# ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
# FOR
# CADMIUM
# (CAS Reg. No. 7440-43-9)

# Cd

# INTERIM

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## PROPOSED

## PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop 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 to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) 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 or milligrams per cubic meter [ppm or mg/m3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory 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/m3) 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/m3) 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 could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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

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# EXECUTIVE SUMMARY

Cadmium (Cd) is a metal used in a variety of consumer and industrial materials with a high percentage used in the production of nickel-cadmium batteries and in electroplating. It is also in pigments used in plastics, ceramics and glasses and is used as a stabilizer for polyvinyl chloride (PVC). World production between 1990 and 2000 was ~19,000 tons/year (Morrow, 2001). Estimated U.S. production of cadmium was about 1450 metric tons in 2003 and 700 metric tons in 2006 (ATSDR 2008).

Human exposure to cadmium can be from inhalation of cadmium containing particles, inhalation of cigarette smoke or inhalation from fumes/dust in an occupational setting. In case reports of accidental acute exposure, cadmium caused respiratory irritation, dyspnea, alveolar damage, pneumonitis, and death. Chronic occupational exposure caused decreased lung function. Cadmium and cadmium compounds are characterized as *"probable human carcinogens"* based on evidence of carcinogenicity in humans (U.S. EPA 1994). Respiratory cancers were increased in workers at a Cd-nickel battery factory, however, chronic Cd exposure was not found to lead to lung carcinogenicity. In animal inhalation studies, cadmium oxide is used as it is the most common airborne form of cadmium. The size of the cadmium particle often determines the extent of absorption and distribution. Cadmium, in various forms, caused respiratory irritation, pulmonary edema, rales, pneumonitis, lacrimation, increased alveolar macrophages, and death in rabbits and rats exposed for 1-6 hours. Rats and mice exposed for 90 days or less exhibited pulmonary inflammation and edema, pulmonary hyperplasia, nasal and respiratory epithelium degeneration, and renal lesions. In carcinogenicity studies, rats exposed to Cd had an increased incidence of primary lung carcinomas.

The AEGL-1 values are based on the experimental concentration, 0.55 mg Cd/$m^3$, that caused slight respiratory irritation in rats (Takenaka et al. 2004). After a 6 hour exposure, increased neutrophils and multifocal alveolar inflammation were observed. At the next higher experimental exposure, pneumonitis was observed (Grose et al. 1987). Although the exposure was a whole-body exposure, the size of the ultrafine particles (51 nM MMAD, 1.7 GSD) would mimic a gaseous state and the majority of the aerosol would be inhaled and not deposited on the fur. An interspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant as indicated by the signs of irritation in rabbits and rats. This mode of action is not expected to differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/$m^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/$m^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. An intraspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant in humans, and this mode of action is not expected to differ among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, 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. The 30-minute AEGL-1 value was adopted as the 10-

minute value due to the added uncertainty of extrapolating from a 6-hour time point to 10 minutes (NRC 2001).

The AEGL-2 values are based on the experimental concentration, 5.3 mg Cd/$m^3$, that caused overt respiratory irritation and pathology in rats (Buckley and Bassett 1987). The 3 hour exposure resulted in reduced weight gain and increased lung weight, protein content, DNA content, number of cuboidal alveolar cells, number of inflammatory cells, and focal areas of interstitial thickening. An interspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant as indicated by the signs of irritation in rabbits and rats. This mode of action is not expected to differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/$m^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/$m^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. An intraspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant in humans, and this mode of action is not expected to differ among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, 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.

The AEGL-3 values are based on the 2 hour $LC_{50}$ for cadmium fume in rats, 112 mg/$m^3$ (Rusch et al. 1986). The $LC_{50}$ was divided by 3 to estimate a threshold of lethality. An interspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant as indicated by the signs of irritation in rabbits and rats. This mode of action is not expected to differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/$m^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/$m^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. An intraspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant in humans, and this mode of action is not expected to differ among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, 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.

The calculated values are listed in the table below.

**TABLE 1. Summary of AEGL Values Cadmium**

| Classification | 10-min | 30-min | 1-hr | 4-hr | 8-hr | Endpoint (Reference) |
|---|---|---|---|---|---|---|
| **AEGL−1 (Nondisabling)** | 0.13 mg/m$^3$ | 0.13 mg/m$^3$ | 0.10 mg/m$^3$ | 0.063 mg/m$^3$ | 0.041 mg/m$^3$ | Respiratory irritation, 0.55 mg Cd/m$^3$ for 6 hr (Takenaka et al. 2004) |
| **AEGL−2 (Disabling)** | 1.4 mg/m$^3$ | 0.96 mg/m$^3$ | 0.76 mg/m$^3$ | 0.40 mg/m$^3$ | 0.20 mg/m$^3$ | Overt respiratory tract irritation and pathology, 5.3 mg/m$^3$ CdO for 3 hr Buckley and Bassett. 1987) |
| **AEGL−3 (Lethal)** | 8.5 mg/m$^3$ | 5.9 mg/m$^3$ | 4.7 mg/m$^3$ | 1.9 mg/m$^3$ | 0.93 mg/m$^3$ | Threshold of lethality based on the 2-hr rat $LC_{50}$ for Cd fumes, 112 mg/m$^3$ (Rusch et al. 1986) |

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## 1. INTRODUCTION

Cadmium is used in a variety of consumer and industrial materials with a high percentage used in the production of nickel-cadmium batteries and in electroplating. It is also in pigments used in plastics, ceramics and glasses and as a stabilizer for polyvinyl chloride (PVC). The demand for cadmium has decreased since the 1990s as lithium-ion and nickel metal hydride batteries become more popular (ATSDR 2008). World production between 1990 and 2000 was ~19,000 tons/year (Morrow 2001). Estimated U.S. production of cadmium was about 1450 metric tons in 2003 and 700 metric tons in 2006 (ATSDR 2008). Human exposure to cadmium can be from consumption of food, drinking water, incidental ingestion of soil or dust, inhalation of cadmium containing particles, inhalation of cigarette smoke, or inhalation from fumes/dust in an occupational setting. Cadmium is usually not present in the environment as pure metal but as a mineral combined with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride) or sulfur (cadmium sulfate/sulfide) (ATSDR 2008). These forms are also solids but some are water soluble.

**TABLE 2. Chemical and Physical Properties**

| Parameter | Value | References |
|---|---|---|
| Synonyms | Colloidal cadmium | |
| Chemical formula | Cd | HSDB 2005 |
| Molecular weight | 112.41 g | HSDB 2005 |
| CAS Reg. No. | 7440-43-9 | HSDB 2005 |
| Physical state | Silver-white, blue-tinged, lustrous metal; solid | HSDB 2005 |
| Solubility in water | Insoluble in water | HSDB 2005 |
| Vapor pressure | 1 mm Hg @ 394°C | ATSDR 2008 |
| Vapor density (air =1) | - | - |
| Liquid density (water =1) | - | - |
| Melting point | 321ºC | HSDB 2005 |
| Boiling point | 765ºC | HSDB 2005 |
| Flammability limits | Powder flammable in air; Auto-ignites at 250 ºC | ACGIH 1996; NIOSH 2005 |
| Conversion factors | 1 ppm = 4.6 mg/$m^3$<br>1 mg/$m^3$ = 0.22 ppm | Calculated by reviewer using<br>1 ppm = mg/$m^3$ x 24.45/112.4 |

**TABLE 3. Chemical and Physical Properties of Cadmium Compounds**

| | Cd carbonate | Cd chloride | Cd oxide | Cd sulfate | Cd sulfide |
|---|---|---|---|---|---|
| Synonyms | Carbonic acid, cadmium salt | Dichlorocadmium | Cadmium fume; cadmium monoxide | Sulfuric acid, cadmium salt | Cadmium yellow; Cadmium orange |
| Chemical formula | $CdCO_3$ | $CdCl_2$ | CdCO | $CdSO_4$ | CdS |
| Molecular wt. | 172.42 | 183.32 | 128.41 | 208.47 | 144.47 |
| CAS No. | 513-78-0 | 10108-64-2 | 1306-19-0 | 10124-36-4 | 1306-23-6 |
| Physical state | White powder or rhombohedral leaflets | Colorless, rhombohedral crystals | Dark brown infusible powder or cubic crystals | Colorless monoclinic crystals | Light yellow or orange cubic or hexagonal structure |
| Solubility in water | Insoluble | Soluble | Insoluble | Soluble | Soluble at 1.3 mg/L @ 18 °C |
| Vapor pressure | – | 10 mm Hg @ 656 °C | 1 mm Hg @ 1000 °C | – | – |
| Vapor density (air =1) | 4.26 g/cm$^3$ @ 4°C | 3.3 g/cm$^3$ @ 20°C | Crystals- 8.15 g/cm$^2$; amorphous powder- 6.95 g/cm$^3$ | 4.69 g/cm$^3$ | Hexagonal structure- 4.82 g/cm$^3$; Cubic structure- 4.5 g/cm$^3$ |
| Liquid density (water =1) | – | – | – | – | – |
| Melting point | Decomposes (< 500 °C) | 568 °C | – | 1000 °C | 1750 °C |
| Boiling point | – | 960 °C | Sublimes at 1559 °C | - | Sublimes in $N_2$ @ 980 °C |
| Flammability limits | – | – | – | – | – |
| Conversion factors | 1 mg/m$^3$ = 0.14 ppm | 1 mg/m$^3$ = 0.13 ppm | 1 mg/m$^3$ = 0.19 ppm | 1 mg/m$^3$ = 0.12 ppm | 1 mg/m$^3$ = 0.17 ppm |

Data from ATSDR, 2008
- No data available

# 2. HUMAN TOXICITY DATA

## 2.1. Acute Lethality

### 2.1.1. Case Reports

Numerous case reports are available on acute inhalation exposure to Cd; while some report the Cd levels in tissues, very few have the actual Cd exposure concentrations. Panchal and Vaideeswar (2006) reported on a man exposed to an unknown concentration of Cd oxide fumes who developed a cough, dyspnea and finally died. Fernández et al. (1996) reported on a man exposed to Cd fumes for approximately 60-75 minutes while flame-cutting an alloy containing about 10% Cd. The man developed dyspnea 4 hours after finishing work, was hospitalized, and on day 15 after exposure, the blood and urine concentration of cadmium was 0.34 µg/100 mL (control = 0.11 µg/100 mL) and creatinine was 17.6 µg/g (control = 0.2 µg/g). He had multi-organ failure and died after 19 days. Autopsy showed diffuse alveolar damage to the lungs with beginning intra-alveolar fibrosis. Concentrations of cadmium in tissues were 823 ng/g liver, 3571 ng/g kidney and 1143 ng/g lung. The author stated that exposures to 200-500 µg/m$^3$ usually result in "metal fume fever" that lasts for one to two days, so this patient was almost certainly exposed to a much higher concentration.

A man was exposed for ~5 hours to a brownish-yellowish smoke during a copper smelting process after which he complained of fatigue and nausea (Yamamoto et al. 1983). The clinical signs continued to worsen with hypoxemia developing. On day 2, Cd was 6 µg/mL in the blood and on day 5 was 332 µg/mL in the urine. Twelve days after the accident, the man died, and the cadmium content of the right upper lung lobe was found to be 1.06 µg/g.

Five workers were accidentally exposed to Cd fumes for 5 hours in a tank while using an oxyacetylene burner to melt off bolts made of cadmium (Beton et al., 1966). Cadmium oxide was released due to the heat of the burner. None of the men except for the burner wore any type of respiratory protection. All men experienced coughing and slight irritation of the throat during exposure with dyspnea developing 4-10 hours later. One man died on post-exposure day 5; all others had degrees of pulmonary edema that resolved over time. The man that died was found to have severe pulmonary edema, alveolar metaplasia of the lungs and bilateral cortical necrosis of the kidneys. The lungs contained 0.25 g CdO per 100 g wet specimen. The author speculated that if 11% of the inhaled CdO was retained in the lungs (% retention was estimated based on earlier work in five animal species), approximately 51.7 mg CdO fume must have been inhaled. Working for 5 hours with a ventilatory rate of 20 L/min, the concentration of CdO in the air would have been about 8.6 mg/$m^3$ or 2,580 minute-mg/$m^3$.

## 2.2. Nonlethal Toxicity

### 2.2.1. Odor Threshold/Odor Awareness

Cadmium is odorless (HSDB 2005).

### 2.2.2. Epidemiologic Studies

Jakubowski et al. (2004) looked at long-term occupational exposure and lung function of 79 workers (median age: 50.4 ± 8.9 years; 35 men and 44 women) to Cd in a cadmium battery factory (mean period of 17.4 ± 9.1 years). For comparison, 159 non-exposed workers (48.4 ± 4.2 years; 91 men and 68 women) were used as controls. Subjects were divided into four groups depending on their cumulative cadmium exposure calculated either by cadmium levels in the blood x time or cadmium levels in the air x time. The range of Cd-Blood (µg/L) x time (years) was < 25, 25-500, > 500-1000 or > 1000 and for Cd-Air (mg Cd/$m^3$) x time (years) was <0.01, 0.10-1.5, > 1.5-4.0 or > 4. Lung function was evaluated using a LUNGTEST 500 spirometer and measuring the following: forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), peak expiratory flow (PEF), mid expiratory flow (MEF) at 25, 50 and 75%, vital capacity (VC), inspiratory capacity (IC) and the percentage of the $FEV_1$/FVC ratio. Statistically significant decreases in $FEV_1$ (85% of predicted values, p=0.0208), PEF (76% of predicted values, p=0.0488), MEF 25% (103 % of predicted values, p=0.0404), MEF 50% (86% of predicted values, p=0.0169) and MEF 75% (78% of predicted values, p= 0.0248) were observed in the workers exposed to >1000 µg/L x years as measured by Cd-blood concentration compared to controls. Workers in the group exposed to > 4 mg Cd-air x time also had a significant decrease in MEF 50% and slight decrease in the $FEV_1$. The results indicated that long-term exposure could cause some decrease in lung function suggestive of mild airway obstruction. Table 4 provides the Cd concentrations in the blood of workers and Cd concentrations found at the plant.

| TABLE 4. Blood Cd Concentrations of Workers and Air Cd Concentrations | | | |
|---|---|---|---|
| **Parameter** | **N** | **Geometric mean ± GSD** | **Range** |
| **1983** | | | |
| Cd x B (µg/L) | 43 | 31.8 ± 2.14 | 9.11 - 166 |
| Cd x A ($mg/m^3$) | | | 0.08 – 0.51 |
| **1986-1988** | | | |
| Cd x B (µg/L) | 91 | 29.1 ± 2.01 | 4.1 – 120.3 |
| Cd x A ($mg/m^3$) | | | 0.03 – 0.38 |
| **1998-1999** | | | |
| Cd x B (µg/L) | 116 | 9.2 ± 2.14 | 0.5 – 42.1 |
| Cd x A ($mg/m^3$) | | | 0.03 – 0.032 |

Data from Jakubowski et al. (2004)
B= Blood; A= Air

Lauwerys et al. (1979) followed eleven male workers in a small factory producing cadmium salts and monitored the cadmium levels in their blood and urine as well as the air exposure levels for 13 months. Nine of eleven men wore personal air monitors and the exposure levels (excluding outliers) ranged from 88 to 6276 $\mu g/m^3$, equivalent to 0.088 to 6.276 $mg/ m^3$. Most of the exposures were to cadmium oxide. Health effects were not evaluated.

## 2.3. Neurotoxicity

No data were located.

