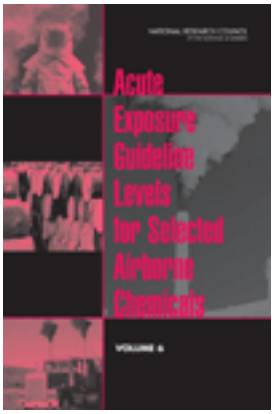

Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6

Committee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 6

Committee on Acute Exposure Guideline Levels

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the sixth volume in the

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for allylamine, ammonia, aniline, arsine, crotonaldehyde, *trans* and *cis* + *trans*, 1, 1-dimethylhydrazine, 1, 2-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Deepak K. Bhalla, Wayne State University; David W. Gaylor, Gaylor and Associates, LLC; and Samuel Kacew, University of Ottawa.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Robert Goyer, University of Western Ontario (Emeritus). Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

After the review of the draft was completed, the committee evaluated AEGLs that were developed for 8 metal phosphides. Because the acute toxicity of metal phosphides results from the phosphine generated from hydrolysis of the metal phosphides, their AEGL values are likewise based upon phosphine AEGLs. Therefore Chapter 10 of this report was expanded to present AEGL values for phosphine and the metal phosphides. We wish to thank Ian Greaves, University of Minnesota, and Wallace Hayes, Harvard School of Public Health, for their review of this revised chapter. The review was overseen by Samuel Kacew.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.); Cheryl Bast, Sylvia Talmage, Robert Young, and Sylvia Milanez (all from Oak Ridge National Laboratory). We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. Other staff members who contributed to this effort are Raymond Wassel (senior program officer), Aida Neel (program associate), Ruth Crossgrove (senior editor), Radiah Rose (senior editorial assistant), and Mirsada Karalic-Loncarevic (manager, Technical Information Center). The committee particularly acknowledges

Kulbir Bakshi, project director for the committee, for bringing the report to completion. Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

William E. Halperin, *Chair*
Committee on Toxicology

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Introduction

This report is the sixth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety and Health in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 hour (h), and

only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November1995 the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from in vivo and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in

laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or exert multiple effects, all endpoints (including reproductive (in both genders), developmental, neurotoxic, respiratory, and other organ-related effects are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, the EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports.

Thus far, the committee has prepared five reports in the series Acute Exposure Guideline Levels for Selected Airborne Chemicals (NRC 2001b, 2002, 2003, 2004, 2007). This report is the sixth volume in that series. AEGL documents for allylamine, ammonia, aniline, arsine, crotonaldehyde, cis/trans-, crotonaldehyde, trans-iso, 1, 1-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides are each published as an appendix to this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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9

Nickel Carbonyl[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population, including infants and children and other individuals who may be sensitive and susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

[1]This document was prepared by AEGL Development Team member Robert Young of Oak Ridge National Laboratory and Ernest Falke (Chemical Manager) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC). The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993; 2001).

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Nickel carbonyl, formed by the reaction of carbon monoxide with metallic nickel, is used in nickel refining, in the synthesis of acrylic and methacrylic esters, and for other organic synthesis. In air, nickel carbonyl rapidly decomposes to metallic nickel and carbon monoxide with a 50% decomposition at room temperature and total decomposition at 150-200 C. Its decomposition is inversely proportional to the concentration of carbon monoxide; in the absence of carbon monoxide, decomposition may occur in approximately 1 min. Thus, potential exposure to the parent nickel carbonyl is limited by its rapid conversion to airborne metallic nickel.

Human data are limited to case reports, primarily of nickel workers, that affirm the extreme toxicity of the compound. Definitive exposure terms are lacking in these reports. Available information suggests that there are very limited or no warning properties associated with exposure to nickel carbonyl. Significant signs and symptoms of toxicity are known to occur in the absence of recognizable odor. Human case studies have shown that a latency period often occurs between initial signs of toxicity and subsequent serious effects that may progress to death. The primary target of nickel carbonyl-induced acute toxicity appears to be the lungs, although extra pulmonary involvement also has been reported. The specific mechanism of toxicity is unclear but appears to involve damage to pulmonary tissue.

Animal data are limited to lethality and developmental toxicity. Lethality values (LC_{50}) are available for rats, mice, cats, and rabbits. Thirty-minute LC_{50}

values for these species range from 33.6 to 266 ppm. These lethality data indicate notable species variability in the lethal response to inhaled nickel carbonyl; smaller species are generally more sensitive. Developmental toxicity has been demonstrated in rats and hamsters following single 30-min (11.2-42 ppm, rats) or 15-min (8.4 ppm, hamsters) exposures of dams during gestation. In hamsters, developmental toxicity was observed in dams following lethal or near-lethal exposures. In rats, developmental toxicity was observed in offspring of dams that were exposed to nonlethal concentrations of nickel carbonyl. Because information on the health status of the rat dams was not provided, it was not possible to determine the relative maternal versus fetal sensitivity to nickel carbonyl challenge.

Epidemiologic data do not support the contention that inhalation of nickel carbonyl is carcinogenic to humans. Studies of respiratory tract cancer in nickel workers suggest that nickel dusts, nickel sulfide, and nickel subsulfide may be more relevant than nickel carbonyl and that nickel carbonyl is not a likely causative agent in the carcinogenicity observed in nickel refinery workers. Limited data for rats have provided equivocal evidence of pulmonary carcinogenicity following acute or long-term exposure to nickel carbonyl. Data are unavailable for a quantitative assessment of the carcinogenic potential of nickel carbonyl in humans or animals.

Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a temporal scaling factor (n) was not possible. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

Neither human nor animal data are available for deriving AEGL-1 values. Both human and animal data affirm the extreme toxicity of nickel carbonyl. Published accounts of human exposures indicate that symptoms of toxicity can occur in the absence of olfactory or other sensory detection. Severe pulmonary edema and hemorrhage can follow initial asymptomatic exposures by as much as 12 h after exposure. Therefore, AEGL-1 values are not recommended.

Teratogenicity and fetotoxicity findings in rats and hamsters following lethal or near-lethal exposures have been reported. No human data are available that specifically identify effects consistent with AEGL-2.

AEGL-2 values for nickel carbonyl were developed based on a 30-min exposure of mice to 2.17 ppm (Kincaid et al. 1953). A concentration-dependent lethal response was observed for exposures to 6.51-12.6 ppm, but the lowest concentration (2.17 ppm) resulted in no deaths. Exposure to 6.51 ppm resulted in the deaths of two of 15 mice, and a 30-min LC_{50} of ~9.4 ppm was estimated by the investigators. Although no histopathology examinations were performed on the mice in the 2.17-ppm group, Kincaid et al. and Barns and Denz (1951) reported findings of pleural effusion, severe pulmonary congestion, and pulmo-

nary edema for rats that died following exposure to nickel carbonyl. Therefore, the 30-min exposure to 2.17 ppm was considered a reasonable estimate of an exposure that might cause pulmonary damage in the mouse (the most sensitive species tested) but not result in irreversible adverse effects. As shown by the multiple-exposure studies of Kincaid et al., repeated exposures of mice to this or greater concentrations did not result in a lethal response. Pulmonary damage appears to be a component in the continuum of the toxic response to nickel carbonyl and an appropriate critical effect for AEGL-2 development. The available lethality data suggest that the mouse represents a sensitive species. Based on this and the analysis conducted by Kincaid et al. indicating an inverse relationship between lethality and body size, the interspecies uncertainty factor of 3 appears to be justified. Although intraspecies variability is difficult to assess based on available data, an uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. Occupational exposure data suggest that the AEGL-2 values are sufficiently protective. A modifying factor of 3 was applied in the development of the AEGL-2 values to account for data deficiencies regarding AEGL-2 specific effects and the possibility of developmental toxicity.

AEGL-3 values were derived based on an estimated lethality threshold in mice (3.17 ppm) exposed to nickel carbonyl for 30 min (Kincaid et al. 1953). Lethality data were available for several species (rats, mice, rabbits, and cats). A total uncertainty adjustment of 10 was applied (each uncertainty factor of 3 is the approximate logarithmic mean of 10, which is 3.16; hence, $3.16 \times 3.16 = 10$). Analysis of the available data indicated that the mouse was the most sensitive species and that larger species tended to be less sensitive. Because data from the most sensitive species were used and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion the uncertainty adjustment between inter- and intraspecies.

Limited data suggest the development of pulmonary tumors in rats inhaling nickel carbonyl. There are equivocal findings suggestive of a tumorigenic response following a single massive exposure of rats to nickel carbonyl. However, a valid quantitative cancer risk assessment is not currently feasible for a single acute exposure. Although some nickel compounds (nickel subsulfide and nickel refinery dust) are considered human carcinogens based on animal data and epidemiological studies, other nickel compounds including nickel carbonyl are considered potential human carcinogens based on limited animal data. The human carcinogen classification is based on animal data and evaluations of epidemiologic data showing an increased risk of pulmonary and sinonasal cancers in nickel refinery workers with exposure to nickel refinery dust, which is primarily nickel subsulfide (EPA 1991). No quantitative carcinogen risk assessment has been conducted for nickel carbonyl due to deficiencies in the available data. Evaluations of epidemiological studies by Doll (1984) and CEC (1990) concluded that nickel carbonyl was an unlikely contributor to the increased risk

of sinonasal cancers in the nickel refinery workers. Therefore, cancer risk was not the basis for AEGL development. The AEGL values and toxicity end points are summarized in Table 9-1.

1. INTRODUCTION

Nickel carbonyl, formed by the reaction of carbon monoxide with metallic nickel, is used in nickel refining, in the synthesis of acrylic and methacrylic esters, and for other organic syntheses (Antonsen 1978; Budavari et al. 1996). Additionally, the compound is used in vapor deposition plating to increase the durability of injection molds for automotive parts (EPA 2002). Although frequently listed as a site-limited intermediate, on-site storage by some users have listed up to 900 pounds of nickel carbonyl (EPA 2002). Upon heating to 200° C, nickel carbonyl decomposes to pure nickel and carbon monoxide, a reaction referred to as the Mond process (Goyer 1991). In air at room temperature, 50% of nickel carbonyl rapidly decomposes to nickel and carbon monoxide. At temperatures of 150-200°C, 100% degradation may occur (Vuopola et al. 1970). The rate of decomposition is inversely dependent on the carbon monoxide concentration; in the absence of carbon monoxide, nickel carbonyl will completely decay in about 1 min (Stedman et al. 1980). An odor threshold of 0.5-3 ppm has been reported for humans but not validated (AIHA 1989). Some inhaled nickel carbonyl is eliminated via expired air, the remainder may dissociate to Ni^0, subsequently oxidized to Ni (II) and released into the blood serum, where it may bind to albumin and nickel-binding substances and be cleared via the kidneys. Nickel carbonyl will, however, damage Type I and Type II alveolar cells of the lungs and may induce pulmonary edema and chemical pneumonitis. Physicochemical data for nickel carbonyl are shown in Table 9-2.

TABLE 9-1 Summary of AEGL Values for Nickel Carbonyl (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.10 (0.69)	0.072 (0.50)	0.036 (0.25)	0.0090 (0.063)	0.0045 (0.031)	NOAEL for severe pulmonary damage in mice; 2.17 ppm, 30 min (Kincaid et al. 1953).
AEGL-3 (lethal)	0.46 (3.2)	0.32 (2.2)	0.16 (1.1)	0.040 (0.27)	0.020 (0.14)	Estimated mouse lethality threshold (LC_{01} of 3.17 ppm; (Kincaid et al. 1953).

