NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

COBALT SULFATE HEPTAHYDRATE

(CAS NO. 10026-24-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

August 1998

NTP TR 471

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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.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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ABSTRACT

$CoSO_4 \cdot 7H_2O$

COBALT SULFATE HEPTAHYDRATE

CAS No. 10026-24-1

Molecular Weight: 281.13

Synonyms: Bieberite; cobalt(II) sulfate (1:1) heptahydrate; cobalt monosulfate heptahydrate; cobalt(II) sulphate heptahydrate; sulfuric acid, cobalt(2+) salt (1:1) heptahydrate

Cobalt sulfate is used in the electroplating and electrochemical industries. It is also used as a coloring agent for ceramics and as a drying agent in inks, paints, varnishes, and linoleum. Cobalt sulfate may be added to animal feed as a mineral supplement and has been used as a top dressing on pasture lands. Cobalt sulfate was nominated by the National Cancer Institute for study based on a lack of information on the toxicity of soluble salts. Male and female F344/N rats and $B6C3F_1$ mice were exposed to cobalt sulfate heptahydrate (approximately 99% pure) by inhalation for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*. The results of prechronic inhalation toxicity studies were reported previously (Bucher *et al.*, 1990; NTP, 1991).

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to aerosols containing 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate heptahydrate 6 hours per day, 5 days per week, for 105 weeks.

Survival and Body Weights

Survival of exposed males and females was similar to that of the chamber controls. Mean body weights of exposed male and female rats were similar to those of the chamber controls throughout the study.

Pathology Findings

The incidences and severities of proteinosis, alveolar epithelial metaplasia, granulomatous alveolar inflammation, and interstitial fibrosis were markedly greater in all exposed groups of male and female rats than in the chamber controls. The incidences of alveolar epithelial hyperplasia in all groups of exposed males and in females exposed to 3.0 mg/m^3 were significantly greater than those in the chamber control groups, as were the incidences of squamous metaplasia in 1.0 mg/m^3 females and atypical alveolar epithelial hyperplasia in 3.0 mg/m^3 females. In 3.0 mg/m^3 males, the combined incidence of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma) was significantly greater than in the chamber controls. In female rats exposed to 1.0 or 3.0 mg/m^3, the

incidences of alveolar/bronchiolar neoplasms were significantly greater than those in the chamber control group and exceeded the NTP historical control ranges. A squamous cell carcinoma was observed in one 1.0 mg/m^3 and one 3.0 mg/m^3 female.

The incidences of benign, complex, or malignant pheochromocytoma (combined) in 1.0 mg/m^3 males and in 3.0 mg/m^3 females were significantly greater than those in the chamber controls and exceeded the historical control ranges.

Hyperplasia of the lateral wall of the nose, atrophy of the olfactory epithelium, and squamous metaplasia of the epiglottis were observed in all exposed groups of males and females, and the severities of these lesions increased with increasing exposure concentration. The incidences of squamous metaplasia of the lateral wall of the nose and metaplasia of the olfactory epithelium were increased in 3.0 mg/m^3 males and females.

2-Year Study in Mice

Groups of 50 male and 50 female mice were exposed to aerosols containing 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate heptahydrate 6 hours per day, 5 days per week, for 105 weeks.

Survival and Body Weights

Survival of exposed males and females was similar to that of the chamber controls. Mean body weights of 3.0 mg/m^3 male mice were less than those of the chamber controls from week 96 until the end of the study. The mean body weights of all exposed groups of female mice were generally greater than those of the chamber controls from week 20 until the end of the study.

Pathology Findings

The incidences of diffuse histiocytic cell infiltration in 3.0 mg/m^3 males and of focal histiocytic cell infiltration in 3.0 mg/m^3 females were significantly greater than those in the chamber controls. The incidences of alveolar/bronchiolar neoplasms in 3.0 mg/m^3 males and females were significantly greater than those in the chamber control groups. The combined incidences of alveolar/bronchiolar adenoma or carcinoma and the incidences of alveolar/bronchiolar carcinoma in 3.0 mg/m^3 males and females and the incidence of alveolar/bronchiolar adenoma in 3.0 mg/m^3 females exceeded the NTP historical control ranges for inhalation studies.

The incidences of atrophy of the olfactory epithelium in 1.0 and 3.0 mg/m^3 males and females and hyperplasia of the olfactory epithelium in 3.0 mg/m^3 males and females were significantly greater than in the chamber controls. Squamous metaplasia of the larynx was observed in all exposed groups of males and females.

Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms within the liver, characteristic of an infection with *Helicobacter hepaticus*. In NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of heman-giosarcoma were seen in the liver of male mice. In this study of cobalt sulfate heptahydrate, incidences of hemangiosarcoma were increased in exposed groups of male mice. Because of the above association, interpretation of the increased incidences of hemangiosarcoma in the livers of male mice was confounded. Incidences of lesions at other sites in this study of cobalt sulfate heptahydrate were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

Genetic Toxicology

Cobalt sulfate heptahydrate was mutagenic in *S. typhimurium* strain TA100 with and without liver S9 metabolic activation enzymes; no mutagenic activity was detected in strain TA98 or TA1535, with or without S9.

Conclusions

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of cobalt sulfate heptahydrate in male F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms. Marginal increases in incidences of pheochromocytomas of the adrenal

medulla may have been related to exposure to cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* in female F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms and pheochromocytomas of the adrenal medulla in groups exposed to cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* of cobalt sulfate heptahydrate in male and female $B6C3F_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms.

Exposure to cobalt sulfate heptahydrate caused a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice.

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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 Cobalt Sulfate Heptahydrate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations	Chamber control, 0.3, 1.0, or 3.0 mg/m^3	Chamber control, 0.3, 1.0, or 3.0 mg/m^3	Chamber control, 0.3, 1.0, or 3.0 mg/m^3	Chamber control, 0.3, 1.0, or 3.0 mg/m^3
Body weights	Exposed groups similar to chamber controls	Exposed groups similar to chamber controls	3.0 mg/m^3 group slightly less than chamber controls	Exposed groups slightly greater than chamber controls
Survival rates	17/50, 15/50, 21/50, 15/50	28/50, 25/49, 26/50, 30/50	22/50, 31/50, 24/50, 20/50	34/50, 37/50, 32/50, 28/50
Nonneoplastic effects	Lung: proteinosis (0/50, 16/50, 40/48, 47/50); alveolar epithelial metaplasia (0/50, 50/50, 48/48, 49/50); granulomatous alveolar inflammation (2/50, 50/50, 48/48, 50/50); interstitial fibrosis (1/50, 50/50, 48/48, 49/50); alveolar epithelial hyperplasia (9/50, 20/50, 20/48, 23/50) Nose: lateral wall hyperplasia (2/50, 14/50, 21/49, 20/50); olfactory epithelial atrophy (8/50, 24/50, 42/49, 48/50); lateral wall squamous metaplasia (1/50, 3/50, 5/49, 8/50); olfactory epithelial metaplasia (5/50, 1/50, 5/49, 30/50) Larynx: epiglottis squamous metaplasia (0/50, 10/49, 37/48, 50/50)	Lung: proteinosis (0/50, 36/49, 49/50, 49/50); alveolar epithelial metaplasia (2/50, 47/49, 50/50, 49/50); granulomatous alveolar inflammation (9/50, 47/49, 50/50, 49/50); interstitial fibrosis (7/50, 47/49, 50/50, 49/50); alveolar epithelial hyperplasia (15/50, 7/49, 20/50, 33/50); squamous metaplasia (0/50, 1/49, 8/50, 3/50); atypical alveolar epithelial hyperplasia (0/50, 0/49, 3/50, 5/50) Nose: lateral wall hyperplasia (1/50, 8/49, 26/50, 38/50); olfactory epithelial atrophy (5/50, 29/49, 46/50, 47/50); lateral wall squamous metaplasia (1/50, 1/49, 4/50, 10/50); olfactory epithelial metaplasia (2/50, 2/49, 3/50, 40/50) Larynx: epiglottis squamous metaplasia (1/50, 22/49, 39/50, 48/50)	Lung: diffuse histiocytic cell infiltrate (1/50, 2/50, 4/50, 10/50) Nose: olfactory epithelial atrophy (0/50, 0/50, 29/48, 48/49); olfactory epithelial hyperplasia (0/50, 0/50, 0/48, 10/49) Larynx: squamous metaplasia (0/48, 37/49, 48/48, 44/49)	Lung: focal histiocytic cell infiltrate (2/50, 5/50, 7/50, 10/50) Nose: olfactory epithelial atrophy (0/50, 2/50, 12/49, 46/48); olfactory epithelial hyperplasia (0/50, 0/50, 0/49, 30/48) Larynx: squamous metaplasia (0/50, 45/49, 40/47, 50/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Cobalt Sulfate Heptahydrate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects	Lung: alveolar/bronchiolar adenoma (1/50, 4/50, 1/48, 6/50); alveolar/bronchiolar carcinoma (0/50, 0/50, 3/48, 1/50); alveolar/bronchiolar adenoma or carcinoma (1/50, 4/50, 4/48, 7/50)	Lung: alveolar/bronchiolar adenoma (0/50, 1/49, 10/50, 9/50); alveolar/bronchiolar carcinoma (0/50, 2/49, 6/50, 6/50); alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, or squamous cell carcinoma (0/50, 3/49, 16/50, 16/50) Adrenal medulla: benign, complex, or malignant pheochromocytoma (2/48, 1/49, 4/50, 10/48)	Lung: alveolar/bronchiolar adenoma (9/50, 12/50, 13/50, 18/50); alveolar/bronchiolar carcinoma (4/50, 5/50, 7/50, 11/50); alveolar/bronchiolar adenoma or carcinoma (11/50, 14/50, 19/50, 28/50)	Lung: alveolar/bronchiolar adenoma (3/50, 6/50, 9/50, 10/50); alveolar/bronchiolar carcinoma (1/50, 1/50, 4/50, 9/50); alveolar/bronchiolar adenoma or carcinoma (4/50, 7/50, 13/50, 18/50)
Uncertain findings	Adrenal medulla: benign, complex, or malignant pheochromocytoma (15/50, 19/50, 25/49, 20/50)	None	None	None
Level of evidence of carcinogenic activity	Some evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Positive in strain TA100 with and without S9 Negative in strains TA98 and TA1535 with and 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 cobalt sulfate heptahydrate on 11 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of cobalt sulfate heptahydrate 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.R. Bucher, NIEHS, introduced the toxicology and carcinogenesis studies of cobalt sulfate heptahydrate 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 the chemical-related neoplastic and nonneoplastic lesions in male and female rats and mice. The proposed conclusions were *some evidence of carcinogenic activity* in male F344/N rats and *clear evidence of carcinogenic activity* in female F344/N rats and male and female $B6C3F_1$ mice.

Dr. Tyson, a principal reviewer, agreed with the proposed conclusions. Concerning the genetic mechanisms involved in murine lung tumorigenesis, he said that although a comprehensive study of K-*ras* activation was done in lung neoplasms, other molecular markers could have been assessed as well. Loss of heterozygosity or homozygous deletions on regions of chromosome 4, which are syntenic to regions of human chromosome 9p21 where frequent deletions are observed in human lung cancer, could have been studied to determine if similar mechanisms are at work in both murine and human lung tumorigenesis via exposure to this chemical. Dr. R.C. Sills, NIEHS, reported that further studies were planned with the next step being to look at loss of heterozygosity not only on chromosome 4, but also to look at chromosomes 6 and 11, where the p53 genes are located.

Dr. Ward, the second principal reviewer, agreed with the proposed conclusions. He agreed with the rationale for the exposure concentrations chosen for the 2-year studies but because there was no concentration-related body weight gain depression, he thought that rats and mice could have tolerated higher concentrations. With regard to the extensive lesions in the nasal cavity and larynx, he stated that this was a classic case showing the association between toxic and regenerative/reparative lesions resulting in no neoplasms.

Dr. Russo, the third principal reviewer, agreed with the proposed conclusions.

Dr. Tyson moved that the Technical Report on cobalt sulfate heptahydrate be accepted with the revisions discussed and with the conclusions as written for male F344/N rats, *some evidence of carcinogenic activity* and for female F344/N rats and male and female $B6C3F_1$ mice, *clear evidence of carcinogenic activity*. Dr. Russo seconded the motion, which was accepted unanimously with eight votes.

INTRODUCTION

$CoSO_4 \cdot 7H_2O$

COBALT SULFATE HEPTAHYDRATE

CAS No. 10026-24-1

Molecular Weight: 281.13

Synonyms: Bieberite; cobalt(II) sulfate (1:1) heptahydrate; cobalt monosulfate heptahydrate; cobalt(II) sulphate heptahydrate; sulfuric acid, cobalt(2 +) salt (1:1) heptahydrate

CHEMICAL AND PHYSICAL PROPERTIES

Cobalt sulfate is a reddish, crystalline, water-soluble powder. It is usually produced as cobalt(II) sulfate but can also exist in the cobalt(III) sulfate form with a formula of $Co_2(SO_4)_3 \cdot 18H_2O$. The heptahydrate salt is reported to have a structure of $[Co(H_2O)_6] \cdot [H_2SO_5]$ (*Merck Index*, 1983). Cobalt(II) salts are stable to autoxidation in air or in solution (Smith and Carson, 1981).

PRODUCTION, USE, AND HUMAN EXPOSURE

The production of cobalt sulfate in the United States in 1983 was estimated to be 450,000 pounds (204,000 kg) (J.V. Gandhi, Hall Chemical Co., personal communication); more recent production estimates are not available. Seven companies were listed as producing or handling cobalt sulfate at 10 facilities in the United States (USDHHS, 1992). Cobalt sulfate has been widely used in the electroplating and electrochemical industries. It is used as a coloring agent for ceramics and as a drying agent in inks, paints, varnishes, and linoleum. Cobalt sulfate may be added to animal feed as a mineral supplement and has been used as a top dressing on pasture lands (De Bie and Doyen, 1962).

Cobalt is an essential trace element because it is an integral part of vitamin B_{12}. The human body burden is approximately 1.1 mg, and the daily intake is about 0.3 mg, primarily via food (Hammond and Beliles, 1980). Cobalt is found in urban air (0.5 to 60 ng/m^3) (Morgan *et al.*, 1970) and has been identified in trace amounts in natural waters; concentrations in excess of 10 µg/L are rare (NRC, 1977). Ocean water contains about 0.3 µg/L (Hamilton, 1994). Cobalt has been identified in chemical waste dumps (Barrett, 1983).

In the 1960s, several breweries added cobalt sulfate to beer at a level of about 1 ppm to counteract the antifoaming activity of detergent residues left on poorly rinsed glasses (Morin and Daniel, 1967). Soon after this, an epidemic of "beer-drinkers' cardiomyopathy" occurred, and cobalt was identified as the causative agent. The addition of cobalt salts to beer was discontinued, and the epidemic ceased. Doses of cobalt chloride of up to 200 to 300 mg per day were given orally to patients as treatment for various types of anemia in the 1950s (Finch, 1980). This practice

has largely stopped because of associated toxicity (gastrointestinal upset, goiter, cardiomyopathies) and the development of less hazardous therapies.

It has been estimated that over 1 million workers in the United States are exposed to cobalt or cobalt compounds (Jensen and Tüchsen, 1990). Occupational exposure to cobalt occurs principally in refining processes, in the production of alloys, and in the tungsten carbide hard metal industry (Kazantzis, 1981). Exposure under these conditions is primarily dermal or via inhalation of cobalt metal dusts or fumes, often in combination with other elements such as nickel, arsenic, or tungsten; adverse respiratory effects (such as pneumoconiosis) have been reported at cobalt concentrations between 0.1 and 2 mg/m^3 (Domingo, 1989). The threshold limit value-timeweighted average for elemental cobalt is 0.02 mg/m^3 (ACGIH, 1996). Airborne levels of cobalt dust from spray painting in a Danish porcelain factory in 1981 were as high as 8.6 mg/m^3 (Jensen and Tüschen, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

The absorption of cobalt salts after oral administration is variable and is influenced by the nature of the salt, the size of the dose, and the presence of food in the gastrointestinal tract (Murdock, 1959; Smith *et al.*, 1972). Clearance of inhaled soluble cobalt salts from the lung has not been studied but is expected to be rapid (Kerfoot *et al.*, 1975). Several processes could contribute to this effect. The water-soluble salts dissolve directly, and certain insoluble salts and cobalt metal powder appear to have an appreciable solubility in protein-containing fluids (Harding, 1950). Clearance by phagocytic alveolar macrophages may also occur (Kerfoot *et al.*, 1975). Cobalt is distributed to all tissues after administration by the oral or inhalation route or by injection (Smith and Carson, 1981). Tissue retention is not marked, but higher concentrations have been noted in the liver, kidney, spleen, and heart than in other organs (Domingo *et al.*, 1984a,b; Llobet *et al.*, 1986).

Experimental Animals

In an unspecified strain of rabbits administered cobalt sulfate at doses of 0.25 mg/kg per day orally or by injection for 2 months, some accumulation of cobalt occurred in the liver, small intestine, lung, blood, kidney, and stomach (Kichina, 1974). Excretion is primarily via the urine and secondarily via the feces. The cobalt content of bile collected for 2 hours after intravenous administration of [^{57}Co] cobalt chloride to Sprague-Dawley rats totaled about 2% to 5% of the dose over a thirty-fold dose range (0.03 mg/kg to 1 mg/kg of Co^{2+}) (Gregus and Klaassen, 1986). Several studies have shown that a small portion of cobalt, given in several forms by parenteral or inhalation routes, is retained in tissues with a biological half-time of several years (IARC, 1991). The form of these materials has not been determined, but this could represent uptake into vitamin B_{12} (Edel *et al.*, 1990).

Humans

A recent report has demonstrated significant dermal absorption of cobalt by humans exposed to mixed cobalt-tungsten carbide powders (Scansetti *et al.*, 1994). The concentration of cobalt in the blood and urine of nonoccupationally exposed humans is 0.2 to 2.0 µg/L (Hamilton, 1994). Cobalt concentrations in the urine of workers in the Italian hard metal industry were between 10 and 100 µg/L at the beginning of the work shift and increased to between 16 and 210 µg/L at the end of the work shift (Sabbioni *et al.*, 1994).

TOXICITY

Experimental Animals

Exposure to cobalt results in a wide spectrum of toxicities in mammals. The ionic radius of cobalt is between that of Mg^{2+} and Ca^{2+}, so cobalt can replace or mimic these ions and also may influence reactions normally involving Fe^{2+}, Zn^{2+}, Cu^{2+}, or Mn^{2+} (Jennette, 1981). For example, cobalt can bind to Ca^{2+}-binding proteins in or near microtubules (Phillips, 1980) and has been shown to block Ca^{2+} channels in squid axons (Baker *et al.*, 1973). Cobalt promotes aberrant microtubule assembly (Buttlaire *et al.*, 1980) and can alter the activity of metalloenzymes such as carboxypeptidase (Jennette, 1981). Cobalt also inhibits the activity of DNA polymerase I from *Micrococcus luteus* (Korman *et al.*, 1978). Cobalt binds to sulfhydryl groups, including those of glutathione and cysteine, and through its binding to lipoic acid inhibits pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, effectively stopping oxidative metabolism (Dingle *et al.*, 1962).

A 250 µmol/kg (approximately 60 mg/kg) dose of cobalt chloride heptahydrate administered by subcutaneous injection to male Sprague-Dawley rats caused a rapid increase in biliary excretion of both reduced and oxidized glutathione, but total hepatic glutathione tended to increase after cobalt exposure (Stelzer and Klaassen, 1985).

A dose of 60 mg cobalt/kg body weight given to an unspecified strain of rats was found to inhibit heme synthesis in the liver (De Matteis and Gibbs, 1977). This apparently results from the formation of cobalt protoporphyrin by ferrochelatase and feedback inhibition of δ-aminolevulinic acid synthetase activity by the abnormal protoporphyrin (Sinclair *et al.*, 1982). Cobalt also induces heme oxygenase (Maines and Kappas, 1976), and the combined effect of these actions is to rapidly decrease the cytochrome P_{450} concentrations in the liver. Other cytochromes appear to be less affected (Tephly and Hibbeln, 1971).

In contrast to its actions on heme synthesis in the liver, cobalt administration promotes polycythemia. This effect is more pronounced in humans than in rodents (Smith and Carson, 1981) and is the basis for the use of cobalt chloride to treat anemia. The oral administration of 10 mg cobalt/kg body weight given as cobalt chloride to male rats of unspecified strain five times per week for 150 days resulted in an increase in the erythrocyte count, hematocrit value, and hemoglobin concentration of the blood; however, the mean cell volume and hemoglobin concentration per cell were unchanged, indicating a simple polycythemic effect (Murdock, 1959). This response is mediated by an increase in circulating erythropoietin, postulated to be a secondary response to a central nervous system effect of cobalt which results in respiratory alkalosis. Alkalosis increases the affinity of heme for oxygen, which is interpreted by tissue "sensors" as hypoxia (Miller *et al.*, 1974).

A second effect of cobalt administration on the blood is an increase in triglycerides, cholesterol, and free fatty acids (Taylor and Marks, 1978). This may be caused by inhibition of tissue lipoprotein lipase, resulting in failure to clear very low-density lipoprotein (Taylor and Marks, 1978), and perhaps by stimulation of lipoprotein synthesis in the liver (Eaton, 1972).

A single injection of 35 mg/kg cobalt chloride caused degranulation and disintegration of the α cells of the pancreatic islets in rabbits (Telib, 1972). This was followed by degranulation of the ß cells.

Although exposure to cobalt affects a wide variety of enzymatic processes, the acute toxicity of cobalt is not as great as might be expected. The oral LD_{50} for anhydrous cobalt sulfate is 420 mg/kg in male and female Wistar rats (Speijers *et al.*, 1982).

Krasovskii and Fridlyand (1971) administered 0.5 or 2.5 mg/kg cobalt chloride by gavage to rats six times per week for 7 months. These investigators found polycythemia and a suppression of leukocyte function. Myocardial histologic changes were seen in 26 of 30 rats given 26 mg/kg cobalt sulfate by gavage once daily for 8 weeks (Grice *et al.*, 1969). This study is representative of a large number of animal studies designed to examine beer-drinkers' cardiomyopathy (cited in Smith and Carson, 1981, and USDHHS, 1992). Overall, these studies indicated that rather large doses of cobalt could mimic the cardiomyopathy caused by cobalt-treated beer, but that cobalt probably acted synergistically in humans with thiamine deficiency and an insufficient intake of sulfur-containing amino acids. Deficits in thyroid function have been shown in l-day-old chicks and guinea pigs but not in young chicks, rats, mice, or rabbits given cobalt (Sederholm *et al.*, 1968).

A variety of cobalt dusts and aerosols have been administered to animals via inhalation. Results of these studies indicate that lung compliance is decreased and that electrical properties of the heart are affected as in beer-drinkers' cardiomyopathy (Kerfoot *et al.*, 1975; Smith, 1980). In general, similar toxicity has been elicited by cobalt whether administered orally or by inhalation. These effects have been seen after exposure of rats to atmospheres containing 0.05 or 0.5 mg/m^3 cobalt for 3 months (Popov, 1977). In addition, specific pulmonary effects in male rabbits exposed to 0.5 mg/m^3 cobalt (as cobalt chloride) by inhalation for 6 hours per day, 5 days per week, for 4 to 6 weeks included a change in the growth pattern of alveolar type II cells, resulting in clusters of cells projecting into the alveolar lumen, and changes in oxidative metabolism of lung macrophages (Johansson *et al.*, 1984, 1986).

Sixteen-day and 13-week inhalation studies with cobalt sulfate heptahydrate in F344/N rats and $B6C3F_1$ mice have been reported (Bucher *et al.*, 1990; NTP, 1991). In the 13-week studies, groups of 10 male and 10 female rats and mice were exposed to cobalt sulfate heptahydrate concentrations ranging from 0 to 30 mg/m^3, 6 hours per day, 5 days per week. Two male mice exposed to 30 mg/m^3 died. All groups at this concentration initially lost weight, but then gained weight at rates similar to controls. At the end of the studies, lung weights were generally increased in rats and mice exposed to 1.0 mg/m^3 and higher, and polycythemia was observed in exposed rats but not in mice. Lesions observed in the respiratory tract of rats and mice included degeneration of the olfactory epithelium, squamous metaplasia of the respiratory epithelium, and inflammation in the nose; inflammation, necrosis, squamous metaplasia, ulcers (rats), and inflammatory polyps (rats) of the larynx; squamous metaplasia of the trachea (mice); and histiocytic infiltrates, bronchiolar regeneration, peribronchiolar and septal fibrosis, and epithelial hyperplasia in the alveoli of the lung. A no-observed-adverse-effect-level (NOAEL) was not reached in these studies as lesions, particularly in the larynx, were observed at the lowest exposure (0.3 mg/m^3) used.

In other NTP studies (unpublished, available upon request), cobalt sulfate elicited contact hypersensitivity. Female Hartley guinea pigs received dermal applications of 100 µL of an aqueous 6% solution once per day for 14 days. A dose-related increase in contact hypersensitivity, as measured by retention of labeled inflammatory cells in the skin, was observed upon challenge application of solutions of 0.3%, 1%, or 3% aqueous cobalt sulfate to a site distant from the induction site 7 days after the last induction dose. Erythema and edema in the ears and paws of rats resulted from the administration of 5 mg cobalt sulfate by injection (Jasmin, 1974).

Humans

Besides myocardial toxicity, as noted above, a second effect of cobalt observed in victims of beer-drinkers' cardiomyopathy was hypothyroidism (Taylor and Marks, 1978). Thyroid function tests, including uptake of [^{131}I]iodide, were also depressed in patients receiving 0.17 to 3.9 mg/kg cobalt per day for treatment of anemia (Paley *et al.*, 1958). It has been proposed that cobalt interferes with binding of inorganic iodide to tyrosine in the thyroid gland.

Hypersensitivity reactions have been observed in patients who received prosthetic implants made of a cobalt alloy and in industrial workers exposed to cobalt dusts (Smith and Carson, 1981). Asthma related to cobalt exposure has also been described (Cirla, 1994).

Most inhalation of cobalt is by workers in the refining and alloy production industries (NIOSH, 1981). The dusts may be in the form of the metal, its alloys, or its salts, but most often the oxide form is present. Consequently, no toxicity studies exist on exposure to pure cobalt metal or to cobalt sulfate. Exposure appears to cause pulmonary fibrosis, splenic enlargement, dermatitis, and losses of appetite and sense of smell (Dorsit *et al.*, 1970). Cobalt is used in the cemented tungsten carbide industry and is thought to be primarily responsible for pulmonary "hard metal disease," consisting of upper respiratory tract irritation, pneumonitis, and pulmonary fibrosis (NIOSH, 1981). However, the actual role of inhaled cobalt versus an interaction of cobalt and other inhaled particles remains a subject of debate (Swennen *et al.*, 1993).

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Experimental Animals

Sprague-Dawley rats maintained on diets containing 265 ppm cobalt for 98 days showed degenerative changes in the testis; these changes were considered secondary to hypoxia (Mollenhaur *et al.*, 1985). Decreases in sperm motility and/or increased abnormal sperm were noted in mice, but not in rats, exposed to 3 mg/m^3 or higher in 13-week inhalation studies with cobalt sulfate (NTP, 1991). Following 13 weeks of chronic exposure to 100 to 400 ppm cobalt chloride in drinking water, male CD-1 mice showed marked dose-related decreases in fertility, testicular weight, and sperm concentration and motility, and increases in circulating levels of testosterone (Pedigo *et al.*, 1988).

Cobalt has been shown to cross the placenta; cobalt chloride and nitrite salt solutions induced fetal cleft

palates when injected alone into mouse dams, but inhibited cleft formation caused by cortisone or phenytoin (Kasirsky *et al.*, 1969; Mitala *et al.*, 1978). Oral exposure of rats to cobalt chloride at daily doses of 5.4 or 21.8 mg cobalt/kg body weight from gestation day 14 through lactation day 21 resulted in stunted growth and/or decreased pup survival, although adverse effects were also evident in the dams at both doses (Domingo *et al.*, 1985). In contrast, Paternain *et al.* (1988) reported that doses of up to 100 mg/kg cobalt chloride administered by gavage to pregnant Sprague-Dawley rats once per day on days 6 to 15 of gestation did not result in significant fetotoxicity or teratogenicity. Similarly, Seidenberg *et al.* (1986) reported no effect on mouse fetal growth or mortality in dams given daily doses of 81.7 mg cobalt/kg on days 8 to 12 of pregnancy.

Humans

Cobalt has not been shown to cause significant teratogenic or reproductive effects in humans (Smith and Carson, 1981). No clinical effects were noted in the babies of women who had taken cobalt chloride to counter anemia while pregnant (Jacobziner and Raybin, 1961).

CARCINOGENICITY

Experimental Animals

There have been no reports of adequate chronic inhalation toxicity or carcinogenicity studies with soluble or insoluble cobalt salts or metal powders (IARC, 1991). Wehner *et al.* (1977) found no increase in tumors in Syrian golden hamsters exposed to 10 mg/m^3 cobalt oxide dust for 7 hours per day, 5 days per week, for life; however, the study was faulted for poor survival (IARC, 1991). Cobalt oxide has been studied by intratracheal administration to groups of 50 male and 50 female Sprague-Dawley rats (Steinhoff and Mohr, 1991). Doses of 2 or 10 mg/kg were given in 19 treatments at 2-week intervals and in 10 treatments at 4-week intervals over 2 years. Two groups of 50 male and 50 female controls received saline or no treatment. Approximately 80% of the material was within the particle size range of 5 to 40 µm. At the end of the study an unspecified bronchioalveolar proliferation was noted in 51 of 100 low-dose rats (male and females combined), in 70 of 100 high-dose rats, and in no controls. One male and one female from the low-dose groups developed a benign lung tumor, and one high-dose female had a bronchioalveolar carcinoma. Three adenocarcinomas and two bronchioalveolar adenomas were observed in high-dose males. No lung tumors occurred in the controls. In a similar but smaller study by the same group, cobalt oxide was found to enhance the lung tumor yield of benzo[a]pyrene treatment (Steinhoff and Mohr, 1991).

Sarcomas in rats have been observed at the site of injection of cobalt salts or cobalt metal powder (IARC, 1991). Heath (1956, 1960) gave an unspecified strain of rats a single injection of 0.28 mg cobalt metal powder in fowl serum into the thigh muscle. Within 2 weeks, atypical myoblasts were observed (Heath, 1960), and between 5 and 12 months, malignant neoplasms developed at the injection site in 17 of 30 rats; 11 were rhabdomyosarcomas (Heath, 1956). Gilman (1962) reported a similar neoplastic response to injections of cobalt sulfide and cobalt oxide in an unspecified strain of rats but saw no neoplasms in an unspecified strain of mice. These materials are relatively insoluble, and Abbracchio *et al.* (1982) suggested that intracellular solubilization of relatively insoluble cobalt salts would favor cellular transformation. Heath and Webb (1967) determined that cobalt is bound intracellularly in primary rhabdomyosarcomas induced by intramuscular injection of metallic cobalt, with 70% to 90% of the bound cobalt found in the nucleus. Further fractionation studies demonstrated that 50% of the nuclear cobalt is bound in the nucleolus (Webb *et al.*, 1972). Similar injection studies have given little evidence of cobalt-induced cancer in mice, hamsters, or guinea pigs (Christensen and Poulsen, 1994).

There is only one report of the formation of neoplasms after injection of a soluble cobalt salt. Shabaan *et al.* (1977) observed fibrosarcomas in 14 of 40 male Wistar rats 8 months to 1 year after administration of 40 mg/kg cobalt chloride by subcutaneous injection once per day for 10 days. Four of these neoplasms were not at the site of injection.

Humans

Cobalt has been used in hundreds of patients as part of an alloy with chromium and molybdenum in prosthetic implants. During the first 14 years of its use for this purpose, no fibrosarcomas were identified in the recipients (McKee, 1971); however, a number of cases of malignant neoplasia have been reported

since that time at the sites of metal-containing fracture plates or joint prostheses, some of which contained cobalt (IARC, 1991).

The IARC (1991) considered the available data inadequate to establish an association between cancer and cobalt exposure to humans. At that time there were two epidemiological studies that were considered adequate for evaluation (Mur *et al.*, 1987; Hogstedt and Alexandersson, 1990). The Mur *et al*. (1987) cohort study was composed of 1,143 workers who were employed for at least a year between 1950 and 1980 in a French electrochemical plant producing cobalt and sodium. For workers employed only in cobalt production, the standard mortality ratio for lung cancer was 466 (95% confidence interval from 146 to 1,064) based on four cases. Hogstedt and Alexandersson (1990) studied a cohort of 3,163 male Swedish workers with at least 1 year of exposure to cobalt-containing, hard-metal dust ore between 1940 and 1982. There were 17 cases of lung cancer versus 12.7 expected (SMR, 134; 95% CI 77 to 213). Interpretation of both studies was made difficult by concurrent exposures to other substances including arsenic and nickel in the French plant and tungsten carbide in the Swedish facility.

Since the IARC evaluation, a follow-up study of the French electrochemical plant workers was completed which extended the period of observation from 1981 to 1988. No additional lung cancers were observed. Based on this and other factors, the authors concluded that the data no longer supported an association of cobalt exposure with lung cancer (Moulin *et al.*, 1993). In contrast, Lasfargues *et al*. (1994) reported on a cohort mortality study carried out on workers at a French hard-metal plant. The study specifically addressed lung cancer risks in relation to cobalt exposure and included 709 male workers who had at least 1 year of employment at the plant and who died between the years 1956 and 1989. While overall mortality was not increased, death due to lung cancer was significantly elevated (SMR=213), with 10 cases observed. This excess was associated with high cobalt exposure, but no effect of employment duration was noted. Smoking did not account for the observed incidence of lung cancer.

GENETIC TOXICITY

Genetic toxicity data for cobalt sulfate heptahydrate are limited to a single publication. Zeiger *et al*. (1992) reported the results of a mutagenicity study with cobalt sulfate heptahydrate which showed a weakly positive response in *Salmonella typhimurium* strain TA100 in the absence of exogenous metabolic activation as well as with hamster or rat liver S9; the authors reported no induction of mutations in strain TA98 or TA1535, with or without S9.

Few studies with other cobalt compounds have been reported. The literature on genetic and related effects of cobalt compounds was reviewed by Beyersmann and Hartwig (1992). Most of the bacterial mutagenicity test results included in this review were negative. However, some positive results were reported for mammalian cell DNA damage studies, including the observation of DNA strand breaks in human cells (McLean *et al.*, 1982; Hamilton-Koch *et al.*, 1986; Hartwig *et al.*, 1990) and sister chromatid exchange induction in human (Anderson, 1983) and hamster cells (Hartwig *et al.*, 1991) treated *in vitro* with cobalt chloride in the absence of exogenous metabolic systems. The authors discussed the possible role of hydroxyl and superoxide radical formation in the generation of DNA breaks (Beyersmann and Hartwig, 1992). Morita *et al*. (1991) reported a weak response in an *in vitro* test designed to detect increased frequencies of 6-thioguanine-resistant mutant FM3A cell colonies. At a concentration of 2×10^{-4} M cobalt chloride (which induced a 50% decrease in cell survival), an increased number of mutant colonies (approximately four to five times the control number) was observed. At concentrations higher and lower than 2×10^{-4} M, the mutagenic response was weaker. The authors suggested, based upon results from the testing of other known mutagens in this assay, that metal ions such as cobalt require relatively high concentrations and long exposure periods to induce an effect and that the induced mutagenic response obtained is weak and seen over a narrow dose range. In the *Drosophila* wing spot test, cobalt chloride was demonstrated to induce a significant, dose-dependent increase in somatic recombination in third instar larvae exposed to cobalt chloride concentrations of 2 to 10 mM during development to the adult stage (Ogawa *et al.*, 1994).

STUDY RATIONALE

Cobalt sulfate was nominated by the National Cancer Institute for study based on a lack of information on the toxicity of soluble cobalt salts. The more common cobalt(II) form and the inhalation route were selected for study to mimic worker exposure. Prechronic studies were previously reported (Bucher *et al.*, 1990; NTP, 1991) with a spectrum of lesions noted in the respiratory tract of rats and mice. Polycythemia was also observed in rats. A NOAEL was not reached in these studies using doses as low as 0.3 mg/m^3. This report documents the findings of 2-year inhalation exposure studies with cobalt sulfate heptahydrate in F344/N rats and $B6C3F_1$ mice.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF COBALT SULFATE HEPTAHYDRATE

Cobalt sulfate heptahydrate was obtained from Curtin Matheson Scientific (Kansas City, MO) in one lot (412092). Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix F). Reports on analyses performed in support of the cobalt sulfate heptahydrate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a red, crystalline solid, was identified as cobalt sulfate heptahydrate by infrared, ultraviolet, and/or visible spectroscopy. The purity of lot 412092 was determined by elemental analysis, Karl Fischer water analysis, and spark source mass spectroscopy. Elemental analyses for sulfur and hydrogen were in agreement with the theoretical values for cobalt sulfate heptahydrate, but results for cobalt were slightly low. Karl Fischer water analysis indicated 44.6% ± 0.5% water. Spark source mass spectroscopy indicated 140 ppm nickel present as an impurity; all other impurities had a combined total of less than 175 ppm. The overall purity was determined to be approximately 99%.

Literature references indicate that cobalt sulfate heptahydrate is stable as a bulk chemical when stored protected from light at normal temperatures. The heptahydrate dehydrates to the hexahydrate at 41.5° C and to the monohydrate when heated to 71° C, with no further changes expected below the decomposition temperature (708° C). Therefore, an accelerated stability study was not conducted. To ensure stability, the bulk chemical was stored in its original shipping containers, metal cans, at room temperature. Stability was monitored during the studies using elemental analysis by inductively coupled plasma/atomic emission spectroscopy (ICP/AES) normalized against a cobalt standard (National Institute of Standards and Technology, Gaithersburg, MD); no degradation of the bulk chemical was detected.

AEROSOL GENERATION AND EXPOSURE SYSTEM

Cobalt sulfate heptahydrate was generated and delivered from an aqueous solution by a system composed of three main components: a compressed-air-driven nebulizer (Model PN7002; RETEC Development Laboratory, Portland, OR), an aerosol charge neutralizer, and an aerosol distribution system. Cobalt sulfate heptahydrate in deionized water was siphoned from the bulk reservoir to the nebulizer reservoir and then aspirated into the nebulizer chamber and expelled as a stream. Shear forces broke the stream into droplets that were evaporated to leave dry particles of cobalt sulfate heptahydrate. The aerosol generation and delivery system included primary and secondary compressed-air-driven nebulizers. The aerosol generated by the compressed-air-driven nebulizer was passed through the aerosol charge neutralizer to remove static charge that formed on the aerosol particles during generation. Detailed descriptions of the inhalation chambers and the vapor generation system are provided in Appendix F.

A distribution line carried aerosol to the Hazleton 2000 inhalation exposure chambers (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) on both sides of the exposure room. At each chamber, aerosol moving through the chamber inlet was further diluted with HEPA-filtered air to the appropriate concentration for the chamber.

AEROSOL CONCENTRATION MONITORING

The chamber concentrations of cobalt sulfate heptahydrate were monitored by computer-controlled real-time aerosol monitors (Model RAM-1; MIE, Inc.,

Bedford, MA). Chamber aerosol concentrations were sampled at least once per hour during each exposure day. Throughout the studies, the background concentrations of total suspended particles in the control chambers were less than the limit of detection. The RAM-1 voltage output was calibrated against cobalt sulfate heptahydrate concentrations of chamber filter samples. Solutions of filter samples in 2% nitric acid were analyzed quantitatively for cobalt sulfate heptahydrate by ICP/AES. The ICP/AES was calibrated with a solution of standard cobalt diluted with nitric acid. Stability studies performed with X-ray diffraction analyses of samples from the 0.3 and 3.0 mg/m^3 chambers indicated that cobalt sulfate hexahydrate was the primary species delivered to the chambers. Chamber concentration uniformity was maintained throughout the 2-year studies. A summary of chamber concentrations is presented in Table F1.

Chamber Atmosphere Characterization

The time required for the chamber concentration to reach 90% of the target value following the beginning of exposure (T_{90}) and the time required for the chamber concentration to reach 10% of the target value following termination of the exposure (T_{10}) were determined for each exposure chamber. Without animals present, T_{90} values ranged from 9 to 11 minutes for rats and from 7 to 12 minutes for mice; T_{10} ranged from 8 to 9 minutes for rats and mice. With animals present, T_{90} values ranged from 11 to 16 minutes for rats and from 8 to 12 minutes for mice; T_{10} ranged from 12 to 13 minutes for rats and from 11 to 12 minutes for mice. A T_{90} of 12 minutes was selected for the 2-year studies.

Aerosol size distribution was determined monthly for each exposure chamber with a Mercer-style seven-stage impactor (In-Tox Products, Albuquerque, NM). Samples were analyzed for cobalt sulfate heptahydrate with ICP/AES. The relative mass on each impactor stage was analyzed by probit analysis; the mass median aerodynamic diameter for the aerosol was within the specified range of 1 to 3 µm (Tables F2 and F3).

Studies of cobalt sulfate heptahydrate degradation and monitoring for impurities were conducted throughout the 2-year studies with ICP/AES. No degradation of cobalt sulfate heptahydrate was observed during the studies. Cageboards were used after the first 8 weeks of the studies to control ammonia in the exposure chambers.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats and mice were exposed to aqueous aerosols containing 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate heptahydrate for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks.

The exposure concentrations for the 2-year cobalt sulfate heptahydrate studies were based on the findings of 16-day and 13-week studies reported previously (NTP, 1991). The most sensitive tissue was the larynx, with squamous metaplasia observed in rats and mice at the lowest exposure concentration of 0.3 mg/m^3. A NOAEL was not reached for this tissue. Inflammatory polyps, some nearly obstructing the esophagus, were observed at 10 and 30 mg/m^3 in rats, while these lesions at the 0.3 and 1.0 mg/m^3 exposure concentrations were composed of mild or minimal squamous metaplasia and/or chronic inflammation in both rats and mice. The severity of the laryngeal changes and other lesions in the respiratory tract at 3.0 mg/m^3 was not considered life threatening, and, therefore, exposure concentrations of 0.3, 1.0, and 3.0 mg/m^3 were chosen for the 2-year study with rats and mice.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Rats and mice were quarantined for 14 days before the beginning of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation 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 H).

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 1. Information on feed composition and contaminants is provided in Appendix G.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded initially, at weeks 5, 9, and 13 (clinical findings) or weekly for 13 weeks (body weights), monthly through week 92, every 2 weeks thereafter, and at the end of the studies.

A complete necropsy and microscopic examination were performed on all rats and mice. 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 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs which included the adrenal medulla, lung, larynx, nose, and all neoplasms in all groups except testicular neoplasms for male and female rats. For male and female mice, the quality assessment pathologist evaluated slides from all tumors and all potential target organs which included the larynx, liver, lung, nose, and trachea, and all neoplasms in all organs. Additionally, all thyroid glands were reviewed for incidences of proliferative lesions of the follicular cells. Renal and iliac lymph nodes of male mice were reviewed when the diagnosis of lymphoid hyperplasia occurred. Ovaries of female mice were reviewed when the diagnoses of cyst, bilateral cyst, or corpus luteum cyst occurred.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues usually 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. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Cobalt Sulfate Heptahydrate

Study Laboratory
Battelle Pacific Northwest Laboratories
(Richland, WA)

Strain and Species
Rats: F344/N
Mice: $B6C3F_1$

Animal Source
Simonsen Laboratories
(Gilroy, CA)

Time Held Before Studies
14 days

Average Age When Studies Began
6 weeks

Date of First Exposure
Rats: 30 August 1990
Mice: 23 August 1990

Duration of Exposure
6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks

Date of Last Exposure
Rats: 28 August 1992
Mice: 21 August 1992

Necropsy Dates
Rats: 1-4 September 1992
Mice: 24-27 August 1992

Average Age at Necropsy
111 weeks

Size of Study Groups
50 males and 50 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights; cages were distributed randomly into groups from another computer-generated list of random numbers.

Animals per Cage
1

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Cobalt Sulfate Heptahydrate

Method of Animal Identification
Tail tattoo

Diet
NIH-07 open formula pellet diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* except during exposure periods, changed weekly

Water Distribution
Tap water (Richland municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*

Cages
Stainless-steel wire-bottom (Hazleton System, Inc., Aberdeen, MD), changed weekly

Bedding
Cageboard (Bunzl Cincinnati Paper Co., Cincinnati, OH), changed daily (15 October 1990 to study termination)

Chamber Air Supply Filters
Single HEPA (Flanders Filters, Inc., San Rafael, CA)

Chambers
Stainless-steel with excreta pan suspended below each cage unit (Harford System Division of Lab Products, Inc., Aberdeen, MD), changed weekly

Chamber Environment
Temperature: 21.3°–26.6° C (rats); 19.5°–27.1° C (mice)
Relative humidity: 31%–89% (rats); 28%–93% (mice)
Room fluorescent light: 12 hours/day
Chamber air changes: 9-23/hour

Exposure Concentrations
0, 0.3, 1.0, or 3.0 mg/m^3

Type and Frequency of Observation
Observed twice daily; animals were weighed and clinical findings were recorded initially, at weeks 5, 9, and 13 (clinical findings) or weekly for 13 weeks (body weights), monthly through week 92, every 2 weeks thereafter, and at the end of the studies.

Method of Sacrifice
CO_2 anesthetization

Necropsy
Necropsy performed on all animals

Histopathology
Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), harderian gland (rats), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lungs/bronchi, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland (except male mice), nose, oral cavity (rats), ovary, pancreas, pancreatic islets, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, sciatic nerve, seminal vesicle, skin, spinal cord, spleen, stomach (forestomach and glandular), testes/epididymides, thymus, thyroid gland, trachea, urinary bladder, and uterus.

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 pregnant 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., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, 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.

Analysis of Continuous Variables

Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

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, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 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 a 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 cobalt sulfate heptahydrate was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of cobalt sulfate heptahydrate 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 molecular structure and the effects 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 chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (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 correlate less 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 the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

RESULTS

RATS

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 2 and in the Kaplan-Meier survival curves (Figure 1). Survival of exposed males and females was similar to that of the chamber controls.

Body Weights and Clinical Findings

Mean body weights of exposed male and female rats were similar to those of the chamber controls throughout the study (Figure 2 and Tables 3 and 4). Irregular breathing was observed more frequently in female rats exposed to 3.0 mg/m^3 than in the chamber controls or other exposed groups.

