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Cadmium-induced Cancers in Animals and in Humans

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Abstract

Discovered in the early 1800s, the use of cadmium and various cadmium salts started to become industrially important near the close of the 19th century, rapidly thereafter began to flourish, yet has diminished more recently. Most cadmium used in the United States is a byproduct from the smelting of zinc, lead, or copper ores, and is used to manufacture batteries. Carcinogenic activity of cadmium was discovered first in animals and only subsequently in humans. Cadmium and cadmium compounds have been classified as known human carcinogens by the International Agency for Research on Cancer and the National Toxicology Program based on epidemiologic studies showing a causal association with lung cancer, and possibly prostate cancer, and studies in experimental animals, demonstrating that cadmium causes tumors at multiple tissue sites, by various routes of exposure, and in several species and strains. Epidemiologic studies published since these evaluations suggest that cadmium is also associated with cancers of the breast, kidney, pancreas, and urinary bladder. The basic metal cationic portion of cadmium is responsible for both toxic and carcinogenic activity, and the mechanism of carcinogenicity appears to be multifactorial. Available information about the carcinogenicity of cadmium and cadmium compounds is reviewed, evaluated, and discussed.

Keywords

cadmium; carcinogenicity; animal studies; environmental exposures; epidemiologic studies; public health; occupational exposures; cancer bioassays; extrapolation

Cadmium, discovered in 1817, was not used commercially until the end of the 19th century.^{1,2} An odorless, silver-white, blue-tinged malleable metal or grayish-white powder, cadmium in the environment occurs as eight stable and two radioactive isotopes.³ Almost all cadmium compounds have an oxidation state of +2. Cadmium is slowly oxidized in moist air but forms cadmium oxide fumes when heated.^{2–4} It is commercially available as powders, foils, ingots, slabs, sticks, and crystals. Commercially important cadmium salts include cadmium chloride, cadmium sulfate, and cadmium nitrate, and to a somewhat lesser extent, cadmium oxide and cadmium sulfide.^{3,4} Toxicology and carcinogenicity of cadmium and other metals, as well as environmental impacts,^{1–4,10,11} have been relatively well studied.^{3–9} Nonetheless, described herein are some alternative and more sensitive carcinogenesis bioassays. Our overview of cadmium 1) describes production, uses, and exposures, and toxicity data; 2) discusses human and animal carcinogenicity; and 3)

comments on the importance of studies in experimental animals in identifying human carcinogens..

Production and Uses

Cadmium is a widely but sparsely distributed element found in the earth's crust at concentrations ranging from 0.1 to 1 ppm, primarily in association with zinc ores,⁴ ranking 67th in abundance among the 90 naturally occurring elements on earth.¹² Though primarily found in zinc-containing ores, it is also found in lead and copper ores. The primary mineral form of the metal is greenockite or cadmium sulfide.¹² Approximately 3 kilograms of cadmium are produced for each ton of zinc, or roughly 0.33%.⁵ U.S. production of cadmium began in 1907 and peaked in 1969 at 5,737 metric tons, but has declined in recent decades and was approximately 892 metric tons in 2006.^{3,13} Worldwide refinery production of cadmium in 2006 was 19,400 metric tons; China was the largest producer, followed by Japan, the Republic of Korea, and Kazakhstan. In 2003, the European Union adopted The Restriction of the Use of Hazardous Substances, which prohibits incorporation of cadmium and other heavy metals in most electrical and electronic equipment (including certain types of portable nickel-cadmium batteries) sold in the European Union after July 1, 2006. U.S. domestic consumption of cadmium metals has also declined due to environmental concerns, dropping about 14% between 2002 and 2006.¹³

The earliest use of cadmium, primarily as sulfide, was in paint pigments, in dental amalgams (minor amounts) in the early 1900s, and as a substitute for tin during World War II. Since World War II, almost all cadmium has been used in batteries, pigments, electroplating and coating, stabilizers for plastics and alloys. All uses except for batteries have declined in the late 20th century, and the major use for cadmium and cadmium compounds today is in battery manufacturing (81%). Cadmium use in batteries increased from 8% in 1970 to 75% in 2000.³ Cadmium also finds use in the green and blue phosphors in color TV tubes. Major uses for some specific compounds are as follows^{3,14}:

- Cadmium chloride—preparation of cadmium sulfide, dying and calico printing, electroplating, pigment manufacture, and vacuum tubes; previously used as a fungicide
- Cadmium hydroxide—alkaline batteries
- Cadmium nitrate—glass and porcelain colorant and photographic emulsions
- Cadmium oxide—silver zinc storage batteries, heat stabilizers for plastics and alloys
- Cadmium sulfate—intermediate and electroplating
- Cadmium stearate—lubricant and plastic stabilizer
- Cadmium sulfide—pigment

Human Exposures

As with most naturally occurring chemicals, such as, for example, asbestos and benzene, humans play a significant role in creating concentrated sources of cadmium and releasing it into the environment through activities such as mining, smelting, and refining metal ores—zinc, lead, arsenic, copper, chromium, and others.¹⁵ Cadmium is emitted from both stationary and mobile sources. Stationary sources likely to emit cadmium include secondary smelters, cement-manufacturing plants, cadmium-electroplating facilities, plants burning oil or coal, and sewage sludge incinerators. Mobile sources that emit cadmium include gasoline and diesel vehicles and particles resulting from tire wear. An emissions inventory compiled

by the California Air Resources Board¹⁰ indicates that 16 to 18 tons/year of cadmium are emitted in California; stationary sources account for 80% or more of the cadmium emissions. Cadmium is also emitted airborne from fossil fuel burning, waste incineration, and steel production. Cadmium emissions from fossil fuel combustion and vehicles are projected to increase due to the expected increase in fuel use.

