II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name:	Cadmium and Compounds
CASRN:	7440-43-9
Preparation Date:	March 4, 1999

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

A *probable human carcinogen by inhalation exposure* (Classification: B1; limited evidence from epidemiologic studies by the inhalation route and sufficient evidence of carcinogenesis in animals by the inhalation route). The evidence for cadmium being carcinogenic via the oral route is inadequate. Except for the designation of route, this assessment essentially reaffirms the previous IRIS evaluation of cadmium.

Basis:

Evidence for human carcinogenicity of cadmium via inhalation is consistent across study investigators and cohorts in occupational epidemiology studies. Exposure to known confounding factors (including arsenic and smoking) are, however, present in several of these occupational studies. There is sufficient evidence of cadmium carcinogenicity in animals, based on induction of lung cancer in two independent rat inhalation studies.

Evidence for carcinogenicity of cadmium via the oral route is inadequate. No compelling evidence exists for human cancers from oral exposure to cadmium either in the lung or in oral portal-of-entry tissues. The only tumors seen in rat oral studies with cadmium are benign testicular tumors that are likely endocrine-mediated.

II.A.2. HUMAN CARCINOGENICITY DATA

A number of epidemiology studies have been conducted to evaluate the carcinogenic potential of occupational exposure to cadmium, with some cohorts followed for extended periods in multiple studies. A series of studies conducted on a cohort at an American cadmium smelter that had also been used as an arsenic smelter reported an increase in lung cancer deaths related to cumulative cadmium exposure (Lemen et al., 1976; Thun et al., 1985; Stayner et al., 1992, 1993; Lamm et al., 1992; Sorahan and Lancashire, 1997). Significant excesses in the number of lung cancer deaths were also observed in cadmium workers in the United Kingdom (Kazantzis et al., 1992) although a number of confounding factors (including arsenic) were cited as potential confounding exposures. Significantly increased mortality from respiratory cancer was observed in a study of nickel cadmium battery workers, but no relationship to exposure duration was observed (Sorahan, 1987). An excess of lung cancer deaths that did not reach statistical significance was also reported in a nickel-cadmium manufacturing plant in Sweden (Elinder et al., 1985). A link between occupational exposure to cadmium and prostate cancer has been suggested (Kipling and Waterhouse, 1967; Lemen et al., 1976; Potts, 1965), but this finding has not been supported by more recent follow-up (Sorahan and Waterhouse, 1985; Thun et al., 1985). Detection of a cadmium-related increase in prostate cancer mortality is complicated by the relatively high prevalence in the general population and by recent improvements in prostate cancer screening.

A series of retrospective mortality studies has been conducted of workers exposed to cadmium dust or cadmium fume at a cadmium smelter in the U.S. that had functioned as an arsenic smelter prior to 1926 (Lemen et al., 1976; Thun et al., 1985; Stayner et al., 1992; Sorahan and Lancashire, 1997). In the initial study, Lemen et al. (1976) studied 292 men from the cohort, with follow-up through 1973. Workers who had been employed for 2 or more years between January 1, 1940, and December 31, 1969 were included in the study; no attempt was made to exclude workers exposed while the plant was an arsenic smelter. Life table analysis comparing mortality with the U.S. white male population found a statistically significant excess of deaths from respiratory cancer (12 Obs, SMR=2.34, $p<0.05$). A nonsignificant excess of prostate cancer deaths was observed for the total cohort (Obs=4, SMR=347, $p>0.05$) which became statistically significant when the analysis was restricted to workers with 20 or more years of exposure (4 Obs, SMR=452, $p<0.05$).