TABLE 2
Survival of Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Animals initially in study	50	50	50	50
Moribund	30	34	26	34
Natural deaths	3	1	3	1
Animals surviving to study termination	17	15	21	15
Percent probability of survival at end of study[a]	34	30	42	30
Mean survival (days)[b]	648	655	663	643
Survival analysis[c]	P=0.723	P=1.000N	P=0.292N	P=0.876
Female				
Animals initially in study	50	50	50	50
Moribund	19	20	20	17
Natural deaths	3	4	4	3
Pregnant[d]	0	1	0	0
Animals surviving to study termination	28	25	26	30
Percent probability of survival at end of study	56	51	52	60
Mean survival (days)	699	677	691	684
Survival analysis	P=0.642N	P=0.583	P=0.756	P=0.959N

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

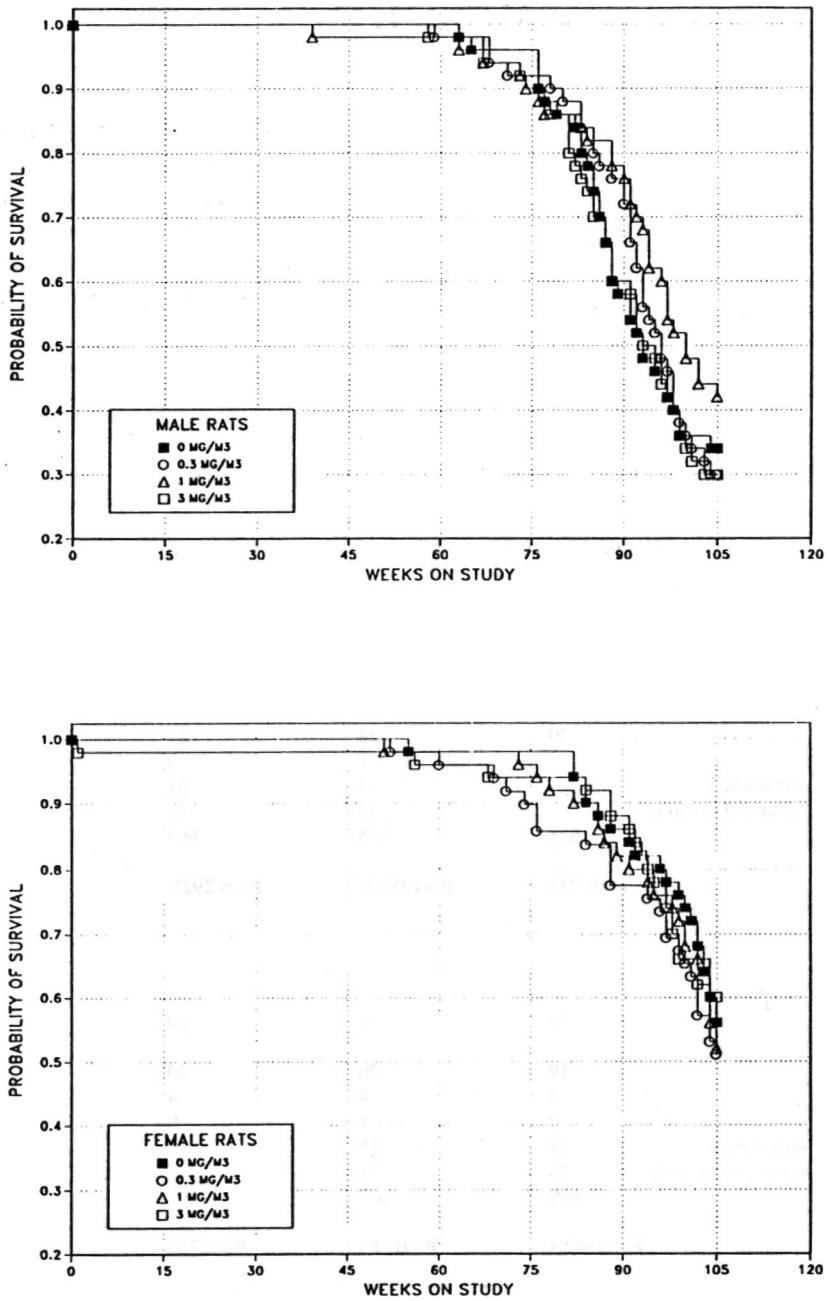
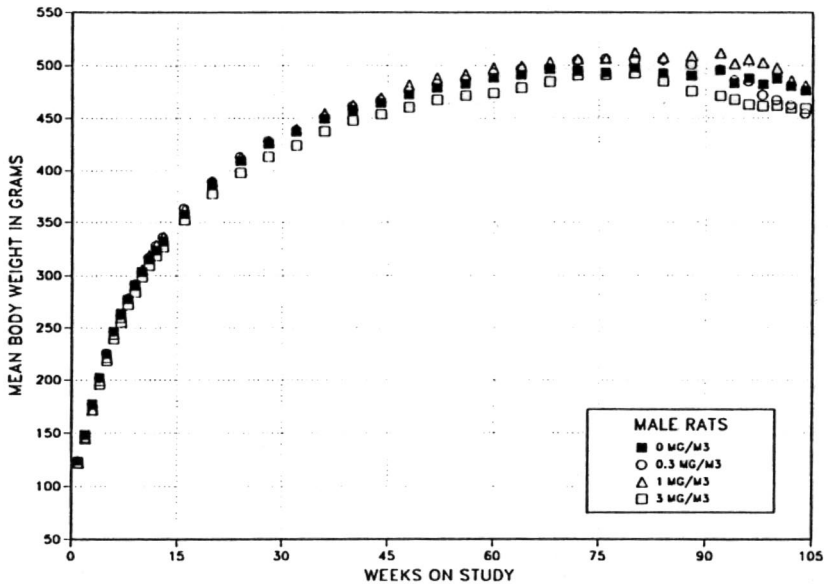


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Cobalt Sulfate Heptahydrate by Inhalation for 2 Years



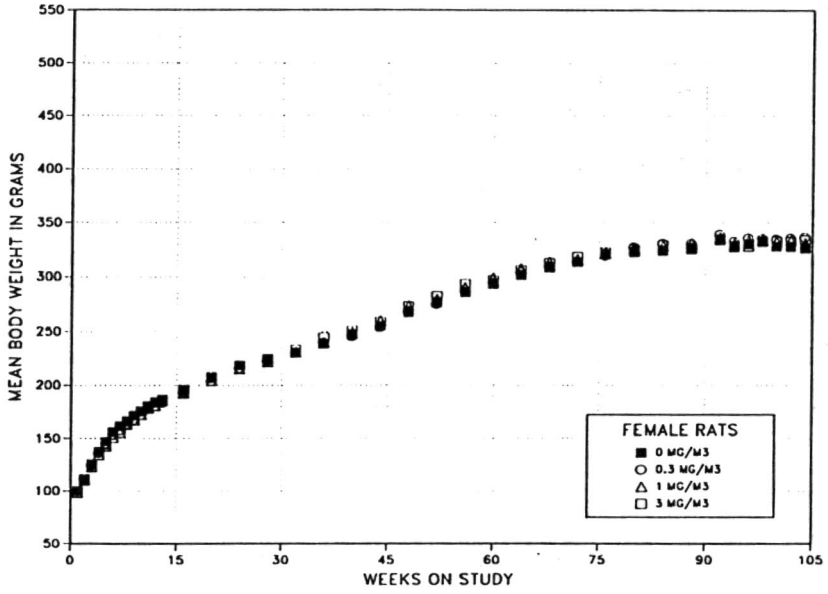


FIGURE 2
Growth Curves for Male and Female Rats
Exposed to Cobalt Sulfate Heptahydrate by Inhalation for 2 Years

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

Weeks on Study	Chamber Control		0.3 mg/m^3			1.0 mg/m^3			3.0 mg/m^3		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	124	50	124	100	50	122	99	50	122	99	50
2	149	50	148	100	50	145	97	50	146	98	50
3	177	50	177	100	50	172	97	50	172	97	50
4	202	50	202	100	50	200	99	50	196	97	50
5	225	50	226	101	50	221	99	50	219	97	50
6	247	50	247	100	50	244	99	50	240	97	50
7	264	50	263	99	50	260	98	50	255	97	50
8	277	50	278	100	50	279	101	50	273	98	50
9	291	50	292	100	50	291	100	50	284	98	50
10	303	50	304	100	50	306	101	50	299	98	50
11	315	50	317	101	50	320	102	50	310	98	50
12	324	50	328	101	50	329	102	50	319	99	50
13	332	50	336	101	50	336	101	50	327	98	50
16	358	50	364	102	50	363	101	50	352	98	50
20	387	50	390	101	50	390	101	50	377	98	50
24	409	50	413	101	50	412	101	50	398	97	50
28	425	50	428	101	50	429	101	50	413	97	50
32	437	50	439	100	50	440	101	50	424	97	50
36	450	50	452	101	50	455	101	50	438	97	50
40	458	50	462	101	50	463	101	49	448	98	50
44	464	50	468	101	50	470	101	49	454	98	50
48	473	50	476	101	50	482	102	49	461	98	50
52	479	50	483	101	50	488	102	49	468	98	50
56	483	50	487	101	50	492	102	49	472	98	50
60	489	50	493	101	49	498	102	49	474	97	49
64	491	49	497	101	49	499	102	48	479	98	49
68	497	48	498	100	49	503	101	47	485	98	47
72	495	48	505	102	46	506	102	47	491	99	47
76	493	48	506	103	46	506	103	45	491	100	46
80	498	43	505	102	45	512	103	43	493	99	43
84	493	40	505	103	42	507	103	42	485	98	38
88	490	32	501	102	39	509	104	41	476	97	33
92	495	27	497	100	33	512	103	36	471	95	29
94	483	24	486	101	28	502	104	34	468	97	25
96	488	23	485	99	26	506	104	31	463	95	24
98	482	21	472	98	23	503	104	27	462	96	21
100	487	18	467	96	19	498	102	26	462	95	18
102	481	18	462	96	17	486	101	24	460	96	16
104	476	18	454	95	16	481	101	22	459	96	15
Mean for weeks											
1-13	248		249	100		248	100		243	98	
14-52	434		438	101		439	101		423	97	
53-104	489		489	100		501	102		474	97	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

Weeks on Study	Chamber Control		0.3 mg/m^3			1.0 mg/m^3			3.0 mg/m^3		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	100	50	100	100	50	99	98	50	99	98	50
2	112	50	112	100	50	110	99	50	111	99	49
3	126	50	125	99	50	123	98	50	123	98	49
4	138	50	136	99	50	134	98	50	134	98	49
5	147	50	145	99	50	143	97	50	144	98	49
6	156	50	154	99	50	151	97	50	154	99	49
7	162	50	158	98	50	156	97	50	158	98	49
8	166	50	164	99	50	163	98	50	166	100	49
9	171	50	168	98	50	168	98	50	170	99	49
10	176	50	173	98	50	173	98	50	176	100	49
11	179	50	178	99	50	179	100	50	181	101	49
12	184	50	181	99	49	181	99	50	184	100	49
13	186	50	184	99	49	186	100	50	187	100	49
16	195	50	193	99	49	193	99	50	196	101	49
20	207	50	204	99	49	205	99	50	208	101	49
24	219	50	216	99	49	215	99	50	219	100	49
28	224	50	223	99	49	222	99	50	225	100	49
32	230	50	230	100	49	231	100	50	233	101	49
36	238	50	240	101	49	241	101	50	244	103	49
40	247	50	246	100	49	249	101	50	251	102	49
44	255	50	254	100	49	260	102	50	259	101	49
48	267	50	269	101	49	273	102	50	273	102	49
52	276	50	275	100	49	279	101	49	282	102	49
56	286	49	288	101	48	290	102	49	293	103	49
60	293	49	294	100	48	299	102	49	297	101	48
64	302	49	304	101	47	307	102	49	306	101	48
68	308	49	310	100	47	313	102	49	312	101	48
72	314	49	314	100	45	316	101	49	318	102	47
76	321	49	320	100	44	322	100	48	323	101	47
80	323	49	328	102	42	326	101	46	325	101	47
84	324	47	331	102	42	329	101	45	329	102	47
88	326	44	331	102	41	331	102	42	327	101	46
92	334	42	339	102	38	337	101	40	335	100	43
94	327	41	333	102	38	331	101	40	328	100	41
96	330	41	336	102	37	334	101	38	328	99	39
98	333	39	336	101	34	334	100	38	333	100	37
100	328	38	335	102	33	333	102	36	333	102	33
102	328	36	336	103	31	334	102	34	333	102	33
104	326	32	337	103	27	331	102	32	334	102	31
Mean for weeks											
1-13	154		152	99		151	98		153	99	
14-52	236		235	100		237	100		239	101	
53-104	319		323	101		323	101		322	101	

Pathology and Statistical Analyses

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

Lung: In all exposed groups of male and female rats, the incidences of proteinosis, alveolar epithelial metaplasia, granulomatous alveolar inflammation, and interstitial fibrosis were significantly greater than those in the chamber controls (Tables 5, A5, and B5). In general, these lung lesions increased in incidence and severity with increased exposure to cobalt sulfate heptahydrate. The incidence of squamous metaplasia in 1.0 mg/m^3 females was significantly greater than in the chamber control group. Multifocally, throughout the lungs, pulmonary architecture was distorted by a combination of inflammatory cells, fibrosis, and epithelial metaplasia. Lesions tended to be subpleural, peripheral, and/or along larger blood vessels and airways. Granulomatous inflammation was characterized by accumulations of alveolar macrophages with foamy cytoplasm, occasional multinucleated giant cells and cholesterol clefts, cell debris and few neutrophils. In these areas, the alveolar interstitium and occasionally the overlying pleura were variably thickened by dense fibrous connective tissue which often effaced alveoli (Plates 1 and 2). Although a diffuse change, aggregates of homogeneous to granular eosinophilic material within alveolar lumens (alveolar proteinosis) were often pronounced within the areas of chronic inflammation. Metaplasia of the alveolar epithelium in alveoli within and at the periphery of foci of inflammation was characterized by replacement of normal Type I epithelial cells with plump cuboidal or ciliated columnar epithelial cells. The incidences of alveolar epithelial hyperplasia in all groups of exposed males and in females exposed to 3.0 mg/m^3 and atypical alveolar epithelial hyperplasia in 3.0 mg/m^3 females were significantly greater than those in the chamber control groups.

The combined incidence of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma) was significantly greater in 3.0 mg/m^3 males than that in the chamber controls and exceeded the historical control range (Tables 5 and A3). In females exposed to 1.0 or 3.0 mg/m^3, the incidences of alveolar/bronchiolar neoplasms were significantly greater than those in the chamber control group and exceeded the historical control ranges (Tables 5, B3, and B4a). Although the incidences of alveolar/bronchiolar adenoma in 3.0 mg/m^3 males and alveolar/bronchiolar carcinoma in 1.0 mg/m^3 males were not significantly increased, they exceeded the historical control ranges for inhalation studies (Tables 5, A3, and A4a).

The spectrum of alveolar/bronchiolar neoplasms and nonneoplastic proliferative lesions observed within the lungs of exposed rats was broad. While many of these lesions were highly cellular and morphologically similar to those observed spontaneously, others were predominantly fibrotic, squamous, or mixtures of alveolar/bronchiolar epithelium and squamous or fibrous components. Hyperplasia generally represented an increase in numbers of epithelial cells along alveolar walls with maintenance of normal alveolar architecture (Plates 3 and 4). Multiple hyperplastic lesions were often observed in animals receiving higher concentrations of cobalt sulfate heptahydrate. The benign neoplasms typical of those observed spontaneously were generally distinct masses that often compressed surrounding tissue (Plates 5 and 6). Component epithelial cells were often arranged in acinar and/or irregular papillary structures and occasionally in a solid cellular pattern. These epithelial cells were typically uniform and similar to hyperplastic counterparts. Malignant alveolar/bronchiolar neoplasms had similar cellular patterns but were generally larger and had one or more of the following histologic features: heterogeneous growth pattern, cellular pleomorphism and/or atypia, and local invasion or metastasis (Plate 7).

In addition to these more typical proliferative lesions, there were “fibroproliferative” lesions ranging from less than 1 mm to greater than 1 cm in diameter. Generally, these lesions had a rounded outline and a central fibrous core containing dispersed glandular (alveolar) structures lined by uniformly cuboidal epithelial cells. Aggregates of mostly necrotic

TABLE 5
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Number Examined Microscopically	50	50	48	50
Alveolar Epithelium, Hyperplasia[a]	9 (1.8)[b]	20* (2.0)	20* (2.1)	23**(2.0)
Alveolar Epithelium, Hyperplasia, Atypical	0	1 (2.0)	2 (3.0)	2 (4.0)
Metaplasia, Squamous	0	1 (1.0)	4 (2.0)	2 (3.0)
Alveolar Epithelium, Metaplasia	0	50**(1.9)	48**(3.1)	49**(3.7)
Inflammation, Granulomatous	2 (1.0)	50**(1.9)	48**(3.1)	50**(3.7)
Interstitium, Fibrosis	1 (1.0)	50**(1.9)	48**(3.1)	49**(3.7)
Proteinosis	0	16**(1.4)	40**(2.3)	47**(3.4)
Cyst	0	0	0	1 (4.0)
Alveolar/bronchiolar Adenoma[c]				
Overall rate[d]	1/50 (2%)	4/50 (8%)	1/48 (2%)	6/50 (12%)
Adjusted rate[e]	2.3%	17.7%	2.4%	28.4%
Terminal rate[f]	0/17 (0%)	2/15 (13%)	0/21 (0%)	2/15 (13%)
First incidence (days)	568	589	611	638
Logistic regression test[g]	P=0.051	P=0.179	P=0.753	P=0.055
Alveolar/bronchiolar Carcinoma[h]				
Overall rate	0/50 (0%)	0/50 (0%)	3/48 (6%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	11.3%	6.7%
Terminal rate	0/17 (0%)	0/15 (0%)	1/21 (5%)	1/15 (7%)
First incidence (days)	—[i]	—	652	734 (T)
Logistic regression test	P=0.360	—	P=0.136	P=0.475
Alveolar/bronchiolar Adenoma or Carcinoma[j]				
Overall rate	1/50 (2%)	4/50 (8%)	4/48 (8%)	7/50 (14%)
Adjusted rate	2.3%	17.7%	13.4%	33.9%
Terminal rate	0/17 (0%)	2/15 (13%)	1/21 (5%)	3/15 (20%)
First incidence (days)	568	589	611	638
Logistic regression test	P=0.032	P=0.179	P=0.163	P=0.029
Female				
Number Examined Microscopically	50	49	50	50
Alveolar Epithelium, Hyperplasia	15 (1.4)	7 (1.6)	20 (1.8)	33**(2.0)
Alveolar Epithelium, Hyperplasia, Atypical	0	0	3 (3.7)	5* (3.2)
Metaplasia, Squamous	0	1 (2.0)	8**(2.3)	3 (1.7)
Alveolar Epithelium, Metaplasia	2 (1.0)	47**(2.0)	50**(3.6)	49**(3.9)
Inflammation, Granulomatous	9 (1.0)	47**(2.0)	50**(3.6)	49**(3.9)
Interstitium, Fibrosis	7 (1.0)	47**(2.0)	50**(3.6)	49**(3.9)
Proteinosis	0	36**(1.2)	49**(2.8)	49**(3.9)
Cyst	0	0	1 (4.0)	0
Alveolar/bronchiolar Adenoma[k]				
Overall rate	0/50 (0%)	1/49 (2%)	10/50 (20%)	9/50 (18%)
Adjusted rate	0.0%	3.4%	36.4%	30.0%
Terminal rate	0/28 (0%)	0/25 (0%)	9/26 (35%)	9/30 (30%)
First incidence (days)	—	714	692	735 (T)
Logistic regression test	P=0.001	P=0.480	P < 0.001	P=0.003

TABLE 5
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Female (continued)				
Alveolar/bronchiolar Carcinoma[l]				
Overall rate	0/50 (0%)	2/49 (4%)	6/50 (12%)	6/50 (12%)
Adjusted rate	0.0%	8.0%	20.2%	17.5%
Terminal rate	0/28 (0%)	2/25 (8%)	4/26 (15%)	4/30 (13%)
First incidence (days)	—	735 (T)	694	610
Logistic regression test	P=0.023	P=0.213	P=0.015	P=0.017
Alveolar/bronchiolar Adenoma or Carcinoma[m]				
Overall rate	0/50 (0%)	3/49 (6%)	15/50 (30%)	15/50 (30%)
Adjusted rate	0.0%	11.2%	50.6%	46.1%
Terminal rate	0/28 (0%)	2/25 (8%)	12/26 (46%)	13/30 (43%)
First incidence (days)	—	714	692	610
Logistic regression test	P < 0.001	P=0.096	P < 0.001	P < 0.001
Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/49 (0%)	1/50 (2%)	1/50 (2%)
Alveolar/bronchiolar Adenoma, Alveolar/bronchiolar Carcinoma, or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	3/49 (6%)	16/50 (32%)	16/50 (32%)
Adjusted rate	0.0%	11.2%	54.1%	49.2%
Terminal rate	0/28 (0%)	2/25 (8%)	13/26 (50%)	14/30 (47%)
First incidence (days)	—	714	692	610
Logistic regression test	P < 0.001	P=0.096	P < 0.001	P < 0.001

* Significantly different (P≤0.05) from the chamber control by the logistic regression test
** P≤0.01
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 17/654 (2.6% ± 3.6%); range 0%-10%
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber 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 chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[h] Historical incidence: 6/654 (0.9% ± 1.0%); range 0%-2%
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 23/654 (3.5% ± 3.7%); range 0%-10%
[k] Historical incidence: 7/650 (1.1% ± 1.6%); range 0%-4%
[l] Historical incidence: 0/650
[m] Historical incidence: 7/650 (1.1% ± 1.6%); range 0%-4%

inflammatory cells were also present in adjacent alveoli and often within the glandular structures. Peripherally, the fibroproliferative lesions had one to several layers of epithelium which coursed along and often extended into adjacent alveoli, frequently forming papillary projections (Plates 8, 9, and 10). These epithelial cells were often slightly pleomorphic with occasional mitotic figures. The smallest of these lesions were usually observed adjacent to areas of chronic inflammation. Small lesions with modest amounts of peripheral epithelial proliferation were diagnosed as atypical hyperplasia, while larger lesions with florid epithelial proliferation, marked cellular pleomorphism, and/or local invasion were diagnosed as alveolar/bronchiolar carcinomas (Plate 11).

While squamous epithelium is not normally observed within the lung, squamous metaplasia of alveolar/ bronchiolar epithelium is a relatively common response to pulmonary injury and occurred in a number of rats in this study (Table 5). Squamous metaplasia was a minor change consisting of a small cluster of alveoli in which the normal epithelium was replaced by multiple layers of flattened squamous epithelial cells (Plate 12) that occasionally formed keratin. One 3.0 mg/m^3 male and one 1.0 mg/m^3 female had a large cystic squamous lesion rimmed by a variably thick (a few to many cell layers) band of viable squamous epithelium with a large central core of keratin (Plate 13). These were diagnosed as cysts. In one 1.0 mg/m^3 and one 3.0 mg/m^3 female, proliferative squamous lesions had cystic areas but also more solid areas of pleomorphic cells and invasion into the adjacent lung; these lesions were considered to be squamous cell carcinomas (Plate 14). In general, diagnoses of squamous lesions were made only when the lesion composition was almost entirely squamous epithelium. However, squamous metaplasia/ differentiation was a variable component of other alveolar/bronchiolar proliferative lesions (Plate 15), including the fibroproliferative lesions, and was clearly a part of the spectrum of lesions resulting from exposure to cobalt sulfate heptahydrate.

Adrenal Medulla: The incidence of benign pheochromocytoma in 3.0 mg/m^3 females was significantly greater than that in the chamber controls and exceeded the historical range for inhalation studies (Tables 6, B3, and B4b). The incidences of benign, complex, or malignant pheochromocytoma (combined) in 1.0 mg/m^3 males and in 3.0 mg/m^3 females were significantly greater than those in the chamber controls and exceeded the historical control ranges (Tables 6, A3, A4b, B3, and B4b).

The incidences of bilateral pheochromocytoma in exposed males slightly exceeded that in the chamber control group. The incidence of hyperplasia was not significantly increased in exposed males or females. Focal hyperplasia and pheochromocytoma are considered to constitute a morphological continuum in the adrenal medulla. Focal hyperplasia consisted of irregular, small foci of small- to normal-sized medullary cells arranged in packets or solid clusters slightly larger than normal; compression of surrounding parenchyma was minimal or absent. Benign pheochromocytomas were well-delineated masses often with altered architecture and variable compression of surrounding parenchyma. Neoplastic cells were arranged in variably sized aggregates, clusters, and/or variably thick trabecular cords. Larger neoplasms usually exhibited greater cellular pleomorphism and atypia than smaller neoplasms. Malignant pheochromocytomas were identified when there was invasion of or beyond the adrenal capsule or when distant metastases were observed. Although a very common spontaneous neoplasm in male F344/N rats, pheochromocytomas have a lower spontaneous occurrence in females. In this study, the incidence of pheochromocytoma in 3.0 mg/m^3 females was considered related to the administration of cobalt sulfate heptahydrate. The marginally increased incidence of pheochromocytoma in males was considered an uncertain finding because it occurred only in the 1.0 mg/m^3 group and was not supported by increased incidence or severity of hyperplasia.

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Number Examined Microscopically	50	50	49	50
Hyperplasia[a]	34 (2.0)[b]	23* (2.5)	29 (2.1)	30 (2.1)
Benign Bilateral Pheochromocytoma				
Overall rate	1/50 (2%)	4/50 (8%)	6/49 (12%)	5/50 (10%)
Benign Pheochromocytoma (includes benign bilateral pheochromocytoma)[c]				
Overall rate[d]	14/50 (28%)	19/50 (38%)	23/49 (47%)	20/50 (40%)
Adjusted rate[e]	51.0%	70.0%	71.9%	71.4%
Terminal rate[f]	6/17 (35%)	8/15 (53%)	13/21 (62%)	8/15 (53%)
First incidence (days)	534	541	526	526
Logistic regression test[g]	P=0.172	P=0.226	P=0.069	P=0.126
Benign, Complex, or Malignant Pheochromocytoma (includes benign bilateral pheochromocytoma)[h]				
Overall rate	15/50 (30%)	19/50 (38%)	25/49 (51%)	20/50 (40%)
Adjusted rate	52.1%	70.0%	74.1%	71.4%
Terminal rate	6/17 (35%)	8/15 (53%)	13/21 (62%)	8/15 (53%)
First incidence (days)	534	541	526	526
Logistic regression test	P=0.218	P=0.295	P=0.045	P=0.180
Female				
Number Examined Microscopically	48	49	50	48
Hyperplasia	8 (1.6)	7 (2.3)	11 (2.1)	13 (2.0)
Benign Pheochromocytoma[i]				
Overall rate	2/48 (4%)	1/49 (2%)	3/50 (6%)	8/48 (17%)
Adjusted rate	5.1%	3.1%	9.3%	26.4%
Terminal rate	0/27 (0%)	0/25 (0%)	1/26 (4%)	7/29 (24%)
First incidence (days)	666	702	694	709
Logistic regression test	P=0.004	P=0.498N	P=0.512	P=0.043
Benign, Complex, or Malignant Pheochromocytoma[j]				
Overall rate	2/48 (4%)	1/49 (2%)	4/50 (8%)	10/48 (21%)
Adjusted rate	5.1%	3.1%	11.7%	31.5%
Terminal rate	0/27 (0%)	0/25 (0%)	1/26 (4%)	8/29 (28%)
First incidence (days)	666	702	685	663
Logistic regression test	P < 0.001	P=0.498N	P=0.323	P=0.014

* Significantly different ($P \leq 0.05$) from the chamber control by the logistic regression test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 163/623 (26.2% ± 13.2%); range 0%-50%
[d] Number of animals with neoplasm per number of animals with adrenal medulla examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber 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 chamber 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**.
[h] Historical incidence: 176/623 (28.3% ± 12.0%); range 8%-50%
[i] Historical incidence: 35/608 (5.8% ± 4.9%); range 0%-14%
[j] Historical incidence: 39/608 (6.4% ± 4.4%); range 2%-14%

Nose: The incidences of hyperplasia of the lateral wall of the nose and atrophy of the olfactory epithelium in all exposed groups of males and females were significantly greater than those in the chamber controls, and the severities of these lesions increased with increasing exposure concentration (Tables 7, A5, and B5). The incidences of squamous metaplasia of the lateral wall of the nose and metaplasia of the olfactory epithelium in 3.0 mg/m^3 males and females were significantly greater than those in the chamber controls.

Although the incidence and severity of nasal lesions increased with increased exposure to cobalt sulfate heptahydrate, they involved limited portions of nasal epithelium and none were severe. Hyperplasia and squamous metaplasia were minimal to mild, unilateral or bilateral, and involved the transitional epithelium along the walls and turbinates of the anterior nasal passage. Hyperplasia was characterized by an increase in thickness of the epithelium from the normal one to two layers to two or more layers, while squamous metaplasia represented areas where the normal transitional epithelium was replaced by multiple layers of flattened epithelial cells. More posterior in the nose, along the dorsal meatus, atrophy of the olfactory epithelium was characterized by loss of cell layers and disorganization of remaining epithelium, and in some instances, increased prominence of sensory cell nuclei. Metaplasia was characterized by replacement of olfactory epithelium with respiratory-type ciliated columnar epithelium.

TABLE 7
Incidences of Nonneoplastic Lesions of the Nose and Larynx in Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Nose[a]	50	50	49	50
Lateral Wall, Hyperplasia[b]	2 (1.5)[c]	14**(1.4)	21**(1.5)	20**(1.6)
Lateral Wall, Metaplasia, Squamous	1 (1.0)	3 (1.3)	5 (1.4)	8* (2.0)
Olfactory Epithelium, Atrophy	8 (1.1)	24**(1.4)	42**(1.5)	48**(2.5)
Olfactory Epithelium, Metaplasia	5 (1.2)	1 (3.0)	5 (1.8)	30**(1.9)
Larynx	50	49	48	50
Epiglottis, Metaplasia, Squamous	0	10**(1.3)	37**(1.8)	50**(2.8)
Female				
Nose	50	49	50	50
Lateral Wall, Hyperplasia	1 (1.0)	8* (1.3)	26**(1.4)	38**(1.7)
Lateral Wall, Metaplasia, Squamous	1 (1.0)	1 (3.0)	4 (1.3)	10**(1.4)
Olfactory Epithelium, Atrophy	5 (1.4)	29**(1.2)	46**(1.6)	47**(2.9)
Olfactory Epithelium, Metaplasia	2 (2.0)	2 (1.5)	3 (1.7)	40**(2.3)
Larynx	50	49	50	50
Epiglottis, Metaplasia, Squamous	1 (1.0)	22**(1.1)	39**(1.4)	48**(2.6)

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

Larynx: The incidences of squamous metaplasia of the epiglottis in all exposed groups of males and females were significantly greater than those in the chamber controls, and the severity of this lesion increased with increasing exposure concentration (Tables 7, A5, and B5). Squamous metaplasia was limited to the base of the epiglottis and was not a severe lesion in exposed rats. It was characterized by replacement of the ciliated respiratory epithelium by one or more layers of flattened epithelial cells overlying a basal layer of cuboidal cells. Keratinization was sometimes observed.

MICE

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 8 and in the Kaplan-Meier survival curves (Figure 3). Survival of exposed males and females was similar to that of the chamber controls.

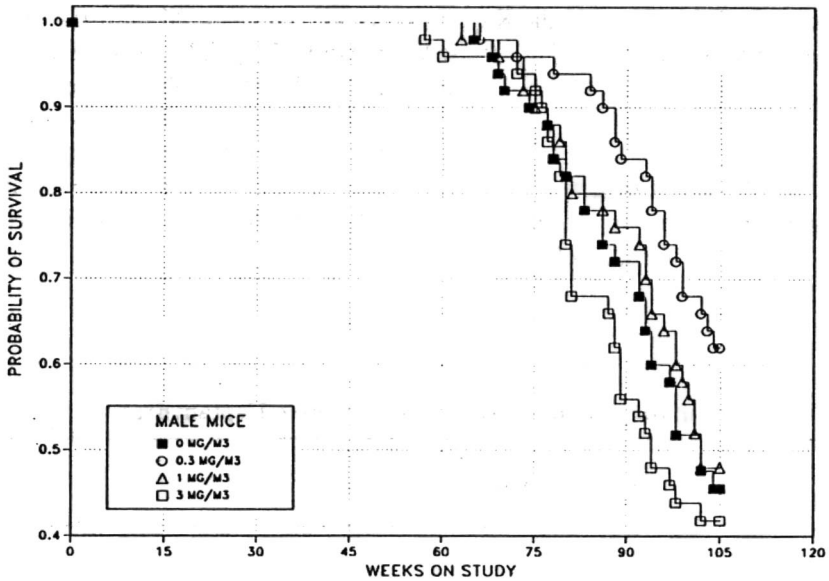
Body Weights and Clinical Findings

Mean body weights are given in Figure 4 and Tables 9 and 10. Mean body weights of 3.0 mg/m^3 male mice were less than those of the chamber controls from week 96 until the end of the study. The mean body weights of all exposed female mice were generally greater than those of the chamber controls from week 20 until the end of the study. Irregular breathing was observed slightly more frequently in female mice exposed to 1.0 mg/m^3 than in the chamber controls or other exposed groups.

TABLE 8
Survival of Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	1	0	0	1
Moribund	19	16	17	23
Natural deaths	8	3	9	6
Animals surviving to study termination	22	31	24	20
Percent probability of survival at end of study[b]	46	62	48	42
Mean survival (days)[c]	662	695	670	643
Survival analysis[d]	P=0.104	P=0.088N	P=0.861N	P=0.577
Female				
Animals initially in study	50	50	50	50
Moribund	11	10	13	16
Natural deaths	5	3	5	6
Animals surviving to study termination	34	37	32	28
Percent probability of survival at end of study	68	74	64	56
Mean survival (days)	694	713	685	680
Survival analysis	P=0.102	P=0.529N	P=0.855	P=0.327

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



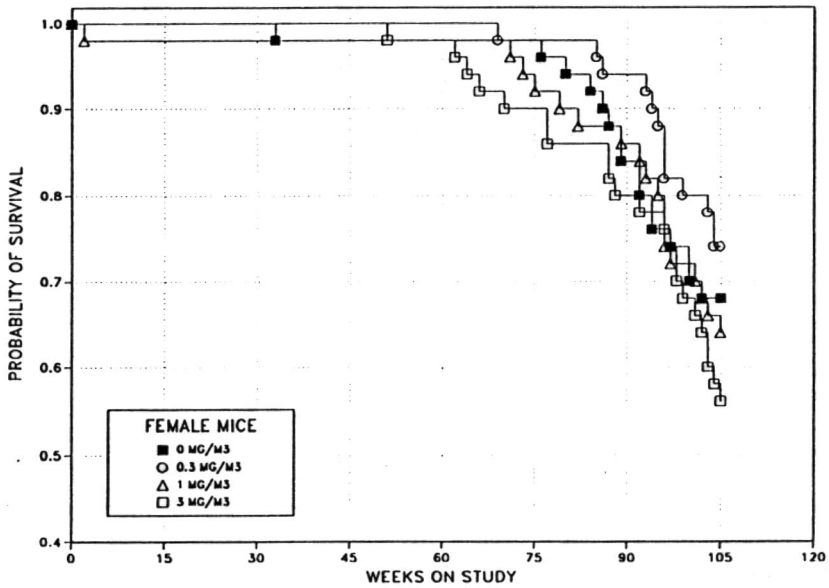
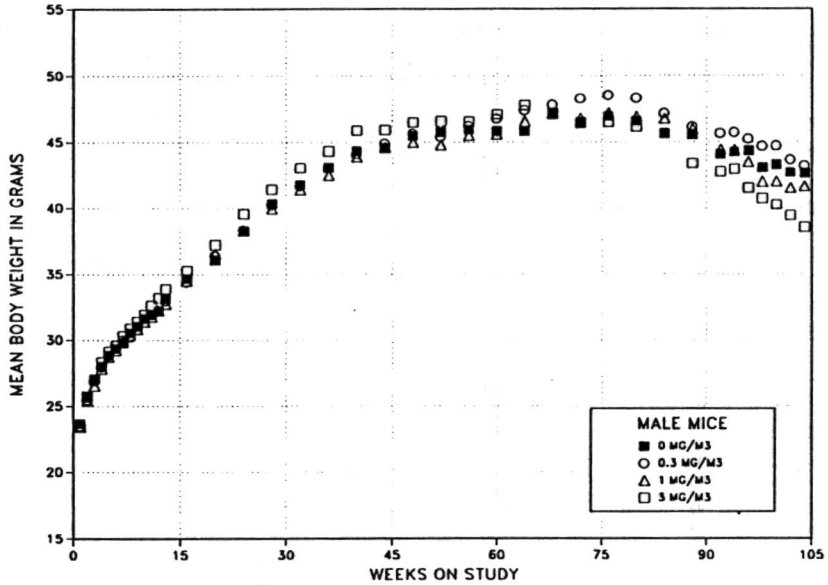


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Cobalt Sulfate Heptahydrate by Inhalation for 2 Years



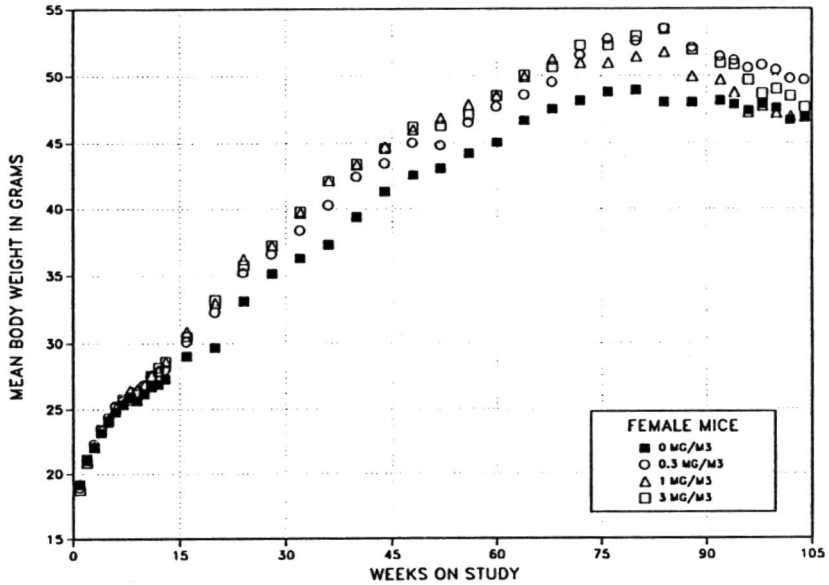


FIGURE 4
Growth Curves for Male and Female Mice Exposed to Cobalt Sulfate Heptahydrate by Inhalation for 2 Years

TABLE 9
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

Weeks on Study	Chamber Control		0.3 mg/m^3			1.0 mg/m^3			3.0 mg/m^3		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.7	50	23.5	99	50	23.4	99	50	23.4	99	50
2	25.8	50	25.5	99	50	25.4	98	50	25.7	100	50
3	27.0	50	26.9	100	50	26.6	99	50	27.1	100	50
4	28.0	50	27.9	100	50	27.8	99	50	28.3	101	50
5	28.8	50	28.8	100	50	28.7	100	50	29.1	101	50
6	29.3	50	29.6	101	50	29.2	100	50	29.6	101	50
7	29.8	50	30.0	101	50	30.0	101	50	30.3	102	50
8	30.5	50	30.2	99	50	30.4	100	50	30.9	101	50
9	31.0	50	30.8	99	50	30.8	99	50	31.4	101	50
10	31.6	50	31.3	99	50	31.4	99	50	31.9	101	50
11	32.0	50	31.9	100	50	31.8	99	50	32.7	102	50
12	32.2	50	32.2	100	50	32.2	100	50	33.2	103	50
13	33.1	50	33.0	100	50	32.7	99	50	33.9	102	50
16	34.7	50	34.4	99	50	34.5	99	50	35.3	102	50
20	36.1	50	36.4	101	50	36.6	101	50	37.2	103	50
24	38.3	50	38.4	100	50	38.3	100	50	39.6	103	50
28	40.3	50	40.3	100	50	40.0	99	50	41.4	103	50
32	41.8	50	41.7	100	50	41.4	99	50	43.1	103	50
36	43.1	50	43.1	100	50	42.5	99	50	44.3	103	50
40	44.3	50	44.1	100	50	43.9	99	50	45.9	104	50
44	44.6	50	44.9	101	50	44.7	100	50	45.9	103	50
48	45.5	50	45.6	100	50	45.0	99	50	46.5	102	50
52	45.8	50	45.4	99	50	44.8	98	50	46.6	102	50
56	45.9	50	46.2	101	50	45.5	99	50	46.5	101	50
60	45.8	50	46.8	102	50	45.6	100	50	47.1	103	48
64	45.8	50	47.4	104	50	46.6	102	49	47.8	104	48
68	47.1	48	47.8	102	49	47.2	100	49	47.2	100	48
72	46.4	46	48.3	104	48	46.8	101	48	46.5	100	48
76	46.9	45	48.5	103	48	47.2	101	45	46.5	99	46
80	46.6	42	48.3	104	47	46.9	101	43	46.1	99	40
84	45.6	39	47.2	104	47	46.7	102	40	45.7	100	34
88	45.5	37	46.1	101	45	46.0	101	38	43.4	95	32
92	44.1	36	45.6	103	42	44.4	101	38	42.8	97	28
94	44.2	32	45.7	103	41	44.4	101	35	42.9	97	26
96	44.3	30	45.2	102	39	43.5	98	33	41.5	94	24
98	43.0	29	44.7	104	37	42.0	98	32	40.7	95	22
100	43.3	25	44.7	103	34	42.0	97	29	40.3	93	21
102	42.7	25	43.7	102	34	41.5	97	26	39.5	93	21
104	42.6	23	43.2	101	32	41.6	98	24	38.5	90	20
Mean for weeks											
1-13	29.4		29.4	100		29.3	100		29.8	101	
14-52	41.5		41.4	100		41.2	99		42.6	103	
53-104	45.0		46.2	103		44.9	100		43.9	98	

TABLE 10
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

Weeks on Study	Chamber Control		0.3 mg/m^3			1.0 mg/m^3			3.0 mg/m^3		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.2	50	18.9	98	50	19.2	100	50	18.7	97	50
2	21.2	50	21.1	100	50	21.1	100	50	20.8	98	50
3	22.0	50	22.3	101	50	22.2	101	49	22.1	101	50
4	23.2	50	23.5	101	50	23.4	101	49	23.5	101	50
5	24.0	50	24.4	102	50	24.3	101	49	24.1	100	50
6	24.8	50	25.3	102	50	25.1	101	49	25.1	101	50
7	25.4	50	25.6	101	50	25.5	100	49	25.8	102	50
8	26.0	50	25.9	100	50	26.5	102	49	25.7	99	50
9	25.6	50	26.2	102	50	26.6	104	49	26.4	103	50
10	26.2	50	26.9	103	50	26.9	103	49	26.8	102	50
11	26.7	50	27.5	103	50	27.6	103	49	27.6	103	50
12	26.9	50	27.9	104	50	28.0	104	49	28.2	105	50
13	27.3	50	28.0	103	50	28.6	105	49	28.6	105	50
16	29.1	50	30.1	103	50	30.9	106	49	30.5	105	50
20	29.7	50	32.3	109	50	33.0	111	49	33.2	112	50
24	33.1	50	35.3	107	50	36.3	110	49	35.8	108	50
28	35.2	50	36.6	104	50	37.3	106	49	37.3	106	50
32	36.3	50	38.4	106	50	39.7	109	49	39.8	110	50
36	37.3	49	40.3	108	50	42.1	113	49	42.1	113	50
40	39.4	49	42.4	108	50	43.3	110	49	43.4	110	50
44	41.3	49	43.4	105	50	44.7	108	49	44.5	108	50
48	42.5	49	45.0	106	50	46.0	108	49	46.2	109	50
52	43.0	49	44.8	104	50	46.9	109	49	46.3	108	49
56	44.2	49	46.5	105	50	47.9	108	49	47.1	107	49
60	45.0	49	47.7	106	50	48.5	108	49	48.5	108	49
64	46.7	49	48.6	104	50	49.9	107	49	50.1	107	47
68	47.5	49	49.5	104	50	51.3	108	49	50.7	107	46
72	48.2	49	51.6	107	49	51.0	106	48	52.3	109	45
76	48.8	49	52.8	108	49	51.0	105	46	52.3	107	45
80	48.9	48	52.6	108	49	51.4	105	45	53.0	108	43
84	48.1	46	53.5	111	49	51.8	108	44	53.5	111	43
88	48.1	44	52.1	108	47	50.0	104	44	51.9	108	41
92	48.2	42	51.5	107	47	49.7	103	43	51.0	106	40
94	47.9	40	51.2	107	46	48.8	102	41	50.8	106	39
96	47.4	38	50.6	107	44	47.3	100	40	49.7	105	39
98	47.9	37	50.8	106	41	47.8	100	36	48.7	102	37
100	47.6	37	50.5	106	40	47.2	99	36	49.0	103	34
102	46.7	35	49.8	107	40	47.0	101	35	48.5	104	33
104	46.9	34	49.7	106	39	46.9	100	33	47.7	102	30
Mean for weeks											
1-13	24.5		24.9	102		25.0	102		24.9	102	
14-52	36.7		38.9	106		40.0	109		39.9	109	
53-104	47.4		50.6	107		49.2	104		50.3	106	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the lung, nose, larynx, thyroid gland, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Lung: In all exposed groups of males and females, the incidences of cytoplasmic vacuolization of the bronchi were significantly greater than those in the chamber control groups (Tables 11, C5, and D5). The incidences of diffuse histiocytic cell infiltration in 3.0 mg/m^3 males and of focal histiocytic cell infiltration in 3.0 mg/m^3 females were significantly greater than those in the chamber controls.

Cytoplasmic vacuolization of the bronchial epithelium was a minimal change of unknown biological significance confined to the epithelial cells lining the apex of the bronchial bifurcation. The affected cells were somewhat larger than normal with a diffusely clear to finely vacuolated cytoplasm. Histiocyte infiltration was characterized by one or more histiocytes with foamy cytoplasm within variable numbers of alveolar lumens. Focal infiltrate was a localized accumulation of histiocytes, while diffuse infiltrate was more widely scattered. The histiocyte infiltrate was very commonly seen in lungs with alveolar/bronchiolar neoplasms, and the increased incidences of infiltrate in the lungs of exposed animals were considered to reflect the higher incidences of lung neoplasms in these animals rather than a primary effect of cobalt sulfate heptahydrate exposure.

The incidences of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma) in 3.0 mg/m^3 males and females and the combined incidence of alveolar/bronchiolar neoplasms in 1.0 mg/m^3 females were significantly greater than those in the chamber control groups and generally exceeded the historical control ranges for inhalation studies (Tables 11, C3, C4a, D3, and D4a). In exposed males and females, the incidences of all lung neoplasms occurred with positive trends.

Unlike in the rat, all the alveolar/bronchiolar proliferative lesions observed within the lungs of exposed mice were typical of those observed spontaneously. Hyperplasia generally represented an increase in numbers of epithelial cells along alveolar walls which retained normal alveolar structure. Adenomas generally were distinct masses that often compressed surrounding tissue (Plate 16). Component cells were arranged in acinar and/or irregular papillary structures and occasionally in a solid cellular pattern. These cells were typically uniform and similar to hyperplastic counterparts. Malignant alveolar/bronchiolar neoplasms had similar cellular patterns but were generally larger (Plate 17) and had one or more of the following: heterogeneous growth pattern, cellular pleomorphism, and/or atypia and local invasion or metastasis.

Although similar in appearance to “spontaneous” lung neoplasms in chamber controls, alveolar/ bronchiolar neoplasms in mice exposed to cobalt sulfate heptahydrate had different molecular lesions in the K*ras* gene (Appendix I). Of the K-*ras* mutations detected at the second base of codon 12, a higher frequency (5/9, 55%) of G to T transversions was detected compared to concurrent (0/1) and historical control lung neoplasms (1/24, 4%). K-*ras* codon 61 CTA or CGA mutations were not present in cobalt sulfate heptahydrate-induced lung neoplasms.

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Number Examined Microscopically	50	50	50	50
Infiltration Cellular, Diffuse, Histiocyte[a]	1 (3.0)[b]	2 (3.0)	4 (2.3)	10**(1.5)
Infiltration Cellular, Focal, Histiocyte	10 (2.7)	5 (2.6)	8 (3.0)	17 (2.7)
Bronchus, Cytoplasmic Vacuolization	0	18**(1.0)	34**(1.0)	38**(1.0)
Alveolar Epithelium Hyperplasia	0	4 (2.3)	4 (1.8)	4 (2.3)
Alveolar/bronchiolar Adenoma[c]				
Overall rate[d]	9/50 (18%)	12/50 (24%)	13/50 (26%)	18/50 (36%)
Adjusted rate[e]	30.4%	30.9%	41.1%	54.6%
Terminal rate[f]	4/22 (18%)	6/31 (19%)	7/24 (29%)	7/20 (35%)
First incidence (days)	600	460	548	524
Logistic regression test[g]	P=0.018	P=0.353	P=0.256	P=0.027
Alveolar/bronchiolar Carcinoma[h]				
Overall rate	4/50 (8%)	5/50 (10%)	7/50 (14%)	11/50 (22%)
Adjusted rate	13.2%	16.1%	25.3%	43.7%
Terminal rate	2/22 (9%)	5/31 (16%)	4/24 (17%)	7/20 (35%)
First incidence (days)	449	733 (T)	687	552
Logistic regression test	P=0.006	P=0.528	P=0.273	P=0.033
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	11/50 (22%)	14/50 (28%)	19/50 (38%)	28/50 (56%)
Adjusted rate	35.5%	36.5%	56.5%	78.8%
Terminal rate	5/22 (23%)	8/31 (26%)	10/24 (42%)	13/20 (65%)
First incidence (days)	449	460	548	524
Logistic regression test	P < 0.001	P=0.345	P=0.071	P < 0.001
Female				
Number Examined Microscopically	50	50	50	50
Infiltration Cellular, Diffuse, Histiocyte	0	0	0	4 (3.3)
Infiltration Cellular, Focal, Histiocyte	2 (2.0)	5 (1.8)	7 (2.9)	10* (2.4)
Bronchus, Cytoplasmic Vacuolization	0	6* (1.0)	31**(1.0)	43**(1.0)
Alveolar Epithelium Hyperplasia	2 (1.5)	3 (1.3)	0	5 (2.0)
Alveolar/bronchiolar Adenoma[j]				
Overall rate	3/50 (6%)	6/50 (12%)	9/50 (18%)	10/50 (20%)
Adjusted rate	8.8%	15.0%	25.2%	32.8%
Terminal rate	3/34 (9%)	4/37 (11%)	6/32 (19%)	8/28 (29%)
First incidence (days)	734 (T)	664	649	706
Logistic regression test	P=0.024	P=0.287	P=0.057	P=0.024
Alveolar/bronchiolar Carcinoma[k]				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	9/50 (18%)
Adjusted rate	2.9%	2.7%	9.2%	25.3%
Terminal rate	1/34 (3%)	1/37 (3%)	1/32 (3%)	4/28 (14%)
First incidence (days)	734 (T)	734 (T)	495	536
Logistic regression test	P < 0.001	P=0.743N	P=0.201	P=0.009

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Female (continued)				
Alveolar/bronchiolar Adenoma or Carcinoma[l]				
Overall rate	4/50 (8%)	7/50 (14%)	13/50 (26%)	18/50 (36%)
Adjusted rate	11.8%	17.5%	32.6%	50.2%
Terminal rate	4/34 (12%)	5/37 (14%)	7/32 (22%)	11/28 (39%)
First incidence (days)	734 (T)	664	495	536
Logistic regression test	P < 0.001	P=0.318	P=0.016	P < 0.001

* Significantly different (P≤0.05) from the chamber control by the logistic regression test
** P≤0.01
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Historical incidence for 2-year NTP inhalation studies with chamber control groups (mean ± standard deviation): 141/947 (14.9% ± 7.0%); range 6%-36%
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber 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 chamber 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**.
[h] Historical incidence: 75/947 (7.9% ± 5.7%); range 0%-16%
[i] Historical incidence: 205/947 (21.7% ± 8.0%); range 10%-42%
[j] Historical incidence: 61/939 (6.5% ± 3.2%); range 0%-14%
[k] Historical incidence: 38/939 (4.1% ± 3.2%); range 0%-12%
[l] Historical incidence: 97/939 (10.3% ± 3.7%); range 0%-16%

Nose: The incidences of atrophy of the olfactory epithelium in 1.0 and 3.0 mg/m^3 males and females and hyperplasia of the olfactory epithelium in 3.0 mg/m^3 males and females were significantly greater than those in the chamber controls. The incidences of suppurative inflammation in 3.0 mg/m^3 males and in 1.0 mg/m^3 females were significantly greater than those in the chamber controls (Tables 12, C5, and D5). The nasal lesions in mice were less severe than in the rats and involved limited segments of the olfactory epithelium located further back in the nasal passage. Atrophy of the olfactory epithelium was characterized by loss of cell layers (sensory cells) and a decrease in the number of axons in the lamina propria. Hyperplasia of the olfactory epithelium was observed only in animals exposed to 3.0 mg/m^3 and was characterized by increased numbers of sensory cells that were usually arranged in nests or rosettes. The suppurative inflammation involved only a few animals and was a very mild change. It primarily involved animals that died prior to the end of the study and consisted of a focal aggregate of inflammatory cells.

Larynx: The incidences of squamous metaplasia in all exposed groups of males and females were significantly greater than those in the chamber controls (Tables 12, C5, and D5). Squamous metaplasia was limited to the base of the epiglottis and was not a severe lesion in exposed mice. It was characterized by replacement of the ciliated respiratory epithelium by one or more layers of flattened epithelial cells overlying a basal layer of cuboidal cells. Keratinization was sometimes observed.

TABLE 12
Incidences of Nonneoplastic Lesions of the Nose and Larynx in Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Nose[a]	50	50	48	49
Olfactory Epithelium, Atrophy[b]	0	0	29**(1.2)[c]	48**(1.8)
Olfactory Epithelium, Hyperplasia	0	0	0	10**(1.0)
Inflammation, Suppurative	0	1 (3.0)	0	6* (2.2)
Larynx	48	49	48	49
Metaplasia, Squamous	0	37**(1.0)	48**(1.0)	44**(1.0)
Female				
Nose	50	50	49	48
Olfactory Epithelium, Atrophy	0	2 (1.5)	12**(1.0)	46**(1.5)
Olfactory Epithelium, Hyperplasia	0	0	0	30**(1.3)
Inflammation, Suppurative	0	1 (1.0)	5* (1.6)	4 (1.5)
Larynx	50	49	47	50
Metaplasia, Squamous	0	45**(1.0)	40**(1.0)	50**(1.1)

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

Thyroid Gland: The incidences of follicular cell hyperplasia in all exposed groups of males were significantly greater than the incidence in the chamber controls (chamber control, 3/49; 0.3 mg/m^3, 17/50; 1.0 mg/m^3, 11/50; 3.0 mg/m^3, 10/50; Table C5). Minimal hyperplasias are commonly observed in untreated male and female mice, suggesting that the rate in the concurrent chamber control group is low. The severity of most hyperplasias in these mice was minimal to mild and did not differ between chamber control and exposed groups. The incidence of hyperplasia did not increase with exposure to cobalt sulfate heptahydrate, nor was the incidence of neoplasms of the follicular cells increased.

Liver: High incidences of chronic inflammation, karyomegaly, oval cell hyperplasia, and regeneration occurred in all groups of male mice and were usually observed together in the same liver (Tables 13 and C5). These changes were generally mild to moderate in severity and observed throughout the liver (usually not within proliferative lesions), but they appeared most pronounced in the portal regions. Similar lesions were observed in only a few females, and the severity was also much less than that observed in most males (Tables 13 and D5). This spectrum of lesions is consistent with those observed with *Helicobacter hepaticus* infection (Appendix J). Liver sections from four of five male mice with liver lesions were positive for bacterial organisms consistent with *H. hepaticus* when examined using Steiner's modification of the Warthin Starry silver stain.