Note: Numerical values for AEGL-1 are not recommended because of the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.
Abbreviations: NR, not recommended; NOAEL, no-observed-adverse-effect level.

TABLE 9-2 Physical and Chemical Data

Property	Descriptor or Value	Reference
Synonyms	Nickel tetracarbonyl	Budavari et al. 1996
Common name	Nickel carbonyl	
Chemical formula	C_4NiO_4	Budavari et al. 1996
Molecular weight	170.73	Budavari et al. 1996
CAS Registry No.	13463-39-3	Budavari et al. 1996
Physical state	Liquid	Budavari et al. 1996
Vapor pressure	28.7 kPa at 20°C 400 mm at 25.8°C	Antonsen 1978 Sax and Lewis 1989
Density	1.318 at 17°C	Budavari et al. 1996
Boiling/melting point	43°C/–19.3°C	Budavari et al. 1996
Solubility	Miscible with organic solvents, soluble to about 5,000 parts in water.	Antonsen 1978; Budavari et al. 1996
Conversion factors in air	1 mg/m^3 = 0.14 ppm 1 ppm = 6.9 mg/m^3	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Nickel carbonyl is known to exhibit extreme toxicity in humans following acute exposure (Antonsen 1978; Budavari et al. 1996; Sunderman 1989; Goyer 1991). Nickel carbonyl is generally considered the most toxic form of nickel (Ellenhorn 1997) and upon inhalation produces both respiratory tract and systemic effects (Shi 1994a). Individuals poisoned by acute exposure to nickel carbonyl exhibit immediate and delayed effects (Kincaid et al. 1953). The acute lethality of nickel carbonyl in humans is well documented (Sunderman 1989; Kurta et al. 1993; Ellenhorn 1997). Lethality appears to be attributed to neurologic and respiratory effects (Sunderman 1989; Kurta et al. 1993).

Several reports are available that document lethal exposure to nickel carbonyl. Sunderman (1989) reported on the exposure of over 100 workers to nickel carbonyl at a Port Arthur, Texas, petroleum refining facility. Thirty-one experienced acute signs and symptoms of toxicity (headache, sternal and epigastric pain, nausea, vomiting, chest constriction, shortness of breath, hacking and unproductive cough, extreme weakness, fatigue), and two subsequently died. Case-specific data were not reported, but pneumonitis, respiratory difficulties (cough, shortness of breath, chest constriction) and neurological signs (convulsions, confusion) were associated with those individuals with severe or lethal

poisoning. It was noted that the signs and symptoms of poisoning could be categorized as immediate or delayed (latency of 1-5 days). The onset of severe symptoms varied from 10 h to 6 days. Convalescence was protracted and the administration of 2,3-dimercaptopropanol was attributed with saving the lives of some of the victims. Kincaid et al. (1956) estimated the human LC_{50} as 3 ppm, and Vuopola et al. (1970) noted that atmospheric concentrations of 30 ppm of nickel carbonyl are probably immediately fatal to humans.

The limited acute lethality values for inhalation exposure of humans to nickel carbonyl are summarized in Table 9-3.

2.2. Nonlethal Toxicity

Shi (1986) reported on 179 cases of nonlethal occupational exposure to nickel carbonyl. Exposure times varied from <30 min to >2 h. The report was primarily a qualitative analysis of the documented exposures. No specific exposure concentration or exposure duration data were provided regarding the signs and symptoms discussed, and therefore there were no data useful for derivation of AEGL values. Exposures were categorized as mild, moderate, or severe based on many clinical signs and symptoms. The onset of signs and symptoms varied from a few minutes to several hours to as long as a week following exposure and included respiratory system, nervous system, digestive tract, and cardiovascular effects. In analyzing the toxic responses in the 179 cases, Shi (1994a) found that there was an immediate stage lasting 4-5, followed by a remission of approximately 12 h that may extend to 2-3 days. The immediate phase was characterized by neurologic disorders and upper-airway irritation, while the delayed phase was generally characterized by chest pain, cough and dyspnea, palpitation, fever, leukocytosis, and some X-ray abnormalities (irregular linear shadow, expansion and increased density of the hilus, diffuse irregular nodular mottling or patchy shadows). The delayed onset of toxicity is consistent with what is observed in animal models.

Sunderman (1992) provided information on the results of a study involving 156 male workers accidentally exposed to nickel carbonyl at the Toa Gosei Chemical plant in Nagoya, Japan. Of the workers exposed, 137 exhibited symptoms of poisoning, but no fatalities occurred, due in part to treatment of the workers with Antabuse and Dithiocarb (diethyldithiocarbamate). Exposure terms were unavailable, but the report served to identify major medical findings for the exposed workers. These included abnormal liver function, renal insufficiencies, skin lesions, abnormal densities in pulmonary x-rays, and symptoms of encephalopathy.

An acute case of nickel carbonyl poisoning involving inhalation and dermal exposure was reported by Kurta et al. (1993). Although exposure terms were unavailable, the report provided a clinical picture of nickel carbonyl poisoning and its outcome following antidote therapy with disulfiram and diethyl-

TABLE 9-3 Acute Lethality of Nickel Carbonyl in Humans

Acute Lethality Value	Reference
30-min LC_{50}: 3 ppm (Estimated)	Kincaid et al. 1956
30 ppm: Immediately Fatal (Estimated)	Vuopola et al. 1970

dithiocarbamate. Twenty-four hours after the exposure, urinary nickel levels were 172 µg/dL (normal is <5 µg/dL). The 46-year-old subject initially experienced headache, chest pains, shortness of breath, and weakness. The subject was aggressively treated with oxygen and other supportive and prophylactic therapy (e.g., antibiotics) as well as disulfiram and diethyldithiocarbamate. An 18-day hospital stay was required, but upon discharge pulmonary function was still moderately impaired.

In a report by Sunderman (1990) on clinical management of nickel carbonyl poisoning with Dithiocarb, reference was made to the inability of human subjects to detect low concentrations of nickel carbonyl. Results of experiments in which six human subjects smelled "whiffs" of 0-5 ppm of nickel carbonyl (no specific exposure durations were provided) were highly variable, with some individuals acknowledging detection of the compound and others being unaware of any odor. The results suggested that nickel carbonyl is unlikely to be detected at low concentrations, especially by those unfamiliar with it.

2.2.1. Epidemiologic Studies

Shi et al. (1986) conducted a study in which serum monoamine oxidase (SMAO) activity and electroencephalograms (EEGs) were evaluated in male and female nickel carbonyl workers. Group A contained 42 workers (average age, 36.2) with 10-20 years of work; Group B had 36 individuals (average age, 29.1) with 2-8 years of work; and Group C included 40 individuals (average age, 28.4) with no possible exposure to nickel carbonyl. It was noted that the average concentration of nickel carbonyl in the work area was 0.007-0.52 mg/m^3 (equivalent to 0.0009-0.073 ppm). Results of the study revealed statistically significant (t-test) decreases in SMAO activity with longer exposure durations. Incidences of abnormal EEGs were significantly increased with longer exposure durations. Although these findings demonstrate nonlethal effects following long-term, low-level exposure to nickel carbonyl, extrapolation to acute exposure situations would be uncertain.

More recently, Shi (1994b) conducted a study of lung function in workers occupationally exposed to nickel carbonyl for 2-20 years. The study groups included workers exposed to nickel carbonyl over 18.6 years (men), 16.6 years (women), 2.5 years (men), or 3.8 years (women). The nickel carbonyl concentration at the workplace, as determined by gas chromatography, ranged from 0.007 to 0.52 mg/m^3 (0.00098-0.072 ppm). Unexposed workers served as controls. For

male workers exposed for more than 14 years and for female workers exposed for more than 10 years, statistically significant ($p < .05$ to $p < .001$) alterations in several lung function measures were noted. For those workers exposed for lesser durations, considerably fewer parameters were altered. Although inadequate for the derivation of AEGL values, the results of this study show that long-term exposure to nickel carbonyl at concentrations of 0.00098-0.072 ppm may affect respiratory function but are not life threatening.

2.3. Reproductive/Developmental Toxicity

Data regarding the reproductive/developmental toxicity of nickel carbonyl in humans were not available.

2.4. Genotoxicity

Decheng et al. (1987) analyzed data from workers occupationally exposed to nickel carbonyl and found no increase in the frequency of chromosomal aberrations but that nickel carbonyl appeared to act synergistically with cigarette smoke in increasing the frequency of sister chromatid exchange in peripheral lymphocytes.

Cytogenetic measurements were evaluated by Shi (1992) in 64 workers (19-48 years old) exposed to nickel carbonyl (0.0043-0.026 mg/m^3; 0.0006-0.0036 ppm) over a period of 10 years. Compared to unexposed workers, the incidences of chromosomal anomalies in peripheral lymphocytes were significantly increased ($p < .01$ to $p < .05$). Anomalies included "teratogenized" cells, chromatic aberrations, chromosomal aberrations, breakage and deletion, sister chromatid exchanges, and increased micronuclei frequency. An increase in dyskaryotic cells in the sputum was also found to be significant ($p < .01$) in workers exposed to nickel carbonyl compared to unexposed workers.

2.5. Carcinogenicity

In an unpublished study (cited in Morgan 1992) using data from the Clydach, Wales, refinery, pulmonary cancer deaths in a group of 69 men occupationally exposed to nickel carbonyl vapor did not exceed those of unexposed workers based on an age-specific status (see Table 9-4). It was not specified if the analysis was adjusted for cigarette smoking or other confounding factors, and definitive exposure data were not available.

IARC (1987) considers nickel and nickel compounds as Group 1 carcinogens (sufficient evidence in humans and animals) and U.S. Environmental Protection Agency (EPA) has classified both nickel subsulfide and nickel refinery

TABLE 9-4 Mortality Data for 69 Workers Occupationally Exposed to Nickel Carbonyl (1933-1964)

Disease Group	Expected	Observed	SMR[a]
All causes	35.8	38	106
Pulmonary cancer	3.9	6	152

[a]Standard mortality ratio; $p > .05$.

dust as human carcinogens (EPA 1991). These assessments are based primarily on epidemiologic data showing an increased risk of pulmonary and sinonasal cancers in nickel refinery workers exposed to nickel refinery dust (which is primarily nickel subsulfide). Nickel carbonyl is considered a potential human carcinogen, although a quantitative assessment has not been conducted due to insufficient data (EPA 1991). However, Doll (1984) and CEC reported that nickel carbonyl was considered an unlikely contributor to the increased risk of sinonasal cancers in the nickel refinery workers. The CEC (1990) concluded that "the available epidemiological studies suggest that the toxicologic properties of nickel tetracarbonyl do not include the potential to cause cancer."

