

Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy



In March, 2022, a Working Group of 31 scientists from 13 countries met remotely at the invitation of the International Agency for Research on Cancer (IARC) to finalise their evaluation of the carcinogenicity of nine agents: cobalt metal (without tungsten carbide or other metal alloys), soluble cobalt(II) salts, cobalt(II) oxide, cobalt(II,III) oxide, cobalt(II) sulfide, other cobalt(II) compounds, trivalent antimony, pentavalent antimony, and weapons-grade tungsten (with nickel and cobalt) alloy. For cobalt metal and the cobalt compounds, particles of all sizes were included in the evaluation. These assessments will be published in Volume 131 of the *IARC Monographs*.¹

Cobalt metal and soluble cobalt(II) salts were classified as “probably carcinogenic to humans” (Group 2A) based on “sufficient” evidence for cancer in experimental animals and “strong” mechanistic evidence in human primary cells. Cobalt(II) oxide and weapons-grade tungsten alloy were classified as “possibly carcinogenic to humans” (Group 2B) based on “sufficient” evidence in experimental animals. Trivalent antimony was classified as “probably carcinogenic to humans” (Group 2A), based on “limited” evidence for cancer in humans, “sufficient” evidence for cancer in experimental animals, and “strong” mechanistic evidence in human primary cells and in experimental systems. Cobalt(II,III) oxide, cobalt(II) sulfide, other cobalt(II) compounds, and pentavalent antimony were each evaluated as “not classifiable as to its carcinogenicity to humans” (Group 3).

Cobalt is used in many industries, including in the manufacture of cutting and grinding tools, in pigments and paints, coloured glass, medical implants, electroplating, and increasingly in lithium-ion battery production. Occupational

exposure to cobalt is expected to occur predominantly during refining of cobalt, production of cobalt metal, cobalt compounds, and dental materials, use of diamond-cobalt tools, plate painting with cobalt pigments, manufacture of nickel–hydrogen batteries, hard-metal production, and electronic waste recycling. Workers can be exposed to various cobalt compounds and metal powders mainly through inhalation, but also by skin or ingestion routes. For the general population, food is usually the primary source of cobalt exposure; exposure can also occur via ambient air, tobacco smoke, and medical implants.

The Working Group concluded that there was “inadequate” evidence regarding cancer in humans for cobalt metal (without tungsten carbide or other metal alloys) and for cobalt(II) and (II,III) compounds. The available studies did not permit the separation of cobalt’s effects from those of the cobalt–tungsten carbide composite or other confounding exposures, or did not show positive associations.

The evidence for cancer in experimental animals was “sufficient” for cobalt metal, for soluble cobalt(II) salts, and for cobalt(II) oxide. In two Good Laboratory Practice (GLP) studies² in mice and rats, inhaled cobalt metal caused bronchioloalveolar carcinoma in male and female mice; bronchioloalveolar carcinoma, and malignant pheochromocytoma of the adrenal medulla in male and female rats; pancreatic islet carcinoma in male rats; and leukaemia in female rats. In two GLP studies in mice and rats, inhaled cobalt(II) sulfate caused bronchioloalveolar carcinoma in male and female mice; bronchioloalveolar tumours in male rats; and bronchioloalveolar carcinoma, and adrenal medulla tumours in female rats. In addition, subcutaneous injection of cobalt(II) chloride

caused local fibrosarcomas in one study in rats. Cobalt(II) oxide caused lung tumours in one intratracheal instillation study, and malignant tumours at the injection site in one intraperitoneal, one subcutaneous, and two intramuscular injection studies in rats. Evidence regarding cancer in experimental animals was “limited” for cobalt(II) sulfide, and “inadequate” for cobalt(II,III) oxide and for other cobalt(II) compounds.

The mechanistic evidence for both cobalt metal and soluble cobalt(II) salts was “strong” in human primary cells and in experimental systems for genotoxicity. Multiple studies in human primary cells showed that cobalt metal and cobalt(II) salts increased DNA strand breaks, chromosomal aberrations, micronucleus formation, or sister-chromatid exchanges. The evidence for cobalt metal was also “strong” in human primary cells and experimental systems for oxidative stress, and in experimental systems for chronic inflammation and alterations in cell proliferation, cell death, or nutrient supply. The mechanistic evidence for cobalt(II) salts was also “strong” in human primary cells and experimental systems for alterations in cell proliferation, cell death, or nutrient supply, and in experimental systems for oxidative stress, chronic inflammation, and immunosuppression. In multiple studies with human primary cells, cobalt(II) salts increased cell viability or proliferation, or the expression of vascular endothelial growth factor. The mechanistic evidence was “limited” for cobalt(II) and cobalt(II,III) oxides, and “inadequate” for cobalt(II) sulfide and other cobalt(II) compounds.