The incidences of hemangiosarcoma in all exposed groups of male mice and in 1.0 mg/m^3 in female mice exceeded the range observed in historical controls for inhalation studies (Tables 13, C3, and C4b). In addition, the incidence of hemangiosarcoma in 1.0 mg/m^3 males was significantly greater than that in

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Male				
Number Examined Microscopically	50	50	50	50
Inflammation, Chronic[a]	33 (1.3)[b]	36 (1.6)	40 (1.7)	39 (1.3)
Karyomegaly	39 (2.3)	35 (2.8)	39 (2.7)	43 (2.7)
Regeneration	32 (2.3)	30 (2.7)	35 (2.4)	38 (2.8)
Bile Duct, Hyperplasia	0	3 (1.3)	6* (1.7)	4 (2.5)
Oval Cell, Hyperplasia	38 (2.6)	36 (2.8)	40 (2.7)	44 (2.7)
Hemangiosarcoma[c]				
Overall rate[d]	2/50 (4%)	4/50 (8%)	8/50 (16%)	7/50 (14%)
Adjusted rate[e]	9.1%	11.5%	23.5%	25.0%
Terminal rate[f]	2/22 (9%)	2/31 (6%)	2/24 (8%)	3/20 (15%)
First incidence (days)	733 (T)	685	523	502
Logistic regression test[g]	P=0.078	P=0.441	P=0.050	P=0.069
Female				
Number Examined Microscopically	50	50	50	49
Inflammation, Chronic	6 (1.7)	1 (1.0)	1 (1.0)	2 (2.0)
Karyomegaly	4 (2.8)	2 (1.5)	0	1 (2.0)
Oval Cell, Hyperplasia	2 (2.0)	1 (2.0)	0	0
Hemangiosarcoma[h]				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted rate	2.9%	0.0%	7.3%	0.0%
Terminal rate	1/34 (3%)	0/37 (0%)	1/32 (3%)	0/28 (0%)
First incidence (days)	734 (T)	—[i]	524	—
Logistic regression test	P=0.431N	P=0.483N	P=0.318	P=0.539N

* Significantly different (P≤0.05) from the chamber control by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Historical incidence for 2-year NTP inhalation studies with chamber control groups (mean ± standard deviation): 12/947 (1.3% ± 1.7%); range 0%-6%
[d] Number of animals with neoplasm per number of animals with liver examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber 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 chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend or lower incidence in an exposure group is indicated by **N**.
[h] Historical incidence: 5/937 (0.5% ± 1.0%); range 0%-3%
[i] Not applicable; no neoplasms in animal group

the chamber controls. Hemangiosarcomas were morphologically similar to those observed spontaneously and consisted of multiple variably sized blood-filled spaces that were separated by cords of hepatocytes and lined by plump endothelial cells.

GENETIC TOXICOLOGY

Cobalt sulfate heptahydrate (3 to 10,000 µg/mL) was mutagenic in *Salmonella typhimurium* strain TA100 in the absence of S9 metabolic activation, and with 5% hamster or rat liver S9; no mutagenicity was detected in strain TA98 or TA1535, with or without S9 (Zeiger *et al.*, 1992; Table E1).

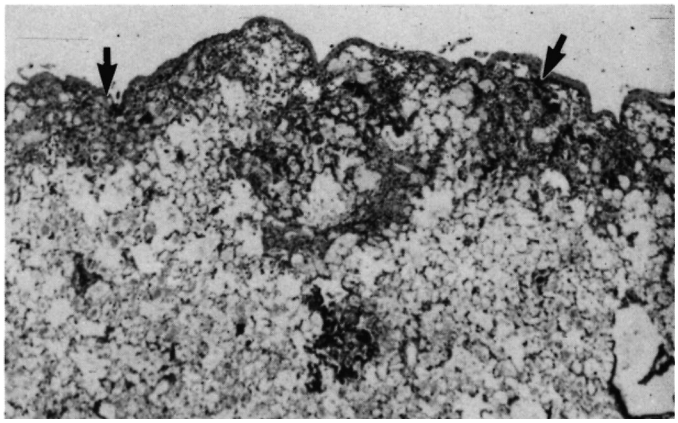


PLATE 1
Low magnification of a typical area of chronic inflammation (arrows) in the lung of a female F344/N rat exposed to 3.0mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 20×

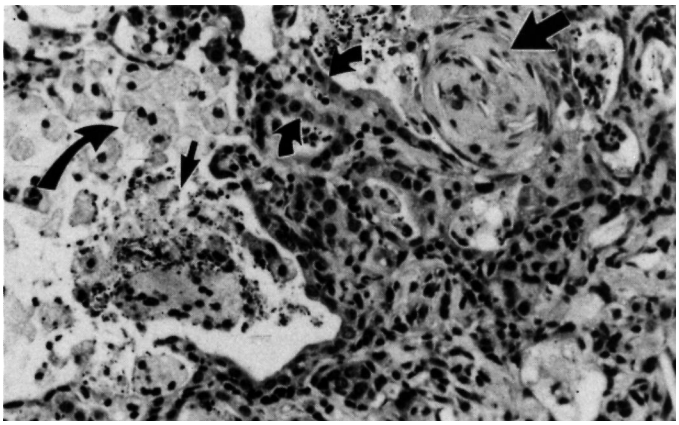


PLATE 2
Higher magnification of an area of chronic inflammation. Note the areas of fibrosis (large arrow), foamy alveolar macrophages (large curved arrow), necrotic cellular debris (small arrow), and epithelial hyperplasia (curved arrows) in the lung of a female F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 160×

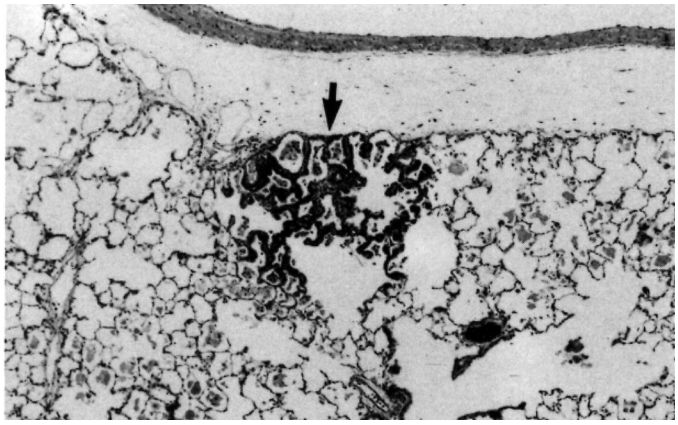


PLATE 3
Hyperplasia (arrow) in the lung of a female F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 20×

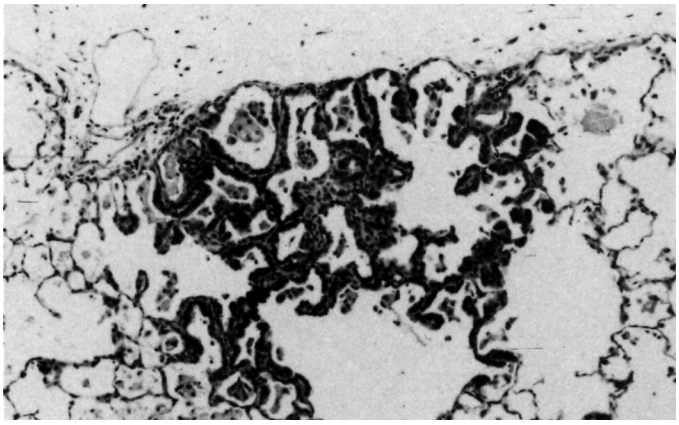


PLATE 4
Higher magnification of Plate 3. Note the proliferation of cells along the alveolar walls, but normal alveolar strucvture is maintained. H&E; 100×

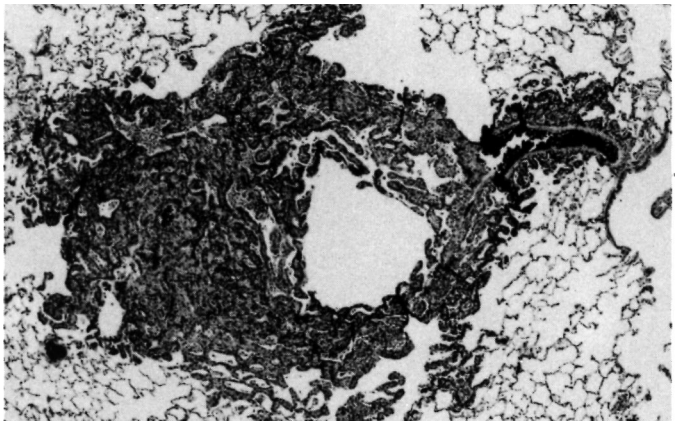


PLATE 5
Alveolar/bronchiolar adenoma in the lung of a male F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 26×

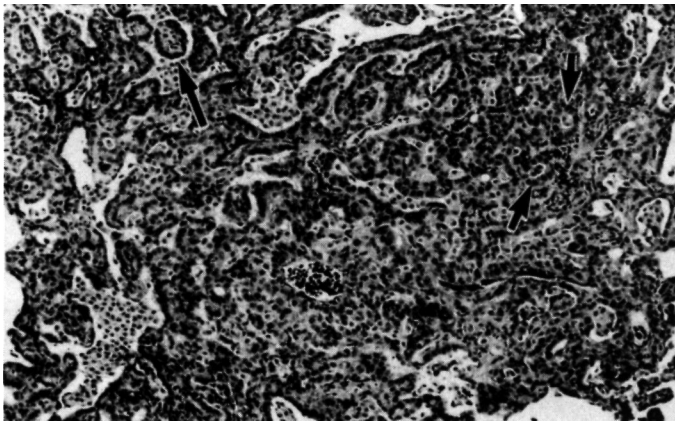


PLATE 6
Higher magnification of Plate 5. Component cells are arranged in acini (small arrows) and papillary projection s (large arrow). H&E; 66×

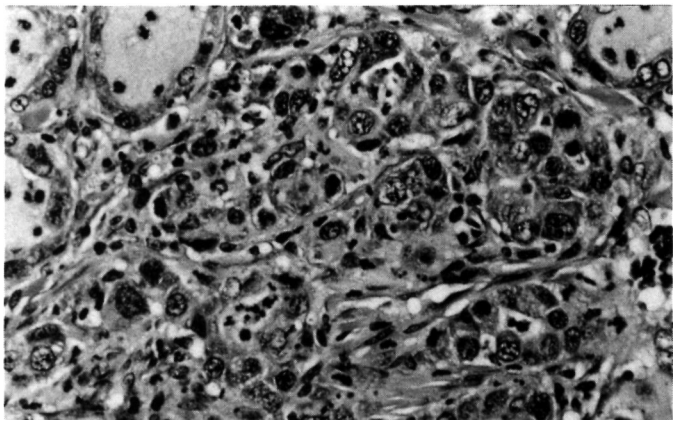


PLATE 7
Alveolar/bronchiolar carcinoma in the lung of a female F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. Note the variation in the size of the cells comprising acini at this high magnification. H&E; 200×

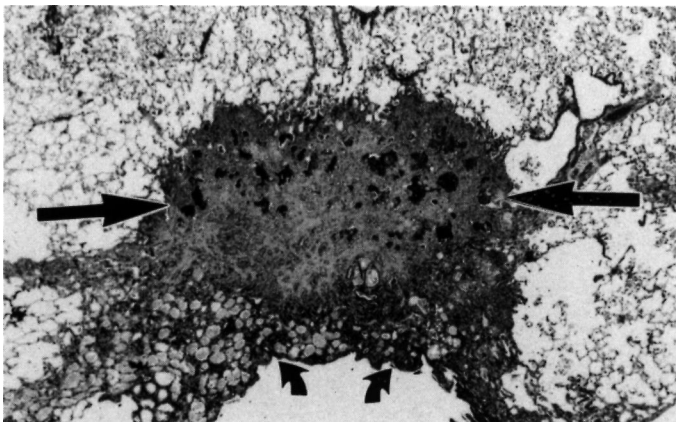


PLATE 8
Atypical hyperplasia (arrows) in the lung of a female F344/N rat exposed to 1.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. The lesion is located within an area of chronic inflammation (curved arrows). H&E; 16×

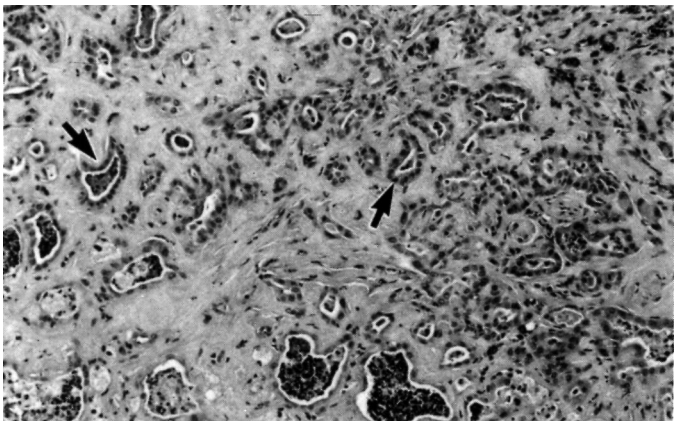


PLATE 9
Higher magnification of Plate 8. Note the glandular structures (arrows) lined by cuboidal epithelium within the fibrotic core. H&E; 80×

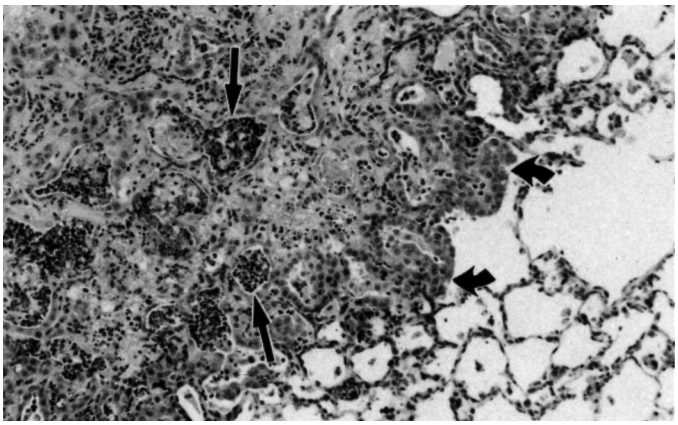


PLATE 10
High magnification of the border of an atypical hyperplasia in the lung of a male F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. Note the necrotic debris within the glandular structure (arrows) and the proliferative epithelium at the periphery (curved arrows). H&E; 80×

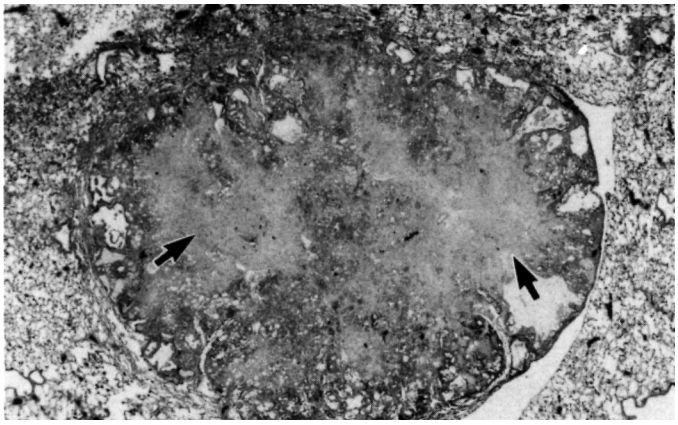


PLATE 11
Alveolar/bronchiolar carcinoma with abundant fibrous connective tissue (arrows) in the lung of a male F344/N rat exposed to 1.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 10×

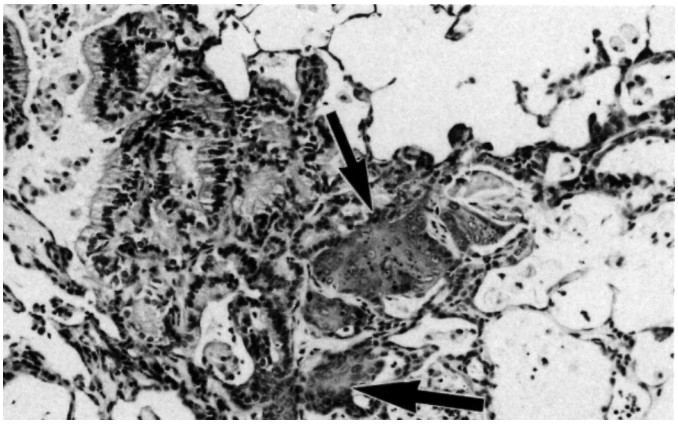


PLATE 12
Squamous metaplasia along the alveolar wall consisting of several layers of squamous epithelium (arrows) in the lung of a female F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 100×

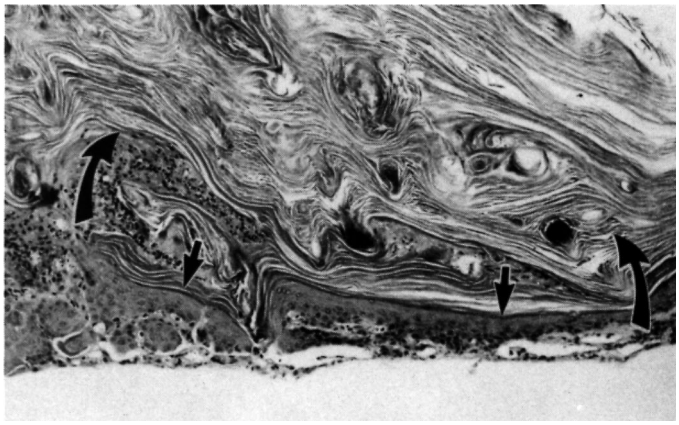


PLATE 13
Squamous cyst rimmed by a variably thick wall of squamous epithelium (large arrows) and filled with keratinous material (curved arrows) in the lung of a male F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 66×

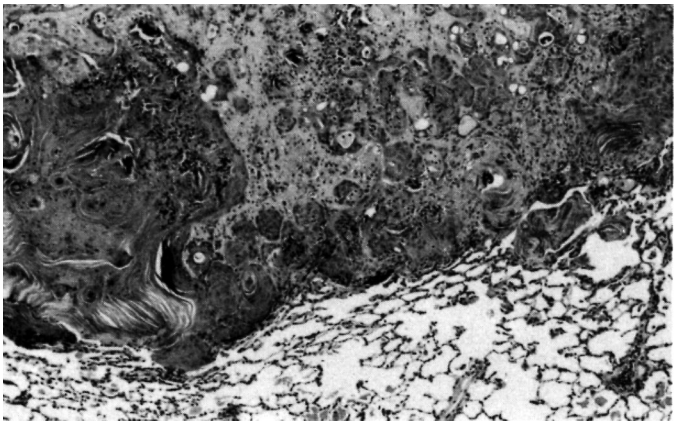


PLATE 14
High magnification of a squamous cell carcinoma in the lung of a female F344/N rat exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 40×

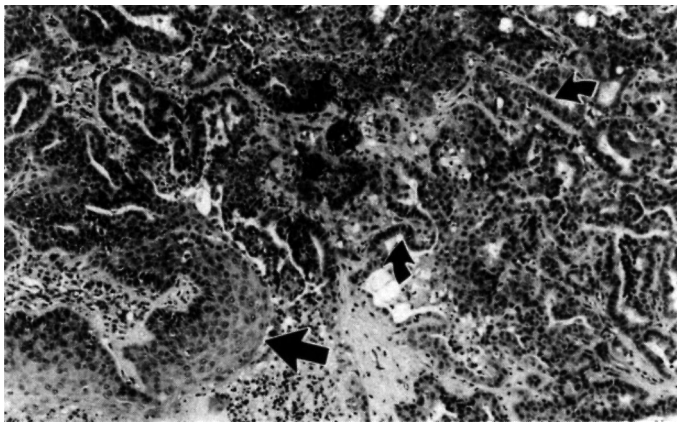


PLATE 15
Alveolar/bronchiolar carcinoma with an area of alveolar/bronchiolar epithelium to the right (curved arrows) and squamous differentiation to the left (arrow) in the lung of a male F344/N rat exposed to 1.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 66×

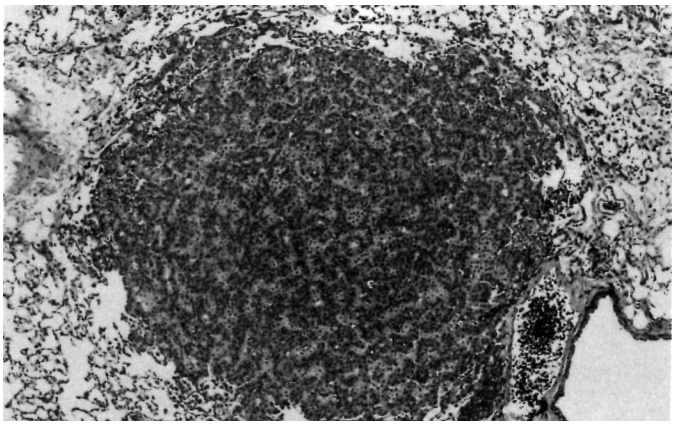


PLATE 16
Alveolar/bronchiolar adenoma in the lung of a female $B6C3F_1$ mouse exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 40×

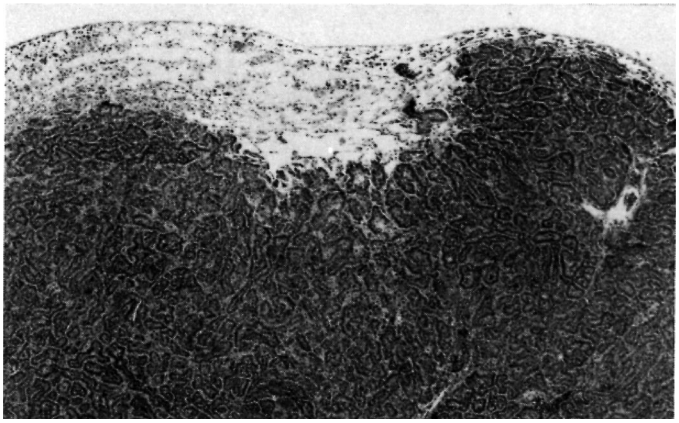


PLATE 17
Section of an alveolar/bronchiolar carcinoma with irregular and variably sized acinar structures in a female $B6C3F_1$ mouse exposed to 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 2 years. H&E; 26×

DISCUSSION AND CONCLUSIONS

This report presents the findings and conclusions of 2-year inhalation studies with cobalt sulfate heptahydrate. A companion report (NTP, 1991) discusses the findings of 16-day and 13-week inhalation studies conducted prior to the 2-year studies at the same laboratory. In all studies, the respiratory tract was the primary site of nonneoplastic lesions and neoplasms. In the 13-week studies, laryngeal lesions ranged from mild squamous metaplasia with or without chronic inflammation at concentrations ultimately selected for the 2-year studies, to large inflammatory polyps present in rats exposed to higher concentrations. Although other respiratory tract lesions were present, the larynx appeared to be the most sensitive to cobalt sulfate heptahydrate exposure, and lesions in this tissue were the determining factor in exposure concentration selection for the 2-year studies.

The highest concentration (3.0 mg/m^3) chosen for the 2-year studies did not affect survival or body weight gains of rats or survival of mice in either the 13-week or 2-year studies. The polycythemia noted in rats in the 13-week study was very mild at 3.0 mg/m^3, and there was no indication that this effect worsened to the point of causing clinical effects with longer exposure, although no hematologic measures were performed during the 2-year study. Similarly, there was no indication that the lesions observed in rats and mice in the 13-week studies in the larynx progressed in extent or changed in character with the prolonged exposures. There was no evidence of laryngeal polyp formation in rats, and the metaplastic and inflammatory changes in rats remained greater than in mice.

In contrast to the findings in the larynx, prolonged exposure to cobalt sulfate heptahydrate aerosol appeared to cause a progressive injury to the nose of rats and mice and to the lung of rats. Olfactory epithelial degeneration occurred primarily in rats and mice exposed to 10 and 30 mg/m^3 in the 13-week studies, but olfactory epithelial atrophy was increased at even the lowest concentration (0.3 mg/m^3) in rats and at 1.0 mg/m^3 in mice in the 2-year studies. Lesions in the lungs of rats changed markedly in character with the prolonged exposure in the 2-year study. Inflammation in the alveoli of rats was much more severe and occurred at lower concentrations than in the prechronic studies, and proteinosis was moderate to marked in the 2-year study rats and not noted in the prechronic study. Interstitial fibrosis is known to be a rather slowly developing lesion, but the extent of this lesion and its occurrence in essentially all rats at all exposure concentrations was not predicted based on the findings of the 13-week study. The alveolar epithelium of rats also displayed a spectrum of proliferative changes ranging from metaplasia through hyperplasia and atypical hyperplasia, and extending to neoplasia.

The spectrum of proliferative lung lesions observed in rats in the 2-year study ranged from highly cellular proliferations (typical of spontaneous lesions) to fibroproliferative and squamous lesions not typical of spontaneous lesions, and morphologic variants in between. The biological behavior of “typical” lung lesions, and to a lesser extent, squamous lesions, is fairly well documented. However, little is known about the biology of fibroproliferative lesions. In this study, many of the smaller lesions were identified within and/or adjacent to areas of chronic inflammation and fibrosis; however, it was clear that these lesions represented proliferative lesions distinct from the inflammation. Based upon the morphologic spectrum observed, it appears that their growth is progressive. There was, however, no clear morphologic correlate signaling autonomy of growth (i.e., consistent with a benign neoplasm) for these fibroproliferative lesions. Therefore, unless growth alterations consistent with a malignant neoplasm were present, all fibroproliferative lesions were diagnosed as atypical hyperplasia. There were several animals that had malignant neoplasms with a very prominent fibrous component; presumably, some of these progressed from atypical hyperplasias. In many respects, the range of proliferative lesions within the lungs of exposed rats resembled those observed in NTP studies of particulates (talc and the nickel compounds; NTP, 1993, 1996a,b,c), and it is clear that all the morphologic variants of proliferative lesions represent a response to cobalt sulfate heptahydrate.

Nonneoplastic lesions in the lungs of mice exposed to cobalt sulfate heptahydrate did not appear to differ appreciably from those expected in mice based on the results of the prechronic study. The lesions were confined primarily to histiocytic infiltration, and there was an absence of fibrosis and only minimal evidence of the nonneoplastic proliferative lesions noted in exposed rats. Most of the diagnoses of histiocytic infiltration were noted in animals that also had an alveolar/bronchiolar neoplasm; this is a frequent observation in mice with lung neoplasms and is not necessarily related to exposure to cobalt sulfate heptahydrate. Thus, it is not possible to clearly attribute the presence of histiocytic infiltration to cobalt sulfate heptahydrate exposure. Nonetheless, the lung changes were clearly much less severe than those seen in rats and differed markedly in character.

While rats and mice exhibited quite different nonneoplastic pulmonary responses to cobalt sulfate heptahydrate, exposed male and female rats and mice developed alveolar/bronchiolar adenomas and carcinomas. The distinction between these neoplasms is largely based on size, and both categories of this neoplasm were increased in exposed male and female rats and mice. In all groups, the neoplasms appeared with a significant positive trend, and the incidences in the 3.0 mg/m^3 groups exceeded the historical control ranges in the respective groups. The magnitude of the neoplastic response was somewhat less in male rats than in the other groups.

The incidences of follicular cell hyperplasia of the thyroid gland were moderately increased in all exposed groups of male mice, although no dose response was observed. Hypothyroidism has been noted in humans who also exhibited cardiomyopathy associated with consumption of cobalt-contaminated beer (Taylor and Marks, 1978).

Incidences of pheochromocytoma of the adrenal medulla were increased in female rats exposed to cobalt sulfate heptahydrate. Pheochromocytomas are relatively common in male F344/N rats, occurring with an historical rate of about 30% in inhalation studies. The historical inhalation chamber control rate in females is much lower (6%), and the incidence in the concurrent chamber control was 4%. While the incidences of this neoplasm were increased in exposed males and females, the strength of the response was much greater in females, and the increase in males was judged equivocal. In the NTP database of chemical carcinogenesis studies of nearly 450 chemicals, pheochromocytomas were part of a carcinogenic response in only 13 rat studies, five of which were inhalation studies. Although the historical control rates of pheochromocytomas do not appreciably differ between inhalation and dosed feed studies, a positive response is more likely to occur in inhalation studies than in studies using other routes of exposure. The reasons for this are not clear. Of the five other positive inhalation studies, two were with nickel compounds (oxide and subsulfide) and one with the particulate, talc.

Although the mechanisms responsible for induction of pheochromocytomas in rats are not understood, it is worth considering whether the adrenal gland and the pulmonary responses to cobalt sulfate heptahydrate in the rat might represent nonspecific responses to the physical inhalation and pulmonary accumulation of a particle, rather than a chemical-specific response. Measures of the possible accumulation of cobalt in the lung were not taken during these studies, although urinary cobalt concentrations have demonstrated dose-related absorption in the prechronic studies. Nickel sulfate hexahydrate is a highly water-soluble salt, as is cobalt sulfate heptahydrate. In similar studies, nickel sulfate hexahydrate did not show evidence of exposure-concentration-related accumulation in the lung of rats or mice exposed to concentrations as high as 30 mg/m^3 (NTP, 1996c). In contrast, the less soluble nickel subsulfide (NTP, 1996b) and the highly insoluble nickel oxide (NTP, 1996a) did accumulate in the lung. Thus, given the similar solubility and use of exposure concentrations ten-fold lower than those used with nickel sulfate hexahydrate, it is unlikely that cobalt would accumulate in the lung unless there was specific toxicity to pulmonary clearance mechanisms. The absence of nonneoplastic changes associated with cobalt sulfate heptahydrate inhalation by mice would argue against impaired clearance. The rather extensive and progressive pulmonary toxicity in the rat could have resulted in impaired clearance of cobalt, but it is unlikely that the toxicity represented a simple inflammatory and fibrotic response to an “overload” situation as has been postulated with chemically inert particles (Morrow *et al.*, 1991). The fact that the entire respiratory tract demonstrated a toxic response to cobalt sulfate heptahydrate argues convincingly that

the chemical has inherent toxicity and is not acting through secondary mechanisms related to its inhalation as a particle.

A number of factors need to be considered to properly address the relationship of these findings to typical human exposures to cobalt. The segments of the human population with the highest potential exposure to significant airborne cobalt concentrations are workers in the hard metal industry, coal mining, and those involved in ore processing (USDHHS, 1992). In these situations cobalt may exist in various forms, primarily as cobalt powder or cobalt oxide. These agents are less soluble than cobalt sulfate heptahydrate, and the toxic response of the respiratory system would likely depend on the combination of inherent toxicity, solubility in biological fluids, and residence time in the tissue. The carcinogenic potential of various cobalt compounds has been perhaps best demonstrated in injection studies in experimental animals (reviewed in IARC, 1991), and both insoluble and soluble forms have been shown to produce injection-site neoplasms.

The present demonstration of alveolar/bronchiolar neoplasms in rats and mice exposed to cobalt sulfate heptahydrate by inhalation confirms the findings of the injection studies and suggests that cobalt is inherently carcinogenic. These findings also lend credence to the epidemiological investigations of Mur *et al.* (1987), Hogstedt and Alexandersson (1990), and Lasfargues *et al.* (1994) that reported increased risks for lung cancer among workers producing cobalt and exposed to cobalt in the hard metal industry. Cobalt concentrations in the urine of workers in the Italian hard metal industry were found to be as high as 0.21 µg/mL at the end of the work shift (Sabbioni *et al.*, 1994). Ichikawa *et al.* (1985) reported even higher concentrations (0.39 µg/mL) in Japanese workers. In prechronic inhalation studies reported previously (NTP, 1991), average urinary cobalt concentrations in rats exposed to 0.3, 1.0, and 3.0 mg/m^3, respectively, were 0.14, 0.32, and 1.77 µg/mL. If urine cobalt concentrations roughly approximate relative inhalation exposures to cobalt, then the results from the current 2-year rat and mouse studies appear similar to occupational exposure levels and suggest that humans and rodents may be similarly sensitive to cobalt carcinogenesis.

The mechanisms of cobalt-induced carcinogenesis are not well understood. The genotoxicity of cobalt compounds has been established in a variety of eukaryotic test systems (reviewed in IARC, 1991), and cobalt has been shown under certain conditions to catalyze the production of oxygen-based free radicals that may underlie some of the observed adverse genetic events (Shi *et al.*, 1993). The observation of a larger than usual number of G to T transversions at the second base of codon 12 of those mouse lung neoplasms carrying a mutated K-*ras* gene (Appendix I) is also consistent with oxidative injury. Similar increases in G to T transversions were seen in lung neoplasms from mice exposed to ozone (NTP, 1994)

The potential contribution of the sulfate moiety to the carcinogenic response is worthy of consideration in that exposures of humans to concentrated inorganic acid mists are recognized as causing respiratory tract neoplasms, primarily in the larynx (IARC, 1992). There are no experimental animal carcinogenicity studies with sulfuric acid mists *per se* (IARC, 1992), but nickel sulfate hexahydrate was studied by inhalation as mentioned earlier (NTP, 1996c). In this instance, there was no evidence of carcinogenicity of nickel sulfate hexahydrate to the respiratory tract or other tissues despite the fact that other nickel salts are carcinogenic. Additionally, nickel sulfate hexahydrate was studied at an equivalent exposure concentration to that which caused significant increases in lung neoplasms in mice exposed to cobalt sulfate heptahydrate (1.0 mg/m^3). Thus, there seems to be little evidence to suggest that the sulfate moiety contributed significantly to the carcinogenic response.

Based on retrospective analyses, *Helicobacter hepaticus* was determined to have infected mice in 12 recent NTP 2-year studies (Appendix J). Of the 12 studies, mice (primarily males) from nine studies (including this study of cobalt sulfate heptahydrate) had a *H. hepaticus*-associated hepatitis. Qualitatively, the hepatitis and silver-staining organisms within the liver were similar among the nine studies. In a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) based assay, *H. hepaticus* was identified in studies from which adequately preserved (frozen) liver tissue was available. In general, efforts to identify *H. hepaticus* from tissue fixed in formalin for over a week were not successful

(Malarkey *et al.*, 1997), which was the case for this study of cobalt sulfate heptahydrate. However, because of the presence of the typical liver lesions and silver-staining helical organisms, mice from the study were presumed to be infected with *H. hepaticus*.

Increases in the incidences of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present (Ward *et al.*, 1994; Fox *et al.*, 1996; Appendix J). Additionally, in NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma were seen in the livers of male mice (Appendix J). Because of the latter association, interpretation of the increased incidences of hemangiosarcoma in the liver of male mice was confounded. Incidences of lesions at other sites in this study of cobalt sulfate heptahydrate were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis (Appendix J).

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of cobalt sulfate heptahydrate in male F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms. Marginal increases in incidences of pheochromocytomas of the adrenal medulla may have been related to exposure to cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* in female F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms and pheochromocytomas of the adrenal medulla in groups exposed to cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* of cobalt sulfate heptahydrate in male and female $B6C3F_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms.

Exposure to cobalt sulfate heptahydrate caused a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice.

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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.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF COBALT SULFATE HEPTAHYDRATE

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	30	34	26	34
Natural deaths	3	1	3	1
Survivors				
Terminal sacrifice	17	15	21	15
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(49)	(50)	(49)	(49)
Intestine large, cecum	(48)	(49)	(48)	(49)
Intestine small, duodenum	(50)	(50)	(48)	(49)
Intestine small, jejunum	(49)	(49)	(47)	(49)
Intestine small, ileum	(50)	(49)	(47)	(48)
Liver	(50)	(50)	(48)	(50)
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Hepatocellular carcinoma		1 (2%)		
Hepatocellular adenoma	1 (2%)		1 (2%)	1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Mesentery	(21)	(14)	(11)	(14)
Carcinoma, metastatic, seminal vesicle		1 (7%)		
Sarcoma, metastatic, uncertain primary site		1 (7%)		
Fat, lipoma			1 (9%)	
Pancreas	(50)	(50)	(48)	(50)
Adenoma			1 (2%)	1 (2%)
Carcinoma			1 (2%)	
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Mixed tumor malignant				1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(49)	(50)
Stomach, glandular	(50)	(50)	(48)	(50)
Schwannoma malignant				1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(48)	(50)
Adenoma			1 (2%)	1 (2%)
Carcinoma		1 (2%)	1 (2%)	
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma malignant		2 (4%)	2 (4%)	2 (4%)
Pheochromocytoma complex	1 (2%)		1 (2%)	
Pheochromocytoma benign	13 (26%)	15 (30%)	17 (35%)	15 (30%)
Bilateral, pheochromocytoma benign	1 (2%)	4 (8%)	6 (12%)	5 (10%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(48)	(50)
Adenoma	1 (2%)	4 (8%)	5 (10%)	5 (10%)
Adenoma, multiple	1 (2%)	1 (2%)		
Carcinoma	3 (6%)	4 (8%)	4 (8%)	7 (14%)
Pituitary gland	(49)	(49)	(50)	(49)
Pars distalis, adenoma	43 (88%)	40 (82%)	42 (84%)	41 (84%)
Thyroid gland	(49)	(50)	(48)	(50)
Bilateral, C-cell, adenoma				1 (2%)
C-cell, adenoma	4 (8%)	2 (4%)	3 (6%)	3 (6%)
C-cell, carcinoma	3 (6%)	3 (6%)	4 (8%)	3 (6%)
Follicular cell, adenoma		1 (2%)		1 (2%)
Follicular cell, carcinoma	1 (2%)	2 (4%)		
General Body System				
Peritoneum		(2)	(1)	(1)
Sarcoma, metastatic, uncertain primary site		1 (50%)		
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(49)	(50)
Adenoma			1 (2%)	1 (2%)
Carcinoma	2 (4%)	2 (4%)		3 (6%)
Bilateral, adenoma			1 (2%)	
Bilateral, carcinoma	1 (2%)			
Prostate	(50)	(50)	(49)	(50)
Adenoma	1 (2%)	2 (4%)	4 (8%)	1 (2%)
Seminal vesicle	(50)	(50)	(49)	(49)
Carcinoma		1 (2%)		
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	26 (52%)	18 (36%)	26 (52%)	19 (38%)
Interstitial cell, adenoma	9 (18%)	13 (26%)	7 (14%)	10 (20%)
Hematopoietic System				
Bone marrow	(50)	(50)	(48)	(50)
Lymph node	(8)	(9)	(9)	(9)
Lymph node, bronchial	(45)	(30)	(41)	(49)
Lymph node, mandibular	(46)	(47)	(47)	(49)
Lymph node, mesenteric	(50)	(50)	(48)	(50)
Lymph node, mediastinal	(47)	(46)	(44)	(49)
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Spleen	(50)	(50)	(49)	(50)
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Fibroma	1 (2%)			
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Thymus	(45)	(42)	(47)	(48)
Thymoma benign			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Integumentary System				
Mammary gland	(30)	(34)	(36)	(38)
Fibroadenoma	3 (10%)	1 (3%)	2 (6%)	3 (8%)
Fibroadenoma, multiple				1 (3%)
Skin	(50)	(48)	(50)	(50)
Basal cell adenoma	2 (4%)			
Basal cell carcinoma				1 (2%)
Keratoacanthoma	2 (4%)	5 (10%)		2 (4%)
Keratoacanthoma, multiple				1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Squamous cell papilloma				1 (2%)
Sebaceous gland, adenoma	1 (2%)	1 (2%)		
Subcutaneous tissue, fibroma		1 (2%)	2 (4%)	2 (4%)
Subcutaneous tissue, fibrosarcoma		2 (4%)	1 (2%)	2 (4%)
Subcutaneous tissue, lipoma		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma				1 (2%)
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Chordoma	1 (2%)	1 (2%)		
Osteosarcoma		3 (6%)		
Skeletal muscle		(2)	(1)	(1)
Carcinoma, metastatic, seminal vesicle		1 (50%)		
Sarcoma				1 (100%)
Sarcoma, metastatic, uncertain primary site		1 (50%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)		1 (2%)	
Spinal cord			(1)	
Respiratory System				
Larynx	(50)	(49)	(48)	(50)
Lung	(50)	(50)	(48)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	4 (8%)	1 (2%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Alveolar/bronchiolar carcinoma			3 (6%)	1 (2%)
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Chordoma, metastatic, bone	1 (2%)			
Osteosarcoma, metastatic, bone		1 (2%)		
Sarcoma, metastatic, skeletal muscle				1 (2%)
Nose	(50)	(50)	(49)	(50)
Nasopharyngeal duct, squamous cell carcinoma				1 (2%)
Pleura	(1)			
Trachea	(50)	(50)	(48)	(50)
Special Senses System				
Zymbal's gland	(1)			(2)
Carcinoma	1 (100%)			2 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Urinary System				
Kidney	(50)	(50)	(48)	(50)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Renal tubule, adenoma	1 (2%)		1 (2%)	
Urinary bladder	(50)	(50)	(48)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	30 (60%)	32 (64%)	29 (58%)	28 (56%)
Mesothelioma malignant	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	50	50
Total primary neoplasms	159	169	173	178
Total animals with benign neoplasms	48	46	47	48
Total benign neoplasms	111	113	124	122
Total animals with malignant neoplasms	38	41	35	38
Total malignant neoplasms	48	56	49	56
Total animals with metastatic neoplasms	1	3		1
Total metastatic neoplasms	1	18		1
Total animals with malignant neoplasms of uncertain primary site		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 Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	435	453	526	526	527	534	548	568	576	579	582	589	593	602	602	603	605	610	610	610	619	631	632	643	645
Carcass ID Number	022	015	044	045	016	014	033	038	048	037	004	012	047	021	041	024	049	029	036	046	035	003	017	043	030
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery		+	+	+				+	+	+	+		+				+	+	+	+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex								X																	
Pheochromocytoma benign						X					X	X									X		X		
Bilateral, pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																									
Carcinoma			X																						X
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X		X	X	X
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
C-cell, carcinoma	X																								
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis		+								+												+			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Bilateral, carcinoma																									

+: 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 Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	649	664	673	679	680	691	692	727	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	
Carcass ID Number	027	026	028	018	023	008	040	042	001	005	006	007	009	010	011	019	020	031	032	039	002	013	025	034	050	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X															1
Mesentery	+		+						+		+				+		+			+		+	+			21
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+																							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign					X		X						X	X			X			X		X	X			13
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Adenoma, multiple													X													1
Carcinoma																								X		3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	43
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma			X									X	X													4
C-cell, carcinoma						X									X											3
Follicular cell, carcinoma																						X				1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma				X		X																				2
Bilateral, carcinoma																			X							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	435	453	526	526	527	534	548	568	576	579	582	589	593	602	602	603	605	610	610	610	619	631	632	643	645
Carcass ID Number	022	015	044	045	016	014	033	038	048	037	004	012	047	021	041	024	049	029	036	046	035	003	017	043	030
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X			X		X	X	X						X				X
Interstitial cell, adenoma									X	X						X		X		X				X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+							+						+	+			+			+			
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X									
Thymus	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M
Integumentary System																									
Mammary gland	M	+	M	M	M	+	M	M	+	+	+	M	M	+	+	M	+	M	M	+	M	M	+	+	M
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, schwannoma, malignant	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Chordoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+		+																	
Zymbal's gland					+																				
Carcinoma					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	649	664	673	679	680	691	692	727	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	
Carcass ID Number	027	026	028	018	023	008	040	042	001	005	006	007	009	010	011	019	020	031	032	039	002	013	025	034	050	Total Tissues/ Tumors
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X		X	X	X	X		X	X	X	X	X		X	X		X	X	X	X		X	26
Interstitial cell, adenoma		X								X						X										9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+					+																		8
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	M	30
Fibroadenoma											X				X							X				3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																X	X									2
Keratoacanthoma								X			X															2
Sebaceous gland, adenoma														X												1
Subcutaneous tissue, schwannoma, malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma														X												1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																						X				1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Chordoma, metastatic, bone														X												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura				+																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye					+					+										+						5
Zymbal's gland																										1
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	435	453	526	526	527	534	548	568	576	579	582	589	593	602	602	603	605	610	610	610	619	631	632	643	645
Carcass ID Number	022	015	044	045	016	014	033	038	048	037	004	012	047	021	041	024	049	029	036	046	035	003	017	043	030
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X		X	X	X		X			X	X	X			X		X	X	X	X	X
Mesothelioma malignant												X										X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	649	664	673	679	680	691	692	727	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735		
Carcass ID Number	027	026	028	018	023	008	040	042	001	005	006	007	009	010	011	019	020	031	032	039	002	013	025	034	050	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X		X	X		X	X		X				X	X	X	X	X				X	30
Mesothelioma malignant				X																						3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	408	471	475	495	541	554	576	579	589	589	600	610	629	629	631	631	632	638	638	645	646	649	652	663	669
Carcass ID Number	233	220	207	246	237	206	229	205	227	249	236	230	222	226	239	240	219	211	247	250	204	232	245	215	248
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle	X																								
Hepatocellular carcinoma																X									
Sarcoma, metastatic, uncertain primary site					X																				
Mesentery	+				+				+					+	+										+
Carcinoma, metastatic, seminal vesicle	X																								
Sarcoma, metastatic, uncertain primary site					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle	X																								
Sarcoma, metastatic, uncertain primary site					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle	X																								
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign					X				X							X		X					X		
Bilateral, pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																				X			
Adenoma, multiple																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X	X	X		X	X	X	X	X		X	X					X	X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma							X																		
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Peritoneum					+																				
Sarcoma, metastatic, uncertain primary site					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	671	678	680	680	681	691	694	701	719	722	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	
Carcass ID Number	210	231	213	224	242	225	228	218	216	217	202	208	212	214	221	223	235	238	243	244	201	203	209	234	241	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, seminal vesicle																										1
Hepatocellular carcinoma																										1
Sarcoma, metastatic, uncertain primary site																										1
Mesentery			+	+							+			+	+			+	+				+			14
Carcinoma, metastatic, seminal vesicle																										1
Sarcoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, seminal vesicle																										1
Sarcoma, metastatic, uncertain primary site																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, seminal vesicle																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant										X	X															2
Pheochromocytoma benign	X				X		X			X	X			X		X		X			X				X	15
Bilateral, pheochromocytoma benign									X				X									X				4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																	X								4
Adenoma, multiple															X											1
Carcinoma			X	X					X					X												4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	48
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																					X				X	2
C-cell, carcinoma							X															X				3
Follicular cell, adenoma				X																						1
Follicular cell, carcinoma									X									X								2
General Body System																										
Peritoneum					+																					2
Sarcoma, metastatic, uncertain primary site																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	408	471	475	495	541	554	576	579	589	589	600	610	629	629	631	631	632	638	638	645	646	649	652	663	669
Carcass ID Number	233	220	207	246	237	206	229	205	227	249	236	230	222	226	239	240	219	211	247	250	204	232	245	215	248
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Sarcoma, metastatic, uncertain primary site					X																				
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X						X	X		X	X			X		X	X
Interstitial cell, adenoma			X											X			X						X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+						+									+		+		+	+		
Lymph node, bronchial	M	+	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	M	+	M	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle	X																								
Sarcoma, metastatic, uncertain primary site					X																				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	M	+	+	+	+	M	+	M	+	+	+	+	M	M	M	+	M	+	M	+	+	M	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Keratoacanthoma									X							X	X								
Sarcoma, metastatic, uncertain primary site					X																				
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																					X				
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma										X															
Osteosarcoma																X									
Skeletal muscle	+				+																				
Carcinoma, metastatic, seminal vesicle	X																								
Sarcoma, metastatic, uncertain primary site					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	671	678	680	680	681	691	694	701	719	722	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	
Carcass ID Number	210	231	213	224	242	225	228	218	216	217	202	208	212	214	221	223	235	238	243	244	201	203	209	234	241	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X	X																	2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X								X														2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Sarcoma, metastatic, uncertain primary site																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X			X			X		X		X		X		X	X	X			X				18
Interstitial cell, adenoma				X	X		X			X		X								X	X		X		X	13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+	+	+																9
Lymph node, bronchial	M	+	+	+	+	M	M	M	+	M	+	M	M	+	+	M	+	M	M	+	+	M	+	M	+	30
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Carcinoma, metastatic, seminal vesicle																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, seminal vesicle																										1
Sarcoma, metastatic, uncertain primary site																										1
Thymus	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	42
Integumentary System																										
Mammary gland	+	+	+	+	M	M	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	34
Fibroadenoma																	X									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Keratoacanthoma			X																				X			5
Sarcoma, metastatic, uncertain primary site																										1
Sebaceous gland, adenoma			X																							1
Subcutaneous tissue, fibroma										X																1
Subcutaneous tissue, fibrosarcoma																					X					2
Subcutaneous tissue, lipoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma																										1
Osteosarcoma			X		X																					3
Skeletal muscle																										2
Carcinoma, metastatic, seminal vesicle																										1
Sarcoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	408	471	475	495	541	554	576	579	589	589	600	610	629	629	631	631	632	638	638	645	646	649	652	663	669
Carcass ID Number	233	220	207	246	237	206	229	205	227	249	236	230	222	226	239	240	219	211	247	250	204	232	245	215	248
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X						X									
Carcinoma, metastatic, seminal vesicle	X																								
Osteosarcoma, metastatic, bone																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X	X	X		X		X	X	X	X	X	X	X	X		X	X	X	X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m^3

Number of Days on Study	671	678	680	680	681	691	694	701	719	722	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	
Carcass ID Number	210	231	213	224	242	225	228	218	116	117	202	208	112	114	221	223	235	238	243	244	201	203	209	234	241	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X									X			4
Carcinoma, metastatic, seminal vesicle																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X	X	X	X	X			X	X			X		X	X		X		X	X	32
Mesothelioma malignant					X										X											2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	272	435	467	509	518	526	534	581	582	611	611	630	631	632	642	649	652	654	657	671	673	673	678	681	694
Carcass ID Number	420	406	438	421	444	422	412	403	401	409	446	448	437	433	441	450	411	417	413	439	425	427	424	434	407
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X																			
Mesentery					+			+					+						+		+				+
Fat, lipoma																									X
Pancreas	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma																				X					
Adrenal medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																					X				
Pheochromocytoma complex																									
Pheochromocytoma benign								X						X	X				X	X		X		X	
Bilateral, pheochromocytoma benign						X						X													
Islets, pancreatic	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X								X													
Carcinoma																			X				X	X	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid gland	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X									
C-cell, carcinoma									X							X									
General Body System																									
Peritoneum																+									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	699	709	713	729	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	
Carcass ID Number	440	418	405	432	402	404	408	410	414	415	419	426	429	430	431	435	436	442	443	445	449	416	423	428	447	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma																										1
Mesentery	+				+											+	+					+				11
Fat, lipoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma							X																			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																+										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant							X																			2
Pheochromocytoma complex				X																						1
Pheochromocytoma benign	X				X		X									X	X		X	X	X	X		X		17
Bilateral, pheochromocytoma benign									X			X	X												X	6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma											X								X			X				5
Carcinoma												X														4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X		X	X	X	X			X	42
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma								X						X												3
C-cell, carcinoma			X																	X						4
General Body System																										
Peritoneum																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	272	435	467	509	518	526	534	581	582	611	611	630	631	632	642	649	652	654	657	671	673	673	678	681	694
Carcass ID Number	420	406	438	421	444	422	412	403	401	409	446	448	437	433	441	450	411	417	413	439	425	427	424	434	407
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Bilateral, adenoma																									X
Prostate	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Seminal vesicle	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X	X	X			X	X		X		X	X	X	X		X
Interstitial cell, adenoma							X										X								
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+					+										+	+		
Lymph node, bronchial	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	A	M	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	M	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	M	+
Fibroadenoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																						X			
Subcutaneous tissue, fibrosarcoma																						X			
Subcutaneous tissue, lipoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							+		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Spinal cord		+																							
Respiratory System																									
Larynx	I	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma																	X								
Nose	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	699	709	713	729	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	
Carcass ID Number	440	418	405	432	402	404	408	410	414	415	419	426	429	430	431	435	436	442	443	445	449	416	423	428	447	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Bilateral, adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X			X			X									4
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X			X		X			X	X	X	X	X			X	X	X		X			X	X	X	26
Interstitial cell, adenoma			X		X									X					X			X				7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node		+	+												+	+				+						9
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	41
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma benign																				X						1
Integumentary System																										
Mammary gland	+	+	M	+	M	+	+	M	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	M	36
Fibroadenoma																							X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																		X								2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma	X																			X						3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye											+															1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	272	435	467	509	518	526	534	581	582	611	611	630	631	632	642	649	652	654	657	671	673	673	678	681	694
Carcass ID Number	420	406	438	421	444	422	412	403	401	409	446	448	437	433	441	450	411	417	413	439	425	427	424	434	407
Urinary System																									
Kidney	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									X
Urinary bladder	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X			X	X		X	X		X		X			X		X	X	X	X	X	
Mesothelioma malignant																X								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m^3