## 2.4. Developmental/Reproductive Toxicity

Fifty seven Japanese women, 58.1% of whom had delivered infants of gestational age of more than 30 weeks, and their infants were tested to determine if maternal urinary levels of Cd had any effect on the infant growth, gestational age at birth and/or the Cd level in the breast milk (Nishijo et al., 2002). All subjects lived in areas close to a Cd polluted region where *itai-itai* disease, the most severe manifestation of chronic cadmium poisoning, is still being eliminated. No differences were found in the women's socioeconomic status, nutrition status or prenatal care. Maternal urine and breast milk samples were taken on the fifth or eighth day post-partum and information about occupational or environmental exposure to Cd, including smoking, was obtained. Eight women were smokers (6 in the low Cd group and 2 in the high Cd group); however, 6/8 had stopped smoking early in pregnancy making smoking less relevant to current Cd levels. Women were divided into two groups based on the samples, those with urinary Cd of $< 2$ µg/g Creatinine (Cr) (n= 45) and those with $\geq 2$ µg/g Cr (n= 12). This value of 2 µg/g Cr was derived from previous studies stating that those exposed to 2 µg/g Cr were found to have 10% proteinuria. In the infants from mothers with higher Cd levels, the mean gestational age at birth (37 weeks vs. 39.1 weeks), height at birth (47.2 cm vs. 49.2 cm) and weight at birth (2663 g vs. 3099g) were significantly lower ($p< 0.01$ and 0.05) than the infants of mothers with Cd levels $< 2$ µg/g Cr. The number of infants delivered by Cesarean section (7 % vs. 4%) was also higher in the high Cd mothers compared to the mothers having lower Cd levels. Multiple regression analysis indicated that an increase of maternal urinary Cd was related to a decrease in gestational age after adjustment for maternal age. Samples of breast milk also had a higher mean concentration of Cd in mothers in the high Cd group. Overall, the study suggested that Cd exposure may increase the possibility of pre-term births thus indirectly causing decreased birth weight.

## 2.5. Genotoxicity

Data are summarized from IARC 2003.

Human female *itai-itai* patients (n=12) exposed to cadmium through the diet had higher incidences of chromosomal aberrations of all types in peripheral blood lymphocytes than age-matched control subjects (n=9). However, there were no differences in the frequencies of cells with structural aberrations in cultures from blood of four female *itai-itai* patients compared to four control subjects.

No differences in chromosomal aberrations of lymphocytes were observed between five alkaline battery factory workers and three office workers. The battery workers had been employed for 5-24 years and the average cadmium concentration in personal air samples was estimated to be 0.70 $mg/m^3$. Blood cadmium concentration in the battery workers was 37.7 ng/g and 2.3 ng/g in the office workers.

No differences were found in chromosomal or chromatid aberration frequency in workers exposed from six weeks to 34 years in a cadmium pigment plant when compared to controls, administrative and laboratory personnel at the same plant.

No difference was observed in the incidence of chromosomal aberrations in workers exposed to cadmium dusts for 6-25 years when compared to the office worker controls.

A small increase in the incidence of chromosomal aberrations was observed in smelter workers when compared to non-smelter control subjects. It was not determined if smoking habits were included as a source of cadmium exposure.

Abnormal metaphase rates were significantly higher in peripheral blood lymphocytes in male workers exposed to cadmium fumes and dusts compared to the age-matched controls.

Cadmium chloride induced sister chromatid exchange in human lymphocytes in vitro.

## 2.6. Carcinogenicity

Sorahan and Esmen (2004) reported on a cohort study occurring from 1947-2000 involving 926 males that worked at a Cd-nickel battery factory. The aim was to investigate mortality of the workers in relation to cumulative cadmium hydroxide exposure. All those included in the study were required to have worked at the factory for a minimum of 12 months. Work histories were available from 1947-1986 and the factory closed in 1992. Two approaches were used to analyze the data: indirect standardization and Poisson regression. Based on the serial mortality rates for England and Wales, significantly increased mortality was observed for cancers of the pharynx (observed 4, expected 0.7; standardized mortality ratio (SMR) 559, $p<0.05$), non-malignant diseases of the respiratory tract (observed 61, expected 43; SMR 142, $p< 0.05$), and non-malignant diseases of the genitourinary system (observed 10, expected 4.1; SMR 243, $p< 0.05$). Non-significantly increased SMRs were observed for lung cancer (observed 45, expected 40.7; SMR 111) and prostate cancer (observed 9, expected 7.5; SMR 116). The results do not indicate that chronic cadmium hydroxide exposure leads to carcinogenicity in the lung,

but that it does lead to increase in non-malignant diseases of the respiratory and genitourinary systems and pharyngeal cancers.

A mortality study of 602 white males with at least 6 months of production work in the same factory between 1940 and 1969 was performed to determine the effects of Cd exposure (Thun et al., 1985). Workers were followed until 1978. Cause-specific mortality rates for seven causes of death were compared between the workers and average US white males. Cadmium inhalation exposure concentrations measured in the plant ranged from 0.007 to 1.5 mg/$m^3$ from pre-1950 to 1976, depending on the area of work. Most of the Cd exposure was to Cd oxide. The study population was obtained from employment histories from the personnel files. Mortality was analyzed with the use of the modified life-table system developed by NIOSH. Of all the workers, 83% had over 20 years of follow-up. For respiratory cancer, the expected rate was 12.15 and the actual rate was 20. All 20 had over 2 years of employment and all mortalities were due to cancers of the lung, trachea and bronchus. Six deaths (expected 4.45) from genitourinary cancer were observed with one due to renal cancer (expected 0.9), two due to cancers of the bladder or other urinary organs (expected 1.10) and three due to prostate cancer (expected 2.20). Nine deaths were from non-malignant gastrointestinal disease (NMGID) and the expected number was 2.35. Even with adjustments to account for the lack of knowledge of the worker's smoking habits and the fact that arsenic was used in the same factory prior to 1926, there is still an increase in the respiratory cancers.

Kjellström et al. (1979) reported on the mortality and cancer incidence of Swedish workers exposed to Cd for more than 5 years. Data were collected from 269 Cd-Ni battery factory workers and 94 Cd-Cu alloy factory workers. At the Cd-Ni factory, the levels of Cd in the air were: before 1947: >1 mg Cd/$m^3$; in the 1950's: 200 µg Cd/$m^3$; between 1962-1974: 50 µg Cd/$m^3$; and 1979: < 5 µg Cd/$m^3$. In this same factory, similar levels of nickel hydroxide were found in the air. In the Cd-Cu factory, cadmium concentrations were not obtained until the 1960s, when the levels were 100-400 µg Cd/$m^3$; since the 1970s, the value has been about 50 µg Cd/$m^3$. An internal reference group from the Cd-Cu factory was used; workers that were involved in processes not exposing them to any Cd. A life-table method with the national average cancer incidence rates for men in different age groups was used to help determine any correlation between Cd exposure and the cancer incidence. Among the cadmium nickel workers, the risk ratio for nasopharyngeal cancer was 10 (2 cases) which was statistically significantly higher than 1, the expected value. However, part of this increase could be attributed to the nickel hydroxide dust they were exposed to as well as the cadmium oxide dust. There was an increased tendency for mortality from prostate cancer (4 cases) in the Cd-Cu alloy workers; however, the risk ratio when calculated was not statistically significantly increased (2.4).

The U.S. EPA (1994) listed cadmium and cadmium compounds as probably human carcinogens based on limited evidence in occupational epidemiologic studies and sufficient evidence of carcinogenicity in rats and mice by inhalation, injection, and subcutaneous injection. An inhalation unit risk factor was calculated based on lung, trachea, and bronchus cancer death data in human males (Thun et al. 1985).

The International Agency for Research on Cancer (IARC 2003) concluded that there is sufficient evidence in humans for carcinogenicity of cadmium and cadmium compounds and categorized cadmium and cadmium compounds as being carcinogenic to humans.

## 2.7. Summary

Case reports, occupational studies, and epidemiological studies showed how inhalation of cadmium affected humans. Although the case reports did not include Cd exposure concentrations, they did show that acute accidental exposure to Cd caused respiratory irritation, dyspnea, alveolar damage, pneumonitis, and death. Chronic exposure to Cd in occupational settings caused decreased lung function and nephrotoxicity. The results of carcinogenicity studies in Cd workers were equivocal, which may be due to concurrent exposures to other metals in the workplace. Respiratory cancers were increased in workers at a Cd-nickel battery factory; although, chronic Cd exposure was not statistically correlated with lung cancer. The U.S. EPA (1994) and IARC (2003) list cadmium and cadmium compounds as being carcinogenic to humans. Maternal urine Cd concentration was associated with decreased gestational age and lower weight at birth.

# 3. ANIMAL TOXICITY DATA

## 3.1. Acute Lethality

### 3.1.1. Rat

Male Crl:CD(SD)Br rats, 24/group, were exposed by nose-only inhalation to 0, 0.25, 0.45 or 4.5 mg/m$^3$ of both $CdCl_2$ and CdO for 2 hours (Grose et al. 1987). The exposure concentrations were given as mg Cd/m$^3$. Animals were killed immediately or 72 hours post-exposure. The following parameters were determined: Cd content in the lungs, lung weight, body weight, biochemical responses and histopathological lesions in the lungs. Concentrations were measured using 47 mm cellulose acetate filters and analyzed by atomic absorption and found to be consistent in the chambers. Three exposed rats died during the study. Two rats in the 0.45 mg/m$^3$ CdO group died; one rat had cardiovascular failure associated with pulmonary congestion and the other had an undetermined cause of death. The exposure group of the third rat was not reported and cause of death was undetermined. It is believed that the rats died from causes related to complications with the exposure apparatus and not from exposure to cadmium. No deaths were reported in rats of the high-dose group.

Twenty six adult Sprague-Dawley CD rats/sex/group were exposed for 2 hours to 97 mg/m$^3$ of cadmium red pigment, 99 mg/m$^3$ cadmium yellow pigment, 132 mg/m$^3$ cadmium carbonate, or 112 mg/m$^3$ cadmium fume (Rusch et al. 1986). The exposure concentrations are based on cadmium content. An air control group was also included. Animals were exposed in a glass and stainless steel exposure chamber that had a total volume of one cubic meter and an effective volume of 760 L. The Cd carbonate and pigments were sieved through a 60-mesh sieve and hand-packed into a Wright dust feed mechanism. Dry air was passed through the dust feed and diluted with room air before being delivered to the chamber. Samples from the chamber were taken with a dust monitor. The Cd fume was derived from a 10% aqueous solution of cadmium acetate dehydrate. An aerosol was created by putting the metered solution and dry air through a nebulizer. No mortality occurred in groups exposed to air (control), Cd red or Cd yellow pigment. In the cadmium carbonate group, one female rat died on Day 4 and one male and one female rat died on day 13. All animals were moribund prior to death. Blood and food matter were found in the gastrointestinal tract, and the lung and liver of the animals were enlarged and discolored. In the cadmium fume group, 25/52 rats died. Six males and one female died on day 2, seven males and five females died on day 3, three females died on day 4, two females died on day 5, and one male rat died on day 6. Lung and liver discoloration and

congestion were observed in the animals that died from the Cd fume group. Based on the study, the $LC_{50}$ for cadmium fume was 112 mg/m$^3$.

## 3.2. Nonlethal Toxicity

### 3.2.1. Rabbit

A maximum of eight male DLA:New Zealand White rabbits (~30 days old) were exposed by nose-only inhalation to 0 (controls), 0.25, 0.45 or 4.5 mg/m$^3$ of both $CdCl_2$ and CdO for 2 hours (Grose et al. 1987). The exposure concentrations were given as mg Cd/m$^3$. Animals were killed immediately or 72 hours post-exposure. The following parameters were determined: Cd content in the lungs, lung weight, body weight, biochemical responses and histopathological lesions in the lungs. Concentrations were measured and found to be consistent in the chambers. Rabbits exposed to 0.45 mg/m$^3$ CdO had a greater number of alveolar macrophages present when compared to controls and those exposed to $CdCl_2$. At 4.5 mg/m$^3$, the lungs of rabbits had moderate to severe multifocal interstitial pneumonitis that was more severe in the CdO group with the presence of fibrocytic-type cells as well as pneumocytes. Rabbits exposed 4.5 mg/m$^3$ of either chemical had increased lung weight and lung-to-body weight ratios. In the rabbit, $CdCl_2$ had an inhibitory effect on pulmonary GSH peroxidase activity at the lowest and highest concentrations. The two highest concentrations of CdO inhibited GSH peroxidase activity. The activity of GSH transferase was increased after treatment with 0.45 mg/m$^3$ $CdCl_2$. The authors hypothesized that the changes in GSH peroxidase and transferase activity could be a response to protect cells against lipid peroxidation.

### 3.2.2. Rat

Twenty-four female Fischer 344 rats were exposed for 6 hours to ultrafine particles of CdO at a concentration of 70 µg Cd/m$^3$ in whole-body chambers (330 L volume; ventilation exchange of 20 times/hour) (Takenaka et al. 2004). The MMAD was 40 nm and the GSD 1.6. Four rats were sacrificed immediately after exposure and on days 1, 4, and 7 for morphology and elemental analysis. Eight rats were sacrificed on day 0 for lung lavage. An additional 16 rats were exposed to 550 µg Cd/m$^3$ in a similar manner. The MMAD was 51 nm and the GSD was 1.7. When converted, 70 µg Cd/m$^3$ is equivalent to 0.07 mg/m$^3$ and 550 µg Cd/m$^3$ is equivalent to 0.550 mg/m$^3$. Eight rats were sacrificed on day 0 for lung lavage and four rats were sacrificed on days 0 and 1 for morphology and elemental analysis. Twelve animals for each exposure were used as controls, and exposed to clean air only. Just after exposure, Cd in the lungs of rats exposed to 0.07 mg/m$^3$ was 19% of the total inhaled dose and this remained the same at the other time points. A slight but significant increase of Cd in the liver was observed only in the rats sacrificed 7 days after exposure. The lung lavage indicated no exposure-related morphological changes in the lungs or inflammatory responses in the low-dose rats. In rats exposed to the higher concentration, 0.550 mg/m$^3$, Cd content was similar in the lungs on day 0 and 1 but was significantly elevated in the liver and kidneys on both days, and 2/4 of the rats had increased blood Cd. Lung lavage of the rats in the high-dose group showed increased neutrophils, and multifocal alveolar inflammation was observed histologically.

Four groups of ten male Long Evans rats were exposed to CdO dust (0.00195 mg/m$^3$), CdO fume (0.00169 mg/m$^3$), CdS (0.00180 mg/m$^3$) or sham-exposed in a nose-only inhalation chamber for 1 hour (Oberdörster et al. 1987). The exposure concentration was not reported as mg Cd/m$^3$, therefore, the concentration of Cd in this study is unknown. The CdO dust was ball-milled for 24 hours and had a mass median aerodynamic diameter (MMAD) of 0.51 µm. The

CdO fume was generated by an electric arc burning off metallic Cd electrodes, producing particles of 0.4 µm. Pure CdS with a MMAD of 0.45 µm was used. Twenty-four hours post-exposure, the animals were sacrificed, and the lungs were lavaged, and the cellular components of the lavage fluid were analyzed. Lung epithelial permeability was also determined by measuring the activity of $^{99m}$Tc-DTPA in the lung lavage fluid; this substance was injected intravenously 10 minutes prior to sacrifice. An increase in activity in the lung lavage fluid indicates a loss of epithelial integrity. Administration of both CdO dust and CdO fume resulted in a significant decrease in the number of alveolar macrophages and a significant increase in numbers of polymorphonuclear neutrophils, with a more pronounced effect observed with the CdO dust. Epithelial permeability was increased with exposure to CdO dust, but not CdO fume. Inhalation exposure to CdS resulted in no differences in rats compared to those in the sham-exposed group. The study report provided very little detail but did help to show that water solubility does not always correlate with increased toxicity.

