Science of the Total Environment 906 (2024) 167667

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

The impact of toxic metal bioaccumulation on colorectal cancer: Unravelling the unexplored connection

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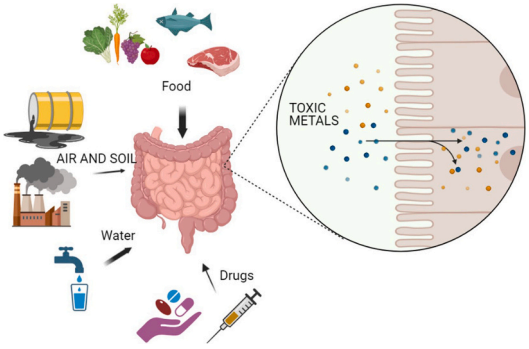
HIGHLIGHTS

- High blood lead levels increase the risk of colorectal cancer.
- Hexavalent chromium exhibits cytotoxic effects due to its oxidizing properties.
- Aluminium and cadmium long-term exposure induces cellular survival and proliferation.
- The long-term exposure to toxic metals could be considered as risk for colon cancer.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Lidia Minguez Alarcon

Keywords:
Colon cancer
Toxic metals
Environmental pollution
Lead
Cadmium
Copper
Aluminium
Chromium
Mercury
Arsenic

ABSTRACT

Colorectal cancer is a major public health concern, with increasing incidence and mortality rates worldwide. Environmental factors, including exposure to toxic metals, such as lead, chromium, cadmium, aluminium, copper, arsenic and mercury, have been suggested to play a significant role in the development and progression of this neoplasia. In particular, the bioaccumulation of toxic metals can play a significant role in colorectal cancer by regulating biological phenomenon associated to both cancer occurrence and progression, such as cell death and proliferation. Also, frequently these metals can induce DNA mutations in well-known oncogenes. This review provides a critical analysis of the current evidence, highlighting the need for further research to fully grasp the complex interplay between toxic metal bioaccumulation and colorectal cancer. Understanding the contribution of toxic metals to colorectal cancer occurrence and progression is essential for the development of targeted preventive strategies and social interventions, with the ultimate goal of reducing the burden of this disease.

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https://doi.org/10.1016/j.scitotenv.2023.167667
Received 12 August 2023; Received in revised form 3 October 2023; Accepted 6 October 2023
Available online 9 October 2023

1. Introduction

Toxic metals have the capacity to accumulate in the body over extended periods, resulting in chronic exposure and potentially serious health consequences (Palma-Lara et al., 2020; Al Osman et al., 2019; Salles et al., 2022). Recent studies suggest that exposure to toxic metals, such as lead (Pb), chromium (Cr), cadmium (Cd), aluminium (Al), copper (Cu), arsenic (As) and mercury (Hg), may contribute to the development and progression of cancers (Scimeca et al., 2018a; Scimeca et al., 2014; Scimeca et al., 2016; Rehman et al., 2018a; Zhu and Costa, 2020). These metals can disrupt cellular homeostasis, trigger oxidative stress, and induce DNA damage, potentially promoting carcinogenesis. Additionally, they may alter key signaling pathways involved in cell proliferation (Gatti et al., 2019; Panatta et al., 2021), epithelial to mesenchymal transition (Bonfiglio et al., 2020; Scimeca et al., 2019a; Scimeca et al., 2018b; Scimeca et al., 2020; Scimeca et al., 2021a; Scimeca et al., 2018c) and apoptosis (Ganini et al., 2022; Urbano et al., 2022; Vitale et al., 2023; Rozenberg et al., 2021; Lena et al., 2021), further exacerbating cancer progression. Occupational exposure and environmental contamination are common routes of toxic metal exposure, making it vital to understand their role in colon etiology and devise preventive strategies.

Anyway, one of the major sources of toxic elements exposure in humans is through the diet (Jose and Ray, 2018; Ventre et al., 2022; Yang et al., 2022; Nakhaee et al., 2023). Although in small amounts, toxic metals are present in various foods, including processed foods, baking powders and drugs such as antacids, astringents, buffered aspirin, vaccines, but also drinking water, food additives, antiperspirants, and cosmetics (Willhite et al., 2014). As a result, the gastrointestinal tract becomes one of the primary targets for toxic metals exposure, primarily through the consumption of food and beverages.

