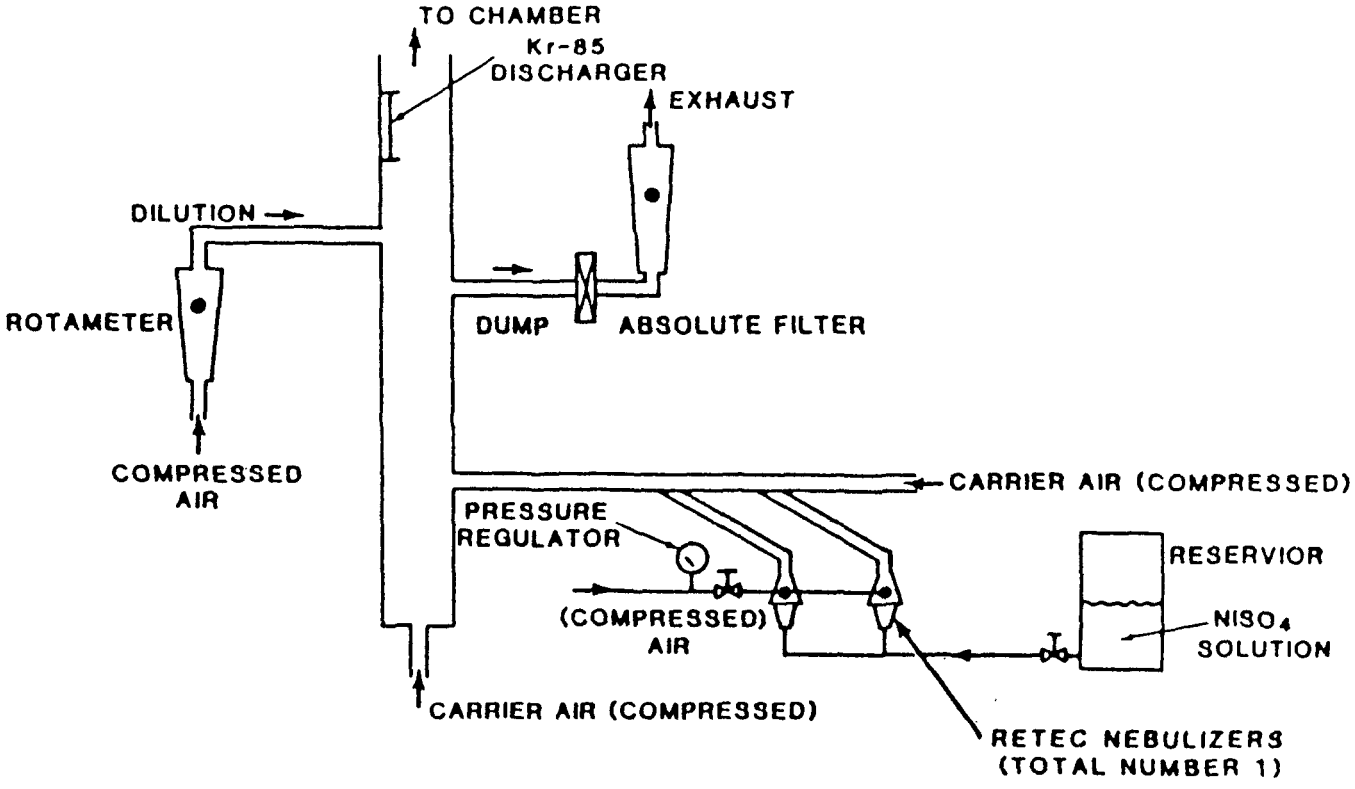

FIGURE K2
Schematic of the Generation System

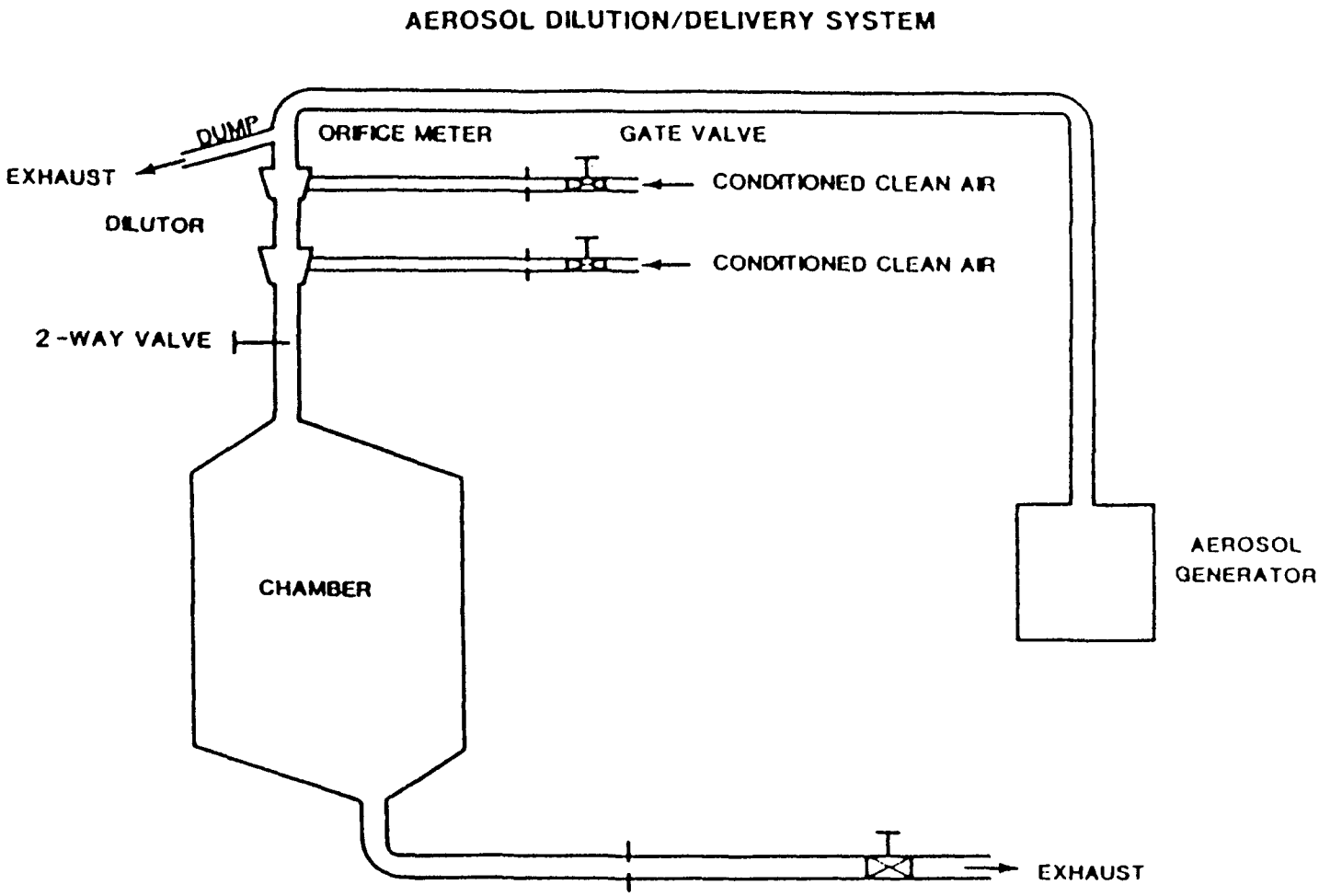

FIGURE K3
Schematic of the Nickel