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Cadmium (Cd)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOREWORD

Current Intelligence Bulletins are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A Current Intelligence Bulletin may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

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The purpose of this bulletin is to disseminate recent information concerning the potential carcinogenic hazard to workers of cadmium (Cd). In 1976, NIOSH published Criteria for a Recommended Standard....Occupational Exposure to Cadmium, recommending a permissible exposure limit of 40 micrograms of cadmium per cubic meter of air (40 $\mu g/m^3$) which was viewed as necessary to prevent chronic renal damage in exposed workers. Epidemiological and toxicological data suggesting an association between cadmium exposure and cancer were cited in that document, but the evidence for carcinogenicity was considered to be inconclusive at that time. Based on subsequent epidemiological and toxicological studies, NIOSH now recommends that cadmium and its compounds be regarded as potential occupational carcinogens.

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CADMIUM

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ABSTRACT

A recent epidemiological study has demonstrated a statistically significant excess of lung cancer mortality among workers exposed to cadmium oxide (CdO). A chronic inhalation exposure study with rats provides toxicological evidence that exposure to cadmium chloride ($CdCl_2$) aerosol can cause a dose-dependent incidence of malignant lung tumors. Based primarily on these data, the National Institute for Occupational Safety and Health (NIOSH) recommends that cadmium and its compounds be regarded as potential occupational carcinogens and that appropriate controls be used to reduce worker exposure.

BACKGROUND

Exposure Standards, Recommendations, and Guides

Based on the 1970 recommended cadmium (Cd) standard of the American National Standards Institute (ANSI) [1], the Occupational Safety and Health Administration (OSHA) promulgated a standard for cadmium which set permissible exposure limits for cadmium fume (as Cd) of 100 micrograms of cadmium per cubic meter of air ($\mu g/m^3$) determined as an 8-hour time-weighted average (TWA) concentration and a ceiling concentration of 300 $\mu g/m^3$ and for cadmium dust (as Cd) of 200 $\mu g/m^3$ (as an 8-hour TWA) with a ceiling concentration of 600 $\mu g/m^3$ [2].

In 1976, the National Institute for Occupational Safety and Health (NIOSH) recommended that exposures to any form of cadmium at concentrations greater

than 40 $\mu g/m^3$ (determined as a TWA for up to a 10-hour workday, 40-hour workweek) or at a ceiling concentration greater than 200 $\mu g/m^3$ for any 15-minute period not be permitted [3].

The 1984-85 American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV®) for cadmium dust and salts (as Cd) is 50 $\mu g/m^3$ for an 8-hour TWA, with a 15-minute Short Term Exposure Limit (STEL) of 200 $\mu g/m^3$; for cadmium oxide (CdO) fume, 50 $\mu g/m^3$ (as Cd) as a ceiling; and for cadmium oxide production, an 8-hour TWA of 50 $\mu g/m^3$ (as Cd) [4].

OSHA, NIOSH, and ACGIH have aimed their standards or recommendations for permissible occupational exposures to cadmium toward prevention of such critical health effects as chronic renal damage and acute pulmonary toxicity [2-4].

Production, Use, and Potential for Occupational Exposure

Cadmium is found primarily as cadmium sulfide (less than 1%) in ores containing zinc, lead, and copper. Cadmium-containing precipitates from ore smelting are processed electrolytically to produce cadmium metal. Because of its low boiling point (767°C) and a high vapor pressure relative to the metals with which it is found, cadmium volatilizes readily during smelting and then condenses to form fine airborne particles that react almost immediately with oxygen to form respirable cadmium oxide fume [5].

Approximately 4,000 metric tons of cadmium are used yearly in the United States, of which about half is used for plating other metals and half is used in pigments, batteries, stabilizers for plastics, metallurgy, nuclear reactor neutron-absorbing rods, and semiconductors and as a catalyst [6].

Based on data from the National Occupational Hazard Survey, NIOSH estimates that approximately 1,500,000 workers may be potentially exposed to cadmium, of which approximately 100,000 are identified with exposure to specific cadmium compounds or with industries that utilize cadmium [7]. Sources of potential worker exposure to cadmium include ore smelting operations, mist from cadmium-containing electroplating baths, calcination (drying) of cadmium pigments, and handling of powdered cadmium oxide in production of cadmium soaps that are used to stabilize plastics [5].