2.6. Summary

The human health effects of inhaled nickel carbonyl have been summarized by Sunderman (1989) and Shi (1994a). Nickel carbonyl is generally considered to be one of the most toxic industrial chemicals. A thorough assessment of the exposure response to nickel carbonyl is complicated by the often asymptomatic delay between initial, mild toxic effects and delayed serious effects that may result in fatal outcomes. Sunderman and co-workers summarized the various signs and symptoms of 350 individuals poisoned by nickel carbonyl. Immediate effects that usually resolved upon removal from exposure included headache, dizziness, sternal and epigastric pain, nausea, and vomiting. Effects that followed a 1- to 5-day latency included chest constriction, chills, shortness of breath, muscle pains, weakness, gastrointestinal disorders, convulsions, delirium, and death. Although some forms of nickel are known and suspected carcinogens, the carcinogenic potential of nickel carbonyl in humans is equivocal and no quantitative data are currently available.

Although specific exposure response data for human health effects are not available, the severity of acute nickel carbonyl poisoning paralleled increases in urinary nickel (Shi 1994a), and correlations between urinary nickel and exposure severity have been determined (Sunderman and Sunderman (1958). For mild, moderately severe, and severe exposures, initial 8-h urinary nickel values were <10 µg/100 mL, >10 µg/100 mL but <50 µg/100 mL, and >50 µg/100 mL, respectively.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Inhalation lethality data are available for several species. Although data from some reports were only semiquantitative and lacked detail, other reports provided definitive data from well-conducted studies.

3.1.1. Rats

In experiments with rats, Barnes and Denz (1951) examined the lethality of nickel carbonyl exposure and the effects of subsequent treatment with 2,3-dimercaptopropanol (British Anti-Lewisite). In this study, groups of 10-76 albino rats (sex and strain not specified) were exposed to nickel carbonyl for periods of 5-30 min (ct of 17×10^3 to 70×10^3 mg•min/m^3; equivalent to 2,380-9,800 ppm•min). Nickel carbonyl concentrations were estimated by chemical analysis and, although capable of detecting nickel concentrations of 1-2 μg, may lack the precision of later reports in which concentrations were determined by gas chromatographic techniques. Only a range of exposure periods and ct values were provided by the authors ($17\text{-}23 \times 10^3$, $29\text{-}38 \times 10^3$, $43\text{-}58 \times 10^3$, and 70×10^3 mg•min/m^3; equivalent to 2,380-3,220, 4,060-5,200, 6,020-8,120, and 9,800 ppm•min, respectively). Mortality in these four exposure groups was 65%, 77%, 84%, and 100%, respectively. Exposed rats exhibited initial postexposure inactivity, followed by apparent recovery. At about 12 h postexposure, the condition of the rats deteriorated, followed by death 18-150 h after exposure. Necropsy findings revealed marked pleural effusion and extensive pulmonary edema. The concentrations reported in this study appear to be extremely high when compared to other experimental data.

Kincaid et al. (1953) conducted acute lethality studies in several species, including rats. In these experiments, groups of 6-21 Wistar rats (gender not specified) were exposed to nickel carbonyl vapor at concentrations of 0.17, 0.20, 0.38, 0.45, or 0.50 mg/L for 30 min (equivalent to 23.8, 28.0, 53.2, 63.0, and 70 ppm, respectively). The report provided detailed information regarding the exposure protocol as well as generation and measurement of the experimental atmosphere. Adjustments were made to account for decomposition of the nickel carbonyl. Results of the experiment with rats are shown in Table 9-5. Using probit analysis, a 30-min LC_{50} of 0.24 mg/L (33.6 ppm) was estimated. The rats were observed for 0.2 h to 6 days after exposure. It was reported that deaths usually occurred 2-3 days after termination of exposure. Animals that died immediately exhibited severe pulmonary congestion and pulmonary edema. In rats that survived for several days, extensive pneumonitis was observed.

In experiments to study the efficacy of dimercaprol in the treatment of nickel carbonyl poisoning, control rats (those not receiving the dimercaprol) were exposed for 30 min to nickel carbonyl at concentrations of 0.20, 0.40, or

0.60 mg/L (equivalent to 28, 56, and, 84 ppm, respectively; Kincaid et al. 1953). The mortality incidences for these exposures were 9/18, 7/9, and 9/9, respectively. Dimercaprol (3-day dosing regimen of 10, 8, and 3.8 mg/kg) reduced the incidences to 0/18, 3/9, and 8/9, respectively.

Sunderman (1964) conducted studies in rats to evaluate the effectiveness of Dithiocarb as an antidote for nickel carbonyl poisoning. Groups of Wistar rats (sex not specified) were exposed by 30-min inhalation to nickel carbonyl at concentrations of 67, 105, 168, or 266 ppm. Chamber concentrations were determined by chemical analysis capable of detecting nickel carbonyl concentrations in the parts per billion ranges. Survival ratios were determined 5 days after the exposure. Results for the control groups (nickel carbonyl exposed with no antidote administration) are shown in Table 9-6. The data show that 30-min exposures of rats to nickel carbonyl concentrations ≥67 ppm produced significant mortality approaching or attaining 100%. All rats (30 per group) receiving the Dithiocarb intraperitoneally were alive at 5 days postexposure, although orally administered Dithiocarb was not as effective (60-90% mortality was still observed following 30-min exposure to 266 ppm nickel carbonyl).

TABLE 9-5 Lethal Response of Rats Exposed to Nickel Carbonyl for 30 min

Exposure Concentration, mg/L (ppm)	Number Dead/ Number Exposed	Probit
0.17 (23.8)	0/6	3.27
0.20 (28.0)	9/18	5.00
0.38 (53.2)	17/21	5.88
0.45 (63.0)	15/18	5.97
0.50 (70.0)	12/12	6.75

Source: Kincaid et al. 1953. Reprinted with permission; copyright 1953, American Medical Association.

TABLE 9-6 Lethality in Rats Following 30-min Inhalation Exposure to Nickel Carbonyl

Nickel Carbonyl Concentration (ppm)	Number Surviving/ Number Exposed	Mortality (%)
67	11/30	63
67	1/10	90
105	6/30	80
168	0/30	100
266	0/30	100
266	0/10	100

Source: Sunderman 1964. Reprinted with permission; copyright 1964, *Journal of New Drugs*.

In carcinogenicity assays, Sunderman and Donnelly (1965) reported that 214 of 285 rats died within 3 weeks of a single 30-min inhalation exposure to nickel carbonyl (80 ppm). None of the 19 control rats died during this time period.

Baselt et al. (1977) tested groups of 8-33 female Fischer-344 rats exposed for 15 min to nickel carbonyl at concentrations of 1.4 (196 ppm) or 4.2 mg/L (588 ppm). Measurement of exposure concentrations was by gas chromatography. Results are shown in Table 9-7. Necropsies were apparently not performed. Separate groups of 20 female F-344 rats were exposed for 15 min to nickel carbonyl at 0.14, 0.28, 0.72, or 1.43 mg/L (19.6, 39.2, 100.8, or 200.2 ppm). The lethality ratios for the 19.6-, 39.2-, 100.8-, and 200.2-ppm exposures were 5/20, 7/20, 12/20, and 15/20, respectively, but no further details were provided. A 15-min LC_{50} of 0.58 mg/L (81.2 ppm) was calculated by the study authors.

In a study by Baselt and Hanson (1982), female Fischer rats (four rats/group) were exposed to nickel carbonyl (1.4- or 1.7- mg/L; 196 or 238 ppm) for 15 min and observed for 1 week after exposure. The mortality ratio for rats not given the chelating agents was 6/14 and 7/8, respectively, for the 1.4 and 1.7 mg/L groups. Specific time-to-death data were not provided. Mortality was limited in rats receiving the chelating agents. Rats given D-penicillamine and diethyldithiocarbamate in the higher-exposure groups exhibited mortality ratios of 4/4 and 1/4, respectively, for the 1.4- and 1.7-mg/L nickel carbonyl groups. Rats receiving disulfiram in the 1.4-mg/L group had a mortality ratio of 1/6 and 3/4 at disulfiram doses of 125 and 1,500 mg/kg (three doses of 500 mg/kg at hourly intervals).

3.1.2. Mice

In the research reported by Kincaid et al. (1953), groups of 10-29 albino mice were exposed to nickel carbonyl vapor at concentrations of 0.0155, 0.0465, 0.056, 0.062, 0.070, 0.078, or 0.090 mg/L for 30 min (equivalent to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, and 12.6 ppm, respectively). The report provided detailed information regarding the exposure protocol as well as generation and measurement of the experimental atmosphere. Adjustments were made to account for decomposition of the nickel carbonyl. The results of the experiment are shown in Table 9-8. Using probit analysis, a 30-min LC_{50} of 0.067 ± 0.003 mg/L (~9.4 ppm) was calculated. Similar to the experiments with rats, deaths in mice occurred 2-3 days after termination of exposure.

In experiments intended to evaluate the effectiveness of edathamil calcium-disodium (calcium disodium EDTA) as a treatment for nickel carbonyl poisoning, West and Sunderman (1958) exposed four groups of 20 mice (strain and sex not specified) for 30 min to 0.06 mg of nickel carbonyl per liter of air (equivalent to 60 mg/m^3 [8.4 ppm]). Ten mice from each group were also given the chelating agent. The 3-day postexposure mortality ratios for the groups of 10

TABLE 9-7 Lethality in Rats Following 15-min Exposure to Nickel Carbonyl

Exposure Concentration (ppm)	Mortality Ratio	Time-to Death (Days)
588	33/33	<1-2
196	19/26	2-5
196	17/26	1-6
196	3/8	4-6

Source: Baselt et al. 1977. Reprinted with permission; copyright 1977, *Research Communications in Chemical Pathology and Pharmacology*.

TABLE 9-8 Lethal Response of Mice Exposed to Nickel Carbonyl for 30 min

Exposure Concentration mg/L (ppm)	Number Dead/ Number Exposed	Probit
0.0155 (2.17)	0/12	2.98
0.0465 (6.51)	2/15	3.89
0.056 (7.84)	3/10	4.48
0.062 (8.68)	10/29	4.60
0.070 (9.80)	10/20	5.00
0.078 (10.9)	12/22	5.11
0.090 (12.6)	10/10	6.96

Source: Kincaid et al. 1953. Reprinted with permission; copyright 1953, American Medical Association.

mice not given the chelating agent are shown in Table 9-9. The edathamil calcium-disodium treatment was ineffective in reducing lethality.

Sunderman (1964) conducted studies in mice to evaluate the effectiveness of sodium dithiocarbamate (Dithiocarb) as an antidote for nickel carbonyl poisoning. In these experiments, groups of C-57 mice (sex not specified) were exposed by 30-min inhalation to nickel carbonyl at concentrations of 6, 8, 10, 16, or 24 ppm. The exposure concentrations were determined by chemical analysis previously shown to be sensitive in the parts per billion ranges (Kincaid et al. 1956). Survival ratios were determined 5 days after the exposure. The results for the control groups (nickel carbonyl exposed with no antidote administration) are shown in Table 9-10. From these experiments it is apparent that 30-min exposures to nickel carbonyl concentrations as low as 6 ppm resulted in substantial mortality. Additionally, the large number of test animals in the 10-ppm exposure group affirms this exposure as being near 100% lethal. No deaths were observed in the Diothiocarb-treated mice.

TABLE 9-9 Mortality Ratio for Mice 3 Days Following 30-min Exposure to Nickel Carbonyl (8.4 ppm)

Experimental Group	Exposure	Mortality Ratio
Group 1	0.06 mg/L (8.4 ppm)	6/10
Group 2	0.06 mg/L (8.4 ppm)	10/10
Group 3	0.06 mg/L (8.4 ppm)	9/10
Group 4	0.06 mg/L (8.4 ppm)	8/10

Source: West and Sunderman 1958.