Sulfate Hexahydrate Aerosol Delivery System

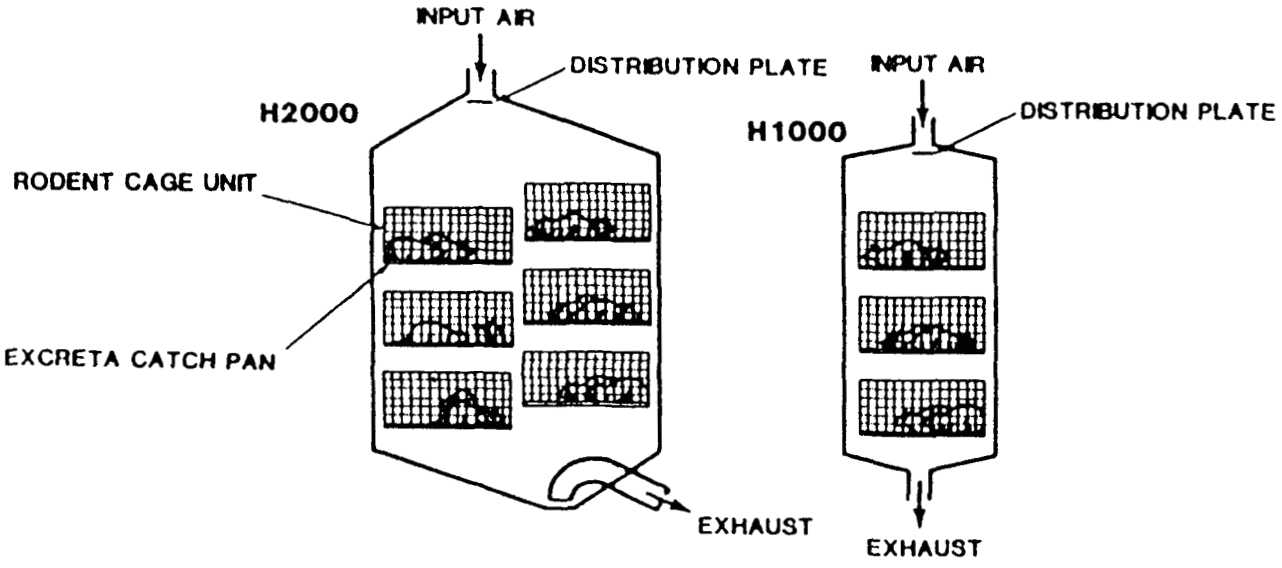

FIGURE K4
Schematic of the H1000 and H2000 Exposure Chambers

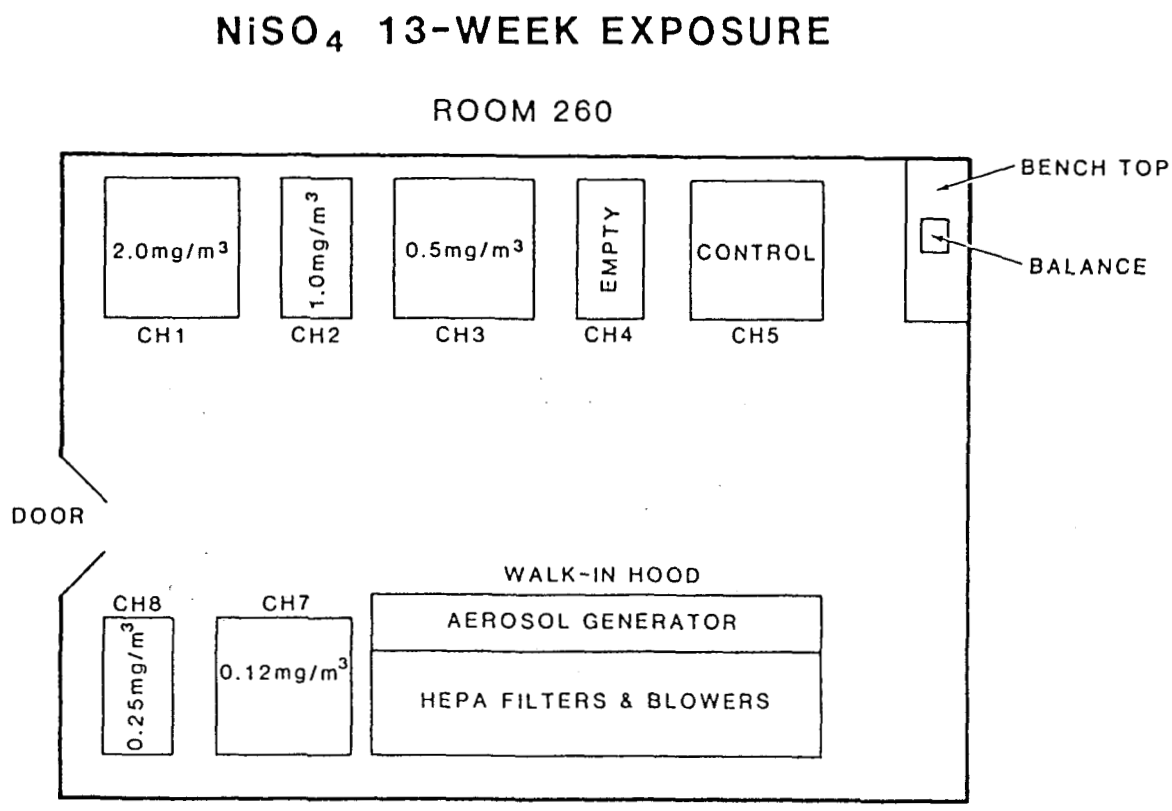

