The Carcinogenic Potential of Cadmium, Arsenic, and
Selenium and the Associated Public Health and
Regulatory Implications

Anna M. Fan, Ph.D.
Pesticide and Environmental Toxicology Section
California Department of Health Services
2151 Berkeley Way
Berkeley, CA 94704
U.S.A.

Introduction

Metals and metalloids are among the first agents reported to be associated with human cancer (Furst, 1984) with skin cancer induction by arsenical mixtures used for medicinal purposes being reported as early as 1888.

The objective of this evaluation is to analyze the carcinogenicity data for three agents namely cadmium, arsenic, and selenium, in order to evaluate their potential for carcinogenicity in humans. Cadmium is selected because of the particular concern as to whether it should be considered carcinogenic by the oral route as oral exposure by dietary ingestion is being evaluated under our food toxicology program. The metalloids arsenic and selenium are chosen because of the great controversy surrounding around these two inorganics. While some consider both elements carcinogenic, selenium has been reported to inhibit carcinogenesis under certain conditions and used as a chemotherapeutic agent in cancer treatment, whereas arsenic has been suggested by some to be an essential nutrient. Both these substances are

being evaluated for drinking water standards development under our drinking water program. Selenium has also been extensively evaluated by the Department because of the recent findings of selenium contamination in the Central Valley of California (Fan et al., 1988).

Cadmium

Most of the epidemiological studies on human exposure to cadmium have reported increased mortality from respiratory cancer in the cadmium exposed worker population by inhalation of cadmium-containing aerosol and dust (IARC, 1987). All of the studies reporting significant increases in the incidences of respiratory cancer have limitations in that potential confounding variables were present.

Mortality from cancers at sites other than the respiratory tract has not been shown to be significantly correlated with exposure to cadmium. Although increased mortality from cancer of the prostate was reported in cadmium exposed workers by Kipling and Waterhouse (1967), this was not confirmed in a follow-up study (Sorahan, 1987).

In experimental animals, cadmium has produced tumors following exposure by inhalation (cadmium chloride) (Takanaka et al., 1983), intramuscular (Gunn et al., 1963; Heath and Daniel, 1964; Furst and Schlauder, 1977; Furst and Fan, 1986), intrathoracic (cadmium) (Furst et

al., 1973), intratracheal (cadmium oxide) (Sanders and Mahaffey, 1984), subcutaneous (cadmium sulfide, cadmium oxide, cadmium sulfate) (Kazantis and Hanbury, 1966; Haddow et al., 1964), but not oral, (cadmium chloride) administrations (Loser, 1980).

The experimental data showed that lung carcinomas were observed in rats following inhalation of cadmium chloride aerosols (Takanaka et al., 1983), local sarcomas following subcutaneous or intramuscular injection in rats or mice (Heath and Daniel, 1964; Gunn et al., 1963; Furst and Schlauder, 1977; Furst and Fan, 1986; Haddow et al., 1964; Kazantis and Hanburg, 1966) of cadmium powder, cadmium sulfate, cadmium oxide, or cadmium sulfide. Most of these were local tumors at the site of cadmium administration. But tumors at distal sites, such as testicular interstitial cell tumors (Levy et al., 1973; Reddy et al., 1973) and pancreatic islet cell tumors (Poirier et al., 1983), were also reported following subcutaneous injection. The study of Loser (1980) which involved dietary administration of cadmium chloride at 0 to 50 ppm cadmium chloride to male and female Wistar rats for two years did not show a significant increase in tumor incidence. Male animals in the high dose group had a reduced weight gain indicating that a maximum tolerated dose was reached. Other lifetime oral bioassays of cadmium in rodents also did not find any increases in tumor incidences (ATSDR, 1989). On the other hand, these studies suffered from various deficiencies such as the limited number of animals and tissue sites examined

microscopically in the studies of Levy et al. (1975) and Levy and Clark (1975).

