International Agency for Research on Cancer

World Health Organization

7 April 2022

IARC Monographs evaluate the carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy

Questions and Answers (Q&A)

The meeting for *IARC Monographs* Volume 131: Cobalt, Antimony Compounds, and Weapons-Grade Tungsten Alloy, convened by the International Agency for Research on Cancer (IARC) and held remotely due to the coronavirus disease (COVID-19) pandemic, took place on 2–18 March 2022.

The Working Group of international experts, including 31 scientists from 13 countries, evaluated the carcinogenicity 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.

More information about the meeting is available on the *IARC Monographs* website: https://monographs.iarc.who.int/iarc-monographs-volume-131/.

The outcome of the assessment has been published in a summary article in *The Lancet Oncology*[1] and will be described in detail in Volume 131 of the *IARC Monographs*, to be published in early 2023.

1. What are the results of the evaluation?

Cobalt metal (without tungsten carbide or other metal alloys) and **soluble cobalt(II) salts** were classified as *probably carcinogenic to humans* (Group 2A) on the basis of *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence (related to key characteristics of carcinogens in human primary cells and in experimental systems). There was *inadequate* evidence regarding cancer in humans.

Cobalt(II) oxide was classified as *possibly carcinogenic to humans* (Group 2B) on the basis of *sufficient* evidence for cancer in experimental animals. There was *limited* mechanistic evidence and *inadequate* evidence regarding cancer in humans.

Cobalt(II,III) oxide was *not classifiable as to its carcinogenicity to humans* (Group 3). There was *inadequate* evidence regarding cancer in humans and in experimental animals and *limited* mechanistic evidence.

Cobalt(II) sulfide was *not classifiable as to its carcinogenicity to humans* (Group 3). There was *limited* evidence for cancer in experimental animals, *inadequate* evidence regarding cancer in humans, and *inadequate* mechanistic evidence.

[1] Karagas MR, Wang A, Dorman DC, Hall AL, Pi J, Sergi CM, et al. (2022). Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy. *Lancet Oncol*, Published online 7 April 2022; https://doi.org/S1470-2045(22)00219-4

Other cobalt(II) compounds were *not classifiable as to their carcinogenicity to humans* (Group 3). There was *inadequate* evidence regarding cancer in humans and in experimental animals and *inadequate* mechanistic evidence.

For cobalt metal, cobalt oxides, and cobalt sulfide, particles of all sizes were included in the evaluation.

Trivalent antimony was classified as *probably carcinogenic to humans* (Group 2A) on the basis of *limited* evidence for cancer in humans (for cancer of the lung), *sufficient* evidence for cancer in experimental animals, and *strong* mechanistic evidence (related to key characteristics of carcinogens in human primary cells and in experimental systems).

Pentavalent antimony was *not classifiable as to its carcinogenicity to humans* (Group 3). There was *inadequate* evidence regarding cancer in humans and in experimental animals and *limited* mechanistic evidence.

Weapons-grade tungsten (with nickel and cobalt) alloy was classified as *possibly carcinogenic to humans* (Group 2B) on the basis of *sufficient* evidence for cancer in experimental animals. There was *limited* mechanistic evidence and *inadequate* evidence regarding cancer in humans.

Table 1 Summary of classifications in *IARC Monographs* Volume 131

Chemical	Evidence stream			Overall evaluation
	Cancer in humans	Cancer in experimental animals	Mechanistic evidence (key characteristics of carcinogens)	
Cobalt metal[a]	Inadequate	Sufficient	Strong – human primary cells	2A
Soluble cobalt(II) salts	Inadequate	Sufficient	Strong – human primary cells	2A
Cobalt(II) oxide	Inadequate	Sufficient	Limited	2B
Cobalt(II,III) oxide	Inadequate	Inadequate	Limited	3
Cobalt(II) sulfide	Inadequate	Limited	Inadequate	3
Other cobalt(II) compounds	Inadequate	Inadequate	Inadequate	3
Trivalent antimony	Limited (lung)	Sufficient	Strong – human primary cells	2A
Pentavalent antimony	Inadequate	Inadequate	Limited	3
Weapons-grade tungsten (with nickel and cobalt) alloy	Inadequate	Sufficient	Limited	2B

[a] Without tungsten carbide or other metal alloys

2. Have these agents previously been evaluated by the *IARC Monographs* programme?

Agents previously evaluated by the *IARC Monographs* programme:

Cobalt metal without tungsten carbide: Group 2B (2003)

Soluble cobalt salts: Group 2B (2003)

Other cobalt(II) compounds: Group 2B (1990)

Trivalent antimony: Group 2B for antimony trioxide (1989); WHO Guideline for drinking-water quality (WHO GDWQ, 2003) tolerable daily intake (TDI) for antimony of 6 µg/kg of body weight

Agents never previously evaluated by the *IARC Monographs* programme:

Pentavalent antimony

Weapons-grade tungsten (with nickel and cobalt) alloy

3. Who is exposed to these agents, and how?

Cobalt is produced mainly as a by-product of the mining and processing of the ores of other metals. Globally, mining and refinery production of cobalt have increased steadily over the past two decades. Cobalt is used in many industries, including in the manufacture of cutting and grinding tools, in pigments and paints, coloured glass, medical implants, batteries, and electroplating.

Occupational exposure can occur during production of hard metal and cobalt powder, use of cobalt-containing pigments and driers, and production and recycling of lithium-ion batteries.

The general population can be exposed via ambient air, drinking-water, tobacco smoke, and food.

Trivalent antimony is a High Production Volume chemical. Trivalent antimony compounds are used in the production of flame retardants, plastics, lead–acid batteries, lead alloys, glass, pigments, and paints.