FIGURE K5
13-Week Nickel Sulfate Hexahydrate Inhalation Suite

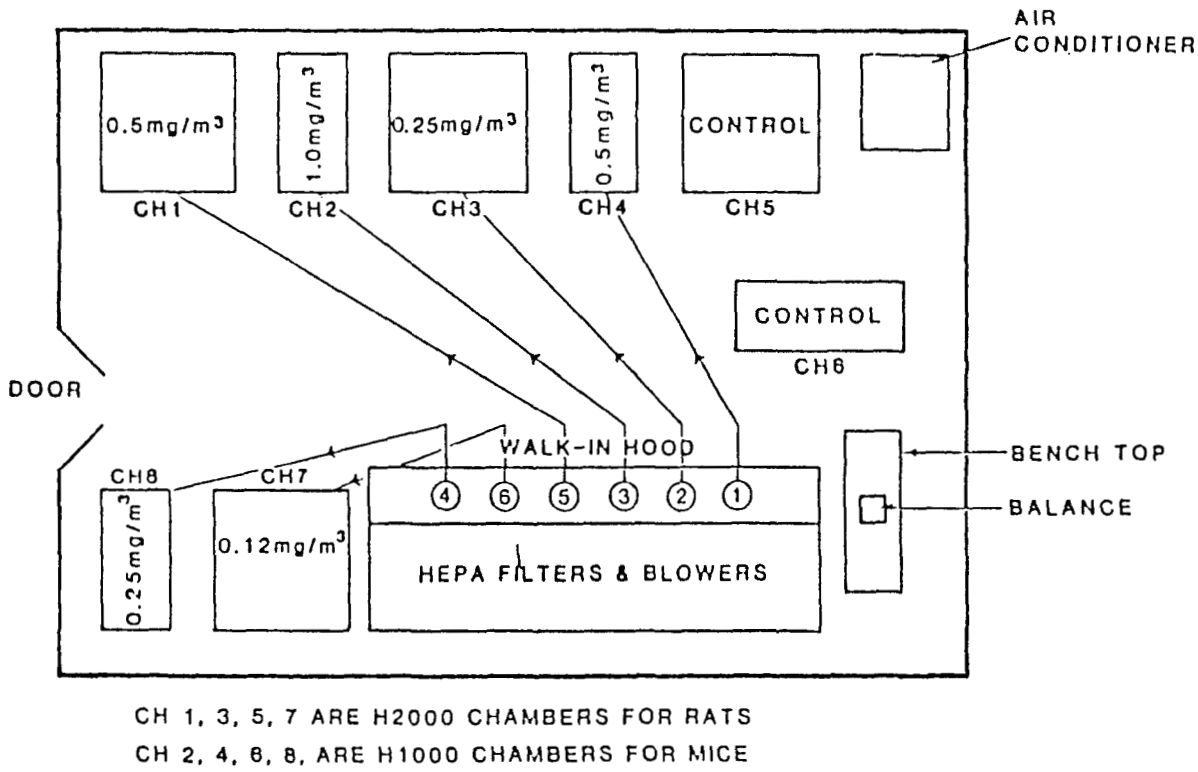

FIGURE K6
2-Year Nickel Sulfate Hexahydrate Inhalation Suite