Despite the low oral bioavailability of the main toxic metals (about 0.1–0.3 % for ingested metals), the colon and kidneys, which act as excretion pathways for unabsorbed substances, can be exposed to relatively high concentrations of these metals. Thus, it is plausible to hypothesize a bioaccumulation of toxic metals in colon and their involvement in the development of colorectal cancer (CRC). CRC is the third most common cancer in both men and women worldwide, with an estimated 1.93 million new cases and 935,000 deaths in 2020 (https://gco.iarc.fr/, n.d.). CRC is the second leading cause of cancer deaths globally, affecting both sexes and all age groups, with an estimated 90 % of cases occurring in individuals over 50 years old, rates higher for men than for women. The higher incidence of CRC in men may be attributed to a greater impact of environmental factors rather than genetic ones (Larsen et al., 2006; Lin, 2009). The distribution of CRC varies widely over time within different geographical areas. The incidence rates of CRC are increasing in countries undergoing rapid socio-economic and environmental changes such as Brazil, China, and Slovakia, while in high-income countries such as North America, Europe, and Oceania, the incidence rates are either decreasing or remaining stable (https://gco.iarc.fr/, n.d.).

Understanding the contribution of toxic metals to CRC occurrence and progression is essential for the development of targeted preventive strategies and therapeutic interventions, with the ultimate goal of reducing the burden of this devastating disease. Accordingly, this review provides a critical analysis of the current evidence, highlighting the need for further research to fully grasp the complex interplay between toxic metals, such as Pb, Cr, Cd, Al, Cu, As and Hg, and colon cancers.

2. The role of toxic metals in the colon cancer occurrence and progression: overview

Toxic metals are chemical elements that are non-essential and have no known physiological function in the body (Sinicropi et al., 2010). In fact, they can cause harmful effects on human health even in small amounts. They are often found in the environment, including water, air, and soil, as well as in certain foods and consumer products. These molecules can contaminate agriculture and the environment through weathering of bedrock, air pollution, and soil irrigation with polluted water (Guerra et al., 2012). Furthermore, human exposure to these chemicals has increased significantly due to their use in domestic and technological applications (Bradl, 2002) since toxic metals can enter the body through ingestion, inhalation, or skin contact and can accumulate over time, leading to long-term health effects. According to the World Health Organization (WHO), Pb, Cr, Cd, Al, Cu, As and Hg, along with other compounds, are considered chemicals of public health concern (World Health Organization (WHO), n.d.; *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.*, 1980). Among these, heavy metals are known for their toxicity and can cause a range of health problems, including cancer, neurological damage and reproductive issues (Rehman et al., 2018a; Tchounwou et al., 2012). Nonetheless, it's important to note that the toxicity of a metal is dose-dependent, meaning that even functional metals can become toxic at high levels. Functional metals are essential to human health in small amounts for proper physiological function in the human body. Examples include iron, zinc, and copper, which are important for various biological functions, such as oxygen transport, immune function, and enzyme activity. However, at high doses, these functional metals can become toxic and increase the risk for several diseases. Therefore, it is important to maintain a balance and adequate intake of both functional and toxic metals in the body to prevent adverse health effects. Some toxic metals, have the ability to bind to hormone receptors and interfere with the normal functioning of the endocrine system, thereby are also known as metalloestrogens or endocrine disruptors (Hartwig and Schwerdtle, 2002; Hartwig et al., 2003). It is known that toxic metals induce oxidative stress, stimulate cell growth, cause genomic instability, and alter cell proliferation (Paithankar et al., 2021; Briffa et al., 2020; Balali-Mood et al., 2021a). All these actions are directly linked to cancer progression. One area of concern is the potential link between toxic metals and CRC. Exposure to certain toxic metals has been linked to an increased CRC risk.

However, it's important to note that the link between these toxic metals and CRC is not yet fully understood, and more research is needed to better understand the relationship between environmental exposures and cancer risk.

2.1. Lead

Pb is one of the most abundant substances on Earth, with unique properties such as ductility, softness, high malleability, low melting point, and resistance to corrosion (Lee et al., 2019). It is widely used in industries such as mining, smelting, refining, battery manufacturing, painting, ceramics, plastics, and more (Flegal and Odigie, 2020). Human exposure to Pb can occur in various forms, including industrial discharge that pollutes nearby water bodies, contamination of soil from pesticides and fertilizers used in agriculture, and atmospheric pollution caused by the combustion of gasoline from intense traffic (Parizanganeh et al., 2010; Jalali and Khanlari, 2008). According to the IARC classification (2006) of carcinogenic agents, inorganic Pb compounds belong to Group 2A, whereas organic Pb compounds belong to Group 3 because the compounds are metabolized at least in part to ionic Pb in humans and animals. In the human body, Pb is primarily absorbed by the kidneys but also by the liver, brain, and heart. Another critical aspect is that Pb accumulates in the skeleton (Flora et al., 2006).