Occupational exposure can occur through mining, copper smelting, production of antimony compounds, manufacture and recycling of batteries and electronic waste, and among firefighters.

The general population can be exposed by inhalation of fuel and coal combustion products and road traffic dust, and via drinking-water and consumer products such as toys and cosmetics.

Pentavalent antimony is used mainly in antileishmanial drugs.

Weapons-grade tungsten (with nickel and cobalt) alloy is used in armour-penetrating munitions as a replacement for depleted uranium.

Occupational exposure can occur during the production, firing, or impact of these weapons, and through war-related injury by retained embedded metal fragments.

4. What does the *IARC Monographs* classification mean in terms of risk?

The *IARC Monographs* classification indicates the strength of the evidence that a substance or agent can cause cancer. The *IARC Monographs* programme seeks to identify cancer hazards, that is, the potential for the exposure to cause cancer. However, the classification does not indicate the level of cancer risk associated with exposure at different levels or in different scenarios. The cancer risk associated with substances or agents that are assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the size of the effect of the agent at a given exposure level.

5. What are the different strength-of-evidence evaluation groups used by the *IARC Monographs*?

The strength-of-evidence groups that contribute to each evaluation are summarized in the following table.

<table>
<tr><th>Evidence of Cancer in Humans</th><th>Evidence of Cancer in Experimental Animals</th><th>Mechanistic Evidence</th><th>Evaluation</th></tr>
<tr><td>Sufficient</td><td></td><td></td><td rowspan="2">Carcinogenic (Group 1)</td></tr>
<tr><td></td><td>Sufficient</td><td>Strong (exposed humans)</td></tr>
<tr><td>Limited</td><td>Sufficient</td><td></td><td rowspan="4">Probably carcinogenic (Group 2A)</td></tr>
<tr><td>Limited</td><td></td><td>Strong</td></tr>
<tr><td></td><td>Sufficient</td><td>Strong (human cells or tissues)</td></tr>
<tr><td></td><td></td><td>Strong (mechanistic class)</td></tr>
<tr><td>Limited</td><td></td><td></td><td rowspan="3">Possibly carcinogenic (Group 2B)</td></tr>
<tr><td></td><td>Sufficient</td><td></td></tr>
<tr><td></td><td></td><td>Strong</td></tr>
<tr><td></td><td>Sufficient</td><td>Strong (does not operate in humans)</td><td rowspan="2">Not classifiable (Group 3)</td></tr>
<tr><td colspan="3">All other situations not listed above</td></tr>
</table>

6. What are the four different categories into which agents are classified by the *IARC Monographs*?

Group 1: The agent is *carcinogenic to humans*.
This category is used when there is *sufficient* evidence for cancer in humans. In other words, there is convincing evidence that the agent causes cancer in humans. The evaluation is usually based on the results of epidemiological studies showing development of cancer in exposed humans. Agents can also be classified in Group 1 on the basis of *sufficient* evidence for cancer in experimental animals supported by *strong* evidence in exposed humans that the agent has mechanistic effects that are important for cancer development.

Group 2: This category includes agents with a range of evidence regarding cancer in humans and in experimental animals. At one extreme of the range are agents with positive but not conclusive evidence regarding cancer in humans. At the other extreme are agents for which evidence in humans is not available but for which there is *sufficient* evidence for cancer in experimental animals. There are two subcategories, which indicate different levels of evidence.

Group 2A: The agent is *probably carcinogenic to humans*.
This category is used in three different scenarios:

1. When there is *limited* evidence for cancer in humans and *sufficient* evidence for cancer in experimental animals ("*limited* evidence for cancer in humans" means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations, technically termed "chance", "bias", or "confounding", could not be ruled out with reasonable confidence);
2. When there is *limited* evidence for cancer in humans and *strong* mechanistic evidence;
3. When there is *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence in human primary cells or tissues.

These scenarios may also occur simultaneously within a Group 2A classification (**as is the case for trivalent antimony**).

Group 2B: The agent is *possibly carcinogenic to humans*.
This category is used when there is *limited* evidence for cancer in humans and less-than-sufficient evidence for cancer in experimental animals. It may also be used when the evidence regarding cancer in humans does not permit a conclusion to be drawn (referred to as *inadequate* evidence) but there is *sufficient* evidence for cancer in experimental animals or *strong* mechanistic evidence.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.
This category is used most commonly when the evidence is *inadequate* regarding cancer in humans and *inadequate* or *limited* for cancer in experimental animals, and mechanistic evidence is less than *strong*. *Limited* evidence for cancer in experimental animals means that the available information suggests a carcinogenic effect but is not conclusive.

7. How was the evidence reviewed in the *IARC Monographs* evaluation?

During an *IARC Monographs* evaluation, experts critically review the scientific evidence according to strict criteria, which focus on determining the strength of the available evidence that the agent causes cancer. These criteria are described in the Preamble to the *IARC Monographs*, which is available on the *IARC Monographs* website: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf.

The experts critically review four types of data:

- the situations in which people are exposed to the agent;
- epidemiological studies on cancer in humans exposed to the agent (scientific evidence regarding cancer in humans);
- experimental studies of cancer in laboratory animals treated with the agent (scientific evidence regarding cancer in experimental animals); and
- studies on how cancer develops in response to the agent (scientific evidence on carcinogen mechanisms).

8. What are IARC's recommendations based on these results?

IARC is a research organization that evaluates the evidence on the causes of cancer but does not make health recommendations. However, the evaluations made by the *IARC Monographs* are often used as a basis for national and international policies, guidelines, and recommendations to minimize cancer risks.

You can find more information on the *IARC Monographs* evaluation process here: https://monographs.iarc.who.int/wp-content/uploads/2018/07/QA_ENG.pdf.

For more information, please contact

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