TABLE 9-10 Lethality in Mice Following 30-min Inhalation Exposure to Nickel Carbonyl

Nickel Carbonyl Concentration (ppm)	Number Surviving/ Number Exposed	Mortality (%)
6	6/30	80
8	0/30	100
10	2/30	99
16	0/30	100
24	0/30	100

Source: Sunderman 1964. Reprinted with permission; copyright 1964, *Journal of New Drugs*.

3.1.3 Rabbits

In addition to studies with rats, Barnes and Denz (1951) examined the effects of nickel carbonyl and subsequent BAL treatment on rabbits. Similar to the previously described experiments in rats, the exposures were reported only as ct values (i.e., 10-37 $\times$ 10^3 mg·min/m^3; equivalent to 1,400-5,180 ppm·min). The mortality in rabbits exposed to nickel carbonyl but not given BAL was 18/23 (62%), with an average survival of 3.3 days.

3.1.4. Cats

With regard to determination of a 30-min LC_{50} for cats in the Kincaid et al. (1953) study, data were less conclusive (see Table 9-11). With the exception of using a larger exposure chamber, the exposure protocol and techniques were the same as for mice and rats, but only a limited number of animals were used (i.e., 1-3). The small sample size precluded an exposure-probit analysis. Because

TABLE 9-11 Lethal Response of Cats Exposed to Nickel Carbonyl for 30 min

Exposure Concentration mg/L (ppm)	Number Dead/Number Exposed	Time to Death (h)
0.19 (26.6)	0/1	–
0.50 (70.0)	0/1	–
1.24 (173.6)	1/1	216
1.94 (271.6)	0/2	–
2.00 (280.0)	3/3	56, 96, 142
2.11 (295.4)	3/3	36, 72, 96
2.43 (340.2)	1/1	40

Source: Kincaid et al. 1953. Reprinted with permission; copyright 1953, American Medical Association.

only one cat died following exposure to <2.00 mg nickel carbonyl/L (280 ppm) and 3/3 died following exposure to 2.11 mg/L (295.4 ppm), it was concluded that the 30-min LC_{50} for cats was <2.00 mg/L (280 ppm). Both cats exposed to 1.94 mg/L (271.6 ppm) survived; therefore, the 30-min LC_{50} was estimated as 1.9 mg/L (266 ppm).

3.1.5. Summary of Lethal Toxicity in Animals

Acute lethality values for nickel carbonyl are summarized in Table 9-12. There appears to be considerable species variability in the lethal response to inhaled nickel carbonyl, and, as noted by Kincaid et al. (1953), the acute lethality of nickel carbonyl appears to be inversely related to body mass. Based on the lethality data for rats, mice, and cats, Kincaid et al. found that the LC_{50} values were proportional to the 2/3 power of the body mass; specifically, $LC_{50} = 0.009 (\text{body mass})^{2/3}$.

3.2. Nonlethal Toxicity

Data regarding nonlethal toxicity of nickel carbonyl in animals are limited. The acute toxicity of nickel carbonyl and the progression of systemic toxicity to lethality limit the identification of critical effects consistent with AEGL-2 end points.

3.2.1. Rats

Kincaid et al. (1953) conducted pathologic evaluations on a series of rats following various exposure protocols. One rat, exposed for 30 min to 0.08 mg

TABLE 9-12 Acute Lethality of Nickel Carbonyl in Animal Species

Species	Acute Lethality Value	Reference
Rat	30-min LC_{50}: 56 ppm	Kincaid et al. 1953; Barnes and Denz 1951[a]
Rat	30-min LC_{50}: 33.6 ppm	Kincaid et al. 1953
Rat	30-min LC_{75}: 80 ppm	Sunderman and Donnelly 1965
Rat	15-min LC_{50}: 81.2 ppm	Baselt et al. 1977
Mouse	30-min LC_{50}: 9.38 ppm	Kincaid et al. 1953
Rabbit	30 min LC_{50}: 42-168 ppm	Kincaid et al. 1953; Barnes and Denz 1951[a]
Cat	30-min LC_{50}: ≈266 ppm[b]	Kincaid et al. 1953

[a]50% mortality value determined by Kincaid et al. (1953) using probit analysis and multiple exposure time data of Barnes and Denz (1951).
[b]Value estimated by authors based on 100% (3/3) mortality at 280 ppm for 30 min but no mortality (0/2) at 271.6 ppm for 30 min.

nickel carbonyl/L (11.2 ppm), survived to 144 h postexposure, whereupon it was killed and examined. Although the rat survived to 144 h, the pathologic findings (pulmonary congestion and edema, extensive pneumonitis) were reportedly similar to those of other rats that died as a result of nickel carbonyl exposure.

Exposure of rats to nickel carbonyl induced transient hyperglycemia, the severity of which was concentration dependent (Horak et al. 1978). In this study, female F-344 rats were exposed to nickel carbonyl at concentrations of 0, 1.2, 3.5, or 6.4 μmoles/L (equivalent to 0, 28.67, 83.66, and 152.97 ppm) for 15 min. The nickel carbonyl concentrations were determined by gas chromatography. Compared to untreated controls, rats of all three nickel carbonyl groups exhibited a significant ($p < .01$, F-test) hyperglycemic response at 0.5-1 h but returned to normal 2 h after the onset of exposure. Plasma glucose was also significantly ($p < .01$; test) increased in the high-exposure (6.4 μmoles/L) group at 30 min and 1 h after initiation of the 15-min exposure. Although these effects per se are indicative of nonlethal responses to nickel carbonyl exposure, the ultimate fate of the exposed rats was not stated. Considering that the two highest exposure concentrations exceed the reported 15-min LC_{50} value for rats (Baselt et al. 1977), it is likely that these exposures would result in fatality.

3.2.2. Mice

In the research reported by Kincaid et al. (1953), groups of 10-29 albino mice were exposed to nickel carbonyl vapor at concentrations of 0.0155, 0.0465, 0.056, 0.062, 0.070, 0.078, or 0.090 mg/L for 30 min (equivalent to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, and 12.6 ppm, respectively). As noted in Section 3.1.2,

Kincaid et al. provided detailed information regarding the exposure protocol as well as generation and measurement of the experimental atmosphere. Adjustments were made to account for decomposition of the nickel carbonyl. Although the experiments were primarily an assessment of lethality, there were no deaths in the lowest concentration group. Histopathologic examinations were not reported for these mice. In another phase of the study, the potential tolerance to nickel carbonyl poisoning was examined, wherein groups of five mice were exposed to increasingly higher levels of the compound (10 30-min exposures over 48 days. The exposure concentrations ranged from 0.016 to 0.19 mg/L (2.24-26.6 ppm). The results of this experiment revealed no deaths until after the tenth exposure, even though the sixth and seventh exposures (9.9 ppm and 9.5 ppm) were equivalent to the LC_{50}.

3.2.3. Summary of Nonlethal Toxicity in Animals

Data regarding nonlethal exposure of laboratory species to nickel carbonyl are extremely limited. A hyperglycemic response was documented for rats but involved exposure concentrations approaching or equivalent to LC_{50} values. The well-documented latency in the lethal response complicates the identification of exposures inducing serious, irreversible effects but not causing death.

3.3. Developmental/Reproductive Toxicity

Sunderman et al. (1980) showed that inhalation of nickel carbonyl is teratogenic and embryotoxic in Syrian hamsters. Groups of pregnant Syrian hamsters were exposed by inhalation to nickel carbonyl (0.06 mg/L [60 mg/m^3; 8.4 ppm]) for 15 min/day on either day 4, 5, 6, 7, or 8 of gestation. Nickel carbonyl concentrations in the exposure chamber were determined by gas chromatography. The dams were killed on day 15 of gestation, and the fetuses were examined for malformations. The statistically significant findings of this experiment (see Table 9-13), showed increased incidences of malformations resulting from exposures on gestation days 4 and 5. In order to study postnatal survival, pregnant Syrian hamsters were exposed similarly but only on day 5 of gestation. Developmental toxicity has been demonstrated in rats and hamsters following single 30-min (11.2-42 ppm, rats) or 15-min (8.4 ppm, hamsters) exposures of dams during gestation. In hamsters, developmental toxicity was observed in dams following lethal or near-lethal exposures. Five of 14 hamsters exposed to 8.4 ppm died by gestation day 16. All 14 dams in the control group (five died by gestation day 16) delivered their litters, and the offspring were observed for 10 weeks. Although there was no significant difference in the average number of live births between the controls and the nickel carbonyl-exposed group, neonatal mortality was significantly increased ($p < .01$) in the nickel carbonyl group by

postpartum day 4 (7.6 ± 1.5 and 9.7 ± 1.8 live pups/litter for the treated and control groups, respectively). Additionally, serous cavity hemorrhage (peritoneal, pleural, pericardial, and subdural spaces) was observed in the fetuses of the treated dams but not the untreated controls.

The teratogenic potential of inhaled nickel carbonyl in rats was evaluated by Sunderman et al. (1979). In this study, pregnant Fischer-344 rats were exposed for 15 min to nickel carbonyl vapor (0.08 mg/L, equivalent to 11.2 ppm) on gestation day 7, 8, or 9 (day 0 determined by sperm in vaginal smear). Groups of pregnant rats were exposed to 0.16 or 0.30 mg nickel carbonyl/L (equivalent to 22.4 and 42 ppm) on gestation days 8 and 7, respectively. Concentrations of nickel carbonyl in chamber air were determined by gas chromatography. Sham-exposed (ambient air) rats and a separate group of pregnant rats exposed to carbon monoxide (0.5%) also were included in the protocol. For the first phase of the study, fetuses were removed by cesarean section on gestation day 20 and examined. Ocular malformations were observed in 22 of 78 (28%) of the fetuses from nickel carbonyl-exposed dams. An exposure-response relationship was observed between the incidences of malformations and the nickel carbonyl exposure concentration (see Table 9-14). The mean body weight of fetuses was significantly reduced ($p < .01$) in all but the lowest exposure group, and the number of live fetuses per conceptuses was significantly reduced ($p <$ .05 to 0.01) in all nickel carbonyl groups and the carbon monoxide groups. No malformations were observed in fetuses of dams exposed on day 9 of gestation, the sham-exposed group, or the carbon monoxide exposure group, indicating that the teratogenic effects were due to nickel carbonyl and not a carbon monoxide biotransformation product. In another phase of the study, dams exposed to

TABLE 9-13 Embryotoxic Effects of Nickel Carbonyl Inhalation (8.4 ppm, 15 min/day) in Pregnant Syrian Hamsters

Parameter	Control	$Ni(CO)_4$-Treated
Total malformations[a]	0% (0/9)	
Day 4 exposure		5.5% (8/146)[b]
Day 5 exposure		5.8% (10/171)[b]
Proportion of litters with malformed fetuses	0% (0/9)	
Day 4 exposure		33% (4/12)[b]
Day 5 exposure		24% (4/17)[b]
Serous cavity hemorrhage	0% (0/9)	
Day 4 exposure		18% (26/146)[b]
Day 5 exposure		25% (42/171)[b]

[a]Included nine fetuses with cystic lungs, seven fetuses with exencephaly, one fetus with exencephaly plus fused rib, and 1 fetus with anophthalmia plus cleft palate; for fetuses of dams exposed on days 6 or 7, there were one fetus with fused ribs and two fetuses with hydronephrosis.