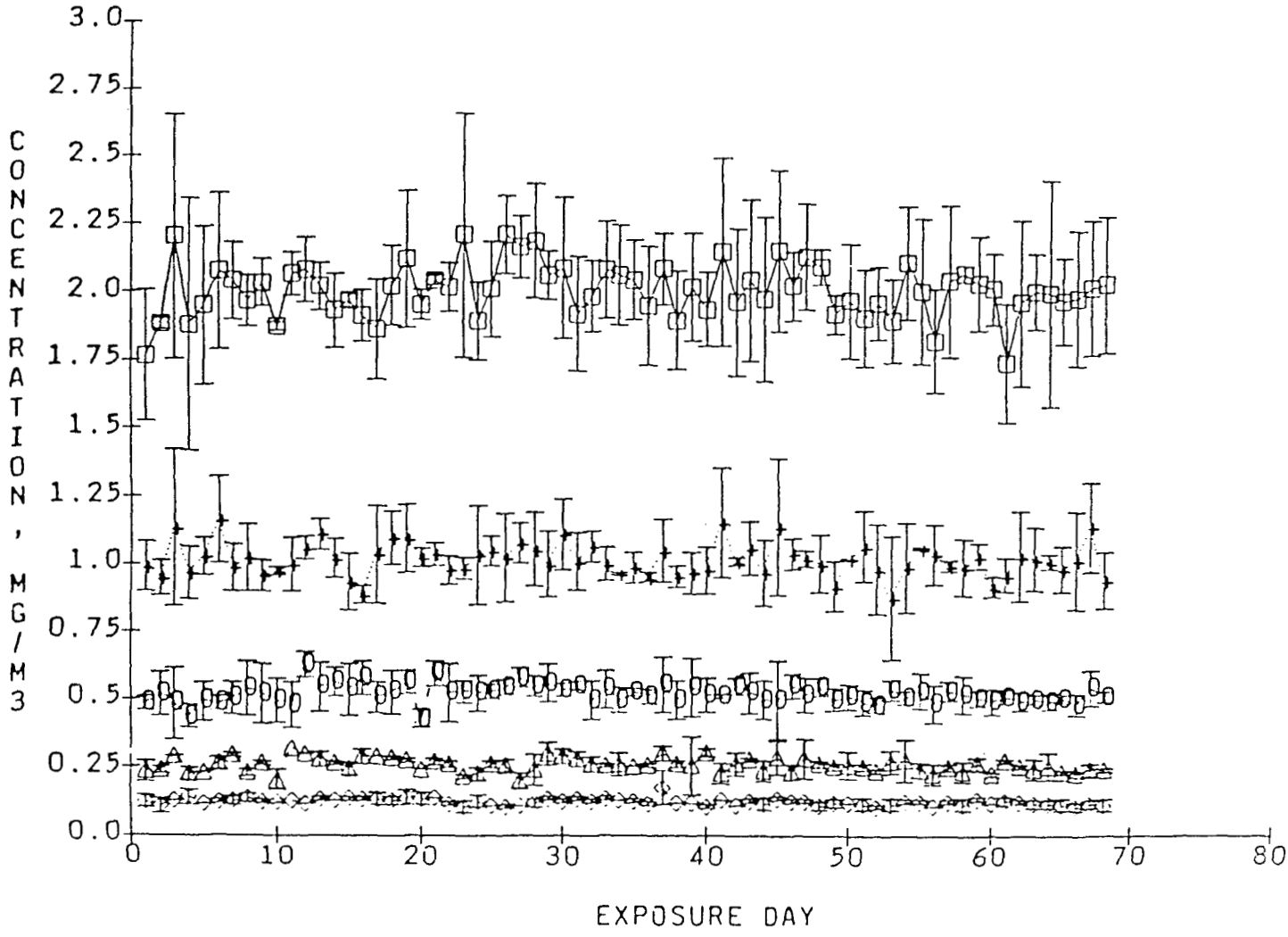

FIGURE K7
Daily Mean Filter Concentrations and Standard Deviations in the 13-Week Inhalation Study in Rats

