

Carcinogenicity of trace elements with reference to evaluations made by the International Agency for Research on Cancer

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BOFFETTA P. Carcinogenicity of trace elements with reference to evaluations made by the International Agency for Research on Cancer. *Scand J Work Environ Health* 1993;19 suppl 1:67-70. The monograph program of the International Agency for Research on Cancer has evaluated many trace elements for their carcinogenicity to humans. Five groups of compounds were considered human carcinogens: arsenic and arsenic compounds, beryllium and beryllium compounds, cadmium and cadmium compounds, hexavalent chromium compounds, and nickel compounds. Antimony trioxide, cobalt and cobalt compounds, lead and inorganic lead compounds, methylmercury compounds, and metallic nickel were considered possibly carcinogenic to humans. Antimony trisulfide, trivalent chromium compounds, metallic chromium, ferric oxide, organolead compounds, metallic mercury, inorganic mercury compounds, selenium and selenium compounds, and titanium dioxide were not classifiable. Trace elements studied to a limited extent include copper, manganese, tin, vanadium, and zinc. Among the problems are the lack of relevant data, the definition of active species, the extrapolation of the results of experimental studies to humans, the methodological problems of epidemiologic studies, and the possible anticarcinogenic activity of some trace elements.

Key terms: cancer, epidemiology, review.

This review considers the evidence of the carcinogenicity of the trace elements and related compounds that have been investigated in epidemiologic or long-term animal studies. Several compounds have been evaluated in the monograph program of the International Agency for Research on Cancer (IARC) (1). In this review, special emphasis is given to IARC monograph evaluations. For a few compounds, however, studies that have been published since the last IARC evaluation and that may be critical for a future reevaluation are briefly mentioned. For the trace elements that have not been considered by IARC, relevant data are mentioned, but no formal evaluation is proposed. Exposure to trace elements also occurs in several occupations and industries which have been evaluated by IARC (eg, iron and steel founding). However, these evaluations do not provide information on the carcinogenicity of specific trace elements, given the complex patterns of exposure encountered in such industries and occupations, and they are not reviewed in this article. Excluded from this review are also some organic compounds containing a trace element, for example, copper 8-hydroxyquinoline, a fungicide, and manganese ethylene bisdithiocarbamate, a pesticide.

Throughout the review, the standard IARC terminology has been used wherever possible, ie, expressions such as "sufficient evidence of carcinogenicity" or "limited evidence of carcinogenicity" refer to IARC evaluations. The IARC criteria used in the evaluation of carcinogenicity are defined in the preamble to the monograph volumes (1). Briefly, data on humans are reviewed and the evidence of carcinogenicity in humans is classified as (i) sufficient, when a causal association is established between exposure to an agent and human cancer, (ii) limited, when an association has been observed but chance, bias and confounding cannot be ruled out, or (iii) inadequate, when the data are of insufficient quality, consistency or statistical power to allow a conclusion. Similarly, the results of long-term experiments are reviewed, and the evidence of carcinogenicity in experimental animals is classified as sufficient, limited, or inadequate. Other data relevant to the evaluation of carcinogenicity are also taken into account (eg, short-term tests, data relevant to the mechanism of carcinogenic action).

The overall evaluation places the agent into one of the following four categories: group 1 (carcinogenic to humans), when the evidence in humans is sufficient; group 2A (probably carcinogenic to humans), mainly for experimental carcinogens with limited data on humans; group 2B (possibly carcinogenic to humans), mainly for experimental carcinogens with less than limited evidence from humans or agents with limited evidence from humans and less than sufficient evidence from animals; and group 3

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(not classifiable as to the carcinogenicity in humans) for agents that do not fall in any other category. It should be noted, however, that there may be exceptions and that it is also possible to classify an agent as probably not carcinogenic (group 4).

Methodological problems

A methodological problem in reviewing data on the carcinogenicity of trace elements is that of speciation. In many cases, data of sufficient quality are available only for a few compounds within a family (eg, a few salts of a metal), and these compounds may not be the most relevant in terms of human exposure. Epidemiologic studies carried out mainly in occupationally exposed populations are rarely able to separate the effects of exposure to individual chemicals within a family. Moreover, in many instances exposure to the chemicals of interest only occurs when they form part of a complex mixture containing known or suspected carcinogens (eg, exposure to cadmium and arsenic among smelters), and the effect of nonoccupational confounders, such as smoking, is seldom taken into account.

The use of data from long-term animal experiments may be problematic because of the questionable relevance of the route of exposure (eg, subcutaneous or intramuscular administration of metallic particles). The degree of solubility often influences the biological effects. Medium-term and short-term experimental studies are also taken into account in the IARC evaluations, but they have not been reviewed in detail in this article.

Table 1. IARC Evaluations made of the carcinogenicity of trace elements and related compounds to humans by the International Agency for Research on Cancer (IARC) (1).