Soil and water near industrial areas or waste sites typically contain higher concentrations of cadmium. From these human activities, an estimated 4,000 to 13,000 tons of cadmium are released into the environment every year.¹² According to the EPA toxic release inventory (TRI), total on- and off-site disposals or other releases of cadmium and cadmium compounds equal close to 5,000,000 pounds, with 80% from cadmium compounds¹⁶; clearly these figures serve as an indication of environmental and population exposures to cadmium, especially near cadmium operations. Cadmium present in soil from industrial emissions or other sources is selectively taken up by edible plants, resulting in levels much higher than those in the surrounding soils. Cadmium has also been shown to bio-concentrate in water plants and in fish. Of special concern are Mollusca and Crustacea; cadmium levels in crab may be as high as 30 to 50 parts per million.¹⁷

Primarily, however, exposures to cadmium and cadmium compounds occur in workplaces—mining, smelting, processing, product formulations, and battery manufacturing, whereas non-occupational exposures come from various foods and tobacco smoke.^{3–5} Occupational exposures to cadmium and cadmium compounds are mainly exposures to airborne dusts and fumes. The highest potential exposures occur in cadmium production and refining, nickel-cadmium battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, soldering, and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased in the last two decades, largely together with decreased demand.^{1–5}

Outside the occupational exposure setting, the main sources of cadmium in air are from zinc, lead, or copper smelters and from burning fossil fuels such as coal or oil and the incineration of municipal waste materials.^{3,5,12} On- and off-site disposal and dispersal represent a sizable source of cadmium exposure.¹⁶ Cadmium levels in some foods can be increased by the application of phosphate fertilizers or sewage sludge to farm fields.⁶ Smoking tobacco is an important source of cadmium exposure, with smokers having twice as much cadmium in their bodies as do nonsmokers. For nonsmokers, food is generally the largest source of non-occupational cadmium exposure. The average person in the United States consumes approximately 30 µg of cadmium per day in food; however, in cadmium-polluted areas intakes may reach several hundred micrograms.¹⁷ Approximately 3–10% of ingested cadmium is absorbed from the gastrointestinal system, whereas 50% of cadmium in inhaled smoke is absorbed into the bloodstream.¹⁸

Toxicity

Public awareness of cadmium's toxic effects rose with the post-World-War-II (1950) outbreak in Toyama Prefecture, Japan, of “itai-itai” disease, which was the first cadmium poisoning in the world. Itai-itai or “ouch-ouch” disease, so named from the painful screams due to severe pain in the joints and the spine, was caused by ingestion of runoff water containing cadmium released from mining companies in surrounding mountains.^{2,12,19} Farmers in the region used the runoff for irrigating rice paddies and other crops. Cadmium concentrated in the crops, and before long local women began to experience pain in bones and joints, eventually becoming so excruciating that they were bedridden. Cadmium interfered with calcium metabolism, leading to reduction in calcium levels and thus reduced

density and strength of bones, often causing the weakened bones to break.¹² In addition, kidney failure caused by cadmium poisoning was common. The mining companies were successfully sued for the damage. Itai-itai disease is one of the four major pollution-related diseases of Japan: 1) minamata disease—mercury poisoning; Chisso's chemical factory; 2) Niigata minamata disease (second minamata disease)—mercury poisoning; Showa Electrical Works; 3) Yokkaichi asthma—sulfur dioxide and nitrogen dioxide; air pollution in Yokkaichi; 4) itai-itai disease—cadmium poisoning; mining in Toyama Prefecture.

Short-term adverse effects of cadmium in humans through inhalational exposures from the environment consist mainly of effects on the lung, such as pulmonary irritation. Long-term inhalation or oral exposure to cadmium leads typically to build-up of cadmium in kidneys, and potential kidney disease.^{3–6} In the workplace, chronic inhalation and oral exposure of humans to cadmium results in adverse effects on the lung, including bronchiolitis and emphysema, and a build-up of cadmium in the kidneys, often resulting in kidney disease, including proteinuria, decrease in glomerular filtration rate, increased frequency of kidney stone formation, and cancer.^{3–5} In animals, long-term inhalation or oral exposure to cadmium results in harmful effects on the kidney, liver, lung, bone, immune system, blood, and nervous system.