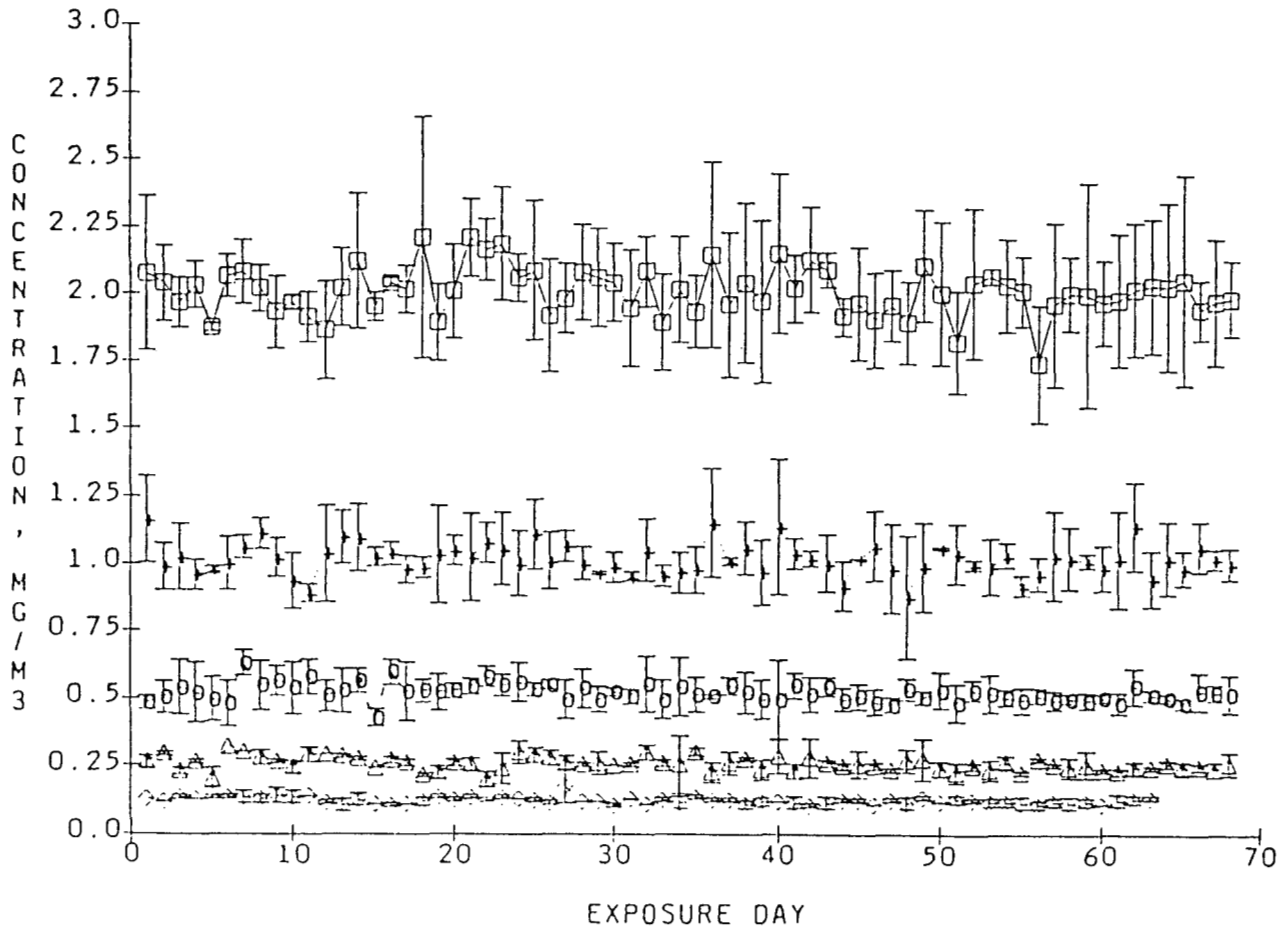

FIGURE K8
Daily Mean Filter Concentrations and Standard Deviations in the 13-Week Inhalation Study in Mice

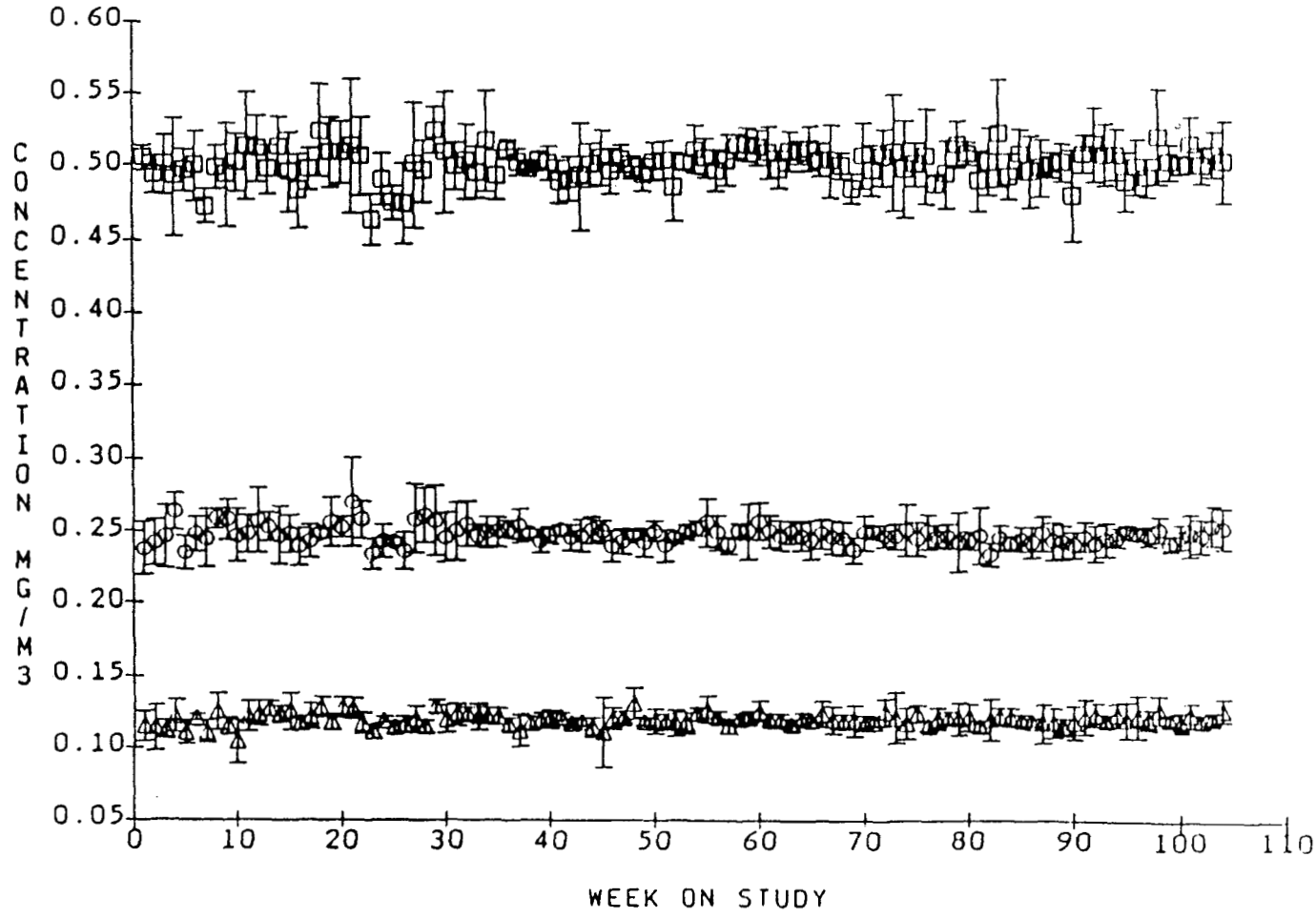

FIGURE K9
Weekly Mean Filter Concentrations and Standard Deviations in the 2-Year Inhalation Study in Rats