Unfortunately, with increased industrialization and modernization, the widespread use of Pb-based materials has led to alarming levels of Pb contamination in the environment, water sources, and even the air we breathe. As a result, the toxic effects of Pb exposure have become a significant public health concern, with the most vulnerable populations, such as children and pregnant women, being at the greatest risk (Levallois et al., 2018; Yu et al., 2023). This essay delves into the complex and multifaceted nature of the cytotoxic effects of Pb, shedding light on the far-reaching consequences of this silent menace.

When ingested or inhaled, Pb is readily absorbed and distributed throughout the body via the bloodstream. Initially, Pb primarily targets the bones, where it competes with calcium, mimicking its role in cellular processes (Scimeca et al., 2017; Visconti et al., 2023). Moreover, Pb crosses the blood-brain barrier and placental barrier, making the central nervous system and developing fetuses exceptionally susceptible to its detrimental effects. Over time, Pb accumulates in soft tissues and organs, leading to chronic exposure and long-term health issues.

Pb's cytotoxicity arises from its ability to disrupt essential cellular functions and interfere with biological pathways (Lee et al., 2019). One primary mechanism of Pb toxicity is oxidative stress. Pb generates reactive oxygen species (ROS) in cells, overwhelming the body's antioxidant defences, which results in oxidative damage to lipids, proteins, and DNA (Balali-Mood et al., 2021b). This leads to cellular dysfunction, apoptosis, and ultimately tissue damage (Guidotti et al., 2008; Piomelli, 2002) (Fig. 1).

Several epidemiological studies have explored the correlation between blood lead levels and the risk of CRC. In this context, Min-Gi Kim et al. (n.d.) identified an association between blood lead levels (BLL) and mortality in inorganic Pb-exposed workers in South Korea. Notable, authors found a significant increase in CRC risk among female workers with BLLs ranging from 10 to 20 micrograms/dl, with a relative risk (RR) of 13.42 (95 % confidence interval: 1.21–149.4). Similar data were reported from CRC patients in Cina and Alexandria (Virginia). Specifically, in a recent study (Lin et al., n.d.) researchers analyzed the possible impact of Pb and Cd exposure on gastrointestinal cancer risk in China population. The study included blood samples from the Chaoshan zone, a region known to be polluted by several toxic metals, including Cd, Cobalt (Co), Cr, Zinc (Zn), Nichel (Ni), and Pb. The samples consisted of individuals with different types of gastrointestinal cancer (70 esophageal cancer, 51 gastric cancer, and 46 colorectal cancer) and healthy controls.

Also, in a study of Soha et al. (*Environmental Risk Factors and Plasma Concentration of Lead and Copper in Colorectal Cancer Patients in Alexandria*, n.d.) authors identified higher levels of Pb and Cu in the blood of CRC patients residents in Alexandria respect to the healthy ones by using atomic absorption spectrometry. The findings of these epidemiological studies indicated that the blood levels of Pb in CRC patients were significantly higher than those in the control group thus suggesting that high concentrations of Pb in the blood might be a risk factor for CRC.

As concern the bioaccumulation in human colon tissues, Gondal et al. (2020) analyzed several cancerous and normal colon tissues collected from the CRC patients aged 40–60 years by using the indigenously developed fast and accurate (calibration-free) laser-induced breakdown spectroscopy (LIBS). Thanks LIBS authors demonstrated the presence of carcinogenic heavy metals including Pb in the malignant colon tissues, while the healthy tissues were devoid of these elements. This study for the first time described the presence of Pb in human colon tissues suggesting its possible role in CRC occurrence.

Another study investigated the specific bioaccumulation of Pb in primary organs and intestinal tissue of mice by administering it in the form of $PbCl_2$ through drinking water (Breton et al., 2013). This allowed researchers to cover both low and critical doses of Pb exposure, as well as to mimic Pb intoxications. After 8 weeks of exposure, authors found that the bioaccumulation of Pb was tissue-specific and increased with its concentration. Specifically, Pb was detected in the duodenum, in the ileum and in the colon. At lower doses of Pb exposure, changes were found in expression of genes involved in transport, oxidative stress, and inflammation. Ileum segments did not respond significantly to the Pb, and most of the significant changes were in the duodenum and colon. Key concepts about the effect of Pb in CRC are listed in Box 1.

