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Research

Assessment of reproductive and developmental toxicity risks of cobalt in medical devices

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Abstract

Cobalt metal is an essential trace element that plays a crucial role in various biological processes, with human exposure arising from diverse sources, including diet, dietary supplements, occupational environment, medical devices. Recently, the European Chemicals Agency (ECHA) classified cobalt as a Reproductive Hazard Category 1B. This classification indicates that cobalt is presumed to be a reproductive toxin, primarily due to adverse effects on the testes in male rodents during clinical trials. To evaluate the significance of this classification. Findings from these evaluations suggest that cobalt-induced reproductive toxicity in rodents is confined to the testes function. The underlying mechanisms of cobalt's reproductive effects, including indirect impacts on testicular function, are discussed in the context of their applicability to human health. Notably, current evidence suggests that the classification of cobalt as a Reproductive Hazard Category 1B may not be entirely appropriate. Instead, a more fitting classification might be as a Reproductive Hazard Category 2, indicating a reproductive toxin. Importantly, for cobalt-containing medical devices, the data do not support its classification as a reproductive hazard, highlighting the need for a refined, evidence-based perspective in regulatory assessments.

Keywords: Cobalt (Co), Reproductive toxicity, Developmental toxicity, Maximum tolerable dose (MTD), European Chemical Agency (ECHA), Reproductive Hazard.

INTRODUCTION

Cobalt is a versatile metal plays a critical role in various medical devices, where it imparts important mechanical and biological properties (Davis, 2003). As with a comprehensive toxicological evaluation of cobalt must take into account several factors, including its chemical form, exposure route, and levels of intake, particularly in comparison to normal levels (Egorova and Ananikov, 2017)1. Cobalt is an integral component of cobalamin or vitamin B12, which was essential for normal red blood cell (RBC) formation and plays a key role in maintaining the health of nerve tissue, thus having well-established pathways for its absorption, metabolism, and elimination within the human body (WHO, 2006). The population is exposed to trace amounts of cobalt through dietary intake and environmental sources, including air, water, and dust, typically in low microgram range (WHO, 2006). Foods such as fish, leafy vegetables, and cereals are the primary sources of cobalt, contributing to daily intake (Hokin et al., 2004a; 2004b; WHO, 2006; Finley et al., 2012b). Historically, cobalt have been used in treatment of anemia due to its ability to stimulate RBC and hemoglobin production (Stokinger, 1962). In industrial settings, however, cobalt exposure is more significant, particularly in occupations where cobalt-containing aerosols or compounds are released during processes like cobalt refining,2,3 alloy production, and the manufacturing of hard metals (IARC, 2006). In these work environments, exposure occurs primarily through the inhalation of dust, making it essential for risk assessments to focus specifically on this inhalation route when evaluating potential hazards.

Cobalt (Co) is a trace element best known for its essential role in the structure of cobalamin, commonly referred to as vitamin B12.[4,5] This vitamin is vital for numerous biological processes, including DNA synthesis, red blood cell formation, and maintaining proper neurological function. Humans cannot produce cobalamin on their own and must rely on dietary sources such as fish, leafy green vegetables, and whole grains or supplementation in the form of cyanocobalamin. Cobalamin serves as a co-factor for methionine synthase (in the form of methylcobalamin) and methylmalonyl-CoA mutase (as adenosylcobalamin), which are critical enzymes in amino acid and fatty acid metabolism.

Dietary cobalt intake, primarily derived from these foods, is the range between 5 and 40 microgram per day in the United States (Hokin et al., 2004; WHO, 2006). Additionally, exposure to cobalt can occur through occupational activities, particularly in industries such as mining, metal processing, and battery manufacturing. This highlights the dual importance of cobalt as both a nutritional necessity and a potential occupational hazard. The role of cobalt (Co) in various industries and its implications for health have been subjects of significant study, particularly regarding its use in medical devices and potential reproductive effects. Cobalt-chromium (Co-Cr) alloys and stainless steel, commonly used in orthopedic implants, prosthetics, and stents, have raised concerns about systemic cobalt exposure through ion release (Dmytriw et al., 2019; Paustenbach et al., 2013; Short et al., 2011).