Carcinogenicity—Experimental Animal Studies

Experimental animal studies demonstrate clearly that cadmium and cadmium compounds (referred to as cadmium) by multiple routes of exposure induce benign and malignant tumor formation at various sites in many species of experimental animals.^{3,4,7–9,20–27} The earliest studies showing cadmium to be a carcinogen were bioassays conducted in the middle 1960s using the injection route of exposure,^{6,28–33} a valid method for screening and identifying carcinogens.³⁴ These findings of cadmium carcinogenicity predated the first accepted epidemiologic study, by Lemen et al. in 1976,³⁵ of human lung and prostate cancers in cadmium workers.

Reported in 1983 by Takenaka et al.,³⁶ the first non-injection cadmium cancer study showed unequivocal positive results (lung cancers) in rats exposed to cadmium chloride aerosol. Earlier oral exposure studies were reported negative, but these suffered from various inadequacies—incomplete experimental details, single exposures or low exposure levels, short exposure durations, inadequate overall length of experiment, too few animals, absence of concurrent controls, limited tissue sampling, and restricted histopathology. Length of experimental duration was the likely reason that Takenaka et al.³⁶ but not Loser³⁷ obtained positive carcinogenicity results.^{15,38–40} That is, Loser³⁷ conducted a two-year feeding study exposing Wistar rats to dietary levels of 0, 1, 3, 10, and 50 ppm cadmium chloride. “Cadmium administered orally was not associated with an increased incidence of total numbers of tumours or of any specific type of neoplasia, although the highest level tested resulted in adverse effects.” On the other hand, Takenaka et al.³⁶ exposed groups of 40 male Wistar rats continuously (23 hours/day, 7 days/week) to cadmium chloride aerosols at cadmium concentrations of 0 (filtered air), 12.5, 25, and 50 $\mu\text{g}/\text{m}^3$ for 18 months, and survivors were killed 13 months after the end of the inhalation experiments, at 31 months. The clear dose-related incidence of lung adenocarcinomas (often multiple) was 71% in the group exposed to 50 $\mu\text{g}/\text{m}^3$, 53% in the group exposed to 25 $\mu\text{g}/\text{m}^3$, and 15% in the group exposed to 12.5 $\mu\text{g}/\text{m}^3$. None of the controls developed lung carcinomas. At the end of the experiment, the cadmium concentrations remaining in the lungs were relatively high, almost at the same level as those in the livers.

There were three major differences between the two studies: 1) aerosol (inhalation) versus dietary (oral) exposures to cadmium chloride; 2) 31 months (18 months exposure plus 13

months non-exposure) versus 24 months experimental duration; and 3) cumulative cadmium exposures were likely greater and more targeted (lung) with the aerosol route than with the dietary mode of exposure. Actually, Loser³⁷ exposed animals to cadmium chloride longer than did Takenaka et al.,³⁶ but for the latter the experiment went longer over all, perhaps allowing development of late-appearing tumors. We believe the key here regarding cadmium carcinogenesis and non-carcinogenesis is duration, as others have found this to be the case for toluene^{41,42} and xylene^{40,43} under like duration differences.^{38–40} Takenaka et al.³⁶ reported that in the highest-exposure group “the first lung carcinomas were noticed 23 months after beginning the experiment. During the following 4 months we found no lung carcinomas; however, after the 27th month 23 lung carcinomas occurred, which means an incidence of more than 90%. If we had killed the animals before the 27th month, we would surely have detected initial stages of lung cancer, but not so many macroscopically and microscopically clear tumors.”

However, this interpretation and clear differentiation becomes a bit complicated, since Waalkes and Rehm²⁵ exposed male Wistar rats to diets containing 0, 25, 50, 100, or 200 ppm cadmium chloride for only 77 weeks, and animals at the higher exposure levels had increased incidences of leukemia (100 ppm), not dose-related, and interstitial cell tumors of the testes (200 ppm). The keen difference here is that exposure concentrations for detecting an effect were two to four times greater than those in earlier experiments.^{36,37} The Waalkes and Rehm study²⁵ (oral exposure) also used a different route of administration than the study of Takenaka et al.³⁶ (inhalation exposure), which may help to explain why the tumors were observed at different organ sites (leukemia and testicular tumors in the oral study and lung tumors in the inhalation study). In later drinking-water studies, Waalkes et al.²³ reported a few rare tumors of the kidney in Noble (NBL/Cr) rats, and most significantly their “results indicate that oral cadmium can induce proliferative lesions in the prostate and kidney of the Noble rat. The finding of proliferative lesions of dorsolateral prostate in rats has presumed relevance to human prostate cancers.”