2.1.1. *Discussion and perspectives*

Pb is a widely used substance with various industrial applications, but its toxic effects on human health and the environment are a growing concern. The extensive use of Pb-based materials in industrial processes and the combustion of leaded gasoline have led to significant contamination of the environment, water sources, and air, posing a serious risk to public health. Vulnerable populations, such as children and pregnant women, are particularly at risk.

Pb's cytotoxic effects result from its ability to interfere with essential cellular functions. Recent studies have shown a possible link between

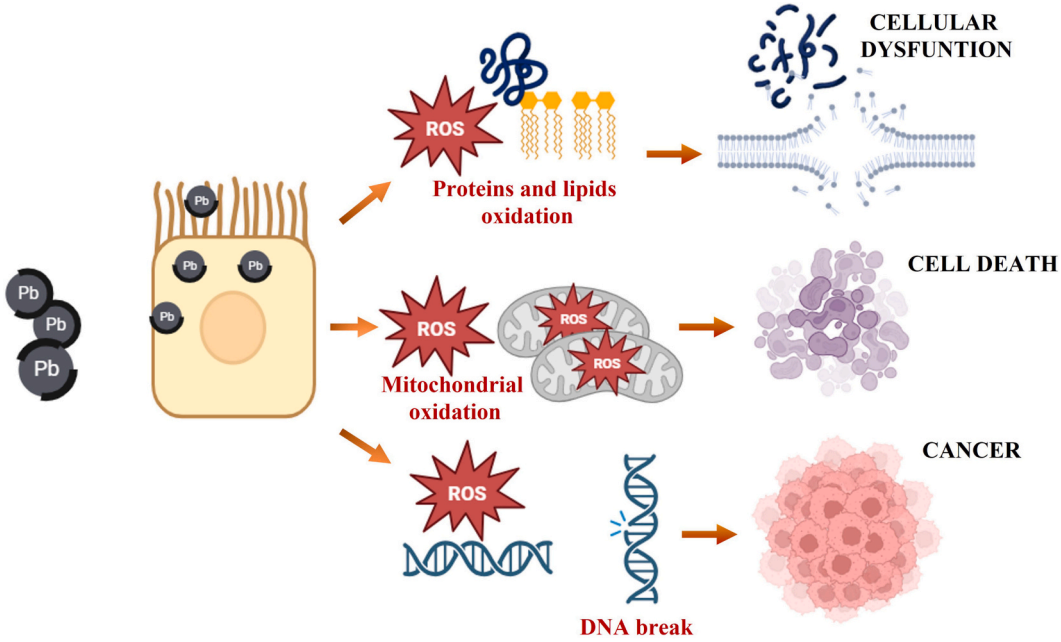

Fig. 1. Cytotoxicity of lead. Lead cytotoxicity is driven by its capacity to disrupt essential cellular functions and interfere with biological pathways. A key mechanism of Lead toxicity involves oxidative stress, where Lead induces the production of reactive oxygen species (ROS) within cells. This oxidative stress overwhelms the body's antioxidant defences, causing damage to lipids, proteins, mitochondrial oxidation and DNA. This cascade of events leads to cellular dysfunction, apoptosis, and ultimately tissue damage.
Fig. 1 has been created by using BioRender.

Box 1
Key points of Pb effects on colon cells.

Key points	References
• Human exposure to Pb can occur in various forms, including industrial discharge, contamination of soil, and atmospheric pollution caused by the combustion of gasoline.	(Parizanganeh et al., 2010; Jalali and Khanlari, 2008)
()	[58]
• Lead can trigger inflammation and oxidative stress in colon cells, promoting chronic cellular damage.	(Breton et al., 2013)

elevated blood levels of Pb and gastrointestinal cancers, including CRC. Furthermore, animal studies have demonstrated tissue-specific bioaccumulation of Pb, particularly in the duodenum and colon, which can lead to changes in gene expression related to transport, oxidative stress, and inflammation.

Overall, the evidence here presented highlights the urgent need for stricter regulations and environmental measures to mitigate Pb exposure and protect human health from the detrimental effects of this silent menace. Further research and awareness are necessary to fully understand the complex interactions between Pb exposure and gastrointestinal cancers, promoting public health initiatives.

