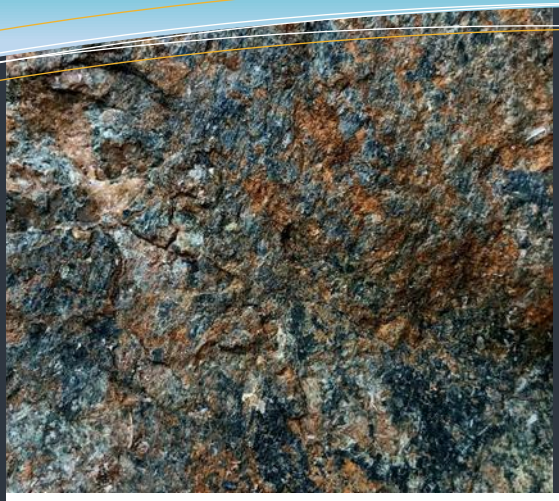
VOLUME
31
May
2025

GT
GERMAN SOCIETY OF
TOXICOLOGY

Poison of the month



The nomination of cobalt as “Toxin of the Month” for May 2025 was put forward by the GT working group Carcinogenesis

…due to its classification as a CMR substance and the resulting current relevance of the debate surrounding differentiated regulatory assessment, particularly in the context of cobalt-containing alloys, which also highlights the stumbling blocks of harmonized classification. The working group aims to draw attention to the challenges of a uniform CMR classification in light of the discrepancy between scientific evidence and legal interpretation.

Cobalt Occurrence

The German name "cobalt" derives from the word Kobold, meaning "goblin" or "evil spirit." In the Middle Ages, miners gave it this name because cobalt-containing ores released toxic fumes when smelted and yielded little useful metal, they suspected a curse or malevolent forces at work.
Cobalt is a naturally occurring trace element that, due to its high reactivity with oxygen, sulfur, and other elements, it is typically bound to other elements. It occurs in minerals such as cobaltite and erythrite. In soil, water, and plants, cobalt is mainly present as a divalent ion (Co^{2+}). In the human body, cobalt exists in a biologically bound form, primarily as the central atom in vitamin B12. Accordingly, the main dietary sources of cobalt are animal products such as liver, meat, fish, eggs, milk, and cheese, in which it is bound within vitamin B12.
Elemental metallic cobalt does not occur naturally and is produced industrially from ores via chemical or electrolytic processes. Additionally, cobalt has been used for centuries, particularly in the form of cobalt blue, as a pigment for ceramics, glazes, and artists' paints. Metallic cobalt is relatively stable and releases ions only slowly. In contrast, cobalt compounds and dissolved cobalt ions are more reactive and more readily bioavailable, which significantly influences their biological effects and toxicity.

Cobalt in Medical Devices: Challenges Arising from Harmonized EU Classification

Cobalt (Co) is a naturally occurring trace element found in the Earth's crust, minerals, soil, seawater, and in small amounts in plants, animals, and the human body. As the central metal atom of vitamin B12 (cobalamin), it is essential for the human body and plays a vital role in blood formation, cell division, and the functioning of the nervous system.

However, depending on its concentration, chemical form, oxidation state, route of exposure, and duration of contact, cobalt can exhibit toxic effects. At high doses, inhalation or oral intake can lead to acute toxicity, with symptoms such as nausea, vomiting, shortness of breath, circulatory failure, or acute kidney damage. Respiratory tract irritation and even toxic pneumonitis are also possible.

Chronic exposure, even at significantly lower concentrations, can damage various organ systems. Particularly affected are the hematopoietic system, the thyroid, the heart, lungs, and kidneys. In animal studies, cobalt(II) compounds such as cobalt sulfate or cobalt chloride have shown tumor-inducing effects upon inhalation or parenteral exposure, especially in the lungs. Accordingly, metallic cobalt has been classified by the European Chemicals Agency (ECHA) in Category 1B ("may cause cancer in humans").

Cobalt(II) ions exert genotoxic effects via the generation of reactive oxygen species (ROS), causing oxidative DNA damage. Various *in vitro* test systems have also demonstrated disrupted spermatogenesis and indications of embryotoxicity, leading to additional classification as a reproductive toxicant (Category 1B) and mutagen (Category 2). As of March 9, 2020, cobalt is officially considered a CMR substance (carcinogenic, mutagenic, toxic to reproduction) with harmonized classification by ECHA. This classification presents significant challenges

VOLUME
31
May
2025

GT
GERMAN SOCIETY OF
TOXICOLOGY

Poison of the month

within the framework of the European Medical Device Regulation (MDR): CMR substances of Categories 1A and 1B may only be present in medical devices in concentrations above 0.1% (w/w) if a specific and scientifically justified exemption applies.