[b]Significantly different from controls ($p < .05$).

Source: Sunderman et al. 1980. Reprinted with permission; copyright 1980, *Teratogenesis, Carcinogenesis and Mutagenesis*.

TABLE 9-14 Malformations in Rats Following 15-min Exposure to Nickel Carbonyl During Gestation

Observation	Treatment Groups						
Exposure (mg/L)	Sham	CO	0.16	0.30[a]	0.08	0.16	0.16
Surviving dams; day 20	12/12	22/22	14/14	10/19**	16/16	13/15	13/13
Exposure day	8	7	7	7	8	8	9
Live fetuses/litter	9.2 ± 2.1	8.3 ± 2.6	8.1 ± 2.6	9.1 ± 1.6	7.6 ± 3.6	8.3 ± 2.6	7.4 ± 4.8
Live fetuses/ conceptuses	110/114	187/215**	113/135**	91/100*	121/134*	108/120*	96/112*
Mean fetus weight (g)	3.4 ± 0.2	3.1 ± 0.7	3.0 ± 0.3**	3.0 ± 0.4**	3.3 ± 0.5	3.1 ± 0.3**	3.2 ± 0.3**
Litters with malformed fetuses	0/12	0/22	9/14***	9/10***	2/16	9/13***	0/13
Total malformations[b]	0	0	15***	29***	2	19***	0

[a]Ten of 19 dams survived to day 20; clinical signs of toxicity were not specified.
[b]Ocular malformations: bilateral anophthalmia, unilateral anophthalmia, bilateral microphthalmia, unilateral microphthalmia, anophthalmia, and microphthalmia; only one incidence each in Group C and Group D was categorized as other than ophthalmic anomalies. * $p < .05$; ** $p < .01$; *** $p < .001$.
Source: Adapted from Sunderman et al. 1979. Reprinted with permission; copyright 1979, Science Magazine.

nickel carbonyl (0.30 mg/L [42 ppm]) for 15 min on gestation day 7 were allowed to deliver and nurse the pups for 4 weeks. The progeny were then observed for 16 weeks after birth. Results of this experiment revealed an increased incidence of total malformations (1/87 and 22/78 in controls and treated rats, respectively; $p < .001$), a significant reduction ($p < .001$) in live pups per litter (10.9 ± 2.5 versus 8.7 ± 2.6), and significantly increased incidence ($p < .001$) of litters with malformed pups (0/8 versus 6/9 in controls and treated rats, respectively). With the exception of increased mortality in some treatment groups, no additional information was provided regarding health effects in the dams. The study authors stated that the observed teratogenic response is likely specific to inhaled nickel carbonyl because such responses were not observed following exposures to divalent nickel salts or parenterally administered nickel carbonyl. The investigators hypothesized that the relatively low absorption of nickel salts from the gastrointestinal tract (compared to inhalation) and consequent lower dose to the fetus, or the conversion to a less active form following gastrointestinal absorption, are plausible explanations for this observation.

Results of a dominant lethal mutation test were reported by Sunderman et al. (1983). In this experiment, 10 male Fischer-344 rats were exposed to 0.05 mg/L (equivalent to 7 ppm) of nickel carbonyl for 15 min and subsequently caged with mature females each week during the following 2-6 weeks. Compared to unexposed controls, there were no significant effects on fertilization rate, live fetuses/litter, live fetuses/corpora lutea/dam, dead fetuses/implants, or dead fetuses/implants/litter.

3.4. Genotoxicity

Both IARC (1987) and EPA (1986) reviewed the genotoxicity of nickel and nickel compounds. In vivo chromosomal aberration studies generally showed a lack of clastogenic activity (EPA 1986), although some studies were equivocal. Bacterial mutagenesis studies revealed nickel compounds to lack mutagenic activity or to be only weakly mutagenic (EPA 1986). Nickel carbonyl, however, was not among the nickel compounds tested.

3.5. Carcinogenicity

Results of two studies by Sunderman and co-workers have shown a carcinogenic response in male Wistar rats following various exposure protocols involving inhalation of nickel carbonyl. These protocols included a single 30-min exposure to a high concentration (80 ppm) and lifetime exposures (30-min, three times/week) to lower concentrations (4 ppm) of nickel carbonyl.

Sunderman et al. (1959) reported on a study wherein groups of 32-64 rats (gender and strain not specified) were exposed three times per week for 1 year to nickel carbonyl concentrations of 0.0, 0.03, or 0.06 mg/L (equivalent to 0.0, 4.2, and 8.4 ppm). Another group of 80 rats was given a single (presumably 30-min exposure, although not specifically stated) to 0.25 mg of nickel carbonyl/L (equivalent to 35 ppm; noted by the investigators as approximately the LD_{50}). Within 1 week, 52 of the 80 rats in the single-exposure group had died; only eight rats survived to 8 months and only three survived to 24 months. At 2 years after the exposure, 3/41, 5/64, and 3/32 rats survived in the control, 4.2-, and 8.4-ppm groups, respectively. Among these survivors, pulmonary tumors were found in one rat each in the 4.2- and 8.4-ppm groups, and two rats of the single-exposure (8.4-ppm) group. None of the three surviving control rats exhibited pulmonary tumors. Although the study authors concluded from these results that nickel carbonyl caused pulmonary tumors in rats, the number of rats remaining alive in each group is insufficient for a statistically and biologically meaningful analysis. Additionally, no time-to-tumor data were provided.

Sunderman and Donnelly (1965) conducted experiments in which various exposure protocols were used to assess the carcinogenic potential of inhaled nickel carbonyl in male Wistar rats. Of relevance to AEGLs was the fact that a single 30-min exposure to 80 ppm was found to induce pulmonary tumors in 3 of the 71 rats that survived beyond 2 years. The tumor types, all of which also involved metastases to the kidneys and liver, included anaplastic carcinomas in two rats and an adenocarcinoma in the third rat. The lesions were found between 24 and 27 months after exposure. Malignant lymphomas were also observed in the nickel carbonyl-treated rats, but because of similar incidences in control rats the investigators concluded that these lesions were not due to nickel carbonyl exposure.

3.6. Summary of Animal Toxicity Data

Experiments in animals have confirmed the extreme toxicity of nickel carbonyl following acute inhalation exposure. Animal data also reflect the latency of severe or lethal effects observed in humans exposed to nickel carbonyl. Data describing nonlethal effects in test animals are limited to the demonstration of a nickel carbonyl-induced hyperglycemia in rats following 15-min inhalation exposure to nickel carbonyl at or near LC_{50} values. Lethality data are available for several species, including rats (30-min LC_{50} values of 33.6 and 56 ppm and a 30-min LC_{75} of 80 ppm), mice (30-min LC_{50} of 9.38 ppm), rabbits (30-min LC_{50} values ranging from 42 to 168 ppm), and cats (estimated 30-min LC_{50} of 266 ppm). Nickel carbonyl has been shown to be teratogenic in rats and hamsters exposed during gestation to concentrations of 22.4 ppm and 8.4 ppm, respectively. In rats the health status of the dams was uncertain, thereby disallowing a definitive determination of the relative maternal versus fetal sensitivity to nickel carbonyl challenge. A single gestational exposure of hamsters (15-min exposure to 8.4 ppm on gestation day 5) resulted in increased neonate mortality by postpartum day 4 but was also maternally toxic. There are limited, equivocal data showing the development of pulmonary tumors in rats exposed chronically to nickel carbonyl and equivocal data suggestive of a tumorigenic response following a single massive exposure of rats to nickel carbonyl.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Following inhalation and oral exposure to most nickel compounds, absorbed nickel is excreted primarily via the urine and feces (summarized in Sunderman 1989). In studies with dogs exposed to nickel carbonyl, Sunderman and co-workers noted that the excretion route varied with the exposure route; fecal excretion accounted for 90% and urinary excretion about 10% following ingestion, while the reverse was found for inhalation exposure. This finding attests to the poor absorption of nickel carbonyl from the gastrointestinal tract. It was also found that urinary excretion of nickel increased sharply immediately after exposure and prior to any signs of toxicity. Results of studies with radiolabeled nickel carbonyl administered to rats have shown that the compound will, upon inhalation, cross the alveolar membrane unchanged (reviewed in Sunderman et al. 1979; NAS 1975). The biologic half-life for nickel carbonyl in the rat is about 0.5 h. Although a substantial amount of nickel carbonyl may be eliminated via the lungs (≈36% in the rat within 4 h), the remainder reportedly undergoes dissociation to nickel nickel and carbon monoxide within erythrocytes and other tissues (NAS 1975). The nickel is subsequently oxidized to Ni (II) and released into the blood serum where it may bind to albumin and nickel-binding substances (nickeloplasmin, an α_2-macroglobulin) and is cleared via the kidneys.

Sunderman (1964) also studied nickel balance in 50 nickel carbonyl-exposed workers. These workers experienced severe exposures (concentrations not provided) that likely would have been fatal without treatment with Dithiocarb. The urinary concentration of nickel was monitored in the 13 most severe exposures. In several subjects (all treated with Dithiocarb), urinary excretion was 100-200 µg/mL for up to 4 days postexposure. A comparison of nickel burden in tissues of humans not exposed to nickel carbonyl (values are the mean of four individuals) and an individual dying from acute nickel carbonyl exposure revealed considerably elevated nickel content in the lung (1.59 µg/100 g versus 17.3 µg/100 g) and liver (0.87 µg/100 g versus 5.3 µg/100 g) (Sunderman 1989).

Using urinary nickel as an index of exposure severity, Sunderman and Sunderman (1958) categorized nickel carbonyl exposure as mild, moderately severe, or severe if urinary nickel concentrations at 18 h were 60-100 µg/L, 100-500 µg/L, or >500 µg/L, respectively. There are currently no reliable correlations between air concentrations of nickel carbonyl and nickel levels in the body fluids or tissues of exposed individuals.

In a time-course analysis with rats exposed by inhalation to nickel carbonyl, Barnes and Denz (1951) reported a rapid uptake of nickel carbonyl. Immediately after a 30-min exposure, nickel was found in the liver and brain, with the liver tissue containing the greatest amounts. The lungs contained very little nickel, indicating exhalation of inhaled nickel carbonyl and/or rapid uptake. Barnes and Denz found that rabbits exhibited very little accumulation of nickel in the brain following lethal exposure to nickel carbonyl. However, Tjälve et al. (1984) found that 1 h after inhalation exposure of mice to radiolabeled nickel carbonyl, the highest $^{63}Ni^{2+}$ levels were found in the lung. High levels were also detected in the brain, heart, and diaphragm.

4.2. Mechanism of Toxicity

In a review of nickel toxicology, Sunderman (1981) summarized research findings conducted with his co-workers on the pathologic reaction of laboratory species to nickel carbonyl. These investigators found that the pulmonary parenchyma was consistently the principal target for nickel carbonyl insult, regardless of the route of exposure. Both Type I and Type II alveolar cells were affected by nickel carbonyl, although the former were reportedly the primary target (Hackett and Sunderman 1968). It has also been shown that pulmonary edema and chemical pneumonitis are characteristic of severe nickel carbonyl poisoning (Shi 1994b). Shi reported impairment of some respiratory functions (spirometric indices) in workers with long-term exposures to low levels (0.00098-0.072 ppm) of nickel carbonyl.