Over all, cadmium exposures of laboratory animals causes tumors of the hematopoietic system (leukemia and lymphoma), local sarcoma, and cancers of the adrenal gland, liver, lung, kidney, pancreas, pituitary, prostate, and testis.^{3,8} Even though cadmium penetrates the placenta and appears in breast milk, there appears to be no longterm cancer study using an inutero exposure design protocol. As cadmium mimics estrogen,⁴⁴ and because children are exposed to cadmium via maternal exposures,⁴⁵ interest in earlier exposure regimens, including in utero, should be considered to obtain a fuller understanding of cadmium carcinogenicity.⁷

Carcinogenicity—Human Epidemiological Studies

Regarding possible causal associations between cadmium exposures and human cancers, the International Agency for Research on Cancer (IARC) in February 1993 reviewed and evaluated the available epidemiologic findings and other relevant information on cadmium exposures and concluded there was sufficient evidence of carcinogenicity in humans for the carcinogenicity of cadmium and cadmium compounds.⁴ Their evaluation was based largely on occupational cohort studies of nickel-cadmium manufacturing, cadmium processing, cadmium-recovery plants, and copper-cadmium alloy plants. Most studies reported excess mortality from lung cancer among cadmium-exposed workers. Limitations included small numbers of long-term highly exposed workers, inadequate exposure assessment data, and potential confounding by cigarette smoking and exposures to other metals. For lung cancer, the IARC concluded that the dose–response relation for workers at a U.S. cadmium-recovery plant was unlikely to be confounded by cigarette smoking, and “the increase in lung cancer risk was unlikely to be explained by exposure to arsenic.” Other studies reported

that risks of lung cancer were greater in highly exposed workers or that there were suggested trends with increased duration of employment or intensity of exposure. The IARC also noted that some studies (mainly earlier ones) reported excesses for prostate cancer.

Despite potential confounding, the IARC considered the totality of available information through early 1993 as being sufficient to place cadmium in its Group 1 category of evidence: “Cadmium and cadmium compounds are carcinogenic to humans.” Their conclusion was based on

- sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds,
- sufficient evidence in experimental animals for the carcinogenicity of cadmium compounds, and
- limited evidence in experimental animals for the carcinogenicity of cadmium metal.

The overall evaluation took into consideration that ionic cadmium causes genotoxic effects in a variety of eukaryotic cell types, including human cells.

In 2000, the National Toxicology Program (NTP)³ independently evaluated the available evidence and concluded “Cadmium and cadmium compounds are known to be human carcinogens based on sufficient evidence of carcinogenicity in humans, including epidemiological and mechanistic information that indicate a causal relationship between exposure to cadmium and cadmium compounds and human cancer.” The NTP concurred with the IARC’s assessment that cohort studies showed an increased lung cancer risk among workers exposed to various cadmium compounds, and while they often were co-exposed to other agents, the increased risks of lung cancer were unlikely due to confounding factors. Additionally, the NTP stated that “Follow-up analyses for some of the cohorts has not definitely eliminated arsenic as a confounding factor but has confirmed that cadmium exposure is causally associated with elevated lung cancer risk under certain industrial exposure circumstances.”^{46,47}

Regarding cadmium-associated prostate cancer, the NTP concurred with the IARC that the increases observed in earlier cohort studies were not confirmed in later studies. However, some case–control or ecologic studies suggest an association between cadmium exposure and cancer of the prostate.^{48,49} Epidemiologic studies have reported possible associations between cadmium exposures and cancers of the kidneys⁵⁰; and of the urinary bladder.⁵¹

Since the NTP review, additional epidemiologic studies, reviews, and meta-analyses have evaluated cancer risks and exposures to cadmium compounds. Most have focused on cancers of the lung, prostate, pancreas, and kidney. Another study looked at cadmium exposure and breast cancer. Several of these are mentioned in brief.

Lung

In 2003, Verougstraete et al.⁵² reviewed the epidemiologic data on exposures to cadmium and lung and prostate cancers and concluded that the cohort studies (including the latest updates) consistently found an increased risk of lung cancer despite different exposure conditions, in different cadmium industries, and in different countries. Mentioned limitations were inconsistencies of exposure–response relationships and potential confounding by arsenic. Since that review, a further update of the U.K. nickel-cadmium factory reported an excess lung cancer mortality (standardized mortality ratio, SMR = 1.11, 95% confidence interval (CI) = 0.81–1.48; 45 observed deaths, for which the authors stated their study weakened the evidence for cadmium as a lung carcinogen.⁵³ However, a later prospective population-based study of environmental exposures to cadmium demonstrated a positive

association between 24-hour urinary cadmium levels (doubling of excretion) and both lung cancer (hazard ratio = 1.70, 95% CI = 1.13–2.57) and total cancer risk (hazard ratio = 1.31, 95% CI = 1.03–1.65) after adjusting for age, sex, and tobacco smoking.⁵⁴ Significant findings were also found for an association between lung cancer and cadmium concentrations in the soil or living in a high-exposure area. Moreover, urinary cadmium excretion was a significant predictor of any cancer (hazard ratio = 1.28, 95% CI = 1.01–1.63) and lung cancer (hazard ratio = 1.60, 95% CI = 1.04–2.45) after adjusting for arsenic exposure. (Urinary arsenic excretion data were available for 26% of the population.) Use of urinary cadmium level to assess exposure alleviates some of the limitations of occupational cohort studies, such as misclassification of exposure and confounding from exposures to other agents or cigarette smoking, and thus strengthens the evidence for cadmium carcinogenicity. The urinary cadmium level is proportional to the cadmium body burden and is considered to be a sensitive dosimeter for lifetime exposure.^{55,56}

