

Cadmium carcinogenesis and its relationship to other health effects in humans

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NORDBERG GF. Cadmium carcinogenesis and its relationship to other health effects in humans. *Scand J Work Environ Health* 1993;19 suppl 1:104-7. Several different adverse health effects can be caused by cadmium exposure to humans and animals. In environmental and occupational health it is important to identify effects that occur at relatively low exposures (ie, the critical effects that are crucial for preventive action). In long-term human exposures to cadmium, effects of cadmium on the kidney have been considered to be critical effects and quantitative risk assessments of these effects have been performed on the basis of both risk modeling and direct epidemiologic observation. However, experimental and epidemiologic studies are providing increasing evidence that cadmium is carcinogenic, and this effect, which is considered to be stochastic in character, can be considered to be the critical effect. A quantitative evaluation of the cancer risk is currently difficult to make, but the preventive action against such effects is usually to limit the exposure as much as possible.

Key terms: critical effects, deterministic effects, dose-response relationships, lung cancer, nephrotoxicity, stochastic effects, toxicology.

The prevention of adverse effects on human health is an important goal in environmental and occupational health. It is thus important to identify effects that occur at relatively low exposures (ie, the critical effects that are crucial for preventive action).

When critical effects are discussed, it is important to distinguish between effects of the deterministic type (ie, effects which have threshold types of dose-response curves) and those of a stochastic type, for which the dose-response curves have no threshold. The concept of critical effect was first developed in relation to deterministic effects (1) and can be understood as the very first effect that occurs at low exposure. The term "critical effect" has recently been defined as follows: "For deterministic effects the first adverse effect that appears when the critical concentration in the critical organ is reached in an individual. It is the adverse effect that occurs as a result of the lowest dose in the critical organ: if cancer is a potential effect of a chemical it is usually regarded as the critical effect" (2). The critical concentration for a cell or organ is the concentration at which a potentially toxic substance causes undesirable or adverse functional changes, whether reversible or irreversible, in the cell or organ. These concepts have been further discussed elsewhere (3).

Toxic effects on humans

Occupational or environmental exposure to cadmium can result in adverse effects on different organs. Effects on the respiratory system can occur in humans after short-term exposure to relatively high concentrations of cadmium in air (in the $\text{mg} \cdot \text{m}^{-3}$ range). These effects are the critical effects for short-term inhalation exposures. With longer exposure at concentrations of cadmium dust above $70 \mu\text{g} \cdot \text{m}^{-3}$, chronic effects on the lung can occur. At lower concentrations, however, lung damage does not usually take place (4). An important consideration in relation to the effects on the tissues of the respiratory tract is to what extent such effects constitute early phases in the process leading to cancer. Deposition patterns of cadmium in the respiratory organs of various animal species and their relationship to the development of lung cancer have been discussed by Oberdörster (5).

When food or drink containing cadmium concentrations above $15 \text{ mg} \cdot \text{l}^{-1}$ is ingested, vomiting and other gastrointestinal symptoms occur. Low concentrations of cadmium in food can also produce some nonspecific symptoms, but it is still uncertain to what extent chronic gastrointestinal symptoms can be induced by cadmium. In exposures that include only a single oral intake, there are no other effects on the organism than acute effects on the gastrointestinal tract. This effect must thus be considered the critical effect of short-term oral exposure.

In long-term low-level exposure, cadmium accumulates in the kidney and gives rise to renal tubular damage. After uptake from the lung or the gastrointestinal tract, it is transported in blood plasma, initially bound to albumin. Cadmium-albumin is pref-

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entially taken up by the liver. Cadmium in the liver then induces the synthesis of metallothionein, and a small proportion of the cadmium-metallothionein is released into plasma. Because of its low molecular weight, cadmium-metallothionein is efficiently filtered through the glomeruli and accumulates in the renal tubules, where it gives rise to renal tubular damage. However, glomerular damage has also been reported in chronic cadmium toxicity (6). In cadmium-exposed industrial workers, cadmium concentrations in the kidney have been measured *in vivo*, and a relationship has been reported between the development of kidney dysfunction and the concentration of cadmium in the renal cortex (7, 8). Approximately 10% of the subjects examined were found to suffer kidney damage when the renal cortical concentration was $200 \text{ mg} \cdot \text{kg wet weight}^{-1}$. By means of a metabolic model (9), it is possible to calculate the exposure that would be required to reach a kidney concentration of $200 \text{ mg} \cdot \text{kg}^{-1}$, either during industrial exposure by inhalation or during exposure of the general population (oral exposures).

