SEVENTH EDITION

Casarett & Doull's

Toxicology

The Basic Science of Poisons

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peripheral vascular disease associated with chronic arsenic exposure is black foot disease, starting with numbness and ulceration of extremities and ending in gangrene and spontaneous amputations (Chen *et al.*, 1988).

Beryllium Beryllium and its salts are not mutagenic and do not appear to induce cellular transformation (IARC, 1993). Mechanistically, beryllium salts bind to nucleoproteins and inhibit enyzmes involved in DNA synthesis, resulting in infidelity of DNA synthesis and also induce gene mutations in cultured cells (Leonard and Lauwerys, 1987). Studies in animal models have consistently reported increases in lung tumors in rodents and nonhuman primates exposed to beryllium or beryllium compounds (IARC, 1993; Finch *et al.*, 1996; NTP, 1998). Beryllium metal and several beryllium compounds (e.g., beryllium–aluminum alloy, beryllium ore, beryllium chloride, beryllium hydroxide, beryllium sulfate tetrahydrate, and beryllium oxide) induced lung tumors in rats. Beryllium oxide and beryllium sulfate produced lung cancer (anaplastic carcinoma) in monkeys after intrabronchial implantation or inhalation. In rabbits, osteosarcomas were reported after exposure to beryllium metal, beryllium carbonate, beryllium oxide, beryllium phosphate, beryllium silicate, or zinc beryllium silicate (IARC, 1993).

Beryllium and beryllium compounds have been classified as human carcinogens based on animal studies and evidence of carcinogenicity in humans. Epidemiological studies indicate an increased risk of lung cancer in occupational groups exposed to beryllium or beryllium compounds (Steenland and Ward, 1991; Ward *et al.*, 1992). Further, an association with lung cancer has consistently been observed in occupational populations exposed to beryllium or beryllium compounds. Acute beryllium pneumonitis, a marker for exposure to beryllium has been shown to be associated with higher lung cancer rates (Steenland and Ward, 1991).

Cadmium Animal studies have shown that cadmium and cadmium compounds induce tumor formation at various sites in multiple species of experimental animals, following multiple exposure routes, including the induction of prostate tumors in rats, testicular tumors in rats and mice, lymphoma in mice, adrenal-gland tumors in hamsters and mice, and lung and liver tumors in mice (IARC, 1993; Waalkes *et al.*, 1994, 1999). It has been suggested that ionic cadmium, or compounds that release ionic cadmium, is the cause of genetic damage and thus the carcinogenic species. Increased frequencies of chromosomal aberrations (changes in chromosome structure or number) have been observed in lymphocytes of workers occupationally exposed to cadmium. Many studies of cultured mammalian cells have shown that cadmium compounds cause genetic damage, including gene mutations, DNA strand breaks, chromosomal damage, cell transformation, and disrupted DNA repair (IARC, 1993).

Cadmium and cadmium compounds have been classified as known human carcinogens based on 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 (IARC, 1993). Epidemiological studies of cadmium workers found that exposure to various cadmium compounds increased the risk of death from lung cancer (IARC, 1993). Follow-up analysis of some of these cohorts has confirmed that cadmium exposure is associated with elevated lung cancer risk under some industrial circumstances (Sorahan *et al.*, 1995; Sorahan and Lancashire, 1997). Some epidemiological evidence has also suggested an association between cadmium exposure and prostate cancer (Shigematsu *et al.*, 1982; van der Gulden *et al.*, 1995), kidney (Mandel *et al.*, 1995), and bladder (Siemiatycki *et al.*, 1994).

Chromium Chromium has multiple oxidation states: from −2 to +6; however, the most common forms are the trivalent (III) and hexavalent (VI) forms. With regard to carcinogenicity, chromium III does not exhibit carcinogenicity in laboratory animals whereas chromium VI has been tested to be positive for genotoxicity and carcinogenicity in a variety of bioassays (Langard, 1988; IARC, 1990). Chromium VI compounds cause genetic damage including gene mutations and DNA damage in bacteria. Several chromium VI compounds also caused mutations in yeast and insects. Many chromium VI compounds caused genetic damage in cultured human and other animal cells and in experimental animals exposed in vivo, including SCE, chromosomal aberrations, and cell transformation. Chromosomal aberrations, SCE, and aneuploidy were observed in workers exposed to chromium VI compounds (IARC, 1990). Chromium VI (calcium chromate, chromium trioxide, sodium dichromate, lead chromates, strontium chromate, or zinc chromates) exposure in rats following inhalation, intrabronchial, intrapleural, intratracheal, intramuscular, or subcutaneous administration resulted in benign and malignant lung tumors in rats in a number of studies. In mice, calcium chromate caused benign lung tumors and chromium trioxide caused malignant lung tumors. Exposure of hamsters, guinea pigs, and rabbits to chromium VI compounds by intratracheal instillation did not cause lung tumors (IARC, 1980, 1990). While the mechanisms for chromium VI carcinogenicity remain unresolved, it has been speculated that the reduction of chromium VI by glutathione is involved (Connett and Whtterhahn, 1985; Kortenkamp and O'Brien, 1994).

Hexavalent chromium (chromium VI) compounds have been classified as known human carcinogens based on data from animal studies and human epidemiological studies. Human epidemiological studies have consistently reported increased risks of lung cancer among chromate workers. Chromate workers are exposed to a variety of chromium compounds, including chromium VI and trivalent (III) compounds. In addition, an increased risk of a rare cancer of the sinonasal cavity was observed in these workers (IARC, 1990). Some studies suggested that exposure to chromium among workers, such as chromium-exposed arc welders, chromate pigment workers, chrome platers, and chromium tanning workers, may be associated with leukemia and bone cancer (Costa, 1997).

Nickel Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, exhibit genotoxicity, producing DNA strand breaks, mutations, chromosomal damage, cell transformation, and modulation of DNA repair. Soluble nickel salts can be complete carcinogens and/or initiators of carcinogenesis (Kasprzak *et al.*, 1990; Diwan *et al.*, 1992). In rats and mice, inhalation or intratracheal instillation of nickel subsulfide or nickel oxide produced dose-related increases of benign and malignant lung tumors (IARC, 1990; NTP, 1996). Inhalation of nickel compounds also caused malignant and benign pheochromocytoma in rats (NTP, 1996). Short-term intraperitoneal exposure during gestation to soluble nickel salt induced malignant pituitary tumors in the offspring. Additionally, exposure to nickel acetate through the placenta followed by exposure of the offspring to barbital (a known tumor promoter) produces kidney tumors (renal cortical and pelvic tumors) (Diwan *et al.*, 1992). In adult rats, injection of soluble nickel salts followed by exposure to a promoting carcinogen resulted in kidney cancer (renal cortical