In studies of the genotoxicity of cadmium, the substances have generally been shown to produce negative responses in mutagenicity assays (IARC, 1987). Some positive responses were seen in cell transformation studies and studies of chromosomal aberrations. Cadmium, therefore, is not mutagenic but is genotoxic in certain studies.

Arsenic

Inorganic arsenic has been shown to cause lung cancer in smelter workers following inhalation and skin cancer in humans following ingestion from drinking water (IARC, 1980). The evidence was obtained from studies in Taiwan (Tseng, 1977; Tseng et al., 1968), Mexico (Cebrian et al., 1983), India (Chakraborty and Saha, 1987), and Chili (Zaldivar et al., 1981). The most relevant information is that from the studies in Taiwan. The prevalence rate in Taiwan was 10.6 per 1,000. The arsenic concentration was in the range of 0.01 to 1.82 mg/l, with an average of 0.4 to 0.6 mg/l. The prevalence rate in Mexico was 14 per 1,000 and the mean arsenic concentration was 0.411 mg/l. The skin cancer is often associated with other skin manifestations such as hyperkeratosis and skin pigmentation. Studies in the United States involving several counties and communities in different states (Oregon, Utah, Alaska, California) did not report an increase in skin cancer incidences (Morton et al., 1976;

Southwick et al., 1983; Harrington, et al., 1978; Valentine et al., 1985; Goldsmith et al., 1972).

Evidence of increases in lung and liver cancer incidences was also suggestive in Taiwan's Blackfoot disease endemic area (Tseng, 1977) and in wine growers in Germany (Roth, 1958) who might have been exposed to arsenical insecticides that were used at one time and arsenic from grapes made into a wine substitute. The data obtained from Taiwan should be examined more closely for kidney and bladder tumor induction.

Contrary to the findings in humans, arsenic has not been shown to be a carcinogen in rodents. In experimental animal studies in which rats and mice were given arsenic in the diet and drinking water, or by parenteral injection and skin painting, the responses were either negative or inconclusive. Inhalation bioassays have generally produced negative results except for the positive findings reported following intratracheal administration (Pershagen et al., 1984; Pershagen and Bjorklund, 1985; Ishinishi, 1983).

Selenium

The carcinogenicity of selenium was first suggested in studies in the 1940s through the 1970s but these studies suffered from deficiencies in experimental design and interpretation of lesions. In particular, some test animals developed neoplastic lesions only when they had

liver cirrhosis produced by frank selenium toxicity. These limitations do not allow for a clear interpretation of the experimental data, and precluded an adequate evaluation of the carcinogenicity of selenium to be made.

Nelson et al. (1943) first reported liver changes in rats following feeding of the animals with seleniferous feedstuff. The study, however, had problems in histopathological diagnosis and was not able to discriminate between hyperplasia and tumor. In other studies, rats administered sodium selenate and sodium selenite were reported to produce a negative response (Tinsley, 1967; Harr, 1967). Further study whereby tumors were reported in uncontrolled trials when rats were fed selenium in the diet was not confirmed when another study using controlled animals was evaluated (Volgarev and Tschevkes, 1967). In addition, when rats were administered sodium selenate and sodium selenite with semi-purified diet containing no selenium and in drinking water, tumors were reported with selenate given the semi-purified diet (Schroeder and Mitchner, 1971). The study used small numbers of test animals and the nutritional status of the animals was not clear.

Selenium sulfide, an ingredient in anti-dandruff shampoo, has been reported to be carcinogenic for rats and female mice when given by gavage (NCI, 1986), producing hepatocellular carcinomas in male and female rats and female mice and alveolar/bronchiolar carcinomas and adenomas in female mice. However, selenium sulfide is a

separate and distinct compound, rather than just another salt of selenium, therefore, the EPA has stated that it cannot be assumed that the results show that other inorganic selenium compounds (selenite or selenate) are carcinogenic (EPA, 1988a). The effect seen appeared to be more of a specific effect of the compound rather than an effect of selenium itself.

