



COBALT, ANTIMONY COMPOUNDS, AND WEAPONS-GRADE TUNGSTEN ALLOY

VOLUME 131

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met remotely, 2–18 March 2022

LYON, FRANCE - 2023

IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS

GENERAL REMARKS

This one-hundred-and-thirty-first volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of 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 oxides, particles of all sizes were included in the evaluation. Due to the coronavirus disease (COVID-19) pandemic, this meeting was held remotely.

Cobalt and cobalt compounds were most recently evaluated by the *IARC Monographs* programme in 2006 ([IARC, 2006](#)). Cobalt metal without tungsten carbide, as well as cobalt sulfate and other soluble cobalt(II) salts were classified as *possibly carcinogenic to humans (Group 2B)*. Metallic cobalt with tungsten carbide (used in the hard-metal industry) was classified as *probably carcinogenic to humans (Group 2A)*. Different cobalt-based alloys were evaluated by the *IARC Monographs* programme in 1999 ([IARC, 1999](#)). Implanted foreign bodies of cobalt-based alloys were evaluated as *not classifiable as to their carcinogenicity to humans (Group 3)* ([IARC, 1999](#)). Antimony trioxide (Sb₂O₃) was previously evaluated as *possibly carcinogenic to humans (Group 2B)* ([IARC, 1989a](#)). Two of these agents – pentavalent antimony and weapons-grade tungsten (with nickel and cobalt) alloy – were evaluated by the Working Group for the first time.

The Advisory Group to Recommend Priorities for the *IARC Monographs* that met in 2019 recommended that cobalt and cobalt compounds, and weapons-grade tungsten (with nickel and cobalt) alloy be evaluated with high priority; and

antimony trioxide with medium priority ([IARC, 2019a](#); [Marques et al., 2019](#)). A summary of the findings of this volume appears in *The Lancet Oncology* ([Karagas et al., 2022](#)).

The history of cobalt classification by the *IARC Monographs* programme

The *IARC Monographs* programme was originally due to consider cobalt at the meeting for Volume 49 (Chromium, nickel, and welding) in 1989; however, during the preparation of that meeting, it was decided the time available was insufficient to consider this topic adequately. In 1991, for Volume 52, the Working Group considered metallic cobalt, cobalt alloys (including cobalt-containing medical implants), and cobalt compounds (but not organic cobalt-containing agents such as vitamin B₁₂) ([IARC, 1991](#)). At this time, the evidence for the carcinogenicity of cobalt and cobalt compounds in humans was found to be *inadequate*, and the evaluation

was based mainly on the results of studies in experimental animals, with *sufficient* evidence for the carcinogenicity of cobalt metal powder and cobalt(II) oxide, and *limited* evidence for cobalt(II) chloride and metal alloys containing cobalt, chromium, and molybdenum. The overall evaluation was that cobalt and cobalt compounds were *possibly carcinogenic to humans (Group 2B)*.

Cobalt was subsequently evaluated as a component of metallic implants and foreign bodies for Volume 74 (Surgical implants and other foreign bodies) in 1999 ([IARC, 1999](#)). At that time there was *inadequate* evidence for the carcinogenicity of metallic implants and metallic foreign bodies in humans. In experimental animals, there was *sufficient* evidence for the carcinogenicity of implants of metallic cobalt, metallic nickel, and nickel alloy powder containing approximately 66–67% nickel, 13–16% chromium, and 7% iron (which were classified as Group 2B, *possibly carcinogenic to humans*), and *limited* evidence for the carcinogenicity of implants of alloys containing cobalt and alloys containing nickel, other than the specific aforementioned alloy. Overall, orthopaedic implants of complex composition and cardiac pacemakers were each evaluated as *not classifiable as to its carcinogenicity to humans (Group 3)*.