Male Wistar rats (16/group) were exposed to 0, 0.5, or 5.3 mg/m$^3$ CdO aerosols for 3 hours in a laminar flow exposure chamber (Buckley and Bassett 1987). The animals were observed for up to 15 days post exposure. Interim sacrifices took place 2, 4, 7, and 15 day post exposure and 4 rats/group were sacrificed at each necropsy. The CdO aerosols were generated by oxidizing cadmium acetate aerosols as they passed through a heated quartz tube. The chamber atmosphere was sampled using 0.22 µm pore diameter polycarbonate filters and determined by gravimetric analysis of aerosol samples. The geometric standard deviations were 2.31 and 3.18 with mass median aerodynamic diameters of 0.26 and 0.33 µm, respectively, for the low and high dose concentrations. Body weight of rats exposed to 0 or 0.5 mg/m$^3$ increased from exposure through the end of the observation period, however, rats exposed to 5.3 mg/m$^3$ did not gain weight until day 7 post exposure. Body weight was similar among all groups on day 15 post exposure. At 0.5 mg/m$^3$, foci of petechial hemorrhage were occasionally observed 2 and 4 days post exposure and were consistently observed at 5.3 mg/m$^3$. Mild hypercellularity at bronchoalveolar junctions and adjacent alveoli and inflammatory cell influx of mononuclear cells were observed at 0.5 mg/m$^3$ prior to day 7 post exposure. Morphology of the lungs was normal in rats exposed to 0.5 mg/m$^3$ 7 days post exposure. Focal areas of interstitial thickening, increases in cuboidal alveolar cells, and numerous inflammatory cells (interstitial mononuclear cells, alveolar macrophages, eosinophils, and basophils) were observed at 5.3 mg/m$^3$ in the bronchoalveolar junctions and peripheral alveoli. Lung weight (dry) and protein content of the lungs were significantly increased in rats exposed to 5.3 mg/m$^3$ compared to those of control on study days 2-15 post exposure, and DNA content was increased days 4-15. Glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase activity were significantly increased in rats exposed to 5.3 mg/m$^3$ compared to the activity levels in control rats.

Male Crl:CD(SD)Br rats, 24/group, were exposed by nose-only inhalation to 0, 0.25, 0.45 or 4.5 mg/m$^3$ of both $CdCl_2$ and CdO for 2 hours (Grose et al. 1987). The exposure concentrations were given as mg Cd/m$^3$. Animals were killed immediately or 72 hours post-exposure. The following parameters were determined: Cd content in the lungs, lung weight, body weight, biochemical responses and histopathological lesions in the lungs. Concentrations were measured and found to be consistent in the chambers. Three rats exposed to cadmium died during the study; only one rat (0.45 mg/m$^3$ CdO group) had cardiovascular failure associated with pulmonary congestion and both others had unknown causes of death. No effects were observed in the lungs at 0 and 72 hours in rats in the 0.45 mg/m$^3$ group. Groups of rats exposed to wither 4.5 mg/m$^3$ $CdCl_2$ or CdO had no lesions observed immediately after exposure, but at 72

hours there was moderate to severe multifocal interstitial pneumonitis that was more severe in the CdO group. It was characterized by the presence of fibrocytic-type cells, alveoli edema, goblet cell hyperplasia, as well as hyperplastic pneumocytes. The pneumonitis observed in rats exposed to $CdCl_2$ presented as thickening of the alveolar walls, edema, hemorrhage, and increases in neutrophils and alveolar macrophages. There was no difference in Cd deposition in the lungs in animals exposed to 0.25 or 0.45 mg/m$^3$ $CdCl_2$ or CdO at either 0 or 72 hours. While there was an increase in Cd deposition in the lungs of the rats exposed to 4.5 mg/m$^3$, at 72 hours there was significantly less Cd in the lungs of rats exposed to 4.5 mg/m$^3$$CdCl_2$ than in those exposed to 1 ppm CdO. Rats exposed to 0.25 mg/m$^3$ $CdCl_2$ had a 13% decrease in lung-to-body weight ratio. Rats exposed to 0.45 mg/m$^3$ group $CdCl_2$ had a decrease in body weight and at 4.5 mg/m$^3$ a 20% decrease in body weight and increased lung and lung-to-body weight ratio 72 hours after exposure. In the 0.45 or 4.5 mg/m$^3$ CdO exposed rats, there was an increase in lung weight but no effect on body weight. Cadmium ($CdCl_2$) had an inhibitory effect (27%) on pulmonary GSH peroxidase activity at the lowest concentration and at 0.45 mg/m$^3$. Cadmium inhibited GSH peroxidase activity at the two highest dose levels.

Twenty six adult Sprague-Dawley CD rats/sex/group were exposed in a single 2-hour exposure to 97 mg/m$^3$ of cadmium red pigment, 99 mg/m$^3$ cadmium yellow pigment, 132 mg/m$^3$ cadmium carbonate, or 112 mg/m$^3$ cadmium fume (Rusch et al. 1986). The exposure concentrations are based on cadmium content. An air control group was also included. Animals were exposed in a glass and stainless steel exposure chamber that had a total volume of one cubic meter and an effective volume of 760L. The Cd carbonate and pigments were sieved through a 60-mesh sieve and hand-packed into a Wright dust feed mechanism. Dry air was passed through the dust feed and diluted with room air before being delivered to the chamber. Samples from the chamber were taken with a dust monitor. The Cd fume was derived from a 10% aqueous solution of cadmium acetate dehydrate. An aerosol was created by putting the metered solution and dry air through a nebulizer.

The rats exposed to Cd fume exhibited clinical signs (hypoactivity and closed eyes) during the exposure. Following exposure, excessive lacrimation was observed in rats exposed to Cd red and yellow, and dry rales and body tremors were observed in the animals exposed to Cd carbonate. Those exposed to Cd fume had dry rales, labored breathing, and excessive lacrimation. Animals exposed to Cd fume also had decreased body weight compared to the controls, with all others maintaining weight similar to that of controls. No gross abnormalities were observed in those sacrificed immediately following exposure. Renal discoloration was observed in the rats in the Cd red pigment group. Pulmonary edema, observed as increased lung weight was seen in the Cd carbonate exposed group starting at 24 hours post-exposure. Exposure to Cd carbonate or Cd fume resulted in an increased incidence of lung discoloration and erosions in the stomach. Blood levels indicated that Cd was absorbed to a greater degree in the carbonate and fume groups when compared to the pigment groups. Urine and feces samples were collected at 0-24 hrs, 24-48 hrs, 48-72 hrs, 6-7 days and 29-30 days post-treatment. Samples indicated that the highest levels of cadmium were excreted in the first 24 hour period and urinary excretion was similar in all three groups while 80% of the red and yellow pigments were excreted in the feces within the first 24 hours. Tissues were collected for cadmium analysis in all but the Cd fume-exposed animals and these were not collected due to the moribund condition of the animals. The Cd carbonate-exposed animals had the greatest amount of cadmium measured in both the kidneys and liver; Cd levels increased initially in the liver and then dropped off but continued to increase in the kidney.

**TABLE 5. Summary of Acute Inhalation Data in Laboratory Animals**

| Species | Concentration (mg Cd/$m^3$) | Exposure Time | Effect | Reference |
|---|---|---|---|---|
| Rabbit | $CdCl_2$<br>0.25<br>0.45<br>4.5 | 2 hr | ↓ Pulmonary GSH peroxidase activity 25%<br>↑ GSH transferase activity<br>Moderate-severe multifocal interstitial pneumonitis; ↑lung weight | Grose et al. 1987 |
| Rabbit | CdO<br>0.25<br>0.45<br>4.5 | 2 hr | No effects<br>↑ Alveolar macrophages; ↓ pulmonary GSH peroxidase activity<br>Moderate-severe multifocal interstitial pneumonitis; ↑lung weight; ↓ pulmonary GSH peroxidase activity | Grose et al. 1987 |
| Rat | CdO<br>0.07<br>0.550 | 6 hr | No morphological changes or inflammatory response<br>↑ Neutrophils and multifocal alveolar inflammation | Takenaka et al. 2004 |
| Rat | 0.00195 Cd dust<br>0.00169 Cd fume<br>0.00180 CdS | 1 hr | ↓ Alveolar macrophages; ↑PMNs; ↑epithelial permeability<br>↓ Alveolar macrophages; ↑PMNs<br>No effect | Oberdörster et al. 1987 |
| Rat | CdO<br>0.5<br>5.3 | 3 hr | Transient mild hypercellularity at bronchoalveolar junctions and adjacent alveoli, inflammatory cell influx<br>Interstitial thickening, ↑ cuboidal alveolar cells, ↑inflammatory cells, ↑dry lung weight, ↑protein content, ↑DNA content, ↑ GP, GR, G6PD, 6PGD activity | Buckley and Bassett 1987 |
| Rat | $CdCl_2$<br>0.25<br>0.45<br>4.5 | 2 hr | ↓ Pulmonary GSH peroxidase activity 27%<br>↓ bw; ↓pulmonary GSH peroxidase activity<br>↓ bw 20%; ↑lung weight; ↓ pulmonary GSH peroxidase activity; pneumonitis | Grose et al. 1987 |
| Rat | CdO<br>0.25<br>0.45<br>4.5 | 2 hr | No effects<br>↑ Lung weight; ↓ pulmonary GSH peroxidase activity; 2 deaths-cardiovascular failure (1)<br>↑ Lung weight; ↓ pulmonary GSH peroxidase activity; pneumonitis | Grose et al. 1987 |
| Rat | 97 Cd red<br>99 Cd yellow<br>132 Cd carbonate<br>112 Cd fume | 2 hr | Lacrimation; renal discoloration<br>Lacrimation<br>Dry rales, body tremors; 5.8% mortality<br>Hypoactivity; closed eyes; lacrimation; dry rales; ↓ bw; ↑ lung discoloration and stomach erosion; 48% mortality; $LC_{50}$ | Rusch et al. 1986 |

## 3.3. Developmental/Reproductive Toxicity

Four female Hartley guinea pigs/group were exposed in late gestation (days 50-55) to 0 or 0.05 mg/$m^3$ cadmium chloride for 4 hours/day for 1 or 5 consecutive days by nose-only inhalation (Trottier et al. 2002). Cadmium aerosol was generated in a nebulizer using a solution

of Cd made from CdCl dissolved in distilled water. Total airflow to the chamber was 22 L air/min and the concentration of Cd in the chamber was monitored by obtaining air samples through filters during the exposure. The mean Cd concentration was 53.2 ± 4.6 μg/$m^3$ and the MMAD was 0.3μm. Twenty-four hours after the last exposure, females were euthanized and the tissues processed. Tissue Cd content was determined by graphite furnace atomic absorption spectrophotometry and placental metallothionein and cadmium content were also determined.

Inhalation exposure did not affect the maternal body weight, fetal body weight, maternal or fetal organ weight, or placental weight when compared to controls. Maternal rats had a significant increase ($p<0.01$) in lung Cd compared to controls after only a single day and a significant increase in both lung and liver after 5 days. In the fetus, brain, liver and heart Cd levels were significantly increased compared to controls after 1 day of exposure, and levels in brain and liver remained elevated after 5 days. Maternal blood Cd increased from 25.6 to 57.3 pg/mg of protein after 5 days of treatment but the fetal blood had no change. The levels of Cd and MT in the placenta did not change upon exposure, but the placental cadmium decreased after the 5-day exposure.

Thirty two pregnant Sprague-Dawley female rats and thirty-three pregnant Swiss (CD-1) mice were exposed to 0, 0.05, 0.5 or 2 mg/$m^3$ cadmium oxide by whole-body inhalation for 6 hours/day, 7 days/week on gestation days (GD) 4-19 in the rats and GD 4-17 in mice (NTP 1995). Generation of the aerosol was by the same methods described in Section 3.5.1. One rat exposed to 2 mg/$m^3$ died on GD 17. Clinical signs observed in rats were dyspnea in all those exposed and hypoactivity at 2 mg/$m^3$, in females. The female rats exposed to 2 mg/$m^3$ had significant decreases ($p\leq 0.01$) in body weight (14% less than controls) and body weight gain (41% less than controls). The high dose female rats also had decreases in absolute and relative liver weight and absolute kidney weight, compared to controls. Developmental toxicity was observed at 2 mg/$m^3$ in rats, and included a decrease in the weight of live fetuses. This concentration also caused significant increases in the mean percent of fetuses per litter with reduced ossification of the pelvis (12 vs. 2.4 in controls) and sternebrae (25 vs. 4.4 in controls). Dyspnea and hypoactivity were observed in mice exposed to concentrations ≥ 0.5 mg/$m^3$ cadmium oxide. At ≥ 0.5 mg/$m^3$, the number of pregnant mice was significantly decreased. Fetal body weight following exposure to 0.5 mg/$m^3$ was significantly less than control fetal body weight. Five mice in the 2 mg/$m^3$ group were euthanized moribund before the end of the study. Maternal body weight gain, absolute and relative gravid uterine weights, and absolute liver weight were significantly lower compared to control values, and relative kidney weight was significantly increased compared to control kidney weight in female mice exposed to 2 mg/$m^3$. The total number of resorptions per litter was significantly increased in this group, and the fetal body weight and percentage of live male fetuses per litter were significantly decreased in the 2 mg/$m^3$ group.

Male and female Fischer 344 rats (10 weeks old) were exposed whole body to 0, 0.3, 1.0 or 2.0 mg $CdCl_2$/$m^3$ for 6 hours/day, 5 days/week for 62 exposures (Kutzman et al. 1986). Twenty male rats were used for multiple pulmonary endpoint assessments, eight males for pathology only, eight male and eight females for reproductive studies and ten males for cytogenetic endpoints. Rats were exposed in a 1.4 $m^3$ stainless steel and Lucite chamber. Airflow was equivalent to 15 chamber volumes/hr. Laskin-type nebulizers were used to generate the aerosol. An optical particle size analyzer was used to characterize the size distribution of the aerosolized particles. RAM-1 aerosol mass monitors were used to continuously monitor the

chamber atmosphere. Chamber atmospheres were 0.33 (± 0.02), 1.06 (± 0.04) and 2.13 (± 0.11) mg Cd $Cl_2/m^3$ in the 0.3, 1.0 and 2.0 $mg/m^3$ chambers, respectively.

All rats exposed to 2.0 $mg/m^3$ lost weight rapidly and died within the first 45 days and were observed to have rapid and shallow breathing and appeared unkempt prior to death. The females averaged a higher survival (40 days; n= 10) compared to the males (32 days; n= 57). At 1.0 $mg/m^3$, five males died and all animals at 0.3 $mg/m^3$ survived. Some exposed males and females were allowed to breed with unexposed mates and there were no decreases in reproductive potential. No findings were associated with treatment in the number of viable embryos, late deaths, early deaths (resorptions), number of corpea lutea, or pre-implantation losses. At necropsy, there was a dose-dependent increase in organ-to-body weight ratio for the lungs, heart, spleen, kidneys, and testis. Also, the liver and brain weight-to-body ratio was increased in the high-dose, compared to the controls. Lesions of type II hyperplasia, alveolar macrophages, and polymorphonuclear leukocytes were observed at the terminal bronchioles of both the low- and mid-dose rats. Areas of fibrosis were also observed in the mid-dose rats. Similar lesions were identified in those that died in the high-dose group. Based on the histopathological findings, the LOAEL was 0.3 $mg/m^3$ $CdCl_2$ and the NOAEL could not be determined.

### 3.4. Genotoxicity

Cadmium oxide was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537 with or without metabolic activation and did not produce micronuclei in erythrocytes of mice exposed by inhalation for 13 weeks (NTP, 1995).

Cadmium chloride induced DNA strand breaks in *Escherichia coli* and induced differential toxicity in *Bacillus subtilis* and *E. coli* strains. It also induced gene conversion in *Saccharomyces cerevisiae*, but did not induce reverse mutation in *S. cerevisiae.* Unscheduled DNA synthesis and DNA strand breaks were observed in primary cultures of rat hepatocytes, but not in primary cultures of rat Leydig cells. Calcium chloride was mutagenic to Chinese hamster V79 cells and mouse lymphoma L5178Y cells (IPCS 1992).