Prostate gland

Although historically prostate cancer was the first cancer identified in association with exposure to cadmium,³⁵ Verougstraete et al.⁵² suggested that their review of cohort studies (the same review as for lung studies discussed above) did not confirm the original findings of high-risk estimates for prostate cancer. Sahmoun et al.¹⁸ reviewed the literature for studies on prostate cancer and exposure to cadmium published between 1966 and 2002, and reported positive associations in three of four descriptive studies, five of ten case-control studies, and three of 11 cohort studies. From their collective findings, they decided the overall evidence of an association between exposure to cadmium and prostate cancer was either weakly positive or negative, but indicated that the studies were limited by potential exposure misclassification, which limits the ability to detect an effect. When they restricted their review to four cohorts of nickel-cadmium battery workers (who the authors stated had the highest and least ambiguous exposures), they calculated an elevated summary SMR of 1.26 (95% CI 0.83–1.84) for prostate cancer. A 1998 case-control study in southeast China with 297 male volunteers from a control area and two cadmium-polluted areas showed a clear dose-response relationship between cadmium exposure and the prevalence of abnormal prostate-specific antigen (PSA).⁵⁷ These results indicate that chronic environmental cadmium exposure is associated with injuries to human prostate. Moreover, cadmium induces prostatic proliferative lesions and cancer in laboratory animals^{20–23,25} and transforms human prostate cells in vitro,⁸ suggesting that more studies, with improved methods to assess exposure, are needed. The available human studies have limited ability to detect an effect and thus reliance on animal findings strengthens the evidence of an association between cadmium exposure and cancer of the prostate in humans.

Kidney

Since the IARC and NTP evaluations, there has been mounting evidence that cadmium may be associated with cancers at other sites, including kidney, pancreas, and breast. Il'yasova and Schwartz⁵⁸ reviewed publications between 1966 and 2003 on exposures to cadmium and renal cancer and reported that three large (935 to 1,732 cases) case-control studies, from different geographic regions and using different methods to assess exposure, found increased risks for renal cancer from occupational exposures to cadmium, odds ratios (ORs) between 1.2 and 5. They identified four other studies with information about cadmium exposures: three had elevated but imprecise risk estimates (as evidenced by wide confidence intervals resulting from small numbers of exposed cases) and the fourth study did not report an increased risk. There is site concordance with animal studies and mechanistic or other data supporting the findings suggested by human studies. Because there is no apparent biological mechanism for excretion of cadmium, this metalloid accumulates in tissues, with the largest amounts deposited in kidneys (half-life in kidney cortex is 10 to 30 years) and

liver, followed by the pancreas and lungs.^{5,17} Cadmium–metallothionein complexes accumulate in the proximal tubules in the kidney, and release of free cadmium is thought to produce renal tubular damage.^{5,17} Cadmium is an established cause of end-stage renal disease in humans.^{58,59}

Pancreas

Schwartz and Reis^{5,17} proposed that cadmium exposure may present a risk for pancreatic cancer. A meta-analysis of studies published between 1966 and 1999 gave a pooled SMR of 1.62 (95 CI = 0.94–2.79) for three cohorts of male workers using the most recent reports giving numbers of observed and expected deaths from pancreatic cancer. However, a meta-analysis by Ojajärvi et al.⁶⁰ did not show an elevated risk for cancer of the pancreas from cadmium exposure, based on two populations. (Cadmium was not the focus of their review, but was one of 23 chemicals or physical agents evaluated.) Additionally, Kriegel et al.⁶¹ measured serum cadmium levels of 31 newly diagnosed pancreatic cancer patients and 52 hospital comparison subjects from Mansoura, Egypt, and found significant differences in serum cadmium (mean $\pm$ SD 11.1 $\pm$ 7.7 ng/mL vs 7.1 $\pm$ 5.0 ng/mL). The OR for pancreatic cancer risk was significant for serum cadmium level, OR 1.12 (95% CI, 1.04–1.23) and farming, OR 3.25 (95% CI, 1.03–11.64) but not for age, sex, residence, or smoking status. From this pilot study, Kriegel et al.⁶¹ suggested that pancreatic cancer in the East Nile Delta region is significantly associated with the highest levels of serum cadmium and farming. As with cancer of the kidney, there is site concordance with animal studies and mechanistic or other data supporting the findings suggested by human studies for the pancreas. Cadmium causes trans-differentiation of pancreatic cells, increases synthesis of pancreatic DNA, and induces or regulates oncogenic activation of several proteins or tumor-suppressor proteins that are over-expressed in human pancreatic cancer.¹⁷