Antimony is used mainly in flame retardants, lead-acid batteries, lead alloys, plastics, brake pads, clutch discs, glass and ceramics, and as an ammunition primer in explosives. Some

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Declaration of interests

All Working Group Members declare no competing interests.

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None

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Declaration of interests

CJB has served as a consultant on human health issues to the International Antimony Association, the Nickel Producers Environmental Research

Association, and the Cobalt Development Institute. SB reports employment by NiPERA. RLO has been the HSE Director of the International Tungsten Industry Association (ITIA) since February, 2013, and as part of this work RLO provides expert opinions as part of regulatory processes and receives travel costs from ITIA when applicable. VV reports contract of employment by, and research funding from, Cobalt Institute and Cobalt Reach Consortium.

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All IARC Secretariat declare no competing interests.

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pentavalent antimony compounds are used in the treatment of leishmaniasis. Industrial workers can be exposed to multiple antimony compounds, mainly by inhalation, during smelting, production of antimony compounds, manufacture of glass, textiles, and batteries, and electronic processing and electrical waste processing. Non-occupational exposures, which occur via contaminated water, air, and soil, and use of consumer products and tobacco, are typically lower than occupational exposures.

Four occupational studies and ten general-population studies investigated the association between antimony exposure and cancer risk. For cancer in humans, the Working Group concluded that there was “limited” evidence for lung cancer. Evidence of positive associations with trivalent antimony exposure was observed in three cohort studies among antimony^{3,4} and tin⁵ smelter workers. One study of antimony smelter workers³ found elevated standardised mortality ratios (SMRs) for lung cancer by job group of antimony workers, early period of hire, and latency from first exposure. Another⁴ found elevated SMRs using ethnicity-specific reference rates and a positive trend in lung cancer risk with increasing duration of exposure (SMR 2.73 [95% CI 1.33–5.01] for >10 years employment). A study of tin smelter workers⁵ found positive trends in risk with increasing cumulative antimony exposure. Overall, the Working Group concluded that a causal association between exposure to trivalent antimony and lung cancer was plausible; however, in view of potential confounding due to co-exposure to arsenic and other lung carcinogens in smelting processes, bias could not be ruled out with reasonable confidence. Evidence for other cancer types was found to be “inadequate”: studies were considered only minimally informative, too few in number, or without consistent evidence to contribute to the evaluation.

The evidence for cancer in experimental animals was “sufficient” for

antimony trioxide. In two GLP studies⁶ in rodents, inhalation exposure caused bronchioloalveolar carcinoma in male and female mice; fibrous histiocytoma and fibrosarcoma of the skin in male mice; lymphoma in female mice; and lung and adrenal medulla tumours in female rats.

The mechanistic evidence for trivalent antimony was “strong” in human primary cells for genotoxicity, and in experimental systems for oxidative stress, chronic inflammation, and alterations in cell proliferation, cell death, or nutrient supply. Multiple studies in human primary cells showed that trivalent antimony increased DNA damage, chromosomal aberrations, micronucleus formation, or sister-chromatid exchanges.

For pentavalent antimony, evidence regarding cancer in humans and cancer in experimental animals was “inadequate”, since no data were available to the Working Group. The mechanistic evidence for pentavalent antimony was “limited”.

Weapons-grade tungsten alloys (91–93% tungsten, 3–5% nickel, and 2–4% cobalt) are used in armour-penetrating munitions. Occupational exposure can occur by inhalation during the production of munitions. Military personnel and civilians can be exposed to metal aerosols generated during munitions firing or impact. Munitions-related injuries with retained embedded fragments can lead to long-term exposure. Exposure data were sparse. The evidence for cancer in experimental animals was “sufficient” because intramuscular implantation of weapons-grade tungsten alloy caused rhabdomyosarcoma at the implantation site in two rat⁷ and one mouse⁸ studies. No human cancer studies were available to the Working Group, and the mechanistic evidence was “limited”.

We declare no competing interests.

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