### 3.5. Repeated Dose

#### 3.5.1. Rat

Male and female F344/N rats (6 wks old) were exposed to cadmium oxide aerosol (99.4% purity; mass median aerodynamic diameter (MMAD) = 1.1-1.6 µgm) for 6 hours/day, 5 days/week for 2 weeks (n = 5/sex/group) or 13 weeks (n= 10/sex/group) (NTP 1995). Animals were exposed to 0, 0.1, 0.3, 1, 3 or 10 $mg/m^3$ for the 2 week studies and 0, 0.025, 0.05, 0.1, 0.25 or 1 $mg/m^3$ for 13 weeks. Animals were exposed in whole-body chambers that had a total volume of 2.3 $m^3$. Chemical concentration, airflow, temperature and relative humidity were controlled and monitored with an automated system. Overall, concentration within the chamber was adequate. Cadmium oxide dust was mixed with compressed air to create an aerosol. The MMAD of the aerosol particles was measured in each exposure chamber before the studies began, once in the 2 week study and monthly in the 13 week study. Blood was obtained to measure hematology and clinical chemistry parameters, urine collected and histopathology performed.

In the rats exposed for 2 weeks, all those exposed to 10 mg/m$^3$ died by day 6; no other deaths occurred. Clinical signs of hypoactivity, dehydration, ruffled fur, dyspnea and nasal discharge were observed in rats at concentrations ≥ 1 mg/m$^3$. Lesions in the lungs including alveolar histiocytic infiltrate, focal inflammation and fibrosis were observed in all of the treated rats with a dose-dependent increase in severity. Effects on the nasal and respiratory epithelium were observed in those exposed to 1 mg/m$^3$ and greater. Based on the findings, the doses were set for the 13 week study. For the two-week study, a LOAEL of 0.1 mg/m$^3$ Cd oxide in rats was established based on histopathological findings; a NOAEL could not be determined.

**TABLE 6. Histopathological Findings in rats Exposed for 2 wks to Cadmium Oxide**

**(# Affected/Total # examined)**

| | 0 mg/m$^3$ | 0.1 mg/m$^3$ | 0.3 mg/m$^3$ | 1 mg/m$^3$ | 3 mg/m$^3$ | 10 mg/m$^3$ |
|---|---|---|---|---|---|---|
| **MALES** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/5 | 5/5 (2.0)[a] | 5/5 (2.0) | 5/5 (3.0) | 5/5 (3.8) | 5/5 (4.0) |
| Focal inflamm/fibrosis | 0/5 | 5/5 (1.0) | 5/5 (2.0) | 5/5 (3.0) | 5.5 (2.8) | 5/5 (4.0) |
| Nose | | | | | | |
| Olfactory epithelium | | | | | | |
| Degeneration | 0/5 | 0/5 | 0/5 | 2/5 (1.0) | 5/5 (2.0) | 5/5 (2.2) |
| Respiratory epithelium | | | | | | |
| Squamous metaplasia | 0/5 | 0/5 | 0/5 | 1/5 (1.0) | 0/5 | 5/5 (1.0) |
| Inflammation | 0/5 | 0/5 | 0/5 | 1/5 (1.0) | 5/5 (1.4) | 3/5 (1.7) |
| **FEMALES** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/5 | 5/5 (2.0) | 5/5 (2.2) | 5/5 (3.0) | 5/5 (4.0) | 5/5 (4.0) |
| Focal inflamm/fibrosis | 0/5 | 3/5 (1.0) | 5/5 (2.0) | 5/5 (3.0) | 5.5 (3.0) | 5/5 (4.0) |
| Nose | | | | | | |
| Olfactory epithelium | | | | | | |
| Degeneration | 0/5 | 0/5 | 0/5 | 4/5 (1.3) | 4/5 (2.3) | 4/4 (3.0) |
| Respiratory epithelium | | | | | | |
| Squamous metaplasia | 0/5 | 0/5 | 0/5 | 0/5 | 4/5 (1.5) | 4/4 (1.5) |
| Inflammation | 0/5 | 0/5 | 0/5 | 0/5 | 4/5 (2.3) | 3/4 (1.0) |

Data from NTP (1995)

[a] Number in parenthesis is severity code: 1= minimal, 2= mild, 3= moderate and 4= marked

All rats survived the 13 week study and all treated rats had a nasal discharge that increased in frequency as the concentration increased. Rats at 1 mg/m$^3$ consistently had lower body weight throughout the study compared to controls, but it was within 10%. No significant findings were observed in the hematology, clinical chemistry or urine parameters. Males and females had statistically significant increases ($p \leq 0.01$ or 0.05) in organ weight at concentrations ≥ 0.05 mg/m$^3$, compared to controls including relative kidney weight, and relative and absolute lung weight; however, there were no treatment-related microscopic findings in the kidney or liver. Blood pressure was measured in the animals and there were no findings observed with treatment. Grossly, the only treatment-related finding was enlargement and paleness of the tracheobronchial and mediastinal lymph nodes. Microscopic lesions were identified in the lungs in all treated animals except those in the 0.025 mg/m$^3$ group. The lesions were similar to those identified in the 2 week study. Based on the histopathological findings, the LOAEL for rats treated for 13 weeks 0.05 mg/m$^3$ cadmium and the NOAEL was 0.025 mg/m$^3$.

1

**TABLE 7. Histopathological Findings in Rats Exposed for 13 wks to Cadmium Oxide**

**(# Affected/Total # examined)**

| | 0 mg/m$^3$ | 0.025 mg/m$^3$ | 0.05 mg/m$^3$ | 0.1 mg/m$^3$ | 0.25 mg/m$^3$ | 1 mg/m$^3$ |
|---|---|---|---|---|---|---|
| **Males** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/10 | 0/10 | 10/10 (1.0)[a] | 10/10 (2.0) | 10/10 (3.0) | 10/10 (3.0) |
| Inflammation | 0/10 | 0/10 | 0/10 | 0/10 | 10/10 (2.6) | 10/10 (2.1) |
| Fibrosis | 0/10 | 5/5 (1.0) | 5/5 (2.0) | 5/5 (3.0) | 5.5 (2.8) | 5/5 (4.0) |
| Tracheobronchial lymph node | | | | | | |
| Inflammation | 0/9 | 0/7 | 0/5 | 3/7 (1.0) | 9/9 (3.0) | 10/10 (3.1) |
| Nose | | | | | | |
| Olfactory epithelium | | | | | | |
| Degeneration | 0/10 | 0/10 | 0/10 | 0/10 | 1/10 (1.0) | 10/10 (3.0) |
| Respiratory epithelium | | | | | | |
| Inflammation | 0/10 | 0/10 | 0/10 | 0/10 | 7/10 (1.0) | 9/10 (2.6) |
| **Females** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/10 | 0/10 | 10/10 (1.0) | 10/10 (2.1) | 10/10 (3.0) | 10/10 (3.0) |
| Inflammation | 0/10 | 0/10 | 0/10 | 0/10 | 10/10 (1.6) | 10/10 (3.5) |
| Fibrosis | 0/10 | 0/10 | 0/10 | 10/10 (1.0) | 10/10 (2.0) | 10/10 (2.1) |
| Tracheobronchial lymph node | | | | | | |
| Inflammation | 0/7 | 0/4 | 0/8 | 6/8 (1.2) | 6/9 (2.8) | 10/10 (3.5) |
| Nose | | | | | | |
| Olfactory epithelium | | | | | | |
| Degeneration | 0/10 | 0/10 | 0/10 | 0/10 | 2/10 (1.0) | 10/10 (2.8) |
| Respiratory epithelium | | | | | | |
| Inflammation | 0/10 | 0/10 | 0/10 | 3/10 (1.0) | 10/10 (1.6) | 10/10 (1.8) |

Data from NTP (1995)

[a] Number in parenthesis is severity code: 1= minimal, 2= mild, 3= moderate and 4= marked

2

3

4 Sixty male Wistar (CHbb:THOM) rats, approximately 8 weeks old, with a mean body
5 weight of 250 g were exposed nose-only 6 hours/day for up to 10 days to 0 (air control),
6 0.3 mg/m$^3$ $CdCl_2$ or 0.2, 1.0 or 8.0 mg/ m$^3$ CdS (Klimisch 1993). Four animals from each group
7 were sacrificed on days 2, 10, 11, 12, 13, 17, 38, 66 and 94. The study was designed to expose
8 rats to soluble ($CdCl_2$) and insoluble (CdS) forms of Cd. Measurements of lung, renal and fecal
9 Cd were obtained. Cadmium chloride was generated as an aerosol by taking an aqueous solution
10 and putting it through an injection pump to a binary nozzle atomizer before diluting with air.
11 Cadmium sulfide was generated as a dust using a rotating brush-type generator and passing the
12 dust directly into the inhalation chamber. All concentrations were sampled and found to be
13 within an acceptable range. Upon sacrifice, the lungs and kidneys were removed and weighed
14 before being processed for Cd content. Feces were collected daily and pooled together.
15
16 No adverse clinical signs or mortalities occurred during the study or post-exposure
17 period. Pooled data from days 0-10 showed a statistically significant increase in mean lung
18 weight and lung to body weight ratio in the $CdCl_2$-exposed rats. Rats exposed to 8.0 mg/m$^3$ CdS
19 also had increased mean lung weight. No effects were observed on kidney weight. Cadmium
20 accumulated in the kidney of all treated animals but at a much greater proportion in those
21 exposed to $CdCl_2$. Cadmium in feces was observed mostly during the exposure and for a few
22 days post-exposure, with the highest amount observed in rats exposed to the highest dose of CdS.
23 The analyzed Cd content of test atmospheres for both compounds was 0.17 µg/L; however, the
24 Cd lung content in the $CdCl_2$-exposed rats was about two times higher than the CdS exposed
25 rats. This could have been caused by either the greater availability of the $CdCl_2$ aerosol

compared to the CdS dust or the fact that $CdCl_2$ is held in the lung longer. Overall the study showed a much higher bioavailability of $CdCl_2$ compared to the soluble CdS upon inhalation exposure.

Three month old female Wistar rats (n= 13-14) were exposed by inhalation to CdO for 5 hours/day, 5 days/week for 20 weeks at concentrations of 0.02, 0.16 or 1 mg/m$^3$ (Barański and Sitarek 1987). A control group was exposed to clean air only. The aerosol concentration was determined by drawing air in an inhalation chamber through Sartorious membrane filters SM11306. Fractions of aerosols with particle sizes below 4.7 µm were determined with the Anderson Impactor 2000. Mortality occurred at 1 mg/m$^3$, although histopathology and gross findings were not described in the report. At 1 mg/m$^3$, mortality was 15% at the end of 7-8 weeks, 38% at the end of 13-14 weeks and 100% at the end of the study. This was compared to 0, 7 and 14% of the controls at the same time points, respectively. A significant decrease ($p< 0.05$) in body weight gain was observed in the rats exposed to 1 mg/m$^3$ throughout the study; at 0.16 mg/m$^3$, exposed rats had a decrease in body weight gain compared to controls, but it was not significant. All treated rats showed an increase in the length of estrous during treatment when compared to pre-treatment, but at 0.02 and 0.16 mg/m$^3$, rats showed this change only at the end of the study (weeks 19-20). At 1.0 mg/m$^3$, exposed rats had an increase in estrous length during the entire study. Based on the increased estrous length, the LOAEL was 0.02 mg/m$^3$ CdO and the NOAEL could not be determined.

Twelve adult female Wistar rats/group were exposed continuously to 0, 25 or 50 µg Cd/m$^3$ for 90 days and to 100 µg Cd/m$^3$ for 63 days (Prigge 1978), equivalent to 0, 0.025, 0.052 and 0.105 mg/m$^3$ administered as CdO. The rats were removed from the chamber for only 10-20 minutes daily to allow for cleaning and food was changed daily to prevent oral contamination. Inhalation chambers were 50 x 50 x 90 cm with a total volume of 225L. Cadmium was nebulized from a 0.2% solution of cadmium acetate. The volume flow into the chambers was about 80 L/min equating to about 21 changes/hour. Aerosol concentrations were checked and found to be within range of the expected values. Size distribution of the particles had a mean aerodynamic diameter of 0.19 µm, and the geometric standard deviation was 1.5. Both are in the range of respirable fine dust in humans. Urine and blood samples were obtained after exposure. A significant dose-dependent decrease ($p<0.05$) in body weight was observed in the rats exposed to 0.052 and 0.105 mg/m$^3$, and 5/12 died at 0.105 mg/m$^3$ between days 45 and 60. A significant increase in lung weight was observed in all of the treated animals. A slight increase was observed in hematocrit or hemoglobin with treatment, but there was no effect on serum iron or alkaline phosphatase activity. A significant ($p<0.05$) decrease in the partial pressure of $O_2$ and an increase in the partial pressure of $CO_2$ were observed in the rats exposed to 0.105 mg/m$^3$. Proteinuria was not observed in any of the treated females. Inhalation uptake of cadmium resulted in increased liver cadmium levels but they were not as high as those observed after oral administration; uptake of cadmium in the kidney was similar with both methods of administration. Histopathology showed a few areas of swellings in the kidney tubuli, no lesions in the liver, emphysematic areas and cell proliferation in the bronchi, bronchiole, alveoli, and histiocytic cell granulomas in the lungs in the treated animals. Based on the histopathological findings, the inhalation LOAEL for cadmium by inhalation in rats was 25 µg/m$^3$ Cd (0.025 mg/m$^3$) and the NOAEL was not established.

### 3.5.2. Mouse

Male and female B6C3F$_1$ mice (6 wks old) were exposed to cadmium oxide aerosol (99.4% purity; MMAD = 1.1-1.6 µgm) for 6 hours/day, 5 days/week for 2 weeks (n = 5/sex/group) or 13 weeks (n= 10/sex/group) (NTP 1995). Animals were exposed to 0, 0.1, 0.3, 1, 3 or 10 mg/m$^3$ for the 2 week studies and 0, 0.025, 0.05, 0.1, 0.25 or 1 mg/m$^3$ for 13 weeks. Animals were exposed in whole-body chambers that had a total volume of 2.3 m$^3$. Chemical concentration, airflow, temperature and relative humidity were controlled and monitored with an automated system. Overall, concentration within the chamber was adequate. Cadmium oxide dust was mixed with compressed air to create an aerosol. The mass median aerodynamic diameter (MMAD) of the aerosol particles was measured in each exposure chamber before the studies began, once in the 2 week study and monthly in the 13 week study. Blood was obtained to measure hematology and clinical chemistry parameters, urine collected and histopathology performed.

Findings similar to those reported in rats (NTP, 1995) were observed in the mice. In the 2 week study, all mice in the 10 mg/m$^3$ group died and death was due to severe respiratory toxicity. Hypoactivity, abnormal posture, rapid breathing, ataxia, nasal discharge, and ruffled fur were observed at 1, 3, and 10 mg/m$^3$. Absolute and relative lung weights were significantly increased at concentrations ≥ 0.3 mg/m$^3$. Alveolar macrophage infiltration, fibrosis, focal inflammation, and necrosis of alveolar duct epithelium were observed. As in the rats, severity of effects increased with increasing concentration. Histopathologic lesions are listed in Table 8. In the 2 week study, a NOAEL could not be established and the LOAEL for mice was 0.1 mg/m$^3$ cadmium based on microscopic lung lesions.