Cobalt is primarily found in medical technology in cobalt-chromium alloys and stainless steels, either as a main component or as a technical impurity. However, stable alloys release significantly fewer cobalt ions in the body compared to pure metallic cobalt, resulting in lower bioavailability. Current regulatory classification, however, does not differentiate between chemical forms or matrices, an approach that many manufacturers consider not proportionate to the actual risk.

Regulatory authorities, on the other hand, emphasize that potential long-term risks, especially in permanently implanted devices, must be taken into account. This precautionary approach is intended to protect patient safety. Currently, professional associations are calling for a more differentiated assessment based on realistic exposure scenarios to enable evidence-based and practical regulation.

By Ute Haßmann

Regulatory Framework

For medical devices, the EU Medical Device Regulation (MDR), which has been fully applicable since May 26, 2021, stipulates in Annex I, Chapter II, 10.4 that carcinogenic, mutagenic, or reprotoxic (CMR) substances of categories 1A and 1B may only be present in concentrations above 0.1% (w/w) if a specific justification is provided. This justification must be scientifically substantiated and documented as part of the conformity assessment process. In addition, special labeling of the product is required.
In practice, this means that manufacturers may have to forgo proven materials or provide extensive evidence to demonstrate the safety of their products despite the presence of cobalt. This requires additional toxicological evaluations, detailed technical dossiers, advanced analytics, and closer coordination with authorities, notified bodies, and users. Cobalt, such as that found in porcelain cups, is classified as a food contact material and is regulated under EU Directive 84/500/EEC in conjunction with Regulation (EC) No. 1935/2004 and the German Consumer Goods Ordinance. These regulations currently do not specify a binding migration limit for cobalt.

Cobalt Cardiomyopathy

Cobalt cardiomyopathy is a pathological enlargement and weakening of the heart muscle that can lead to heart failure in many affected individuals. It first appeared as a form of food poisoning in the 1960s among heavy beer drinkers in Quebec, whose beer had been treated with cobalt salts as a foam stabilizer.

Sensitization

Cobalt is among the most significant triggers of allergic contact dermatitis. Highly sensitized individuals may react even to minute traces. For this reason, cobalt is also strictly regulated in cosmetics, where technically unavoidable trace amounts may be tolerated, provided they pose no health risk.

Literature and links:

- ECHA Europa, 2021
- Alexander CS. Cobalt-beer cardiomyopathy. A clinical and pathologic study of twenty-eight cases. Am J Med. 1972 Oct;53(4):395-417. doi: 10.1016/0002-9343(72)90136-2. PMID: 4263183.
- https://www.fda.gov/cosmetics/potential-contaminants-cosmetics/fdas-testing-cosmetics-arsenic-cadmium-chromium-cobalt-lead-mercury-and-nickel-content
- Eichenbaum, Gary, et al. "An integrated benefit-risk assessment of cobalt-containing alloys used in medical devices: Implications for regulatory requirements in the European Union." *Regulatory Toxicology and Pharmacology* 125 (2021): 105004.
- Kovochich, Michael, et al. "Carcinogenic hazard assessment of cobalt-containing alloys in medical devices: review of in vivo studies." *Regulatory Toxicology and Pharmacology* 122 (2021): 104910.
- Monnot, Andrew D., et al. "A hazard evaluation of the reproductive/developmental toxicity of cobalt in medical devices." *Regulatory Toxicology and Pharmacology* 123 (2021): 104932.
- Zhang, Shumin, et al. "Carcinogenic assessment of cobalt-containing alloys in medical devices or cobalt in occupational settings: A systematic review and meta-analysis of overall cancer risk from published epidemiologic studies." *Regulatory Toxicology and Pharmacology* 125 (2021): 104987.
- Microsoft Word - 2016-10-25 Zweiseiter Position_Cobalt Einstufung clear
- Bewertung von Cobalt als Bestandteil in Dentallegierungen | Quintessenz Verlags-GmbH
- Foto von Hwang sanguk auf Unsplash