Thun et al. (1985) conducted a study extending the cohort, with additional follow-up time. The study population consisted of 602 white men who worked in a production area at the smelter for at least 6 months between 1940 and 1969, with followup through 1978. Separate analyses were conducted for the pre- and post-1926 cohorts to reduce the confounding effects of arsenic. A statistically significant exposure-response relationship was observed between lung cancer deaths and cumulative exposure to cadmium (SMR=229, 95% CI=131-371). The study authors also reported total deaths from respiratory cancer, including cancers of the lung, trachea, and bronchus, but 16/20 respiratory cancers were lung cancers and no exposure-response analysis was conducted for total respiratory cancers. They also noted that, because national lung cancer death rates overestimated regional rates by 10-25%, the measured excess of lung cancer deaths was probably an underestimate. There was no significant increase in mortality from prostate cancer, nonmalignant respiratory disease, nonmalignant renal disease, or hypertension. From the separate analyses for arsenic exposure the authors noted that levels of arsenic in the areas of highest exposure were as high as 300 to 700 ug/m^3 in the 1950's, but was much lower, due to respirator use and decreasing air levels, in later years where the average air concentration was estimated from air and urine sampling to be in the range of 14- 25 ug/m^3 The study authors estimated from these data that arsenic exposure should have resulted in no more than 0.77 lung cancers due to arsenic; this value was updated to 0.52-0.97 by OSHA (1992). The percent of smoking in the workers was also estimated (based on 70% of survivors or next-of-kin) to be comparable to that in the general population.

Stayner et al. (1992) published a follow-up through 1984 of the Thun cohort, including 162 deaths. A modified life table analysis was conducted comparing mortality to that of the U.S. white males. Person-years were categorized in four ways: cumulative exposure, latency (elapsed years since first exposure), year of observation, and age. Separate analyses were conducted on Hispanics and non-Hispanics, to account for the fact that Hispanics smoke less and have a lower lung cancer death rate than non-Hispanic whites. Respiratory cancer mortality (including cancer of the lung, trachea, and bronchus, henceforth termed "lung cancer" for this cohort) was significantly increased in the non-Hispanic population (SMR = 211, 95% CI = 131-323), while a reduction was seen in the Hispanic population. This decrease in the Hispanic population was attributed to the overall lower cancer death rate in Hispanics compared to non-Hispanic whites, and the use of a life table based on all white males. An exposure-response relationship between respiratory cancer mortality and cumulative cadmium exposure was observed for the top three cumulative exposure groups among non-Hispanics (585-1460 mg/m^3 -days and up), and among all workers in the highest exposure group ($\geq$2921 mg/m^3 -days). When person-years were stratified by latency, a significant response was observed only for a latency $\geq$20 years, consistent with findings for other chemical-induced lung cancers. These data were used for the quantitation of this assessment (below). The authors attempted to address the issue of arsenic confounding with indirect procedures. However, they did not

consider these procedures sufficient to rule out arsenic as a confounder mostly due to the lack of specific information on individual worker exposure.

An exhaustive re-analysis of individual exposures of the U.S. cohort was conducted by Sorahan and Lancashire (1994, 1997), based on the principal departments reported in individual time sheets. This re-analysis allowed assignment of individual worker exposure based on over 600 job titles and 22 departments compared to the 7 broad categories used by Stayner (1992) and Thun (1985) and accounted for a total of 105 433 man-half-months. Additional information on arsenic exposure was also given in this report including airborne levels of arsenic trioxide and statements indicating that arsenic was present in feedstocks until 1958, with the annual mean percentage being 1% to 4% between 1940 and 1958. These data also allowed for cadmium exposure evaluation by speciation as either cadmium oxide, cadmium sulfide or cadmium sulfate. These newly derived data allowed for 4 groups of cumulative exposure to cadmium (< 400, 400-99, 1000-1999, >2000 $mg.m^3$ days). Modeling results demonstrated there to be a significant positive trend between cumulative exposure to cadmium and risks of mortality from lung cancer. The relative the risks for the cumulative groups were 2.3 (95% CI, 0.72-7.36), 2.83 (95% CI, 0.75-10.72), and 3.88 (95% CI, 1.04-14.46), respectively. A separate analysis examined the independent effects of exposure to cadmium in the presence of high exposures to arsenic trioxide and exposure to cadmium received in the absence of arsenic trioxide; a significant trend for a risk of lung cancer was found only for variable 4, in the presence of arsenic. Several hypotheses are consistent with these results and include; cadmium (oxide) in the presence of arsenic trioxide is a human lung carcinogen; cadmium (oxide) and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulfide are not; arsenic trioxide is a human lung carcinogen and cadmium (as oxide, sulphate or sulfide) is not. The limited number of deaths from lung cancer in this cohort to date (twenty one) are insufficient to determine further which of these hypotheses, if any, is correct. Complete smoking histories are lacking for this cohort. These results indicate that the confounding influences of both smoking and arsenic exposure on the lung cancer mortality seen in this cohort are yet to be totally resolved.