Breast

McElroy et al.⁶² reported in 2006 that cadmium exposures are associated with cancer of the breast. These authors carried out a population-based case–control study of 246 women, aged 20–69 years, with breast cancer and 254 age-matched controls. Cadmium levels in urine were measured and telephone interviews conducted to obtain information about known breast cancer risk factors. Women in the highest quartile of creatinine-adjusted cadmium level ($> 0.58 \mu\text{g/g}$) had twice the breast cancer risk of those in the lowest quartile ($< 0.26 \mu\text{g/g}$; OR = 2.29, 95% CI 1.3–4.2) after adjusting for other breast cancer risk factors. Notably, there was a significant increase in risk with increasing cadmium level, $P(\text{trend}) = 0.01$. Nonetheless, McElroy et al.⁶² hedge a bit by concluding “whether increased cadmium is a causal factor for breast cancer or reflects the effects of treatment or disease remains to be determined.” No investigation of this target site in animal experiments on the effects of cadmium has been reported. However, there are other hormone-dependent cancers observed in animals, affecting the adrenal and pituitary glands, prostate, and testes, and evidence in rats indicates that cadmium at very low doses acts estrogenically in the uterus and mammary glands.⁴⁴ Nagato et al.⁶³ reported a positive association between urinary cadmium and serum testosterone levels after controlling for age and body index. Cadmium exposure may affect the mechanism that maintains the estrogen–androgen balance, and epidemiologic studies have shown that high testosterone levels have been associated with breast cancer risk.⁶⁴

Urinary bladder

A new study was published while this publication was in proof; see note added in proof.

In contrast to the IARC and NTP evaluations, both of which have classified cadmium as a known human carcinogen, the U.S. Environmental Protection Agency has classified

cadmium as a “probable” human carcinogen, indicating a lower level of concern.⁶⁵ Further, in 1986 the California EPA under Proposition 65 listed cadmium and cadmium salts as known to the State to cause cancer, and “Based on available scientific information, a cadmium exposure level below which carcinogenic effects are not expected to occur cannot be identified.”^{66,67} This difference between the concordant evaluations by IARC and NTP and that of the EPA is significant with regard to:

- regulatory categorization and enforcement levels of exposure,
- occupational and environmental standard setting,
- primary prevention initiatives, and
- exposure-caused cancer victims' recourse.

The IARC and the NTP cited primarily cadmium-induced lung cancers as clearly demonstrating causation and incorporated mechanistic data in making their final evaluations. Recent studies suggest that cadmium may also be associated with cancers of the kidney, pancreas, and breast.

Mechanistic Considerations

Cadmium (i.e., cadmium or cadmium compounds) is poorly excreted and has a long biological half-life. Accumulating mainly in the liver and kidney, cadmium is bound to metallothionein (a metal-binding protein), which may serve to temporarily detoxify the metal.⁸

As discussed previously, cadmium causes cancers in experimental animals at many tissue sites, and thus it is likely that the mechanism of carcinogenicity is multi-factorial. Like other toxic metals, cadmium may act by molecular/atomic mimicry of essential nutrient metals; that is, it competes for binding at sites (specifically with a zinc finger motif) that are important in gene regulation, enzyme activity, or maintenance of genomic stability.^{8,68} Numerous studies have shown that zinc reduces the carcinogenic effect of cadmium at some sites (such as lung, testes and injection sites) but not all (such as prostate).⁸

In vitro, cadmium can transform a variety of cells, including human prostate epithelial cells, demonstrating its oncogenic properties.⁸ It has a wide spectrum of cellular and molecular effects, including both genetic and epigenetic, which could affect all stages in the carcinogenic process. Potential molecular and cellular mechanisms of cadmium that mediate carcinogenesis have been reviewed extensively in the last several years^{8,68,69} and thus will be discussed only briefly.

Most of the reviews have concluded that cadmium is weakly genotoxic.^{4,7,8,69} Cadmium causes genetic damage in cultured mammalian cells but is not mutagenic in bacteria. Cadmium compounds are co-mutagens in mammalian cells when combined with genotoxic agents.⁶⁹ Cadmium also causes genetic damage (micronuclei, sister chromatid exchanges, and single-strand breaks) in experimental animals exposed by intraperitoneal injection but not in inhalational studies.⁵² Verougstraete et al.⁵² reviewed studies that evaluated cytogenetic effects in humans exposed occupationally and environmentally to cadmium. These authors concluded that the reported results of the human studies were conflicting and no definite conclusion could be reached. A contemporary study of workers exposed to cadmium, cobalt, and lead reported a positive correlation between cadmium concentrations in air and blood and DNA damage (single-strand breaks).⁷⁰

Waisberg and colleagues stated, “Various studies have shown that cadmium carcinogenicity seems to be crucially mediated by the production of reactive oxygen species.” Cadmium

induces the production of hydroxyl radicals, superoxide anions, nitric oxide, and hydrogen peroxide. It also increases lipid peroxidation levels in the liver and liver mitochondria in rats, and in cultured rat hepatocytes. Cadmium is not a Fenton metal, and induces reactive oxygen species by indirect mechanisms.⁶⁹

In experimental systems, cadmium induces many biochemical changes, including aberrant gene expression and signal transduction, E-cadherin (protein important in (3-catenin signaling pathway and possibly tumor invasion) dysfunction, inhibition of DNA methylation, disruption of DNA repair, and cell death.⁶⁹ Cadmium modifies the expression of several genes related to carcinogenesis, including intermediate early-response genes such as c-fos, c-jun, and c-myc; stress-response genes such as metallothionein, and heat-shock genes; genes controlling glutathione and related proteins; and transcription and translation factors.⁶⁹ At low, non-cytotoxic concentrations, cadmium inhibits DNA repair including mismatch repair, nucleotide-excision repair, and base-excision repair. Inhibition of DNA repair in combination with increased oxidative stress causes DNA damage, cell cycle arrest, mutagenesis, and genomic instability, leading to cancer or cell death.⁶⁸