2.2. Chromium

Cr is a rare element found in nature, its most stable forms being trivalent, Cr(III), and hexavalent chromium, Cr(VI), due to their stability in the presence of water and oxygen they are considered biologically and environmentally relevant (Vincent and Lukaski, 2018). Cr(III) is a necessary trace element in the human diet, it supports glucose metabolism and intervenes in the regulation of blood glucose because it has a synergic action with insulin. Conversely, Cr(VI) is carcinogenic if inhaled and/or ingested in large amounts. Cr's cytotoxicity refers to its ability to cause damage to living cells, particularly in higher concentrations. In its hexavalent form, Cr exhibits potent cytotoxic effects due to its strong oxidizing properties. Upon exposure, Cr(VI) can penetrate cell membranes and convert to Cr(III) inside the cell. This conversion generates reactive intermediates and free radicals, leading to oxidative stress and subsequent cellular damage (Mezencev and Gibbons, 2023). Cr(VI) interferes with essential cellular processes, disrupts DNA repair mechanisms, and induces genotoxicity, ultimately contributing to the development of cancer (Metropulos et al., 2022). Additionally, Cr(VI) can lead to the production of ROS, causing lipid peroxidation and protein damage (Fig. 2).

Given its cytotoxic nature, proper handling and regulation of Cr exposure are crucial in occupational settings and environmental contexts to safeguard human health. In the latter case, industrial activities are the main sources of Cr(VI) (Mezencev and Gibbons, 2023). Commercial applications of Cr include tanning, corrosion inhibition, plating, glassware-cleaning solutions, wood preservatives, safety match manufacture, metal finishing and pigments (Barceloux, 1999a). According to these evidences, the International Agency for Research on Cancer (IARC) suggests that Cr(VI) is a carcinogenic element of Group 1, and this claim has been confirmed by numerous studies (Welling et al., 2015; Rinaldi et al., 2015).

A biological monitoring study conducted in Taranto, a southern Italian city known for the presence of a large steel mill, revealed the exposure of the resident population to Cr. (Vimercati et al., 2017) According to the Environmental Protection Agency (APAT), steel plant in Taranto in 2005 emitted 3800.8 kg of Cr into the air and up to 20,407.3 kg into water (APAT, 2005). Through atomic absorption spectrophotometry, higher urinary levels of Cr were detected in people who had lived near industrial plants for at least 10 years thus demonstrating the accumulation of Cr in subject with high exposure.

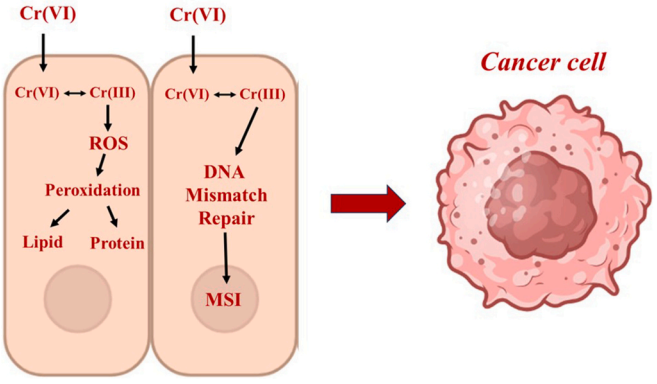

Fig. 2. Cytotoxicity of hexavalent chromium on colon cells. The image illustrates the cytotoxic effects of hexavalent chromium (Cr(VI)) on colon cells. Trivalent chromium (Cr(III)) present in the environment can be transformed into Cr(VI) within colon cells through processes of oxidation, such as the action of cytochrome P450 enzymes. Once converted into Cr(VI), this metal generates elevated levels of oxygen-free radicals, known as reactive oxygen species (ROS). The increased ROS levels induce oxidative stress, leading to lipid peroxidation and cellular protein degradation. Additionally, Cr(VI) can directly act on DNA, impairing DNA mismatch repair, and consequently causing genomic instability. These combined effects contribute to the cytotoxicity of Cr(VI), which may play a crucial role in the pathogenesis of colon-related disorders, particularly the development of CRC.

As concern the possible effect of Cr in CRC carcinogenesis, Rinaldi et al. (2015) examined a cohort of 104 patients with various colon-rectal diseases, out of which 76 were diagnosed with CRC. The primary objective of their research was to investigate the potential association between the Cr bioaccumulation and the risk of CRC incidence by using inductively coupled plasma atomic emission spectrometry. To achieve this, the researchers compared the levels of Cr in both tumor and non-tumor tissues of the patients. Surprisingly, they observed a significantly higher presence of Cr in the CRC biopsies compared to the non-cancerous ones. This intriguing finding prompted the scientists to consider the possibility of exogenous sources of Cr such as industrial pollution, playing a significant role in the heightened risk of developing colorectal cancer.

Similarly, a possible association between Cr exposure and CRC was investigated in Iran (Kiani et al., 2021). In particular, CRC and normal colon mucosa biopsies have been analyzed to detect the presence of several toxic metals including the Cr. The presence of Cr was frequently in CRC biopsies respect to the normal ones. Thus, also this study highlights the possible role of Cr bioaccumulation in CRC.