**TABLE 8. Histopathological Findings in Mice Exposed for 2 wks to Cadmium Oxide**

| | # Affected/Total # examined | | | | | |
|---|---|---|---|---|---|---|
| | **0 mg/m$^3$** | **0.1 mg/m$^3$** | **0.3 mg/m$^3$** | **1 mg/m$^3$** | **3 mg/m$^3$** | **10 mg/m$^3$** |
| **MALES** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/5 | 5/5 (1.2)[a] | 5/5 (2.0) | 5/5 (3.0) | 5/5 (3.0) | 0/5 |
| Focal inflamm/fibrosis | 0/5 | 0/5 | 5/5 | 5/5 | 5/5 | 0/5 |
| Necrosis | 0/5 | 0/5 | 1/5 (1.0) | 5/5 (2.0) | 5/5 (2.2) | 5/5 (3.0) |
| Acute inflammation | 0/5 | 0/5 | 0/5 | 0/5 | 5/5 | 5/5 (4.0) |
| Nose | | | | | | |
| Olfactory epithelium | | | | | | |
| Degeneration | 0/5 | 0/5 | 0/5 | 5/5 (1.4) | 5/5 (3.0) | 3/5 (3.0) |
| Tracheobronchial lymph node hyperplasia | 0/5 | 3/5 (1.0) | 5/5 (1.0) | 5/5 (2.0) | 5/5 (2.0) | 1/5 (3.0) |
| **FEMALES** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/5 | 5/5 (1.0) | 5/5 (1.8) | 5/5 (3.0) | 5/5 (3.0) | 0/5 |
| Focal inflamm/fibrosis | 0/5 | 0/5 | 5/5 | 5/5 | 5.5 | 0/5 |
| Necrosis | 0/5 | 0/5 | 1/5 (1.0) | 5/5 (2.0) | 5/5 (2.0) | 5/5 (3.0) |
| Acute inflammation | 0/5 | 0/5 | 0/5 | 0/5 | 0/5 | 5/5 (4.0) |
| Nose | | | | | | |
| Olfactory epithelium | | | | | | |
| Degeneration | 0/5 | 0/5 | 0/5 | 5/5 (2.0) | 5/5 (3.0) | 5/5 (3.0) |
| Tracheobronchial lymph node hyperplasia | 0/5 | 4/5 (1.0) | 4/5 (1.0) | 4/4 (1.5) | 5/5 (1.8) | 0/4 |

Data from Table 16, p. 69 in NTP 1995.
[a] Number in parenthesis is severity code: 1= minimal, 2= mild, 3= moderate and 4= marked

In the 13 week study, one mouse from the control group died with no deaths in the treated animals. No clinical signs of toxicity were observed. Lung lesions were similar to those of the rat and consisted of macrophage infiltrates, hyperplasia, inflammation and fibrosis, although fibrosis was more prevalent in the rat as shown in Table 9. The absolute and relative lung weight of both sexes, absolute and relative kidney and thymus weights in male rats, and absolute and relative kidney, liver, and spleen weights in female rats in all treatment groups were increased compared to control weights. No microscopic changes were found in the liver, kidney, spleen, or thymus. In the 13 week study, a NOAEL could not be established and the LOAEL for mice was 0.025 mg/m$^3$ cadmium based on microscopic lung lesions.

**TABLE 9. Histopathological Findings in Mice Exposed for 13 wks to Cadmium Oxide**

**(# Affected/Total # examined)**

| | **0 mg/m$^3$** | **0.025 mg/m$^3$** | **0.05 mg/m$^3$** | **0.1 mg/m$^3$** | **0.25 mg/m$^3$** | **1 mg/m$^3$** |
|---|---|---|---|---|---|---|
| **MALES** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/10 | 9/10 (1.1)[a] | 10/10 (1.0) | 10/10 (2.0) | 10/10 (2.0) | 10/10 (3.0) |
| Alveolar hyperplasia | 0/10 | 1/10 (1.0) | 10/10 (1.0) | 10/10 (1.8) | 10/10 (1.8) | 10/10 (2.0) |
| Inflammation | 0/10 | 0/10 | 0/10 | 8/10 (3.0) | 10/10 (2.2) | 10/10 (2.7) |
| Fibrosis | 0/10 | 0/10 | 2/10 (1.0) | 10/10 /1.0) | 10/10 (1.0) | 10/10 (1.0) |
| Tracheobronchial lymph node hyperplasia | 0/6 | 0/8 | 4/9 (1.0) | 9/9 (2.3) | 8/10 (2.4) | 9/10 (2.7) |
| Larynx squamous metaplasia | 0/9 | 10/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) | 9/10 (1.0) |
| Nose | | | | | | |
| Olfactory epithelium Degeneration | 0/10 | 0/10 | 0/10 | 4/10 (1.0) | 10/10 (1.7) | 10/10 (2.0) |
| Respiratory epithelium hyaline droplets | 0/10 | 0/10 | 0/10 | 0/10 | 2/10 (1.0) | 10/10 (1.0) |
| **FEMALES** | | | | | | |
| Lung | | | | | | |
| Alveolar infiltrate | 0/10 | 9/10 (1.0) | 10/10 (1.0) | 10/10 (2.0) | 10/10 (2.0) | 10/10 (3.0) |
| Alveolar hyperplasia | 0/10 | 0/10 | 0/10 | 10/10 (1.4) | 10/10 (2.0) | 10/10 (2.0) |
| Inflammation | 0/10 | 0/10 | 0/10 | 6/10 (2.3) | 8/10 (2.1) | 8/10 (2.9) |
| Fibrosis | 0/10 | 0/10 | 1/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) |
| Tracheobronchial lymph node hyperplasia | 0/6 | 0/6 | 2/9 (1.0) | 8/9 (1.5) | 9/10 (2.0) | 10/10 (2.4) |
| Larynx squamous metaplasia | 0/10 | 10/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) |
| Nose | | | | | | |
| Olfactory epithelium Degeneration | 0/10 | 0/10 | 0/10 | 1/10 (1.0) | 10/10 (1.0) | 10/10 (1.0) |
| Respiratory epithelium hyaline droplets | 0/10 | 0/10 | 0/10 | 0/10 | 2/10 (1.0) | 10/10 (1.0) |

Data from Table 19, p. 76 in NTP 1995.

[a] Number in parenthesis is severity code: 1= minimal, 2= mild, 3= moderate and 4= marked

The repeat dose studies are summarized in Table 10.

**TABLE 10. Summary of Repeat Dose Inhalation Data in Laboratory Animals**

| Species | Concentration ($mg/m^3$) | Exposure Time | Effect | Reference |
|---|---|---|---|---|
| Rat | CdO aerosol<br>0.1<br>0.3<br>1<br>3<br>10 | 6 hr/d<br>5 d/wk<br>2 wk | All: Alveolar histiocytic infiltrate, pulmonary focal inflammation, pulmonary fibrosis<br>0.1: LOAEL<br>≥ 1: Hypoactivity, dehydration, dyspnea, nasal discharge, olfactory epithelium degeneration, inflammation<br>10: 100% mortality | NTP 1995 |
| Rat | CdO aerosol<br>0.025<br>0.05<br>0.1<br>0.25<br>1 | 6 hr/d<br>5 d/wk<br>13 wk | 0.025: NOAEL<br>0.05: LOAEL<br>≥ 0.05: ↑ organ weight, pulmonary fibrosis, alveolar infiltrate<br>≥ 0.1: Tracheobronchial lymph node inflammation, respiratory epithelium inflammation, pulmonary fibrosis, alveolar infiltrate<br>≥ 0.25: Tracheobronchial lymph node inflammation, pulmonary fibrosis, alveolar infiltrate , respiratory epithelium inflammation, olfactory epithelium degeneration | NTP 1995 |
| Rat | 0.3 CdCl2<br>CdS<br>0.2<br>1.0<br>8.0 | 6 hr/d<br>10 d | 0.3 $CdCl_2$: ↑ absolute and relative lung weight<br>8.0 CdS: ↑ absolute lung weight | Klimisch 1993 |
| Rat | CdO aerosol<br>0.02<br>0.16<br>1 | 5 hr/d<br>5 d/wk<br>20 wk | 0.02: LOAEL<br>All: ↑ increased length of estrous (0.02, 0.16 at end of the study)<br>1: 15% mortality at 7-8 wk, 38% mortality at 13-14 wk, ↓ body weight | Barański and Sitarek 1987 |
| Rat | mg $Cd/m^3$<br>0.025<br>0.052<br>0.105 | Continuous<br>63 d | All: Focal kidney tubuli swelling, emphysematic areas and cell proliferation in bronchi<br>0.025: LOAEL, ↑ lung weight,<br>0.052: ↓ body weight, ↑ lung weight,<br>0.105: 42% mortality between days 45 and 60, ↓ body weight, ↓ $pO_2$, ↑$pCO_2$, ↑ lung weight | Prigge 1978 |
| Mouse | CdO aerosol<br>0.1<br>0.3<br>1<br>3<br>10 | 6 hr/d<br>5 d/wk<br>2 wk | 0.1: LOAEL<br>≥ 0.1: Alveolar infiltrate, tracheobronchial lymph node hyperplasia<br>≥ 0.3: ↑ absolute and relative lung weight, alveolar duct epithelium necrosis<br>≥ 1: Hypoactivity, abnormal posture, ataxia, rapid breathing, olfactory epithelium degeneration<br>10: 100% mortality, severe respiratory toxicity | NTP 1995 |
| Mouse | CdO aerosol<br>0.025<br>0.05<br>0.1<br>0.25<br>1 | 6 hr/d<br>5 d/wk<br>13 wk | 0.025: LOAEL, alveolar infiltrate, larynx squamous metaplasia<br>≥ 0.05: alveolar infiltrate, larynx squamous metaplasia, tracheobronchial lymph node hyperplasia<br>≥ 0.1: Olfactory epithelium degeneration<br>≥ 0.25: Respiratory epithelium hyaline droplets | NTP 1995 |

## 3.6. Chronic Toxicity/Carcinogenicity

As a follow-up to the Takenaka et al. (1983) study described below Oldiges et al. (1989) exposed thirty four groups of twenty male and female SPF Wistar rats/sex/group (8 wks old) to a variety of Cd compounds in aerosol, dust or fume form (Table 11). The animals were exposed 22 hours a day, 7 days a week for 18 months. A few groups had discontinuous exposure for 40 hours a week for 6 months. Inhalation and observation periods were terminated at mortality rates of more than 25% during the inhalation period and 75% during the observation period to assure a carcinogenic result. In addition, an aerosol combination with the antagonistic zinc oxide aerosol was used in some of the exposures. Results were similar to those from the Takenaka et al. (1983) study in that no primary lung tumors were identified in the control rats, but were identified in the Cd exposed animals. Lung tumors rats were increased for all Cd compounds. The inhalation period was shorter for the water insoluble Cd compounds CdS and CdO because of mortality, but primary lung tumors were still observed in the rats of these groups.

1

**TABLE 11. Observations after Inhalation Exposures of Rats to Various Cd Compounds**

**# Affected/Total # examined**

| Group No. | Compound | Concentration ($mg/m^3$) | Duration (month) | | Lung Nodules (n/n) | Primary lung tumors[a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Exposure | Study | | A | B | C | D |
| | | | | | | n/n | | | |
| **Males** | | | | | | | | | |
| 1 | Control | – | – | 31 | 0/20 | 0 | 0 | 0 | 0 |
| | | | | | | 0/20 | | | |
| 3 | $CdCl_2$ | 0.03 | 18 | 30[b] | 18/20 | 2 | 12 | 0 | 1 |
| | | | | | | 15/20 | | | |
| 5 | $CdCL_2$ | 0.09 | 6 | 30[b] | 12/20 | 3 | 5 | 3 | 0 |
| | | | | | | 11/20 | | | |
| 7 | $CdSO_4$ | 0.09 | 14[b] | 31 | 10/20 | 2 | 7 | 0 | 2 |
| | | | | | | 11/20 | | | |
| 9 | CdS | 0.09 | 18 | 30[b] | 16/20 | 4 | 9 | 2 | 2 |
| | | | | | | 17/20 | | | |
| 11 | CdS | 0.27 | 16[b] | 30[b] | 11/19 | 1 | 8 | 2 | 3 |
| | | | | | | 14/19 | | | |
| 13 | CdS | 0.81 | 7[b] | 30[b] | 7/20 | 2 | 5 | 2 | 2 |
| | | | | | | 11/20 | | | |
| 15 | CdS | 2.43 | 4[b] | 30[b] | 6/16 | 1 | 2 | 1 | 3 |
| | | | | | | 7/16 | | | |
| 17 | CdS | 0.27 | 6 | 27[b] | 2/20 | 3 | 0 | 0 | 0 |
| | | | | | | 3/20 | | | |
| 19 | CdO dust | 0.03 | 18 | 31 | 15/20 | 4 | 6 | 1 | 4 |
| | | | | | | 15/20 | | | |
| 21 | CdO dust | 0.09 | 7[b] | 31[b] | 11/15 | 2 | 5 | 0 | 2 |
| | | | | | | 9/17 | | | |
| 23 | CdO dust | 0.09 | 6 | 31 | 8/20 | 1 | 2 | 1 | 0 |
| | | | | | | 4/20 | | | |
| 25 | CdO dust | 0.03 | 18 | 29[b] | 13/18 | 5 | 7 | 0 | 1 |
| | | | | | | 13/18 | | | |
| 26 | CdO dust | 0.01 | 18 | 29[b] | 13/20 | 6 | 5 | 0 | 1 |
| | | | | | | 12/20 | | | |
| 27 | CdO dust | 0.03 | 18 | 31 | 1/19 | 0 | 0 | 0 | 0 |
| | | | | | | 0/19 | | | |
| 28 | CdO dust | 0.03 | 18 | 31 | 1/19 | 0 | 0 | 0 | 0 |
| | | | | | | 0/19 | | | |
| 29 | CdO dust | 0.03 | 18 | 31 | 8/19 | 2 | 1 | 0 | 0 |
| | | | | | | 3/20 | | | |
| 30 | CdO dust | 0.09 | 18 | 31 | 5/17 | 3 | 1 | 0 | 0 |
| | | | | | | 4/17 | | | |
| 31 | CdO/ZnO dust | | 18 | 31 | 1/20 | 0 | 0 | 0 | 0 |
| | | | | | | 0/20 | | | |
| 33 | CdO/ZnO dust | | 18 | 31 | 11/20 | 1 | 3 | 2 | 2 |
| | | | | | | 8/20 | | | |
| **Females** | | | | | | | | | |
| 2 | Control | – | - | 31 | 0/20 | 0 | 0 | 0 | 0 |
| | | | | | | 0/20 | | | |
| 4 | $CdCl_2$ | 0.03 | 18 | 31 | 15/20 | 4 | 7 | 0 | 2 |
| | | | | | | 13/18 | | | |

**TABLE 11. Observations after Inhalation Exposures of Rats to Various Cd Compounds**

**# Affected/Total # examined**

| Group No. | Compound | Concentration ($mg/m^3$) | Duration (month) | | Lung | Primary lung tumors[a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Exposure | Study | Nodules (n/n) | A | B | C | D |
| | | | | | | n/n | | | |
| 6 | $CdCl_2$ | 0.09 | 6 | 29[b] | 6/18 | 0 | 1 | 2 | 0 |
| | | | | | | 3/18 | | | |
| 8 | $CdSO_4$ | 0.09 | 18 | 29[b] | 17/20 | 4 | 6 | 2 | 6 |
| | | | | | | 18/20 | | | |
| 10 | CdS | 0.09 | NR | NR | 17/20 | 0 | 9 | 1 | 5 |
| | | | | | | 15/20 | | | |
| 12 | CdS | 0.27 | 16[b] | 30[b] | 17/19 | 1 | 8 | 2 | 5 |
| | | | | | | 16/19 | | | |
| 14 | CdS | 0.81 | 10[b] | 29[b] | 11/20 | 3 | 5 | 1 | 4 |
| | | | | | | 13/20 | | | |
| 16 | CdS | 2.43 | 3[b] | 31 | 9/19 | 3 | 3 | 0 | 0 |
| | | | | | | 6/19 | | | |
| 18 | CdS | 0.27 | 6 | 29[b] | 6/20 | 1 | 1 | 0 | 1 |
| | | | | | | 3/20 | | | |
| 20 | CdO dust | 0.03 | 18 | 31 | 15/20 | 3 | 7 | 1 | 4 |
| | | | | | | 15/20 | | | |
| 22 | CdO dust | 0.09 | 11[b] | 3[b] | 14/15 | 2 | 8 | 1 | 0 |
| | | | | | | 11/16 | | | |
| 24 | CdO dust | 0.09 | 6 | 31 | 6/20 | 0 | 2 | 1 | 0 |
| | | | | | | 3/20 | | | |
| 32 | CdO/ZnO dust | | 18 | 31 | 4/20 | 0 | 0 | 0 | 0 |
| | | | | | | 0/20 | | | |
| 34 | CdO/ZnO dust | | 18 | 31 | 11/20 | 1 | 3 | 1 | 2 |
| | | | | | | 7/20 | | | |

NR = not reported

Data from Oldiges et al. 1989

[a] Type of tumors: A- bronchioalveolar adenomas; B- adenocarcinomas; C- squamous cell tumors; D- combined forms

[b] The exposure and the study were stopped after 25% and 75% morality, respectively.