CARCINOGENICITY

Epidemiological and toxicological data suggesting an association between cadmium exposure and cancer were included in the 1976 NIOSH document Criteria for a Recommended Standard....Occupational Exposure to Cadmium [3]. In that document, several toxicological studies showed that injection of cadmium metal

or its salts (oxide, chloride, sulfide, and sulfate) into laboratory rats produced local sarcomas and Leydig cell (interstitial cell) testicular tumors, but oral ingestion studies with rats and mice did not demonstrate an increased incidence of malignant tumors. Two epidemiological studies of a single cohort of battery plant workers exposed to airborne cadmium reported an association between cadmium exposure and prostatic cancer [8,9]. In a study of 292 cadmium production workers who had a minimum of 2 years of employment between 1940 and 1969, a statistically significant excess of deaths from all malignancies and from lung cancer was observed in the entire cohort. In addition, a statistically significant excess of deaths from prostate cancer was detected among workers who lived for at least 20 years after the date of first working in a cadmium production facility. Some of these workers had been hired prior to 1926, when arsenic (a known human lung carcinogen) was produced in the plant [10].

NIOSH considered the body of toxicological and epidemiological evidence for carcinogenicity to be inconclusive and recommended against basing a standard on potential human carcinogenicity. However, the criteria document stated, "This recommendation should be reconsidered if additional data on these points that warrant such reconsideration are developed" [3].

Recent Epidemiological Evidence

A recent epidemiological study provides more persuasive evidence for the carcinogenicity of cadmium oxide. Subsequent to the 1976 report of a study of workers in a cadmium production facility [10], the cohort was expanded from the original 292 workers to 602 white males who had worked at least six months between 1940-1969 in the cadmium production area of the cadmium smelting plant [11]. This expanded cohort was followed through 1978. Of the 602 workers, 345 had two or more years of total employment, including some for whom records were not available at the time of the earlier study; the remaining 257 were short-term workers employed for 6 months to 2 years. Mortality from cancer of the respiratory tract was significantly greater in the entire cohort than would have been expected from rates in the general U.S. population (20 observed vs. 12.15 expected, standardized mortality ratio [SMR]=165, 95% confidence interval [CI]=101-254). All respiratory cancer deaths were due to cancer of the lung, trachea, or bronchus. Within the subset of cadmium production workers employed at least two years, the SMR for lung cancer was 265 (20 observed vs. 7.60 expected, 95% CI=162-409) and a significant excess was seen among those hired both before (4 observed vs. 0.56 expected, SMR=714, 95% CI=195-1829) and after (16 observed vs. 7.00 expected, SMR=229, 95% CI=131-371) the cessation of arsenic smelting.

In this study, lung cancer mortality was also found to increase with increasing cumulative exposure to cadmium. Using categories based on a 40 year TWA at a given exposure concentration, SMR's were 53 at $\leq$40 $\mu g/m^3$, 152 at 41-200 $\mu g/m^3$, and 280 at >200 $\mu g/m^3$; the 95% CI

at >200 $\mu g/m^3$ was 113-577. A regression slope calculated for directly standardized rate ratios (SRR) was 7.33×10^{-7} ($p=0.0001$) with elevated lung cancer mortality at 41-200 $\mu g/m^3$ and >200 $\mu g/m^3$. The investigators stated that data provided by the company on smoking and on exposure to residual arsenic did not appear to account for the observed excess of lung cancer mortality.

The findings of other recent epidemiological studies [12-15] are compatible with these results and provide limited additional epidemiological evidence for excess lung cancer mortality. A study of 3,025 nickel-cadmium battery workers potentially exposed to cadmium oxide dust for at least one month between 1923 and 1975 with vital status determined through January 1981 showed significantly increased numbers of deaths from respiratory cancer (89 observed vs. 70.2 expected, SMR=127, $p<0.05$) [12]. However, the possible contribution of nickel hydroxide and oxy-acetylene welding fume exposures to lung cancer mortality was not assessed.

A study of 6,995 cadmium-exposed workers from 17 facilities engaged in primary cadmium production and production of alloys, cadmium soap, and pigments demonstrated no statistically significant tumor excess, but lung cancer mortality was slightly above that expected (199 observed vs. 185.6 expected) [13,14]. The study had limited power to detect elevated lung cancer because only 210 workers (3% of the cohort) were classified as "ever highly exposed," which was defined by the researchers as having had a job title for at least one year that was judged likely to lead to cadmium in urine concentrations of over 20 µg/liter following chronic exposure [14]. In a preliminary report on workers in two cadmium-copper alloy plants, no excess lung cancer mortality was detected in production workers (10 observed vs. 13.4 expected), but a statistically significant excess of lung cancer deaths (36 observed vs. 26.08 expected, SMR=138, $p<0.05$) was observed among workers in one of the two plants who worked in proximity to the cadmium-copper process and had potential exposure to arsenic [15].