Cadmium-induced biochemical changes may play roles in all stages of carcinogenicity (initiation, promotion, and progression). For example: 1) induction of oxidative stress in combination with decreased DNA repair can lead to DNA damage, and gene mutation, resulting in preneoplastic lesions; 2) aberrant gene expression and signaling in combination with inhibition of DNA methylation induces proto-oncogenes, resulting in cell proliferation; and 3) E-cadherin dysfunction disrupts cell adhesion and causes tumor progression.⁶⁹

Cadmium also affects apoptosis. In cultured cells, exposure to cadmium causes an increase in apoptotic cells in a concentration-related matter. In some experimental systems, the increase in cell death is associated with increased p53 protein and mRNA levels, whereas in other cell lines, cadmium-induced apoptosis is p53-independent and related to reactive oxygen production. However, the induction of apoptosis is probably not protective against malignant transformation, because some studies have found that only a small fraction of cadmium-treated cells undergo apoptosis and the remaining cells may acquire apoptotic resistance.⁶⁹ Moreover, cadmium-transformed cells such as prostate, epithelial, or rat liver or cadmium-adapted cells (lung cells) acquire resistance to apoptosis.^{69,71,72} Apoptotic resistance allows for the accumulation of critical mutations, or preneoplastic or early neoplastic cells.^{8,69}

Calepa Risk Due to Atmospheric Cadmium

Hazards posed by atmospheric cadmium to residents of California were estimated by applying the unit risk estimate to cadmium concentrations measured in the state. The upper-bound excess lifetime cancer risk from atmospheric concentrations of cadmium in California has been estimated to be 30 per million. Near emission sources of cadmium, the upper-bound estimated excess lifetime cancer risk from 24-hour-per-day exposure to an average of 40 ng/m³ of cadmium is 480 per million persons exposed. These are health-conservative estimates; the actual risks may lie below these values. The CalEPA Board^{10,66,67} thus finds:

- cadmium is an animal carcinogen with epidemicologic evidence of carcinogenicity in humans;
- there is not sufficient available scientific evidence to support the identification of a threshold exposure level for cadmium; and
- cadmium is an air pollutant which, because of its carcinogenicity, may cause or contribute to an increase in mortality and an increase in serious illness, and poses a hazard to human health.

Remarks

Like many other carcinogens, cadmium and cadmium compounds have long been known to cause cancers in laboratory animals, and are another example of chemicals first identified as being carcinogenic in animals and only subsequently in humans.^{15,73–75} In fact, nearly 25–30% of known human carcinogens were first discovered in long-term bioassays in animals.^{15,74} This phenomenon typically results from an increasing debate regarding whether chemical carcinogenesis bioassay findings are relevant and validated to predict human cancer risks.^{76,77} The overwhelming majority of governmental and nongovernmental organizations support and endorse the biologic concept that animal bioassay results are the most reasonable and reliable means to identify likely human carcinogens.³ The endorsement from the IARC/WHO states: “In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence in experimental animals as if they presented a carcinogenic risk to humans.”⁷³

As one example whereby convincing animal carcinogenicity data have been repudiated, the editor of *Science* wrote two editorials in the 1990s^{78,79} criticizing us for declaring 1,3-butadiene as a unique and dangerous carcinogen. Others view this industrial hazard differently.^{80,81} We found this industrial chemical caused multiple cancers in only 60 weeks at and below (650 and 1,250 ppm)⁸² the then OSHA workplace standard (1,000 ppm); in further more definitive experiments the lowest exposure (6.5 ppm) tested was also considerably carcinogenic.^{83,84} OSHA eventually lowered its occupational exposure standard to 1 ppm, which is not likely to prevent completely further excess cancers in workers since every exposure level yet tested causes significant cancers in animals.⁸⁴ Subsequently, of course, leukemias (also seen in animals) were found in butadiene workers,^{85–88} and this is another example whereby animal evidence was disregarded, trumping worker safety. The NTP declared butadiene a human carcinogen in 2000,⁸⁷ but the IARC, after much debate and controversy, retained its classification of “probably carcinogenic to humans.”^{89–94} IARC will reevaluate the carcinogenicity data of 1,3-butadiene in June 2007.