Molecular data about the effect of Cr on colon have been obtained in both in vivo and in vitro studies. In this context, Bian et al. (2022) examined the mechanism through which Cr induces centrosome amplification (CA) in HCT116 colon cancer cells. It is known that CA playing a role in tumorigenesis and the invasiveness of cancer cells. In this study, authors found that Cr(VI) is able to induce CA and thus facilitating cancer progression via the ROS-ATF6-PLK4 pathway. Noteworthy, the inhibition of ROS, ATF6 activation, or PLK4 upregulation reduced the formation of Cr(VI)-related CA. However, the most comprehensive and exhaustive molecular investigation on the effects of Cr in the gastrointestinal system can be found in the study of Der-An Tsao et al. (2011). In particular, authors present novel insights into the expression of RKIP, RhoGDIα, galectin, c-Myc, and p53 in the stomach and colon of rats subjected to Cr(VI) treatment. By examining the correlation between Cr(VI) levels and the expression of these markers, it was evident that Cr(VI) exposure in drinking water may indeed contribute to the formation of stomach and CRC in rats. Molecular investigations have revealed that Cr exposure leads to a decrease in the expression of p53 and RKIP, while an increase in galectin and c-myc was observed. Of note, the impairment of p53 expression related to Cr exposure could drastically impact the occurrence of CRC. Loss of p53 function due to mutations or decreased expression significantly impacts CRC pathogenesis (Nakayama and Oshima, 2019; Rufini et al., 2013; Amelio and Melino, 2015; Melino, 2020). Reduced p53 expression disrupts cell cycle control, allowing uncontrolled proliferation and tumor growth (Nicolai et al., 2015; Chillemi et al., 2017; Pitolli et al., 2019). Moreover, impaired p53 function compromises DNA repair mechanisms, leading to the accumulation of genetic aberrations and increased tumor aggressiveness. Thus, according to the data of Der-An Tsao et al. it is possible hypothesize a mutagenic effect of Cr on TP53 gene. This study contributes valuable information to our understanding of the potential health risks associated with Cr(VI) exposure and underscores the importance of further research in this area. Key concepts about the effect of Cr in CRC are listed in Box 2.

2.2.1. Discussion and perspectives

Numerous studies have linked Cr bioaccumulation to an increased risk of CRC, with industrial pollution being a potential exogenous source. Molecular investigations have shown that Cr exposure leads to the downregulation of tumor suppressor gene p53, which is critical in CRC pathogenesis as it controls cell cycle arrest, apoptosis, and DNA repair.

The findings here reported emphasize the need for stringent handling and regulation of Cr exposure, especially in occupational settings and industries where Cr is commonly used. Efforts to minimize environmental Cr pollution are crucial to safeguarding public health. Additionally, the association between Cr exposure and CRC warrants further exploration, particularly in terms of identifying potential biomarkers and therapeutic targets.

2.3. Cadmium

Cd is a heavy metal that naturally occurs in Earth's crust and in ocean water, in several forms: as ores with other metals, such as Zn, Pb and Cu, as pure Cd, a soft, silver-white metal, or as water-soluble Cd chloride and sulfate (ATSDR, 2012). This metal is carcinogenic for human, in fact it is classify as class 1 cancerogenic element by International Agency for Research on Cancer (IARC) (IARC, 2012). Especially near metal industries and polluted areas, high levels of Cd have been registered in soil, water, and air too, as particles or vapors (https://www.atsdr.cdc.gov/index.html). Anthropological sources of Cd are mainly connected to industry because of its numerous employments: the principal use of Cd is related to nickel-Cd rechargeable batteries, followed by electroplating in galvanized steel; furthermore, it is used as pigment, plastic stabilizer, in solar panels and in cosmetics, but also in agriculture as fertilizing compounds (Nordberg and Costa, 2021). Ingestion of contaminated foodstuff and smoking of cigarettes represent the primary source of non-working exposure to Cd. The former is due to agricultural and industrial activities which could lead to air, water, and soil contamination, introducing Cd in food chain: crustaceans, leafy vegetables (as lettuce and spinach), potatoes and grains, peanut, rice, and offal are most frequently Cd-contaminated foods, in addition to water (Bernhoft, 2013). Concerning occupational exposure to Cd, it is mainly related to smelting and electroplating, two processes which involve heating cadmium-containing materials. In this case, the principal way of exposure is through inhalation of dust and fumes, although personal protective equipment, good industrial hygiene practices, and reduction of Cd emission in general could reduce all the related risks (ATSDR, 2012).