On the other hand, selenium has been reported to inhibit experimental carcinogenesis by other chemicals in laboratory animals and it has been used in clinical trials for cancer prevention (Fan and Kizer, 1990). It needs to be pointed out that the dose levels at which tumor inhibition was seen occurred at levels which were toxic to the experimental animals. The chemotherapeutic level suggested is not likely to provide an adequate safety margin to protect from the adverse effects of selenium (e.g., nail and hair changes) that can result from long-term exposure and, therefore, would be much higher than that permissible for daily exposure for the general population.

Epiemiological studies have suggested an inverse relationship between environmental selenium levels and the incidences of certain types of cancer but a casual relationship has not been established.

Summary and Discussion

The available evidence for carcinogenicity of cadmium, arsenic, and selenium and their public health evaluation status in California are summarized in table 1.

Table 1. Carcinogenicity and public health evaluation for cadmium, arsenic and selenium

Evidence for carcinogenicity¹

<u>Chemical</u>	<u>In Animals</u>	<u>In Humans</u>	<u>CDHS² Public Health Evaluation</u>
Cadmium	Sufficient	Limited	Ingestion from food (e.g., Cd in fish and waterfowl, or leached from ceramic tableware).
Arsenic	Inadequate	Sufficient	Drinking water standard development.
Selenium	Inadequate	Inadequate	Drinking water standard development. Ingestion from food (e.g., selenium in fish, ducks, agricultural crops, animals and animal products).

¹IARC classification scheme

²CDHS - California Department of Health Services

For cadmium, there is limited evidence that inhalation causes respiratory cancer in humans. There is sufficient evidence that it causes respiratory cancer in laboratory animals following inhalation. Local sarcomas were induced in laboratory animals following intramuscular and subcutaneous injection. Oral administration did not induce carcinogenesis at any site in rats. Cadmium is generally not mutagenic but shows genotoxic activity in

some studies. The available data are not sufficient to permit a definitive evaluation of the carcinogenicity of cadmium by the oral route. On the other hand, although the weight of evidence shows that cadmium is a probable human carcinogen by the inhalation route especially under conditions of occupational exposure, it also suggests that cadmium is not a human carcinogen by the oral route in the general population. This view may be modified if deemed appropriate when new data provide new evidence otherwise. Public health evaluation of ingestion of cadmium from food would, therefore, likely be based on the evaluation of the systemic effects of cadmium. The issue exposure route is being addressed by an internal working group.

For arsenic, there is sufficient evidence for carcinogenicity in humans primarily based on its association with skin cancer induction. Drinking water standard development would likely be based on providing adequate protection from increased cancer risk from arsenic in considering the revision of the current drinking water standard of 50 µg/L. Although animal data have suggested that inorganic arsenic may be an essential nutrient (EPA, 1988b), the relevance of the animal data to humans is unclear and a specific biochemical or physiological role for arsenic has not yet been determined. No arsenic deficiency syndrome in humans has yet been reported.

For selenium, there is inadequate data for the evaluation of its carcinogenicity. Human epidemiologic studies

suggested an inverse relationship between selenium levels and certain types of cancer but a casual relationship has not been established. The published laboratory studies suffered from various flaws and limitations. Although selenium has been reported to inhibit experimental carcinogenesis under certain conditions, this effect occurred only at dose levels that were toxic to the animals. Dose levels suggested in clinical research generally aim to achieve biologic activity of selenium but do not consider providing an adequate safety margin to protect from the chronic, adverse effects of overexposure to selenium. Evaluation of the public health implications of exposure to selenium from various sources, and the revision of the existing drinking water standard of 10 µg/l, would be based on the evaluation of the systemic effects of the chemical and the consideration of the regular dietary intake by general population of selenium, which is also a beneficial micronutrient.

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