Number of Days on Study	699	709	713	729	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	
Carcass ID Number	440	418	405	432	402	404	408	410	414	415	419	426	429	430	431	435	436	442	443	445	449	416	423	428	447	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X			X				X	X			X	X	X	X		X	X	X	X		X	29
Mesothelioma malignant																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	401	463	463	511	526	534	545	562	562	567	574	579	586	589	593	603	604	611	611	611	632	638	638	643	646
Carcass ID Number	628	612	615	607	618	621	604	620	630	641	637	619	634	601	625	635	633	645	647	649	614	624	639	623	613
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery			+					+							+			+		+				+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Mixed tumor malignant																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Tongue																									
Tooth																									
Cardiovascular System																									
Blood vessel											+														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign							X													X		X		X	
Bilateral, pheochromocytoma benign					X																		X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X			X			
Carcinoma																							X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X		X	X			X	X	X	X	X	X		X	X	X	X	X	X			X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma													X												
C-cell, carcinoma									X																
Follicular cell, adenoma																									
General Body System																									
Peritoneum																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	663	666	669	673	680	692	693	694	706	720	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	
Carcass ID Number	643	631	608	644	610	650	648	605	606	622	609	611	616	617	629	632	638	640	642	646	602	603	626	627	636	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X																						1
Mesentery						+		+					+			+	+						+		+	14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Mixed tumor malignant																				X						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant										X																1
Tongue												+									+					2
Tooth																							+			1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant	X								X																	2
Pheochromocytoma benign	X		X		X				X	X	X		X		X								X	X	X	15
Bilateral, pheochromocytoma benign				X																	X	X				5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X						X					X														5
Carcinoma				X			X		X	X											X		X			7
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	41
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma								X																		1
C-cell, adenoma														X										X		3
C-cell, carcinoma											X														X	3
Follicular cell, adenoma																		X								1
General Body System																										
Peritoneum														+												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	401	463	463	511	526	534	545	562	562	567	574	579	586	589	593	603	604	611	611	611	632	638	638	643	646
Carcass ID Number	628	612	615	607	618	621	604	620	630	641	637	619	634	601	625	635	633	645	647	649	614	624	639	623	613
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis														+						+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma				X																					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X	X								X				X			X			
Interstitial cell, adenoma					X			X					X	X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+		+						+							+				
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	M	M	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	M
Fibroadenoma																				X					
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																									
Keratoacanthoma, multiple																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+						
Sarcoma																			X						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	663	666	669	673	680	692	693	694	706	720	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	
Carcass ID Number	643	631	608	644	610	650	648	605	606	622	609	611	616	617	629	632	638	640	642	646	602	603	626	627	636	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma				X																			X			3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X		X		X					X	X	X	X	X		X	X	X			X		X	X	19
Interstitial cell, adenoma					X		X	X	X							X							X			10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+													+		+							+	9
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	38
Fibroadenoma															X		X									3
Fibroadenoma, multiple										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																X										1
Keratoacanthoma															X						X					2
Keratoacanthoma, multiple																	X									1
Squamous cell papilloma														X												1
Subcutaneous tissue, fibroma	X																							X		2
Subcutaneous tissue, fibrosarcoma										X										X						2
Subcutaneous tissue, lipoma																						X				1
Subcutaneous tissue, sarcoma						X																				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	401	463	463	511	526	534	545	562	562	567	574	579	586	589	593	603	604	611	611	611	632	638	638	643	646
Carcass ID Number	628	612	615	607	618	621	604	620	630	641	637	619	634	601	625	635	633	645	647	649	614	624	639	623	613
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Sarcoma, metastatic, skeletal muscle																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasopharyngeal duct, squamous cell carcinoma							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland	+									+															
Carcinoma	X									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		
Mesothelioma malignant																X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m^3

Number of Days on Study	663	666	669	673	680	692	693	694	706	720	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	
Carcass ID Number	643	631	608	644	610	650	648	605	606	622	609	611	616	617	629	632	638	640	642	646	602	603	626	627	636	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X				X						X					X						5
Alveolar/bronchiolar adenoma, multiple				X																						1
Alveolar/bronchiolar carcinoma																					X					1
Sarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasopharyngeal duct, squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																			+							1
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X				X			X			X		X		X	X	X				X	X	28
Mesothelioma malignant														X												2

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	14/50 (28%)	19/50 (38%)	23/49 (47%)	20/50 (40%)
Adjusted rate[b]	51.0%	70.0%	71.9%	71.4%
Terminal rate[c]	6/17 (35%)	8/15 (53%)	13/21 (62%)	8/15 (53%)
First incidence (days)	534	541	526	526
Life table test[d]	P=0.166	P=0.220	P=0.214	P=0.134
Logistic regression test[d]	P=0.172	P=0.226	P=0.069	P=0.126
Cochran-Armitage test[d]	P=0.229			
Fisher exact test[d]		P=0.198	P=0.041	P=0.146
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	15/50 (30%)	19/50 (38%)	25/49 (51%)	20/50 (40%)
Adjusted rate	52.1%	70.0%	74.1%	71.4%
Terminal rate	6/17 (35%)	8/15 (53%)	13/21 (62%)	8/15 (53%)
First incidence (days)	534	541	526	526
Life table test	P=0.206	P=0.285	P=0.188	P=0.182
Logistic regression test	P=0.218	P=0.295	P=0.045	P=0.180
Cochran-Armitage test	P=0.279			
Fisher exact test		P=0.263	P=0.027	P=0.201
Bone: Osteosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	11.4%	0.0%	0.0%
Terminal rate	0/17 (0%)	0/15 (0%)	0/21 (0%)	0/15 (0%)
First incidence (days)	—[e]	631	—	—
Life table test	P=0.258N	P=0.146	—	—
Logistic regression test	P=0.257N	P=0.123	—	—
Cochran-Armitage test	P=0.255N			
Fisher exact test		P=0.121	—	—
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	4/50 (8%)	1/48 (2%)	6/50 (12%)
Adjusted rate	2.3%	17.7%	2.4%	28.4%
Terminal rate	0/17 (0%)	2/15 (13%)	0/21 (0%)	2/15 (13%)
First incidence (days)	568	589	611	638
Life table test	P=0.042	P=0.187	P=0.726N	P=0.056
Logistic regression test	P=0.051	P=0.179	P=0.753	P=0.055
Cochran-Armitage test	P=0.055			
Fisher exact test		P=0.181	P=0.742	P=0.056
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/48 (6%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	11.3%	6.7%
Terminal rate	0/17 (0%)	0/15 (0%)	1/21 (5%)	1/15 (7%)
First incidence (days)	—	—	652	734 (T)
Life table test	P=0.355	—	P=0.181	P=0.475
Logistic regression test	P=0.360	—	P=0.136	P=0.475
Cochran-Armitage test	P=0.382			
Fisher exact test		—	P=0.114	P=0.500

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	4/50 (8%)	4/48 (8%)	7/50 (14%)
Adjusted rate	2.3%	17.7%	13.4%	33.9%
Terminal rate	0/17 (0%)	2/15 (13%)	1/21 (5%)	3/15 (20%)
First incidence (days)	568	589	611	638
Life table test	P=0.027	P=0.187	P=0.263	P=0.030
Logistic regression test	P=0.032	P=0.179	P=0.163	P=0.029
Cochran-Armitage test	P=0.038			
Fisher exact test		P=0.181	P=0.168	P=0.030
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate	17.6%	6.7%	7.6%	21.2%
Terminal rate	3/17 (18%)	1/15 (7%)	1/21 (5%)	2/15 (13%)
First incidence (days)	734 (T)	734 (T)	652	611
Life table test	P=0.199	P=0.346N	P=0.391N	P=0.449
Logistic regression test	P=0.203	P=0.346N	P=0.398N	P=0.475
Cochran-Armitage test	P=0.240			
Fisher exact test		P=0.309N	P=0.500N	P=0.500
Pancreatic Islets: Adenoma				
Overall rate	2/50 (4%)	5/50 (10%)	5/48 (10%)	5/50 (10%)
Adjusted rate	10.2%	21.3%	18.3%	20.5%
Terminal rate	1/17 (6%)	2/15 (13%)	3/21 (14%)	1/15 (7%)
First incidence (days)	679	471	509	611
Life table test	P=0.278	P=0.217	P=0.301	P=0.222
Logistic regression test	P=0.304	P=0.224	P=0.226	P=0.208
Cochran-Armitage test	P=0.316			
Fisher exact test		P=0.218	P=0.201	P=0.218
Pancreatic Islets: Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	4/48 (8%)	7/50 (14%)
Adjusted rate	11.4%	19.8%	14.3%	33.2%
Terminal rate	1/17 (6%)	1/15 (7%)	1/21 (5%)	2/15 (13%)
First incidence (days)	526	680	657	638
Life table test	P=0.089	P=0.501	P=0.611	P=0.149
Logistic regression test	P=0.091	P=0.515	P=0.489	P=0.149
Cochran-Armitage test	P=0.110			
Fisher exact test		P=0.500	P=0.477	P=0.159
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	9/50 (18%)	9/48 (19%)	11/50 (22%)
Adjusted rate	20.7%	37.6%	30.6%	44.7%
Terminal rate	2/17 (12%)	3/15 (20%)	4/21 (19%)	3/15 (20%)
First incidence (days)	526	471	509	611
Life table test	P=0.101	P=0.202	P=0.328	P=0.088
Logistic regression test	P=0.107	P=0.205	P=0.192	P=0.077
Cochran-Armitage test	P=0.127			
Fisher exact test		P=0.194	P=0.172	P=0.086

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	43/49 (88%)	40/49 (82%)	42/50 (84%)	41/49 (84%)
Adjusted rate	97.4%	100.0%	89.3%	95.1%
Terminal rate	15/16 (94%)	15/15 (100%)	16/21 (76%)	13/15 (87%)
First incidence (days)	435	471	467	401
Life table test	P=0.455	P=0.340N	P=0.121N	P=0.509N
Logistic regression test	P=0.485N	P=0.269N	P=0.376N	P=0.386N
Cochran-Armitage test	P=0.474N			
Fisher exact test		P=0.288N	P=0.403N	P=0.387N
Preputial Gland: Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	0/49 (0%)	3/50 (6%)
Adjusted rate	14.7%	11.1%	0.0%	12.8%
Terminal rate	1/17 (6%)	0/15 (0%)	0/21 (0%)	1/15 (7%)
First incidence (days)	679	701	—	511
Life table test	P=0.472	P=0.512N	P=0.087N	P=0.632
Logistic regression test	P=0.486	P=0.229N	P=0.093N	P=0.657
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.500N	P=0.125N	P=0.661N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/49 (4%)	4/50 (8%)
Adjusted rate	14.7%	11.1%	6.8%	15.8%
Terminal rate	1/17 (6%)	0/15 (0%)	0/21 (0%)	1/15 (7%)
First incidence (days)	679	701	654	511
Life table test	P=0.292	P=0.512N	P=0.380N	P=0.478
Logistic regression test	P=0.305	P=0.229N	P=0.329N	P=0.494
Cochran-Armitage test	P=0.320			
Fisher exact test		P=0.500N	P=0.510N	P=0.500
Prostate Gland: Adenoma				
Overall rate	1/50 (2%)	2/50 (4%)	4/49 (8%)	1/50 (2%)
Adjusted rate	5.9%	10.7%	17.1%	6.7%
Terminal rate	1/17 (6%)	1/15 (7%)	3/21 (14%)	1/15 (7%)
First incidence (days)	734 (T)	680	673	734 (T)
Life table test	P=0.537N	P=0.481	P=0.250	P=0.736
Logistic regression test	P=0.533N	P=0.508	P=0.251	P=0.736
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.500	P=0.175	P=0.753N
Skin: Keratoacanthoma				
Overall rate	2/50 (4%)	5/50 (10%)	0/50 (0%)	3/50 (6%)
Adjusted rate	11.1%	17.8%	0.0%	20.0%
Terminal rate	1/17 (6%)	1/15 (7%)	0/21 (0%)	3/15 (20%)
First incidence (days)	727	589	—	734 (T)
Life table test	P=0.602	P=0.231	P=0.196N	P=0.437
Logistic regression test	P=0.608N	P=0.227	P=0.183N	P=0.445
Cochran-Armitage test	P=0.582N			
Fisher exact test		P=0.218	P=0.247N	P=0.500

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	2/50 (4%)	5/50 (10%)	0/50 (0%)	4/50 (8%)
Adjusted rate	11.1%	17.8%	0.0%	26.7%
Terminal rate	1/17 (6%)	1/15 (7%)	0/21 (0%)	4/15 (27%)
First incidence (days)	727	589	—	734 (T)
Life table test	P=0.385	P=0.231	P=0.196N	P=0.272
Logistic regression test	P=0.400	P=0.227	P=0.183N	P=0.271
Cochran-Armitage test	P=0.429			
Fisher exact test		P=0.218	P=0.247N	P=0.339
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	4/50 (8%)	5/50 (10%)	0/50 (0%)	5/50 (10%)
Adjusted rate	22.2%	17.8%	0.0%	33.3%
Terminal rate	3/17 (18%)	1/15 (7%)	0/21 (0%)	5/15 (33%)
First incidence (days)	727	589	—	734 (T)
Life table test	P=0.406	P=0.493	P=0.040N	P=0.413
Logistic regression test	P=0.420	P=0.526	P=0.033N	P=0.414
Cochran-Armitage test	P=0.458			
Fisher exact test		P=0.500	P=0.059N	P=0.500
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	9.8%	3.3%	16.9%
Terminal rate	0/17 (0%)	1/15 (7%)	0/21 (0%)	1/15 (7%)
First incidence (days)	—	646	673	692
Life table test	P=0.113	P=0.245	P=0.553	P=0.113
Logistic regression test	P=0.113	P=0.246	P=0.509	P=0.109
Cochran-Armitage test	P=0.132			
Fisher exact test		P=0.247	P=0.500	P=0.121
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted rate	0.0%	15.4%	7.9%	25.9%
Terminal rate	0/17 (0%)	1/15 (7%)	1/21 (5%)	2/15 (13%)
First incidence (days)	—	646	673	663
Life table test	P=0.033	P=0.120	P=0.293	P=0.031
Logistic regression test	P=0.031	P=0.126	P=0.272	P=0.028
Cochran-Armitage test	P=0.044			
Fisher exact test		P=0.121	P=0.247	P=0.028
Testes: Adenoma				
Overall rate	35/50 (70%)	31/50 (62%)	33/50 (66%)	29/50 (58%)
Adjusted rate	94.3%	90.5%	88.7%	92.7%
Terminal rate	15/17 (88%)	12/15 (80%)	17/21 (81%)	13/15 (87%)
First incidence (days)	568	475	534	526
Life table test	P=0.369N	P=0.321N	P=0.093N	P=0.319N
Logistic regression test	P=0.236N	P=0.142N	P=0.185N	P=0.145N
Cochran-Armitage test	P=0.179N			
Fisher exact test		P=0.263N	P=0.415N	P=0.149N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/49 (8%)	2/50 (4%)	3/48 (6%)	4/50 (8%)
Adjusted rate	18.8%	13.3%	12.1%	20.3%
Terminal rate	2/17 (12%)	2/15 (13%)	2/21 (10%)	2/15 (13%)
First incidence (days)	645	734 (T)	649	586
Life table test	P=0.391	P=0.358N	P=0.368N	P=0.602
Logistic regression test	P=0.406	P=0.316N	P=0.426N	P=0.634
Cochran-Armitage test	P=0.447			
Fisher exact test		P=0.329N	P=0.512N	P=0.631N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	3/49 (6%)	3/50 (6%)	4/48 (8%)	3/50 (6%)
Adjusted rate	12.4%	13.6%	13.6%	15.3%
Terminal rate	1/17 (6%)	1/15 (7%)	1/21 (5%)	2/15 (13%)
First incidence (days)	435	576	582	562
Life table test	P=0.569	P=0.647	P=0.597	P=0.631
Logistic regression test	P=0.587N	P=0.656N	P=0.479	P=0.655N
Cochran-Armitage test	P=0.582N			
Fisher exact test		P=0.651N	P=0.488	P=0.651N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/49 (14%)	5/50 (10%)	6/48 (13%)	7/50 (14%)
Adjusted rate	29.5%	25.9%	22.3%	34.1%
Terminal rate	3/17 (18%)	3/15 (20%)	3/21 (14%)	4/15 (27%)
First incidence (days)	435	576	582	562
Life table test	P=0.394	P=0.408N	P=0.349N	P=0.558
Logistic regression test	P=0.430	P=0.353N	P=0.479N	P=0.609
Cochran-Armitage test	P=0.466			
Fisher exact test		P=0.365N	P=0.516N	P=0.597N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/49 (2%)	3/50 (6%)	0/48 (0%)	1/50 (2%)
Adjusted rate	5.9%	16.0%	0.0%	6.7%
Terminal rate	1/17 (6%)	1/15 (7%)	0/21 (0%)	1/15 (7%)
First incidence (days)	734 (T)	680	—	734 (T)
Life table test	P=0.453N	P=0.288	P=0.458N	P=0.736
Logistic regression test	P=0.448N	P=0.309	P=0.458N	P=0.736
Cochran-Armitage test	P=0.423N			
Fisher exact test		P=0.316	P=0.505N	P=0.747N
All Organs: Mononuclear Cell Leukemia				
Overall rate	30/50 (60%)	32/50 (64%)	29/50 (58%)	28/50 (56%)
Adjusted rate	77.3%	80.6%	74.9%	75.6%
Terminal rate	9/17 (53%)	8/15 (53%)	12/21 (57%)	8/15 (53%)
First incidence (days)	453	475	435	463
Life table test	P=0.468N	P=0.501	P=0.199N	P=0.507N
Logistic regression test	P=0.313N	P=0.433	P=0.467N	P=0.420N
Cochran-Armitage test	P=0.297N			
Fisher exact test		P=0.418	P=0.500N	P=0.420N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
All Organs: Malignant Mesothelioma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	10.2%	11.1%	6.5%	9.3%
Terminal rate	0/17 (0%)	1/15 (7%)	0/21 (0%)	1/15 (7%)
First incidence (days)	589	681	649	603
Life table test	P=0.523N	P=0.477N	P=0.397N	P=0.517N
Logistic regression test	P=0.498N	P=0.494N	P=0.507N	P=0.501N
Cochran-Armitage test	P=0.491N			
Fisher exact test		P=0.500N	P=0.500N	P=0.500N
All Organs: Osteosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	11.4%	0.0%	0.0%
Terminal rate	0/17 (0%)	0/15 (0%)	0/21 (0%)	0/15 (0%)
First incidence (days)	—	631	—	—
Life table test	P=0.258N	P=0.146	—	—
Logistic regression test	P=0.257N	P=0.123	—	—
Cochran-Armitage test	P=0.255N			
Fisher exact test		P=0.121	—	—
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	46/50 (92%)	47/50 (94%)	48/50 (96%)
Adjusted rate	97.9%	100.0%	97.9%	100.0%
Terminal rate	16/17 (94%)	15/15 (100%)	20/21 (95%)	15/15 (100%)
First incidence (days)	435	471	467	401
Life table test	P=0.317	P=0.419N	P=0.125N	P=0.437
Logistic regression test	P=0.385	P=0.319N	P=0.517N	P=0.687
Cochran-Armitage test	P=0.434			
Fisher exact test		P=0.339N	P=0.500N	P=0.691N
All Organs: Malignant Neoplasms				
Overall rate	38/50 (76%)	42/50 (84%)	35/50 (70%)	38/50 (76%)
Adjusted rate	89.9%	93.1%	78.9%	87.5%
Terminal rate	13/17 (76%)	12/15 (80%)	12/21 (57%)	10/15 (67%)
First incidence (days)	435	408	272	401
Life table test	P=0.490	P=0.386	P=0.115N	P=0.469
Logistic regression test	P=0.396N	P=0.241	P=0.329N	P=0.592N
Cochran-Armitage test	P=0.395N			
Fisher exact test		P=0.227	P=0.326N	P=0.592N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	17/17 (100%)	15/15 (100%)	21/21 (100%)	15/15 (100%)
First incidence (days)	435	408	272	401
Life table test	P=0.361	P=0.510N	P=0.146N	P=0.438
Logistic regression test	—[f]	—	—	—
Cochran-Armitage test	—			
Fisher exact test		P=1.000N	P=1.000N	P=1.000N

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

TABLE A4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile (CS2)	4/50	0/50	4/50
Acetonitrile	1/48	1/48	2/48
2-Chloroacetophenone	1/49	1/49	2/49
l-Epinephrine Hydrochloride	4/50	1/50	5/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	5/50	0/50	5/50
Ozone	1/50	1/50	2/50
Overall Historical Incidence			
Total	17/654 (2.6%)	6/654 (0.9%)	23/654 (3.5%)
Standard deviation	3.6%	1.0%	3.7%
Range	0%-10%	0%-2%	0%-10%

[a] Data as of 12 May 1995

TABLE A4b
Historical Incidence of Neoplasms of the Adrenal Medulla in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls	
	Benign Pheochromocytoma	Benign, Complex, or Malignant Pheochromocytoma[b]
Historical Incidence at Battelle Pacific Northwest Laboratories		
o-Chlorobenzalmalononitrile (CS2)	18/42	20/42
Acetonitrile	4/48	4/48
2-Chloroacetophenone	14/46	15/46
l-Epinephrine Hydrochloride	11/50	11/50
Chloroethane	8/36	8/36
Hexachlorocyclopentadiene	15/50	16/50
Ozone	17/50	17/50
Overall Historical Incidence		
Total	163/623 (26.2%)	176/623 (28.3%)
Standard deviation	13.2%	12.0%
Range	0%-50%	8%-50%

[a] Data as of 12 May 1995
[b] Seven unspecified pheochromocytomas are included in the overall incidence.

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate[a]

	Chamber Control	0.3 mg/m³	1.0 mg/m³	3.0 mg/m³
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	30	34	26	34
Natural deaths	3	1	3	1
Survivors				
Terminal sacrifice	17	15	21	15
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Intestine small, jejunum	(49)	(49)	(47)	(49)
Inflammation, chronic active		1 (2%)		
Liver	(50)	(50)	(48)	(50)
Angiectasis	5 (10%)	1 (2%)		1 (2%)
Basophilic focus	13 (26%)	16 (32%)	23 (48%)	21 (42%)
Clear cell focus	8 (16%)	5 (10%)	8 (17%)	6 (12%)
Degeneration, cystic	10 (20%)	11 (22%)	16 (33%)	10 (20%)
Degeneration, fatty	6 (12%)	5 (10%)	5 (10%)	6 (12%)
Eosinophilic focus	2 (4%)		3 (6%)	5 (10%)
Hepatodiaphragmatic nodule	1 (2%)	4 (8%)	4 (8%)	6 (12%)
Mixed cell focus	3 (6%)	3 (6%)	4 (8%)	5 (10%)
Necrosis		2 (4%)	1 (2%)	1 (2%)
Regeneration	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Thrombosis	1 (2%)	1 (2%)		
Bile duct, hyperplasia	41 (82%)	42 (84%)	34 (71%)	35 (70%)
Centrilobular, necrosis	17 (34%)	19 (38%)	5 (10%)	11 (22%)
Mesentery	(21)	(14)	(11)	(14)
Fat, hemorrhage	1 (5%)		1 (9%)	
Fat, necrosis	20 (95%)	11 (79%)	9 (82%)	13 (93%)
Pancreas	(50)	(50)	(48)	(50)
Angiectasis		1 (2%)		
Atrophy	25 (50%)	25 (50%)	20 (42%)	28 (56%)
Basophilic focus	3 (6%)	2 (4%)	6 (13%)	3 (6%)
Hyperplasia	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Metaplasia, hepatocyte		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	2 (4%)		1 (2%)
Stomach, forestomach	(50)	(50)	(49)	(50)
Hyperplasia, basal cell		1 (2%)		
Hyperplasia, squamous		1 (2%)		
Necrosis	6 (12%)	5 (10%)	10 (20%)	3 (6%)
Stomach, glandular	(50)	(50)	(48)	(50)
Inflammation, acute		1 (2%)		
Mineralization	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Necrosis	3 (6%)	2 (4%)	5 (10%)	2 (4%)
Tongue	(1)			(2)
Hyperplasia, squamous	1 (100%)			1 (50%)
Epithelium, cyst				1 (50%)
Tooth			(1)	(1)
Developmental malformation			1 (100%)	1 (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 Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m³	1.0 mg/m³	3.0 mg/m³
Cardiovascular System				
Blood vessel				(1)
Aorta, mineralization				1 (100%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	38 (76%)	46 (92%)	45 (90%)	38 (76%)
Atrium, thrombosis	2 (4%)	4 (8%)	1 (2%)	4 (8%)
Endocrine System				
Adrenal cortex	(50)	(50)	(48)	(50)
Hyperplasia	26 (52%)	24 (48%)	26 (54%)	24 (48%)
Hypertrophy	2 (4%)	5 (10%)	5 (10%)	5 (10%)
Necrosis	2 (4%)	1 (2%)		3 (6%)
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	6 (12%)	4 (8%)	3 (6%)	3 (6%)
Adrenal medulla	(50)	(50)	(49)	(50)
Cyst				1 (2%)
Hyperplasia	34 (68%)	23 (46%)	29 (59%)	30 (60%)
Islets, pancreatic	(50)	(50)	(48)	(50)
Hyperplasia		1 (2%)		
Parathyroid gland	(48)	(48)	(49)	(49)
Hyperplasia	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Pituitary gland	(49)	(49)	(50)	(49)
Pars distalis, hyperplasia	4 (8%)	5 (10%)	4 (8%)	5 (10%)
Thyroid gland	(49)	(50)	(48)	(50)
C-cell, hyperplasia	31 (63%)	32 (64%)	32 (67%)	34 (68%)
Follicular cell, hyperplasia	2 (4%)		1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)	3 (6%)		
Preputial gland	(50)	(50)	(49)	(50)
Hyperplasia	1 (2%)			
Inflammation, chronic active	11 (22%)	10 (20%)	3 (6%)	12 (24%)
Prostate	(50)	(50)	(49)	(50)
Hyperplasia	12 (24%)	8 (16%)	5 (10%)	9 (18%)
Inflammation, chronic active	3 (6%)	4 (8%)	1 (2%)	1 (2%)
Necrosis				1 (2%)
Seminal vesicle	(50)	(50)	(49)	(49)
Inflammation, chronic active			1 (2%)	
Necrosis				1 (2%)
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	4 (8%)	5 (10%)	
Artery, inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Interstitial cell, hyperplasia	13 (26%)	10 (20%)	6 (12%)	10 (20%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Hematopoietic System				
Bone marrow	(50)	(50)	(48)	(50)
Necrosis		1 (2%)		
Lymph node	(8)	(9)	(9)	(9)
Iliac, ectasia				1 (11%)
Iliac, hemorrhage				1 (11%)
Pancreatic, ectasia			1 (11%)	
Renal, hemorrhage			1 (11%)	
Lymph node, bronchial	(45)	(30)	(41)	(49)
Inflammation, suppurative			1 (2%)	
Lymph node, mandibular	(46)	(47)	(47)	(49)
Infiltration cellular, plasma cell				1 (2%)
Lymph node, mediastinal	(47)	(46)	(44)	(49)
Hemorrhage		1 (2%)		1 (2%)
Spleen	(50)	(50)	(49)	(50)
Accessory spleen	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Depletion cellular			1 (2%)	
Fibrosis	16 (32%)	16 (32%)	12 (24%)	13 (26%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, focal				1 (2%)
Necrosis	2 (4%)		1 (2%)	2 (4%)
Integumentary System				
Mammary gland	(30)	(34)	(36)	(38)
Galactocele	2 (7%)	1 (3%)		1 (3%)
Hyperplasia, atypical			1 (3%)	
Skin	(50)	(48)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Inflammation, chronic	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)	2 (4%)		3 (6%)
Subcutaneous tissue, edema				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy			2 (4%)	
Hyperostosis	2 (4%)	2 (4%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Developmental malformation		1 (2%)		
Gliosis	1 (2%)	1 (2%)	1 (2%)	
Mineralization		1 (2%)		
Necrosis	2 (4%)	1 (2%)		
Respiratory System				
Larynx	(50)	(49)	(48)	(50)
Epiglottis, metaplasia, squamous		10 (20%)	37 (77%)	50 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Respiratory System (continued)				
Lung	(50)	(50)	(48)	(50)
Cyst				1 (2%)
Foreign body				1 (2%)
Hemorrhage	1 (2%)			
Hyperplasia, atypical			1 (2%)	1 (2%)
Infiltration cellular, histiocyte		1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative				1 (2%)
Metaplasia, squamous		1 (2%)	4 (8%)	2 (4%)
Mineralization				1 (2%)
Proteinosis		16 (32%)	40 (83%)	47 (94%)
Thrombosis		1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	9 (18%)	20 (40%)	20 (42%)	23 (46%)
Alveolar epithelium, hyperplasia, atypical		1 (2%)	2 (4%)	2 (4%)
Alveolar epithelium, metaplasia		50 (100%)	48 (100%)	49 (98%)
Alveolus, inflammation, granulomatous	2 (4%)	50 (100%)	48 (100%)	50 (100%)
Artery, mediastinum, mineralization				1 (2%)
Bronchiole, inflammation, chronic				1 (2%)
Interstitium, fibrosis	1 (2%)	50 (100%)	48 (100%)	49 (98%)
Mediastinum, inflammation, suppurative			1 (2%)	
Nose	(50)	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)			
Inflammation, suppurative	4 (8%)	15 (30%)	5 (10%)	6 (12%)
Metaplasia, squamous	1 (2%)			
Thrombosis	14 (28%)	18 (36%)	3 (6%)	9 (18%)
Glands, cyst	1 (2%)			
Lateral wall, hyperplasia	2 (4%)	14 (28%)	21 (43%)	20 (40%)
Lateral wall, inflammation				1 (2%)
Lateral wall, metaplasia, squamous	1 (2%)	3 (6%)	5 (10%)	8 (16%)
Olfactory epithelium, atrophy	8 (16%)	24 (48%)	42 (86%)	48 (96%)
Olfactory epithelium, metaplasia	5 (10%)	1 (2%)	5 (10%)	30 (60%)
Respiratory epithelium, hyperplasia, focal	6 (12%)	1 (2%)	3 (6%)	2 (4%)
Respiratory epithelium, inflammation	4 (8%)			1 (2%)
Respiratory epithelium, metaplasia, squamous	1 (2%)			1 (2%)
Pleura	(1)			
Trachea	(50)	(50)	(48)	(50)
Mineralization				1 (2%)
Special Senses System				
Eye	(5)		(1)	(1)
Cataract	5 (100%)		1 (100%)	1 (100%)
Retina, atrophy	5 (100%)		1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(48)	(50)
Cyst	1 (2%)			1 (2%)
Hydronephrosis		1 (2%)		1 (2%)
Infarct	4 (8%)	1 (2%)	1 (2%)	3 (6%)
Nephropathy	49 (98%)	49 (98%)	48 (100%)	50 (100%)
Thrombosis			1 (2%)	
Papilla, necrosis				1 (2%)
Renal tubule, hyperplasia	2 (4%)	4 (8%)	2 (4%)	2 (4%)
Urinary bladder	(50)	(50)	(48)	(50)
Necrosis				1 (2%)
Transitional epithelium, hyperplasia				1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF COBALT SULFATE HEPTAHYDRATE

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	19	20	20	17
Natural deaths	3	4	4	3
Survivors				
Terminal sacrifice	28	25	26	30
Pregnant		1		
Animals examined microscopically	50	49	50	50
Alimentary System				
Intestine large, colon	(48)	(45)	(48)	(48)
Intestine large, cecum	(48)	(45)	(47)	(47)
Intestine small, duodenum	(49)	(46)	(48)	(48)
Intestine small, ileum	(49)	(45)	(47)	(47)
Liver	(50)	(49)	(50)	(49)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Mesentery	(5)	(8)	(6)	(13)
Sarcoma stromal, metastatic, uterus		1 (13%)		
Oral mucosa	(1)	(2)		
Pharyngeal, squamous cell papilloma	1 (100%)	2 (100%)		
Pancreas	(49)	(49)	(50)	(48)
Salivary glands	(50)	(49)	(50)	(50)
Adenoma				1 (2%)
Sarcoma, metastatic, eye				1 (2%)
Stomach, forestomach	(50)	(49)	(50)	(50)
Leiomyoma				1 (2%)
Stomach, glandular	(49)	(49)	(49)	(48)
Carcinoid tumor benign		1 (2%)		
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, thyroid gland	1 (2%)			
Schwannoma benign	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(49)
Adenoma		1 (2%)		1 (2%)
Carcinoma, metastatic, kidney	1 (2%)			
Adrenal medulla	(48)	(49)	(50)	(48)
Pheochromocytoma malignant			1 (2%)	1 (2%)
Pheochromocytoma complex				1 (2%)
Pheochromocytoma benign	2 (4%)	1 (2%)	3 (6%)	7 (15%)
Bilateral, pheochromocytoma benign				1 (2%)
Islets, pancreatic	(49)	(49)	(50)	(48)
Adenoma	4 (8%)	1 (2%)		
Carcinoma	2 (4%)		1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m³	1.0 mg/m³	3.0 mg/m³
Endocrine System (continued)				
Pituitary gland	(50)	(49)	(50)	(49)
Pars distalis, adenoma	40 (80%)	39 (80%)	38 (76%)	40 (82%)
Thyroid gland	(49)	(49)	(50)	(48)
C-cell, adenoma	6 (12%)	6 (12%)	7 (14%)	3 (6%)
C-cell, carcinoma	3 (6%)		2 (4%)	3 (6%)
Follicular cell, adenoma		1 (2%)		1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(48)	(48)	(49)
Adenoma	5 (10%)	7 (15%)	3 (6%)	3 (6%)
Carcinoma	2 (4%)	3 (6%)	4 (8%)	3 (6%)
Bilateral, adenoma			2 (4%)	
Ovary	(50)	(49)	(50)	(49)
Granulosa cell tumor benign	1 (2%)			
Bilateral, granulosa-theca tumor benign		1 (2%)		
Uterus	(50)	(49)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Leiomyoma				1 (2%)
Polyp stromal	8 (16%)	7 (14%)	10 (20%)	4 (8%)
Polyp stromal, multiple			1 (2%)	
Sarcoma stromal	1 (2%)	2 (4%)		
Hematopoietic System				
Bone marrow	(49)	(49)	(50)	(50)
Lymph node	(2)	(3)	(3)	(2)
Lymph node, bronchial	(30)	(30)	(37)	(37)
Lymph node, mandibular	(44)	(40)	(47)	(45)
Sarcoma, metastatic, eye				1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Lymph node, mesenteric	(49)	(49)	(50)	(48)
Lymph node, mediastinal	(43)	(38)	(43)	(45)
Spleen	(49)	(48)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Thymus	(42)	(45)	(45)	(44)
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Adenoma	2 (4%)			
Carcinoma	2 (4%)	2 (4%)	5 (10%)	4 (8%)
Carcinoma, multiple	1 (2%)			1 (2%)
Fibroadenoma	18 (36%)	18 (37%)	13 (26%)	20 (41%)
Fibroadenoma, multiple	4 (8%)	4 (8%)	7 (14%)	7 (14%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Integumentary System (continued)				
Skin	(50)	(49)	(50)	(50)
Basal cell adenoma				1 (2%)
Squamous cell papilloma	1 (2%)			
Sebaceous gland, adenoma		1 (2%)		1 (2%)
Subcutaneous tissue, fibroma				1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, lipoma	2 (4%)			
Subcutaneous tissue, sarcoma				1 (2%)
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Sarcoma, metastatic, eye				1 (2%)
Skeletal muscle			(1)	(1)
Carcinoma, metastatic, lung				1 (100%)
Rhabdomyosarcoma			1 (100%)	
Nervous System				
Brain	(50)	(49)	(50)	(50)
Astrocytoma benign				1 (2%)
Astrocytoma malignant		1 (2%)		
Oligodendroglioma benign			1 (2%)	
Respiratory System				
Larynx	(50)	(49)	(50)	(50)
Lung	(50)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	9 (18%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma		2 (4%)	6 (12%)	6 (12%)
Carcinoma, metastatic, mammary gland	1 (2%)			
Histiocytic sarcoma				1 (2%)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Sarcoma, metastatic, eye				1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Squamous cell carcinoma			1 (2%)	1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Nose	(50)	(49)	(50)	(50)
Pleura		(1)		
Special Senses System				
Eye	(1)	(5)	(3)	(3)
Sarcoma				1 (33%)
Zymbal's gland		(1)	(1)	
Carcinoma		1 (100%)	1 (100%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Urinary System				
Kidney	(49)	(49)	(50)	(48)
Histiocytic sarcoma				1 (2%)
Lipoma	1 (2%)			1 (2%)
Mesenchymal tumor benign		1 (2%)		
Bilateral, renal tubule, carcinoma, multiple	1 (2%)			
Urinary bladder	(49)	(49)	(50)	(47)
Systemic Lesions				
Multiple organs[b]	(50)	(49)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Leukemia mononuclear	15 (30%)	16 (33%)	19 (38%)	10 (20%)
Lymphoma malignant				1 (2%)
Mesothelioma malignant		1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]	48	47	50	46
Total primary neoplasms	123	122	141	139
Total animals with benign neoplasms	45	44	47	44
Total benign neoplasms	96	94	97	105
Total animals with malignant neoplasms	25	23	32	27
Total malignant neoplasms	27	28	44	34
Total animals with metastatic neoplasms	3	3	1	3
Total metastatic neoplasms	3	3	2	9
Total animals with malignant neoplasms of uncertain primary site		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 Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	385	569	572	582	582	602	610	632	638	666	679	692	694	705	709	709	719	721	727	727	733	733	735	735	735
Carcass ID Number	148	150	107	116	142	118	114	126	136	110	102	131	138	101	104	143	128	122	121	141	123	144	103	108	115
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+																			+		
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Schwannoma benign																			X						
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Carcinoma, metastatic, kidney																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Pheochromocytoma benign										X					X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Adenoma																									
Carcinoma			X																						
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
C-cell, adenoma																							X		
C-cell, carcinoma																		X							
General Body System																									
Peritoneum																				+					
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X		X	X	X		
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X						X											X					X	
Sarcoma stromal																				X					

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	
Carcass ID Number	125	127	134	140	145	149	105	106	112	113	119	129	130	132	135	137	139	146	109	111	117	120	124	133	147	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery					+		+	+																		5
Oral mucosa								+																		1
Pharyngeal, squamous cell papilloma								X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland												X														1
Schwannoma benign																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney																				X						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X																			X	X		X	4
Carcinoma												X														2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X		40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma						X		X			X			X								X				6
C-cell, carcinoma			X									X														3
General Body System																										
Peritoneum																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							5
Carcinoma							X	X																		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign												X														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal								X						X							X		X			8
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	385	569	572	582	582	602	610	632	638	666	679	692	694	705	709	709	719	721	727	727	733	733	735	735	735
Carcass ID Number	148	150	107	116	142	118	114	126	136	110	102	131	138	101	104	143	128	122	121	141	123	144	103	108	115
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lymph node										+				+											
Lymph node, bronchial	M	M	+	M	+	+	M	M	+	+	M	+	M	+	+	M	M	+	+	+	M	M	M	+	M
Lymph node, mandibular	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																X						
Carcinoma																X									
Carcinoma, multiple									X																
Fibroadenoma		X		X			X			X	X	X		X	X	X					X				
Fibroadenoma, multiple																			X				X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, lipoma																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lipoma																									
Bilateral, renal tubule, carcinoma, multiple																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X							X		X	X		X	X	X		X			X		X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	
Carcass ID Number	125	127	134	140	145	149	105	106	112	113	119	129	130	132	135	137	139	146	109	111	117	120	124	133	147	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										2
Lymph node, bronchial	M	+	M	+	M	M	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	30
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Carcinoma											X															2
Carcinoma, multiple																										1
Fibroadenoma		X				X									X	X	X					X	X		X	18
Fibroadenoma, multiple										X									X							4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																						X				1
Subcutaneous tissue, lipoma									X																	2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lipoma				X																						1
Bilateral, renal tubule, carcinoma, multiple																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X				X											X	X	15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	362	420	483	491	517	526	526	585	610	610	610	652	670	673	673	687	694	702	709	709	714	722	728	731
Carcass ID Number	336	327	310	350	322	318	340	311	303	307	312	304	315	306	348	331	313	308	323	335	319	334	342	301
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A
Intestine small, ileum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+													+						+	+	+		
Sarcoma stromal, metastatic, uterus	X																							
Oral mucosa																								
Pharyngeal, squamous cell papilloma																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor benign													X											
Tooth												+												
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign					X																			
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X	X		X		X		X	X	X	X	X		X	X		X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X		X																	X
Follicular cell, adenoma							X																	
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X		X	X									
Carcinoma									X								X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, granulosa-theca tumor, benign							X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X	X							X		X											
Sarcoma stromal	X									X														

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	
Carcass ID Number	302	324	325	326	330	337	338	341	344	349	309	316	320	328	332	333	339	345	346	347	305	317	321	329	343	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery		+		+									+													8
Sarcoma stromal, metastatic, uterus																										1
Oral mucosa					+											+										2
Pharyngeal, squamous cell papilloma					X											X										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoid tumor benign																										1
Tooth										+																2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma benign																			X							2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	39
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma						X								X										X		6
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma					X		X							X		X										7
Carcinoma																								X		3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, granulosa-theca tumor, benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal		X										X							X							7
Sarcoma stromal																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	362	420	483	491	517	526	526	585	610	610	610	652	670	673	673	687	694	702	709	709	714	722	728	731
Carcass ID Number	336	327	310	350	322	318	340	311	303	307	312	304	315	306	348	331	313	308	323	335	319	334	342	301
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+								+													
Lymph node, bronchial	M	+	+	M	M	M	M	+	+	+	+	+	M	M	M	+	+	+	M	+	M	+	M	M
Lymph node, mandibular	M	+	+	+	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X												X					
Fibroadenoma										X	X	X		X										X
Fibroadenoma, multiple									X										X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																								
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X			
Alveolar/bronchiolar carcinoma																								
Mesothelioma malignant, metastatic, pleura									X															
Sarcoma, metastatic, uncertain primary site																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura									+															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye				+					+													+		
Zymbal's gland											+													
Carcinoma											X													
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenchymal tumor benign																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X				X		X	X			X	X		X	X		X		X		
Mesothelioma malignant									X															

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	
Carcass ID Number	302	324	325	326	330	337	338	341	344	349	309	316	320	328	332	333	339	345	346	347	305	317	321	329	343	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										3
Lymph node, bronchial	M	M	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	30
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	M	+	+	+	+	M	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	M	M	38
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	M	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										2
Fibroadenoma	X		X	X	X	X							X		X	X		X	X			X	X	X		18
Fibroadenoma, multiple							X																		X	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sebaceous gland, adenoma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma malignant	X																									1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma				X																X						2
Mesothelioma malignant, metastatic, pleura																										1
Sarcoma, metastatic, uncertain primary site													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye								+							+											5
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesenchymal tumor benign						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear			X										X				X			X					X	16
Mesothelioma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	355	510	526	541	568	596	600	603	619	632	652	659	685	692	694	695	709	722	722	722	723	727	729	732	735
Carcass ID Number	525	546	530	527	514	519	526	548	547	507	531	523	518	512	508	503	541	521	528	536	539	540	537	535	502
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Pheochromocytoma malignant, metastatic, adrenal medulla													X												
Mesentery											+														+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel		+																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant													X												
Pheochromocytoma benign															X					X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X					X	X	X	X	X			X	X	X	X	X	X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X			X		
C-cell, carcinoma																	X							X	
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																						X		X	
Carcinoma															X							X			
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X	X				X													
Polyp stromal, multiple																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	511	517	549	550	504	505	513	515	524	529	532	533	538	542	543	544	501	506	509	510	516	520	522	534	545	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							1
Histiocytic sarcoma										X																1
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Mesentery	+							+								+							+			6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign							X																X			2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign			X																							3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X			X	X	X	X	38
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X			X												X		X			X			7
C-cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma												X														3
Carcinoma				X																		X				4
Bilateral, adenoma							X		X																	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X		X	X		X	X		X								X			10
Polyp stromal, multiple					X																					1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	355	510	526	541	568	596	600	603	619	632	652	659	685	692	694	695	709	722	722	722	723	727	729	732	735
Carcass ID Number	525	546	530	527	514	519	526	548	547	507	531	523	518	512	508	503	541	521	528	536	539	540	537	535	502
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+			+								+								
Lymph node, bronchial	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X			X		X				
Fibroadenoma		X			X			X											X	X					
Fibroadenoma, multiple									X			X										X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Rhabdomyosarcoma	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign																					X				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma															X		X								
Pheochromocytoma malignant, metastatic, adrenal medulla													X												
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Zymbal's gland																						+			
Carcinoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
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 Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	511	517	549	550	504	505	513	515	524	529	532	533	538	542	543	544	501	506	509	510	516	520	522	534	545	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, bronchial	+	+	M	M	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	M	37
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X												X			5
Fibroadenoma		X		X		X			X	X					X						X	X				13
Fibroadenoma, multiple												X	X	X		X										7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma benign																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X		X			X		X				X	X	X	X		9
Alveolar/bronchiolar adenoma, multiple									X																	1
Alveolar/bronchiolar carcinoma				X												X				X	X					6
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Squamous cell carcinoma								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+										+															3
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																1
Leukemia mononuclear	X	X								X	X	X			X					X						19

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	006	386	470	585	610	611	632	642	650	652	663	673	679	680	686	692	693	709	709	722	735	735	735	735	735
Carcass ID Number	743	730	742	701	749	721	736	717	707	726	747	733	711	744	708	704	709	710	739	729	712	716	718	719	728
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+	+								+	+									+		
Pancreas	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Sarcoma, metastatic, eye								X																	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Stomach, glandular	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																						+			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung					X																				
Schwannoma benign																								X	
Endocrine System																									
Adrenal cortex	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant											X														
Pheochromocytoma complex																									
Pheochromocytoma benign																			X						X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X				X	X	X	X	X	X		X	X	X	X	X	X		X		X	X	X	X
Thyroid gland	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X												X							
C-cell, carcinoma															X										
Follicular cell, adenoma										X															
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma														X					X						
Carcinoma																									
Ovary	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Leiomyoma																									
Polyp stromal																					X	X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	735	738	702	703	705	706	715	720	723	724	725	731	732	745	746	750	713	714	722	727	734	737	740	741	748	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery				+			+		+				+		+					+		+		+		13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Sarcoma, metastatic, eye																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, lung																										1
Schwannoma benign																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Pheochromocytoma malignant																										1
Pheochromocytoma complex													X													1
Pheochromocytoma benign						X		X									X			X			X			7
Bilateral, pheochromocytoma benign																						X				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma													X													3
C-cell, carcinoma						X			X																	3
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													3
Carcinoma		X													X	X										3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Leiomyoma															X											1
Polyp stromal																						X				4

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	006	386	470	585	610	611	632	642	650	652	663	673	679	680	686	692	693	709	709	722	735	735	735	735	735
Carcass ID Number	743	730	742	701	749	721	736	717	707	726	747	733	711	744	708	704	709	710	739	729	712	716	718	719	728
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																			+	+					
Lymph node, bronchial	M	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	M	+	M	+	M	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Sarcoma, metastatic, eye								X																	
Sarcoma, metastatic, skin							X																		
Lymph node, mesenteric	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Thymus	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, multiple																	X								
Fibroadenoma		X						X	X	X								X	X	X			X	X	X
Fibroadenoma, multiple																X					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																				X					
Sebaceous gland, adenoma																									X
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, sarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, eye								X																	
Skeletal muscle					+																				
Carcinoma, metastatic, lung					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign									X																
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		X
Alveolar/bronchiolar adenoma, multiple																					X				
Alveolar/bronchiolar carcinoma					X									X											
Histiocytic sarcoma															X										
Sarcoma, metastatic, eye								X																	
Sarcoma, metastatic, skin							X																		
Squamous cell carcinoma																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+			+																	
Sarcoma								X																	
Lacrimal gland																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	735	738	702	703	705	706	715	720	723	724	725	731	732	745	746	750	713	714	722	727	734	737	740	741	748	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	M	37
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	45
Sarcoma, metastatic, eye																										1
Sarcoma, metastatic, skin																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma			X										X									X	X			4
Carcinoma, multiple																										1
Fibroadenoma			X	X				X					X	X			X	X			X		X		X	20
Fibroadenoma, multiple	X					X	X								X	X										7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma												X														1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, eye																										1
Skeletal muscle																										1
Carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma benign																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X		X											X		X	X	7
Alveolar/bronchiolar adenoma, multiple																	X									2
Alveolar/bronchiolar carcinoma	X		X													X			X							6
Histiocytic sarcoma																										1
Sarcoma, metastatic, eye																										1
Sarcoma, metastatic, skin																										1
Squamous cell carcinoma																					X					1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+																							3
Sarcoma																										1
Lacrimal gland																				+			+			2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m^3

Number of Days on Study	006	386	470	585	610	611	632	642	650	652	663	673	679	680	686	692	693	709	709	722	735	735	735	735	735
Carcass ID Number	743	730	742	701	749	721	736	717	707	726	747	733	711	744	708	704	709	710	739	729	712	716	718	719	728
Urinary System																									
Kidney	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Lipoma																									
Urinary bladder	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Leukemia mononuclear			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 Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	735	738	702	703	705	706	715	720	723	724	725	731	732	745	746	750	713	714	722	727	734	737	740	741	748	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Lipoma								X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear																	X							X		10
Lymphoma malignant																										1