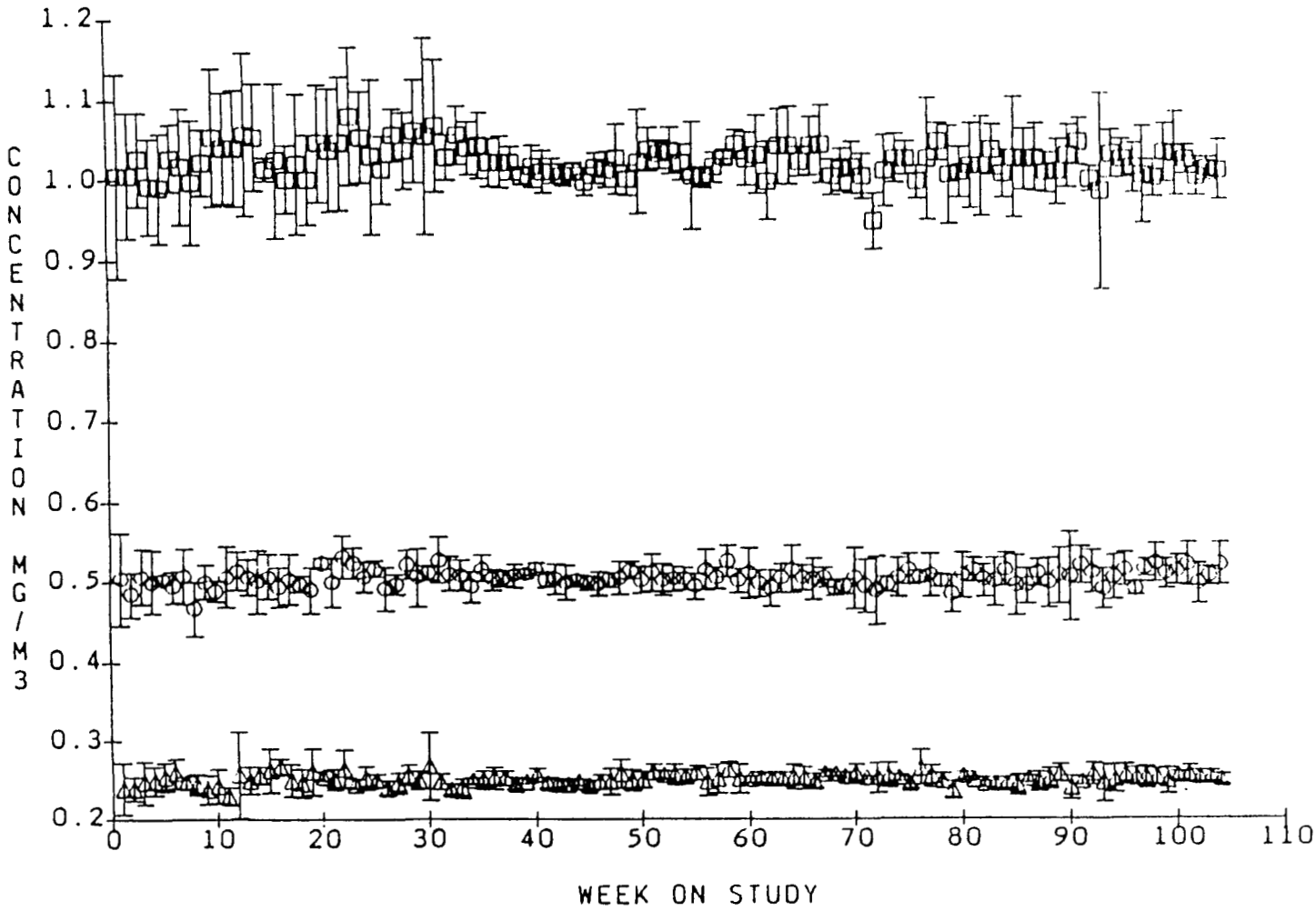

FIGURE K10
Weekly Mean Filter Concentrations and Standard Deviations in the 2-Year Inhalation Study in Mice

TABLE K1
Summary of Aerosol Size Measurements for the Rat and Mouse Chambers in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate

Target Concentration (mg/m^3)	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation
0.12	2.31	2.1
0.25	2.11	2.7
0.5	3.08	2.9
1.0	1.81	2.2
2.0	2.01	2.0

TABLE K2
Summary of Aerosol Size Measurements for the 0.12, 0.25, and 0.5 mg/m³ Rat Chambers in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