Forty male inbred Wistar rats/group (6 weeks old) were exposed to $CdCl_2$ aerosol at concentrations of 0 (n=41), 12.5, 25 or 50 µg/$m^3$ for 23 hrs/day, 7 days/week for 18 months (Takenaka et al. 1983). After exposure, animals were kept for another 13 months under normal laboratory conditions. Equivalent concentrations were 0.0125, 0.025 or 0.050 mg/$m^3$, respectively. Exposures took place in a 225 L inhalation chamber and the aerosol was generated by atomizing a solution of $CdCl_2$ with an ultrasonic atomizer. Air flow through the atomizer was 700 L/min and the aerosol flow through the inhalation chamber was 80 L/min. The aerosol was diluted at the lower concentrations with filtered air. Air samples were drawn through membrane filters twice weekly from the intake and exhaust of the chamber to check chamber concentration. The mass of Cd on the filters was determined by atomic absorption spectrometry. The mass median diameter was 0.55 µm and the geometric standard deviation was 1.8. Animals were weighed every 3 months and any animals dying were examined as soon as possible.

Histopathology was performed as well as measurement of the Cd content in the lungs, livers and kidneys.

During and after the exposure, there was no difference in body weight between the control and treated rats. Mean survival time at 0.050 mg/m$^3$ was slightly below that of the others but the difference was not significant. Compared to the controls (0.03 µg/g), the Cd concentration in the lungs was higher in treated rats, 5.6 µg/g in the low-dose group, 4.7 µg/g in the mid-dose group and 10.4 µg/g in the high-dose group. Similar values were found in the liver, and the kidney values were 0.3, 13.5, 16.4 and 33.6 µg/g Cd in the control, low-, mid- and high-dose groups, respectively. After the 13 month waiting period, the study reported that 0/38 in the control group; 6/39 (15.4%) at 0.0125 mg/m$^3$, 20/38 (52.6%) at 0.025 mg/m$^3$, and 25/35 (71.4%) at 0.050 mg/m$^3$ had primary lung carcinomas. These tumors were identified as adenocarcinomas, epidermoid carcinomas and combined epidermoid and adenocarcinomas. Some of the rats also had metastases in the regional lymph nodes and the kidneys. Other tumors were noted but either lacked a dose response or did not appear to be treatment-related. Limited data were provided on all other histopathological findings.

### 3.7. Summary

Cadmium, in various forms, caused respiratory irritation, pulmonary edema, rales, pneumonitis, lacrimation, increased alveolar macrophages, and death in rabbits and rats exposed for 1-6 hours. Rats and mice exposed for 90 days or less exhibited pulmonary inflammation and edema, pulmonary hyperplasia, and nasal and respiratory epithelium degeneration. Kidney weight was also increased with limited microscopic changes observed. In carcinogenicity studies, rats exposed to Cd had an increased incidence of primary lung carcinomas. Reproductive studies in rats resulted in decreased weight of live fetuses and reduced ossification of the pelvis and sternebrae. In mice, the number of pregnant mice decreased with exposure to Cd and fetal body weight was decreased.

## 4. SPECIAL CONSIDERATIONS

### 4.1. Metabolism and Disposition

Cadmium can be absorbed by inhalation, oral and dermal routes of exposure; however, dermal absorption is relatively insignificant (ATSDR 2008). In humans, acute oral exposure to cadmium causes severe nausea, vomiting, diarrhea and salivation. Cadmium fumes may produce a metal fume fever, or at higher doses, pulmonary edema, inflammation and emphysema (U.S. EPA, 1986). In humans, cadmium adsorption in the gastrointestinal tract has been reported to be low, only about 3-8%, and dependent upon several blood and dietary factors. In contrast, 30-64% of inhaled cadmium can be absorbed (Morrow, 2001). For the non-smoker, 95% of the total cadmium intake comes from ingestion of terrestrial foods or meat from animals that ate plants grown in cadmium-containing soil. For a smoker, 50% of cadmium intake is through cigarettes. Based on a 50% absorption rate, a person smoking one pack a day will absorb about 1-3 µg cadmium (Wittman and Hu 2002).

Järup et al. (1983) determined the half-life of cadmium in the blood of workers after exposure had ended. Five men were exposed to cadmium for 4-7 years and then followed up to 13 years after cessation of exposure. The estimated total inhaled amounts of cadmium during their exposures ranged from 399 to 865 mg x hr/m$^3$. Two of the five men had developed renal tubular damage. The best fit with the data was a two compartment model with the biological

half-life of cadmium in the blood being 75-128 days in the first compartment and 7.4 to 16.0 years in the second.

Once absorbed, cadmium is distributed to most tissues in the body but concentrates in the liver and kidneys of all animals (ATSDR 2008). Once in the blood, cadmium is not known to undergo any direct metabolic conversion, but the sulfhydryl groups in albumin and metallothionein have a high affinity for cadmium so it can adhere to plasma proteins (mostly albumin), plasma metallothionein or directly to the erythrocyte. Since cadmium is not easily absorbed in the GI tract, most is excreted in the feces. In the lungs, some clearance occurs but absorption can take place. In chronic exposure, approximately 1/3 of the cadmium in the body is stored in the kidney and biological half-lives are on the order of 10-30 years (Wittman and Hu 2002).

Absorbed cadmium is excreted from the body primarily in urine. The excretion rate is low and as stated above, the half-life in humans can be 10-30 years (U.S. EPA 1986; Wittman and Hu 2002).

Hadley et al. (1980) dosed male Wistar rats by intratracheal instillation with 15 µg $^{109}$CdO having a particle size of approximately 1.0 µm. Rats were sacrificed 1, 2, 4, 6, 12, 24, 48, 168, and 336 hours after instillation. At approximately 6 hours post instillation, 50% instilled $^{109}$CdO was no longer present in the lungs and 70% of that which had left the lungs was found in the liver. At 24 hours, 80% instilled $^{109}$CdO had left the lung. At the end of the 2 week period, 20% instilled $^{109}$CdO remained in the lungs. Approximately 8% of the instilled $^{109}$CdO was distributed to the kidney over 2 weeks, and the cumulative total eliminated in the urine and feces was less than 10% of total body burden.

## 4.2. Mechanism of Toxicity

Acute exposure to cadmium by the inhalation route has produced inflammatory cell influx, pneumonitis, respiratory irritation, and pulmonary edema in humans, rabbits, and rats (Beton et al. 1966; Rusch et al. 1986; Grose et al. 1987). Chronic exposure to cadmium by the oral or inhalation route has produced renal proximal tubule damage, proteinuria, polyuria and glycosuria. Cadmium-induced renal injury initially presents as tubular proteinuria which can be quantified by measurement of low molecular weight proteins such as $\beta_2$-microglobulin, retinol binding protein and protein HC. With continued exposure, the progression continues and glomerular damage occurs with a characteristic decrease in the glomerular filtration rate. For the most part, this damage is irreversible (Wittman and Hu 2002). Pneumonitis, inflammation, and fibrosis have been observed following chronic inhalation exposure (Prigge 1978; IPCS 1992; Klimisch 1993). Very little is known, however, regarding the biochemical mechanisms by which cadmium causes toxicity at the cellular level (U.S. EPA 1986).

## 4.3. Structure Activity Relationships

No data were located.

## 4.4. Other Relevant Information

### 4.4.1. Species Variability

Acute exposure to cadmium caused pneumonitis, increased lung weight, and pulmonary inflammatory cell influx in rabbits and rats (Rusch et al. 1986; Buckley and Bassett 1987; Grose et al. 1987; Takenaka et al. 2004).

In a 4-week study, male Fisher 344 rats and Balb-c mice (number of animals not specified) were exposed to $CdCl_2$ aerosols at a concentration of 0 or 100 µg $Cd/m^3$ for 6 hours/day, 5 days/week to determine if the amount of metallothionein (MT) produced was substantially different between the species (Oberdörster et al. 1994). The study found a significant species difference in the pulmonary response which may explain the pulmonary carcinogenicity observed in long-term Cd exposure in rats, whereas there is none in mice. Cadmium exposure significantly increased MT in both species in the total lung, persisting for a 28 day post-exposure period, however, the baseline MT level was higher in mice. Mice showed a 3 fold increase in MT in the lavaged lung compared to rats, the increase in mice persisted for 28-days. Histochemical staining showed that the epithelial cells of mice in the conducting airways and alveolar region had a greater induction of MT compared to those of rats, and that mice had more effects on proliferative cells compared to rats. Overall, the study suggested species difference in carcinogenicity susceptibility to Cd exposure and recommended further human research to help determine the extent of MT induction in humans.

To help further distinguish species differences observed in pulmonary inflammation, McKenna et al. (1997) exposed forty-three 15-week old male Wistar Furth rats, and sixty 17-week old mice/strain (C57 and DBA) to 1.0 $mg/m^3$ (0.22 ppm) of CdO fumes for 3 hours by nose-only inhalation. Control animals were exposed to a mixture of air and argon. Animals were sacrificed at 0, 1, 3 or 5 days post-exposure and control animals at one time point only. Overall, there were interspecies and interstrain differences observed, further indicating the wide range of effects that could be possible with human exposures. The main findings were that C57 mice had higher cell proliferation in lung tissue and neutrophil influx in the bronchoalveolar lavage fluid (BALF) compared to DBA mice and Wistar rats, DBA mice had a higher percentage of Cd dose in lung and higher levels of biochemical indices of injury in BALF, and rats responded to Cd inhalation with a more transient response in BALF and a higher degree of acute inflammatory lesions in the lung than mice.

### 4.4.2. Susceptible Populations

In acute inhalation studies, cadmium caused respiratory irritation and adverse pulmonary effects, therefore, those with lung-associated diseases or conditions (such as asthma and COPD) could be affected more. Children may be slightly more sensitive to cadmium by inhalation exposure as the rate of respiration is usually higher than that of adults. Exposure to cadmium as a child may also increase susceptibility to renal toxicity later in life (ATSDR 2008). Women with low iron stores or iron deficiency typically show increased cadmium intake; however, very little is transferred through the placenta or breast milk (Schoeters et al., 2006). Those with pre-existing renal and/or hepatic conditions would be more at risk in chronic exposures. Smokers would also be at more risk of toxicity as they are already receiving doses of cadmium from cigarettes. Other factors found to affect susceptibility to cadmium include: diet, age, sex and genetic background (U.S. EPA 1986). The factors may result in increased absorption, decreased detoxification or excretion, or compromised organ function. People living close to sources of

cadmium pollution, especially in industrialized areas, are subjected to higher exposures than those in non-industrialized areas (ATSDR 2008).

### 4.4.3. Concentration-Exposure Duration Relationship

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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, 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.

### 4.4.4. Concurrent Exposure Issues

In occupational settings, workers are exposed to other metals in addition to cadmium. Smokers inhale cadmium along with other chemicals and compounds.

## 5. DATA ANALYSIS FOR AEGL-1

### 5.1. Summary of Human Data Relevant to AEGL-1

No data were located.

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

Female Fischer 344 rats exposed (whole body) to 0.07 mg/m$^3$ Cd for 6 hours showed no morphological changes in the lungs or inflammatory response (Takenaka et al. 2004). Rabbits and rats exposed (nose-only) to 0.25 mg/m$^3$ $CdCl_2$ or CdO for 2 hours had inhibited pulmonary GSH peroxidase activity (Grose et al. 1987). Rabbits and rats exposed (nose-only) to 0.45 mg/m$^3$ $CdCl_2$ or CdO for 2 hours had increased inflammatory response (Grose et al. 1987). Deaths were observed in rats exposed to 0.45 mg/m$^3$ but no deaths were observed in rats exposed to 4.5 mg/m$^3$, and those deaths may be associated with the exposure apparatus. The mortality observed was also inconsistent with the data for rats exposed to similar concentrations. After exposure to 0.5 mg/m$^3$ CdO for 3 hours, rats had increased inflammatory cell influx and transient hypercellularity, but no mortality (Buckley and Bassett 1987). After whole-body exposure to 0.55 mg/m$^3$ CdO for 6 hours, rats had increased neutrophils and multifocal alveolar inflammation and no mortality (Takenaka et al. 2004).

### 5.3. Derivation of AEGL-1

The AEGL-1 values are based on the experimental concentration, 0.55 mg Cd/m$^3$, that caused slight respiratory irritation in rats (Takenaka et al. 2004). After a 6 hour exposure, increased neutrophils and multifocal alveolar inflammation were observed. At the next higher experimental exposure, pneumonitis was observed (Grose et al. 1987). Although the exposure was a whole-body exposure, the size of the ultrafine particles (51 nM MMAD, 1.7 GSD) would mimic a gaseous state and the majority of the aerosol would be inhaled and not deposited on the fur. An interspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant as indicated by the signs of irritation in rabbits and rats. This mode of action is not expected to differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/m$^3$ displayed similar histological and biochemical pulmonary effects including

pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 $mg/m^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987 ; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. An intraspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant in humans, and this mode of action is not expected to differ among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, 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. The 30-minute AEGL-1 value was adopted as the 10-minute value due to the added uncertainty of extrapolating from a 6-hour time point to 10 minutes (NRC 2001). The calculations for the AEGL-1 values are in Appendix A.

**TABLE 12. AEGL-1 Values for Cadmium**

| 10-min | 30-min | 1-hr | 4-hr | 8-hr |
|---|---|---|---|---|
| 0.13 $mg/m^3$ | 0.13 $mg/m^3$ | 0.10 $mg/m^3$ | 0.063 $mg/m^3$ | 0.041 $mg/m^3$ |

## 6. DATA ANALYSIS FOR AEGL-2

### 6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to AEGL-2 were located.

### 6.2. Summary of Animal Data Relevant to AEGL-2

Rabbits and rats exposed for 2 hours to 4.5 $mg/m^3$ $CdCl_2$ or CdO exhibited increased lung weight and moderate-severe pneumonitis characterized by alveolar wall thickening, hemorrhage, and edema (Grose et al. 1987). At 5.3 $mg/m^3$, focal areas of interstitial thickening, an increase in cuboidal alveolar cells, numerous inflammatory cells (interstitial mononuclear cells, alveolar macrophages, eosinophils, and basophils), and increase in lung weight and protein content were observed (Buckley and Bassett 1987).

### 6.3. Derivation of AEGL-2

The AEGL-2 values are based on the experimental concentration, 5.3 mg $Cd/m^3$, that caused overt respiratory irritation and pathology in rats (Buckley and Bassett 1987). The 3 hour exposure resulted in reduced weight gain and increased lung weight, protein content, DNA content, number of cuboidal alveolar cells, number of inflammatory cells, and focal areas of interstitial thickening. An interspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant as indicated by the signs of irritation in rabbits and rats. This mode of action is not expected to differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 $mg/m^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 $mg/m^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987 ;

Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. An intraspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant in humans, and this mode of action is not expected to differ among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, 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. The calculations for the AEGL-2 values are in Appendix A.