Trace element	Chemical or group of chemicals	Evaluation ^a
Sb	Antimony trioxide	2B
	Antimony trisulfide	3
As	Arsenic and arsenic compounds	1 ^b
Be	Beryllium and beryllium compounds	1
Cd	Cadmium and cadmium compounds	1
Cr	Hexavalent chromium compounds	1
	Trivalent chromium compounds	3
	Metallic chromium	3
Co	Cobalt and cobalt compounds	2B
Fl	Inorganic fluorides used in drinking water	3
Fe	Ferric oxide	3
	Hematite	3
Pb	Inorganic lead compounds	2B
	Organolead compounds	3
Hg	Methylmercury compounds	2B
	Metallic mercury	3
	Inorganic mercury compounds	3
Ni	Nickel compounds	1
	Metallic nickel	2B
Pl	Cisplatin	2A
Se	Selenium and selenium compounds	3
Ti	Titanium dioxide	3

^a 1: carcinogenic to humans, 2A: probably carcinogenic to humans, 2B: possibly carcinogenic to humans, 3: not classifiable as to carcinogenicity to humans. Details on the classification are available in the preamble of the volumes of the IARC monograph series (1).

^b The evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.

In a few cases, data on the mechanism of carcinogenesis are available, such as studies on deoxyribonucleic acid (DNA) or protein adducts. Although studies of these types may provide additional evidence, it is inadvisable to reach conclusions as to the carcinogenicity of a compound solely on the basis of such results.

There is both human and experimental evidence that some trace elements (eg, selenium, zinc) may have anticarcinogenic activity. No formal evaluation of anticarcinogenic activity is made by IARC. Although the trace elements for which anticarcinogenic activity has been suggested are not established carcinogens, some data indicating the possibility of a carcinogenic effect have been reported. Currently no one knows how the evidence of concomitant carcinogenic and anticarcinogenic effects should be evaluated.

Carcinogenicity of trace elements

Table 1 shows the IARC evaluations of the carcinogenicity of trace elements and related compounds.

Only two *antimony* compounds have been studied in animals. Antimony trioxide is carcinogenic in experimental animals, whereas, for antimony trisulfide, there is only limited evidence of carcinogenicity. No adequate data are available on humans (2).

Arsenic and arsenic compounds are carcinogenic to humans. The evidence comes mainly from studies showing an increase in skin cancer among patients treated with inorganic trivalent arsenic compounds, skin (and possibly other) cancer from exposure to drinking water containing high concentrations of arsenic, and cancer, mainly of the lung, from occupational exposure to inorganic arsenic compounds in mining and copper smelting. According to studies of intratracheal instillation in hamsters and rats, perinatal exposure of mice (lung adenomas), and stomach implantation in rats (3), there is limited evidence of carcinogenicity in animals.

There is sufficient evidence of the carcinogenicity of *beryllium and several beryllium compounds* in experimental animals from the results of inhalation and intratracheal studies on rats, intrabronchial studies on monkeys, and intravenous or intramedullary administration to rabbits. Results for two industrial cohorts and one study of a register of berylliosis cases showed an increased risk of lung cancer, and therefore IARC has evaluated beryllium as having sufficient evidence of carcinogenicity in humans (4).

Cadmium and cadmium compounds are carcinogenic in experimental animals. They cause neoplasms in rats after subcutaneous, intramuscular, and intraprostatic injection. Cadmium chloride causes respiratory tumors in rats by inhalation, but it is not carcinogenic when given in the diet of rats. Epidemiologic studies are available on nickel-cadmium bat-

tery workers and metal smelting workers. These studies had inconsistent results regarding the risk of prostate and kidney cancer but showed an increased risk of lung cancer that could not be explained by a confounding effect of smoking or exposure to other metals (5, 6).

Chromium and chromium compounds have been extensively studied. There is sufficient evidence for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate, and lead chromates in experimental animals, but only limited evidence of carcinogenicity for other hexavalent chromium compounds, and inadequate evidence for barium chromate, metallic chromium, and trivalent chromium compounds. In humans, hexavalent chromium compounds, as encountered in chromate production, chromate pigment production, and chromium plating industries, cause cancer of the lung, nose, and nasal sinuses. The evidence for the carcinogenicity of metallic chromium and trivalent chromium compounds in humans is inadequate. IARC concluded from the evaluation that hexavalent chromium ions generated at critical sites are responsible for the carcinogenic action (7).