Several studies that have been conducted of a British cohort of nickel cadmium battery workers, who were exposed to cadmium oxide dust, suggest a link between cadmium exposure and prostate cancer (Kipling and Waterhouse, 1967; Potts, 1965; Sorahan and Waterhouse, 1983; Sorahan, 1987). Cadmium exposure was estimated to be 600-2800 ug/m^3 in 1949 (Potts, 1965). After installation of local exhaust ventilation in 1950, cadmium concentrations were reduced to 500 ug/m^3 or less in 1950-1967. Further improvements decreased concentrations to <200 ug/m^3 1968-1975, and <50 ug/m^3 after 1975 (Sorahan and Waterhouse, 1983).

In an early study of this plant, Potts (1965) found three prostate cancer deaths and one lung cancer death among 74 men who had been exposed for at least 10 years, but no comparisons to an unexposed population were conducted. Kipling and Waterhouse (1967) compared cancer incidence among 248 men from this factory who had worked for at least one year at this plant (including the 74 men analyzed by Potts) with incidence rates from a regional cancer registry. They found one new case of prostate cancer, in addition to the three reported by Potts (1965), (O/E=7, p=0.003), but no significant effect on lung cancer (Obs=5, Exp=4.4, p=0.45).

Sorahan and Waterhouse (1983) expanded the Potts cohort to 3025 workers (2559 men and 466 women) who were employed at the factory for at least 1 month during the period 1923-1975 (excluding office workers). A statistically significant relationship was noted between respiratory system cancer deaths and duration of employment in medium- or high-exposure jobs.

In a follow-up study (Sorahan,1987) of the cohort during the period 1946-1984 , mortality from cancer of the lung and bronchus was significantly increased in the entire cohort (Obs=110, SMR=130, $p<0.01$) but duration of employment in a high-exposure job was not significantly correlated with cancer mortality.

A series of studies (Armstrong and Kazantzis, 1983, 1985; Kazantzis et al., 1992) analyzed worker mortality in a cohort of 6995 men in 17 United Kingdom plants where cadmium was produced or used in association with other metals, including arsenic. The cohort included men born before 1940 and employed for at least one year between 1942 and 1970. The study population was divided into "ever high" exposure (3%), "ever medium" (17%), and "always low" (80%), where exposure for at least a year was required for categorization as "ever high" or "ever medium." Mortality rates were compared to those for the population of England and Wales, accounting for regional variation. Armstrong and Kazantzis (1983) found no significant increase in the number of deaths from lung (SMR=107, CI=92-122) or prostate cancer (SMR=99) in the overall cohort In a follow-up of the Armstrong and Kazantzis (1983) cohort through 1989 (Kazantzis et al., 1992), there was a statistically significantly increased risk of lung cancer overall (SMR=1.12, CI=1.00-1.24), with some evidence of increased risk with increased exposure levels or exposure duration, but these relationships did not attain statistical significance. Most of the lung cancer deaths occurred at a zinc-lead-cadmium smelter, where there was also exposure to arsenic. There was no increased prostate cancer mortality in the overall cohort, or in the high or medium exposure groups.