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/48 (4%)	1/49 (2%)	3/50 (6%)	8/48 (17%)
Adjusted rate[b]	5.1%	3.1%	9.3%	26.4%
Terminal rate[c]	0/27 (0%)	0/25 (0%)	1/26 (4%)	7/29 (24%)
First incidence (days)	666	702	694	709
Life table test[d]	P=0.006	P=0.546N	P=0.483	P=0.054
Logistic regression test[d]	P=0.004	P=0.498N	P=0.512	P=0.043
Cochran-Armitage test[d]	P=0.003			
Fisher exact test[d]		P=0.492N	P=0.520	P=0.045
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	2/48 (4%)	1/49 (2%)	4/50 (8%)	10/48 (21%)
Adjusted rate	5.1%	3.1%	11.7%	31.5%
Terminal rate	0/27 (0%)	0/25 (0%)	1/26 (4%)	8/29 (28%)
First incidence (days)	666	702	685	663
Life table test	P=0.001	P=0.546N	P=0.325	P=0.019
Logistic regression test	P < 0.001	P=0.498N	P=0.323	P=0.014
Cochran-Armitage test	P < 0.001			
Fisher exact test		P=0.492N	P=0.359	P=0.014
Clitoral Gland: Adenoma				
Overall rate	5/50 (10%)	7/48 (15%)	5/48 (10%)	3/49 (6%)
Adjusted rate	16.0%	23.4%	17.8%	8.8%
Terminal rate	2/28 (7%)	4/24 (17%)	3/26 (12%)	1/30 (3%)
First incidence (days)	727	652	727	680
Life table test	P=0.160N	P=0.289	P=0.567	P=0.360N
Logistic regression test	P=0.182N	P=0.286	P=0.581	P=0.384N
Cochran-Armitage test	P=0.189N			
Fisher exact test		P=0.351	P=0.603	P=0.369N
Clitoral Gland: Carcinoma				
Overall rate	2/50 (4%)	3/48 (6%)	4/48 (8%)	3/49 (6%)
Adjusted rate	7.1%	9.3%	13.4%	10.0%
Terminal rate	2/28 (7%)	1/24 (4%)	2/26 (8%)	3/30 (10%)
First incidence (days)	735 (T)	610	694	735 (T)
Life table test	P=0.548	P=0.439	P=0.305	P=0.532
Logistic regression test	P=0.504	P=0.459	P=0.301	P=0.532
Cochran-Armitage test	P=0.499			
Fisher exact test		P=0.480	P=0.319	P=0.490
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	10/48 (21%)	8/48 (17%)	6/49 (12%)
Adjusted rate	22.5%	31.1%	27.0%	18.2%
Terminal rate	4/28 (14%)	5/24 (21%)	5/26 (19%)	4/30 (13%)
First incidence (days)	727	610	694	680
Life table test	P=0.234N	P=0.207	P=0.429	P=0.480N
Logistic regression test	P=0.280N	P=0.205	P=0.432	P=0.545N
Cochran-Armitage test	P=0.291N			
Fisher exact test		P=0.266	P=0.465	P=0.516N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	1/49 (2%)	10/50 (20%)	9/50 (18%)
Adjusted rate	0.0%	3.4%	36.4%	30.0%
Terminal rate	0/28 (0%)	0/25 (0%)	9/26 (35%)	9/30 (30%)
First incidence (days)	—[e]	714	692	735 (T)
Life table test	P=0.003	P=0.468	P < 0.001	P=0.003
Logistic regression test	P=0.001	P=0.480	P < 0.001	P=0.003
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.495	P < 0.001	P=0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	2/49 (4%)	6/50 (12%)	6/50 (12%)
Adjusted rate	0.0%	8.0%	20.2%	17.5%
Terminal rate	0/28 (0%)	2/25 (8%)	4/26 (15%)	4/30 (13%)
First incidence (days)	—	735 (T)	694	610
Life table test	P=0.033	P=0.213	P=0.015	P=0.022
Logistic regression test	P=0.023	P=0.213	P=0.015	P=0.017
Cochran-Armitage test	P=0.022			
Fisher exact test		P=0.242	P=0.013	P=0.013
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/49 (6%)	15/50 (30%)	15/50 (30%)
Adjusted rate	0.0%	11.2%	50.6%	46.1%
Terminal rate	0/28 (0%)	2/25 (8%)	12/26 (46%)	13/30 (43%)
First incidence (days)	—	714	692	610
Life table test	P < 0.001	P=0.101	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P=0.096	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P=0.117	P < 0.001	P < 0.001
Lung: Alveolar/bronchiolar Adenoma, Alveolar/bronchiolar Carcinoma, or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	3/49 (6%)	16/50 (32%)	16/50 (32%)
Adjusted rate	0.0%	11.2%	54.1%	49.2%
Terminal rate	0/28 (0%)	2/25 (8%)	13/26 (50%)	14/30 (47%)
First incidence (days)	—	714	692	610
Life table test	P < 0.001	P=0.101	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P=0.096	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P=0.117	P < 0.001	P < 0.001
Mammary Gland: Fibroadenoma				
Overall rate	22/50 (44%)	22/49 (45%)	20/50 (40%)	27/50 (54%)
Adjusted rate	54.6%	67.3%	56.5%	70.5%
Terminal rate	11/28 (39%)	15/25 (60%)	12/26 (46%)	19/30 (63%)
First incidence (days)	569	610	510	386
Life table test	P=0.291	P=0.386	P=0.524N	P=0.280
Logistic regression test	P=0.147	P=0.439	P=0.435N	P=0.182
Cochran-Armitage test	P=0.153			
Fisher exact test		P=0.545	P=0.420N	P=0.212

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	23/50 (46%)	22/49 (45%)	20/50 (40%)	27/50 (54%)
Adjusted rate	55.6%	67.3%	56.5%	70.5%
Terminal rate	11/28 (39%)	15/25 (60%)	12/26 (46%)	19/30 (63%)
First incidence (days)	569	610	510	386
Life table test	P=0.334	P=0.452	P=0.457N	P=0.343
Logistic regression test	P=0.179	P=0.535	P=0.349N	P=0.244
Cochran-Armitage test	P=0.186			
Fisher exact test		P=0.537N	P=0.343N	P=0.274
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	2/49 (4%)	5/50 (10%)	5/50 (10%)
Adjusted rate	8.5%	5.4%	15.9%	15.9%
Terminal rate	1/28 (4%)	0/25 (0%)	2/26 (8%)	4/30 (13%)
First incidence (days)	638	526	695	693
Life table test	P=0.247	P=0.555N	P=0.333	P=0.370
Logistic regression test	P=0.216	P=0.471N	P=0.341	P=0.342
Cochran-Armitage test	P=0.217			
Fisher exact test		P=0.510N	P=0.357	P=0.357
Mammary Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/49 (4%)	5/50 (10%)	5/50 (10%)
Adjusted rate	13.2%	5.4%	15.9%	15.9%
Terminal rate	1/28 (4%)	0/25 (0%)	2/26 (8%)	4/30 (13%)
First incidence (days)	572	526	695	693
Life table test	P=0.423	P=0.280N	P=0.589	P=0.621N
Logistic regression test	P=0.390	P=0.182N	P=0.626	P=0.622
Cochran-Armitage test	P=0.393			
Fisher exact test		P=0.226N	P=0.630N	P=0.630N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	25/50 (50%)	23/49 (47%)	24/50 (48%)	29/50 (58%)
Adjusted rate	59.2%	68.1%	65.0%	74.0%
Terminal rate	12/28 (43%)	15/25 (60%)	14/26 (54%)	20/30 (67%)
First incidence (days)	569	526	510	386
Life table test	P=0.324	P=0.511	P=0.528	P=0.348
Logistic regression test	P=0.160	P=0.527N	P=0.513N	P=0.242
Cochran-Armitage test	P=0.168			
Fisher exact test		P=0.459N	P=0.500N	P=0.274
Pancreatic Islets: Adenoma				
Overall rate	4/49 (8%)	1/49 (2%)	0/50 (0%)	0/48 (0%)
Adjusted rate	14.3%	4.0%	0.0%	0.0%
Terminal rate	4/28 (14%)	1/25 (4%)	0/26 (0%)	0/30 (0%)
First incidence (days)	735 (T)	735 (T)	—	—
Life table test	P=0.049N	P=0.212N	P=0.071N	P=0.053N
Logistic regression test	P=0.049N	P=0.212N	P=0.071N	P=0.053N
Cochran-Armitage test	P=0.058N			
Fisher exact test		P=0.181N	P=0.056N	P=0.061N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	6/49 (12%)	1/49 (2%)	1/50 (2%)	0/48 (0%)
Adjusted rate	19.6%	4.0%	3.4%	0.0%
Terminal rate	5/28 (18%)	1/25 (4%)	0/26 (0%)	0/30 (0%)
First incidence (days)	572	735 (T)	727	—
Life table test	P=0.023N	P=0.078N	P=0.073N	P=0.015N
Logistic regression test	P=0.025N	P=0.069N	P=0.059N	P=0.019N
Cochran-Armitage test	P=0.027N			
Fisher exact test		P=0.056N	P=0.053N	P=0.014N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	40/50 (80%)	39/49 (80%)	38/50 (76%)	40/49 (82%)
Adjusted rate	86.8%	95.0%	90.3%	90.8%
Terminal rate	22/28 (79%)	23/25 (92%)	22/26 (85%)	26/30 (87%)
First incidence (days)	569	420	510	386
Life table test	P=0.350N	P=0.336	P=0.530	P=0.491N
Logistic regression test	P=0.450	P=0.451	P=0.474N	P=0.449
Cochran-Armitage test	P=0.450			
Fisher exact test		P=0.579N	P=0.405N	P=0.520
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/49 (12%)	6/49 (12%)	7/50 (14%)	3/48 (6%)
Adjusted rate	21.4%	19.1%	24.5%	8.3%
Terminal rate	6/28 (21%)	3/25 (12%)	5/26 (19%)	1/30 (3%)
First incidence (days)	735 (T)	517	722	611
Life table test	P=0.139N	P=0.540	P=0.449	P=0.220N
Logistic regression test	P=0.177N	P=0.597	P=0.469	P=0.254N
Cochran-Armitage test	P=0.184N			
Fisher exact test		P=0.620N	P=0.516	P=0.254N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	3/49 (6%)	0/49 (0%)	2/50 (4%)	3/48 (6%)
Adjusted rate	10.0%	0.0%	6.5%	9.3%
Terminal rate	2/28 (7%)	0/25 (0%)	0/26 (0%)	2/30 (7%)
First incidence (days)	721	—	709	686
Life table test	P=0.365	P=0.147N	P=0.528N	P=0.651N
Logistic regression test	P=0.340	P=0.140N	P=0.511N	P=0.653
Cochran-Armitage test	P=0.323			
Fisher exact test		P=0.121N	P=0.490N	P=0.651
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	9/49 (18%)	6/49 (12%)	9/50 (18%)	6/48 (13%)
Adjusted rate	30.7%	19.1%	29.4%	17.0%
Terminal rate	8/28 (29%)	3/25 (12%)	5/26 (19%)	3/30 (10%)
First incidence (days)	721	517	709	611
Life table test	P=0.277N	P=0.376N	P=0.543	P=0.263N
Logistic regression test	P=0.339N	P=0.326N	P=0.578	P=0.303N
Cochran-Armitage test	P=0.357N			
Fisher exact test		P=0.288N	P=0.584N	P=0.303N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Uterus: Stromal Polyp				
Overall rate	8/50 (16%)	7/49 (14%)	11/50 (22%)	4/50 (8%)
Adjusted rate	23.9%	20.0%	35.6%	13.3%
Terminal rate	5/28 (18%)	3/25 (12%)	8/26 (31%)	4/30 (13%)
First incidence (days)	569	483	600	735 (T)
Life table test	P=0.113N	P=0.585N	P=0.254	P=0.159N
Logistic regression test	P=0.146N	P=0.467N	P=0.294	P=0.189N
Cochran-Armitage test	P=0.144N			
Fisher exact test		P=0.517N	P=0.306	P=0.178N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	9/50 (18%)	9/49 (18%)	11/50 (22%)	4/50 (8%)
Adjusted rate	26.3%	23.6%	35.6%	13.3%
Terminal rate	5/28 (18%)	3/25 (12%)	8/26 (31%)	4/30 (13%)
First incidence (days)	569	362	600	735 (T)
Life table test	P=0.059N	P=0.507	P=0.341	P=0.108N
Logistic regression test	P=0.071N	P=0.513N	P=0.387	P=0.126N
Cochran-Armitage test	P=0.074N			
Fisher exact test		P=0.584	P=0.402	P=0.117N
All Organs: Mononuclear Cell Leukemia				
Overall rate	15/50 (30%)	16/49 (33%)	19/50 (38%)	10/50 (20%)
Adjusted rate	37.4%	41.1%	47.7%	25.6%
Terminal rate	5/28 (18%)	5/25 (20%)	7/26 (27%)	3/30 (10%)
First incidence (days)	385	483	526	470
Life table test	P=0.107N	P=0.367	P=0.242	P=0.217N
Logistic regression test	P=0.091N	P=0.529	P=0.273	P=0.166N
Cochran-Armitage test	P=0.095N			
Fisher exact test		P=0.473	P=0.263	P=0.178N
All Organs: Benign Neoplasms				
Overall rate	45/50 (90%)	44/49 (90%)	47/50 (94%)	44/50 (88%)
Adjusted rate	93.7%	95.6%	100.0%	97.8%
Terminal rate	25/28 (89%)	23/25 (92%)	26/26 (100%)	29/30 (97%)
First incidence (days)	569	420	510	386
Life table test	P=0.259N	P=0.318	P=0.275	P=0.420N
Logistic regression test	P=0.483N	P=0.566	P=0.248	P=0.636N
Cochran-Armitage test	P=0.418N			
Fisher exact test		P=0.617N	P=0.357	P=0.500N
All Organs: Malignant Neoplasms				
Overall rate	25/50 (50%)	23/49 (47%)	32/50 (64%)	27/50 (54%)
Adjusted rate	58.3%	54.9%	72.0%	65.0%
Terminal rate	11/28 (39%)	8/25 (32%)	14/26 (54%)	16/30 (53%)
First incidence (days)	385	362	355	470
Life table test	P=0.472	P=0.513	P=0.129	P=0.464
Logistic regression test	P=0.341	P=0.376N	P=0.119	P=0.402
Cochran-Armitage test	P=0.337			
Fisher exact test		P=0.459N	P=0.113	P=0.421

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	47/49 (96%)	50/50 (100%)	46/50 (92%)
Adjusted rate	96.0%	95.9%	100.0%	97.9%
Terminal rate	26/28 (93%)	23/25 (92%)	26/26 (100%)	29/30 (97%)
First incidence (days)	385	362	355	386
Life table test	P=0.216N	P=0.310	P=0.280	P=0.365N
Logistic regression test	P=0.228N	P=0.655N	P=0.254	P=0.450N
Cochran-Armitage test	P=0.180N			
Fisher exact test		P=0.684N	P=0.247	P=0.339N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, lung, pancreatic islets, 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 chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile (CS2)	2/49	0/49	2/49
Acetonitrile	0/48	0/48	0/48
2-Chloroacetophenone	1/49	0/49	1/49
l-Epinephrine Hydrochloride	0/50	0/50	0/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	1/50	0/50	1/50
Ozone	0/50	0/50	0/50
Overall Historical Incidence			
Total	7/650 (1.1%)	0/650 (0.0%)	7/650 (1.1%)
Standard deviation	1.6%		1.6%
Range	0%-4%		0%-4%

[a] Data as of 12 May 1995

TABLE B4b
Historical Incidence of Neoplasms of the Adrenal Medulla in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls	
	Benign Pheochromocytoma	Benign, Complex, or Malignant Pheochromocytoma[b]
Historical Incidence at Battelle Pacific Northwest Laboratories		
o-Chlorobenzalmalononitrile (CS2)	5/37	5/37
Acetonitrile	1/48	1/48
2-Chloroacetophenone	5/49	5/49
l-Epinephrine Hydrochloride	1/50	1/50
Chloroethane	1/35	1/35
Hexachlorocyclopentadiene	6/47	6/47
Ozone	6/50	6/50
Overall Historical Incidence		
Total	35/608 (5.8%)	39/608 (6.4%)
Standard deviation	4.9%	4.4%
Range	0%-14%	2%-14%

[a] Data as of 12 May 1995
[b] One unspecified pheochromocytoma is included in the overall incidence.

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate[a]

	Chamber Control	0.3 mg/m³	1.0 mg/m³	3.0 mg/m³
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	19	20	20	17
Natural deaths	3	4	4	3
Survivors				
Terminal sacrifice	28	25	26	30
Pregnant		1		
Animals examined microscopically	50	49	50	50
Alimentary System				
Esophagus	(50)	(49)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Intestine large, cecum	(48)	(45)	(47)	(47)
Necrosis			1 (2%)	
Liver	(50)	(49)	(50)	(49)
Angiectasis	6 (12%)	4 (8%)	1 (2%)	2 (4%)
Basophilic focus	39 (78%)	37 (76%)	45 (90%)	41 (84%)
Clear cell focus	7 (14%)	6 (12%)	5 (10%)	11 (22%)
Cyst			1 (2%)	
Degeneration, fatty	8 (16%)	9 (18%)	8 (16%)	2 (4%)
Eosinophilic focus	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Hepatodiaphragmatic nodule	6 (12%)	6 (12%)	8 (16%)	4 (8%)
Inflammation, chronic active		1 (2%)		
Mixed cell focus	11 (22%)	11 (22%)	18 (36%)	15 (31%)
Necrosis		1 (2%)		
Regeneration		1 (2%)	2 (4%)	
Thrombosis	1 (2%)			
Bile duct, hyperplasia	5 (10%)	6 (12%)	9 (18%)	7 (14%)
Centrilobular, necrosis	5 (10%)	6 (12%)	7 (14%)	5 (10%)
Mesentery	(5)	(8)	(6)	(13)
Inflammation, chronic active				1 (8%)
Artery, inflammation, chronic active		1 (13%)		
Fat, necrosis	5 (100%)	6 (75%)	6 (100%)	12 (92%)
Pancreas	(49)	(49)	(50)	(48)
Atrophy	22 (45%)	11 (22%)	16 (32%)	16 (33%)
Basophilic focus				3 (6%)
Hyperplasia				1 (2%)
Artery, inflammation			1 (2%)	
Salivary glands	(50)	(49)	(50)	(50)
Atrophy	3 (6%)	4 (8%)	1 (2%)	
Stomach, forestomach	(50)	(49)	(50)	(50)
Hyperplasia, basal cell		1 (2%)		
Hyperplasia, squamous			1 (2%)	
Necrosis	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Stomach, glandular	(49)	(49)	(49)	(48)
Mineralization	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis	4 (8%)		1 (2%)	
Tooth		(2)		(1)
Developmental malformation		1 (50%)		
Inflammation, chronic active		1 (50%)		1 (100%)

[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 Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Cardiovascular System				
Blood vessel			(1)	
Aorta, inflammation, chronic active			1 (100%)	
Heart	(50)	(49)	(50)	(50)
Cardiomyopathy	29 (58%)	24 (49%)	29 (58%)	23 (46%)
Atrium, thrombosis		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(49)
Hyperplasia	21 (43%)	21 (43%)	25 (50%)	23 (47%)
Hypertrophy	5 (10%)	3 (6%)	8 (16%)	9 (18%)
Necrosis	1 (2%)			
Vacuolization cytoplasmic	11 (22%)	5 (10%)	10 (20%)	12 (24%)
Adrenal medulla	(48)	(49)	(50)	(48)
Hyperplasia	8 (17%)	7 (14%)	11 (22%)	13 (27%)
Pituitary gland	(50)	(49)	(50)	(49)
Pars distalis, angiectasis			2 (4%)	
Pars distalis, cyst				1 (2%)
Pars distalis, hyperplasia	5 (10%)	5 (10%)	8 (16%)	5 (10%)
Thyroid gland	(49)	(49)	(50)	(48)
C-cell, hyperplasia	37 (76%)	42 (86%)	37 (74%)	38 (79%)
Follicular cell, hyperplasia	2 (4%)			1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(48)	(48)	(49)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic active	2 (4%)	6 (13%)	2 (4%)	6 (12%)
Ovary	(50)	(49)	(50)	(49)
Cyst	5 (10%)	1 (2%)	3 (6%)	
Uterus	(50)	(49)	(50)	(49)
Hydrometra				2 (4%)
Cervix, hypertrophy		1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(49)	(50)	(50)
Atrophy	2 (4%)			1 (2%)
Hyperplasia, histiocytic			1 (2%)	1 (2%)
Lymph node	(2)	(3)	(3)	(2)
Renal, hemorrhage		1 (33%)		
Lymph node, mandibular	(44)	(40)	(47)	(45)
Infiltration cellular, plasma cell				1 (2%)
Lymph node, mesenteric	(49)	(49)	(50)	(48)
Hemorrhage		1 (2%)		1 (2%)
Infiltration cellular, eosinophil				1 (2%)
Lymph node, mediastinal	(43)	(38)	(43)	(45)
Hemorrhage	1 (2%)			1 (2%)
Infiltration cellular, plasma cell			1 (2%)	1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m³	1.0 mg/m³	3.0 mg/m³
Hematopoietic System (continued)				
Spleen	(49)	(48)	(50)	(49)
Accessory spleen	1 (2%)	2 (4%)		
Fibrosis		4 (8%)	2 (4%)	
Hematopoietic cell proliferation	3 (6%)	2 (4%)	4 (8%)	3 (6%)
Hemorrhage	2 (4%)		3 (6%)	1 (2%)
Hyperplasia, focal				1 (2%)
Necrosis				1 (2%)
Thrombosis				1 (2%)
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Galactocele		2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active				1 (2%)
Skin	(50)	(49)	(50)	(50)
Hyperkeratosis		1 (2%)		
Inflammation, chronic				1 (2%)
Inflammation, chronic active		4 (8%)	3 (6%)	3 (6%)
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Hyperostosis	4 (8%)	5 (10%)	5 (10%)	3 (6%)
Nervous System				
Brain	(50)	(49)	(50)	(50)
Gliosis				1 (2%)
Hemorrhage	2 (4%)			
Respiratory System				
Larynx	(50)	(49)	(50)	(50)
Epiglottis, metaplasia, squamous	1 (2%)	22 (45%)	39 (78%)	48 (96%)
Lung	(50)	(49)	(50)	(50)
Congestion, chronic		1 (2%)		
Cyst			1 (2%)	
Metaplasia, osseous				1 (2%)
Metaplasia, squamous		1 (2%)	8 (16%)	3 (6%)
Pigmentation, hemosiderin		1 (2%)		
Proteinosis		36 (73%)	49 (98%)	49 (98%)
Alveolar epithelium, hyperplasia	15 (30%)	7 (14%)	20 (40%)	33 (66%)
Alveolar epithelium, hyperplasia, atypical			3 (6%)	5 (10%)
Alveolar epithelium, metaplasia	2 (4%)	47 (96%)	50 (100%)	49 (98%)
Alveolus, inflammation, granulomatous	9 (18%)	47 (96%)	50 (100%)	49 (98%)
Interstitium, fibrosis	7 (14%)	47 (96%)	50 (100%)	49 (98%)
Perivascular, inflammation, chronic active				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Respiratory System (continued)				
Nose	(50)	(49)	(50)	(50)
Inflammation, suppurative	6 (12%)	10 (20%)	2 (4%)	4 (8%)
Thrombosis	4 (8%)	4 (8%)	3 (6%)	2 (4%)
Lateral wall, hyperplasia	1 (2%)	8 (16%)	26 (52%)	38 (76%)
Lateral wall, metaplasia, squamous	1 (2%)	1 (2%)	4 (8%)	10 (20%)
Nasolacrimal duct, metaplasia, squamous		1 (2%)		
Olfactory epithelium, atrophy	5 (10%)	29 (59%)	46 (92%)	47 (94%)
Olfactory epithelium, metaplasia	2 (4%)	2 (4%)	3 (6%)	40 (80%)
Respiratory epithelium, hyperplasia, focal	1 (2%)			
Respiratory epithelium, metaplasia, squamous	2 (4%)			
Pleura		(1)		
Special Senses System				
Eye	(1)	(5)	(3)	(3)
Cataract	1 (100%)	4 (80%)	3 (100%)	2 (67%)
Cornea, edema		1 (20%)		
Retina, atrophy	1 (100%)	4 (80%)	3 (100%)	1 (33%)
Urinary System				
Kidney	(49)	(49)	(50)	(48)
Hyperplasia, stromal				1 (2%)
Infarct	1 (2%)		2 (4%)	2 (4%)
Nephropathy	47 (96%)	48 (98%)	45 (90%)	48 (100%)
Renal tubule, hyperplasia			1 (2%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF COBALT SULFATE HEPTAHYDRATE

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1			1
Moribund	19	16	17	23
Natural deaths	8	3	9	6
Survivors				
Terminal sacrifice	22	31	24	20
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(45)	(49)	(45)	(46)
Intestine small, duodenum	(45)	(49)	(42)	(45)
Polyp adenomatous		1 (2%)		
Intestine small, jejunum	(45)	(48)	(42)	(45)
Carcinoma		1 (2%)		
Intestine small, ileum	(45)	(49)	(43)	(44)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)	4 (8%)	8 (16%)	7 (14%)
Hepatoblastoma	4 (8%)		2 (4%)	2 (4%)
Hepatocellular carcinoma	16 (32%)	32 (64%)	29 (58%)	26 (52%)
Hepatocellular carcinoma, multiple	7 (14%)	1 (2%)	1 (2%)	4 (8%)
Hepatocellular adenoma	14 (28%)	12 (24%)	16 (32%)	6 (12%)
Hepatocellular adenoma, multiple	8 (16%)	9 (18%)	9 (18%)	7 (14%)
Hepatocholangiocarcinoma	1 (2%)			
Histiocytic sarcoma	1 (2%)			1 (2%)
Sarcoma				1 (2%)
Mesentery	(3)	(4)	(5)	(4)
Hemangiosarcoma		1 (25%)		1 (25%)
Hepatocellular carcinoma, metastatic, liver			1 (20%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (33%)			
Sarcoma, metastatic, liver				1 (25%)
Pancreas	(48)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, liver				1 (2%)
Stomach, forestomach	(49)	(50)	(50)	(50)
Sarcoma, metastatic, liver				1 (2%)
Squamous cell carcinoma		2 (4%)		
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(48)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Serosa, hepatocellular carcinoma, metastatic, liver		1 (2%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma		1 (2%)		
Sarcoma, metastatic, liver				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Endocrine System				
Adrenal cortex	(49)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Adrenal medulla	(48)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Pheochromocytoma benign	1 (2%)			1 (2%)
Islets, pancreatic	(48)	(50)	(49)	(50)
Adenoma		1 (2%)		
Thyroid gland	(49)	(50)	(50)	(50)
Follicular cell, adenoma				1 (2%)
Follicular cell, carcinoma			1 (2%)	
General Body System				
Peritoneum	(1)			
Hepatocholangiocarcinoma, metastatic, liver	1 (100%)			
Tissue NOS	(1)		(1)	
Hemangioma	1 (100%)			
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Leiomyoma			1 (2%)	
Testes	(49)	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hemangiosarcoma		2 (4%)		1 (2%)
Lymph node	(1)	(1)	(2)	(2)
Iliac, sarcoma, metastatic, liver				1 (50%)
Renal, histiocytic sarcoma	1 (100%)			
Lymph node, bronchial	(21)	(24)	(28)	(25)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (4%)
Histiocytic sarcoma	1 (5%)			
Sarcoma, metastatic, liver				1 (4%)
Lymph node, mesenteric	(49)	(48)	(43)	(47)
Hemangiosarcoma		1 (2%)		
Hepatoblastoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, liver				1 (2%)
Lymph node, mediastinal	(43)	(28)	(31)	(35)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, liver				1 (3%)
Spleen	(47)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Histiocytic sarcoma	1 (2%)			1 (2%)
Thymus	(28)	(31)	(33)	(28)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Integumentary System				
Skin	(49)	(50)	(49)	(49)
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)	1 (2%)		2 (4%)
Subcutaneous tissue, carcinoma				1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Skeletal muscle	(1)			(2)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (50%)
Hepatocholangiocarcinoma, metastatic, liver	1 (100%)			
Nervous System				
None				
Respiratory System				
Larynx	(48)	(49)	(48)	(49)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	9 (18%)	9 (18%)	11 (22%)	13 (26%)
Alveolar/bronchiolar adenoma, multiple		3 (6%)	2 (4%)	5 (10%)
Alveolar/bronchiolar carcinoma	3 (6%)	5 (10%)	5 (10%)	9 (18%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)		2 (4%)	2 (4%)
Hemangiosarcoma, metastatic, liver				1 (2%)
Hepatoblastoma, metastatic, liver	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	5 (10%)	5 (10%)	6 (12%)	7 (14%)
Histiocytic sarcoma	1 (2%)			
Nose	(50)	(50)	(48)	(49)
Trachea	(49)	(50)	(50)	(50)
Special Senses System				
Harderian gland	(4)	(4)	(4)	(6)
Adenoma	4 (100%)	2 (50%)	2 (50%)	1 (17%)
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Histiocytic sarcoma				1 (2%)
Renal tubule, adenoma		1 (2%)		1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			1 (2%)
Lymphoma malignant	1 (2%)	1 (2%)	1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	48	47	46
Total primary neoplasms	77	94	92	95
Total animals with benign neoplasms	30	30	30	27
Total benign neoplasms	38	39	42	35
Total animals with malignant neoplasms	33	39	41	38
Total malignant neoplasms	39	55	50	60
Total animals with metastatic neoplasms	7	6	7	9
Total metastatic neoplasms	14	6	7	21

[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 Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	449	470	482	486	516	533	541	541	555	575	579	600	600	611	640	643	649	651	652	652	676	680	685	686	688
Carcass ID Number	015	007	033	044	042	043	016	019	029	009	047	004	010	050	027	048	028	013	001	032	026	005	025	012	038
Alimentary System																									
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	A	+	A	A	+	+	M	M	+	+	+	+	A	+	A	+	M	+	+	M	+	+
Intestine large, colon	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	+	+	A	A	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatoblastoma						X					X								X						
Hepatocellular carcinoma			X		X		X		X	X			X		X	X						X	X		X
Hepatocellular carcinoma, multiple								X																X	
Hepatocellular adenoma				X							X														X
Hepatocellular adenoma, multiple		X										X					X					X			
Hepatocholangiocarcinoma							X																		
Histiocytic sarcoma																									
Mesentery							+																		
Hepatocholangiocarcinoma, metastatic, liver							X																		
Pancreas	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Salivary glands	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver							X																		
Adrenal medulla	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver							X																		
Pheochromocytoma benign																									
Islets, pancreatic	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	I	A	M	M	I	M	M	M	M	M	+	M	+	M	+	M	+	+	M	+	M	+	M	+
Pituitary gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Peritoneum							+																		
Hepatocholangiocarcinoma, metastatic, liver							X																		
Tissue NOS																									
Hemangioma																									

+: 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 Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	708	711	725	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	022	036	040	008	011	014	018	020	021	023	024	030	035	041	045	002	003	006	017	031	034	037	039	046	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	37
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X								X														2
Hepatoblastoma					X																					4
Hepatocellular carcinoma	X											X		X								X			X	16
Hepatocellular carcinoma, multiple								X			X						X	X	X							7
Hepatocellular adenoma			X			X			X		X					X			X	X	X	X	X		X	14
Hepatocellular adenoma, multiple					X			X		X			X													8
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma		X																								1
Mesentery	+																		+							3
Hepatocholangiocarcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma		X																								1
Salivary glands	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+		+	+	+	+	+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma		X																								1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																										1
Pheochromocytoma benign								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	M	M	M	M	+	M	M	M	+	+	M	M	+	+	M	M	+	+	+	M	+	+	M	+	19
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
Peritoneum																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Tissue NOS															+											1
Hemangioma															X											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	449	470	482	486	516	533	541	541	555	575	579	600	600	611	640	643	649	651	652	652	676	680	685	686	686
Carcass ID Number	015	007	033	044	042	043	016	019	029	009	047	004	010	050	027	048	028	013	001	032	026	005	025	012	038
Genital System																									
Epididymis	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis													+												
Preputial gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Renal, histiocytic sarcoma																									
Lymph node, bronchial	+	+	M	+	M	+	M	M	M	M	+	+	M	I	+	M	M	+	+	M	+	M	M	M	M
Histiocytic sarcoma																									
Lymph node, mandibular	+	M	A	M	M	M	M	+	M	M	M	+	+	M	M	+	M	M	+	M	M	+	M	+	+
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver																			X						
Histiocytic sarcoma																									
Lymph node, mediastinal	+	M	A	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver					X																				
Hepatocholangiocarcinoma, metastatic, liver							X																		
Histiocytic sarcoma																									
Spleen	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Histiocytic sarcoma																									
Thymus	M	+	A	+	M	+	+	M	+	M	+	+	+	+	+	M	M	+	+	+	M	I	M	M	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																		X							
Subcutaneous tissue, sarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Hepatocholangiocarcinoma, metastatic, liver							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X			X		X						X		
Alveolar/bronchiolar carcinoma	X																								
Alveolar/bronchiolar carcinoma, multiple												X													
Hepatoblastoma, metastatic, liver																			X						
Hepatocellular carcinoma, metastatic, liver					X				X	X						X									
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	708	711	725	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	022	036	040	008	011	014	018	020	021	023	024	030	035	041	045	002	003	006	017	031	034	037	039	046	049	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node		+																								1
Renal, histiocytic sarcoma		X																								1
Lymph node, bronchial	+	+	M	I	M	M	M	+	+	+	M	M	+	I	+	M	M	M	M	+	M	+	+	+	M	21
Histiocytic sarcoma		X																								1
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	M	+	M	+	M	M	M	M	+	M	M	M	+	+	M	+	22
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatoblastoma, metastatic, liver																										1
Histiocytic sarcoma		X																								1
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma		X																								1
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Histiocytic sarcoma		X																								1
Thymus	+	M	+	+	M	+	M	+	+	+	M	M	+	I	+	M	+	I	M	+	+	+	M	+	+	28
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma					X																					1
Hemangiosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X						X						X								X	X				9
Alveolar/bronchiolar carcinoma																						X			X	3
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																		X								5
Histiocytic sarcoma		X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	449	470	482	486	516	533	541	541	555	575	579	600	600	611	640	643	649	651	652	652	676	680	685	686	688
Carcass ID Number	015	007	033	044	042	043	016	019	029	009	047	004	010	050	027	048	028	013	001	032	026	005	025	012	038
Special Senses System																									
Eye													+												
Harderian gland													+							+					+
Adenoma													X							X					X
Urinary System																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
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 Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	708	711	725	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	022	036	040	008	011	014	018	020	021	023	024	030	035	041	045	002	003	006	017	031	034	037	039	046	049	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland																								+		4
Adenoma																								X		4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								1
Lymphoma malignant																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	460	501	541	583	599	611	614	617	649	652	653	666	666	685	687	690	709	720	726	733	733	733	733	733	733
Carcass ID Number	213	225	201	216	242	205	241	210	230	248	247	209	237	232	224	219	226	207	221	202	203	204	206	211	215
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	A	+	+	M	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X	X										
Hepatocellular carcinoma	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X		X	X			X	X	X
Hepatocellular carcinoma, multiple																					X				
Hepatocellular adenoma								X			X							X				X	X		
Hepatocellular adenoma, multiple							X					X								X					
Mesentery				+									+		+										
Hemangiosarcoma															X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma													X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, hepatocellular carcinoma, metastatic, liver														X											
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	M	+	M	M	+	+	I	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	223	228	229	231	233	234	235	238	240	245	249	250	208	212	214	217	218	220	222	227	236	239	243	244	246	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous											X															1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma				X																						1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X													X						4
Hepatocellular carcinoma			X		X			X			X	X	X	X	X	X				X				X	X	32
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X									X		X	X		X				X				X	12
Hepatocellular adenoma, multiple		X			X					X	X							X	X							9
Mesentery																					+					4
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma					X																					2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, hepatocellular carcinoma, metastatic, liver																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X																			1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Parathyroid gland	M	M	+	M	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma										X																1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	460	501	541	583	599	611	614	617	649	652	653	666	666	685	687	690	709	720	726	733	733	733	733	733	733
Carcass ID Number	213	225	201	216	242	205	241	210	230	248	247	209	237	232	224	219	226	207	221	202	203	204	206	211	215
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Lymph node								+																	
Lymph node, bronchial	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	M	M	+	+	M	M	M	M	M	+
Lymph node, mandibular	M	M	M	M	M	+	M	M	M	+	M	+	M	M	M	M	+	+	M	+	+	M	M	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Hemangiosarcoma																									
Lymph node, mediastinal	M	+	+	+	+	M	+	+	M	+	M	+	+	M	M	+	M	M	M	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X	X										
Thymus	M	M	I	+	+	M	+	+	M	+	+	+	+	M	M	M	M	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X					X				X	X								X						
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma																					X				
Hepatocellular carcinoma, metastatic, liver											X												X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear															+										
Harderian gland		+							+												+				
Adenoma																					X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																			X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	223	228	229	231	233	234	235	238	240	245	249	250	208	212	214	217	218	220	222	227	236	239	243	244	246	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X																			2
Lymph node																										1
Lymph node, bronchial	+	M	+	M	M	M	+	+	M	+	M	+	M	+	M	M	M	+	M	M	+	M	+	I	M	24
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	M	M	+	M	M	M	M	+	+	M	M	+	+	+	M	M	21
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma					X																					1
Lymph node, mediastinal	M	M	+	M	M	+	M	M	+	M	M	M	+	+	+	M	M	M	+	+	+	+	+	+	+	28
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X																			3
Thymus	M	+	+	+	+	M	M	+	+	+	+	M	M	+	M	+	+	+	M	+	+	I	+	M	+	31
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X	X								X								X			9
Alveolar/bronchiolar adenoma, multiple																	X					X				3
Alveolar/bronchiolar carcinoma											X				X							X	X			5
Hepatocellular carcinoma, metastatic, liver																				X				X	X	5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Harderian gland																									+	4
Adenoma																									X	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	440	483	505	510	523	534	548	555	560	561	597	610	639	645	645	652	653	670	681	681	687	699	705	706	708
Carcass ID Number	437	442	408	404	445	409	416	424	441	446	447	428	438	432	434	435	440	406	413	430	436	448	423	431	419
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	A	M	A	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	I	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	M	+	A	+	+	+	+	+	+	+	+	+	A	A	A	A	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A	A	A	A	+	+	+	+	+
Intestine small, ileum	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A	A	A	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X							X	X						X		X				
Hepatoblastoma																							X		
Hepatocellular carcinoma	X	X	X			X	X	X	X	X	X	X	X	X	X		X	X		X	X	X			X
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma	X		X						X		X							X						X	
Hepatocellular adenoma, multiple					X								X												
Mesentery				+																				+	
Hepatocellular carcinoma, metastatic, liver																									
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel					+																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	M	M	M	+	M	M	+	M	M	+	M	M	+	+	M	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS							+																		
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma			X																						
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	M	+	+	+	I	+	M	+	+	+	+	A	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	709	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	
Carcass ID Number	411	401	402	405	410	412	414	417	420	421	422	425	426	427	433	443	450	403	407	415	418	429	439	444	449	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X							X													X					8
Hepatoblastoma			X																							2
Hepatocellular carcinoma	X		X	X			X		X	X				X					X			X			X	29
Hepatocellular carcinoma, multiple																X										1
Hepatocellular adenoma		X			X		X				X	X								X	X		X	X	X	16
Hepatocellular adenoma, multiple	X			X				X							X		X		X			X				9
Mesentery		+														+									+	5
Hepatocellular carcinoma, metastatic, liver																X										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma											X															1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel					+								+													3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	+	M	+	+	+	+	M	M	+	M	M	M	M	M	M	M	+	+	+	+	+	+	24
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma											X															1
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	440	483	505	510	523	534	548	555	560	561	597	610	639	645	645	652	653	670	681	681	687	699	705	706	708
Carcass ID Number	437	442	408	404	445	409	416	424	441	446	447	428	438	432	434	435	440	406	413	430	436	448	423	431	419
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node													+			+									
Lymph node, bronchial	M	M	M	M	M	+	M	M	M	+	+	+	+	+	+	+	+	A	+	+	+	M	+	+	M
Lymph node, mandibular	+	M	M	M	M	M	M	+	+	+	+	M	M	M	+	M	+	+	M	+	M	M	M	+	+
Lymph node, mesenteric	+	+	+	M	+	M	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	+	M	M	M	+	+	+	+	M	+	+	+	+	M	+	+	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Hemangiosarcoma																			X						
Thymus	M	M	M	M	+	M	M	+	M	M	+	M	+	+	+	+	M	+	M	+	+	I	+	M	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X	X										X	X				X		X
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																					X				
Alveolar/bronchiolar carcinoma, multiple																						X			
Hepatocellular carcinoma, metastatic, liver		X					X					X								X		X			X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	I	+	+	+	+	A	A	A	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																X									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m^3

Number of Days on Study	709	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	744	744	734	734	734	734	734	
Carcass ID Number	411	401	402	405	410	412	414	417	420	421	422	425	426	427	433	443	450	403	407	415	418	429	439	444	449	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, bronchial	M	M	+	+	M	M	+	+	+	+	+	M	+	+	M	M	M	M	+	+	+	+	+	M	M	28
Lymph node, mandibular	+	M	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+	M	+	+	+	+	29
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Lymph node, mediastinal	+	+	+	+	+	M	+	+	M	+	M	M	+	M	M	+	M	I	M	+	+	M	+	+	+	31
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	33
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X								X		X	X	X		11
Alveolar/bronchiolar adenoma, multiple											X													X		2
Alveolar/bronchiolar carcinoma					X												X	X		X						5
Alveolar/bronchiolar carcinoma, multiple	X																									2
Hepatocellular carcinoma, metastatic, liver																										6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								1
Harderian gland	+	+						+													+					4
Adenoma		X						X																		2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter			+																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	399	414	502	524	527	533	536	541	552	555	555	555	560	561	561	566	608	611	613	618	618	622	639	649	652
Carcass ID Number	647	606	626	616	614	602	622	612	621	618	639	641	613	645	648	644	643	604	605	632	636	640	646	631	630
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	+	+	+	+	M	+	M	A	+	M	+	M	A	+	+	A	+	M	A	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	A	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	A	+	+	A	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	A	+	+	A	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	A	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X														X			X					
Hepatoblastoma																									
Hepatocellular carcinoma			X	X	X		X		X		X	X	X		X	X	X			X	X		X	X	
Hepatocellular carcinoma, multiple								X		X															
Hepatocellular adenoma						X										X		X						X	
Hepatocellular adenoma, multiple									X													X			
Histiocytic sarcoma																									
Sarcoma				X																					
Mesentery				+									+												
Hemangiosarcoma																									
Sarcoma, metastatic, liver				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, liver				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, liver				X																					
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Sarcoma, metastatic, liver				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	M	+	+	+	+	+	+	+	M	+	+	M	+	M	+	M	+	M	M	+	M	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	653	673	678	686	713	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	
Carcass ID Number	624	633	638	634	623	601	603	607	609	610	620	625	628	635	637	642	649	608	611	615	617	619	627	629	650	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X													X				X						X		7
Hepatoblastoma										X	X															2
Hepatocellular carcinoma	X		X	X	X	X		X	X					X		X					X		X			26
Hepatocellular carcinoma, multiple										X									X							4
Hepatocellular adenoma							X											X								6
Hepatocellular adenoma, multiple	X	X															X				X	X				7
Histiocytic sarcoma				X																						1
Sarcoma																										1
Mesentery							+											+								4
Hemangiosarcoma																		X								1
Sarcoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, liver																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																				+						1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Sarcoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	M	M	M	+	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	M	+	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																		X								1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	399	414	502	524	527	533	536	541	552	555	555	555	560	561	561	566	608	611	613	618	618	622	639	649	652
Carcass ID Number	647	606	626	616	614	602	622	612	621	618	639	641	613	645	648	644	643	604	605	632	636	640	646	631	630
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node				+	+																				
Iliac, sarcoma, metastatic, liver				X																					
Lymph node, bronchial	M	+	M	+	M	+	+	+	+	M	M	M	M	+	M	M	M	+	M	M	+	M	+	M	M
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Sarcoma, metastatic, liver				X																					
Lymph node, mandibular	+	M	+	+	A	+	+	M	M	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Sarcoma, metastatic, liver				X																					
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	I	+	+	+	M	+	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Sarcoma, metastatic, liver				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	M	M	M	M	+	M	+	M	+	+	+	A	+	+	+	M	+	M	+	+	M	M	+	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Subcutaneous tissue, carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Skeletal muscle									+					+											
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																				+					
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X	X		X							X				X			X		X	X	
Alveolar/bronchiolar adenoma, multiple																									X
Alveolar/bronchiolar carcinoma									X										X						
Alveolar/bronchiolar carcinoma, multiple																									
Hemangiosarcoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver				X							X		X		X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	653	673	678	686	713	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	
Carcass ID Number	624	633	638	634	623	601	603	607	609	610	620	625	628	635	637	642	649	608	611	615	617	619	627	629	650	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Lymph node																										2
Iliac, sarcoma, metastatic, liver																										1
Lymph node, bronchial	I	M	+	M	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	M	+	+	25
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Sarcoma, metastatic, liver																										1
Lymph node, mandibular	+	M	+	+	M	+	+	M	M	M	+	+	+	M	I	M	+	+	+	+	+	M	M	+	+	31
Lymph node, mesenteric	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, liver																										1
Lymph node, mediastinal	+	+	M	I	+	+	+	M	+	M	+	+	+	M	+	M	M	+	+	+	+	+	+	+	M	35
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Sarcoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X								X												2
Histiocytic sarcoma				X																						1
Thymus	M	M	+	+	+	M	+	+	+	+	M	+	M	+	+	+	M	+	+	M	+	M	M	M	+	28
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma						X																				2
Subcutaneous tissue, carcinoma		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Skeletal muscle																										2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X							X			X				X						X					13
Alveolar/bronchiolar adenoma, multiple				X					X									X		X						5
Alveolar/bronchiolar carcinoma		X	X			X	X	X						X					X							9
Alveolar/bronchiolar carcinoma, multiple																						X			X	2
Hemangiosarcoma, metastatic, liver																								X		1
Hepatocellular carcinoma, metastatic, liver														X		X			X							7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m^3

Number of Days on Study	399	414	502	524	527	533	536	541	552	555	555	555	560	561	561	566	608	611	613	618	618	622	639	649	652
Carcass ID Number	647	606	626	616	614	602	622	612	621	618	639	641	613	645	648	644	643	604	605	632	636	640	646	631	630
Special Senses System																									
Eye	+																								
Harderian gland	+															+							+		
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Histiocytic sarcoma																									
Renal tubule, adenoma																									
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m^3

Number of Days on Study	653	673	678	686	713	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	
Carcass ID Number	624	633	638	634	623	601	603	607	609	610	620	625	628	635	637	642	649	608	611	615	617	619	627	629	650	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland		+		+																					+	6
Adenoma				X																						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma				X																						1
Renal tubule, adenoma									X																	1
Ureter																			+							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma				X																						1

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rate[b]	13.2%	6.5%	8.3%	4.5%
Terminal rate[c]	1/22 (5%)	2/31 (6%)	2/24 (8%)	0/20 (0%)
First incidence (days)	600	733 (T)	733 (T)	686
Life table test[d]	P=0.270N	P=0.221N	P=0.306N	P=0.239N
Logistic regression test[d]	P=0.229N	P=0.307N	P=0.324N	P=0.192N
Cochran-Armitage test[d]	P=0.185N			
Fisher exact test[d]		P=0.339N	P=0.339N	P=0.181N
Liver: Hemangiosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	8/50 (16%)	7/50 (14%)
Adjusted rate	9.1%	11.5%	23.5%	25.0%
Terminal rate	2/22 (9%)	2/31 (6%)	2/24 (8%)	3/20 (15%)
First incidence (days)	733 (T)	685	523	502
Life table test	P=0.036	P=0.500	P=0.071	P=0.064
Logistic regression test	P=0.078	P=0.441	P=0.050	P=0.069
Cochran-Armitage test	P=0.096			
Fisher exact test		P=0.339	P=0.046	P=0.080
Liver: Hepatocellular Adenoma				
Overall rate	22/50 (44%)	21/50 (42%)	25/50 (50%)	13/50 (26%)
Adjusted rate	71.4%	57.5%	74.0%	42.3%
Terminal rate	14/22 (64%)	16/31 (52%)	16/24 (67%)	5/20 (25%)
First incidence (days)	470	614	440	533
Life table test	P=0.192N	P=0.102N	P=0.473	P=0.123N
Logistic regression test	P=0.061N	P=0.290N	P=0.389	P=0.067N
Cochran-Armitage test	P=0.026N			
Fisher exact test		P=0.500N	P=0.344	P=0.046N
Liver: Hepatocellular Carcinoma				
Overall rate	23/50 (46%)	33/50 (66%)	30/50 (60%)	30/50 (60%)
Adjusted rate	60.8%	69.5%	66.5%	71.2%
Terminal rate	9/22 (41%)	17/31 (55%)	10/24 (42%)	9/20 (45%)
First incidence (days)	482	460	440	502
Life table test	P=0.074	P=0.398	P=0.262	P=0.094
Logistic regression test	P=0.471	P=0.017	P=0.097	P=0.143
Cochran-Armitage test	P=0.303			
Fisher exact test		P=0.035	P=0.115	P=0.115
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	38/50 (76%)	41/50 (82%)	43/50 (86%)	38/50 (76%)
Adjusted rate	89.8%	85.2%	93.2%	83.9%
Terminal rate	18/22 (82%)	24/31 (77%)	21/24 (88%)	13/20 (65%)
First incidence (days)	470	460	440	502
Life table test	P=0.134	P=0.161N	P=0.425	P=0.338
Logistic regression test	P=0.375N	P=0.284	P=0.155	P=0.591
Cochran-Armitage test	P=0.399N			
Fisher exact test		P=0.312	P=0.154	P=0.592N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Liver: Hepatoblastoma				
Overall rate	4/50 (8%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adjusted rate	11.8%	0.0%	7.6%	10.0%
Terminal rate	1/22 (5%)	0/31 (0%)	1/24 (4%)	2/20 (10%)
First incidence (days)	533	—[e]	705	733 (T)
Life table test	P=0.596	P=0.043N	P=0.313N	P=0.390N
Logistic regression test	P=0.567N	P=0.095N	P=0.342N	P=0.345N
Cochran-Armitage test	P=0.549N			
Fisher exact test		P=0.059N	P=0.339N	P=0.339N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	27/50 (54%)	33/50 (66%)	31/50 (62%)	31/50 (62%)
Adjusted rate	66.6%	69.5%	67.7%	73.8%
Terminal rate	10/22 (45%)	17/31 (55%)	10/24 (42%)	10/20 (50%)
First incidence (days)	482	460	440	502
Life table test	P=0.106	P=0.458N	P=0.436	P=0.190
Logistic regression test	P=0.500N	P=0.062	P=0.221	P=0.328
Cochran-Armitage test	P=0.414			
Fisher exact test		P=0.154	P=0.272	P=0.272
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	40/50 (80%)	41/50 (82%)	44/50 (88%)	39/50 (78%)
Adjusted rate	90.3%	85.2%	93.5%	86.2%
Terminal rate	18/22 (82%)	24/31 (77%)	21/24 (88%)	14/20 (70%)
First incidence (days)	470	460	440	502
Life table test	P=0.134	P=0.100N	P=0.488	P=0.383
Logistic regression test	P=0.340N	P=0.423	P=0.204	P=0.494N
Cochran-Armitage test	P=0.376N			
Fisher exact test		P=0.500	P=0.207	P=0.500N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	9/50 (18%)	12/50 (24%)	13/50 (26%)	18/50 (36%)
Adjusted rate	30.4%	30.9%	41.1%	54.6%
Terminal rate	4/22 (18%)	6/31 (19%)	7/24 (29%)	7/20 (35%)
First incidence (days)	600	460	548	524
Life table test	P=0.005	P=0.589	P=0.308	P=0.024
Logistic regression test	P=0.018	P=0.353	P=0.256	P=0.027
Cochran-Armitage test	P=0.029			
Fisher exact test		P=0.312	P=0.235	P=0.035
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	5/50 (10%)	7/50 (14%)	11/50 (22%)
Adjusted rate	13.2%	16.1%	25.3%	43.7%
Terminal rate	2/22 (9%)	5/31 (16%)	4/24 (17%)	7/20 (35%)
First incidence (days)	449	733 (T)	687	552
Life table test	P=0.004	P=0.603N	P=0.313	P=0.031
Logistic regression test	P=0.006	P=0.528	P=0.273	P=0.033
Cochran-Armitage test	P=0.021			
Fisher exact test		P=0.500	P=0.262	P=0.045