Recent Experimental Evidence

A recent toxicological study provides persuasive evidence for the carcinogenicity of cadmium chloride [16]. Rats exposed to cadmium chloride aerosols by inhalation at concentrations of 12.5, 25, and 50 $\mu g/m^3$ for 23 hours daily, 7 days per week for 18 months and observed for an additional 13 months developed primary lung carcinomas in 25 of 35 (71.4%) rats in the 50 $\mu g/m^3$ exposed group, 20 of 38 (52.6%) in the 25 $\mu g/m^3$ group, 6 of 39 (15.4%) in rats exposed at 12.5 $\mu g/m^3$, and 0 of 38 in unexposed controls. Lung cadmium concentrations at necropsy were 10.4 ± 4.2, 4.7 ± 1.5, 5.6 ± 1.0, and <0.03 µg/g wet weight in the four groups, respectively. This study was the first lifetime study of animals exposed by inhalation to a cadmium-containing compound.

Data from two recent toxicological studies contribute information of importance to the biological evaluation of the carcinogenic potential of cadmium. Unexpected (but not statistically significant) cases of lung carcinoma were observed following administration of cadmium oxide to rats by a single inhalation exposure [17] and by multiple intratracheal injections [18].

A recent study in rats chronically exposed through oral ingestion of cadmium chloride dissolved in drinking water did not demonstrate an increased incidence of malignant tumors [19]. However, because the total doses delivered and terminal tissue concentrations of cadmium were not measured, the applicability of these data to an assessment of carcinogenicity is uncertain.

RESEARCH NEEDS

Research is necessary to further assess the carcinogenicity of cadmium in animals and to ascertain the mechanisms by which cadmium causes these effects. Testing of other cadmium compounds and studying the relationship of calcium, zinc, and other metal ions to the potential carcinogenicity of cadmium are of particular importance. Recent data on pulmonary uptake of cadmium compounds [20-23] and on the effects of solubility, particle charge, and crystallinity of cadmium compounds [24-26] suggest the need to better characterize the extent of workers' biological exposure to cadmium in various work settings. In vitro studies should focus on factors that affect cell uptake and intracellular activity of cadmium.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the National Toxicology Program [27], the International Agency for Research on Cancer [28], and OSHA in its "Identification, Classification, and Regulation of Potential Occupational Carcinogens" 29 CFR 1990 [29], also known as "The OSHA Cancer Policy" [30]. NIOSH considers the OSHA classification the most appropriate for use in identifying potential occupational carcinogens* [31]. Cadmium chloride has been shown to be carcinogenic in an experimental animal study; an

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*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" (29 CRF 1990.103).

epidemiological study has demonstrated excess lung cancer mortality among workers exposed to cadmium oxide. Based on these data, and given that no studies have been performed to assess the potential hazards from long-term exposure to other cadmium-containing compounds, NIOSH recommends that cadmium and its compounds be considered as potential occupational carcinogens.

The excess risk of cancer in workers exposed to cadmium at specific airborne concentrations has not yet been fully characterized; nonetheless the risk of developing cancer would be reduced by decreasing exposure. NIOSH recommends that the present OSHA standard for cadmium be reexamined, based on new evidence which supports the conclusion that cadmium and its compounds are potential carcinogens and supplements other data on health effects supporting previous NIOSH recommendations [3]. As prudent public health policy, NIOSH urges employers to assess the conditions under which their workers may be exposed to cadmium and take all reasonable precautions to reduce these exposures to the fullest extent feasible.

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CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS

1.	Chloroprene	- January 20, 1975
2.	Trichloroethylene (TCE)	- June 6, 1975
3.	Ethylene Dibromide (EDB)	- July 7, 1975
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		- October 7, 1975
		- October 8, 1976
5.	Asbestos - Asbestos Exposure during Servicing of Motor Vehicle Brake and Clutch Assemblies	- August 8, 1975
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39.	The Glycol Ethers, with Particular Reference to 2-Methoxyethanol and 2-Ethoxyethanol: Evidence of Adverse Reproductive Effects	- May 2, 1983
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41.	1,3-Butadiene	- February 9, 1984
42.	Cadmium	- September 27, 1984

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