By Volume 86 (Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide, and vanadium pentoxide) ([IARC, 2006](#)), the *IARC Monographs* programme was able to evaluate cobalt in hard metals (with or without tungsten carbide) because of the availability of new epidemiology studies on workers in the hard-metal production industry. The evaluation of cobalt sulfate was updated because a new inhalation bioassay on cobalt sulfate heptahydrate had become available. The Working Group found that the evidence for cancer in humans was *limited* for cobalt metal with tungsten carbide and *inadequate* for cobalt metal without tungsten carbide. In experimental animals, there

was *sufficient* evidence for cobalt sulfate and cobalt metal powder, and *limited* evidence for metal alloys containing cobalt. Overall, cobalt metal with tungsten carbide was evaluated as *probably carcinogenic to humans (Group 2A)*, whereas cobalt metal without tungsten carbide was *possibly carcinogenic to humans (Group 2B)*. Cobalt sulfate and other soluble cobalt(II) salts were *possibly carcinogenic to humans (Group 2B)*.

For the present volume, new evidence on cobalt was available in the form of bioassay and mechanistic data and new epidemiological studies of cobalt exposure without tungsten carbide in occupational cohorts and the general population. The Working Group elected not to re-evaluate cobalt metal with tungsten carbide because of a lack of new informative studies that could have changed the classification ([IARC, 2019a](#)).

Evaluation of trivalent and pentavalent antimony

In the present volume, the Working Group evaluated trivalent antimony and pentavalent antimony separately. There were some data suggesting that there is interconversion of pentavalent antimony and trivalent antimony, but this was overall considered to be an evidence gap. In humans given a single intramuscular injection, about 23.3% of the administered pentavalent antimony compound was reduced to trivalent antimony in the blood ([Vásquez et al., 2006](#)). In monkeys given repeated intramuscular injections of a pentavalent antimony compound, the proportion of trivalent antimony in the plasma increased from 5% to 50% between day 1 and day 9 ([Friedrich et al., 2012](#)). In experimental systems, *in vitro* reduction occurred in the presence of glutathione, cysteine, or cysteinyl-glycine ([Frézard et al., 2001](#)). The valence state of

antimony also affects its distribution and excretion ([NTP, 2018](#)).

The Working Group noted differences in the genotoxic effects induced by the two valent forms. There was consistent and coherent evidence in human primary cells in multiple studies and in human cell lines that trivalent antimony induces DNA damage, chromosomal aberrations, micronucleus formation, and/or increased frequency of sister-chromatid exchange ([Paton & Allison, 1972](#); [Gebel et al., 1997](#); [Elliott et al., 1998](#)); however, the findings for genotoxicity were mixed in mice and rats. For pentavalent antimony, the results were mixed in human primary cells ([Migliore et al., 1999](#); [Lima et al., 2010](#)), but consistent in mice. Pentavalent antimony induced DNA damage and micronucleus formation in mice exposed by intraperitoneal injection in several studies ([Lima et al., 2010](#); [Cantanhêde et al., 2015](#); [Moreira et al., 2017](#); [de Jesus et al., 2018](#)).

Considering that the standard treatment for leishmaniasis in humans involves the administration of pentavalent antimony compounds and that there is suggestive evidence that these pentavalent forms exhibit key characteristics of carcinogens, the Working Group concluded that it was important to evaluate pentavalent antimony and trivalent antimony separately.

Exposure data for cobalt and antimony

Identification of the agent

While chemical names may be reported as a “synonym” of a particular agent, such reporting may not always be accurate, and relevant papers may be silent on characterizations, such as speciation, particle size, or trace element impurities that may be critical to informing understanding of the reactivity or toxicity of the agent within

the product or of the product overall ([Gaultieri, 2017](#)). In studies of human exposure, many of the analytical methods used quantified total cobalt, and did not allow for the identification of different species or types of compound. This is particularly relevant to occupational settings and where exposures are mainly through inhalation of airborne particles. Similarly, the Working Group noted that most of the available data on antimony exposure of the general population consisted of measurements of total antimony concentrations (e.g. in urine), which reflect exposure to any of the individual compounds within the scope of this evaluation. For population-based studies, without information on the exposure source, it is difficult to attribute total antimony concentrations to a particular agent.