Cadmium-induced damage to the kidney is characterized by tubular dysfunction, which gives rise to a decreased reabsorption of plasma proteins filtered through the glomeruli. There is also an increased excretion of glucose, amino acids, calcium, and phosphate. Increased excretion of proteins and enzymes originating from the kidney tubules has also been reported (4). A 10% prevalence of kidney damage above the background prevalence among industrial workers has been observed at a cadmium concentration in the renal cortex of $200 \text{ mg} \cdot \text{kg wet weight}^{-1}$; the corresponding concentration of cadmium in urine is $10 \mu\text{g} \cdot \text{g creatinine}^{-1}$ (4). In the general population in Belgium (6, 10) there was a 10% probability of tubular proteinuria (5% above the background prevalence) at urinary cadmium concentrations between 2 and $4 \mu\text{g} \cdot 24 \text{ h}^{-1}$. This finding indicates that the general population may include persons of higher sensitivity than are found in the industrial population.

A characteristic feature of chronic cadmium poisoning, as seen in a cadmium-contaminated area in Japan, was osteoporosis and osteomalacia. The finding of renal calculi in industrial workers indicates that effects related to an increased excretion of calcium and phosphorus may also occur in such workers. The occurrence of various manifestations of disturbed bone mineral metabolism is dependent on the dietary intake of calcium, vitamin D, and phosphorus via food in the population in question, as discussed recently by Kjellström (11) and Tsuchiya (12).

Among experimental animals, injection of sublethal doses of cadmium can give rise to dramatic effects on both the male and female reproductive organs, but such effects have not been observed in animals or humans exposed for long periods to cadmium. These effects will therefore not be further discussed.

Carcinogenic and genotoxic effects

The first report relating cancer of the prostate to occupational cadmium exposure was published by Potts (13); later, similar associations were found in cadmium smelter workers in the United States (14). However, in follow-up studies of these and other groups of workers, a clearly increased occurrence of prostatic cancer was not confirmed. (For a review, see reference 15.) Sorahan & Waterhouse (16) found a significant increase in prostatic cancers among workers in a British cadmium battery plant, and Elghany et al (17) found a marginally increased odds ratio for aggressive forms of prostatic cancer, but exposure to cadmium was not well documented.

In the early studies on cancer mortality, there was no obvious indication of an increased risk of lung cancer among cadmium workers. It was not until the study in the United States by Lemen et al (14) that a statistically significant increase in the risk of lung cancer was reported. In Swedish studies, for example, that of Elinder et al (18), eight cases of lung cancer were reported (standardized mortality ratio 133, not statistically significant). In the study by Sorahan & Waterhouse (16), a statistically significant increase in the number of lung cancer cases was found in cadmium-nickel battery factory workers in England. In other studies in England (19, 20) a significantly increased risk of lung cancer was also reported, with a tendency towards a dose-response relationship (standardized mortality ratios 112, 121 and 194 in the "always low", "ever medium" and "ever high" exposure categories, respectively). In the studies by Thun et al (21), a statistically significant excess risk was reported for lung cancer in cadmium smelter workers in the United States. There are thus several studies reporting a positive association between cadmium exposure and lung cancer. When the causality of this relationship is discussed, it is important to consider the problems of confounding factors in the work environment, as discussed in detail by Kazantzis et al (22), Boffetta (23), and Doll (15). On the basis of all the evidence available, the International Agency for Research on Cancer recently classified cadmium as carcinogenic to humans (24).