In 2017, the European Chemicals Agency (ECHA) published an opinion recommending the classification of cobalt metal as a Reproductive Hazard Category 1B, based on studies indicating adverse reproductive effects in rodents. These findings, derived primarily from over 20 animal studies, included investigations adhering to OECD guidelines, such as prenatal developmental toxicity (PNDT) studies and oral gavage experiments using cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_2O$) and other cobalt salts. However, these conclusions were not based on human studies, and no conclusive evidence has been documented regarding adverse reproductive effects in humans due to cobalt exposure via inhalation or ingestion (ECHA, 2017; ATSDR, 2004; Paustenbach et al., 2013).[7]

MATERIALS AND METHODS

Literature search

A through literature reviews was conducted to identified on the reproductive and developmental toxicity of cobalt exposure. Using of “cobalt,” “cobalt-chromium-molybdenum,” “Co-Cr,” developmental toxicity, fertility, reproduction and related terms. Both human and animal studies evaluating reproductive and developmental outcomes were included for comprehensive analysis.

Cobalt exposure and its potential reproductive and developmental risks: A Review

Cobalt (Co) is a metal with a broad range of applications, from its use in industrial settings to its incorporation into medical devices such as orthopedic implants, prosthetics, and stents. These medical devices, often made from cobalt-chromium, (CoCr) alloys have raised concerns about the potential risks associated with cobalt exposure, particularly in relation to reproductive and developmental toxicity.[8,9]

Cobalt is commonly introduced into the body either through the consumption of cobalt-containing food or through the release of cobalt ions from medical devices. Although cobalt is a trace element, its accumulation in the body, especially in high concentrations, can lead to adverse health effects. While cobalt in the production of vitamin B12 and is necessary for various biological processes, [10]exposure to excessive amounts has been linked to a range of toxic effects, including neurological, hematological, immunological, and reproductive issues.

Table 1: Cobalt containing materials and example of cobalt use in medical devices

Materials Used					Examples of Specific Devices/ Instruments	Co (%)	Cr (%)	Ni (%)	Mo (%)
Syringe/catheter	Surgical Instrument	Cardiovas. Implant	Prosthetic	Other					
CoCr Alloy (Long-Term Contact Devices)									
			•		In orthopedic surgery	Bal. (57–69)	26–30	0.5–1	5–7
			•		Stem components in hip arthroplasty	Bal. (29–39)	19–21	33–37	9–10.5
			•		Tibial and femoral components of partial and total knee arthroplasty	Bal. (57–69)	26–30	0.5–1	5–7
			•		Extremity systems (e.g., shoulder, elbow, ankle)	Bal. (57–69)	26–30	0.5–1	5–7
		•		•	Stents	Bal. (45.5–57)	19–21	9–11	NS
		•			Cardiac and peripheral stents	Bal. (29–39)	19–21	33–37	9–10.5

Materials Used					Examples of Specific Devices/ Instruments	Co (%)	Cr (%)	Ni (%)	Mo (%)
Syringe/catheter	Surgical Instrument	Cardiovas. Implant	Prosthetic	Other					
		•		•	Heart valve and valve repair	Bal. (29–39)	19–21	33–37	9–10.5
			•	•	Rod, screws, tibial plates	Bal. (57–69)	26–30	0.5–1	5–7
			•	•	Fixator components, pins	Bal. (29–39)	19–21	33–37	9–10.5
				•	Trauma - cerclage cables	Bal (45.5–57)	19–21	9–11	NS
CoCr Alloy (Limited Exposure Devices)									
				•	Guide wires	Bal. (57–69)	26–30	0.5–1	5–7
	•			•	Trials, provisional's, Kirschner wires, guide wires, implant wires, cardiac leads	Bal. (29–39)	19–21	33–37	9–10.5
				•	Instrument springs	Bal. (45.5–57)	19–21	9–11	NS
Stainless Steel (Long-Term Contact Devices)									
			•		Orthopedic surgery	<1[a]	19–22	9–11	2–3
			•		Acetabular shells	<1[a]	21	9–11	2.2
				•	Osteosynthesis plate implants	<1[a]	20.5–23.5	11.5–13.5	2–3
				•	External fixator components	<1[a]	19–23	0.05	0.5–1.5
•		•			Occluders, heart valves	<1[a]	17–20	8–12	0.75–1.25
		•			Stents	<1[a]	17–19	13–15	2.25–3
Stainless Steel (Limited Exposure Devices)									
•	•			•	Blades/lancets, actuators, tunneler, stylets, guidewires, implant tools	<1[a]	15–21	4–15	0.5–4
	•			•	Wires, stylets, implant tools	<1[a]	17–19	8–10	NS