Although carbon monoxide is a biotransformation product of nickel carbonyl, it is not considered responsible for the pronounced toxicity of nickel carbonyl (Sunderman et al. 1979).

4.3. Structure-Activity Relationships

The physicochemical properties of nickel carbonyl are sufficiently different from other nickel compounds to preclude the use of structure-activity relationships in the derivation of AEGL values for the title compound.

4.4. Other Relevant Information

4.4.1. Species Variability

Generally, the lethality values presented in Section 3.1 for various species suggest that smaller species may be more sensitive to the lethal effects of nickel carbonyl. Based on data for rats, mice, and cats, Kincaid et al. (1953) determined that the lethality of nickel carbonyl was directly proportional to the 2/3 power of the body weight. Using this relationship, Kincaid et al. projected an LC_{50} (no duration specified) of 15 mg/L (2,100 ppm) for a 70-kg human.

4.4.2. Concurrent Exposure Issues

No concurrent exposure issues of special concern have been identified that influence the derivation of AEGL values for nickel carbonyl.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Quantitative data pertinent to AEGL-1 effects in humans are not available. Many of the reports describing human exposures to nickel carbonyl involved serious health effects of a severity above and beyond that consistent with the AEGL-1. Human poisonings in the absence of detection also have been documented. Furthermore, nickel carbonyl poisoning characteristically exhibits a latency period, which may be asymptomatic, between the initial exposure and subsequent severe effects that may be lethal.

5.2. Summary of Animal Data Relevant to AEGL-1 Values

Neither quantitative nor qualitative data in animals were available that were consistent with AEGL-1 effects.

5.3. Derivation of AEGL-1

Qualitative data are limited, and quantitative data consistent with AEGL-1 effects are unavailable. Odor detection does not appear to be a valid end point for derivation of AEGL-1 values for nickel carbonyl because toxic effects have occurred in subjects unaware of its presence (Sunderman 1990). Available data also indicate that severe toxicity (i.e., lethality) may occur days after exposures that are initially suggestive of little or no toxicity. Therefore, AEGL-1 values are not recommended for nickel carbonyl (see Table 9-15). This contention is justified by findings from a previous accidental exposure in which more than 100 workers were exposed to nickel carbonyl (some as long as 12 h) with no knowledge of its presence until there were severe signs and symptoms of illness (Kincaid et al. 1956).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative data regarding AEGL-2 level effects in humans following acute exposures were unavailable.

6.2. Summary of Animal Data Relevant to AEGL-2

Animal data regarding serious but nonlethal effects of acute inhalation exposure to nickel carbonyl were limited to studies examining the developmental toxicity of nickel carbonyl in Syrian hamsters (Sunderman et al. 1980) and F-344 rats (Sunderman et al. 1979), and to nonlethal effects in the lower exposure groups of lethality experiments (Kincaid et al. 1953). Exposure of pregnant Syrian hamsters to nickel carbonyl (0.06 mg/L equivalent to 8.4 ppm) for 15 min per day on gestation days 4 or 5 killed four of five dams and resulted in a significant ($p < .05$) increase in the number of litters with malformed fetuses and serous cavity hemorrhage compared to unexposed controls (Sunderman et al. 1980; see Table 9-13). A significant increase ($p < .01$) in neonate mortality was also observed on postpartum day 4 in an experiment in which the dams were permitted to deliver and nurse their pups. These data indicate that these exposure conditions were embryotoxic in the Syrian hamster under conditions that produced concomitant overt maternal toxicity.

In the study reported by Sunderman et al. (1979), a significant increase ($p < .001$) in the numbers of litters with malformed offspring of rats exposed to concentrations as low as 0.16 mg/L nickel carbonyl (equivalent to 22.4 ppm) for 15-min on gestation day 7 was observed. An additional group of dams were exposed to 0.3 mg/L (42 ppm) for 15 min but were allowed to deliver and nurse

TABLE 9-15 AEGL-1 for Nickel Carbonyl

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR

Note: NR, not recommended. Numerical values for AEGL-1 are not recommended because of the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 concentration is without adverse effects.

their pups for 4 weeks. Litters from the nickel carbonyl-treated dams had a significant decrease ($p < .001$) in live pups per litter. There was a significantly increased incidence of ocular malformations ($p < .001$) in these litters and significantly lower pup weight ($p < .001$) at 4 and 16 weeks. Nine of 19 dams exposed to 0.3 mg of nickel carbonyl/L and 9 of 14 dams exposed for 15 min to 0.06 mg/L died.

In the lethality experiments reported by Kincaid et al. (1953), none of the 15 mice in the lowest exposure group (2.17 ppm for 30 min) died, whereas two of 15 mice exposed to 6.51 ppm died. Although no pathologic examinations were reported, these investigators and Barnes and Denz (1951) reported that rats killed by inhalation of nickel carbonyl exhibited pleural effusion, severe pulmonary congestion, and edema. It may be assumed that the mice receiving nonlethal exposures were likely to have some level of pulmonary damage that would be consistent with a critical effect appropriate for AEGL-2 development.

6.3. Derivation of AEGL-2

The development of the AEGL-2 values for nickel carbonyl is based on the toxic response of mice following 30-min inhalation exposures at seven concentrations: 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, or 12.6 ppm (Kincaid et al. 1953). A concentration-dependent lethal response was observed for exposures to 6.51-12.6 ppm, but the lowest exposure (2.17 ppm) resulted in no deaths. Exposure to 6.51 ppm resulted in the deaths of two of 15 mice. A 30-min LC_{50} of ~9.4 ppm was estimated by the investigators. Although no histopathology examinations were performed on the mice in the 2.17-ppm group, Kincaid et al. (1953) and Barns and Denz (1951) reported findings of pleural effusion, severe pulmonary congestion, and pulmonary edema in rats that died following exposure to nickel carbonyl. Therefore, the 30-min exposure to 2.17 ppm was considered a reasonable estimate of an exposure that may cause pulmonary damage in the mouse (most sensitive species tested) but not result in irreversible adverse effects. As shown by the multiple-exposure studies of Kincaid et al. (1953), repeated exposures of mice to this or greater concentrations did not result in a lethal response. Pulmonary damage appears to a component in the continuum of the toxic response to nickel carbonyl and an appropriate critical effect for AEGL-2 development. The 30-min exposure to 2.17 ppm was considered a point-of-departure

representative of a no-observed-adverse-effect level (NOAEL) for AEGL-2 effects.

Exposure-response data over multiple time periods were unavailable for nickel carbonyl, and therefore empirical derivation of a scaling factor (n) was not possible. The concentration exposure-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of an empirically derived exponent, and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. A total uncertainty factor adjustment of 10 was applied. An uncertainty factor of 3 was applied to account for interspecies variability. The available lethality data, however, do suggest that the mouse represents a sensitive species. Based on available lethality data and the analysis conducted by Kincaid et al. (1953) indicating an inverse relationship between lethality and body size (see Section 4.4.1.), the interspecies uncertainty factor of 3 appears to be justified. Although intraspecies variability is difficult to assess based on available data, an uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. The occupational exposure data reported by Shi et al. (1994b) suggest that the AEGL-2 values are sufficiently protective. The overall dataset for nickel carbonyl is deficient regarding nonlethal effects of nickel carbonyl inhalation. Therefore, a modifying factor of 3 was applied in the development of the AEGL-2 values to account for these deficiencies and the possibility of developmental toxic effects reported by Sunderman and colleagues. The resulting AEGL-2 values are shown in Table 9-16 and their derivations in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Quantitative data regarding human lethality following inhalation exposure to nickel carbonyl are unavailable. The available data on human exposures qualitatively define initial effects of varying severity often followed by an asymptomatic latency prior to the onset of more serious effects and possible lethal response. Kincaid et al. (1956) estimated a 30-min LC_{50} of 3 ppm for humans, and Vuopola et al. (1970) estimated that exposure to 30 ppm would be immediately fatal. These estimates do not appear to have been quantitatively derived.

7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data are available for rats, mice, rabbits, and cats. Based on comparison of 30-min LC_{50} values, the mouse appears to be the most sensitive

TABLE 9-16 AEGL-2 Values for Nickel Carbonyl

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-2 (disabling)	0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

species: 9.38 ppm for mice, 33.6 and 56 ppm for rats, 42-168 ppm for rabbits, and 266 ppm for cats (Kincaid et al. 1953). A developmental toxicity study in Syrian hamsters showed that a single 15-min exposure to 0.06 mg/L (8.4 ppm) during gestation resulted in teratogenic effects and increased neonate mortality (Sunderman et al. 1980). Data defining a lethality threshold or those that could be used to estimate a lethality threshold were not available. Lethality data for varying exposure durations were also deficient for defining a temporal extrapolation function.

7.3. Derivation of AEGL-3 Values

As previously noted, lethality data are available for several species but are limited to LC_{50} determinations. Kincaid et al. (1953) suggest that sensitivity to nickel carbonyl may be a function of body mass, and as a result, lethal exposures for humans have been estimated. Based on data from mice, rats, and cats, these investigators estimated that the lethality of nickel carbonyl was directly proportional to body weight to the 2/3 power. Human exposure reports suggest a wide range of nonlethal responses to acute exposure to nickel carbonyl as well as a characteristic latency period between initial exposure and subsequent, more serious effects.

The mouse represents the most sensitive species, and therefore a lethality threshold (LC_{01}) was estimated from the mouse data of Kincaid et al. (1953) (Appendix A). The lethality threshold was estimated using the method of Litchfield and Wilcoxon (1949). This value was determined to be 3.17 ppm for 30 min (Appendix D). Exposure response data over multiple time periods are unavailable for nickel carbonyl, and therefore temporal scaling to AEGL-specific exposure durations necessitated the assumption of default values for n in the exponential temporal scaling equation, $C^n \times t = k$. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data and to obtain protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time periods and n = 1 when extrapolating to longer time periods. A total uncertainty factor of 10 has been applied for developing the AEGL-3 values. Lethality data from the smallest and, according to Kincaid et al. (1953), the most sensitive species were used for development of the AEGL-3. In the Kincaid et al. report, a body mass-based extrapolated plot was provided for hu-

man lethality that predicted an LC_{50} two orders of magnitude greater than the experimentally derived LC_{50} for mice. For this reason, and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion uncertainty adjustment between inter- and intraspecies. The resulting AEGL-3 values are summarized in Table 9-17.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Only AEGL-2 and AEGL-3 values have been derived for nickel carbonyl. Neither human nor animal data were available for the derivation of AEGL-1 values, and therefore they are not recommended. Data consistent with AEGL-2 effects were limited to developmental toxicity data in rats and hamsters and absence of lethal effect in mice and rats (and evidence for tolerance) following multiple exposures. Significant fetotoxicity and teratogenicity following single 15-min gestational exposures at 0.16 mg/L (22.4 ppm) in rats and 8.4 ppm in Syrian hamsters have been reported, but absence of maternal toxicity data precludes a definitive determination of the relative maternal/fetal sensitivity. Data for rats were also inconclusive regarding nickel carbonyl as a selective developmental toxicant following a single exposure during pregnancy. These exposures were also associated with neonate lethality and for the hamsters represented lethal or near-lethal exposures for the dams. The AEGL-2 values were developed to account for possible (and often latently occurring) pulmonary damage. Lethality data were available for four animal species. Analysis of these data also suggested that the larger species were somewhat less sensitive regarding the lethal response to nickel carbonyl following acute inhalation exposure. The AEGL-3 values were derived from mouse lethality data, the most sensitive species tested.