Tumors can be induced in animals by exposure to cadmium both at the injection site (sarcomas) and after systemic distribution. The latter type occurs as Leydig cell tumors of the testicles (25) and as prostatic tumors (26, 27). After inhalation exposure of long duration to relatively low concentrations of cadmium chloride, $12.5\text{--}50 \mu\text{g} \cdot \text{m}^{-3}$, it was found that rats developed lung tumors (28). Findings of cancer are less consistent in other animal species than in the rat (29); this difference may be partly due to differences in pulmonary deposition and disposition (5).

Genetic and related effects of cadmium have been examined in various *in vitro* and *in vivo* test systems. The results have varied. No effects have usually been found in procaryote test systems, while effects have

sometimes been observed in lower eucaryotes and mammalian cells in vitro and mammals in vivo (30). One factor which may explain part of the variation is the induction of metallothionein. Andersen et al (31) found initial changes in the average chromosome length of human lymphocytes when they were treated with cadmium. Later this effect disappeared, probably due to metallothionein synthesis and complexing with cadmium.

Critical effects and dose-response relationships

Critical effects of short-term exposure to cadmium can be identified as toxic effects occurring in the lung or the gastrointestinal tract, depending on the route of exposure. Effects of long-term exposure are, however, more important for preventive action. The effects that occur on the kidney after long-term accumulation of cadmium in that organ have usually been considered to be the critical effects in long-term exposure. Increasing evidence of carcinogenicity, recently reported, needs to be taken into account, however, and the possibility of lung cancer as a critical effect in long-term inhalation exposure should also be considered.

Nephrotoxic effects

An estimate of the risk for the development of nephrotoxicity in humans as a result of long-term exposure to cadmium can be obtained the most directly from epidemiologic observations of the occurrence of tubular proteinuria among workers occupationally exposed to airborne cadmium for long periods of time. The lowest exposure giving rise to an increased prevalence of proteinuria is considered to be 5–10 years of exposure to $100 \mu\text{g} \cdot \text{m}^{-3}$ of cadmium dust. If increased excretion of low molecular-weight proteins is used instead as the critical effect, the data indicate that 10–20 years of inhalation exposure to $50 \mu\text{g} \cdot \text{m}^{-3}$ of cadmium dust or more than $20 \mu\text{g} \cdot \text{m}^{-3}$ of cadmium fumes would give rise to an increased prevalence of such proteinuria (4). Long-term oral intake of cadmium from the general environment in Japan can give rise to tubular proteinuria. Over a period of 50 years an intake of 140–260 μg of cadmium per day or a cumulative cadmium intake of 2000 mg gives rise to an increased prevalence of low molecular-weight proteinuria (4, 32). Studies in China (33) have found a similar relationship. In Belgium (6, 10), low molecular-weight proteinuria occurred with increased prevalence even at lower doses.

Another method of estimating the risk of development of nephrotoxicity from cadmium exposure is to use model calculations based on information on the chemobiokinetics of cadmium and on the critical concentration of cadmium in the renal cortex. (See the section on the toxic effects on humans.)

Such model calculations indicate that exposure to a cadmium concentration of $14 \mu\text{g} \cdot \text{m}^{-3}$ in industrial air during the workdays of the year for 25 years would give rise to an accumulation of cadmium in the renal cortex of $200 \mu\text{g} \cdot \text{kg}^{-1}$, corresponding to approximately a 10% excess risk of low molecular-weight proteinuria.

Lung cancer

Quantitative estimates have been presented of the risk of lung cancer as a result of human exposure to cadmium by inhalation (34). There are, however, considerable uncertainties about both the causal (15, 22) and the quantitative (3, 35) aspects of this relationship.

The quantitative model suggested is based on a stochastic mechanism, and the dose-response curve presented (34) describes risks that exceed the risk estimated for renal effects of cadmium at very low exposures (ie, in the range of $1 \mu\text{g} \cdot \text{m}^{-3}$ and lower). If evidence for the quantitative model for cadmium-induced lung cancer in humans were to be found in the future, especially with regard to its stochastic nature, the quantitative dose-response relationship alluded to would support the notion that the carcinogenic effect should be regarded as the critical effect of cadmium exposure by inhalation.

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