Materials Used					Examples of Specific Devices/ Instruments	Co (%)	Cr (%)	Ni (%)	Mo (%)
Syringe/catheter	Surgical Instrument	Cardiovas. Implant	Prosthetic	Other					
	•		•		Needles, stylets, guidewires, implant tools	<0.5	17–19	8–11	≤0.50
	•		•		Stylets and guide-wires, implant tools	<1[a]	17–20	8–12	0.75–1.25

Overview on CMR health point

The European Chemicals Agency (ECHA) has currently classified cobalt (Co) metal (CAS# 7440-48-4) as a Category 1B carcinogen, Category 1B reproductive hazard, and Category 2 mutagen. However, it is important to note that the ECHA evaluation specifically excluded data related to alloys such as cobalt-chromium alloys (Co-CA), which are used in medical devices (ECHA, 2017b). While certain medical devices may contain pure cobalt as part of their composition—such as cobalt-chromium-molybdenum (CoCrMo) alloys—or as a trace residual in materials are stainless steel, the alloying process significantly alters the physical and chemical properties of cobalt compared to its pure metallic or soluble compound forms (Al Jabbari, 2014; Chen and Thouas, 2015; Klarstrom and Crook, 2001).[11] The distinctive material properties of cobalt within these alloys—such as enhanced wear resistance, high-temperature strength, and corrosion resistance—are primarily due to the unique crystalline structure that cobalt forms within the alloy matrix (Al Jabbari, 2014; Chen and Thouas, 2015; Klarstrom and Crook, 2001). This variation in physical and chemical properties between cobalt alloys and pure cobalt underscores the need for a separate toxicological evaluation, as the health impacts may differ significantly

.

Reproductive Impacts of Cobalt Exposure : Mechanisms and Effects

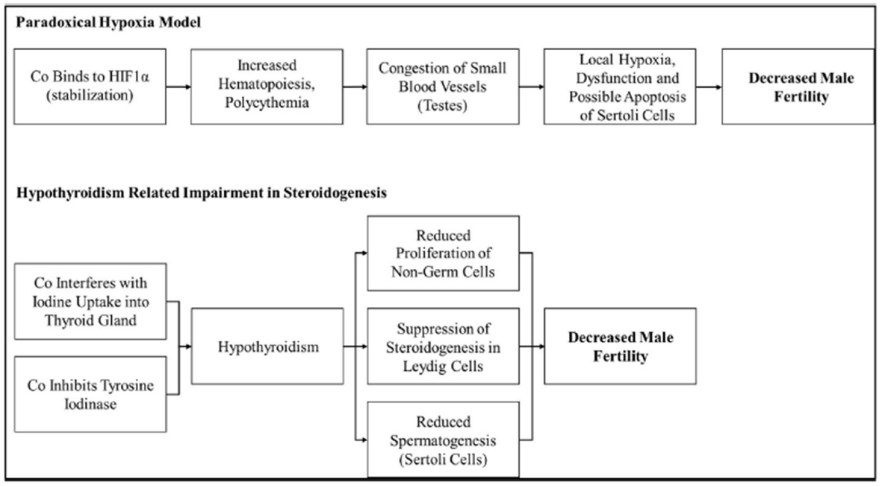
Reproductive Responses Associated with Cobalt-Induced Polycythemia

Cobalt exposure have been induced polycythemia, a condition characterized by an increase in the number of red blood cells in circulation, which can leads to adverse reproductive effects in animals. A study by Mollenhauer et al. (1985) indicated that the harmful effects on testicular function in rodents were a secondary consequence of polycytemia rather than a direct result of cobalt itself. Specifically, the research suggests that testicular degeneration occurred due to hypoxia, which resulted from a blockage of blood vessels by red blood cells and changes in the permeability of blood vessel membranes.[12,13] Interestingly, no cobalt residues were found within the tests, but collagen deposits were noted to contribute to thickening of the basal lamia.

Reproductive Responses Associated with Cobalt-Induced Hypothyroidism

Cobalt exposure has been linked to hypothyroidism, a condition where the thyroid gland produces insufficient thyroid hormones, which are essential for regulating metabolism and growth. This effect has been documented in humans since the 1950s (Finley et al., 2012a; Roche and Layrisse, 1956). High cobalt exposure can cause the development of goiter and reduce thyroid hormone production (Sarne, 2000). While the precise mechanism behind cobalt-induced hypothyroidism is not fully understood, it is believed that cobalt interferes with the uptake of iodine by the thyroid, which is necessary for the synthesis of thyroid hormones.