Sorahan et al. (1995) analyzed cancer mortality among a group of 347 male copper-cadmium alloy workers in a rural and an urban factory and found no increase in lung cancer deaths in the cadmium-exposed groups, even in a lagged analysis after adjusting for age. However, no adjustment was made for rural versus urban location.

Elinder et al. (1985) reported on cancer mortality among 522 male workers in a Swedish cadmium-nickel battery factory. Although the SMRs for lung and prostate cancer were increased, a statistically significant increase in the number of deaths from these causes was not observed, even when the analysis was confined to workers with at least 5 years of exposure and a 20-year latency period was incorporated into the analysis.

Non-occupational data on the carcinogenic potential of cadmium is very limited. Abd Elghany et al. (1990) conducted a case-control study on cases of prostatic cancer newly diagnosed in one year in four urban Utah counties, and 679 age-matched controls. Analyses were conducted based on self-reported exposure, employment in an industry involving cadmium exposure, high dietary intake of cadmium, and smoking. Because some of the controls may have had latent tumors, a separate analysis was conducted for aggressive tumors. There was a borderline significant association with high dietary intake of cadmium (odds ratio=1.4, CI=1.0-2.1), but there was no association with jobs with potential cadmium exposure or with cigarette smoking. Increased tumors overall were not observed in the group with occupational exposure, exposure from cigarette smoking, or elevated dietary exposure, but this combined group did have an increased risk of aggressive tumors (odds ratio 1.7, CI=1.0-3.1).

Overall, these studies show a relationship between occupational exposure to cadmium and lung cancer that is related to cumulative exposure, but that may also be related to known confounding factors. Early reports of an association between cadmium exposure and prostate cancer have not been supported by more recent follow-ups with the same cohorts..

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient: Cadmium is carcinogenic in rats by the inhalation route. Injection site tumors and distant site tumors (e.g., testicular tumors) have been reported by a number of authors as a consequence of intramuscular or subcutaneous administration of cadmium metal, or cadmium chloride, sulfate, oxide, or sulfide to rats and mice (U.S. EPA, 1985).

The results of inhalation studies conducted in rats support the human data in indicating an association between cadmium exposure and lung cancer (Glaser et al., 1990; Oldiges et al., 1989; Takenaka et al., 1983). Species-related differences have been observed. No evidence was found for an association between cadmium inhalation exposure and lung cancer in hamsters (Aufderheide et al., 1989; Heinrich et al., 1989), and the evidence in mice (Heinrich et al., 1989), is inconclusive. However, study design and reporting inadequacies limit the conclusions of the studies conducted in these species. Increased incidences of benign testicular tumors and leukemia have been reported in animals following oral administration of cadmium (Waalkes and Rehm, 1992). A follow-up study showed the testicular tumors to be endocrine-mediated and did not reproduce the leukemia response (Waalkes and Rehm, 1997).

Takenaka et al. (1983) exposed groups of 40-41 male Wistar rats to cadmium chloride aerosol at 0, 13.4, 25.7, and 50.8 ug/m^3 for 23 hours/day, 7 days/week for 18 months, and observed the animals for an additional 13 months. Concentration-related increases in the incidence of adenocarcinomas, squamous cell (epidermoid) carcinoma, and mucoepidermoid carcinoma were observed. No exposure-related increases in the incidence of tumors in other tissues, or cadmium-related increases in non-neoplastic lesions were reported. These data are analyzed further below.

Glaser et al. (1990) and Oldiges et al. (1989) reported a later study using the same protocol as Takenaka et al. (1983) where male and female Wistar rats (20/sex/group) were exposed to clean air or cadmium chloride aerosol at 30 or 90 ug Cd/m^3, cadmium sulfate aerosol at 90 ug Cd/m^3, cadmium sulfide at 90 ug Cd/m^3, cadmium oxide dust at 30 or 90 ug Cd/m^3, or cadmium oxide fume at 10 or 30 ug Cd/m^3. Except for a markedly lower response with cadmium oxide fume, similar lung tumor responses were observed for all of the compounds, with increased levels of brochio-alveolar adenomas, adenocarcinomas, and squamous cell carcinomas although the existence of a concentration-related response could not be evaluated. Non-neoplastic lesions among rats exposed to cadmium oxide dust included bronchiolo-alveolar hyperplasia, squamous metaplasia, interstitial fibrosis, and focal inflammatory cell infiltration.