Category plots depicting the relationship of the AEGL values to one another and to the available data are shown in Appendix E. Because most of the available data were generated from exposure durations of 30 min or less, a plot with an expanded lower timeframe is included for clarity.

The available evidence does not support a definitive assessment of cancer risk in humans for a single once-in-a-lifetime acute exposure. Epidemiologic data do not support the contention that inhalation of nickel carbonyl is carcinogenic to humans. Based on inadequate human data and limited data in animals, the EPA (2003) categorizes nickel carbonyl as B2 (potential human carcinogen), while IARC (1987) specifically stated that nickel carbonyl was considered unlikely to be involved in causing cancers among nickel refinery workers.

8.2. Comparison with Other Standards and Criteria

Several organizations have developed standards and criteria for nickel carbonyl (see Table 9-18). Most values are expressed as nickel equivalents. The occupational exposure standard (OES) for the United Kingdom. is 0.1 ppm for 10 min (Morgan and Usher 1994). There are currently no ERPG values, Dutch MAC values, or German MAK values for nickel carbonyl.

Cancer risk estimates have not been developed for nickel carbonyl (ATSDR 2005).

TABLE 9-17 AEGL-3 Values for Nickel Carbonyl

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-3 (Lethality)	0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm

TABLE 9-18 Extant Standards and Guidelines for Nickel Carbonyl

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.10 ppm	0.072 ppm	0.036 ppm	0.0090ppm	0.0045 ppm
AEGL-3	0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm
ERPG-1 (AIHA)[a]	-	-	-	-	-
ERPG-2 (AIHA)	-	-	-	-	-
ERPG-3 (AIHA)	-	-	-	-	-
EEGL (NRC)[b]	-	-	-	-	-
PEL-TWA (OSHA)[c]	-	-	-	-	0.001 ppm[m]
PEL-STEL (OSHA)[d]	-	-	-	-	-
IDLH (NIOSH)[e]	-	2 ppm[m]	-	-	-
REL-TWA (NIOSH)[f]	-	-	-	-	0.001 ppm[m]
REL-STEL (NIOSH)[g]	-	-	-	-	-
TLV-TWA (ACGIH)[h]	-	-	-	-	0.05 ppm[m]
TLV-STEL (ACGIH)[i]	-	-	-	-	-
MAK (Germany)[j]	-	-	-	-	-
MAK Spitzenbegrenzung (Germany)[k]	-	-	-	-	Cat. III
Einsaztoleranzwert (Germany)[l]	-	-	-	-	-

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 1994). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-2 is the maximum airborne concentration below which it

(Continued)

TABLE 9-18 Continued

is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life threatening health effects.

[b]EEGL (Emergency Exposure Guidance Levels, National Research Council) (NRC 1985) is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace but avoids death, other severe acute effects, and long-term or chronic injury.

[c]OSHA PEL-TWA (Occupational Safety and Health and Administration, Permissible Exposure Limits–Time-Weighted Average) (OSHA 1993) is defined analogous to the ACGIH-TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.

[d]OSHA PEL-STEL (Permissible Exposure Limits–Short-Term Exposure Limit) (OSHA 1993) is defined analogous to the ACGIH TLV-STEL.

[e]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects. The revised IDLH for nickel carbonyl is 2 ppm based on being 2,000 times the current OSHA permissible exposure limit (PEL) of 0.001 ppm. (2,000 is an assigned protection factor for respirators; only the most reliable respirators are recommended above 2,000 times the OSHA PEL). NIOSH recommends, as part of its carcinogen policy, that the most protective respirator be worn for nickel carbonyl at concentrations above 0.001 ppm.

[f]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits–Time-Weighted Average) (NIOSH 1994) is defined analogous to the ACGIH-TLV-TWA.

[g]NIOSH REL-STEL (Recommended Exposure Limits–Short-Term Exposure Limit) (NIOSH 1994) is defined analogous to the ACGIH TLV-STEL.

[h]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–Time-Weighted Average) (ACGIH 1997) is the time-weighted average concentration for a normal 8-h workday and a 40-h work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[i]ACGIH TLV-STEL (Threshold Limit Value–Short-Term Exposure Limit) (ACGIH 1997) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

[j]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany) (DFG 1999) is defined analogous to the ACGIH-TLV-TWA.

[k]MAK Spitzenbegrenzung (Kategorie II,2) (Peak Limit Category II,2) (DFG 1999) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min, with no more than two exposure periods per work shift; total exposure may not exceed 8-h MAK. Category III indicates possible significant contribution to cancer risk.

TABLE 9-18 Continued

[l]Einsatztoleranzwert (Action Tolerance Levels) (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 h without any health risks.
[m]As nickel.
Note: NR: not recommended. Numerical values for AEGL-1 are not recommended because of the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

8.3. Data Adequacy and Research Needs

There were insufficient data to develop of AEGL-1 values. Lethality studies in four species and developmental toxicity studies in two rodent species provided data that were sufficient for the development of AEGL-2 and AEGL-3 values. Human data indicated the extreme toxicity of nickel carbonyl but lacked definitive exposure terms with which to develop AEGL values. Both human and animal data affirm the progressive toxicity of nickel carbonyl following a single exposure and the inherent asymptomatic latency between initial exposure and more severe and often lethal effects. Analysis of occupational exposure data based on area samples of workers exposed to nickel carbonyl indicated that minor respiratory effects (altered spirometric indices) were associated with long-term low-level (up to 0.07 ppm) exposure. Data were lacking for evaluating species variability and individual variability in the nonlethal toxic response to nickel carbonyl.

Data limitations regarding nonlethal exposure responses may be due to the extreme toxicity of the compound, whereby manifestation of any signs and symptoms of toxicity is indicative of exposures great enough to induce lethal effects. The latency period between what initially appear to be relatively mild effects and subsequent lethality also contributes to the difficulty in developing AEGL values, especially for AEGL-1 and AEGL-2 levels. Lethality data currently imply that the mouse is the most sensitive species (the lowest 30-min LC_{50} is for the mouse), but no developmental toxicity studies or other toxicity assays have been reported for this species; therefore, it is uncertain whether this sensitivity is also reflected in nonlethal end points. More definitive information on mechanism of action would be useful for understanding the toxic responses to nickel carbonyl.

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APPENDIX A

Derivation of AEGL-1 Values

Quantitative data regarding responses consistent with the AEGL-1 definition were not available for acute inhalation exposure to nickel carbonyl. Available data indicate that toxic effects in humans may occur in the absence of detection. Because of the lack of appropriate data, AEGL-1 values could not be determined and, due to the extreme toxicity of nickel carbonyl and the documented latency between relatively asymptomatic exposures and severe toxicity, are not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Derivation of AEGL-2 Values

Key study:	Kincaid et al. 1953.
Toxicity end point:	Estimated threshold for pulmonary damage in mice exposed to 2.17 ppm for 30 min.
Scaling:	Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a scaling factor (n) was not possible. The concentration exposure-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. $(2.17 \text{ ppm})^1 \times 0.5 \text{ h} = 1.09 \text{ ppm h}$ $(2.17 \text{ ppm})^3 \times 0.5 \text{ h} = 5.1 \text{ ppm}^3 \text{ h}$
Uncertainty factors:	3 for interspecies variability. The available lethality data suggest that the mouse represents a sensitive species. Based on available lethality data and the analysis conducted by Kincaid et al. (1953) indicating an inverse relationship between lethality and body size (see Section 4.4.1.), the interspecies uncertainty factor of 3 appears to be justified.

	3 for intraspecies variability. Although intraspecies variability is difficult to assess based on available data, an uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. Additionally, the occupational exposure data reported by Shi et al. (1994b) suggest that the AEGL-2 values are sufficiently protective.
Modifying factor:	A modifying factor of 3 was applied to account for data deficiencies regarding AEGL-2 specific effects and to account for the possible developmental toxic effects.
10-min AEGL-2:	$C^3 \times 0.167$ h = 5.1 ppm^3·h C = 3.1 ppm 10-min AEGL-2 = 3.1 ppm/30 = 0.10 ppm (0.69 mg/m^3)
30-min AEGL-2:	$C^1 \times 0.5$ h = 1.09 ppm·h C = 2.17 ppm 30-min AEGL-2 = 2.17 ppm/30 = 0.072 ppm (0.50 mg/m^3)
1-h AEGL-2:	$C^1 \times 1$ h = 1.09 ppm·h C = 1.03 ppm 1-h AEGL-2 = 1.09 ppm/30 = 0.036 ppm (0.25 mg/m^3)
4-h AEGL-2	$C^1 \times 4$ h = 1.09 ppm·h C = 0.27 ppm 4-h AEGL-2 = 0.27 ppm/30 = 0.0090 ppm (0.063 mg/m^3)
8-h AEGL-2:	$C^1 \times 8$ h = 1.09 ppm·h C = 0.136 ppm 8-h AEGL-2 = 0.136 ppm/30 = 0.0045 ppm (0.031 mg/m^3)

Derivation of AEGL-3 Values

Key study:	Kincaid et al. 1953
Toxicity end point:	Estimated 30-min lethality threshold in mice: 3.17 ppm, using the mouse lethality data from Sunderman et al. (1980) and the method of Litchfield and Wilcoxon (1949) (see Appendix D).
Scaling:	$C^n \times t = k$ (ten Berge 1986). Data were unavailable for determining the exponent n. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent *n* ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. $(3.17 \text{ ppm})^1 \times 0.5 \text{ h} = 1.58 \text{ ppm}\cdot\text{h}$ $(3.17 \text{ ppm})^3 \times 0.5 \text{ h} = 15.93 \text{ ppm}^3\cdot\text{h}$
Uncertainty factors:	Total uncertainty adjustment of 10 (each uncertainty factor of 3 is the logarithimic mean of 10, which is 3.16; hence, 3.16. × 3.16 = 10). Lethality data from the smallest and, according to Kincaid et al. (1953), the most sensitive species was used for development of the AEGL-3. For this reason, and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion adjustment between inter- and intraspecies uncertainty.
10-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 15.93 \text{ ppm}^3\cdot\text{h}$ C = 4.57 ppm 10-min AEGL-3 = 4.57 ppm/10 = 0.46 ppm (3.2 mg/m^3)

30-min AEGL-3: $C^1 \times 0.5$ h = 1.58 ppm·h
C = 3.17 ppm
30-min AEGL-3 = 3.17 ppm/10 = 0.32 ppm
(2.2 mg/m^3)

1-h AEGL-3: $C^1 \times 1$ h = 1.58 ppm·h
C = 1.58 ppm
1-h AEGL-3 = 1.58 ppm/10 = 0.16 ppm (1.1 mg/m^3)

4-h AEGL-3: $C^1 \times 4$ h = 1.59 ppm·h
C = 0.398 ppm
4-h AEGL-3 = 0.398 ppm/10 = 0.040 ppm
(0.27 mg/m^3)

8-h AEGL-3: $C^1 \times 8$ h = 1.59 ppm·h
C = 0.198 ppm
8-h AEGL-3 = 0.198 ppm/10 = 0.020 ppm
(0.14 mg/m^3)

APPENDIX B

CARCINOGENICITY ASSESSMENT FOR NICKEL CARBONYL

CANCER ASSESSMENT OF NICKEL CARBONYL

Quantitative data regarding the carcinogenicity of nickel carbonyl in humans and laboratory species are unavailable, and therefore neither a cancer slope factor nor unit risk can be derived. The available evidence does not support a definitive assessment of cancer risk in humans for a single once-in-a-lifetime acute exposure. Epidemiologic data do not support the contention that inhalation of nickel carbonyl is carcinogenic to humans. Based on inadequate human data and limited data in animals, EPA (2003) categorizes nickel carbonyl as B2 (potential human carcinogen), while the IARC (1987) specifically states that nickel carbonyl was considered unlikely to be involved in causing cancers among nickel refinery workers.