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	11/50 (22%)	14/50 (28%)	19/50 (38%)	28/50 (56%)
Adjusted rate	35.5%	36.5%	56.5%	78.8%
Terminal rate	5/22 (23%)	8/31 (26%)	10/24 (42%)	13/20 (65%)
First incidence (days)	449	460	548	524
Life table test	P < 0.001	P=0.544N	P=0.122	P < 0.001
Logistic regression test	P < 0.001	P=0.345	P=0.071	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P=0.322	P=0.063	P < 0.001
Spleen: Hemangiosarcoma				
Overall rate	1/47 (2%)	3/50 (6%)	1/49 (2%)	2/50 (4%)
Adjusted rate	3.0%	8.5%	3.1%	10.0%
Terminal rate	0/22 (0%)	1/31 (3%)	0/24 (0%)	2/20 (10%)
First incidence (days)	651	685	681	733 (T)
Life table test	P=0.454	P=0.419	P=0.739N	P=0.450
Logistic regression test	P=0.524	P=0.337	P=0.754N	P=0.465
Cochran-Armitage test	P=0.596			
Fisher exact test		P=0.332	P=0.742N	P=0.523
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	6/50 (12%)	8/50 (16%)	9/50 (18%)
Adjusted rate	11.8%	17.6%	23.5%	31.1%
Terminal rate	2/22 (9%)	4/31 (13%)	2/24 (8%)	4/20 (20%)
First incidence (days)	651	685	523	502
Life table test	P=0.025	P=0.423	P=0.139	P=0.047
Logistic regression test	P=0.061	P=0.344	P=0.103	P=0.054
Cochran-Armitage test	P=0.079			
Fisher exact test		P=0.243	P=0.100	P=0.061
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	5/50 (10%)	6/50 (12%)	8/50 (16%)	9/50 (18%)
Adjusted rate	20.7%	17.6%	23.5%	31.1%
Terminal rate	4/22 (18%)	4/31 (13%)	2/24 (8%)	4/20 (20%)
First incidence (days)	651	685	523	502
Life table test	P=0.060	P=0.528N	P=0.338	P=0.149
Logistic regression test	P=0.120	P=0.605N	P=0.289	P=0.162
Cochran-Armitage test	P=0.160			
Fisher exact test		P=0.500	P=0.277	P=0.194
All Organs: Benign Neoplasms				
Overall rate	30/50 (60%)	30/50 (60%)	30/50 (60%)	27/50 (54%)
Adjusted rate	84.8%	74.3%	77.7%	73.0%
Terminal rate	17/22 (77%)	21/31 (68%)	16/24 (67%)	11/20 (55%)
First incidence (days)	470	460	440	524
Life table test	P=0.276	P=0.086N	P=0.430N	P=0.538
Logistic regression test	P=0.437N	P=0.353N	P=0.542N	P=0.444N
Cochran-Armitage test	P=0.279N			
Fisher exact test		P=0.581N	P=0.581N	P=0.343N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
All Organs: Malignant Neoplasms				
Overall rate	33/50 (66%)	39/50 (78%)	41/50 (82%)	38/50 (76%)
Adjusted rate	73.8%	79.4%	85.1%	87.8%
Terminal rate	11/22 (50%)	21/31 (68%)	17/24 (71%)	15/20 (75%)
First incidence (days)	449	460	440	502
Life table test	P=0.053	P=0.374N	P=0.270	P=0.141
Logistic regression test	P=0.412	P=0.042	P=0.037	P=0.205
Cochran-Armitage test	P=0.318			
Fisher exact test		P=0.133	P=0.055	P=0.189
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	48/50 (96%)	47/50 (94%)	46/50 (92%)
Adjusted rate	100.0%	96.0%	95.9%	95.8%
Terminal rate	22/22 (100%)	29/31 (94%)	22/24 (92%)	18/20 (90%)
First incidence (days)	449	460	440	502
Life table test	P=0.114	P=0.028N	P=0.283N	P=0.435
Logistic regression test	P=0.238N	P=0.527N	P=0.297N	P=0.279N
Cochran-Armitage test	P=0.143N			
Fisher exact test		P=0.500N	P=0.309N	P=0.181N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and spleen; 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 chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The 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 Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	18/50	5/50	21/50
Acetonitrile	6/50	4/50	10/50
Allyl Glycidyl Ether	7/50	0/50	7/50
2-Chloroacetophenone	7/50	6/50	11/50
l-Epinephrine Hydrochloride	11/50	5/50	15/50
Chloroethane	3/50	2/50	5/50
Hexachlorocyclopentadiene	11/49	0/49	11/49
o-Chlorobenzalmalononitrile (CS2)	7/49	7/49	14/49
Ozone	6/50	8/50	14/50
Overall Historical Incidence			
Total	141/947 (14.9%)	75/947 (7.9%)	205/947 (21.7%)
Standard deviation	7.0%	5.7%	8.0%
Range	6%-36%	0%-16%	10%-42%

[a] Data as of 12 May 1995

TABLE C4b
Historical Incidence of Hemangiosarcoma of the Liver in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	0/50
Acetonitrile	1/50
Allyl Glycidyl Ether	0/49
2-Chloroacetophenone	0/50
l-Epinephrine Hydrochloride	1/50
Chloroethane	0/50
Hexachlorocyclopentadiene	0/50
o-Chlorobenzalmalononitrile (CS2)	0/49
Ozone	0/50
Overall Historical Incidence	
Total	12/947 (1.3%)
Standard deviation	1.7%
Range	0%-6%

[a] Data as of 12 May 1995

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate[a]

	Chamber Control	0.3 mg/m³	1.0 mg/m³	3.0 mg/m³
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1			1
Moribund	19	16	17	23
Natural deaths	8	3	9	6
Survivors				
Terminal sacrifice	22	31	24	20
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(37)	(41)	(38)	(38)
Degeneration, hyaline	1 (3%)	1 (2%)	2 (5%)	
Infiltration cellular, lymphocyte			1 (3%)	
Intestine small, duodenum	(45)	(49)	(42)	(45)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, chronic			1 (2%)	
Necrosis, focal			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	1 (2%)			
Clear cell focus		3 (6%)	2 (4%)	
Clear cell focus, multiple			1 (2%)	
Cyst				1 (2%)
Eosinophilic focus	8 (16%)	7 (14%)	9 (18%)	2 (4%)
Eosinophilic focus, multiple	1 (2%)	1 (2%)	3 (6%)	
Infiltration cellular, lymphocyte	1 (2%)			
Inflammation, chronic	33 (66%)	36 (72%)	40 (80%)	39 (78%)
Karyomegaly	39 (78%)	35 (70%)	39 (78%)	43 (86%)
Mineralization	1 (2%)			
Mitotic alteration				1 (2%)
Necrosis, focal	3 (6%)	3 (6%)	6 (12%)	1 (2%)
Regeneration	32 (64%)	30 (60%)	35 (70%)	38 (76%)
Vacuolization cytoplasmic, diffuse		3 (6%)	1 (2%)	
Vacuolization cytoplasmic, focal			1 (2%)	
Bile duct, hyperplasia		3 (6%)	6 (12%)	4 (8%)
Oval cell, hyperplasia	38 (76%)	36 (72%)	40 (80%)	44 (88%)
Mesentery	(3)	(4)	(5)	(4)
Inflammation, chronic	1 (33%)			1 (25%)
Mineralization			1 (20%)	
Artery, fibrosis	1 (33%)			1 (25%)
Artery, inflammation, chronic		1 (25%)		
Fat, necrosis	1 (33%)	2 (50%)	3 (60%)	
Pancreas	(48)	(50)	(49)	(50)
Acinus, atrophy		1 (2%)		
Stomach, forestomach	(49)	(50)	(50)	(50)
Cyst			1 (2%)	
Hyperplasia, squamous	4 (8%)	2 (4%)		2 (4%)
Inflammation				1 (2%)

[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 Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Alimentary System (continued)				
Stomach, glandular	(48)	(50)	(50)	(50)
Mineralization				1 (2%)
Tooth				(1)
Inflammation				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Inflammation, chronic			1 (2%)	
Artery, inflammation, chronic			1 (2%)	
Atrium, thrombosis	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Endocrine System				
Adrenal cortex	(49)	(50)	(49)	(50)
Accessory adrenal cortical nodule			1 (2%)	
Hyperplasia	3 (6%)	4 (8%)	5 (10%)	2 (4%)
Inflammation		1 (2%)		
Necrosis		1 (2%)		
Necrosis, diffuse			1 (2%)	
Adrenal medulla	(48)	(50)	(49)	(50)
Hyperplasia	1 (2%)			5 (10%)
Necrosis, diffuse			1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
Inflammation				1 (2%)
Follicular cell, hyperplasia	3 (6%)	17 (34%)	11 (22%)	10 (20%)
General Body System				
Tissue NOS	(1)		(1)	
Inflammation, chronic			1 (100%)	
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Degeneration				1 (2%)
Granuloma sperm	1 (2%)			
Inflammation, chronic			1 (2%)	2 (4%)
Mineralization		2 (4%)	1 (2%)	
Penis	(1)			
Inflammation, chronic	1 (100%)			
Preputial gland	(49)	(50)	(50)	(49)
Cyst	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic	13 (27%)	12 (24%)	9 (18%)	5 (10%)
Inflammation, suppurative		2 (4%)	2 (4%)	
Prostate	(46)	(50)	(44)	(49)
Inflammation	2 (4%)		2 (5%)	1 (2%)
Seminal vesicle	(48)	(50)	(49)	(49)
Inflammation, chronic			1 (2%)	
Testes	(49)	(50)	(50)	(50)
Atrophy		2 (4%)		2 (4%)
Degeneration, focal			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Hematopoietic System				
Lymph node	(1)	(1)	(2)	(2)
Iliac, hyperplasia, lymphoid		1 (100%)		1 (50%)
Iliac, infiltration cellular, histiocyte			1 (50%)	
Renal, hyperplasia, lymphoid		1 (100%)		
Lymph node, bronchial	(21)	(24)	(28)	(25)
Infiltration cellular, plasma cell		1 (4%)		
Infiltration cellular, histiocyte	1 (5%)			1 (4%)
Lymph node, mesenteric	(49)	(48)	(43)	(47)
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage	2 (4%)	2 (4%)	4 (9%)	3 (6%)
Hyperplasia, lymphoid		1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)		2 (5%)	2 (4%)
Lymph node, mediastinal	(43)	(28)	(31)	(35)
Hyperplasia, lymphoid		1 (4%)	4 (13%)	
Infiltration cellular, plasma cell	1 (2%)	1 (4%)		
Infiltration cellular, histiocyte	2 (5%)		1 (3%)	
Inflammation, chronic			1 (3%)	1 (3%)
Spleen	(47)	(50)	(49)	(50)
Angiectasis	1 (2%)			1 (2%)
Hematopoietic cell proliferation	10 (21%)	6 (12%)	6 (12%)	14 (28%)
Hyperplasia, lymphoid		4 (8%)		1 (2%)
Integumentary System				
Skin	(49)	(50)	(49)	(49)
Inflammation, chronic		1 (2%)		2 (4%)
Inflammation, suppurative		1 (2%)		
Ulcer		1 (2%)	2 (4%)	
Epidermis, hyperplasia			1 (2%)	1 (2%)
Prepuce, inflammation, chronic		1 (2%)		
Prepuce, ulcer	4 (8%)	1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture				1 (2%)
Skeletal muscle	(1)			(2)
Inflammation, chronic, focal				1 (50%)
Nervous System				
None				
Respiratory System				
Larynx	(48)	(49)	(48)	(49)
Foreign body	1 (2%)			
Metaplasia, squamous		37 (76%)	48 (100%)	44 (90%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Respiratory System (continued)				
Lung	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, diffuse, histiocyte	1 (2%)	2 (4%)	4 (8%)	10 (20%)
Infiltration cellular, focal, histiocyte	10 (20%)	5 (10%)	8 (16%)	17 (34%)
Inflammation, chronic		1 (2%)	1 (2%)	3 (6%)
Alveolar epithelium, hyperplasia		4 (8%)	4 (8%)	4 (8%)
Alveolar epithelium, goblet cell, metaplasia, focal		1 (2%)		
Artery, thrombosis			1 (2%)	
Bronchus, hyperplasia			1 (2%)	
Bronchus, vacuolization cytoplasmic		18 (36%)	34 (68%)	38 (76%)
Nose	(50)	(50)	(48)	(49)
Hemorrhage				1 (2%)
Inflammation, suppurative		1 (2%)		6 (12%)
Olfactory epithelium, atrophy			29 (60%)	48 (98%)
Olfactory epithelium, degeneration, hyaline			2 (4%)	2 (4%)
Olfactory epithelium, hyperplasia				10 (20%)
Olfactory epithelium, metaplasia				2 (4%)
Respiratory epithelium, degeneration, hyaline				1 (2%)
Trachea	(49)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			
Special Senses System				
Eye	(1)		(1)	(1)
Degeneration	1 (100%)			1 (100%)
Hemorrhage				1 (100%)
Inflammation				1 (100%)
Cornea, inflammation			1 (100%)	
Harderian gland	(4)	(4)	(4)	(6)
Inflammation, acute		1 (25%)		
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Cyst		1 (2%)		1 (2%)
Infiltration cellular, mixed cell	5 (10%)	1 (2%)	5 (10%)	3 (6%)
Inflammation, chronic	1 (2%)		1 (2%)	
Metaplasia, osseous			1 (2%)	
Mineralization				1 (2%)
Nephropathy	11 (22%)	13 (26%)	7 (14%)	9 (18%)
Glomerulus, amyloid deposition		1 (2%)		2 (4%)
Medulla, inflammation, chronic				1 (2%)
Renal tubule, hyperplasia				1 (2%)
Urinary bladder	(46)	(49)	(45)	(48)
Inflammation	3 (7%)		3 (7%)	3 (6%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF COBALT SULFATE HEPTAHYDRATE

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	10	13	16
Natural deaths	5	3	5	6
Survivors				
Terminal sacrifice	34	37	32	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(43)	(43)	(38)	(43)
Intestine large, cecum	(49)	(49)	(48)	(47)
Leiomyoma				1 (2%)
Intestine small, duodenum	(47)	(48)	(47)	(45)
Intestine small, jejunum	(48)	(49)	(47)	(44)
Hemangiosarcoma			1 (2%)	
Intestine small, ileum	(48)	(48)	(47)	(45)
Liver	(50)	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)		3 (6%)	
Hepatocellular carcinoma	12 (24%)	9 (18%)	16 (32%)	4 (8%)
Hepatocellular adenoma	7 (14%)	7 (14%)	11 (22%)	9 (18%)
Hepatocellular adenoma, multiple	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Hepatocholangiocarcinoma	2 (4%)			
Histiocytic sarcoma	3 (6%)	2 (4%)		2 (4%)
Mesentery	(10)	(12)	(8)	(7)
Hemangioma				1 (14%)
Hemangiosarcoma		1 (8%)	1 (13%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (10%)			
Histiocytic sarcoma		1 (8%)		
Sarcoma	1 (10%)			
Pancreas	(50)	(50)	(49)	(49)
Histiocytic sarcoma	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)		1 (2%)
Stomach, glandular	(50)	(50)	(49)	(50)
Muscularis, serosa, sarcoma	1 (2%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Histiocytic sarcoma		1 (2%)		
Capsule, adenoma		1 (2%)		
Adrenal medulla	(49)	(50)	(49)	(49)
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(50)	(50)	(49)	(49)
Adenoma	1 (2%)			1 (2%)
Pituitary gland	(48)	(47)	(47)	(48)
Pars distalis, adenoma	11 (23%)	8 (17%)	7 (15%)	8 (17%)
Thyroid gland	(50)	(49)	(49)	(49)
Follicular cell, adenoma	3 (6%)			5 (10%)
Follicular cell, carcinoma	1 (2%)		2 (4%)	
General Body System				
None				
Genital System				
Ovary	(48)	(49)	(49)	(48)
Arrhenoblastoma benign	1 (2%)			
Cystadenocarcinoma		1 (2%)		
Cystadenoma	2 (4%)	3 (6%)	3 (6%)	3 (6%)
Granulosa cell tumor benign	1 (2%)		1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Luteoma	1 (2%)		1 (2%)	
Teratoma benign	1 (2%)	1 (2%)	1 (2%)	
Yolk sac carcinoma			1 (2%)	
Uterus	(50)	(50)	(49)	(49)
Hemangioma		1 (2%)	2 (4%)	
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma	1 (2%)			1 (2%)
Leiomyoma	1 (2%)			
Leiomyosarcoma				1 (2%)
Polyp stromal		2 (4%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)			2 (4%)
Lymph node	(3)	(6)	(3)	(4)
Histiocytic sarcoma	1 (33%)			
Lumbar, histiocytic sarcoma	1 (33%)			
Renal, histiocytic sarcoma	2 (67%)			
Lymph node, bronchial	(30)	(34)	(27)	(35)
Hepatocholangiocarcinoma, metastatic, liver	2 (7%)			
Histiocytic sarcoma	1 (3%)	1 (3%)		1 (3%)
Lymph node, mandibular	(37)	(37)	(36)	(36)
Histiocytic sarcoma	2 (5%)	2 (5%)		1 (3%)
Lymph node, mesenteric	(46)	(45)	(46)	(44)
Histiocytic sarcoma	3 (7%)	2 (4%)		1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Hematopoietic System (continued)				
Lymph node, mediastinal	(41)	(36)	(28)	(34)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Hepatocholangiocarcinoma, metastatic, liver	2 (5%)			
Histiocytic sarcoma	3 (7%)	2 (6%)		1 (3%)
Spleen	(50)	(50)	(49)	(49)
Histiocytic sarcoma	3 (6%)	2 (4%)		1 (2%)
Thymus	(41)	(44)	(41)	(41)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Integumentary System				
Mammary gland	(47)	(50)	(50)	(50)
Adenoma				1 (2%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Skin	(49)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Squamous cell carcinoma	1 (2%)			
Subcutaneous tissue, mast cell tumor benign			1 (2%)	
Subcutaneous tissue, sarcoma	6 (12%)	2 (4%)		
Musculoskeletal System				
Skeletal muscle		(1)	(2)	(1)
Sarcoma			1 (50%)	1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Larynx	(50)	(49)	(47)	(50)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	8 (16%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	4 (8%)	9 (18%)
Hepatocellular carcinoma, metastatic, liver	3 (6%)		5 (10%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)			
Histiocytic sarcoma	3 (6%)	2 (4%)		1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Nose	(50)	(50)	(49)	(48)
Special Senses System				
Harderian gland	(2)	(2)		(1)
Adenoma	2 (100%)	2 (100%)		1 (100%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)		1 (2%)
Urinary bladder	(48)	(47)	(45)	(46)
Histiocytic sarcoma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)	2 (4%)		3 (6%)
Lymphoma malignant	4 (8%)	7 (14%)	7 (14%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	41	43	39
Total primary neoplasms	70	61	76	68
Total animals with benign neoplasms	25	32	27	27
Total benign neoplasms	36	36	38	44
Total animals with malignant neoplasms	27	22	31	21
Total malignant neoplasms	34	25	38	24
Total animals with metastatic neoplasms	6		5	3
Total metastatic neoplasms	12		5	3

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	225	531	559	583	596	609	619	620	639	643	652	656	667	699	699	713	734	734	734	734	735	735	735	735	735
Carcass ID Number	136	127	137	115	106	148	102	146	107	128	121	104	109	125	150	145	110	111	119	139	101	108	112	113	114
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	A	+	A	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma						X	X									X	X		X				X		X
Hepatocellular adenoma																X									
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma								X							X										
Histiocytic sarcoma												X	X	X											
Mesentery			+					+									+			+		+			
Hepatocholangiocarcinoma, metastatic, liver								X																	
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Muscularis, serosa, sarcoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	+	M	M	+	M	+	M	+	M	M	+	M	+	M	+	M	M	+	M	+	+	+
Pituitary gland	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Pars distalis, adenoma					X										X	X			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma							X																		
Follicular cell, carcinoma																X									
General Body System																									
None																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	116	117	122	124	126	129	133	135	141	144	103	105	118	120	123	130	131	132	134	138	140	142	143	147	149	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
Hepatocellular carcinoma					X	X													X	X	X					12
Hepatocellular adenoma		X			X							X		X		X									X	7
Hepatocellular adenoma, multiple			X																							1
Hepatocholangiocarcinoma																										2
Histiocytic sarcoma																										3
Mesentery			+	+							+								+				+			10
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma																							X			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Muscularis, serosa, sarcoma																							X			1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Parathyroid gland	+	+	+	+	M	M	M	M	M	+	M	M	+	M	M	+	+	+	+	M	+	M	M	+	M	25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X						X	X				X				X			X		X					11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X													X											3
Follicular cell, carcinoma																										1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	225	531	559	583	596	609	619	620	639	643	652	656	667	699	699	713	734	734	734	734	735	735	735	735	735
Carcass ID Number	136	127	137	115	106	148	102	146	107	128	121	104	109	125	150	145	110	111	119	139	101	108	112	113	114
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	M	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Arrhenoblastoma benign																									
Cystadenoma																									
Granulosa cell tumor benign																					X				
Histiocytic sarcoma														X											
Luteoma																			X						
Teratoma benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Leiomyoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Lymph node												+		+											
Histiocytic sarcoma														X											
Lumbar, histiocytic sarcoma														X											
Renal, histiocytic sarcoma												X		X											
Lymph node, bronchial	M	M	M	M	M	M	M	+	M	M	M	M	+	M	+	+	+	M	+	M	+	+	M	+	+
Hepatocholangiocarcinoma, metastatic, liver								X							X										
Histiocytic sarcoma													X												
Lymph node, mandibular	M	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X	X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	I	+
Histiocytic sarcoma												X	X	X											
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver								X							X										
Histiocytic sarcoma												X	X	X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X	X	X											
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+	M	M	+	+	+	+
Histiocytic sarcoma														X											
Integumentary System																									
Mammary gland	M	+	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma									X																
Subcutaneous tissue, sarcoma	X															X						X		X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord															+										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	116	117	122	124	126	129	133	135	141	144	103	105	118	120	123	130	131	132	134	138	140	142	143	147	149	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	48
Arrhenoblastoma benign																								X		1
Cystadenoma			X							X																2
Granulosa cell tumor benign																										1
Histiocytic sarcoma																										1
Luteoma																										1
Teratoma benign															X											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leiomyoma													X													1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node											+															3
Histiocytic sarcoma																										1
Lumbar, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										2
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	M	M	30
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	M	M	+	+	+	M	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	M	+	37
Histiocytic sarcoma																										2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	I	+	+	+	+	46
Histiocytic sarcoma																										3
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	M	M	+	M	M	M	M	+	+	+	M	+	+	+	41
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	41
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Subcutaneous tissue, sarcoma											X												X			6
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	225	531	559	583	596	609	619	620	639	643	652	656	667	699	699	713	734	733	734	734	735	735	735	735	735	735
Carcass ID Number	136	127	137	115	106	148	102	146	107	128	121	104	109	125	150	145	110	111	119	139	101	108	112	113	114	
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																								X	X	
Alveolar/bronchiolar carcinoma																										
Hepatocellular carcinoma, metastatic, liver																	X						X			
Hepatocholangiocarcinoma, metastatic, liver								X							X											
Histiocytic sarcoma												X	X	X												
Sarcoma, metastatic, skin	X																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																										
Harderian gland																					+					
Adenoma																					X					
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma													X	X												
Urinary bladder	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma														X												
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma												X	X	X												
Lymphoma malignant				X																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: Chamber Control

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	116	117	122	124	126	129	133	135	141	144	103	105	118	120	123	130	131	132	134	138	140	142	143	147	149	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														3
Alveolar/bronchiolar carcinoma					X																					1
Hepatocellular carcinoma, metastatic, liver																				X						3
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										3
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																1
Harderian gland										+																2
Adenoma										X																2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Lymphoma malignant		X				X					X															4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	481	593	596	649	652	664	666	666	666	693	720	726	727	734	734	734	734	734	734	735	735	735	735	735	735
Carcass ID Number	314	334	327	309	308	326	303	333	347	443	332	331	341	320	321	323	329	338	340	344	301	304	306	310	313
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	M	+	A	+	M	A	+	+	+	+	+	+	+	+	+	M	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X			X					X				X				X	X
Hepatocellular adenoma		X					X																X		
Hepatocellular adenoma, multiple																					X				
Histiocytic sarcoma				X																		X			
Mesentery		+		+	+		+	+				+				+									
Hemangiosarcoma					X																				
Histiocytic sarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	M	M	M	M	+	+	+	M	M	M	M	+	M	M	I	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Pars distalis, adenoma																		X		X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma															X										
Cystadenoma																	X				X				
Histiocytic sarcoma																						X			
Teratoma benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									X
Polyp stromal													X												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	316	317	322	328	330	335	337	339	342	345	348	349	350	302	305	307	311	312	315	318	319	324	325	336	346	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																				X			X		9
Hepatocellular adenoma											X				X	X								X		7
Hepatocellular adenoma, multiple						X				X																3
Histiocytic sarcoma																										2
Mesentery								+			+	+				+		+								12
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Capsule, adenoma																					X					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	M	M	M	+	+	M	+	M	M	+	M	M	M	+	M	+	+	M	+	+	+	+	23
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma			X		X		X					X											X	X		8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	49
Cystadenocarcinoma																										1
Cystadenoma																			X							3
Histiocytic sarcoma																										1
Teratoma benign	X																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																				X						1
Hemangiosarcoma																										1
Polyp stromal								X																		2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 0.3 mg/m³

Number of Days on Study	481	593	596	649	652	664	666	666	666	693	720	726	727	734	734	734	734	734	734	734	735	735	735	735	735
Carcass ID Number	314	334	327	309	308	326	303	333	347	343	332	331	341	320	321	323	329	338	340	344	301	304	306	310	313
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+				+	+												
Lymph node, bronchial	M	+	M	M	M	M	M	+	M	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Histiocytic sarcoma																						X			
Lymph node, mandibular	M	+	M	+	M	+	M	+	+	+	M	+	M	M	+	+	M	+	+	+	+	+	+	+	M
Histiocytic sarcoma				X																		X			
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																		X			
Lymph node, mediastinal	+	M	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	M	M	+	+	+	+	M	M
Histiocytic sarcoma				X																		X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																		X			
Thymus	M	+	+	+	M	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma		X							X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X					X				X										
Alveolar/bronchiolar adenoma, multiple														X											
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma				X																		X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																		+							
Adenoma																		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Urinary bladder	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Cobalt Sulfate Heptahydrate: 0.3 mg/m^3

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	316	317	322	328	330	335	337	339	342	345	348	349	350	302	305	307	311	312	315	318	319	324	325	336	346	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+			+																			6
Lymph node, bronchial	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	M	+	+	+	+	34
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	M	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	37
Histiocytic sarcoma																										2
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	45
Histiocytic sarcoma																										2
Lymph node, mediastinal	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	+	36
Histiocytic sarcoma																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																X										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X				X								5
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma			X																							1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland									+																	2
Adenoma									X																	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant	X																X									7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	009	495	505	524	548	569	622	640	649	659	666	666	667	674	703	709	720	733	734	734	734	735	735	735	735
Carcass ID Number	520	507	519	522	537	544	538	548	543	510	513	535	530	505	523	529	514	509	503	511	518	539	501	502	504
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	M	A	+	+	+	+	M	M	A	+	M	A	+	M	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X			X																		
Hepatocellular carcinoma								X		X	X		X		X		X	X			X	X			X
Hepatocellular adenoma							X		X	X		X						X			X	X	X	X	
Hepatocellular adenoma, multiple																			X						
Mesentery							+										+			+	+				
Hemangiosarcoma							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	M	+	M	M	+	M	M	M	+	+	M	A	+	M	+	+	+	+	M	M	I	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X		X							X						X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																									
Luteoma																									
Teratoma benign																				X					
Yolk sac carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangioma																X									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m^3

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	506	508	515	516	521	524	531	536	541	542	549	550	512	517	525	526	527	528	532	533	534	540	545	546	547	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								3
Hepatocellular carcinoma		X		X			X								X		X		X							16
Hepatocellular adenoma								X							X											11
Hepatocellular adenoma, multiple											X															2
Mesentery							+		+		+										+					8
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	M	M	M	+	M	M	28
Pituitary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Pars distalis, adenoma			X												X					X						7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma	X																						X			2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	43
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma								X													X	X				3
Granulosa cell tumor benign					X																					1
Luteoma	X																									1
Teratoma benign																										1
Yolk sac carcinoma																		X								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma															X											2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	0	4	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	0	9	0	2	4	6	2	4	4	5	6	6	6	7	4	0	0	2	3	3	3	3	3	3	3
	9	5	5	4	8	9	2	0	9	9	6	6	7	4	3	9	0	3	3	4	4	4	4	5	5	5
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	2	0	1	2	3	4	3	4	4	1	1	3	3	0	5	2	2	1	0	0	1	1	3	0	0
	0	7	9	2	7	4	8	8	3	0	3	5	0	5	3	3	9	4	9	3	1	8	9	1	2	4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node													+												
Lymph node, bronchial	+	M	M	+	M	M	M	M	M	M	M	+	+	M	M	M	+	M	+	+	M	+	+	+	M
Lymph node, mandibular	+	+	I	M	M	+	M	+	M	+	M	+	+	+	+	M	+	M	M	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	+	+	M	+	M	+	+	+	M	M	+	+	A	M	+	M	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	M	+	A	M	M	M	+	M	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Subcutaneous tissue, mast cell tumor benign																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	I	+	+	+	+	+	+	A	+	+	+	+	+	I	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X							X	X							X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma		X			X	X																			
Hepatocellular carcinoma, metastatic, liver								X			X		X		X				X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	I	+	+	A	+	+	A	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X				X						X	X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 1.0 mg/m³

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	506	508	515	516	521	524	531	536	541	542	549	550	512	517	525	526	527	528	532	533	534	540	545	546	547	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node		+																							+	3
Lymph node, bronchial	+	+	+	+	M	M	M	+	+	+	M	+	+	+	M	M	M	M	+	+	+	+	+	+	+	27
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mediastinal	+	+	+	+	M	+	+	+	M	+	+	+	M	M	+	M	+	M	M	M	M	+	M	M	M	28
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma			X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	1
Subcutaneous tissue, mast cell tumor benign																				X						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																				+						2
Sarcoma																				X						1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X				X									X									X	8
Alveolar/bronchiolar adenoma, multiple													X													1
Alveolar/bronchiolar carcinoma												X														4
Hepatocellular carcinoma, metastatic, liver																										5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant		X					X										X									7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	356	429	443	462	484	536	539	606	609	611	639	667	675	680	686	692	706	712	717	719	726	732	734	734	734
Carcass ID Number	707	731	713	720	722	726	703	708	727	740	746	749	733	702	718	711	704	717	743	723	742	710	714	730	738
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	+	+	+	M	A	+	M	+	+	A	A	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	A	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+
Leiomyoma																	X								
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	+	A	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	A	+	A	A	+	+	A	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	A	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hepatocellular carcinoma												X			X							X			
Hepatocellular adenoma							X			X				X									X		X
Hepatocellular adenoma, multiple								X																	
Histiocytic sarcoma												X						X							
Mesentery	+																								
Hemangioma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	+	M	+	M	+	+	I	M	M	+	I	+	+	M	+	+	+	+	+	I	M
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Pars distalis, adenoma													X		X					X			X		X
Thyroid gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma															X										X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	A	+	+	+	+	+	+
Cystadenoma																									X
Histiocytic sarcoma											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Histiocytic sarcoma											X														
Leiomyosarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	706	709	715	719	721	732	735	736	737	750	701	705	712	716	724	725	728	729	734	739	741	744	745	747	748	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma										X																4
Hepatocellular adenoma		X																			X	X		X		9
Hepatocellular adenoma, multiple																	X		X							3
Histiocytic sarcoma																										2
Mesentery	+			+			+			+											+	+				7
Hemangioma										X																1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																	X									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																	X									1
Parathyroid gland	+	M	M	M	+	M	M	+	+	M	M	M	I	M	M	M	+	+	+	+	+	M	+	+	M	26
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma															X					X		X				8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma														X	X						X					5
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	M	M	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	M	+	+	+	M	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma								X																	X	3
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Leiomyosarcoma										X																1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m³

Number of Days on Study	356	429	443	462	484	536	539	606	609	611	639	667	675	680	686	692	706	712	717	719	726	732	734	734	734
Carcass ID Number	707	731	713	720	722	726	703	708	727	740	746	749	733	702	718	711	704	717	743	723	742	710	714	730	738
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X							X							
Lymph node									+								+				+				
Lymph node, bronchial	+	M	+	M	+	+	M	M	+	M	M	M	M	+	M	M	M	+	M	M	+	M	+	+	+
Histiocytic sarcoma																		X							
Lymph node, mandibular	M	+	+	+	+	+	+	M	+	+	M	+	M	+	M	+	+	+	+	+	M	+	M	+	+
Histiocytic sarcoma																		X							
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	A	+	+	I	+	+	+
Histiocytic sarcoma																		X							
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	M	M
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Histiocytic sarcoma																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Thymus	+	M	M	+	+	+	+	M	M	+	+	M	M	+	M	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord							+																		
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma						X			X				X						X	X			X		
Hepatocellular carcinoma, metastatic, liver												X			X										
Histiocytic sarcoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Urinary bladder	+	+	A	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m^3

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	706	709	715	719	721	732	735	736	737	750	701	705	712	716	724	725	728	729	734	739	741	744	745	747	748	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymph node																							+			4
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	35
Histiocytic sarcoma																										1
Lymph node, mandibular	+	M	M	+	+	+	+	+	+	M	M	I	+	M	+	+	+	+	+	+	M	+	+	+	+	36
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	44
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	M	M	M	M	+	+	+	M	+	M	M	+	M	+	M	+	+	+	M	M	+	+	+	+	34
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle													+													1
Sarcoma													X													1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X	X									X				X			X			X		X			8
Alveolar/bronchiolar adenoma, multiple																				X						2
Alveolar/bronchiolar carcinoma	X						X		X																	9
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland															+											1
Adenoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m^3

Number of Days on Study	356	429	443	462	484	536	539	606	609	611	639	667	675	680	686	692	706	712	717	719	726	732	734	734	734
Carcass ID Number	707	731	713	720	722	726	703	708	727	740	746	749	733	702	718	711	704	717	743	723	742	710	714	730	738
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X	X						X							
Lymphoma malignant	X								X								X				X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate: 3.0 mg/m^3

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	706	709	715	719	721	732	735	736	737	750	701	705	712	716	724	725	728	729	734	739	741	744	745	747	748	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Lymphoma malignant																							X			5

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Liver: Hemangiosarcoma				
Overall rate[a]	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted rate[b]	2.9%	0.0%	7.3%	0.0%
Terminal rate[c]	1/34 (3%)	0/37 (0%)	1/32 (3%)	0/28 (0%)
First incidence (days)	734 (T)	—[e]	524	—
Life table test[d]	P=0.499N	P=0.483N	P=0.298	P=0.539N
Logistic regression test[d]	P=0.431N	P=0.483N	P=0.318	P=0.539N
Cochran-Armitage test[d]	P=0.455N			
Fisher exact test[d]		P=0.500N	P=0.309	P=0.505N
Liver: Hepatocellular Adenoma				
Overall rate	8/50 (16%)	10/50 (20%)	13/50 (26%)	12/49 (24%)
Adjusted rate	22.9%	25.0%	34.0%	35.3%
Terminal rate	7/34 (21%)	8/37 (22%)	8/32 (25%)	8/28 (29%)
First incidence (days)	713	593	622	539
Life table test	P=0.103	P=0.480	P=0.150	P=0.128
Logistic regression test	P=0.174	P=0.466	P=0.152	P=0.180
Cochran-Armitage test	P=0.221			
Fisher exact test		P=0.398	P=0.163	P=0.212
Liver: Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	9/50 (18%)	16/50 (32%)	4/49 (8%)
Adjusted rate	31.7%	22.7%	40.5%	11.8%
Terminal rate	9/34 (26%)	7/37 (19%)	9/32 (28%)	1/28 (4%)
First incidence (days)	609	666	640	667
Life table test	P=0.094N	P=0.240N	P=0.235	P=0.063N
Logistic regression test	P=0.051N	P=0.258N	P=0.238	P=0.037N
Cochran-Armitage test	P=0.036N			
Fisher exact test		P=0.312N	P=0.252	P=0.030N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	18/50 (36%)	18/50 (36%)	24/50 (48%)	16/49 (33%)
Adjusted rate	48.1%	43.3%	56.7%	43.8%
Terminal rate	15/34 (44%)	14/37 (38%)	14/32 (44%)	9/28 (32%)
First incidence (days)	609	593	622	539
Life table test	P=0.444	P=0.451N	P=0.145	P=0.530
Logistic regression test	P=0.474N	P=0.488N	P=0.137	P=0.506N
Cochran-Armitage test	P=0.374N			
Fisher exact test		P=0.582N	P=0.156	P=0.445N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	6/50 (12%)	9/50 (18%)	10/50 (20%)
Adjusted rate	8.8%	15.0%	25.2%	32.8%
Terminal rate	3/34 (9%)	4/37 (11%)	6/32 (19%)	8/28 (29%)
First incidence (days)	734 (T)	664	649	706
Life table test	P=0.014	P=0.297	P=0.056	P=0.016
Logistic regression test	P=0.024	P=0.287	P=0.057	P=0.024
Cochran-Armitage test	P=0.045			
Fisher exact test		P=0.243	P=0.061	P=0.036

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	9/50 (18%)
Adjusted rate	2.9%	2.7%	9.2%	25.3%
Terminal rate	1/34 (3%)	1/37 (3%)	1/32 (3%)	4/28 (14%)
First incidence (days)	734 (T)	734 (T)	495	536
Life table test	P < 0.001	P=0.743N	P=0.173	P=0.007
Logistic regression test	P < 0.001	P=0.743N	P=0.201	P=0.009
Cochran-Armitage test	P < 0.001			
Fisher exact test		P=0.753N	P=0.181	P=0.008
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	7/50 (14%)	13/50 (26%)	18/50 (36%)
Adjusted rate	11.8%	17.5%	32.6%	50.2%
Terminal rate	4/34 (12%)	5/37 (14%)	7/32 (22%)	11/28 (39%)
First incidence (days)	734 (T)	664	495	536
Life table test	P < 0.001	P=0.322	P=0.016	P < 0.001
Logistic regression test	P < 0.001	P=0.318	P=0.016	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P=0.262	P=0.016	P < 0.001
Ovary: Cystadenoma				
Overall rate	2/48 (4%)	3/49 (6%)	3/49 (6%)	3/48 (6%)
Adjusted rate	6.3%	8.3%	9.4%	10.7%
Terminal rate	2/32 (6%)	3/36 (8%)	3/32 (9%)	3/28 (11%)
First incidence (days)	734 (T)	734 (T)	734 (T)	734 (T)
Life table test	P=0.390	P=0.554	P=0.500	P=0.439
Logistic regression test	P=0.390	P=0.554	P=0.500	P=0.439
Cochran-Armitage test	P=0.487			
Fisher exact test		P=0.510	P=0.510	P=0.500
Ovary: Cystadenoma or Cystadenocarcinoma				
Overall rate	2/48 (4%)	4/49 (8%)	3/49 (6%)	3/48 (6%)
Adjusted rate	6.3%	11.1%	9.4%	10.7%
Terminal rate	2/32 (6%)	4/36 (11%)	3/32 (9%)	3/28 (11%)
First incidence (days)	734 (T)	734 (T)	734 (T)	734 (T)
Life table test	P=0.390	P=0.395	P=0.500	P=0.439
Logistic regression test	P=0.390	P=0.395	P=0.500	P=0.439
Cochran-Armitage test	P=0.487			
Fisher exact test		P=0.349	P=0.510	P=0.500
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	11/48 (23%)	8/47 (17%)	7/47 (15%)	8/48 (17%)
Adjusted rate	30.0%	22.2%	20.7%	24.7%
Terminal rate	8/33 (24%)	8/36 (22%)	5/30 (17%)	5/28 (18%)
First incidence (days)	596	734 (T)	659	675
Life table test	P=0.538N	P=0.236N	P=0.271N	P=0.426N
Logistic regression test	P=0.430N	P=0.255N	P=0.248N	P=0.343N
Cochran-Armitage test	P=0.355N			
Fisher exact test		P=0.323N	P=0.231N	P=0.305N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	6/50 (12%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rate	16.0%	4.3%	0.0%	0.0%
Terminal rate	4/34 (12%)	0/37 (0%)	0/32 (0%)	0/28 (0%)
First incidence (days)	225	593	—	—
Life table test	P=0.022N	P=0.116N	P=0.022N	P=0.029N
Logistic regression test	P=0.012N	P=0.210N	P=0.014N	P=0.014N
Cochran-Armitage test	P=0.015N			
Fisher exact test		P=0.134N	P=0.013N	P=0.013N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	0/49 (0%)	0/49 (0%)	5/49 (10%)
Adjusted rate	8.0%	0.0%	0.0%	16.7%
Terminal rate	2/34 (6%)	0/36 (0%)	0/32 (0%)	4/28 (14%)
First incidence (days)	619	—	—	686
Life table test	P=0.026	P=0.113N	P=0.130N	P=0.274
Logistic regression test	P=0.038	P=0.126N	P=0.125N	P=0.323
Cochran-Armitage test	P=0.046			
Fisher exact test		P=0.125N	P=0.125N	P=0.346
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	0/49 (0%)	2/49 (4%)	5/49 (10%)
Adjusted rate	10.6%	0.0%	6.3%	16.7%
Terminal rate	2/34 (6%)	0/36 (0%)	2/32 (6%)	4/28 (14%)
First incidence (days)	619	—	734 (T)	686
Life table test	P=0.081	P=0.056N	P=0.360N	P=0.407
Logistic regression test	P=0.108	P=0.065N	P=0.351N	P=0.462
Cochran-Armitage test	P=0.130			
Fisher exact test		P=0.061N	P=0.349N	P=0.487
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	2.9%	4.8%	10.3%	0.0%
Terminal rate	1/34 (3%)	1/37 (3%)	2/32 (6%)	0/28 (0%)
First incidence (days)	734 (T)	652	524	—
Life table test	P=0.321N	P=0.536	P=0.173	P=0.539N
Logistic regression test	P=0.250N	P=0.505	P=0.184	P=0.539N
Cochran-Armitage test	P=0.263N			
Fisher exact test		P=0.500	P=0.181	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	6/50 (12%)	1/50 (2%)
Adjusted rate	2.9%	7.5%	15.8%	3.6%
Terminal rate	1/34 (3%)	2/37 (5%)	3/32 (9%)	1/28 (4%)
First incidence (days)	734 (T)	652	524	734 (T)
Life table test	P=0.499N	P=0.342	P=0.057	P=0.718
Logistic regression test	P=0.406N	P=0.319	P=0.059	P=0.718
Cochran-Armitage test	P=0.403N			
Fisher exact test		P=0.309	P=0.056	P=0.753N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted rate	7.7%	4.8%	0.0%	7.9%
Terminal rate	0/34 (0%)	1/37 (3%)	0/32 (0%)	0/28 (0%)
First incidence (days)	656	649	—	639
Life table test	P=0.456	P=0.452N	P=0.126N	P=0.644
Logistic regression test	P=0.496	P=0.396N	P=0.118N	P=0.644N
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.500N	P=0.121N	P=0.661N
All Organs: Malignant Lymphoma				
Overall rate	4/50 (8%)	7/50 (14%)	7/50 (14%)	5/50 (10%)
Adjusted rate	10.8%	16.8%	19.8%	13.4%
Terminal rate	3/34 (9%)	3/37 (8%)	5/32 (16%)	1/28 (4%)
First incidence (days)	583	666	649	356
Life table test	P=0.492	P=0.327	P=0.240	P=0.429
Logistic regression test	P=0.524N	P=0.267	P=0.255	P=0.527
Cochran-Armitage test	P=0.528N			
Fisher exact test		P=0.262	P=0.262	P=0.500
All Organs: Benign Neoplasms				
Overall rate	25/50 (50%)	32/50 (64%)	27/50 (54%)	27/50 (54%)
Adjusted rate	65.5%	76.0%	68.9%	72.1%
Terminal rate	21/34 (62%)	27/37 (73%)	20/32 (63%)	18/28 (64%)
First incidence (days)	596	593	622	539
Life table test	P=0.185	P=0.242	P=0.336	P=0.163
Logistic regression test	P=0.408	P=0.220	P=0.390	P=0.305
Cochran-Armitage test	P=0.465N			
Fisher exact test		P=0.113	P=0.421	P=0.421
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	22/50 (44%)	31/50 (62%)	21/50 (42%)
Adjusted rate	58.5%	47.6%	68.3%	49.5%
Terminal rate	15/34 (44%)	13/37 (35%)	18/32 (56%)	7/28 (25%)
First incidence (days)	225	593	495	356
Life table test	P=0.530N	P=0.154N	P=0.268	P=0.368N
Logistic regression test	P=0.187N	P=0.266N	P=0.276	P=0.147N
Cochran-Armitage test	P=0.199N			
Fisher exact test		P=0.212N	P=0.272	P=0.158N

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

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	41/50 (82%)	43/50 (86%)	39/50 (78%)
Adjusted rate	89.3%	87.2%	91.4%	84.8%
Terminal rate	29/34 (85%)	31/37 (84%)	28/32 (88%)	21/28 (75%)
First incidence (days)	225	593	495	356
Life table test	P=0.213	P=0.255N	P=0.387	P=0.395
Logistic regression test	P=0.366N	P=0.422N	P=0.459	P=0.353N
Cochran-Armitage test	P=0.258N			
Fisher exact test		P=0.500N	P=0.500	P=0.306N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The 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 D4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	4/50	0/50	4/50
Acetonitrile	7/49	1/49	8/49
Allyl Glycidyl Ether	0/50	0/50	0/50
2-Chloroacetophenone	4/50	3/50	6/50
l-Epinephrine Hydrochloride	3/50	2/50	5/50
Chloroethane	2/49	3/49	5/49
Hexachlorocyclopentadiene	4/48	3/48	7/48
o-Chlorobenzalmalononitrile (CS2)	4/50	1/50	5/50
Ozone	4/50	2/50	6/50
Overall Historical Incidence			
Total	61/939 (6.5%)	38/939 (4.1%)	97/939 (10.3%)
Standard deviation	3.2%	3.2%	3.7%
Range	0%-14%	0%-12%	0%-16%

[a] Data as of 12 May 1995

TABLE D4b
Historical Incidence of Hemangiosarcoma of the Liver in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	1/49
Acetonitrile	0/49
Allyl Glycidyl Ether	0/50
2-Chloroacetophenone	0/50
l-Epinephrine Hydrochloride	1/50
Chloroethane	0/49
Hexachlorocyclopentadiene	0/49
o-Chlorobenzalmalononitrile (CS2)	0/50
Ozone	0/50
Overall Historical Incidence	
Total	5/937 (0.5%)
Standard deviation	1.0%
Range	0%-3%

[a] Data as of 12 May 1995

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate[a]

	Chamber Control	0.3 mg/m³	1.0 mg/m³	3.0 mg/m³
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	10	13	16
Natural deaths	5	3	5	6
Survivors				
Terminal sacrifice	34	37	32	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(49)	(48)	(47)
Inflammation			1 (2%)	
Intestine small, ileum	(48)	(48)	(47)	(45)
Peyer's patch, hyperplasia, lymphoid			1 (2%)	
Liver	(50)	(50)	(50)	(49)
Basophilic focus		1 (2%)		
Clear cell focus	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Clear cell focus, multiple				1 (2%)
Cyst			1 (2%)	1 (2%)
Eosinophilic focus	9 (18%)	7 (14%)	8 (16%)	9 (18%)
Eosinophilic focus, multiple				1 (2%)
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hemorrhage		1 (2%)		
Infiltration cellular, lymphocyte	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, mixed cell		1 (2%)		
Inflammation, chronic	6 (12%)	1 (2%)	1 (2%)	2 (4%)
Karyomegaly	4 (8%)	2 (4%)		1 (2%)
Mineralization			1 (2%)	
Necrosis	1 (2%)			
Necrosis, focal	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Regeneration	1 (2%)			
Thrombosis				1 (2%)
Vacuolization cytoplasmic		1 (2%)		
Vacuolization cytoplasmic, diffuse			1 (2%)	1 (2%)
Oval cell, hyperplasia	2 (4%)	1 (2%)		
Serosa, fibrosis				1 (2%)
Mesentery	(10)	(12)	(8)	(7)
Angiectasis	1 (10%)			
Hemorrhage				1 (14%)
Infiltration cellular, lymphocyte		1 (8%)		
Inflammation, chronic		1 (8%)		
Fat, necrosis	7 (70%)	8 (67%)	7 (88%)	5 (71%)
Pancreas	(50)	(50)	(49)	(49)
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)		
Acinus, atrophy	1 (2%)	2 (4%)		3 (6%)
Duct, cyst	1 (2%)	2 (4%)	1 (2%)	
Stomach, forestomach	(50)	(50)	(49)	(50)
Cyst		1 (2%)		
Hyperplasia, squamous	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Inflammation		2 (4%)		

[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 Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
Artery, inflammation, chronic	1 (2%)		1 (2%)	
Epicardium, fibrosis				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Accessory adrenal cortical nodule				1 (2%)
Angiectasis	1 (2%)			
Cyst, focal			1 (2%)	
Degeneration, cystic, focal		1 (2%)		
Inflammation	1 (2%)			1 (2%)
Vacuolization cytoplasmic			1 (2%)	1 (2%)
Capsule, hyperplasia			1 (2%)	
Pituitary gland	(48)	(47)	(47)	(48)
Angiectasis	2 (4%)	5 (11%)	1 (2%)	2 (4%)
Pars distalis, angiectasis	1 (2%)			
Pars distalis, hyperplasia	12 (25%)	1 (2%)	7 (15%)	6 (13%)
Thyroid gland	(50)	(49)	(49)	(49)
Cyst			1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation				1 (2%)
Follicular cell, hyperplasia	20 (40%)	17 (35%)	14 (29%)	19 (39%)
General Body System				
None				
Genital System				
Clitoral gland	(41)	(40)	(43)	(40)
Cyst	1 (2%)			
Inflammation	1 (2%)	1 (3%)		
Ovary	(48)	(49)	(49)	(48)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Atrophy			2 (4%)	
Cyst	9 (19%)	12 (24%)	16 (33%)	15 (31%)
Thrombosis		1 (2%)		
Bilateral, cyst			1 (2%)	
Uterus	(50)	(50)	(49)	(49)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Hydrometra		3 (6%)	3 (6%)	2 (4%)
Hyperplasia, cystic	37 (74%)	41 (82%)	38 (78%)	37 (76%)
Inflammation				2 (4%)
Inflammation, suppurative		1 (2%)		
Thrombosis	1 (2%)		1 (2%)	1 (2%)
Cervix, hemorrhage		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Inflammation, chronic			1 (2%)	
Lymph node	(3)	(6)	(3)	(4)
Hyperplasia, lymphoid		1 (17%)		
Iliac, ectasia			1 (33%)	
Renal, hyperplasia, lymphoid		1 (17%)		
Lymph node, bronchial	(30)	(34)	(27)	(35)
Hyperplasia, lymphoid	1 (3%)	2 (6%)	2 (7%)	3 (9%)
Infiltration cellular, histiocyte				1 (3%)
Lymph node, mandibular	(37)	(37)	(36)	(36)
Hyperplasia, lymphoid		1 (3%)		
Lymph node, mesenteric	(46)	(45)	(46)	(44)
Hyperplasia, lymphoid	1 (2%)	5 (11%)	2 (4%)	
Infiltration cellular, histiocyte	1 (2%)			
Inflammation, chronic	1 (2%)			
Necrosis		1 (2%)		
Lymph node, mediastinal	(41)	(36)	(28)	(34)
Hemorrhage				1 (3%)
Hyperplasia, lymphoid	3 (7%)	5 (14%)	1 (4%)	3 (9%)
Spleen	(50)	(50)	(49)	(49)
Hematopoietic cell proliferation	3 (6%)	11 (22%)	9 (18%)	3 (6%)
Hyperplasia, lymphoid	1 (2%)	5 (10%)	1 (2%)	2 (4%)
Thymus	(41)	(44)	(41)	(41)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Necrosis			1 (2%)	
Integumentary System				
Mammary gland	(47)	(50)	(50)	(50)
Hyperplasia	3 (6%)	4 (8%)	2 (4%)	
Skin	(49)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		
Inflammation, suppurative			1 (2%)	
Ulcer		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, hemorrhage			1 (2%)	
Subcutaneous tissue, inflammation, chronic		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)	1 (2%)	1 (2%)	5 (10%)
Fracture			1 (2%)	1 (2%)
Maxilla, inflammation, chronic				1 (2%)
Skeletal muscle		(1)	(2)	(1)
Hemorrhage			1 (50%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Spinal cord	(1)			(1)
Degeneration				1 (100%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	Chamber Control	0.3 mg/m^3	1.0 mg/m^3	3.0 mg/m^3
Respiratory System				
Larynx	(50)	(49)	(47)	(50)
Inflammation, chronic				1 (2%)
Metaplasia, squamous		45 (92%)	40 (85%)	50 (100%)
Lung	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)	1 (2%)		4 (8%)
Infiltration cellular, diffuse, histiocyte				4 (8%)
Infiltration cellular, focal, histiocyte	2 (4%)	5 (10%)	7 (14%)	10 (20%)
Inflammation, chronic			1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	3 (6%)		5 (10%)
Bronchus, vacuolization cytoplasmic		6 (12%)	31 (62%)	43 (86%)
Capillary, thrombosis, diffuse				1 (2%)
Nose	(50)	(50)	(49)	(48)
Hemorrhage			1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, suppurative		1 (2%)	5 (10%)	4 (8%)
Olfactory epithelium, atrophy		2 (4%)	12 (24%)	46 (96%)
Olfactory epithelium, degeneration, hyaline	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Olfactory epithelium, hyperplasia				30 (63%)
Olfactory epithelium, metaplasia		1 (2%)	1 (2%)	
Respiratory epithelium, degeneration, hyaline	20 (40%)	16 (32%)	14 (29%)	11 (23%)
Respiratory epithelium, metaplasia, squamous				4 (8%)
Special Senses System				
Eye	(1)			
Degeneration	1 (100%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	1 (2%)			2 (4%)
Infarct				1 (2%)
Infiltration cellular, mixed cell	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic		1 (2%)	1 (2%)	
Metaplasia, osseous		1 (2%)	1 (2%)	
Mineralization				1 (2%)
Nephropathy	5 (10%)	6 (12%)	7 (14%)	3 (6%)
Pigmentation, hemosiderin				1 (2%)
Urinary bladder	(48)	(47)	(45)	(46)
Edema		1 (2%)		

APPENDIX E
GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL 210
RESULTS 210
TABLE E1 Mutagenicity of Cobalt Sulfate Heptahydrate in *Salmonella typhimurium* 211

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

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

Each trial consisted of triplicate plates of concurrent positive and negative controls and of five doses of cobalt sulfate heptahydrate. The high dose was limited by experimental design to 10,000 µg/plate. All positive assays were repeated under the conditions that elicited the positive response.