In another related study, male and female Wistar rats (39-40/sex/group) were exposed to clean air or cadmium oxide dust at 30 or 90 ug Cd/m^3 for a maximum of 18 months (Takenaka et al., 1990) with an intermediate sacrifice at 6 months in the 30 ug^3 group. The 90 ug/m^3 group, exposure was terminated at 7 months, due to increased mortality in the animals. Morphological changes progressed from inflammation and bronchiolo-alveolar hyperplasia at 6 months, to abnormal epithelial proliferation (including basophilic foci of cuboidal epithelia and adenomatous proliferation of epithelia, and squamous metaplasia) at 18 months. Lung tumors (bronchiolo-alveolar adenomas and carcinomas, benign and malignant squamous cell tumors, and an adenosquamous carcinoma) occurred in 72% and 31% of the low- and high-concentration groups, respectively, but in none of the controls. Decreased survival was noted at the high concentration.

Aufderheide et al. (1989) exposed groups of 24 Syrian golden hamsters (sex not reported) to air, cadmium oxide aerosol at 10, 90, or 270 ug Cd/m^3, cadmium sulfide aerosol at 90 or 270 ug Cd/m^3, cadmium chloride at 30 or 90 ug Cd/m^3, or cadmium sulfate 30 or 90 ug Cd/m^3 for 8 hours/day, (19 hours/day for high-concentration cadmium chloride or sulfate) 5 days/week for about 65 weeks. Animals were held after exposure until they died, and the lungs and trachea were examined. Proliferative lesions (bronchiolization, consisting of proliferation of bronchiolar epithelium into the alveolar ducts) were

reported in groups exposed to the high concentrations of cadmium oxide or cadmium sulfide, but it appears that only 5 animals/group were examined. The study authors concluded that inhalation of cadmium oxide and cadmium sulfide by hamsters results in hyperplasia, but no tumor development. However, the conclusion is limited by the lack of a complete histopathological examination.

Oral dosing cancer studies included that of Waalkes and Rehm (1992) in which groups of 22-28 male Wistar (WF/NCr) rats were provided 0, 25, 50, 100, or 200 ppm cadmium in the diet as cadmium chloride for 77 weeks. Body weight was decreased 12-17% at the high dose and about 10% at 100 ppm. Statistically significant increases in leukemia incidence were observed at the 50 and 100 ppm dose levels, but not at the highest dose level of 200 ppm (possibly due to cadmium toxicity). Focal atypical hyperplasia and adenomas were observed in the ventral prostate. However, there was no clear dose-response, with a significant increase observed only for the combined incidence of hyperplasia and adenomas at 50 ppm. There were no lesions observed in the dorsolateral prostate lobes (where prostate cancer is seen in humans). No prostatic carcinomas were observed, probably due to the less-than-lifetime duration of exposure. A statistically significant increase in the incidence of interstitial cell tumors of the testes was observed at the highest dose tested. A dose-related increase in testicular tumors (which did not achieve statistical significance in pair-wise comparisons) was also observed at the two highest doses in a parallel study with rats fed the same cadmium doses, but kept on a zinc-deficient diet. No association between testicular atrophy and cadmium exposure was observed, but moderate to severe testicular atrophy was observed in about 50% of the males in all dose groups. In a subsequent study Waalkes and Rehm (1997) conducted a chronic rat study designed to elucidate the role of cadmium in perturbating the hypothalamic-pituitary-testes axis the results of which clearly indicated that cadmium induction of Leydig cell tumors (such as those occurring in Waalkes and Rehm, 1992) is endocrine-mediated and that the occurrence of such tumors appears to depend on reduced circulating testosterone levels stemming from cadmium-induced testicular hypofunction, most likely through perturbation of the hypothalamic-pituitary-testes axis.