Paucity and representativeness of the data

The data on exposure reported in this volume may not be fully comprehensive of industries and exposure contexts in which cobalt and antimony are currently being used. While several publications reported antimony concentrations in the environment (soil, sediment, water including drinking-water, and food), few quantitative data were available on occupational exposure in mining. There has been increasing use of cobalt in battery manufacture in recent years. However, there is lack of data on cobalt exposure in the battery-manufacturing or electroplating industries.

There are data indicating that mining and refining of both cobalt and antimony are widespread throughout the world, but few exposure or epidemiology studies were available in these contexts.

Few data were available on exposure to nanoparticles. Many studies in humans did not provide details on the size distribution of particulate exposures. The use of biological samples,

as was the case in many studies, cannot provide insight into this.

There was sparse information available to the Working Group on the role of ingestion resulting from hand-to-mouth contact as an exposure route in the workplace.

Geographical and sociodemographic aspects

People with low incomes are more likely to live in polluted areas and be exposed to unsafe food, drinking-water, and consumer products ([Vaccarella et al., 2019](#)). However, few data were available on cobalt exposure in different socio-economic strata. There is a particularly notable gap in exposure data among children and elderly people, who may be at higher risk of health problems related to pollutants.

Exposure data for weapons-grade tungsten (with nickel and cobalt) alloy

Few exposure data for this alloy were available to the Working Group. The information on current and historical use of the alloy within munitions around the world is also sparse. This leads to challenges in identifying groups of people who may potentially be exposed during production, combat, or training. Exposure assessment data, where available, are often limited to measuring the concentrations of each individual element contained in the alloy.

The Working Group also noted that there was little information available on the relative concentrations of the tungsten, nickel, and cobalt metals and metallic species involved in exposure to the alloy.

Lack of epidemiological studies in low- and middle-income countries

The Working Group noted a lack of epidemiological studies available from low- and middle-income countries, where personal safety measures and working environments may be different from those in high-income countries.

There was also a lack of epidemiological studies of workers involved in mining activities and of those environmentally exposed from mining operations. In certain parts of the world, such as in the African Copperbelt, there are a few studies suggesting that people may be occupationally and environmentally exposed to elevated levels of cobalt. However, although a few biomonitoring surveys have indicated elevated cobalt concentrations in biological specimens collected from workers at some mining sites, the Working Group was unable to identify cancer epidemiology studies or mechanistic studies in humans in these places.

Other issues with epidemiological studies

The epidemiological studies evaluated in the present volume were largely occupational studies of workers exposed to cobalt metal and to trivalent antimony. Studies of the general population reported on concentrations of biomarkers of exposure to cobalt and antimony, including in the urine, plasma, and toenail clippings, without specification of chemical form. Levels in urine and plasma represent relatively short-term biomarkers, whereas levels in toenails generally reflect exposure in the previous 3–12 months. The reliability of these markers (i.e. in comparison with other measures) has been studied to a limited extent, and scant data were available on the reproducibility of these measures over time.

Two studies included in this volume suggest that toenail clipping measurements in women are correlated with exposure to cobalt over a period of several years ([Garland et al., 1993](#); [O'Brien et al., 2019](#)).

Some of the available population-based studies had limited statistical power due to the narrow (and vastly lower) range of exposure compared with that in occupational studies. It was not possible to assess the role of dietary exposures in any of the cancer epidemiology studies.

For epidemiological studies of cobalt metal in the hard-metal industry, the main challenge was intractable confounding by co-exposure to the composite material, cobalt with tungsten carbide.