	0.12 mg/m³		0.25 mg/m³		0.5 mg/m³	
Date	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation
July 1988	3.14	2.29	2.41	2.78	2.27	2.21
August 1988	2.22	2.32	2.11	2.12	2.36	2.09
September 1988	3.08	2.07	1.95	2.81	2.25	2.33
October 1988	2.70	2.75	1.82	2.33	2.26	2.28
November 1988	2.74	2.86	2.10	2.55	1.85	2.43
December 1988	3.17	2.64	2.90	2.54	2.34	2.18
January 1989	2.88	2.88	2.24	2.37	2.15	2.03
February 1989	2.06	2.31	2.28	2.16	2.09	2.01
March 1989	2.26	2.15	2.59	1.81	2.17	2.04
April 1989	1.98	2.41	2.30	1.93	2.15	1.90
May 1989	2.64	2.36	1.93	2.31	2.31	2.01
June 1989	2.45	2.43	1.97	1.79	2.12	2.17
July 1989	2.44	2.32	1.92	2.20	2.15	2.27
August 1989	2.25	2.32	2.20	2.08	2.23	2.06
September 1989	1.91	2.43	2.66	1.95	2.15	2.08
October 1989	2.86	2.16	2.54	2.13	2.39	1.94
November 1989	2.20	2.54	2.38	2.08	2.47	1.91
December 1989	2.58	2.41	2.30	2.12	2.09	2.21
January 1990	2.05	2.52	2.49	2.22	2.46	2.26
February 1990	3.00	2.05	2.22	2.03	2.23	1.92
March 1990	2.61	2.61	2.07	2.19	2.32	2.03
April 1990	2.25	2.38	2.19	2.24	2.58	2.05
May 1990	2.18	1.65	2.26	2.27	2.44	1.71
June 1990	2.34	2.34	2.12	2.07	2.21	1.90
Mean ± standard deviation	2.50 ± 0.38	2.38 ± 0.27	2.24 ± 0.26	2.21 ± 0.26	2.25 ± 0.16	2.08 ± 0.17

TABLE K3
Summary of Aerosol Size Measurements for the 0.25, 0.5, and 1 mg/m³ Mouse Chambers in the 2-Year Inhalation Study of Nickel Sulfate Hexahydrate

	0.25 mg/m³		0.5 mg/m³		1 mg/m³	
Date	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation
June 1988	2.46	2.25	2.42	2.19	2.11	2.18
July 1988	2.33	2.36	2.22	2.12	2.69	2.32
August 1988	2.23	2.46	2.10	2.14	2.54	2.06
September 1988	2.13	2.38	2.31	2.11	2.51	2.01
October 1988	2.09	2.65	2.18	2.06	2.55	2.18
November 1988	2.36	2.32	2.17	2.33	2.67	2.17
December 1988	2.71	2.02	2.23	2.19	2.73	1.78
January 1989	2.23	2.26	2.06	1.99	2.36	2.11
February 1989	2.38	2.16	2.11	2.08	2.41	1.93
March 1989	2.24	2.19	2.38	1.93	2.46	2.05
April 1989	2.31	2.05	2.09	2.00	2.54	1.96
May 1989	2.22	2.37	2.29	2.15	2.90	1.65
June 1989	2.39	2.32	2.41	1.89	2.67	1.95
July 1989	2.27	2.33	1.87	2.23	2.15	2.18
August 1989	2.08	2.04	2.30	2.09	2.40	2.05
September 1989	2.16	2.18	2.18	2.07	2.78	2.09
October 1989	2.47	2.01	2.68	1.83	2.16	2.20
November 1989	2.55	1.83	2.57	1.91	2.69	1.95
December 1989	2.21	2.29	2.22	2.13	2.55	1.91
January 1990	2.91	2.33	2.42	2.05	2.67	2.11
February 1990	2.31	2.29	2.41	2.35	2.68	1.99
March 1990	2.70	2.22	2.22	2.02	2.64	1.87
April 1990	2.49	2.20	2.41	1.94	2.44	1.95
May 1990	2.04	2.28	2.13	1.93	2.33	1.90
Mean ± standard deviation	2.34 ± 0.21	2.24 ± 0.17	2.27 ± 0.18	2.07 ± 0.13	2.53 ± 0.20	2.02 ± 0.15

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)	23.10 ± 0.74	21.80 — 24.20	27
Crude fat (% by weight)	5.34 ± 0.30	4.60 — 5.90	27
Crude fiber (% by weight)	3.67 ± 0.41	2.80 — 4.30	27
Ash (% by weight)	6.57 ± 0.30	6.11 — 7.30	27
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)	6,665 ± 1,833	4,180 — 12,140	27
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)	19.00 ± 2.26	16.0 — 28.0	27
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 (%)	1.23 ± 0.11	1.06 — 1.54	27
Phosphorus (%)	0.95 ± 0.03	0.89 — 1.00	27
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)	0.24 ± 0.18	0.05 — 0.60	27
Cadmium (ppm)	0.08 ± 0.02	0.05 — 0.10	27
Lead (ppm)	0.25 ± 0.17	0.10 — 1.00	27
Mercury (ppm)	0.04 ± 0.02	0.02 — 0.11	27
Selenium (ppm)	0.41 ± 0.24	0.16 — 1.21	27
Aflatoxins (ppb)[c]	<5.0		26
Nitrate nitrogen (ppm)[d]	16.60 ± 3.93	8.60 — 24.0	27
Nitrite nitrogen (ppm)[d]	0.23 ± 0.19	0.01 — 0.07	27
BHA (ppm)[e]	1.44 ± 0.63	0.10 — 3.00	27
BHT (ppm)[e]	1.30 ± 0.60	0.10 — 3.00	27
Aerobic plate count (CFU/g)	42,755 ± 23,943	6,700 — 120,000	27
Coliform (MPN/g)	45 ± 210	3 — 1,100	27
Escherichia coli (MPN/g)	<3		27
Salmonella (MPN/g)	Negative		27
Total nitrosoamines (ppb)[f]	7.83 ± 3.00	3.60 — 16.50	27
N-Nitrosodimethylamine (ppb)[f]	5.83 ± 2.59	2.60 — 13.00	27
N-Nitrosopyrrolidine (ppb)[f]	2.00 ± 1.14	0.90 — 5.20	27
Pesticides (ppm)			
α-BHC	<0.01		27
β-BHC	<0.02		27
γ-BHC	<0.01		27
δ-BHC	<0.01		27
Heptachlor	<0.01		27
Aldrin	<0.01		27
Heptachlor epoxide	<0.01		27
DDE	<0.01		27
DDD	<0.01		27
DDT	<0.01		27
HCB	<0.01		27
Mirex	<0.01		27
Methoxychlor	<0.05		27
Dieldrin	<0.01		27
Endrin	<0.01		27
Telodrin	<0.01		27
Chlordane	<0.05		27
Toxaphene	<0.1		27
Estimated PCBs	<0.2		27
Ronnel	<0.01		27
Ethion	<0.02		27
Trithion	<0.05		27
Diazinon	<0.1		27
Methyl parathion	<0.02		27
Ethyl parathion	<0.02		27
Malathion	0.23 ± 0.22	0.05 — 1.00	27
Endosulfan I	<0.01		27
Endosulfan II	<0.01		27
Endosulfan sulfate	<0.03		27