Loser (1980) found no evidence of cadmium-related cancer in a 2-year study with groups of 50 male and 50 female Wistar rats administered 1, 3, 10, or 50 ppm cadmium in the diet as cadmium chloride even though body weights in high-dose males were significantly reduced, indicating that these animals were at or above their maximum tolerated dose for cadmium.

II.A.4 SUPPORTING DATA FOR CARCINOGENICITY

Cadmium has been extensively tested in genotoxicity assays, with mixed results. However, positive results, including mutations and chromosomal aberrations, have been observed in vitro, in mammalian and bacterial cells, and in vivo, in mice. Increases in chromosome aberrations that correlated with worker cumulative cadmium exposure levels, although other worker studies reported small, and occasionally statistically significant, increases in the incidences of chromosomal aberrations and sister chromatid exchanges or no effect (reviewed in IARC, 1993).

Mutagenicity tests with cadmium compounds in bacteria give conflicting results apparently due to the influence of buffers and other components in the medium of these assays (Pagano and Zieger, 1992).

Micronucleated polychromatic erythrocytes (PCEs) were significantly increased in mice administered 3-12 mg/kg cadmium as cadmium chloride, although there was no clear dose-response relationship (Marrazzini et al. 1994). Cadmium is a suspected spindle poison, and induction of aneuploidy was observed (based on the results of a trend test) in spermatocytes of mice injected i.p. with 1-6 mg/kg

cadmium as cadmium chloride, and harvested 6-22 hours after dosing (Miller and Adler, 1992). Mixed results were obtained for cadmium chloride in a multi-laboratory analysis of a battery of in vivo tests for aneuploidy, but the predominance of the results were negative, except in one laboratory (Adler, 1993).

A number of mechanisms have been proposed for the development of mutations from exposure to cadmium. Although cadmium can destabilize DNA by binding to the bases and phosphate groups, exposure of isolated DNA to cadmium does not result in production of direct DNA damage, such as DNA adducts or strand breaks. Therefore, it has been proposed that the observed genotoxic effects of cadmium are mediated by oxidative damage (reviewed by Rossman et al., 1992), such as from inflammation related to insoluble cadmium particles. Cadmium treatment reduces cellular glutathione levels, and catalase (a scavenger of hydrogen peroxide) inhibited production of chromosome aberrations by cadmium. Alternatively, an altered DNA conformation could lead to decreased fidelity of DNA replication or repair, or cadmium could affect the activity of a zinc-binding regulatory protein (reviewed in Waalkes et al., 1992). Cadmium has been observed to increase the mutagenic activity of other chemicals, suggesting that it can act by inhibiting DNA repair.

The sensitivity of certain tissues to cadmium carcinogenesis may be related to the poor inducibility of metallothionein in these tissues (Cherian et al., 1994). For example, tumors have been observed in the testes and ventral prostate in rats, and metallothionein levels are low in these tissues. Higher metallothionein production in the lungs of mice compared to rats has been proposed as an explanation for the apparent resistance of mice to cadmium-induced lung cancer (Oberdorster et al., 1994).

II.B QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1 SUMMARY OF RISK ESTIMATES

Oral Slope Factor: Not calculated.