Cd is mainly absorbed through inhalation and ingestion, although somewhat is also absorbed through the skin. The former represents the main mechanism by which Cd enters in the body and occurs when metal presents an aerosol form, such as low weight particle. From 10 % to 50 % of inhaled Cd is absorbed by alveolar mucosa cells, then released in blood flow. Absorption by ingestion is about 5 % to 10 %, and people with Zn, iron (Fe) or calcium (Ca) deficiency have higher absorption of this metal (Nordberg et al., 2014). After reaching blood circulation, Cd bind albumin and metallothioneins, produced by liver, forming sulfhydryl-groups. Metallothioneins (MTs) bind bivalent metal ions (as Fe, Zn, Cu and Cd) with high affinity and play central role in homeostasis, transport, regulation ability of Zn and Cu in MTs gene expression, and protection against toxic metal and free radicals (Sabolić et al., 2010). Cd toxicity in living organisms is related to ability of alter several cellular processes, due to its ionic mimicry ability, modification of biophysical properties of lipid membranes and interactions with thiol groups of macromolecules, such as cysteine residues of proteins (Lee and

Box 2
Key points of Cr effects on colon cells.

Key points	References
• Industrial activities are the main sources of Cr(VI). Commercial applications of Cr include tanning, corrosion inhibition, plating, glassware-cleaning solutions, wood preservatives, safety match manufacture, metal finishing and pigments.	(Mezencev and Gibbons, 2023)
• Cr(VI) interferes with essential cellular processes, disrupts DNA repair mechanisms, and induces genotoxicity, ultimately contributing to the development of cancer.	(Metropulos et al., 2022; Barceloux, 1999a)
• Cr exposure leads to a decrease in the expression of p53 thus influencing the cell death phenomenon.	(Tsao et al., 2011)

Thévenod, 2020). As other heavy metals, Cd enhances the production of ROS, not primarily, but by inhibiting antioxidant enzymes such as superoxide dismutase (SOD), and depleting glutathione (GSH) (Matović et al., 2011), so unbalanced detoxification and increased levels of oxidative stress are fundamental mechanisms of Cd toxicity. On DNA, Cd impairment is determined by both ROS damage, leading to aberration of DNA repair systems, alteration in chromosome separation during cellular division and epigenetic changes, and competitive Zn displacement from several DNA repair enzymes, due to Cd ionic mimicry ability. Besides, Cd blocks the mitochondrial electron-transfer chain by impairing electron flow, inhibits Adenosine diphosphate (ADP)- and uncoupler-stimulated respiration and boosts ion permeability within inner mitochondrial membrane, leading to apoptotic activation (Genchi et al., 2020). Cd can also modify intracellular signaling pathways through interaction with Ca^{2+} metabolism, playing a role as a partial blocker/agonist at its intracellular binding sites. Lastly, due to its characteristic, Cd falls into the group of endocrine disruptor chemicals, meaning compounds able to mimic or block endogenous activity of hormones, leading to adverse health outcomes in humans and animals (Bimonte et al., 2021). This exogenous interaction between Cd and hormone receptors, as estrogens or androgens receptors, causes blocking of hormones interactions with their natural counterpart and the improper activation of specific signaling pathways (Brama et al., 2007; Gore et al., 2015).

As for CRC, the role of environmental and occupational exposure to Cd remains not fully elucidated, and the available epidemiological data appear conflicting.

In a study conducted in 1979, the first occupational association between Cd exposure and CRC was investigated (Kjellström et al., 1979). This epidemiological study examined the incidence of CRC, along with other cancers, among Cd-nickel battery factory workers. While no statistical significance was reported, it was observed that battery factory workers exhibited a higher incidence of CRC compared to the general population.

A long exposure to Cd in the close proximity to industries releasing this metal could determine an higher risk in developing CRC (García-Pérez et al., 2020). In a hospital-based case-control study, Lin et al. found higher Cd levels in the blood of esophageal and CRC patients whit more advanced clinical stages compared to control patients (Lin et al., 2018). Despite this evidence, a significantly association between Cd exposure and CRC mortality has not been reached in the prospective study conducted by García-Esquinas et al. (2014). However, possible correlation between colon cell transformation and long-term exposure to Cd could be assumed. In a toxicogenomic in vitro study by Kwon et al. (2013), the authors investigated the deleterious effects of chronic low-dose exposure to Cd (cadmium) and Ni (nickel) on global profiling of DNA copy number variation, mRNA, and proteins in p53-proficient human colon carcinoma RKO cells. The study found that the 24-hour low-dose exposure to Cd led to the activation of a metal-specific signature involving stress proteins such as heat shock proteins (HSPs), phosphatases, kinases, and enzymes associated with cell proliferation, malignant transformation, and apoptosis networks. Specifically, the Cd-treated cells showed activation of a caspase (CASP)-associated apoptotic pathway, which included CASP3, CASP7, and CASP9. These findings provide valuable insights into the molecular mechanisms by which chronic low-dose Cd exposure can induce cellular stress and apoptosis in CRC cells.