**TABLE 13. AEGL-2 Values for Cadmium**

| 10-min | 30-min | 1-hr | 4-hr | 8-hr |
|---|---|---|---|---|
| 1.4 mg/m$^3$ | 0.96 mg/m$^3$ | 0.76 mg/m$^3$ | 0.40 mg/m$^3$ | 0.20 mg/m$^3$ |

## 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Summary of Human Data Relevant to AEGL-3

Workers (n=5) exposed for 5 hours to Cd oxide fumes inhaled an estimated 8.6 mg/m$^3$. One worker died 5 days after the exposure with severe pulmonary edema, alveolar metaplasia of the lungs, and bilateral cortical necrosis of the kidneys (Beton et al. 1966). The other four workers had pulmonary edema that resolved over time.

### 7.2. Summary of Animal Data Relevant to AEGL-3

Mortality occurred in rats exposed to cadmium carbonate (5.8%) or cadmium fume (48%) for 2 hours. The $LC_{50}$ for the study was 112 mg/m$^3$ (Rusch et al. 1986). One rat exposed to 0.45 mg/m$^3$ Cd died of cardiovascular failure associated with pulmonary congestion (Grose et al. 1987). Two other rats died of unknown causes in the same study. Although death occurred at 0.45 mg/m$^3$, this value was not used to derive AEGL-3. The deaths may be associated with the exposure apparatus and may not be the result of exposure to cadmium. Lack of mortality in rats exposed to similar concentrations (0.5 mg/m$^3$, Buckley and Bassett 1987; 0.55 mg/m$^3$, Takenaka et al. 2004) and at a higher experimental dose within the same study, 4.5 mg/m$^3$, further support the dismissal of the mortality data from Grose et al. (1987) from being considered for derivation of AEGL-3 values.

### 7.3. Derivation of AEGL-3

The AEGL-3 values are based on the 2 hour $LC_{50}$ for cadmium fume in rats, 112 mg/m$^3$ (Rusch et al. 1986). The $LC_{50}$ was divided by 3 to estimate a threshold of lethality. An intraspecies uncertainty factor of 3 was applied because in acute exposures, cadmium is a direct-acting respiratory irritant. An interspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant as indicated by the signs of irritation in rabbits and rats. This mode of action is not expected to differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/m$^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and

decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/m$^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987 ; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. An intraspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant in humans, and this mode of action is not expected to differ among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, 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. The calculations for the AEGL-3 values are in Appendix A.

**TABLE 14. AEGL-3 Values for Cadmium**

| 10-min | 30-min | 1-hr | 4-hr | 8-hr |
|---|---|---|---|---|
| 8.5 mg/m$^3$ | 5.9 mg/m$^3$ | 4.7 mg/m$^3$ | 1.9 mg/m$^3$ | 0.93 mg/m$^3$ |

## 8. SUMMARY OF AEGLS

### 8.1. AEGL Values and Toxicity Endpoints

Cadmium was shown to be an irritating metal that caused developmental, respiratory, and renal effects following multiple exposures. The derived AEGL values would prevent these effects. The AEGL-1 values were based upon the experimental concentration that caused slight respiratory irritation in rats, 0.55 mg Cd/m$^3$, following a 6 hour exposure. The AEGL-2 values were based upon the experimental concentration that caused overt respiratory tract irritation and pathology in rats, 5.3 mg/m$^3$, following a 3 hour exposure. The AEGL-3 values were a based upon the estimated threshold of lethality from cadmium fumes from the 2-hour $LC_{50}$, 112 mg/m$^3$, in rats. AEGL values are summarized in Table 15.

**TABLE 15. Summary of AEGL Values**

| Classification | Exposure Duration | | | | |
|---|---|---|---|---|---|
| | 10-min | 30-min | 1-hr | 4-hr | 8-hr |
| **AEGL-1 (Notable Discomfort)** | 0.13 mg/m$^3$ | 0.13 mg/m$^3$ | 0.10 mg/m$^3$ | 0.063 mg/m$^3$ | 0.041 mg/m$^3$ |
| **AEGL-2 (Disabling)** | 1.4 mg/m$^3$ | 0.96 mg/m$^3$ | 0.76 mg/m$^3$ | 0.40 mg/m$^3$ | 0.20 mg/m$^3$ |
| **AEGL-3 (Lethal)** | 8.5 mg/m$^3$ | 5.9 mg/m$^3$ | 4.7 mg/m$^3$ | 1.9 mg/m$^3$ | 0.93 mg/m$^3$ |

### 8.2. Comparison with Other Standards and Guidelines

AEGL values for cadmium are compared to other guidelines and standards in Table 16. The OSHA values were established to protect against lung cancer and kidney dysfunction (OSHA 2005). The IDLH was based upon acute inhalation toxicity in workers (NIOSH 1996). The ACGIH TWA inhalable particulate value was established to minimize kidney dysfunction and

the respirable fraction value was set to minimize pulmonary accumulation of cadmium that could act as a carcinogen (ACGIH 1996).

**TABLE 16. Extant Standards and Guidelines for Cadmium**

| Guideline | Exposure Duration | | | | |
|---|---|---|---|---|---|
| | 10 min | 30 min | 1 hr | 4 hr | 8 hr |
| **AEGL-1** | 0.13 mg/m$^3$ | 0.13 mg/m$^3$ | 0.10 mg/m$^3$ | 0.063 mg/m$^3$ | 0.041 mg/m$^3$ |
| **AEGL-2** | 1.4 mg/m$^3$ | 0.96 mg/m$^3$ | 0.76 mg/m$^3$ | 0.40 mg/m$^3$ | 0.20 mg/m$^3$ |
| **AEGL-3** | 8.5 mg/m$^3$ | 5.9 mg/m$^3$ | 4.7 mg/m$^3$ | 1.9 mg/m$^3$ | 0.93 mg/m$^3$ |
| PEL-TWA (OSHA)[a] (fume) | | | | | 0.1 mg/m$^3$<br>0.3 mg/m$^{3C}$ |
| PEL-TWA (OSHA)[b] (dust) | | | | | 0.2 mg/m$^3$<br>0.6 mg/m$^{3C}$ |
| IDLH (NIOSH)[c] | 9 mg/m$^3$ | | | | |
| TLV-TWA (ACGIH)[d] | | | | | 0.01 mg/m$^{3I}$<br>0.002 mg/m$^{3R}$ |
| MAC-Peak Category (The Netherlands)[e] | | | | | 0.005 mg/m$^3$ |

[a] OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA, 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week. $^C$-Acceptable ceiling concentration.

[b] OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit) (OSHA, 2005) is defined analogous to the ACGIH-TLV-STEL. $^C$-Acceptable ceiling concentration.

[c] 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 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH, 2008) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. $^I$- Inhalable particulate; $^R$- Respirable fraction

[e]MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration - Peak Category]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-Ceiling.

## 8.3. Data Adequacy and Research

Toxicity data for cadmium are available for humans and animals. Most of the acute inhalation data for humans do not provide cadmium exposure concentrations, but report signs and symptoms of toxicity which are useful for noting effects of exposure. Short-term and chronic epidemiological studies in workers were available; however, the workers may have had concurrent exposures to other chemicals. Animal studies were conducted in at least three species and range from acute to chronic. The acute studies in rabbits and rats provide data suitable for deriving AEGL values and highlight the differences between the effects that occur following acute and chronic cadmium exposure.

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# APPENDIX A: Derivation of AEGL Values

## Derivation of AEGL-1

| | |
|---|---|
| Key Study: | Takenaka, S., E. Karg, W.G. Kreyling, B. Lentner, H. Schultz, A. Ziesenis, P. Schramel and J. Heyder. 2004. Fate and toxic effects of inhaled ultrafine cadmium oxide particles in the rat lung. Inhal. Toxicol. 16 (suppl.1): 83-92. |
| Toxicity endpoint: | The experimental concentration, 0.55 mg Cd/$m^3$ caused slight respiratory irritation in female rats exposed for 6 hours. |
| Time scaling: | $C^n \times t = k$; n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. |
| Uncertainty factors: | |
| Interspecies: | 3, Cadmium is a direct-acting respiratory irritant and it is not expected that toxicity would differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/$m^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/$m^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. |
| Intraspecies: | 3, Cadmium is a direct-acting respiratory irritant, and respiratory effects due to irritation are not expected to differ greatly among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. |
| Modifying factor: | None applied. |
| Calculations: | 0.55 mg/$m^3$ / 10 = 0.055 mg/$m^3$<br>$C^3 \times t = k$<br>(0.055 mg/$m^3$)$^3$ x 360 min = 0.059895 mg/$m^3$-min<br><br>$C^1 \times t = k$<br>0.0055 mg/$m^3$ x 360 min = 19.8 mg/$m^3$-min |
| 10-min AEGL-1 | 30-min value adopted as 10-min value = 0.13 mg/$m^3$ |
| 30-min AEGL-1 | $C^3$ x 30 min= 0.059895 mg/$m^3$-min<br>C = 0.13 mg/$m^3$ |
| 1-hr AEGL-1 | $C^3$ x 60 min= 0.059895 mg/$m^3$-min<br>C = 0.10 mg/$m^3$ |
| 4-hr AEGL-1 | $C^3$ x 240 min= 0.059895 mg/$m^3$-min |

| | | |
|---|---|---|
| 1 | | $C = 0.063\ mg/m^3$ |
| 2 | | |
| 3 | 8-hr AEGL-1 | $C^1 \times 480\ min = 19.8\ mg/m^3\text{-min}$ |
| 4 | | $C = 0.041\ mg/m^3$ |

**Derivation of AEGL-2**

| | |
|---|---|
| Key Studies: | Buckley, B.J. and D.J.P. Bassett. 1987. Pulmonary cadmium oxide toxicity in the rat. J. Toxicol. Environ. Health. 21: 233-250. |
| Toxicity endpoints: | The experimental concentration, 5.3 mg Cd/$m^3$ caused overt respiratory irritation and pathology in exposed for 3 hours. |
| Time scaling: | $C^n \times t = k$; n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. |
| Uncertainty factors: | |
| Interspecies: | 3, Cadmium is a direct-acting respiratory irritant and it is not expected that toxicity would differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/$m^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/$m^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. |
| Intraspecies: | 3, Cadmium is a direct-acting respiratory irritant, and respiratory effects due to irritation are not expected to differ greatly among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. |
| Modifying factor: | None applied. |
| Calculations: | 5.3 mg/$m^3$ / 10 = 0.53 mg/$m^3$<br>$C^3 \times t = k$<br>(0.53 mg/$m^3$)$^3$ x 180 min = 26.79786 mg/$m^3$-min<br><br>$C^1 \times t = k$<br>0.53 mg/$m^3$ x 180 min = 95.4 mg/$m^3$-min |
| 10-min AEGL-2 | $C^3 \times 10$ min= 26.79786 mg/$m^3$-min<br>C = 1.4 mg/$m^3$ |
| 30-min AEGL-2 | $C^3 \times 30$ min= 26.79786 mg/$m^3$-min<br>C = 0.96 mg/$m^3$ |
| 1-hr AEGL-2 | $C^3 \times 60$ min= 26.79786 mg/$m^3$-min<br>C = 0.76 mg/$m^3$ |
| 4-hr AEGL-2 | $C^1 \times 240$ min = 95.4 mg/$m^3$-min<br>C = 0.40 mg/$m^3$ |
| 8-hr AEGL-2 | $C^1 \times 480$ min = 95.4 mg/$m^3$-min |

1 $C = 0.20\ mg/m^3$
2
3

**Derivation of AEGL-3**

Key Studies: Rusch, G.M., J.S. O'Grodnick and W.E. Rinehart. 1986. Acute inhalation study in the rat of comparative uptake, distribution and excretion for different cadmium containing materials. Am. Ind. Hyg. Assoc. J. 47: 754-763.

Toxicity endpoint: The threshold of lethality was calculated from the 2-hr $LC_{50}$ for cadmium fume in rats, 112 mg/m$^3$.

Time scaling: $C^n \times t = k$; n=3 when extrapolating to shorter time points, and n = 1 when extrapolating to longer time points.

Uncertainty factors:

Interspecies: 3, Cadmium is a direct-acting respiratory irritant and it is not expected that toxicity would differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/m$^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/m$^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study.

Intraspecies: 3, Cadmium is a direct-acting respiratory irritant, and respiratory effects due to irritation are not expected to differ greatly among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation.

Modifying factor: None applied.

Calculations

112 mg/m$^3$ /3/10= 3.733 mg/m$^3$

$C^3 \times t = k$

$(3.733 \text{ mg/m}^3)^3 \times 120 \text{ min} = 6242.45206 \text{ mg/m}^3\text{-min}$

$C^1 \times t = k$

$3.733 \text{ mg/m}^3 \times 120 \text{ min} = 447.96 \text{ mg/m}^3\text{-min}$

10-minute AEGL-3

$C^3 \times 10 \text{ min} = 6242.45206 \text{ mg/m}^3\text{-min}$

$C = 8.5 \text{ mg/m}^3$

30-minute AEGL-3

$C^3 \times 30 \text{ min} = 6242.45206 \text{ mg/m}^3\text{-min}$

$C = 5.9 \text{ mg/m}^3$

1-hr AEGL-3

$C^3 \times 60 \text{ min} = 6242.45206 \text{ mg/m}^3\text{-min}$

$C = 4.7 \text{ mg/m}^3$

4-hr AEGL-3

$C^1 \times 240 \text{ min} = 44.796 \text{ mg/m}^3\text{-min}$

$C = 1.9 \text{ mg/m}^3$

| | |
|---|---|
| 8-hr AEGL-3 | $C^1$ x 480 min = 44.796 mg/$m^3$-min |
| | C = 0.93 mg/$m^3$ |

# APPENDIX B: Time-Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule (i.e., $C \times t = k$, where $C$ = exposure concentration, $t$ = exposure duration, and $k$ = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant ($k$) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of $LC_{50}$ data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where $n$ represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically in the form of a linear regression analysis of the log-log transformation of a plot of C vs. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of $n$ ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent ($n$) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of $n$ increases, the plot of concentration vs. time yields a progressive decrease in the slope of the curve.

The available data do not allow for empirical derivation of a temporal scaling factor ($n$) for cadmium. The exposure concentration-exposure duration 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 from the experimental durations of the respective PODs to AEGL-specific durations 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.

## APPENDIX C: Carcinogenicity Assessment

The carcinogenicity data are summarized in Section 3.6 and Table 9. The U.S. EPA (1994) concluded that cadmium is a "probable human carcinogen" based on evidence of carcinogenicity in animals and limited evidence of carcinogenicity in an exposed human population. The inhalation unit risk calculated is $1.8 \times 10^{-3}$ µg/m$^3$, and the concentration associated with a risk level of 1 in 10,000 is $6 \times 10^{-2}$ µg/m$^3$.