The link between cobalt exposure, hypothyroidism, and reproductive function is complex, but it is clear that thyroid hormones play a crucial role in regulating reproductive health. Thyroid dysfunction can impact reproductive cycles, reduce fertility, and affect the development and function of the reproductive organs. Further research is needed to fully understand how cobalt-induced hypothyroidism might contribute to reproductive toxicity, particularly in the context of male fertility.



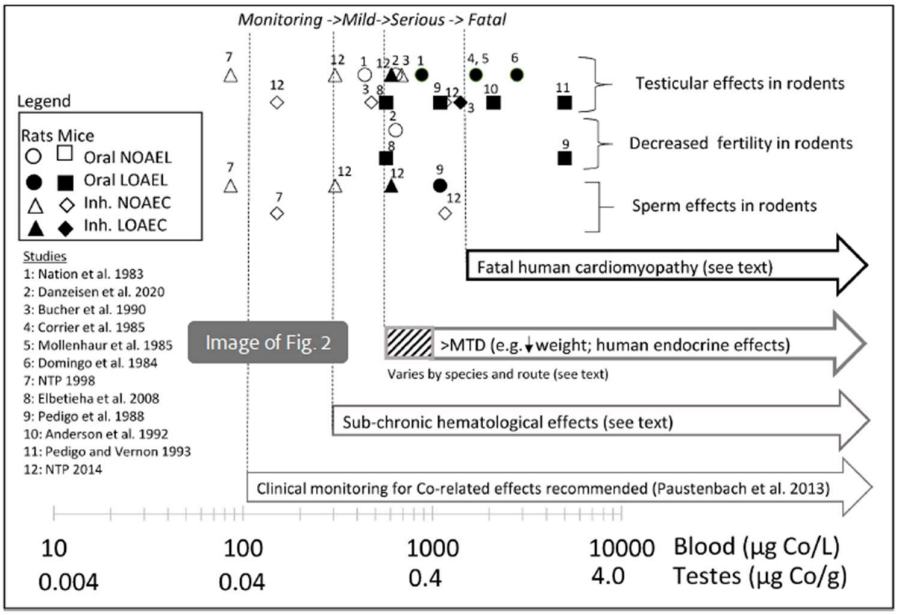
Reproductive and Toxicological Effects of Cobalt Exposure

Evaluation of Cobalt

The reproductive hazard of a substance is typically assessed based on the total body of evidence, considering the compound's ability to adversely affect reproductive function and offspring development. In the case of cobalt (Co), studies indicate that cobalt does not present a significant reproductive hazard to humans at typical exposure levels. Reproductive toxicity in animals has only been observed at doses above the Maximum Tolerated Dose (MTD) or as a non-specific consequence of systemic effects resulting from cobalt exposure. For example, in the study of Danzeisen et al. (2020) concluded that cobalt did not impact sexual performance or reproduction in rodents at tolerable doses.

To evaluate the potential reproductive risks to humans, researchers often consider various factors, including the toxicokinetics of the compound, the target organ or site of action, and the mechanisms of action across species. If the identified mechanisms of action in animals do not have relevance in humans, or if there are significant differences in how the compound is metabolized or distributed across species, then the potential reproductive toxicity may be considered less concerning.[14] In the case of cobalt, research has shown that rodents can tolerate systemic cobalt concentrations of approximately 640 µg/L without experiencing overt toxicity. At this concentration, the estimated cobalt concentration in the testes is about 0.3 µg/g.

This analysis highlights the need for further investigation into the full scope of cobalt's health effects, with particular attention to its potential to cause reproductive toxicity at levels that are below those required to cause fatal cardiac effects.



Regulatory Toxicology and Pharmacology: Cobalt and Reproductive Toxicity

Cobalt (Co) exposure has been linked to various health effects, with particular concern regarding its potential to cause reproductive toxicity. The substances have been studied for its impact on male fertility, through findings are primarily based on animal models. These studies have shown that high doses of cobalt can adversely affect the testes, reducing sperm production and motility, as well as altering hormonal profiles, including testosterone levels. However, the evidence supporting cobalt as a reproductive toxin in humans remains inconclusive.

Excessive cobalt exposure can have significant effects on the thyroid gland and the production of thyroid hormones, raising concerns about its impact on overall health. Prolonged or high levels of cobalt have been linked to the development of goiter and a reduction in thyroid hormone synthesis, which can, in turn, affect various physiological processes, including reproductive health. Thyroid hormones play a crucial role in regulating normal testicular function, influencing key processes such as steroidogenesis and sperm motility. [15,16]Studies have shown that hypothyroidism can disrupt the balance of sex hormone-binding globulin (SHBG), which plays a pivotal role in regulating the bio availability of sex hormones like testosterone and estrogen. This imbalance in hormone levels may subsequently affect fertility and reproductive function. While there is growing evidence of the relationship between cobalt-induced hypothyroidism and male reproductive toxicity, further research is needed to clarify the precise mechanisms and long-term effects.