Role of nanoparticles in cancer pathology

Regular exposure to airborne particles is known to cause cancer (e.g. [IARC, 2015](#)). Most of the effects of nanoparticles are long-term and difficult to discern from those of microparticles. There is an arbitrary and loose definition of nano-dimensionality, which is usually that one dimension of the particle should measure less than 100 nm (or 0.1 μm). Microparticles are particles with a size ranging from about 1 to 1000 μm . Microparticles and nanoparticles may be either natural or man-made. For any given particle exposure setting, determining which is the dominant mechanism of tissue damage that could potentially lead to carcinogenesis may be challenging. The inhalation of microparticles and nanoparticles is associated with reactive changes (i.e. inflammation) in the epithelium of the upper respiratory tract (microparticles) and alveolar changes in the epithelium of the lower respiratory tract (nanoparticles and respirable microparticles). Pro-inflammatory signalling, inflammasome activation, and modulation of

programmed cell death are topics of intense research at the present time. It has been proved that inert particles in a large range of sizes (with a diameter of more than 50 nm to micron-sized particles) can convey therapeutic antigens and become ensnared in the airways ([Morris et al., 2017](#); [Jalikus & Reyes Gil, 2019](#); [Mishra & Singh, 2020](#); [Singhvi et al., 2020](#)). In conclusion, nano-particle size-dependent effects will need to be addressed in detail in future monographs on particles, as far as the available studies on nanoparticles will allow, as noted in the Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 ([IARC, 2019a](#)).

Data from high-throughput screening assays

The analysis of the in vitro bioactivity of the evaluated agents was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA ([Thomas et al., 2018](#)).

The compound cobalt(II) sulfate heptahydrate was considered active in small numbers of assay end-points mapped to two key characteristics of carcinogens ([Smith et al., 2016](#)): “induces oxidative stress” (two assays), and “modulates receptor-mediated effects” (one assay). The four antimony(III) compounds, including acetic acid, antimony(III) salt; antimony(III) potassium tartrate trihydrate; antimony(III) trichloride; and antimony(III) potassium tartrate hydrate, were tested in assays mapped to the key characteristics “is genotoxic”, “induces oxidative stress”, “modulates receptor-mediated effects”, and “alters cell proliferation, cell death, or nutrient supply”. The results were considered uninformative, except for the key characteristic “modulates

receptor-mediated effects”. The antimony(IV) compounds and antimony(V) sulfide were inactive for any key characteristic, while the results for antimony(V) compounds were uninformative for all key characteristics.

The results were generated with the software “kc-hits” (key characteristics of carcinogens – high-throughput screening discovery tool) (available from: <https://gitlab.com/i1650/kc-hits>; Reisfeld et al., 2022). The mapping of assay end-points to each key characteristic follows that described in *IARC Monographs* Volume 123 (IARC, 2019b). All ToxCast/Tox21 data were obtained from the United States Environmental Protection Agency CompTox Chemicals Dashboard 10th Release (US EPA, 2022) at the time of the evaluations performed for the *IARC Monographs* Volume 131 in March 2022. These programmes are constantly being improved and new assays are added over time. However, at present, the general lack of metabolic activation and the small number of genotoxicity assays in these high-throughput screening programmes restrict their value in determining whether a chemical is genotoxic as part of an assessment of carcinogenicity.

Scope of systematic review

Standardized searches of the PubMed database (NCBI, 2021) were conducted for each agent and for each outcome (cancer in humans, cancer in experimental animals, and mechanistic evidence, including the key characteristics of carcinogens). The literature trees for the agent, including the full set of search terms for the agent name and each outcome type, are available online.¹

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¹ The literature trees for the present volume are available at: <https://hawcproject.iarc.who.int/assessment/678/> (cobalt and cobalt compounds), <https://hawcproject.iarc.who.int/assessment/673/> (trivalent and pentavalent antimony), <https://hawcproject.iarc.who.int/assessment/677/> (weapons-grade tungsten (with nickel and cobalt) alloy).

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