To convert a 70-year (25,600 days) exposure to a 24-hr exposure:

24-hr exposure = d x 25,600; where d = $6 \times 10^{-2}$ µg/m$^3$
= ($6 \times 10^{-2}$ µg/m$^3$) x 25,600 days
= 1536 µg/m$^3$ = 1.54 mg/m$^3$

To account for uncertainty regarding the variability in the stage of the cancer process at which cadmium may act, a multi-stage factor of 6 is applied (Crump and Howe, 1984):

$$1.54 \text{ mg/m}^3 / 6 = 0.26 \text{ mg/m}^3$$

Therefore, a single exposure to cadmium at 0.26 mg/m$^3$ for 24 hrs would represent a cancer risk of $10^{-4}$. If the exposure is limited to a fraction (f) of a 24-hr period, the fractional exposure becomes 1/f x 24 hr (NRC 1985).

| | | |
|---|---|---|
| 24 hr exposure | = | 0.26 mg/m$^3$ |
| 8 hr exposure | = | 0.78 mg/m$^3$ |
| 4 hr exposure | = | 1.56 mg/m$^3$ |
| 1 hr exposure | = | 6.24 mg/m$^3$ |
| 30 min exposure | = | 12.48 mg/m$^3$ |
| 10 min exposure | = | 36.66 mg/m$^3$ |

The AEGL values for 10 minutes, 30 minutes, 1, 4, and 8 hours are presented below for risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$

| Time (h) | $10^{-4}$ | $10^{-5}$ | $10^{-6}$ |
|---|---|---|---|
| 0.17 | 36.7 | 3.67 | 0.367 |
| 0.5 | 12.5 | 1.25 | 0.125 |
| 1 | 6.24 | 0.624 | 0.0624 |
| 4 | 1.56 | 0.156 | 0.0156 |
| 8 | 0.78 | 0.078 | 0.0078 |

These values based on carcinogenicity are not proposed for AEGL values.

# APPENDIX D: Derivation Summary for Cadmium AEGLs

## ACUTE EXPOSURE GUIDELINE LEVELS FOR CADMIUM (CAS Reg. No. 7440-43-9) DERIVATION SUMMARY

| AEGL-1 VALUES | | | | |
|---|---|---|---|---|
| **10-min** | **30-min** | **1-hr** | **4-hr** | **8-hr** |
| **0.13 mg/m$^3$** | **0.13 mg/m$^3$** | **0.10 mg/m$^3$** | **0.063 mg/m$^3$** | **0.041 mg/m$^3$** |

**Key Reference**:
Takenaka, S., E. Karg, W.G. Kreyling, B. Lentner, H. Schultz, A. Ziesenis, P. Schramel and J. Heyder. 2004. Fate and toxic effects of inhaled ultrafine cadmium oxide particles in the rat lung. Inhal. Toxicol. (suppl.1): 83-92.

**Test Species/Strain/Number:** Rat/Fischer 344/24/group

**Exposure Route/Concentrations/Duration:** Inhalation/0.07, 0.550 mg/m$^3$/ 6 hr

Effects:
- 0.07 mg/m$^3$ No morphological changes or inflammatory response
- 0.550 mg/m$^3$ Increased neutrophils and multifocal alveolar inflammation

**Endpoint/Concentration/Rationale**: Slight respiratory irritation /0.55 mg Cd/m$^3$ administered as CdO

**Uncertainty Factors/Rationale:**
**Total uncertainty factors:** 10

Interspecies: 3, Cadmium is a direct-acting respiratory irritant and it is not expected that toxicity would differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/m$^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/m$^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study.

Intraspecies: 3, Cadmium is a direct-acting respiratory irritant, and respiratory effects due to irritation are not expected to differ greatly among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation.

**Modifying Factor**: None

**Animal to Human Dosimetric Adjustment**: None

**Time Scaling:** $C^n \times t = k$; n=3 when extrapolating to shorter time points (10-, 30-, and 60- min, and 4-hr), and n = 1 when extrapolating to longer time points (8 hr). The 30-minute AEGL-1 value was adopted as the 10-minute value due to the added uncertainty of extrapolating from a 6-hr time point to 10 min.

**Data Adequacy**: Data were available and adequate for deriving AEGL-1 values.

1
2

| AEGL-2 VALUES | | | | |
|---|---|---|---|---|
| **10-min** | **30-min** | **1-hr** | **4-hr** | **8-hr** |
| **1.4 mg/m$^3$** | **0.96 mg/m$^3$** | **0.76 mg/m$^3$** | **0.40 mg/m$^3$** | **0.20 mg/m$^3$** |

**Key Reference:**
Buckley, B.J. and D.J.P. Bassett. 1987. Pulmonary cadmium oxide toxicity in the rat. J. Toxicol. Environ. Health. 21: 233-250.

**Test Species/Strain/Number:** Rats/Wistar/16/group

**Exposure Route/Concentrations/Duration:** Inhalation/0.0.5, 5.3 mg/m$^3$ CdO/ 3 hr

**Effects**:

| | |
|---|---|
| 0. 5 mg/m$^3$ | Transient mild hypercellularity at bronchoalveolar junctions and adjacent alveoli, inflammatory cell influx |
| 5.3 mg/m$^3$ | Interstitial thickening, ↑ cuboidal alveolar cells, ↑inflammatory cells, ↑dry lung weight, ↑protein content, ↑DNA content, ↑ GP, GR, G6PD, 6PGD activity |

**Endpoint/Concentration/Rationale**: Overt respiratory tract irritation and pathology /5.3 mg/m$^3$ administered as CdO

**Uncertainty Factors/Rationale:**
**Total uncertainty factors:** 10

| | |
|---|---|
| Interspecies: | 3, Cadmium is a direct-acting respiratory irritant and it is not expected that toxicity would differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/m$^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/m$^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. |
| Intraspecies: | 3, Cadmium is a direct-acting respiratory irritant, and respiratory effects due to irritation are not expected to differ greatly among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. |

**Modifying Factor**: None

**Animal to Human Dosimetric Adjustment**: None

**Time Scaling:** $C^n \times t = k$; n=3 when extrapolating to shorter time points (10, 30, and 60 min), and n = 1 when extrapolating to longer time points (4 hr, 8 hr).

**Data Adequacy:** Data were available and adequate for deriving AEGL-2 values.

1
2
3

| AEGL-3 VALUES | | | | |
|---|---|---|---|---|
| **10-min** | **30-min** | **1-hr** | **4-hr** | **8-hr** |
| **8.5 mg/m$^3$** | **5.9 mg/m$^3$** | **4.7 mg/m$^3$** | **1.9 mg/m$^3$** | **0.93 mg/m$^3$** |

**Key Reference**:
Rusch, G.M., J.S. O'Grodnick, and W.E. Rinehart. 1986. Acute inhalation study in the rat of comparative uptake, distribution and excretion for different cadmium containing materials. Am. Ind. Hyg. Assoc. J 47: 754-763.

**Test Species/Strain/Number**: Rat/Sprague-Dawley/26/group

**Exposure Route/Concentrations/Duration:** Inhalation/97 mg/m$^3$ Cd red, 99 mg/m$^3$ Cd yellow, 132 mg/m$^3$ Cd carbonate, 112 mg/m$^3$ Cd fume/2 hr

**Effects**:

| | |
|---|---|
| 97 mg/m$^3$ Cd red | Lacrimation, renal discoloration |
| 99 mg/m$^3$ Cd yellow | Lacrimation |
| 132 mg/m$^3$ Cd carbonate | 5.8% mortality, dry rales, pulmonary edema |
| 112 mg/m$^3$ Cd fume | 48% mortality, hypoactivity, closed eyes, dry and moist rales, $LC_{50}$ |

**Endpoint/Concentration/Rationale:** Threshold of lethality based on 2-hr $LC_{50}$ 112 mg/m$^3$ for cadmium fumes

**Uncertainty Factors/Rationale:**
**Total uncertainty factors:** 10

| | |
|---|---|
| Interspecies: | 3, Cadmium is a direct-acting respiratory irritant and it is not expected that toxicity would differ among species. Rabbits and rats exposed for 2 hours to 0.25-4.5 mg/m$^3$ displayed similar histological and biochemical pulmonary effects including pneumonitis, increased lung weight, pulmonary inflammatory cell influx, and decreased glutathione peroxidase activity (Grose et al. 1987). Rats exposed to cadmium (0.00169-5.3 mg/m$^3$) from 1-6 hours (Buckley and Bassett 1987; Oberdörster et al. 1987; Takenaka et al. 2004) exhibited the same effects as those observed in the Grose et al. (1987) study. |
| Intraspecies: | 3, Cadmium is a direct-acting respiratory irritant, and respiratory effects due to irritation are not expected to differ greatly among individuals. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966) which are signs of respiratory irritation. |

**Modifying Factor:** None

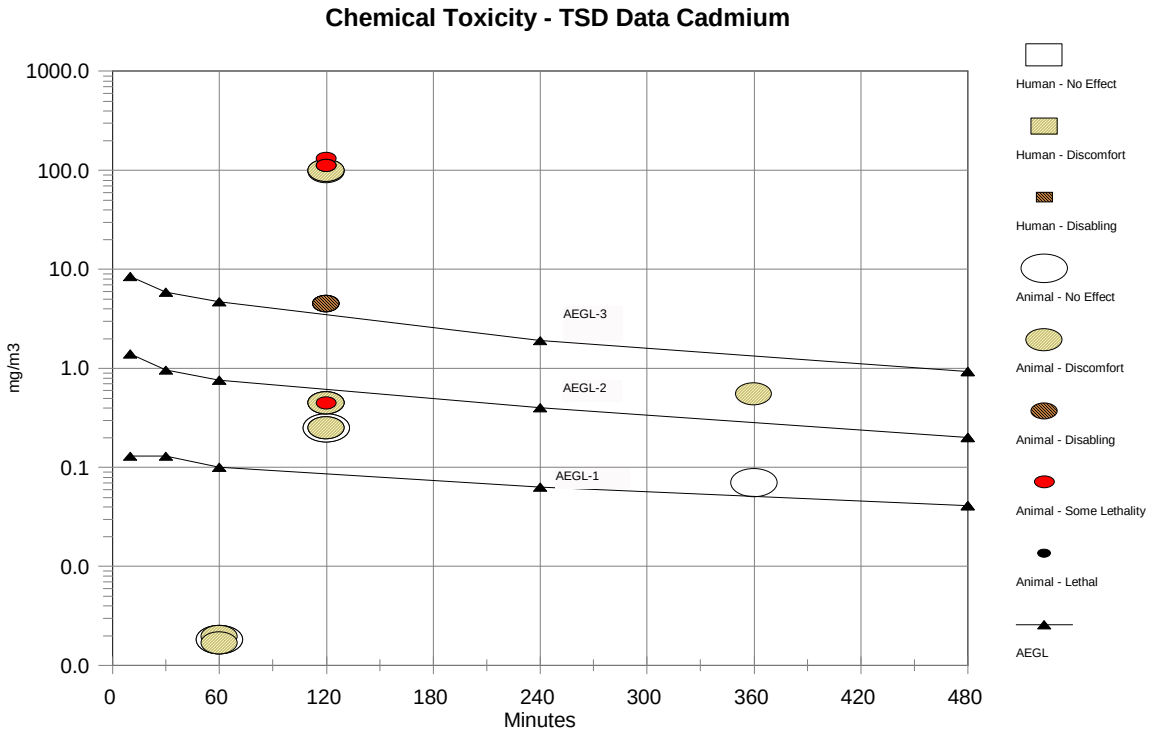
Animal to Human Dosimetric Adjustment:

**Time Scaling:** $C^n \times t = k$; n=3 when extrapolating to shorter time points (10-, 30-, and 60- min), and n = 1 when extrapolating to longer time points (4-hr, 8 hr).

**Data Adequacy:** Data were available and adequate for deriving AEGL-3 values.

4

# APPENDIX E: Category Plot for Cadmium




The values for AEGL-2 and AEGL-3 are above a concentration, 0.45 mg Cd/$m^3$, at which 2 animals died. Based on the information provided in the study (Grose et al. 1987), it is possible that the animal deaths were not the result of exposure to cadmium but were the result of exposure apparatus difficulties (reversal of animal body and resulting asphyxiation). The mortality at this concentration was inconsistent with the other animal data resulting from exposures at similar concentrations. There was also a lack of dose response as no mortality occurred following exposure to a higher dose of cadmium.

1

| **Category Plot Data** | | | | | | | |
|---|---|---|---|---|---|---|---|
| For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal | | | | | | | |
| Source | Species | Sex | # Exposures | $mg/m^3$ | Min | Category | Comments |
| NAC/AEGL-1 | | | | 0.13 | 10 | AEGL | |
| NAC/AEGL-1 | | | | 0.13 | 30 | AEGL | |
| NAC/AEGL-1 | | | | 0.10 | 60 | AEGL | |
| NAC/AEGL-1 | | | | 0.063 | 240 | AEGL | |
| NAC/AEGL-1 | | | | 0.041 | 480 | AEGL | |
| | | | | | | | |
| NAC/AEGL-2 | | | | 1.4 | 10 | AEGL | |
| NAC/AEGL-2 | | | | 0.96 | 30 | AEGL | |
| NAC/AEGL-2 | | | | 0.76 | 60 | AEGL | |
| NAC/AEGL-2 | | | | 0.40 | 240 | AEGL | |
| NAC/AEGL-2 | | | | 0.20 | 480 | AEGL | |
| | | | | | | | |
| NAC/AEGL-3 | | | | 8.5 | 10 | AEGL | |
| NAC/AEGL-3 | | | | 5.9 | 30 | AEGL | |
| NAC/AEGL-3 | | | | 4.7 | 60 | AEGL | |
| NAC/AEGL-3 | | | | 1.9 | 240 | AEGL | |
| NAC/AEGL-3 | | | | 0.93 | 480 | AEGL | |
| Beton et al. 1966 | Human | m | 1 | 8.6 | 300 | SL | 20% mortality, pulmonary edema, dyspnea in others |
| Grose et al. 1987 | Rabbit | m | 1 | 0.25 | 120 | 1 | Decreased GSH peroxidase activity |
| Grose et al. 1987 | Rabbit | m | 1 | 0.45 | 120 | 1 | Increased GSH transferase activity |
| Grose et al. 1987 | Rabbit | m | 1 | 4.5 | 120 | 2 | Pneumonitis |
| Grose et al. 1987 | Rabbit | m | 1 | 0.25 | 120 | 0 | No effects |
| Grose et al. 1987 | Rabbit | m | 1 | 0.45 | 120 | 1 | Increase alveolar macrophages |
| Grose et al. 1987 | Rabbit | m | 1 | 4.5 | 120 | 2 | Pneumonitis |
| Grose et al. 1987 | Rat | m | 1 | 0.25 | 120 | 1 | Decreased GSH peroxidase activity |
| Grose et al. 1987 | Rat | m | 1 | 0.45 | 120 | 1 | Decreased GSH peroxidase activity; body weight |
| Grose et al. 1987 | Rat | m | 1 | 4.5 | 120 | 2 | Pneumonitis |
| Grose et al. 1987 | Rat | m | 1 | 0.25 | 120 | 0 | No effects |
| Grose et al. 1987 | Rat | m | 1 | 0.45 | 120 | SL | Pulmonary congestion |
| Grose et al. 1987 | Rat | m | 1 | 4.5 | 120 | 2 | Pneumonitis |
| Takenaka et al 2004 | Rat | f | 1 | 0.07 | 360 | 0 | No effects |
| Takenaka et al 2004 | Rat | f | 1 | 0.55 | 360 | 1 | Alveolar inflammation, neutrophils |
| Oberdorster et al. 1987 | Rat | m | 1 | 0.00195 | 60 | 1 | Decreased alveolar macrophages, |
| Oberdorster et al. 1987 | Rat | m | 1 | 0.00169 | 60 | 1 | Decreased alveolar macrophages, |
| Oberdorster et al. 1987 | Rat | m | 1 | 0.00182 | 60 | 0 | No effects |
| Rusch et al. 1986 | Rat | b | 1 | 97 | 120 | 1 | Lacrimation; renal discoloration |
| Rusch et al. 1986 | Rat | b | 1 | 99 | 120 | 1 | Lacrimation |
| Rusch et al. 1986 | Rat | b | 1 | 132 | 120 | SL | 5.8% mortality, dry rales; pulmonary edema |
| Rusch et al. 1986 | Rat | b | 1 | 112 | 120 | SL | 48% mortality; hypoactivity, LC50 |

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