Co-CA benefit- risk assessment

A comprehensive benefit- risk assessment of cobalt- containing medical devices in outlined below, covering several critical aspects: (1) considerations and implications in the context of the Medical Device Regulation (MDR) (2) key physical and chemical properties of cobalt-chromium alloys (Co-Cr) , (3) evaluation of cobalt exposure linked to various medical devices, (4) an overview of the systemic effects resulting trom cobalt exposure, and (5) risk assessment of Co-Cr based medical devices in compliance with MDR guidelines. This assessment aims to ensure that the benefits of using cobalt-containing materials in medical devices any outweigh potential risks to patient safety and health. The evaluation will take into account the regulatory frame work out lined in the MDR, which emphasizes the need for through risk analysis and monitoring of the potential adverse effects of materials like cobalt.

Consideration and implications in the context of the MDR

The EU Medical Device Regulation (EU MDR, 2017/745) mandates an evaluation of the positive health impact of a device compared to the probability and severity of any potential harm. The regulation emphasizes that devices must remain suitable for their intended purpose under normal usage conditions, ensuring a high level of health and safety protection. The acceptable risk determination should consider potential hazards within the context of the current state of the art. While medical interventions aim to improve quality of life and reduce pain, they inherently carry some risk of adverse outcomes. [17,18]Therefore, devices must be designed to minimize risks without compromising the overall benefit-risk balance. Achieving an acceptable benefit-risk ratio depends on available alternatives and innovations that offer necessary material benefits, such as corrosion resistance. Biomaterials, including metals, polymers, ceramics, and composites, have become widely accepted for replacing or augmenting tissues and functions due to favorable material and the benefits they provide to patients, despite associated risks. The use of biomaterials has significantly improved the quality of life, particularly in older populations, by addressing medical needs effectively (Agrawal et al., 2014; O'Brien, 2011).

Key physical and chemical properties of cobalt- chromium alloy (Co-CA)

Cobalt (Co) used in medical devices is typically found in specific cobalt-chromium alloys (CoCr), such as CoCrMo, where the Co content plays a key role in determining the alloy's physicochemical properties. Other alloys used in medical devices, like stainless steel, contain much lower levels of Co, often as an unintended impurity from source ores. [19]Regardless of the alloy, the alloying process results in material that differ from those of pure Co or soluble cobalt compounds. These distinct properties significantly influence the toxicokinetics and toxicodynamics of Co in various forms, such as Co metal versus CoCrMo alloys. The unique physical properties of Co-containing alloys, such as resistance, high-temperature strength and corrosion resistance, stem from the crystalline structure of the alloy.[20] Additionally, CoCA surfaces have different morphologies compared to pure cobalt or soluble cobalt compounds, primarily in the presence of a passing surface layer that reduces Co bio-availability.

Properties[a]	Co Alloy (e.g., CoCrMo)	Pure Metallic Co
Face-centered cubic (fcc) crystal structure 	Yes	No
Hexagonal close-packed (hcp) crystal structure 	Yes	Yes
Ability to absorb stresses, high yield strength, limited fatigue damage under cyclic stresses, and high work-hardening rates	Yes	No
Solid solution strengthening effects of chromium, tungsten, molybdenum, and metal carbides	Yes	No
Chromium oxide passivation layer and strong repassivation	Yes	No
Corrosion resistance	Yes	No
Limited Co bioavailability	Yes	No

[a] Properties at room temperature

CONCLUSION

In 2016, the Netherlands submitted a Harmonised Classification and Labeling (CLH) report on cobalt metal, raising concerns about its carcinogenicity, mutagenic, and reproductive toxicity potential. Following this, ECHA proposed classifying Co metal as a Category 1B carcinogen, Reproductive Hazard Category 1B, and a Category 2 mutagen. However, the safety data on Co-containing alloys used in medical devices were excluded from this evaluation. Several studies, including this one, have reviewed the potential carcinogenicity and reproductive toxicity of Co-containing alloys used in medical devices, based on both preclinical and clinical data, as well as epidemiological evidence on cancer risk. Evidence of reproductive or developmental toxicity has mainly been observed in clinical studies involving high systemic Co exposures, exceeding the maximum tolerable dose. Epidemiological reviews, however, found no significant evidence linking Co-containing orthopedic implants with an increased cancer risk. These findings are supported by animal studies, which showed no increase in local or systemic tumors in relevant exposure scenarios. Additionally, local tissue sarcomas near metal implants were found to be extremely rare. This aligns with FDA's recent analysis, which found no increased cancer risk associated with metal implants, despite isolated reports of cancer linked to them.