APPENDIX C

DETERMINATION OF LETHALITY THRESHOLDS

Mouse lethality data: Kincaid et al. (1953) (see Table 9-8).

Dose (ppm)	Mortality	Observed, %	Expected, %	Observed	Expected Chi-Square
2.170	0/12	0 (0.30)	0.21	0.09	0.0004
6.510	2/15	13.33	16.46	–3.13	0.0071
7.840	3/10	30.00	29.83	0.17	0.0000
8.680	10/29	34.48	39.30	–4.82	0.0097
9.800	10/20	50.00	51.68	–1.68	0.0011
10.900	12/22	54.55	62.41	–7.86	0.0264
12.600	10/10	100 (92.20)	75.14	17.06	0.1558

Values in parentheses are corrected for 0 or 100 percent. Total = 0.2005.
LC_{50} = 9.642(8.609 – 10.800)*
Slope = 1.49(1.37 – 1.63)*
*These values are 95 percent confidence limits.
Total animals = 118. Total doses = 7. Animals/dose = 16.86.
Chi-square = total chi-square × animals/dose = 3.3800.
Table value for Chi-square with 5 degrees of freedom = 11.0700.
LC_{84} = 14.398. LC_{16} = 6.457

Expected Lethal Concentration Values (ppm)	
$LC_{0.1}$	1.814
$LC_{1.0}$	3.174
$LC_{5.0}$	4.731
LC_{10}	5.668
LC_{25}	7.392
LC_{50}	9.642
LC_{75}	12.577
LC_{90}	16.404
LC_{99}	29.296

Rat lethality data: Kincaid et al. (1953) (see Table 9-6).

Dose (ppm)	Mortality	Observed, %	Expected, %	Observed Expected	Chi-Square
67.000	19/30	94.00	89.13	4.87	0.0245
67.000	9/10	90.00	89.13	0.87	0.0008
105.000	24/30	80.00	90.66	–10.66	0.1342
168.000	30/30	100 (94.30)	92.05	2.25	0.0069
266.000	30/30	100 (94.30)	93.22	1.08	0.0018
266.000	10/10	100 (94.30)	93.22	1.08	0.0018

Values in parentheses are corrected for 0 or 100 percent: Total = 0.1700.
LC_{50} = 0.246(0.057 – 1.062)*
Slope = 82.91(0.00 – 450639439.54)*.
*These values are 95 percent confidence limits.
Total animals = 140. Total doses = 6. Animals/dose = 23.33.
Chi-square = Total chi-square × animals/dose = 3.9672.
Table value for chi-square with 4 degrees of freedom = 9.4900.
LC_{84} = 20.398: LC_{16} = 0.003

Expected Lethal Concentration Values (ppm)	
$LC_{0.1}$	0.000
$LC_{1.0}$	0.000
$LC_{5.0}$	0.000
LC_{10}	0.000
LC_{25}	0.013
LC_{50}	0.246
LC_{75}	4.596
LC_{90}	85.860
LC_{99}	511.48

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR NICKEL CARBONYL

Derivation Summary for Nickel Carbonyl AEGLS

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
NR	NR	NR	NR	NR

Key reference: NA

Test species/Strain/Number: NA

Exposure route/Concentrations/Durations: NA

Toxicity end point: NA

Time scaling: NA

Concentration/Time selection/Rationale: NA

Uncertainty factors/Rationale
Total uncertainty factor: NA

Modifying factor: NA

Animal to human dosimetric adjustments: NA

Data adequacy: Quantitative data regarding responses consistent with the AEGL-1 definition were not available for acute inhalation exposure to nickel carbonyl, and therefore AEGL-1 values are not recommended (NR). Available data indicate that toxic effects in humans may occur in the absence of detection. Because of the lack of appropriate data, AEGL-1 values could not be determined and, due to the extreme toxicity of nickel carbonyl and the documented latency between relatively asymptomatic exposures and severe toxicity, are not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentrations are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

Key reference: Kincaid, J.F., J.S. Strong, and F.W. Sunderman. 1953. Nickel poisoning. 1. Experimental study of the effects of acute and subacute exposure to nickel carbonyl. Arch. Ind. Hyg. Occup. Med. 8:48-60.

Test species/Strain/Number: albino mice; gender and strain not specified

Exposure route/Concentrations/Durations: inhalation, 2.17 ppm 30 min

Toxicity end point: Exposure to 2.17 ppm for 30 min caused no deaths and was considered a NOAEL for severe damage pulmonary tissue. Exposure to 6.51 ppm resulted in the death of 2/15 mice. Although no pathology examinations were performed on the mice, lethal exposure of rats to nickel carbonyl caused

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

Toxicity end point *(continued)*: severe pulmonary edema, pulmonary congestion, and pleural effusion. It is assumed that mice (most sensitive species) exposed to 2.17 ppm for 30 min would exhibit some effects on pulmonary tissue. Pulmonary damage appears to be a component in the continuum of the toxic response to nickel carbonyl and an appropriate critical effect for AEGL-2 development. The 30-min exposure to 2.17 ppm was considered a point-of-departure representative of a NOAEL for AEGL-2 effects.

Time scaling: Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a scaling factor (n) was not possible. The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5. In the absence of an empirically derived exponent n, and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

Concentration/Time selection/Rationale: Groups of 15 mice exposed for 30 min to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, or 12.6 ppm. A concentration-dependent lethal response was observed for exposures to 6.51-12.6 ppm, but the lowest exposure (2.17 ppm) resulted in no deaths. Exposure to 6.51 ppm resulted in the death of 2/15 mice. The 2.17 ppm exposure for 30 min was considered a NOAEL for severe damage to pulmonary tissue.

Uncertainty factors/Rationale:
Total uncertainty: 10

- Interspecies: An uncertainty factor of 3 was applied to account for interspecies variability. The available lethality data suggest that the mouse represents a sensitive species. Based on available lethality data and the analysis conducted by Kincaid et al. (1953) indicating an inverse relationship between lethality and body size (see Section 4.4.1.), the interspecies uncertainty factor of 3 appears to be justified.
- Intraspecies: An uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. The occupational exposure data reported by Shi et al. (1994b) suggest that the AEGL-2 values are sufficiently protective.

Modifying factor: 3; the overall dataset for nickel carbonyl is deficient regarding nonlethal effects of nickel carbonyl inhalation. Therefore, a modifying factor of 3 was applied in the development of the AEGL-2 values to account for these

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

Modifying factor *(continued)*: deficiencies and the possibility of developmental toxic effects reported by Sunderman and colleagues.

Animal to human dosimetric adjustments: None applied; insufficient data.

Data adequacy: Data regarding AEGL-2 specifics effects are lacking. The AEGL-2 is based on an estimated threshold for severe pulmonary damage with considerations based on selection of a sensitive species and a critical effect and point of departure appropriate for AEGL-2 development. The data deficiencies have been acknowledged by application of a modifying factor.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm

Key reference: Kincaid et al. 1953.

Test species/Strain/Number: 10-20 albino mice (age, gender and strain not specified)

Exposure route/Concentrations/Durations: Inhalation (whole-body exposure) exposure to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, or 12.6 ppm for 30 min

Toxicity end point: Lethality; LC_{01} estimated by method of Litchfield and Wilcoxon (1949)

Concentration (ppm)	Response (Number Dead/Number Exposed)
2.17	
6.51	
7.84	
8.68	
9.80	
10.9	
12.6	

0-min LC_{01} estimated at 3.17 ppm was used as the determinant of AEGL-3.

Time scaling: Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a scaling factor (n) was not possible. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5. In the absence of an empirically derived exponent n, and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (ten Berge et al. 1986).

Concentration/Time selection/Rationale: Estimated 30-min LC_{01} (3.17 ppm)

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm

Uncertainty factors/Rationale:
Total Uncertainty Factor: 10 (Each uncertainty factor of 3 is the approximate logarithmic mean of 10, which is 3.16; hence, 3.16. × 3.16 = 10. Lethality data from the smallest and the most sensitive species were used for development of the AEGL-3. For this reason, and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion adjustment between inter- and intraspecies uncertainty.

Modifying factor: None.

Animal to human dosimetric adjustments: None applied; insufficient data.

Data adequacy: The AEGL-3 values were based on a reasonable estimate of the lethality threshold in a sensitive species. The key study was properly designed and conducted.

APPENDIX E

CATEGORY PLOT FOR NICKEL CARBONYL AEGLS

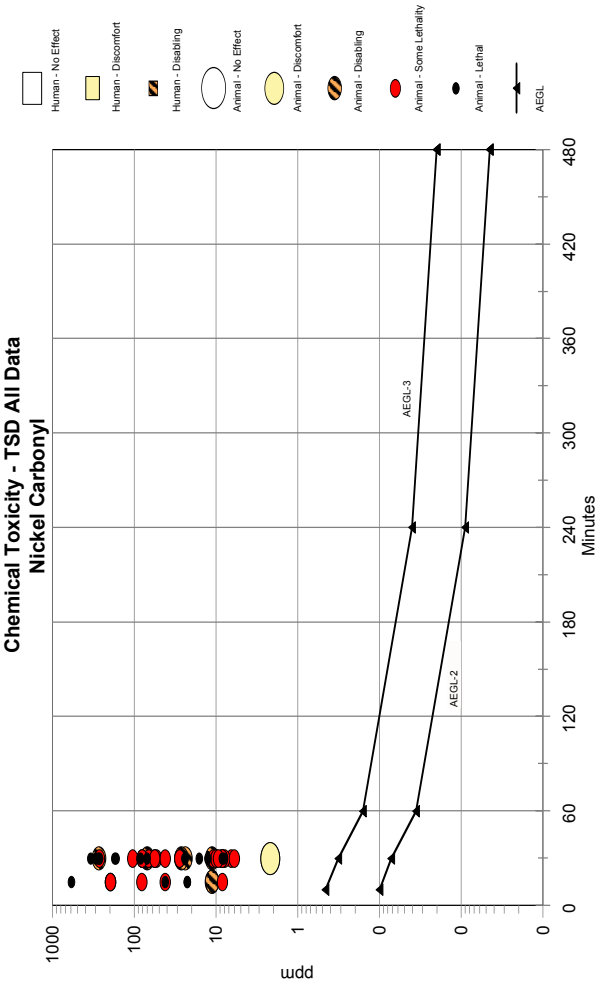

FIGURE 9-1 Chemical toxicity; TSD all data, nickel carbonyl.