[a] CFU = colony forming units, MPN = most probable number, BHC = hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] No aflatoxin measurement was recorded for the lot milled 2 October 1989.
[d] Sources of contamination: alfalfa, grains, and fish meal.
[e] Sources of contamination: soy oil and fish meal.
[f] 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 of Analysis	Time of Analysis
RATS	
13-Week Study	
ELISA	
CARB (cilia-associated respiratory bacillus)	Study termination
Mycoplasma arthritidis	Quarantine and study initiation
Mycoplasma pulmonis	Quarantine and study initiation
PVM (pneumonia virus of mice)	Quarantine, study initiation, and study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	Quarantine, study initiation, and study termination
Sendai	Quarantine, study initiation, and study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Quarantine, study initiation, and study termination
KRV (Kilham rat virus)	Quarantine, study initiation, and study termination
Immunofluorescence Assay	
RCV (rat coronavirus)	Study initiation
2-Year Study	
ELISA	
Ectromelia virus	Study initiation
GDVII (mouse encephalomyelitis virus)	Study initiation
LCM (lymphocytic choriomeningitis virus)	Study initiation
MVM (minute virus of mice)	Study initiation
Mouse adenoma virus	Study initiation
MHV (mouse hepatitis virus)	Study initiation
M. arthritidis	24 months
M. pulmonis	24 months
PVM	Study initiation, 6, 15, and 24 months
RCV/SDA	Study initiation, 6, 15, and 24 months
Sendai	Study initiation, 6, 15, and 24 months

RATS (continued)
2-Year Study (continued)

Hemagglutination Inhibition	
H-1	Study initiation, 6, 15, and 24 months
K (papovavirus)	Study initiation
KRV	Study initiation, 6, 15, and 24 months
Polyoma virus	Study initiation
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study initiation
Reovirus 3	Study initiation

MICE
13-Week Study

Complement Fixation	
LCM	Quarantine and study termination
ELISA	
CARB	Study termination
Ectromelia virus	Quarantine and study termination
GDVII	Quarantine and study termination
MVM	Quarantine and study termination
Mouse adenoma virus	Quarantine and study termination
MHV	Quarantine and study termination
M. arthritidis	Quarantine
M. pulmonis	Quarantine
PVM	Quarantine and study termination
Sendai	Quarantine and study termination
Hemagglutination Inhibition	
K	Quarantine and study termination
Polyoma virus	Quarantine and study termination
Immunofluorescence Assay	
EDIM	Quarantine and study termination
Reovirus 3	Quarantine and study termination

2-Year Study

ELISA	
Ectromelia virus	Study initiation, 7, 15, and 24 months
EDIM	24 months
GDVII	Study initiation, 7, 15, and 24 months
LCM	Study initiation, 15, and 24 months
MVM	Study initiation, 7, and 15 months
Mouse adenoma virus	Study initiation, 7, 15, and 24 months
MHV	Study initiation, 7, 15, and 24 months
M. arthritidis	24 months
M. pulmonis	24 months
PVM	Study initiation, 7, 15, and 24 months
Reovirus 3	7, 15, and 24 months
Sendai	Study initiation, 7, 15, and 24 months

MICE (continued)
2-Year Study (continued)

Hemagglutination Inhibition	
K	Study initiation, 7, 15, and 24 months
Polyoma virus	Study initiation, 7, 15, and 24 months
Immunofluorescence Assay	
EDIM	Study initiation, 7, and 15 months
LCM	7 months
MVM	24 months
Reovirus 3	Study initiation, 7, and 24 months

Results of 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 Sulfate Hexahydrate

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
Rats		
Quarantine screening	0/10	None positive
Week 1	1/10	RCV/SDA
Study termination	10/10	RCV/SDA
	10/10	Sendai
Mice		
Quarantine screening	0/10	None positive
Study termination	0/10	None positive
2-Year Studies		
Rats		
Quarantine screening	0/10	None positive
6 Months	0/16	None positive
15 Months	0/16	None positive
24 Months	6/16	*M. arthritidis*[a]
Mice		
Quarantine screening	0/10	None positive
7 Months	4/16	Reovirus 3
15 Months	0/16	None positive
24 Months	1/16	Reovirus 3

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may be due to 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.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD E1-02
Research Triangle Park, NC 27709

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