REFERENCES

1. Afolaranmi, G.A., Helen Grant, M., 2011. The effect of ascorbic acid on the distribution of soluble Cr and Co ions in the blood and organs of rats. J. Appl. Toxicol. 33 (3), 260-226.
2. Anderson, M.B., Pedigo, N.G., Katz, R.P., George, W.J., 1992. Histopathology of testes from mice chronically treated with cobalt. Reprod. Toxicol. 6 (1), Arch. Toxicol. 87 (7), 1201–1218.
3. Brodner, W., Bitzan, P., Meisinger, V., Kaider, A., Gottsauner-Wolf, F., Kotz, R., 2003. Serum cobalt levels after metal-on-metal total hip arthroplasty.
4. Thompson, M.B., Chou, B.J., Renne, R., Ragan, H.A., 1990. Inhalation toxicity studies of cobaltChen,
5. Z., Zuo, Q., Song, F., Fan, W., Wang, Z., Wu, D., Cheng, W., 2013. Reproductive toxicity in adult male rats following intra-articular injection of cobalt–chromium nanoparticles. J. Orthop. Sci. 18 (6), 1020–1026.
6. CI, 2017. Cobalt: Human Health – Reproduction. Retrieved Jan. 17, 2020 from:. Cobalt Institute, UK (CI). https://www.cobaltinstitute.org/cobalt-and-reproduction.html
7. Mayo Clinic, 2020. Abnormal sperm morphology: what does it mean?, 2020 from: Retrived Dec10. https://www.mayoclinic.org/diseases-conditions/male-infertility/expert-answers/sperm-morphology/faq-20057760.
8. Nelson, R.J., 1988. Restricted water intake influences male reproduction in two strains of house mice (Mus musculus). Physiol. Behav. 43(2), 217–21. https://doi.org/ 10.1016/0031-9384(88)90241-7.
9. Nelson, R.J., Desjardins, C., 1987. Detection of metallic cobalt and chromium liver deposition following failed hip replacement using T, R magnetic resonanceJ. Cardiovasc. Magn. Reson., 18 (2016), pp. 1-5
10. ACGIH, 2001AcgihCobalt and Inorganic Compounds: TLV American Conference of Governmental Industrial Hygienists, Cincinnati, OH (2001).

11. Physico-mechanical properties and prosthodontic applications of Co-Cr dental alloys: a review of the literatureThe journal of advanced prosthodontics, 6 (2014), pp. 138-14
12. Toxicological Profile for Cobalt U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA (2004).
13. Assessing for cardiotoxicity from metal-on-metal hip implants with advanced multimodality imaging techniquesThe Journal of bone and joint surgery. American, 99 (2017), p. 1827.
14. C.S. Alexander Cobalt-beer cardiomyopathy. A clinical and pathological study of twenty-eight cases Am. J. Med.(1972).
15. A.M. Cirla Cobalt related asthma: clinical and immunological aspects Sci. Total Environ. (1994)
16. A. Forni Bronchoalveolar lavage in the diagnosis of hard metal disease Sci. Total Environ. (1994)
17. A. Kennedy *et al.*Fatal myocardial disease associated with industrial exposure to cobalt. No superiority of cemented metal-on-metal over metal-on-polyethylene THA in a randomized controlled trial at 10-year follow-up Orthopedics, 33 (2010).
18. 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 StudiesRegul. Toxicol. Pharmacol. (2021), p. 104987
19. Revision of recalled modular neck rejuvenate and ABG femoral implants blinded manuscriptJ. Arthroplasty, 30 (2014), pp. 822-826.
20. The tissue reaction induced in rats and Guinea-pigs by polymethylmethacrylate (acrylic) and stainless steel (18/8/Mo) Br. J. Exp. Pathol., 45 (1964), p. 21
21. Toxicology studies of cobalt metal (CAS No. 7440-48-4) in F344/N rats and B6C3F1 mice and toxicology and carcinogenesis studies of cobalt metal in F344/NTac rats and B6C3F1 mice (inhalation studies)