In addition to butadiene, other animal carcinogens have also been impugned.⁹⁵ “Questionable assessments involving liver cancer in B6C3F₁ mice include the risks posed by trichloroethylene, perchloroethylene, methylene chloride, butadiene, and phenobarbital.”⁹⁶ Certainly none of these chemicals caused liver tumors in mice only, and all of them (with the possible exception of phenobarbital) have now been evaluated and judged scientifically to be likely or known carcinogens to humans (e.g., TCE⁹⁷). These among others are examples of likely carcinogenic hazards ignored until cancers occur in workers.⁹⁸

As significant and further support of the biologically credible animal-to-human correlation, all known human carcinogens that have been evaluated experimentally are also carcinogenic to animals, and target sites are similar to a fault.^{99,100} Does this mean that all chemicals causing cancer in animals should be regulated or banned? No, all carcinogens are not equally potent carcinogenically, nor do all represent similar carcinogenic hazards to humans. As with most biology, there are gradations of adverse effects, and these must be evaluated accordingly.^{15,101,102}

Epidemiologic findings of cancers in humans exposed to cadmium and cadmium compounds are supported by studies in experimental animals demonstrating that cadmium and cadmium compounds induce benign and malignant tumor formation by multiple routes, at various exposure concentrations, and at various and diverse sites in different species of experimental animals. Cadmium-inhalation-exposed animals develop lung cancers. As has been further

supported and confirmed using other routes of exposures in animals, intra-tracheal exposure to cadmium also caused lung tumors; oral exposure caused leukemia and tumors of the testes, prostate, pituitary, and kidney; and subcutaneous exposure caused lymphoma, local sarcomas (also observed in other types of injection studies), and tumors of the prostate, testes, lung, liver, pancreas, pituitary, and adrenal gland.^{3,8,23} Route of exposure gently impacts “sites” of chemical carcinogenic activity, and has relatively little effect regarding the finding of carcinogenicity.¹⁰³

In humans, cadmium and cadmium compounds are causally associated with cancers, mainly of the lung, with suggestive evidence for cancers of the breast, pancreas, kidney, and prostate (although the strength of the evidence for the latter site appears to have decreased in recent studies). Of these sites, only breast has not been investigated or observed in animals. Once again, concordance between animals and humans is upheld, and points to other sites in humans that may be prone to cadmium-associated cancers. Moreover, Sanner and Dybing¹⁰⁴ found good agreement between hazard characterization for cadmium (lifetime cancer of 10^{-3}) based on epidemiologic studies and animal experiments.

To reiterate, cadmium and cadmium salts were shown to cause cancer first in laboratory animals and only subsequently in humans. As in the case of butadiene (and others), the prudent course of action for operations involving exposures to cadmium and cadmium compounds would have been to take the collective results from animals seriously and act accordingly and more rapidly in the highest principled interests of public and worker health.^{105,106} The initial failure to find cancer in humans might reflect simply a lack of looking for other cancers in workers in cadmium industries. Epidemiologic studies of occupational exposures are likely to be spurred by clear evidence of carcinogenicity in animals.¹⁰⁷ Moreover, occupational epidemiologic studies are often limited in their abilities to detect an effect because of poor exposure assessment, small numbers of exposed cases, and confounding by exposures to other agents. Also, individuals may be exposed to cadmium from non-occupational sources, such as food and cigarette smoking; therefore, occupational studies usually do not measure cumulative exposures to cadmium. The use of biomarkers to measure cadmium exposure, such as urinary cadmium excretion and blood or serum cadmium levels, may help address some of these limitations. As discussed above, three recent studies using exposure biomarkers have shown a positive association between cadmium exposure and cancer risks (lung, breast or pancreatic). Although epidemiology is the best means to unequivocally identify human carcinogens, as Hill has said, “All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.”¹⁰⁸

Fundamentally there is no convincing evidence to suggest that mechanisms thought to account for the multi-organ carcinogenicity of cadmium (and other chemical carcinogens) in experimental animals would not also operate in humans. Correlations between species exist, with first evidence being observed in animals. Thus, further reductions in allowable workplace and environmental exposures to cadmium and cadmium compounds should be actively pursued. This proposed action of occupational surveillance of adverse health effects and cancer and exposure reduction is especially relevant for developing countries.^{109–115} Only by preventing, minimizing, or eliminating exposures to known and suspected chemical carcinogens will there be a significant lessening in the number of these workplace and environmental cancers and their attendant suffering.^{116–119}

Urinary bladder

Kellen et al.¹²⁰ conducted a case-control study in Belgium, one of the most important cadmium-producing countries worldwide, to assess an association between blood cadmium levels and risk of urinary bladder cancer. Blood cadmium reflects current exposure rather than whole-body burdens, while urinary cadmium reflects total burden.⁵ Blood cadmium levels were measured in 172 urinary bladder cancer cases and 359 population controls. Bladder cancer risk increased with increasing levels of blood cadmium ($P_{\text{trend}} < 0.001$), and the risk was greater than eightfold in the highest tertile of blood cadmium levels after adjusting for sex, age, and occupational exposure to PAHs or aromatic amines (OR = 8.3, 95% CI = 5.0–13.8). The OR decreased somewhat after further adjustment for cigarette smoking but was still significant (OR = 5.3, 95% CI = 3.3–9.9). This study supports the findings from an earlier case-control study (that was reviewed by NTP), which reported an association between occupational exposure to cadmium and bladder cancer risk.⁵¹ These epidemiologic findings are further supported mechanistically by studies showing that cadmium malignantly transforms human urothelial cells.¹²¹ Additionally, Sens et al.¹²² reported that tumor heterotransplants produced by these cadmium-transformed cells were epithelial in character and had features consistent with those expected of undifferentiated transitional-cell carcinomas of the urinary bladder.

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