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

RESULTS

Cobalt sulfate heptahydrate (3 to 10,000 µg/mL) was mutagenic in *S. typhimurium* strain TA100 in the absence of S9 metabolic activation, and with 5% hamster or rat liver S9; no mutagenicity was detected in strain TA98 or TA1535, with or without S9 (Zeiger *et al.*, 1992; Table E1).

TABLE E1
Mutagenicity of Cobalt Sulfate Heptahydrate in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/plate[b] S9 Trial 1	S9 Trial 2	S9 Trial 3	+ hamster S9 5%	+ hamster S9 5%
TA100	0	102 ± 6.4	113 ± 6.8	107 ± 8.5	117 ± 9.6	98 ± 6.4
	3					119 ± 11.9
	10		143 ± 4.7	134 ± 6.8		137 ± 13.7
	33		155 ± 1.7	160 ± 10.2	118 ± 5.6	162 ± 8.4
	100	201 ± 15.3	152 ± 7.9	163 ± 2.2	175 ± 1.5	176 ± 14.8
	333	217 ± 7.0	208 ± 11.7	204 ± 9.4	188 ± 6.2	163 ± 1.5
	1,000	204 ± 14.7	206 ± 17.6	152 ± 9.0	187 ± 6.1	
	3,333	126 ± 15.3			176 ± 7.3	
	10,000	101 ± 10.3[c]				
Trial summary		Positive	Weakly Positive	Weakly Positive	Weakly Positive	Weakly Positive
Positive control[d]		429 ± 7.8	312 ± 2.9	290 ± 20.1	922 ± 44.3	897 ± 57.6

Strain	Dose (µg/plate)	+ hamster S9 10%	+ hamster S9 30%	+ hamster S9 30%	+ rat S9 5%	+ rat S9 5%
TA100 (continued)	0	130 ± 15.0	139 ± 11.2	159 ± 3.9	116 ± 8.7	117 ± 10.6
	10					133 ± 1.5
	33	134 ± 9.8		168 ± 15.0	143 ± 12.2	164 ± 4.7
	100	156 ± 2.8	194 ± 9.0	166 ± 0.7	176 ± 8.0	188 ± 7.5
	333	187 ± 2.5	179 ± 6.0	193 ± 4.0	189 ± 15.9	201 ± 1.2
	1,000	159 ± 5.0	176 ± 3.0	160 ± 14.0	168 ± 8.2	143 ± 24.2
	3,333	160 ± 3.1	188 ± 18.4	161 ± 5.8	146 ± 9.8	
	10,000		123 ± 3.8			
Trial summary		Equivocal	Equivocal	Negative	Weakly Positive	Weakly Positive
Positive control		577 ± 10.9	462 ± 31.2	457 ± 22.2	909 ± 16.2	1,011 ± 25.0

Strain	Dose (µg/plate)	+ rat S9 10%	+ rat S9 30%	+ rat S9 30%
TA100 (continued)	0	124 ± 10.7	151 ± 12.3	131 ± 3.0
	33	122 ± 4.4		123 ± 14.8
	100	142 ± 5.8	179 ± 16.6	144 ± 10.7
	333	154 ± 4.9	223 ± 6.9	138 ± 8.4
	1,000	133 ± 5.5	191 ± 0.0	137 ± 11.2
	3,333	124 ± 4.3	202 ± 1.9	135 ± 5.3
	10,000		176 ± 12.5	
Trial summary		Negative	Equivocal	Negative
Positive control		556 ± 32.4	244 ± 6.7	521 ± 41.2

TABLE E1
Mutagenicity of Cobalt Sulfate Heptahydrate in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/plate: S9	+ hamster S9 5%	+ rat S9 5%
TA1535	0	16 ± 1.2	12 ± 3.3	11 ± 1.5
	3		10 ± 2.6	
	10	17 ± 2.0	9 ± 2.6	8 ± 1.3
	33	14 ± 2.3	8 ± 0.3	10 ± 1.5
	100	9 ± 1.2	5 ± 0.6	8 ± 0.9
	333	8 ± 1.7	4 ± 1.2	9 ± 0.3
	1,000	9 ± 1.3		8 ± 1.5
Trial summary		Negative	Negative	Negative
Positive control		213 ± 24.0	64 ± 4.9	186 ± 35.6

Strain	Dose (µg/plate)	S9	+ hamster S9 5%	10%	30%	30%
TA98	0	22 ± 2.3	32 ± 2.2	32 ± 0.6	32 ± 3.8	24 ± 1.7
	10		36 ± 2.7	28 ± 0.9		20 ± 2.3
	33		31 ± 4.4	38 ± 2.7		24 ± 1.9
	100	26 ± 0.5	45 ± 4.1	39 ± 4.6	44 ± 4.7	23 ± 3.5
	333	25 ± 4.0	40 ± 1.2	43 ± 0.0	53 ± 4.2	34 ± 2.6
	1,000	19 ± 0.6	42 ± 2.8	48 ± 7.6	47 ± 7.3	29 ± 4.8
	3,333	16 ± 3.4			44 ± 4.7	
	10,000	5 ± 2.7[c]			31 ± 3.8	
Trial summary		Negative	Negative	Negative	Equivocal	Negative
Positive control		372 ± 12.5	671 ± 34.6	687 ± 24.7	328 ± 4.3	542 ± 38.5

Strain	Dose (µg/plate)	+ rat S9 5%	10%	30%	30%	30%
TA98 (continued)	0	36 ± 1.8	28 ± 1.7	32 ± 3.3	32 ± 4.2	34 ± 1.5
	10	33 ± 4.9	29 ± 2.1			27 ± 1.2
	33	42 ± 3.0	38 ± 3.8			24 ± 2.3
	100	41 ± 4.7	45 ± 7.5	26 ± 1.2	44 ± 3.5	37 ± 3.5
	333	55 ± 5.6	46 ± 4.5	26 ± 0.6	54 ± 8.5	37 ± 3.3
	1,000	55 ± 2.9	33 ± 1.8	14 ± 0.6[c]	28 ± 1.5	34 ± 3.8
	3,333			16 ± 4.0[c]	21 ± 2.0	
	10,000			7 ± 2.6[c]	24 ± 3.7	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		742 ± 14.8	451 ± 12.5	104 ± 5.9	105 ± 6.5	208 ± 15.8

[a] Study performed at SRI International. The detailed protocol and these data are presented in Zeiger *et al*. (1992).
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535) and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

APPENDIX F
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

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CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF COBALT SULFATE HEPTAHYDRATE

Cobalt sulfate heptahydrate was obtained from Curtin Matheson Scientific (Kansas City, MO) in one lot (412092), which was used during the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the cobalt sulfate heptahydrate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a red, crystalline solid, was identified as cobalt sulfate heptahydrate by infrared, ultraviolet and/or visible spectroscopy. The spectra were consistent with the structure of cobalt sulfate heptahydrate. No literature references were found. The infrared spectrum is presented in Figure F1.

The purity of lot 412092 was determined by elemental analysis, Karl Fischer water analysis, and spark source mass spectroscopy. Elemental analyses for sulfur and hydrogen were in agreement with the theoretical values for cobalt sulfate heptahydrate, but values for cobalt were slightly low. Karl Fischer water analysis indicated 44.6% ± 0.5% water. Spark source mass spectroscopy indicated 140 ppm nickel present as an impurity; all other impurities had a combined total of less than 175 ppm. The overall purity was determined to be approximately 99%.

Literature references indicate that cobalt sulfate heptahydrate is stable as a bulk chemical when stored protected from light at normal temperatures (*Merck Index*, 1989). The heptahydrate dehydrates to the hexahydrate at 41.5° C and to the monohydrate at 71° C, with no further changes expected below the decomposition temperature (708° C). Therefore, an accelerated stability study was not conducted. To ensure stability, the bulk chemical was stored in its original shipping containers, metal cans, at room temperature. Stability was monitored during the 2-year studies using elemental analysis by inductively coupled plasma/atomic emission spectroscopy, normalized against a cobalt standard (National Institute of Standards and Technology, Gaithersburg, MD); no degradation of the bulk chemical was detected.

AEROSOL GENERATION AND EXPOSURE SYSTEM

A diagram of the cobalt sulfate heptahydrate aerosol generation and delivery system is shown in Figure F2. Cobalt sulfate heptahydrate aerosol was generated and delivered from an aqueous solution by a system composed of three main components: a compressed-air-driven nebulizer, an aerosol charge neutralizer, and an aerosol distribution system.

The nebulizer (Model PN7002; RETEC Development Laboratory, Portland, OR), shown in Figure F3, consisted of two orifices of different sizes aligned on opposite sides of a small chamber. Compressed air entered the chamber through the small orifice and, on entering the larger orifice, induced a negative pressure. Cobalt sulfate heptahydrate in deionized water (approximately 400 g/L) was siphoned from the bulk reservoir to the nebulizer reservoir and then aspirated into the nebulizer chamber and expelled as a stream through the larger orifice. Shear forces broke the stream into droplets that were evaporated to leave dry particles of cobalt sulfate heptahydrate. The aerosol generation and exposure system included primary and secondary compressed-air-driven nebulizers. The mass concentration of the dry particles in the feed solution was used to determine aerosol particle size. The generator output was controlled by adjusting the compressed air pressure.

The aerosol generated by the compressed-air-driven nebulizer was passed through the aerosol charge neutralizer to remove static charge that formed on the aerosol particles during generation, reducing adhesion of the droplets to the walls of the delivery system. This neutralizer consisted of a length of plastic duct with two 10-mCi ^{63}Ni-plated foils suspended in the center of the tube. The activity of the foils was matched to the diameter of the duct to allow adequate time for the aerosol to approach Boltzmann equilibrium at the system flow rate.

A distribution line carried aerosol (20 mg/m^3) to exposure chambers on both sides of the exposure room. Aerosol was siphoned from the branches of the distribution line by pneumatic pumps (one pump per exposure chamber). The flow rate in each branch of the distribution line was controlled by an Air-Vac pump (Air-Vac Engineering, Milford, CT) and monitored by a photohelic differential pressure gauge (Dwyer Instruments, Inc., Michigan City, IN) coupled to a Venturi tube. At each chamber, aerosol moving through the chamber inlet was further diluted with HEPA-filtered air to the appropriate concentration for the chamber. A diagram of the inhalation suite is shown in Figure F4. The Hazleton 2000 inhalation exposure chambers (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) were designed so that uniform aerosol concentrations could be maintained throughout each chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3.

AEROSOL CONCENTRATION MONITORING

The chamber aerosol concentrations of cobalt sulfate heptahydrate were monitored by real-time aerosol monitors (Model RAM-1; MIE, Inc., Bedford, MA) controlled by a Hewlett-Packard HP-85B computer (Hewlett-Packard Company, Palo Alto, CA). The RAM-1s detected aerosol particles ranging from 0.1 to 20 µm in diameter. Three RAM-1s were employed in the monitoring system (Figure F5); these monitors were exchanged with different RAM-1s when the on-line monitor performance deteriorated. Chamber aerosol concentrations were sampled at least once per hour during each exposure day. Sample lines connecting the exposure chambers to the RAM-1s were designed to minimize aerosol particle losses due to settling or impaction. Throughout the 2-year studies, the background concentrations of total suspended particles in the control chambers were less than the limit of detection. A summary of chamber concentrations is presented in Table F1.

The RAM-1 voltage output was calibrated against cobalt sulfate heptahydrate concentrations of chamber filter samples. Samples were collected on Teflon®-coated, glass-fiber filters with a calibrated flow sampler. Equations for the calibration curves contained in the HP-85B computer converted the RAM-1 voltages into exposure concentrations. Solutions of filter samples in 2% nitric acid were analyzed quantitatively for cobalt sulfate heptahydrate by inductively coupled plasma/atomic emission spectroscopy (ICP/AES). Calibration samples were collected every 2 weeks. Additional samples for monitoring the accuracy of calibration were collected daily from at least one chamber monitored by each RAM-1 and were analyzed two to three times per week. The ICP/AES was calibrated with a solution of standard cobalt diluted with nitric acid.

The stability of aerosol concentrations in the 0.3 and 3.0 mg/m^3 chambers was monitored by analyzing samples collected on Gelman A/E glass fibers using a calibrated flow sampler. X-ray diffraction analyses were performed by a Philips 3600 diffraction unit with Cu Ka radiation. Results indicated that cobalt sulfate hexahydrate was the primary species delivered to the chambers.

CHAMBER ATMOSPHERE CHARACTERIZATION

The time required for the chamber concentration to reach 90% of the target value following the beginning of exposure (T_{90}) and the time required for the chamber concentration to reach 10% of the target value following termination of the exposure (T_{10}) were determined for each exposure chamber. Without animals present, T_{90} values ranged from 9 to 11 minutes for the rat chambers and from 7 to 12 minutes for mouse

chambers; T_{10} ranged from 8 to 9 minutes for rats and mice. With animals present, T_{90} values ranged from 11 to 16 minutes for rats and from 8 to 12 minutes for mice; T_{10} ranged from 12 to 13 minutes for rats and from 11 to 12 minutes for mice. Variations in these values were considered to be due to differences in discrete sampling times, different flow rates for each chamber, fluctuations in generator output, and differing transit times for the aerosol through the delivery system. A T_{90} of 12 minutes was selected for the 2-year studies.

Aerosol size distribution was determined monthly for each exposure chamber with a Mercer-style seven-stage impactor (In-Tox Products, Albuquerque, NM). Samples were collected on glass coverslips sprayed with silicone and were analyzed for cobalt sulfate heptahydrate with ICP/AES. The relative mass on each impactor stage was analyzed by probit analysis; the mass median aerodynamic diameter for the aerosol was within the specified range of 1 to 3 µm (Tables F2 and F3).

The uniformity of aerosol concentration in the inhalation exposure chambers was measured approximately every 3 months. Aerosol concentration was determined with the RAM-1s, with an extension tube fitted to the sampling lines to allow sampling from ports in the front and back of each chamber. Chamber concentration uniformity was acceptable throughout the studies except for measurements taken from the 0.3 mg/m^3 mouse exposure chamber during 1 month of the study; however, these measurements were within the specified 5% variability when repeated.

At the beginning of the studies and approximately every 90 days thereafter, the persistence of cobalt sulfate heptahydrate aerosol in the 3.0 mg/m^3 rat chamber with and without animals present was determined by monitoring the concentration overnight with two RAM-1s. The average time for the concentration to decrease to 1% of the target concentration was approximately 20 minutes.

Before the exposures began, a solution of cobalt sulfate heptahydrate was analyzed for purity by ICP/AES; mean concentration of cobalt sulfate heptahydrate was found to be 99% of the theoretical value. Another sample from this original solution was analyzed after approximately 10 weeks, and the concentration of cobalt sulfate heptahydrate was 103% of the theoretical value. Thus, cobalt sulfate heptahydrate in the generator reservoir solution was considered to be stable for up to 10 weeks. New formulations were prepared at approximately 8-week intervals thereafter. Because the purity information supplied by the manufacturer and determined by the analytical chemistry laboratory indicated possible sulfuric acid contamination from the manufacturing process, the pH of the cobalt sulfate heptahydrate solution in the generator reservoir was analyzed to determine the extent of contamination. The pH was approximately 4.5, compared to 6.0 for the deionized water used to prepare the solution. From the pH of 4.5, the sulfuric acid content of the solution was calculated to be 0.0004% by weight. This value corresponded to a molar concentration of 1.6×10^{-5} sulfuric acid.

The aerosol stoichiometry was determined by measuring the number of moles of cobalt, sulfate, and water associated with samples from the chambers and distribution line. Filters were obtained from the 3.0 mg/m^3 rat and mouse chambers and from the distribution line. The total mass of collected aerosol was determined by ICP/AES. The mass of water on each filter was determined gravimetrically, and the masses of cobalt and sulfate on each filter were determined as the difference between the net aerosol mass and the combined masses of cobalt and sulfate. The results indicated that the average number of moles of cobalt, sulfate, and water associated with each mole of aerosol were 1.00 ± 0.00, 1.01 ± 0.01, and 5.9 ± 0.8, respectively. These results show that aerosol delivered to the exposure chambers is primarily cobalt sulfate hexahydrate, which is in good agreement with results obtained by X-ray diffraction.

Samples from the occupied 0.3 and 3.0 mg/m^3 rat exposure chambers, distribution line, and the generator reservoir were analyzed for ammonia by an Orion Model 512 ammonia electrode (Orion Research, Beverly, MA) with an internal reference. The electrode was calibrated against gravimetrically prepared ammonium

chloride solutions ranging from 0.1 to 100 mg ammonia per liter. Samples were collected on Teflon®-coated glass fibers with calibrated flow samplers. Filters were extracted with deionized water, and cobalt in the samples was quantified by ICP/AES. The filters were then extracted in an ionic strength adjustment buffer and ammonia in the sample was quantified with the ammonia-selective electrode. The concentration of ammonia relative to the amount of cobalt sulfate heptahydrate determined stoichiometrically from the ICP/AES cobalt measurements was approximately 0.9% by weight in the 0.3 mg/m^3 exposure chamber, approximately 1.8% in the 3.0 mg/m^3 chamber, and below detection limits in the distribution line and generator reservoir. The ammonia values in the exposure chambers were slightly above allowable impurity concentrations; this was attributed to the absence of cageboards during the first 8 weeks of the study. Thereafter, cageboards were used and the ammonia concentrations were expected to be significantly lower.

Due to the possibility of contamination of aerosol with carbon eroded from the organic polymers found in the components of the generation and delivery system, samples from the occupied chambers, distribution line, and reservoir were analyzed for carbon. Samples were collected from the occupied and unoccupied 0.3 and 3.0 mg/m^3 mouse exposure chambers, the distribution line, and the generator reservoir on Gelman A/E glass fiber filters using calibrated flow samplers. The filters were extracted with deionized water and aliquots from the extracts were analyzed for cobalt by ICP/AES. The remainder of the extract was made acidic to remove carbonate, and the extract was analyzed for total organic carbon by a Dohrmann Carbon Analyzer System (Dohrmann Division, Xertex Corporation, Santa Clara, CA). The instrument was calibrated against gravimetric standards prepared from potassium hydrogen phthalate.

The concentrations of total organic carbon in samples from the occupied exposure chamber were 8% in the 0.3 mg/m^3 chamber and 2.1% in the 3.0 mg/m^3 chamber. Carbon concentrations in other parts of the generation and delivery system and from empty chambers before exposure began were less than 0.5%. The high levels of organic carbon detected in the occupied mouse chambers were considered to be due to the presence of animals in the chambers. To verify that possibility, the analysis was repeated with samples from the occupied 0.3 and 3.0 mg/m^3 rat exposure chambers, the distribution line, and the generator reservoir. The results (9% and 2.1% total organic carbon in the 0.3 and 3.0 mg/m^3 rat chambers, respectively) were similar to those found for the mouse exposure chamber analysis, with negligible amounts again found in the generation and delivery system components. Thus, the carbon was concluded to be derived from the animals rather than from contamination of the aerosol.

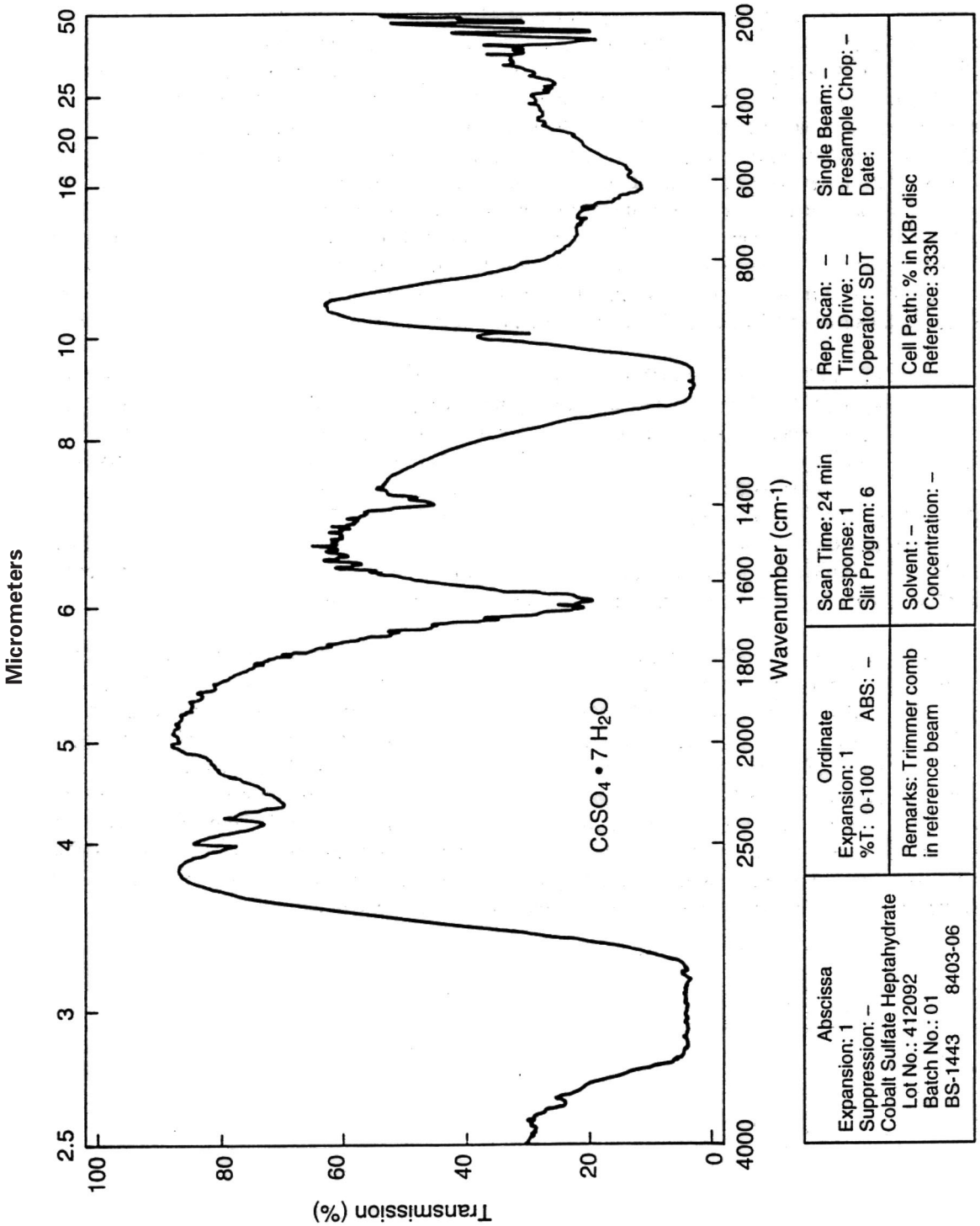


FIGURE F1
Infrared Absorption Spectrum of Cobalt Sulfate Heptahydrate

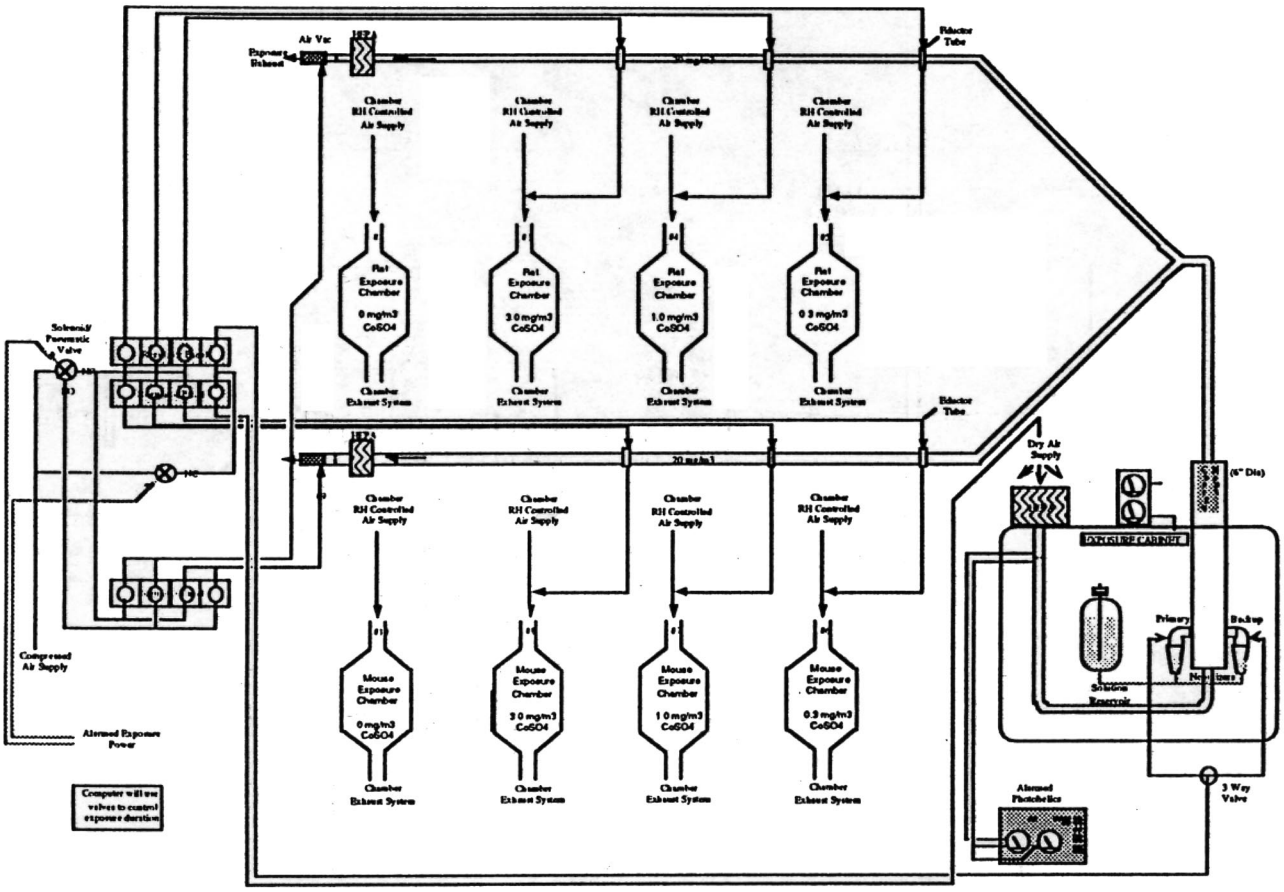


FIGURE F2
Schematic of the Aerosol Generation and Delivery System

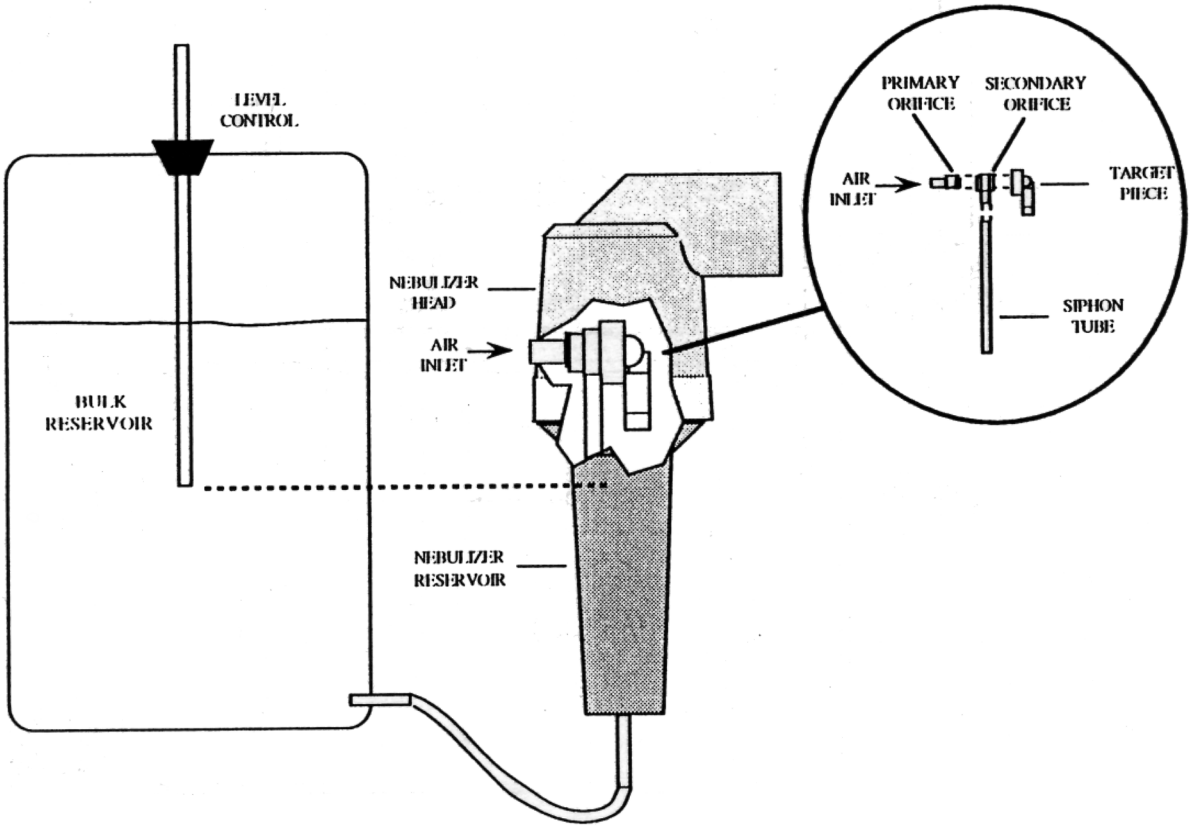


FIGURE F3
Schematic of the RETEC Compressed-Air-Driven Nebulizer

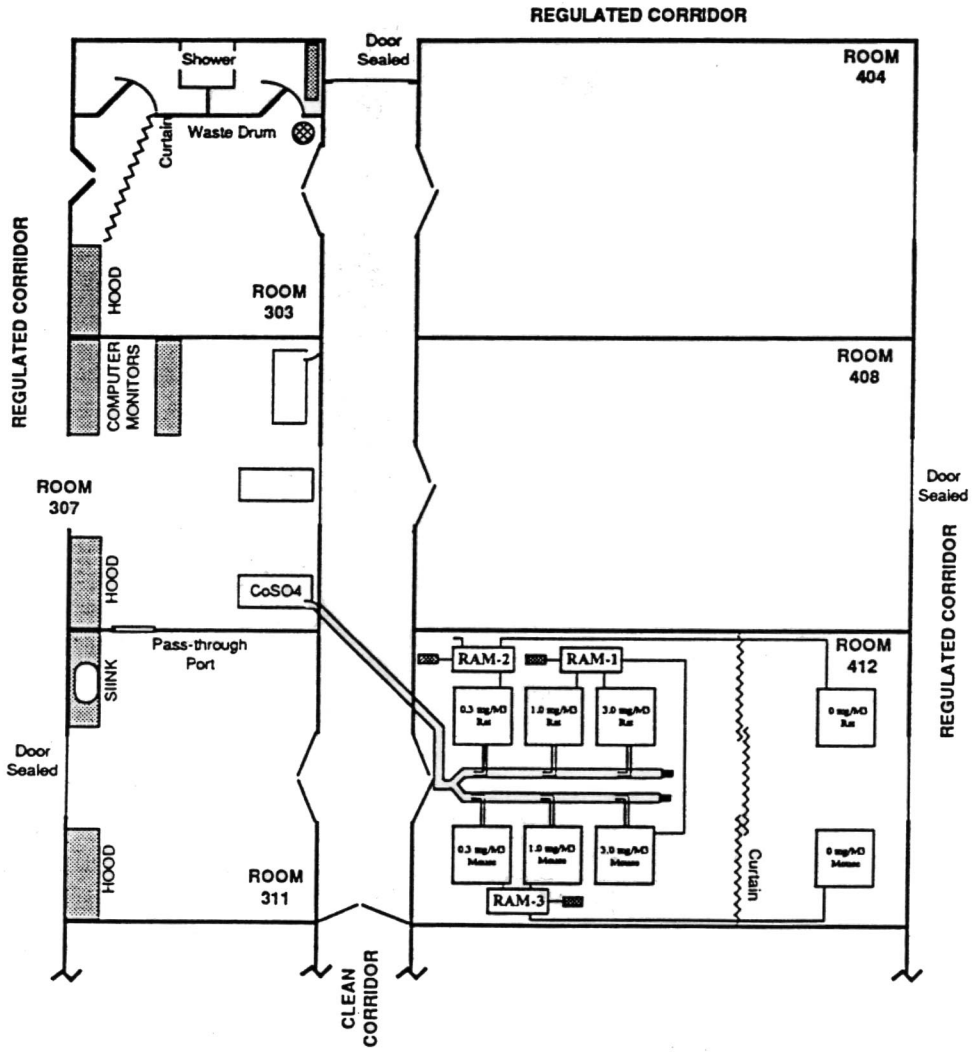
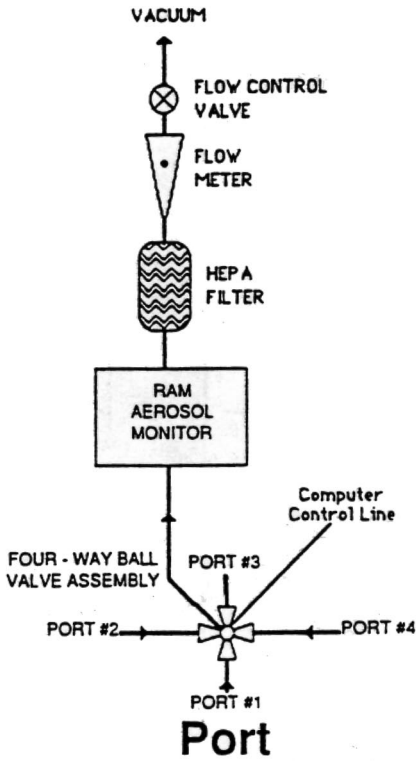


FIGURE F4
Inhalation Suite



RAM	1	2	3	4
1	MICE 3.0 mg/m^3	RATS 3.0 mg/m^3	RATS 1.0 mg/m^3	HEPA filtered Room Air
2	RATS 0 mg/m^3	RATS 0.3 mg/m^3	ROOM RATS 1.0 mg/m3 (calibration only)	HEPA filtered Room Air
3	MICE 1.0 mg/m^3	MICE 0.3 mg/m^3	MICE 0 mg/m^3	HEPA filtered Room Air

FIGURE F5
Schematic of the Concentration Monitoring System

TABLE F1
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Cobalt Sulfate Heptahydrate

Target Concentration (mg/m^3)	Total Number of Readings	Average Concentration[a] (mg/m^3)
Rat Chambers		
0.3	4,574	0.31 ± 0.03
1.0	4,574	1.03 ± 0.10
3.0	4,580	2.98 ± 0.20
Mouse Chambers		
0.3	4,571	0.30 ± 0.04
1.0	4,609	1.02 ± 0.08
3.0	4,605	3.01 ± 0.19

[a] Mean ± standard deviation

TABLE F2
Summary of Aerosol Size Measurements for the Rat Exposure Chambers in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	0.3 mg/m^3		1.0 mg/m^3		3.0 mg/m^3	
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
September 1990	1.7	2.4	1.2	2.2	1.6	2.2
October 1990	1.5	2.0	1.2	2.1	1.6	2.1
November 1990	1.6	2.1	1.3	2.2	1.6	2.1
December 1990	1.3	2.1	1.1	2.0	1.1	1.9
January 1991	1.5	2.1	1.2	2.1	1.6	2.0
February 1991	1.5	2.2	1.4	2.2	1.5	2.1
March 1991	1.5	2.2	1.4	2.2	1.6	2.1
April 1991	1.6	2.1	1.4	2.2	1.6	2.1
May 1991	1.5	2.0	1.4	2.0	1.7	2.0
June 1991	1.6	2.1	1.5	2.3	1.7	2.1
July 1991	1.6	2.1	1.3	2.0	1.6	2.1
August 1991	1.5	2.0	1.4	1.9	1.7	1.9
September 1991	1.5	2.1	1.4	1.9	1.6	2.1
October 1991	1.5	2.2	1.5	2.0	1.7	2.3
November 1991	1.5	2.6	1.6	2.2	1.8	2.4
December 1991	1.3	2.2	1.5	2.0	1.7	2.3
January 1992	1.5	2.1	1.5	2.2	1.7	2.2
February 1992	1.4	2.3	1.4	2.3	1.6	2.3
March 1992	1.3	2.3	1.4	2.3	1.6	2.3
April 1992	1.6	1.9	1.5	2.3	1.6	2.3
May 1992	1.4	2.2	1.5	2.4	1.6	2.3
June 1992	1.4	2.2	1.5	2.1	1.6	2.2
July 1992	1.6	2.2	1.4	2.1	1.6	2.1
August 1992	1.5	2.2	1.3	2.2	1.6	2.2
Mean ± standard deviation	1.5 ± 0.10	2.2 ± 0.14	1.4 ± 0.12	2.1 ± 0.13	1.6 ± 0.12	2.2 ± 0.13

TABLE F3

Summary of Aerosol Size Measurements for the Mouse Exposure Chambers in the 2-Year Inhalation Study of Cobalt Sulfate Heptahydrate

	0.3 mg/m³		1.0 mg/m³		3.0 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**
September 1990	1.3	3.0	1.3	2.6	1.5	2.4
October 1990	1.6	2.6	1.7	2.2	1.9	2.1
November 1990	1.4	2.4	1.6	2.5	1.7	2.3
December 1990	1.2	2.4	—[a]	—[a]	1.1	2.2
January 1991	1.4	2.4	1.6	2.3	1.6	2.2
February 1991	1.6	2.3	1.5	2.3	1.7	2.2
March 1991	1.5	2.3	1.5	2.3	1.6	2.1
April 1991	1.6	2.4	1.5	2.4	1.8	2.3
May 1991	1.6	2.2	1.6	2.2	1.8	2.1
June 1991	1.4	2.3	1.4	2.4	1.6	2.2
July 1991	1.6	2.3	1.4	2.1	1.7	2.1
August 1991	1.6	2.1	1.5	2.1	1.6	2.2
September 1991	1.6	2.2	1.5	2.3	1.7	2.2
October 1991	1.7	2.2	1.7	2.3	1.7	2.3
November 1991	1.7	2.4	1.6	2.4	1.8	2.2
December 1991	1.7	2.2	1.6	2.1	1.7	2.3
January 1992	1.7	2.3	1.5	2.4	1.6	2.3
February 1992	1.7	2.2	1.7	2.4	1.6	2.3
March 1992	1.7	2.4	1.4	2.4	1.5	2.3
April 1992	1.7	2.5	1.6	2.5	1.5	2.6
May 1992	1.6	2.1	1.7	2.2	1.6	2.5
June 1992	1.5	2.2	1.5	2.3	1.6	2.2
July 1992	1.6	2.3	1.3	2.3	1.6	2.2
August 1992	2.0	2.3	1.5	2.3	1.5	2.2
Mean ± standard deviation	1.6 ± 0.16	2.3 ± 0.19	1.5 ± 0.12	2.3 ± 0.13	1.6 ± 0.15	2.3 ± 0.12

[a] No data available due to incomplete stage analysis

APPENDIX G
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

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TABLE G1
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 G2
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 G3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.40 ± 0.56	22.2 – 24.3	25
Crude fat (% by weight)	5.31 ± 0.19	5.00 – 5.90	25
Crude fiber (% by weight)	3.36 ± 0.33	2.60 – 4.30	25
Ash (% by weight)	6.43 ± 0.20	6.12 – 6.81	25
Amino Acids (% of total diet)			
Arginine	1.280 ± 0.083	1.110 – 1.390	11
Cystine	0.308 ± 0.071	0.181 – 0.400	11
Glycine	1.158 ± 0.048	1.060 – 1.220	11
Histidine	0.584 ± 0.027	0.531 – 0.630	11
Isoleucine	0.917 ± 0.033	0.867 – 0.965	11
Leucine	1.975 ± 0.051	1.850 – 2.040	11
Lysine	1.274 ± 0.049	1.200 – 1.370	11
Methionine	0.437 ± 0.109	0.306 – 0.699	11
Phenylalanine	0.999 ± 0.120	0.665 – 1.110	11
Threonine	0.904 ± 0.058	0.824 – 0.985	11
Tryptophan	0.218 ± 0.153	0.107 – 0.671	11
Tyrosine	0.685 ± 0.094	0.564 – 0.794	11
Valine	1.086 ± 0.055	0.962 – 1.170	11
Essential Fatty Acids (% of total diet)			
Linoleic	2.407 ± 0.227	1.830 – 2.570	10
Linolenic	0.259 ± 0.065	0.100 – 0.320	10
Vitamins			
Vitamin A (IU/kg)	6,738 ± 1,318	5,730 – 11,450	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	35.43 ± 8.98	22.5 – 48.9	11
Thiamine (ppm)	17.48 ± 2.10	14.0 – 22.0	25
Riboflavin (ppm)	7.83 ± 0.923	6.10 – 9.00	11
Niacin (ppm)	99.22 ± 24.27	65.0 – 150.0	11
Pantothenic acid (ppm)	30.55 ± 3.52	23.0 – 34.6	11
Pyridoxine (ppm)	9.11 ± 2.53	5.60 – 14.0	11
Folic acid (ppm)	2.46 ± 0.63	1.80 – 3.70	11
Biotin (ppm)	0.268 ± 0.047	0.190 – 0.354	11
Vitamin B_{12} (ppb)	40.5 ± 19.1	10.6 – 65.0	11
Choline (ppm)	2,991 ± 382	2,300 – 3,430	10
Minerals			
Calcium (%)	1.16 ± 0.10	1.00 – 1.49	25
Phosphorus (%)	0.92 ± 0.05	0.76 – 1.00	25
Potassium (%)	0.886 ± 0.063	0.772 – 0.971	9
Chloride (%)	0.529 ± 0.087	0.380 – 0.635	9
Sodium (%)	0.316 ± 0.033	0.258 – 0.371	11
Magnesium (%)	0.166 ± 0.010	0.148 – 0.181	11
Sulfur (%)	0.272 ± 0.059	0.208 – 0.420	10
Iron (ppm)	350.5 ± 87.3	255.0 – 523.0	11
Manganese (ppm)	92.48 ± 5.14	81.7 – 99.4	11
Zinc (ppm)	59.33 ± 10.2	46.1 – 81.6	11
Copper (ppm)	11.81 ± 2.50	9.09 – 15.4	11
Iodine (ppm)	3.54 ± 1.19	1.52 – 5.83	10
Chromium (ppm)	1.66 ± 0.46	0.85 – 2.09	11
Cobalt (ppm)	0.76 ± 0.23	0.49 – 1.15	7

TABLE G4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.42 ± 0.20	0.10 – 0.70	25
Cadmium (ppm)	0.13 ± 0.07	0.04 – 0.20	25
Lead (ppm)	0.35 ± 0.24	0.10 – 1.00	25
Mercury (ppm)[c]	0.02	0.02 – 0.03	25
Selenium (ppm)	0.33 ± 0.11	0.05 – 0.40	25
Aflatoxins (ppm)	< 5.0		25
Nitrate nitrogen (ppm)[d]	8.99 ± 4.49	2.90 – 17.0	25
Nitrite nitrogen (ppm)[d]	0.15 ± 0.08	0.10 – 0.40	25
BHA (ppm)[e]	1.80 ± 1.94	1.00 – 10.0	25
BHT (ppm)[e]	1.56 ± 1.58	1.00 – 8.00	25
Aerobic plate count (CFU/g)	95,908 ± 162,569	4,100 – 710,000	25
Coliform (MPN/g)	3 ± 0.3	3 – 4	25
Escherichia coli (MPN/g)	< 3		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[f]	7.36 ± 1.75	4.70 – 11.40	25
N-Nitrosodimethylamine (ppb)[f]	5.40 ± 1.18	2.90 – 8.20	25
N-Nitrosopyrrolidine (ppb)[f]	1.96 ± 1.05	1.00 – 4.30	25
Pesticides (ppm)			
α-BHC	< 0.01		25
β-BHC	< 0.02		25
γ-BHC	< 0.01		25
δ-BHC	< 0.01		25
Heptachlor	< 0.01		25
Aldrin	< 0.01		25
Heptachlor epoxide	< 0.01		25
DDE	< 0.01		25
DDD	< 0.01		25
DDT	< 0.01		25
HCB	< 0.01		25
Mirex	< 0.01		25
Methoxychlor	< 0.05		25
Dieldrin	< 0.01		25
Endrin	< 0.01		25
Telodrin	< 0.01		25
Chlordane	< 0.05		25
Toxaphene	< 0.10		25
Estimated PCBs	< 0.20		25
Ronnel	< 0.01		25
Ethion	< 0.02		25
Trithion	< 0.05		25
Diazinon	< 0.10		25
Methyl parathion	< 0.02		25
Ethyl parathion	< 0.02		25
Malathion	0.23 ± 0.23	0.05 – 0.97	25
Endosulfan I	< 0.01		25
Endosulfan II	< 0.01		25
Endosulfan sulfate	< 0.03		25

[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] All values except for the September, November, and December 1991 milling dates (0.03 ppm) were less than the detection limit. The detection limit is given as the mean.
[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 H
SENTINEL ANIMAL PROGRAM

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TABLE H1 Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Studies of Cobalt Sulfate Heptahydrate 232

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 2-year studies of cobalt sulfate heptahydrate. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
RCV/SDA	6 months
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, and 18 months, study termination
KRV (Kilham rat virus)	6, 12, and 18 months, study termination

MICE

ELISA

Ectromelia virus	6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

Immunofluorescence Assay

EDIM	18 months and study termination
LCM	6 months
MHV	Study termination
Reovirus 3	18 months and study termination

Hemagglutination Inhibition

K (papovavirus)	6, 12, and 18 months, study termination
MVM (minute virus of mice)	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table H1.

TABLE H1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Studies of Cobalt Sulfate Heptahydrate

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats		
6 Months	0/16	None positive
12 Months	0/16	None positive
18 Months	0/16	None positive
Study termination	6/10	*M. arthriditis*[a]
Mice		
6 Months	0/10	None positive
12 Months	0/9	None positive
18 Months	0/10	None positive
Study termination	3/10	*M. arthriditis*

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.

APPENDIX I
K-*RAS* MUTATION FREQUENCY AND SPECTRA IN LUNG NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO COBALT SULFATE HEPTAHYDRATE FOR 2 YEARS

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K-*RAS* MUTATION FREQUENCY AND SPECTRA IN LUNG NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO COBALT SULFATE HEPTAHYDRATE FOR 2 YEARS

INTRODUCTION

Lung neoplasms occur in B6C3F$_1$ mice with a typical incidence of 20% in control males and 10% in control females by 2 years of age. Molecular analysis of lung neoplasms for genetic alterations in cancer genes such as the *ras* proto-oncogene provides additional mechanistic information to help distinguish spontaneous neoplasms from chemical-induced neoplasms. For example, chemical-induced neoplasms in mice may have a higher frequency of proto-oncogene activation, particularly by point mutations in codon 12, 13, or 61 of K-*ras* genes (Sills *et al.*, 1995). The frequency of *ras* activation in these neoplasms is often greater than that detected in neoplasms occurring in control animals (Devereux *et al.*, 1991), and there is evidence for chemical specificity in the pattern of mutations. The specific types of oncogene-activating mutations induced by a chemical carcinogen often agree with what is expected based on the DNA adducts formed by the agent (Devereux *et al.*, 1993a). Even for "nongenotoxic carcinogens," patterns of *ras* gene mutations in neoplasms can give clues about the mechanism of tumorigenesis (Devereux *et al.*, 1993b).

MATERIALS AND METHODS

Lung neoplasms: Male and female B6C3F$_1$ mice were exposed to 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate heptahydrate by inhalation for 6 hours per day, 5 days per week for 2 years. At necropsy, lung neoplasms were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, sectioned to a thickness of 5 µm, and stained with hematoxylin and eosin. Subsequently, six unstained serial sections (10 µm thick) were prepared from paraffin blocks containing alveolar/bronchiolar adenomas or carcinomas for isolation of DNA for polymerase chain reaction (PCR)-based assays. In order to isolate adequate amounts of DNA, lung neoplasms greater than 1 mm in diameter were identified for analysis. A total of 32 paraffin-embedded neoplasms were examined for genetic alterations in the K-*ras* gene. This included 26 neoplasms from cobalt sulfate heptahydrate-exposed mice and six neoplasms from control mice.

DNA isolation: The DNA isolation procedure is described in Marmur (1961) and Sills *et al.* (1995). The paraffin-embedded tissue was deparaffinized and rehydrated before digesting with proteinase K (Wright and Manos, 1990). The neoplasm tissue was digested with 10 mg/mL pronase in 1% sodium dodecyl sulfate in TNE buffer (10 mM Tris; 150 mM NaCl; and 2 mM EDTA disodium salt, pH 7.5). DNA was extracted with phenol and chloroform and precipitated with ethanol. DNA was quantified by optical density at 260 nm, and 200 ng/µL was used for amplification.

DNA amplification: DNA was amplified by PCR (Saiki *et al.*, 1988; Sills *et al.*, 1995); details of the use of nested primers are described in Devereux *et al.* (1991, 1993b).

Restriction fragment length polymorphic identification: For identification of K-*ras* mutations at codon 61, restriction fragment length polymorphism (RFLP) was used, and most of exon 2 surrounding codon 61 was amplified (Sukumuar and Barbacid, 1990). The sense primer used for amplification of exon 2 was 5′-GACATCTTAGACACAGCAGTT-3′. A restriction site for XbaI or TaqI enzyme (New England Biolaboratory, Beverly, MA) is created by the presence of an A to T or A to G mutation in the second base of codon 61. By using this technique, codon 61 CTA and CGA mutations were detected by XbaI and TaqI digestion, respectively; the normal sequence (CAA) of codon 61 is not cut by these enzymes. The reaction

was incubated at 37° C (XbaI) or 60° C (TaqI) for 2 hours. Fifteen µL of the mixture with bromophenol blue dye was loaded onto the 6% acrylamide tris-borate-EDTA (TBE) gel (8 × 8 cm × 1 mm; 15 wells) (Novex, San Diego, CA). The gel was run at 100 volts for 1 hour on the Novex gel electrophoresis unit. Gels were stained with a 5 µg/mL solution of ethidium bromide for 20 minutes and then destained in distilled water. Ethidium bromide-stained bands were visualized using a 312 nm ultraviolet viewing box and photographed.