The carcinogenicity of *cobalt and several cobalt compounds* has been studied in experimental animals. Metallic cobalt and bivalent cobalt oxide are carcinogenic in rats and produce sarcomas at the injection site. There is limited evidence of the carcinogenicity of cobalt-containing metal alloys, bivalent cobalt sulfide, and bivalent cobalt chloride after subcutaneous or intramuscular administration and inadequate evidence of carcinogenicity for bivalent and trivalent cobalt oxide, cobalt naphthenate, and trivalent cobalt acetate. For humans, there is a suggestion of an increased risk of sarcomas and blood neoplasms in patients after the implantation of cobalt-containing prostheses. Two cohort studies of electrochemical and hard-metal workers suggested an increased risk of lung cancer (8).

No human data are available on the carcinogenicity of *copper and copper compounds*. Local tumors were produced at the site of injection of copper chloride and copper sulfate. Negative results with metallic copper, copper acetate, and copper sulfide have been reported (9).

Correlation studies in human populations exposed to different levels of inorganic *fluorides* in drinking water, and studies in areas before and after fluoridation did not show any consistent excess of any type of tumor. However, these studies were not considered to be of sufficient quality to enable the compounds to be classified as probably not carcinogenic. Data on experimental animals are inadequate (3). Recently, a cohort study of fluoride-exposed workers suggested an increased risk of respiratory and urinary cancers (10).

Studies on workers exposed to ferric oxide gave inconsistent results, whereas experimental studies suggested that the compound was not carcinogenic

(3). Although underground hematite mining involving exposure to radon is carcinogenic, surface hematite mining and mining with low exposure to radon and silica were not associated with an increased risk of cancer (3). Two epidemiologic studies suggested an increased risk of cancer associated with a high iron body burden (11, 12).

The cancer risk from exposure to *lead and inorganic lead compounds* has been studied in smelter and battery workers. There is a suggestion of an increased risk of lung, stomach, kidney, and bladder cancer, but the results are not consistent and thus provide inadequate evidence of carcinogenicity in humans. Lead acetate, lead subacetate, and lead phosphate cause tumors in the kidneys of rats and, to a less extent, in the kidneys of mice. Data on the carcinogenicity of metallic lead, lead oxide, and organolead compounds are inadequate (3).

There are no adequate data on humans exposed to *manganese and manganese compounds*. Metallic manganese caused tumors after intraperitoneal administration in one study (9).

Limited epidemiologic data suggest a possible increase in lung, brain, and kidney tumors among dentists, disinfectant applicators, miners, chloralkali workers, and nuclear weapon workers exposed to *mercury and mercury compounds*, but the evidence is currently inadequate (13, 14). Mercury chloride showed some carcinogenic activity in the kidney of male rats. However the evidence for female rats and male mice was equivocal, and no evidence of carcinogenicity was found in female mice. Methylmercury chloride is carcinogenic in male mice (13, 14).

The evidence for the carcinogenicity of *nickel compounds* in humans comes from studies of workers employed in the high-temperature oxidation of nickel matte and nickel-copper matte, in electrolytic refining, in copper plants, and in the extraction of nickel salts in the hydrometallurgic industry. The highest risk of lung and nasal cancer was found among nickel refinery workers exposed to nickel sulfate and to combinations of nickel sulfides and oxides. There is inadequate evidence of the carcinogenicity of metallic nickel and nickel alloys in humans. Metallic nickel, nickel monoxides, nickel hydroxides, and crystalline nickel sulfides are carcinogenic in experimental animals. The evidence for the carcinogenicity of other nickel compounds in experimental animals is limited (nickel alloys, nickel carbonyl, nickel arsenides, nickel antimonide, nickel selenides, nickel telluride) or inadequate (nickel trioxide, amorphous nickel sulfide, nickel titanate). In the IARC evaluation, nickel compounds were considered to generate nickel ions at critical target sites during the carcinogenic process (15).

The only *platinum compound* for which data are available is cisplatin, a drug used in chemotherapy. It causes leukemia in rats and lung and skin tumors in mice, but the available studies on humans were

not able to separate the effect of cisplatin from that of other such drugs (3).

Selenium and selenium compounds were evaluated by IARC in 1975 (16). At that time, there was inadequate evidence of carcinogenicity in experimental animals and no convincing evidence of a protective effect in humans. Since then, studies have suggested an anticarcinogenic effect in both humans and experimental animals (17).

Inorganic *tin* and stannous chloride were negative in experimental studies (18). An increased risk of lung cancer among tin miners is attributed to concomitant exposure to arsenic and radon (19). No other data are available on humans.

Titanium dioxide is carcinogenic by inhalation in rats but does not cause an increase in tumors in rodents by other routes of administration (20). Local sarcomas are produced after intramuscular injection of metallic titanium or titanocene (18). No data are available on humans.

Negative experimental studies are available for metallic vanadium, vanadyl ions, and trivalent vanadium 2,4-pentanedione. No data on humans exposed to *vanadium and its compounds* are available (18).

Intratesticular injection of *zinc* chloride and zinc sulfate caused local tumors in rodents (9).

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