II.C QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1 SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk: 4.4E-3 per ug/m^3
Extrapolation Method: Poisson regression model, relative risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-2 ug/m^3
E-5 (1 in 100,000)	2E-3 ug/m^3
E-6 (1 in 1,000,000)	2E-4 ug/m^3

II.C.2 DOSE-RESPONSE DATA (CARCINOGENICITY, INHALATION EXPOSURE)

Tumor Type: Lung, trachea, bronchus cancer deaths
Test Animals: Human/non-Hispanic white male
Route: Inhalation, occupational exposure
Reference: Stayner et al., 1992; Thun et al., 1985; OSHA, 1992

Cumulative Exposure (mg/m^3-day)	Median Exposure (ug/m^3-year)	Adjusted for Continuous Exposure (ug/m^3-year)	Expected Lung, Trachea, and Bronchus Cancer Deaths	Observed Number of Lung, Trachea, and Bronchus Cancer Deaths
≤584	795	182	3.35	1
585-1460	2466	566	2.64	7
1461-2920	5699	1308	1.55	6
>2920	10,836	2488	2.41	7

Adjusted for continuous exposure = Median Exposure (occup) x 10/20 x 45/70 x 5/7

Findings in animals support the lung as a target for kidney carcinogenicity:

Tumor Type: Lung carcinomas, including adenocarcinomas, squamous cell carcinomas, and mucoepidermoid carcinoma
Test Animals: Male Wistar rats
Route: Inhalation
Reference: Takenaka et al., 1983

Actual Exposure Level (ug/m^3)	Human Equivalent Concentration (ug/m^3)	Tumor Incidence
0	0.0	0/38
13.4	4.07	6/39
25.7	7.80	20/38
50.8	15.42	25/35

II.C.3 ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The inhalation unit risk was calculated using a Poisson regression model on the occupational epidemiology data of Stayner et al. (1992). The possible need for an adjustment for deposition of cadmium particles under occupational versus environmental exposure scenarios was investigated by comparing the range of deposition fractions under various conditions. Because both the range and midpoint for the estimated deposition fractions under environmental and occupational exposure scenarios were similar, no adjustment for deposition under different conditions was made.

The unit risk should not be used if the air concentration exceeds 2E+1 ug/m^3, since above this concentration the slope factor may differ from that stated.

II.C.4 DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

The study used as the basis for the inhalation dose-response assessment (Stayner et al., 1992) was conducted on an appropriate and adequate cohort (602 white men, with 162 deaths), characterized exposure on an individual basis, and observed an exposure-response relationship between lung cancer mortality and cumulative cadmium exposure. The study also attempted to address potential confounding by smoking and by concurrent exposure to arsenic. Although exposure-response relationships were not well-characterized and may be confounded in the studies of Kazantzis et al. (1992) and Sorahan (1987), positive associations between cumulative cadmium exposure and lung cancers were observed in these cohorts and thus support this association. It is acknowledged, however, that the associations between cadmium exposure and lung cancer in the cohort of Stayner (Sorahan and Lancashire, 1994,1997) and others may be confounded at least in part by exposure to other known lung carcinogens such as arsenic and cigarette smoke.

Takenaka et al. (1983) conducted a 2-year inhalation study in rats exposed to cadmium chloride in which a clear dose-response was observed for lung carcinomas. The unit risk calculated from this study was 4.1E-2 per (ug/m^3), about 10-fold higher than that calculated based on the epidemiology data. This calculation of the risk from the animal study includes accounting for (1) differing particle deposition in the test animals and humans, and (2) differences between the particle characteristics used in the animal study and particle characteristics under ambient exposure conditions. Although the risk calculated using the animal data is higher, and thus more conservative, the estimate from the human data was considered more reliable because (1) good-quality occupational data are available, (2) the cadmium forms in the occupational studies are more environmentally relevant (cadmium oxide and fume vs. cadmium chloride in the animal study), and (3) there are uncertainties in the dosimetric extrapolation from animals to humans.

II.D EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1 EPA DOCUMENTATION

U.S.EPA Toxicological Review for Cadmium

U.S. EPA. 1985. Updated Mutagenicity and Carcinogenicity Assessment of Cadmium: Addendum to the Health Assessment Document for Cadmium (May 1981, EPA 600/B-B1-023). EPA 600/B-83-025F.

II.D.2 REVIEW (CARCINOGENICITY ASSESSMENT)

II.D.3 U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

VI. REFERENCES

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