"Cold" single-strand conformation polymorphism analysis (SSCP): A mixture consisting of 5 µL of PCR product (double-stranded DNA), 0.6 µL of 1M methylmercury hydroxide, 1 µL of 15% W/V Ficoll (molecular weight 400,000) loading buffer containing 0.25% bromophenol blue and 0.25% xylene cyanol, and 13.4 µL of 1X TBE buffer (Novex, San Diego, CA) was prepared to yield a total volume of 20 µL. This nonradioactive mixture was heated to 85° C for 5 minutes and then plunged into ice prior to loading the entire 20 µL into the gel. A 20% polyacrylamide TBE gel was used for K-*ras* with the matching gel electrophoresis unit (Novex, San Diego, CA). The buffer chamber was filled with 1.5X TBE buffer. The gel was run at 300 volts in a 5° C cold room until a light blue marker reached the bottom of the gel. A positive control for K-*ras* mutations and one undenatured DNA control (without methylmercury hydroxide and no heat) were run with unknown samples. Gels were stained with a 0.5 µg/mL solution of ethidium bromide for 20 minutes and destained in distilled water for 5 minutes. The stained bands were visualized under a UV viewing box and photographed. For identification of K-*ras* mutation at codon 61, RFLP was used with XbaI enzyme digestion and "cold" SSCP analysis was performed on the same 20% gel.

Direct sequencing: Direct sequencing of the amplified first and second exon of the K-*ras* gene was performed as described by Tindall and Stankowski (1989) using previously described sequencing primers (Devereux *et al.*, 1991).

RESULTS

In order to determine if the cobalt sulfate heptahydrate-induced neoplasms contained a K-*ras* mutation profile similar to that observed with "spontaneous" neoplasms, sample groups of six neoplasms consisting of adenomas and carcinomas from the chamber control, seven, eight, and 11 neoplasms from the 0.3 mg/m^3, 1.0, and 3.0 mg/m^3 dose groups, respectively, were evaluated by PCR amplification of K-*ras* exon 1 or K-*ras* exon 2 followed by RFLP for the two codon 61 mutations CTA and CGA in the B6C3F$_1$ mouse (Table I1). SSCP was used as an alternative screening method for detection of K-*ras* mutations in DNA, and mutations were confirmed by direct sequencing. Mutation spectra in codons 12, 13, and 61 of the K-*ras* gene had some similarity to those identified in spontaneous lung neoplasms.

Of the K-*ras* mutations detected, a higher frequency (5/9, 55%) of G to T transversions was detected at the second base of codon 12 compared to 0/1 (0%) for chamber controls or 1/24 (4%) for NTP historical controls. K-*ras* codon 61 CTA or CGA mutations were not present in the cobalt sulfate heptahydrate-induced lung neoplasms. A trend toward a dose-response relationship in the frequency of K-*ras* mutations was observed in cobalt sulfate heptahydrate-induced lung neoplasms: 14% versus 38% versus 45% for the 0.3, 1.0, and 3.0 mg/m^3 doses, respectively (Table I2). There were generally no differences in the mutation frequency or spectra between benign and malignant lung neoplasms (data not shown).

DISCUSSION

In examining the K-*ras* mutations detected in the cobalt sulfate heptahydrate study, a higher frequency (5/9, 55%) of G to T transversions was detected at codon 12 compared to 0/1 (0%) for chamber controls or 1/24 (4%) for historical controls. These findings are consistent with the work of Zeiger *et al*. (1992), in which cobalt sulfate heptahydrate showed a weakly positive response in *Salmonella typhimurium* strain TA100 in the absence of exogenous metabolic activation as well as with hamster or rat liver S9.

The higher number of G to T transversions at codon 12 is supportive evidence that cobalt sulfate heptahydrate may indirectly damage DNA by oxidative stress. GGT to GTT mutations appear to be infrequent in spontaneous lung neoplasms from $B6C3F_1$ mice (Table I1). However, G to T transversions are commonly detected DNA base changes associated with active oxygen species and are consistent with 8-OH-G adducts produced during oxidative damage to DNA (Tchou *et al.*, 1991; Shigenaga and Ames, 1991; Janssen *et al.*, 1993). 8-OH-G is a suspect lesion in the formation of both spontaneous cancers and those induced by various agents such as 4-nitroquinoline oxide, ionizing radiation, $KBrO_3$, and 2-nitropropane (Floyd, 1990; Foley *et al.*, 1993). Thus, cobalt sulfate heptahydrate exposure in $B6C3F_1$ mice may have resulted in the generation of hydroxyl radicals that could have enhanced G to T transversions at the second base of codon 12. Consistent with these findings is the work of Shi *et al.* (1993), in which cobalt sulfate heptahydrate was shown to catalyze the production of oxygen-based free radicals.

The observation of similar frequencies and spectra of mutations in cobalt sulfate heptahydrate-induced alveolar/bronchiolar adenomas and carcinomas is consistent with other studies showing that K-*ras* activation occurs early and may be an initiating event in murine lung carcinogenesis (Sills *et al.*, 1995). If mutations in the K-*ras* gene occurred later, an increased frequency of K-*ras* mutations would be expected in carcinomas. In $B6C3F_1$ mice exposed to cobalt sulfate heptahydrate, specific K-*ras* mutations did not correlate with specific morphological patterns or sizes of lung neoplasms, a finding supported by Ohmori (1992).

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TABLE I1
K-*ras* Mutations in Lung Neoplasms of B6C3F$_1$ Mice

Treatment	Activated K-*ras* (%)	Codon 12 N=GGT GTT	GAT	TGT	CGT	CTT	ATT	Codon 13 N=GGC CGC	GAC	Codon 61 N=CAA CTA	CAT	CAC	CGA
Control, Historical	24/75 (33%)	1	9	4	0	0	0	3	0	0	4	1	2
Control, Chamber	1/6 (17%)	0	0	1	0	0	0	0	0	0	0	0	0
Cobalt Sulfate Heptahydrate[a]	9/26 (35%)	5	2	1	0	0	0	1	0	0	0	0	0
Ozone	19/27 (70%)	5	3	2	0	0	0	0	1	8	0	0	0
1,3-Butadiene	6/9 (67%)	0	0	0	0	0	0	6	0	0	0	0	0
Tetranitromethane	10/10 (100%)	0	10	0	0	0	0	0	0	0	0	0	0
Methylene Chloride	11/54 (20%)	1	1	1	0	0	0	1	0	1	1	4	1

[a] One animal had two neoplasms of the same type and mutation (GTT) which were counted as one neoplasm. If counted as two neoplasms, the activated K-*ras* would be 10/27 (37%), and there would be 6 codon 12 GTT mutations.

TABLE I2
K-*ras* Mutation Profile in Lung Neoplasms of B6C3F$_1$ Mice

Treatment Concentration (mg/m^3)	Activated K-*ras* (%)	Codon 12 N=GGT GTT	GAT	TGT	CGT	CTT	ATT	Codon 13 N=GGC CGC	Codon 61 N=CAA CTA	CAT	CAC	CGA
Chamber and Historical Control												
	25/81 (31%)	1 (1%)	9 (11%)	5 (6%)	0	0	0	3 (4%)	0	4 (5%)	1 (1%)	2 (2%)
Cobalt Sulfate Heptahydrate												
0.3	1/7 (14%)	1 (14%)	0	0	0	0	0	0	0	0	0	0
1.0	3/8 (38%)	2 (25%)	0	0	0	0	0	1 (13%)	0	0	0	0
3.0	5/11 (45%)	2 (18%)	2 (18%)	1 (9%)	0	0	0	0	0	0	0	0
Total[a]	9/26 (35%)	5 (19%)	2 (8%)	1 (4%)	0	0	0	1 (4%)	0	0	0	0

[a] One animal had two neoplasms of the same type and mutation (GTT) which were counted as one neoplasm. If counted as two neoplasms, the activated K-*ras* would be 10/27 (37%), and there would be 6 codon 12 GTT mutations.

APPENDIX J
IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

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IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

ABSTRACT

Male and female B6C3F$_1$ mice from 12 NTP 2-year carcinogenesis studies were found to be infected with *Helicobacter hepaticus*. Many of the male mice from nine of these studies ("affected" studies) had an associated hepatitis. The current evaluations were performed in an attempt to determine if the data from the *H. hepaticus*-affected NTP B6C3F$_1$ mouse studies were compromised and unsuitable for cancer hazard identification. The incidences of neoplasms of the liver (both hepatocellular neoplasms and hemangiosarcoma), but not of other organs in control male B6C3F$_1$ mice, were found to be increased in affected studies compared to control males from unaffected studies. The increased incidence of hepatocellular neoplasms was observed in those males exhibiting *H. hepaticus*-associated hepatitis. Other observations further differentiated control male mice from affected and unaffected studies. H-*ras* codon 61 CAA-to-AAA mutations were less common in liver neoplasms in males from affected studies compared to historical and unaffected study controls. In addition, increases in cell proliferation rates and apoptosis were observed in the livers of male mice with *H. hepaticus*-associated hepatitis. These data support the hypothesis that the increased incidence of liver neoplasms is associated with *H. hepaticus* and that hepatitis may be important in the pathogenesis. Therefore, interpretation of carcinogenic effects in the liver of B6C3F$_1$ mice may be confounded if there is *H. hepaticus*-associated hepatitis.

INTRODUCTION

Helicobacter-Induced Diseases

Since the bacterium *H. pylori* was isolated from humans in 1983, numerous *Helicobacter* species have been identified in several laboratory and domestic animal species. Their pathogenicity varies, with some species inducing significant disease while others appear merely to colonize the gastrointestinal tract. *H. pylori* is known to cause chronic gastritis and peptic ulcers in humans (Marshall and Warren, 1984; Graham, 1989; Lee *et al.*, 1993) and, more recently, has been linked to adenocarcinoma and mucosa-associated lymphoma of the stomach (Fox *et al.*, 1989; Nomura *et al.*, 1991; Parsonnet *et al.*, 1991; Wotherspoon *et al.*, 1993). Based on epidemiological and pathology findings, the International Agency for Research on Cancer (1994) has classified *H. pylori* as a group 1 carcinogen in humans. *H. hepaticus* is associated with an increase in liver neoplasm incidences in A/JCr mice (Ward *et al.*, 1994a; Fox *et al.*, 1996).

H. hepaticus commonly colonizes the gastrointestinal tract of many strains of mice from many sources (Fox *et al.*, 1994; Ward *et al.*, 1994b; Shames *et al.*, 1995). It has been shown to be pathogenic, with hepatitis highly prevalent in some strains of mice (A/JCr, BALB/cAnNCr, C3H/HeNCr, SJL/NCr, and SCID/NCr) (Ward *et al.*, 1994b). Intestinal colonization does not necessarily result in subsequent hepatitis, and the conditions that lead to migration of the organism from the intestine to the liver have not been determined. *H. hepaticus* appears to reside primarily within the bile canaliculi. Male mice were reported to have a greater incidence and severity of hepatitis than female mice, and this finding occurred in NTP studies as well. The recently identified *H. bilis*, like *H. hepaticus*, colonizes the biliary tract, liver, and intestine of mice. While *H. bilis* has been identified in animals with chronic hepatitis, whether it caused the hepatitis is not known (Fox *et al.*, 1995).

The pathogenesis of *H. hepaticus*-induced disease has not been fully characterized. In susceptible strains of mice, *H. hepaticus* can cause acute, focal, nonsuppurative, necrotizing hepatitis, which progresses to chronic, active hepatitis characterized by minimal necrosis, hepatocytomegaly, oval cell hyperplasia, and

cholangitis. *H. hepaticus* has been found to possess high levels of urease (Fox *et al.*, 1994). *H. hepaticus* is often isolated from the cecum and colon but is not necessarily isolated from the liver of A/JCr mice, even though these animals develop severe hepatitis. Culture supernatants from several strains of *H. hepaticus* and several other *Helicobacter* species were shown to cause cytopathic effects in a rodent hepatocyte cell line (Taylor *et al.*, 1995). Ward *et al*. (1996) suggested that autoimmunity may play a role in the progressive hepatitis and carcinogenesis in livers infected with *H. hepaticus*.

NTP Infectious Disease Surveillance

In 1993, during the histological evaluation of an NTP 2-year study, pathologists identified a constellation of liver lesions (hepatitis) in control and treated male mice that was consistent with what would later be described in mice infected with *H. hepaticus* (Ward *et al.*, 1993, 1994a; Fox *et al.*, 1994). Subsequently, pathology results from all mouse studies begun since 1984 (67 two-year studies) were reviewed for diagnoses of the characteristic hepatitis; the lesions were identified in nine studies (NTP, 1998a,b,c,d,e,f). Silver stains revealed helical bacteria consistent with *Helicobacter* present in the liver of male mice in the nine studies.

Every reasonable measure is taken to prevent the occurrence of infectious diseases during NTP 2-year carcinogenicity studies. When infections occasionally occur, care is taken to identify the causal agent and its source, measures are taken to ensure that animals in later studies will not be infected, and the potential impact on biological parameters (primarily neoplastic endpoints) important in interpretation of the study is determined. To date, animals (control and treated) from a few studies have had a mild pulmonary inflammatory response presumed to be caused by an infectious agent. In other studies, there have been utero-ovarian infections with *Klebsiella* sp. (Rao *et al.*, 1987) and fungal infections of the nasal cavity. For scientifically valid reasons, interpretation of chemical-related effects was not considered significantly compromised in any of these studies. Unlike the previous infections, *H. hepaticus* involves the liver, the major metabolic organ, and has been associated with an increase in incidences of liver neoplasms in the A/JCr mouse (Ward *et al.*, 1994a). Therefore, when the contemporary epizootic of *H. hepaticus* infection in the United States affected several NTP studies, use of the data for hazard identification was questioned. The first step was to determine the extent of the infection within NTP studies and then evaluate the impact the infection had on biological parameters important in interpretation of the carcinogenic potential of test chemicals.

MATERIALS AND METHODS

Histologic Examination

Studies in which mice were potentially infected with *H. hepaticus* were identified by reviewing the summary pathology tables for characteristic diagnoses: oval and/or biliary epithelial hyperplasia, hepatocyte enlargement (often diagnosed as karyomegaly), chronic inflammation, and regenerative hyperplasia. All 13-week and 2-year studies begun by the NTP since 1984 and for which complete pathology data were available (67 two-year studies) were examined. Eight contemporary studies in which the characteristic lesions were not identified from pathology tables were randomly selected for histologic reevaluation. Slides containing sections of hematoxylin- and eosin-stained livers from 20 to 25 control and 20 to 25 high-dose male mice from each of seven 2-year studies and one 13-week study (10 animals from each group) were reexamined microscopically for the presence of hepatitis potentially related to *H. hepaticus* infection. Hepatitis consistent with that observed with *H. hepaticus* infection was not observed in any of these studies.

Liver sections from five or more animals from each of nine 2-year studies in which hepatitis was observed were prepared using the Warthin-Starry silver stain or Steiner's modification to identify silver-positive helical bacteria.

PCR-RFLP Detection of *Helicobacter* DNA

Assays based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were conducted at the NIEHS (Malarkey *et al.*, 1997) and the University of Missouri Research Animal Diagnostic and Investigative Laboratory (MU-RADIL) (Riley *et al.*, 1996) on liver tissue from approximately 20 animals from each of 32 NTP 2-year studies (including the nine affected studies) and three NTP 13-week studies. The majority of these studies were selected because they were begun at approximately the same time (1988-1990) as the nine affected studies. Also, two earlier studies (1984-1985; mouse life-span and *p*-nitroaniline studies) and one later study (1993; methyleugenol) were selected. The mouse life-span study was designed to evaluate the incidences of spontaneous changes associated with age; therefore, there is no NTP Technical Report. Pathology peer review is not complete for the methyleugenol study, and the NTP Technical Report (NTP, 1998g) has not been completed. Frozen tissue was available from 22 of these studies, while only formalin-fixed tissue was available for the remaining ten 2-year studies and the three 13-week studies. Most of the assays were conducted by MU-RADIL, which used *Helicobacter* genus-specific primers; MU-RADIL used restriction endonucleases on a subset of positives to determine if the species was *H. hepaticus*. DNA was isolated from frozen liver samples with a QIAamp Tissue Kit (Qiagen Inc., Chatsworth, CA) according to the manufacturer's recommendations or routine phenol/chloroform extraction (Malarkey *et al.*, 1997). DNA content and purity were determined spectrophotometrically by measuring the A_{260}/A_{280} optical density ratio. To isolate DNA from paraffin-embedded samples, five 10-µm sections were washed twice with 1 mL xylene and twice with 500 µL ethanol. Tissues were then dried within a vacuum centrifuge prior to DNA isolation as described above. Routine measures were taken to avoid contamination at every step from tissue collection to PCR amplification, and concurrently run controls without DNA were consistently negative.

Statistical Analyses

Multiple regression procedures were used to compare control neoplasm rates in the nine affected studies with the 26 unaffected contemporary studies which had no histologic evidence of *H. hepaticus*-associated liver disease. While frozen liver tissue was unavailable from 13 of these 26 studies, none showed the hepatitis indicative of *H. hepaticus* and thus were assumed to be unaffected. Potential confounding factors such as body weight, date study was begun, route of administration, and animal supplier were included as covariables in the statistical analysis.

Analysis for H-*ras* Codon 61 CAA-to-AAA Mutations

For analyses of formalin-fixed tissue, three to five unstained serial sections (10 µm thick) were cut from paraffin blocks containing hepatocellular adenomas or carcinomas. Paraffin-embedded tissues were deparaffinized and rehydrated prior to being digested with proteinase k overnight at 55° C to isolate DNA. Frozen tissues were digested with 10 mg/mL pronase in 1% sodium dodecyl sulfate in TNE buffer (10 mM TRIS, 150 mM NaCl, and 2 mM EDTA; pH 7.5) overnight at 37° C; DNA was isolated by phenol chloroform extraction and precipitated with ethanol (Marmur, 1961; Sills *et al.*, 1995).

Nested primers were used for amplification of exon 2 of H-*ras* by PCR. The outer primers were 5'-CCA CTA AGC CTG TTG TGT TTT GCA G-3' (forward primer) and 5'-CTG TAC TGA TGG ATG TCC TCG AAG GA-3' (reverse primer). The inner primers (second round of amplification) were 5'-GAC ATC TTA GAC ACA GCA GTT-3' (forward primer) and 5'-GGT GTT GTT GAT GGC AAA TAC-3' (reverse primer). Although the normal sequence of codon 60 is GCT, the forward PCR primer is made with a T at the penultimate 3' base to create the restriction site for Mse1.

A nonradioactive RFLP method was employed to identify CAA-to-AAA mutations in the H-*ras* gene at codon 61 in liver neoplasms (Lee and Drinkwater, 1995). This was based on Mse1 enzyme restriction cutting only the sequence 5'-TTAA-3'. Thus, Mse1 will detect C→A conversion mutation at the first position of codon 61.

Analysis of PCNA and Apoptosis

Detailed methods are included in a report by Nyska *et al*. (1997). Cell proliferation was assessed in nonneoplastic areas of the liver, kidney, and lung by determining a PCNA S-phase labeling index (the percentage of cells in S phase). The identification of apoptotic cells was based on morphologic criteria (Garewal *et al.*, 1996; Goldsworthy *et al.*, 1996) and confirmed immunohistochemically by the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) procedure (Gavrieli *et al.*, 1992).

RESULTS AND DISCUSSION

Identification of *H. hepaticus* Infection in NTP Studies

Determining the extent of *H. hepaticus* infection involved a three-pronged approach of histologic evaluation, silver stains, and PCR-RFLP based assays; all were necessary because of the limitations identified for each. In NTP studies, and as reported in other studies (Ward *et al.*, 1994b), there were no obvious clinical signs of infection, and the only significant histologic lesion (hepatitis) was observed in the liver, primarily in males. Therefore, summary pathology tables were reviewed to identify studies that may have been affected by *H. hepaticus*-associated hepatitis. Male mice from nine studies were identified (Table J1) as having the hepatitis. Eight of the nine studies were begun during a time span of about 6 months (July 1990 to January 1991), while the other study was begun much earlier (October 1988). The hepatitis was not observed in any 13-week studies. Use of histologic evaluation for identification of infected animals has limitations, however. It is somewhat insensitive, as *H. hepaticus* has been cultured and identified by PCR-RFLP methods within livers of animals with no histological evidence of infection (Fox *et al.*, 1998). This may be explained in part by the limited sampling (two liver sections) and the sometimes focal nature of *H. hepaticus*-associated hepatitis. Also, while in the more severely affected animals the hepatitis appears somewhat characteristic, component lesions of the hepatitis are not pathognomonic, and, when the hepatitis is subtle in 2-year old animals, it is more difficult to recognize or attribute to *H. hepaticus*.

Within affected studies, the incidences of the hepatitis in male mice varied from 16% to 78% (Table J1). While generally mild to moderate, the hepatitis varied in severity from barely detectable in some animals to extensive liver involvement and regeneration in others. Only a few females were identified as having the characteristic hepatitis (Table J1). In general, the incidences and severities of *H. hepaticus*-associated hepatitis were similar between control and treated groups. This constellation of nonneoplastic liver lesions, while not pathognomonic, was certainly suggestive of an *H. hepaticus* infection, particularly when observed in control animals. Characteristic lesions included proliferation of oval and/or biliary epithelial cells, hepatocyte enlargement (diagnosed as karyomegaly), and chronic inflammation. In many instances, areas of regenerative hyperplasia were identified within diseased liver.

Helicobacter spp. are not usually observed on routine histologic examination of hematoxylin and eosin-stained sections of liver. The methods for confirmation of infection with *Helicobacter* include Warthin-Starry silver stain or Steiner's modification (Garvey *et al.*, 1985) of this stain for direct microscopic observation of the organisms in tissue; however, this can be a relatively insensitive technique when few organisms are present. In most instances, histologic differentiation between *Helicobacter* species is not possible. Speciation can usually be accomplished with electron microscopy, but this technique is both time consuming and labor intensive. Microbiologic culture of feces, cecal smears, and fresh or frozen liver is also possible. Currently, assays involving amplification of the DNA of the organism using PCR are the most rapid and perhaps the most sensitive methods of detection, and the use of restriction endonucleases has allowed a determination of the species present. PCR-based methods also can be used on feces, cecal contents, or liver homogenates and are most sensitive when using fresh or frozen tissue (Riley *et al.*, 1996; Malarkey *et al.*, 1997).

Using Warthin-Starry silver stains or Steiner's modification on the livers of five or more animals per study, helical bacteria (*Helicobacter*) were identified in animals from the nine affected studies. In some animals, helical bacteria were numerous, suggesting a heavy bacterial burden in these infected animals. However, even in these animals with abundant organisms, few to none were observed in proliferative hepatic lesions such as foci and neoplasms. Helical bacteria were not identified in approximately 25% of males with moderate hepatitis and were rarely identified in males without hepatitis or in females. The absence of identification of helical organisms by silver stains does not preclude infection, nor does the presence of organisms confirm *H. hepaticus*. Based upon current knowledge, however, the characteristic liver lesions in $B6C3F_1$ mice, coupled with the presence of silver-positive helical organisms, are highly suggestive of *H. hepaticus* infection.

As the NTP evaluation evolved, PCR-based assays were developed that appeared more sensitive than histologic evaluation and silver stains for identification and speciation of *Helicobacter*. Therefore, PCR-RFLP-based assays were used to confirm the presence of pathogenic *Helicobacter* (primarily *H. hepaticus*) within the nine affected studies and to determine whether there was *H. hepaticus* infection in other NTP studies. Unfortunately, none of the PCR-based assays had been specifically developed for, or proven reliable for use with, formalin-fixed tissue. Frozen tissue was available from a limited number of animals from a limited number of NTP studies, including only three of the nine affected studies. Furthermore, available frozen liver was almost always limited to tissue from a neoplasm, and, based upon results obtained with silver stains, organisms are generally not readily observed within proliferative hepatic lesions, even when organisms are abundant in adjacent liver tissue. Because the availability of frozen tissue was limited, a PCR-RFLP-based assay was developed and evaluated (Malarkey *et al.*, 1997) for use with frozen or formalin-fixed tissue.

The NIEHS and MU-RADIL laboratories conducted PCR-RFLP-based assays on 32 NTP 2-year studies and three NTP 13-week studies (data not shown); frozen tissues from 22 of the 2-year studies were available. All three bioassays in which hepatitis was identified and for which frozen tissue was available were positive for *H. hepaticus* by the PCR-RFLP-based assays (Table J2). At a third laboratory, *H. hepaticus* was also cultured from the liver tissue of animals in one of these studies (Fox *et al.*, 1998). Formalin-fixed tissues from two of the three studies were evaluated and were also positive; these tissues had been fixed in formalin for less than 48 hours. In the other six affected studies, for which only formalin-fixed tissue was available, *H. hepaticus* was identified in only 1 of 120 animals (Table J2). This decreased sensitivity was considered to be related to the prolonged formalin fixation (Malarkey *et al.*, 1997) rather than proof of an absence of *H. hepaticus*. The presence or absence of *H. hepaticus* apparently cannot be confirmed with current PCR-RFLP-based assays in liver that has been fixed in formalin for long periods (weeks or months). In the three 13-week studies with formalin-fixed tissue, only 1 of 30 animals was positive for *H. hepaticus*.

Within the three affected, PCR-RFLP-positive 2-year studies, *H. hepaticus* was often identified by PCR in frozen livers of mice that had no overt hepatitis. In fact, based upon the combined data from two studies (including PCR results from three laboratories), of 57 animals without characteristic liver lesions, 13 of 24 male mice (54%) and 17 of 33 female mice (52%) were positive for *H. hepaticus*. Furthermore, *H. hepaticus* was identified by PCR in frozen liver of several animals from three "unaffected" studies in which hepatitis typical of that associated with *H. hepaticus* was not observed (Table J2). Apparent variability occurs between various strains of mice and between individual mice from affected studies in developing hepatitis in response to *H. hepaticus* infection. One would assume that, within affected studies, most or all animals have been exposed to the organism, and even animals resistant to developing hepatitis may have organisms within the liver. This assumption is supported by the fact that animals without hepatitis are often positive with PCR-RFLP-based assays. Therefore, although alternative explanations are possible, the three PCR-RFLP-positive studies in which liver lesions are absent are assumed to be true positives. In fact, helical organisms were identified with a silver stain in one animal from one of these studies (Malarkey *et al.*, 1997). Therefore, in addition to assessing the affect of H. hepaticus in the nine affected 2-year

studies, the significance of a positive PCR-RFLP assay for *H. hepaticus* in the absence of liver lesions is also an important question.

Inconsistent Results with PCR-Based Methods

As with any technique, the PCR-RFLP-based assays have limitations even when used to assay fresh and frozen tissue. One assessment of the variability in results of PCR and serologic analyses for *Helicobacter* among three commercial laboratories revealed significant inconsistencies (Dew *et al.*, 1997). Others (J.M. Ward and J. Thigpen, personal communications) have obtained similarly inconsistent results when sending replicate samples to different laboratories. Though the number of samples evaluated by both the NIEHS and MU-RADIL laboratories was limited, there was good, but not complete, correlation of PCR-RFLP results. Also, within the affected studies, the PCR assays were not positive in some animals with liver disease. This result may be explained, in part, by the fact that the only frozen tissues available were neoplasms; as described above, neoplasms are expected to have fewer organisms.

Analysis of *H. hepaticus*-Affected and Unaffected Studies for Incidence of Common Neoplasms

To determine whether the incidences of various neoplasms were different between control groups from affected and unaffected studies, the nine affected studies were compared to 26 unaffected studies begun at relatively similar times (Table J3). There were no statistically significant differences in body weight or survival among the affected and unaffected studies. The neoplasms evaluated represent those that occurred at high enough incidences in various organs for statistically significant differences to be detected. Using multiple regression procedures, male mice in the nine affected studies were demonstrated to have a significantly ($P < 0.05$) increased incidence of only two neoplasm types, both of which were in the liver (hepatocellular neoplasms and hemangiosarcoma), when compared to the unaffected studies. Because of these differences, there was also a corresponding significant difference in the overall incidence of malignant neoplasms (all sites) as well as in the overall proportion of neoplasm-bearing animals. No other tissue site showed a significant difference in the incidence of neoplasms. For female mice, the slightly increased incidence of hepatocellular neoplasms observed in the affected studies was not statistically significant.

This seemingly simple analysis is complicated by several potential confounding variables. There have been coordinate, time-related increases in body weight and in the incidence of liver neoplasms in mice in NTP studies (Haseman, 1992). Table J4 presents the liver neoplasm incidences in relation to the dates the studies began and clearly shows the increases in liver neoplasm incidences and body weights (Seilkop, 1995). In assessing differences in neoplasm incidences between *H. hepaticus*-affected and unaffected studies, the most relevant comparison would be between studies begun at approximately the same time. The starts of 20 of the 26 unaffected studies were clustered near the early part of the time frame (April 1988 to June 1990), while the starts of the affected studies were clustered toward the later end, with eight of the nine studies begun between July 1990 and January 1991; incidences of liver neoplasms in these later studies are expected to be higher based on trends in body weight alone. While the slightly increased incidences of liver neoplasms observed in female control mice in the nine affected studies is likely due to clustering in time, clearly, this alone cannot account for the increased liver neoplasm incidences observed in control male mice in the affected studies (Table J3).

Ideally, unaffected studies used in the above comparison should not only be free of histologic evidence of infection with *H. hepaticus* but should be confirmed as negative by PCR assays. Thirteen of these 26 studies could not be confirmed as negative by PCR because frozen tissue was not available; however, *H. hepaticus*-associated hepatitis was not present in any of the 26 studies. Because these and other data reported to date suggest that hepatitis is associated with neoplasm development in the liver, it seems reasonable to include those 13 studies, unconfirmed by PCR, in this analysis. The majority of the 13 studies confirmed as negative by PCR were begun much earlier than the clearly affected studies, and, therefore, comparing them alone to the nine affected studies is not reasonable. Although not presented here, a number

of comparisons were made with various groupings of studies based on the degree of confidence in their infection status. Although the outcomes of the various comparisons varied somewhat, incidences of hepatocellular neoplasms and hemangiosarcomas of the liver were consistently increased in control male mice from affected studies compared to control males from unaffected studies. Significantly increased liver neoplasm incidences generally were not observed in females. Importantly, the following data corroborate the findings and association with *H. hepaticus* identified in these analyses.

Analysis of Hepatitis-Positive and Hepatitis-Negative Mice for Liver Neoplasm Incidence

Several infectious agents known to be associated with increased incidences of neoplasms cause chronic inflammation in the target tissue or organ. It is commonly hypothesized that this inflammatory process may cause or contribute to the development of neoplasms. One approach to address this was to stratify the mice from the affected studies according to the severity of hepatitis and examine liver neoplasm incidences in relation to these groupings. Thus, animals within the nine affected studies were placed into three groups: 1) animals with mild to moderate hepatitis considered related to *H. hepaticus* infection (+), 2) animals with minimal to mild hepatitis that may have been associated with *H. hepaticus* (±), and 3) animals with no hepatitis that was considered to be associated with *H. hepaticus* (–). Within these groupings, the incidence of liver neoplasms was significantly increased ($P < 0.05$) in males with mild to moderate *H. hepaticus*-associated hepatitis (+) when compared to animals without such hepatitis (Table J5). The neoplasm incidence in animals with minimal lesions (±) was also increased. The liver neoplasm incidence in males without hepatitis (58%) was similar to the incidence (54.8%) in males from the 26 unaffected studies (Table J3). This analysis clearly suggests an association of *H. hepaticus*-associated hepatitis with increased liver neoplasm incidences. Females showed a similar trend, albeit not significant; however, these comparisons are weak because of the low numbers of females with hepatitis.

Analysis of H-*ras* Oncogene Mutations in Liver Neoplasms in Mice from Affected and Unaffected Studies

Liver neoplasms commonly occur in control $B6C3F_1$ mice in 2-year studies. In the historical database of 333 male and female mice with liver neoplasms, 106 (32%) had H-*ras* codon 61 CAA-to-AAA mutations (Maronpot *et al.*, 1995). This historical control database is composed primarily of male data; however, adequate numbers of females have been assayed, and there was no significant difference in the incidences of CAA-to-AAA mutations between males and females.

In an attempt to examine further whether *H. hepaticus* infection had an effect on the development of hepatocellular neoplasms, neoplasms from control male mice from selected affected (NTP, 1998a,b,c) and unaffected (NTP, 1993, 1998h) studies were evaluated for H-*ras* codon 61 CAA-to-AAA mutations (Table J6). Only 6% (2/33) of the hepatocellular neoplasms from control males with hepatitis from three affected studies had this mutation. This percentage is significantly ($P < 0.01$) less than the 32% (11/34) observed in males from the two unaffected studies and less than the 32% (106/333) that occurred in historical control animals. In addition, neoplasms from males without hepatitis from the affected, PCR-positive triethanolamine study (NTP, 1998a) and the unaffected, PCR-positive methyleugenol study (NTP, 1998g) were evaluated; the incidences of mutations in those groups were 3/14 (21%) and 2/17 (12%), respectively.

Neoplasms from control female mice (none had hepatitis) from affected and unaffected studies were evaluated for the CAA-to-AAA mutation (Table J6). The mutation rate was low in both the affected studies (1/25; 4%) and the unaffected study (1/11; 9%) when compared to the 32% observed in the historical control groups.

The finding of a different H-*ras* mutation profile in neoplasms of male mice from affected studies tends to support the association of increased neoplasm incidences with *H. hepaticus*, although there is no mechanistic understanding behind this observation. In a study of *H. hepaticus*-infected A/JCr mice, *ras* mutations were

not detected in the 25 hepatocellular neoplasms analyzed using a PCR/single-strand conformation polymorphism assay (Sipowicz *et al.*, 1997). Because of the low spontaneous rate of liver neoplasms in the A/JCr mouse, there are few or no conclusive data on *ras* mutations in uninfected animals, however. Point mutations at codons 12, 13, and 61 of the Ki-, Ha- and N-*ras* genes were not identified in 45 early gastric carcinomas in humans, whether or not *H. pylori* was present (Craanen *et al.*, 1995). If the increased incidence of hepatocellular neoplasms is associated with hepatitis, as many suspect, then one would expect the neoplasms from animals without hepatitis to have a similar mutational profile as that of the historical controls. The data do not provide a clear answer, because the hepatitis-free males from the affected triethanolamine study (NTP, 1998a) and the males from the methyleugenol study (NTP, 1998g), which were positive by PCR but lacked hepatitis, had mutation frequencies between those of the unaffected controls and the hepatitis-positive mice. Furthermore, mutations in neoplasms from females, none of which had hepatitis, from two affected and one unaffected study were very low compared to the historical controls. These findings were unexpected, and their significance is not understood.

H. hepaticus-Associated Alterations in Cell Kinetics

Studies evaluating cell kinetics were completed to explore further the link between hepatitis and the increased incidence of liver neoplasms (Table J7; Nyska *et al.*, 1997). One of the major objectives was to determine whether there were differences between PCNA labeling indices in the livers of animals with hepatitis from three affected studies, cobalt sulfate heptahydrate, chloroprene, and triethanolamine (NTP, 1998a,b,c), compared to animals without hepatitis, whether from the same three affected studies or from an unaffected study, 1-trans-delta^9-tetrahydrocannabinol (NTP, 1996). Male mice with hepatitis from the three affected studies had a significantly increased ($P < 0.001$) labeling index, with a 24-fold increase over males from the unaffected study and a sixfold increase over males without hepatitis from the same three affected studies (Table J7). The labeling index increase in these mice was substantial and was considered biologically significant. Male mice without hepatitis from the three affected studies had a significantly greater labeling index (increased fourfold) than male mice from the unaffected study (Table J7). The significance of this finding is uncertain, as differences of a similar magnitude were observed in other comparisons. For example, the labeling index of females from the unaffected 1-trans-delta^9-tetrahydrocannabinol study (Table J7; NTP, 1996) was increased fivefold over females from the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (NTP, 1997). Such differences may be within the limits of normal variability for 2-year-old animals.

A second objective of the cell proliferation studies of the liver was to determine if labeling indices were increased in animals from the PCR-positive, hepatitis-negative methyleugenol (NTP, 1998g), scopolamine hydrobromide trihydrate (NTP, 1997), and mouse life-span studies compared to an unaffected PCR-negative and hepatitis-negative 1-trans-delta^9-tetrahydrocannabinol study (NTP, 1996). The scopolamine hydrobromide trihydrate study was evaluated and included in the study by Nyska *et al*. (1997), while the methyleugenol and mouse life-span studies were completed later and are included in Table J7. The labeling indices of males from two of these three studies were almost identical to those of males from the unaffected study. However, the labeling index of males from the mouse life-span study is increased approximately fivefold over that of males from the unaffected study as well as fivefold over the labeling indices of males from the two like studies of scopolamine hydrobromide trihydrate and methyleugenol. This finding suggests that the increase observed in the mouse life-span study is not attributable to the presence of *H. hepaticus*, as two other studies also positive for *H. hepaticus* did not show a similar increase.

The cell proliferation data for the liver from NTP studies are consistent with data from a study by Fox *et al*. (1996) in which cell proliferation indices were evaluated at 8, 10, and 13 months in the A/JCr mouse, which is generally believed to be more susceptible to *H. hepaticus*-associated hepatitis than the B6C3F$_1$ mouse. In the study by Fox *et al*. (1996), cell proliferation rates were significantly increased at all time points in males. Some increases were observed in females in that study but did not reach statistical significance. An increased

incidence of hepatocellular neoplasms was observed only in the males. Though liver lesions were observed in females in that study, they were less severe than those in males.

In addition to the liver, cell proliferation indices (PCNA) were evaluated in the kidneys and lungs of male and female mice in affected studies versus those in unaffected studies (Nyska *et al.*, 1997). No apparent effect of *H. hepaticus* infection or the presence of hepatitis on PCNA indices was observed for the kidneys or lungs.

Apoptosis (programmed cell death) is another important parameter in evaluations of cell kinetics. The apoptotic index in the liver of male mice with hepatitis from an affected study, cobalt sulfate heptahydrate (NTP, 1998b), was significantly ($P < 0.01$) greater than that observed in males from the unaffected 1-trans-delta^9-tetrahydrocannabinol study and the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (Nyska *et al.*, 1997). For females, there were no significant differences among the three studies.

Two 13-week studies which were begun during the same time as the nine affected studies were randomly selected for evaluation of PCNA indices. *H. hepaticus* was not identified in either of the studies by PCR-RFLP; however, as with all NTP 13-week studies, only tissue fixed in formalin for an unspecified period was available. Because of this, no true negative control group was available; therefore, the labeling index of these 19- to 20-week-old animals was compared to values cited in the literature (Eldridge and Goldsworthy, 1996) for 20-week-old B6C3F$_1$ mice. The labeling index in the NTP studies clearly was not increased (data not shown).

The Impact of *H. hepaticus* on the Interpretation of 2-Year Carcinogenesis Studies

Increases in the incidences of neoplasms are associated with a number of infectious agents. The chronic inflammation caused by these agents has been hypothesized to be important in the pathogenesis of the increased neoplasm incidences (e.g., gastric cancer associated with *H. pylori*). The increased incidences of liver neoplasms in male mice from the nine affected NTP studies were observed in the animals with *H. hepaticus*-associated hepatitis. Neoplasms from males with hepatitis tended to have an H-*ras* mutation profile different from that of animals from unaffected studies. Further, cell replication rates at 2 years were significantly higher in males with hepatitis compared to those in males without hepatitis. The data suggest that *H. hepaticus*-associated hepatitis is associated with the increased incidences of liver neoplasms in the male B6C3F$_1$ mouse. Therefore, the most important consideration in evaluating the impact of *H. hepaticus* infection on the interpretation of study results appears to be the presence or absence of significant hepatitis.

For any carcinogenicity study, data within and specific to the individual study provide the greatest basis for an accurate interpretation. However, it is prudent to consider and evaluate all data or information which may affect the interpretation. Based upon the data presented in this and other reports, general guidelines emerge that may be useful in interpreting potential chemical-associated carcinogenic effects in *H. hepaticus*-infected B6C3F$_1$ mice. In a study with sufficient evidence of *H. hepaticus*-associated hepatitis (> 10% of the animals having the characteristic hepatitis may be a reasonable guideline), interpretation of increased incidences of liver neoplasms (hepatocellular neoplasms and hemangiosarcoma) of male mice is considered to be potentially confounded.

Altered chemical uptake and metabolism, due to the intestinal load of *H. hepaticus* and to *H. hepaticus*-associated liver disease, respectively, are possible reasons for considering that the male mouse response to chemical administration at sites other than the liver should also be considered confounded. Data do not currently exist that definitively answer this question. In this group of nine studies, however, there is no evidence to suggest that affected mice responded to chemical treatment in organs other than the liver in a manner different from mice in nonaffected studies. Within each study, there was excellent concordance in chemical-associated neoplasms between the male mice and the females, which had little or no hepatitis

(Table J8). Furthermore, analyses indicate that *H. hepaticus* is not associated with neoplastic responses outside the liver; incidences of neoplasms at sites other than the liver were not different between control groups from affected and unaffected studies (Table J3). Cell replication rates in two major organs (lung and kidney) also were not increased in control groups from affected studies compared to those from unaffected studies.

One of the more difficult issues to address is whether interpretation of a treatment-related increase in liver neoplasm incidences in the female mouse is confounded when *H. hepaticus*-associated hepatitis is present within the male mice in the study. Most evidence to date links hepatitis with the increased liver neoplasm incidences observed in males, and female $B6C3F_1$ mice in affected studies do not have significant hepatitis at 2 years. The lack of hepatitis in females, however, is based on an analysis in which only late time points were evaluated histologically. Therefore, it is conceivable that hepatitis along with increased cell proliferation could have occurred earlier and resolved by 18 months to 2 years. Data collected to date, however, suggest that *H. hepaticus*-associated hepatitis is a late-developing and persistent disease in the $B6C3F_1$ mouse. *H. hepaticus*-associated hepatitis has never been observed in any NTP 13-week studies, including five begun during the same 6-month time span as eight of the nine affected 2-year studies. Also, within affected 2-year studies, more males (51%) that were 18 to 24 months of age had hepatitis than those (34%) that were 12 to 18 months of age. This is consistent with a report by Ward *et al.* (1994b) that *H. hepaticus*-associated liver lesions are not observed at early time points in the $B6C3F_1$ mouse.

Nonetheless, within affected studies, female control mice did have a slightly elevated incidence of liver neoplasms when compared to control mice from unaffected studies, and the data derived from the H-*ras* mutation frequency analysis were inconclusive. The possibility that *H. hepaticus*-infected female mice from affected studies may respond differently to a liver carcinogen than mice from unaffected studies cannot be eliminated at this time. However, because within an affected study hepatitis is observed only rarely in females, until definitive data suggest otherwise, it is concluded that the interpretation of an apparent chemical-induced neoplastic effect in the liver of female mice is not confounded. To censor the few females with *H. hepaticus*-associated hepatitis from any statistical analyses of hepatocellular neoplasms would be prudent. Studies in the ostensibly more sensitive A/JCr mouse (Fox *et al.*, 1996) also showed significant increases in neoplasm incidences and cell proliferation rates in the liver of *H. hepaticus*-infected males, but not females.

Another concern is how to interpret possible chemical-related effects in a study in which the status of *H. hepaticus* infection cannot be determined by PCR-RFLP because only tissues fixed in formalin for more than 48 hours are available. While histologic evaluation is inadequate to identify infection, it appears adequate for identifying hepatitis severe enough to alter the outcome of the study. Therefore, in the absence of significant histologic evidence of *H. hepaticus*-associated hepatitis, the outcome of a 2-year study should not be considered potentially compromised.

The causality between *H. hepaticus* infection and neoplasia has not been proven in the $B6C3F_1$ mouse in these studies, nor has the mechanism of this association been determined; further studies are needed. However, sufficient information exists to make reasonable scientific judgments relative to the interpretation of data from the nine 2-year carcinogenicity studies in the $B6C3F_1$ mouse. Refinements to the above interpretive positions may occur if warranted by future information.

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TABLE J1
Incidence of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine NTP 2-Year Studies[a]

Study	Incidence of Hepatitis (%)	
	Males	Females
Sodium xylenesulfonate	78	4
AZT/5,000 U α-interferon A/D	76	4
Cobalt sulfate heptahydrate	72	8
AZT/500 U α-interferon A/D	66	0
Chloroprene	54	0
Theophylline	32	0
α-Interferon A/D	22	4
Triethanolamine	20	0
AZT	16	2
Average	48	2

[a] Includes regeneration and mild to marked (excludes minimal) chronic inflammation, karyomegaly, oval cell hyperplasia, and bile duct hyperplasia. AZT=3′-azido-3′-deoxythymidine

TABLE J2
Identification of *Helicobacter hepaticus* with PCR-RFLP-Based Assays in Control B6C3F$_1$ Mice from 32 NTP 2-Year Studies and Three NTP 13-Week Studies[a]

Type of Sample	Total Studies	*H. hepaticus*-Positive Studies[b]	
		Affected Studies	Unaffected Studies
13-Week Studies			
Formalin-fixed liver	3	—	1/3[c]
2-Year Studies			
Frozen liver	22	3/3	3/19
Formalin-fixed liver	10	1/6[c]	0/4

[a] PCR-RFLP=polymerase chain reaction-restriction fragment length polymorphism
[b] Number of *H. hepaticus*-positive studies/number of affected or unaffected studies. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[c] Only one animal in the positive study was positive for *H. hepaticus*.

TABLE J3
Comparison of Neoplasm Incidences in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

	Males		Females	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Number of studies	9	26	9	26
Survival (%)	64	71	68	68
12-Month body wt (g)	48.0	48.3	48.1	47.0
Neoplasm incidence (%)				
Liver	71.3*	54.8	50.3	40.5
Lung	26.6	23.2	7.6	10.3
Pituitary gland	0.4	0.8	14.7	14.3
Harderian gland	5.6	6.1	6.0	4.9
Lymphoma	6.9	6.3	16.2	15.5
Circulatory system	9.8	6.0	5.3	4.7
liver only	7.1*	2.5	—	—
All benign	61.8	57.2	59.1	54.6
All malignant	61.3*	40.9	50.0	44.2
All neoplasms	88.0*	77.4	82.7	75.4

* Significantly different ($P \leq 0.05$) from the unaffected studies
[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE J4
Liver Neoplasm Incidences and Body Weights of Control B6C3F$_1$ Mice in Relation to Study Start Dates of *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies[a]

Study Start Date	Liver Neoplasm Incidence (%)		Mean Body Weight (g)	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Male				
April to September 1988	—	43.8 (8)[b]	—	46.2 (8)
October 1988	62.0 (1)	—	48.3 (1)	—
November 1988 to September 1989	—	52.6 (7)	—	48.7 (7)
October 1989 to June 1990	—	61.2 (5)	—	48.9 (5)
July 1990 to January 1991	72.5 (8)	66.2 (4)	48.0 (8)	49.0 (4)
February 1991 to April 1992	—	68.0 (2)	—	52.8 (2)
Average	71.3	54.8	48.0	48.3
Female				
April to September 1988	—	31.1 (8)	—	44.8 (8)
October 1988	46.0 (1)	—	46.4 (1)	—
November 1988 to September 1989	—	39.9 (7)	—	47.2 (7)
October 1989 to June 1990	—	38.6 (5)	—	45.9 (5)
July 1990 to January 1991	50.9 (8)	54.2 (4)	48.3 (8)	48.0 (4)
February 1991 to April 1992	—	58.0 (2)	—	55.6 (2)
Average	50.3	40.5	48.1	47.0

[a] Includes nine affected studies (those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice) and 26 unaffected studies
[b] Number of studies is given in parentheses.

TABLE J5
Association of Liver Neoplasm Incidence and Severity of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine Affected NTP 2-Year Studies[a]

Severity of Hepatitis	Liver Neoplasm Incidence	
	Males	Females
Absent	101/175 (58%)	196/396 (49%)
Minimal	44/57 (77%)	23/42 (55%)
Mild/moderate	176/218 (81%)	7/11 (64%)
Significance of association	$P < 0.05$	NS[b]

[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[b] NS=not significant

TABLE J6
H-*ras* Codon 61 AAA Mutations in Spontaneous Liver Neoplasms in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

Study	Affected[a]	H-*ras* AAA Mutations
Male		
Cobalt sulfate heptahydrate	+	0/10 (0%)
Chloroprene	+	1/13 (8%)
Triethanolamine	+	1/10 (10%)
Oxazepam	—	7/18 (39%)
Diethanolamine	—	4/16 (25%)
Historical control database		106/333 (32%)
Female		
Chloroprene	+	0/10 (0%)
Triethanolamine	+	1/15 (7%)
Diethanolamine	—	1/11 (9%)
Historical control database		106/333 (32%)

[a] +=affected; —=not affected. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE J7
Proliferating Cell Nuclear Antigen Labeling Indices in the Liver of Control B6C3F$_1$ Mice[a]

	Hepatitis	No. of Animals	PCNA Labeling Index[b]	Average PCNA Labeling Index[c]
Male				
Cobalt sulfate heptahydrate[d]	+	15	0.535 ± 0.129	
Chloroprene[d]	+	12	1.452 ± 0.386	
Triethanolamine[d]	+	9	1.215 ± 0.374	1.011
Cobalt sulfate heptahydrate	—	7	0.175 ± 0.117	
Chloroprene	—	10	0.296 ± 0.124	
Triethanolamine	—	12	0.100 ± 0.042	0.186
1-Trans-delta^9-tetrahydrocannabinol[e]	—	15	0.042 ± 0.011	
Scopolamine hydrobromide trihydrate[f]	—	14	0.043 ± 0.012	
Methyleugenol[f]	—	14	0.077 ± 0.020	
Mouse life-span study[f]	—	15	0.217 ± 0.880	
Female				
Cobalt sulfate heptahydrate	+	5	0.161 ± 0.062	
Cobalt sulfate heptahydrate	—	17	0.055 ± 0.015	
Chloroprene	—	12	0.154 ± 0.050	
Triethanolamine	—	12	0.138 ± 0.053	0.108
1-Trans-delta^9-tetrahydrocannabinol	—	13	0.156 ± 0.047	
Scopolamine hydrobromide trihydrate	—	15	0.032 ± 0.009	

[a] A portion of these data are presented in Nyska *et al*. (1997). +=hepatitis present; —=no hepatitis present
[b] Mean ± standard error; PCNA=proliferating cell nuclear antigen
[c] Average of the mean labeling indices for animals from all three studies
[d] Affected study (one in which hepatitis typical of that associated with *H. hepaticus* occurred in many male mice)
[e] Unaffected study (one in which the typical hepatitis did not occur in mice)
[f] Unaffected study with no typical hepatitis, but positive for *H. hepaticus* by polymerase chain reaction-restriction fragment length polymorphism-based assay

TABLE J8
Summary of Target Sites of Carcinogenicity in B6C3F$_1$ Mice from NTP 2-Year Studies with *Helicobacter hepaticus*-Associated Hepatitis

	Males	Females
Chloroprene	Lung Circulatory system[a] Harderian gland Forestomach Kidney	Lung Circulatory system Harderian gland Forestomach Liver Skin Mesentery Zymbal's gland Mammary gland
Cobalt sulfate heptahydrate[b]	Lung	Lung
Triethanolamine	Liver	Liver
AZT[c]	None	Vagina
Sodium xylenesulfonate	None	None
Theophylline	None	None

[a] Hemangioma and hemangiosarcoma of the liver were excluded from the analysis in males.
[b] An apparent treatment-related increase in the incidence of hemangiosarcoma of the liver was discounted in male mice because of the presence of *H. hepaticus*.
[c] AZT=3′-azido-3′-deoxythymidine. Includes four studies: AZT; α-interferon A/D; AZT/500 U α-interferon A/D; and AZT/5,000 U α-interferon A/D