Similar effect on CASP3, 7 and 9 has been showed in the study of Hajrezaie et al. (2015). In this work, the authors evaluated the cytotoxic ability of $CdCl_2(C_{14}H_{21}N_3O_2)$, a Schiff based complex, in activating apoptosis in HT-29 human colorectal adenocarcinoma cells. After 24 h, 3 μg/ml Cd treatment trigger Lactate dehydrogenase (LDH) release, increased ROS and cytochrome *c* levels, Matrix metalloproteinase (MMP) suppression, and activation of caspases after suppression of the NF-kB signaling pathway.

In contrast to these findings, the in vitro study by Naji et al. (2019) evaluated effects of Cd low levels on HT-29, demonstrating increased migratory activity of CRC cells. Notably, by analyzing molecular features of treated HT-29 cells, the authors demonstrated that 100 nM Cd increased ROS levels within the cells and activated both the p38-COX-2-PGE2 and the ROS-Akt pathway, thus enhancing migration cell capability. Activation of COX-2 by Cd has been demonstrated by Lu et al. (2015).

In this study, CRL1807 human colon cells were cultured for two months in a medium containing 5 or 10 μM of cadmium, which approximated doses of human non-occupational exposure, leading to cancer transformation. After transformation, these cells were injected into nude mice, where Cd-treated cells developed tumors that grew faster than those from mice injected with untreated cells. Proteomic analysis of transformed cells identified differentially expressed proteins in Cd-treated and untreated CRL807 cells, including RhoA, RalA, RhoGDI1, CSN, COX2, and NEDD9 proteins, along with associated signaling pathways. These findings provide insights into the mechanisms of Cd-induced colon cell transformation.

The health impact of Cd is huge and involves several organs. Toxicity on bone (Umemura and Wako, 2006; Schutte et al., 2008), kidneys and central nervous system (CNS), and also cardiovascular and reproductive toxicology has been proved (Rehman et al., 2018b).

Interestingly, Cd seems to have a dual effect on colon cells, depending on the time and concentration of in vitro treatment. Higher doses of the metal induce toxic and apoptotic responses within the cells, while lower doses activate cellular survival responses and stimulate proliferation. This suggests that Cd can modulate and transform colon cells in a dose-dependent manner.

In conclusion, the health impact of Cd is huge and involves several organs. Toxicity on bone (Umemura and Wako, 2006; Schutte et al., 2008), kidneys (Järup et al., 2000) and central nervous system (CNS), and also cardiovascular and reproductive toxicology has been proved (Rehman et al., 2018b).

Key concepts about the effect of Cd in CRC are listed in Box 3.

2.3.1. *Discussion and perspectives*

The health impact of Cd is extensive, affecting various organs such as bones, kidneys, the central nervous system, and cardiovascular and reproductive systems. Although the role of Cd exposure in CRC remains not fully elucidated, some studies suggest a possible correlation between long-term exposure to Cd and colon cell transformation.

In vitro studies have provided valuable insights into the molecular mechanisms underlying Cd-induced toxicity in CRC cells. Chronic low-dose Cd exposure has been shown to activate stress proteins and apoptotic pathways, while higher doses induce toxic and apoptotic responses. Moreover, Cd-treated cells exhibited altered protein expression and signaling pathways associated with colon cell transformation.

Future perspectives should focus on further investigating the relationship between Cd exposure and CRC development, with particular attention to different concentrations and durations of exposure. Understanding the dose-dependent effects of Cd and identifying specific molecular targets involved in Cd-induced transformation could lead to potential therapeutic interventions for CRC prevention and treatment. Additionally, efforts should be directed towards promoting industrial hygiene practices and reducing environmental Cd pollution to mitigate the adverse health effects of Cd exposure on human populations.

2.4. *Aluminium*

Al represents the 8.3 % of the total weight of earth's crust and it is widely distributed in nature (Chappard, 2016). Al is a very reactive element, and it combines with other elements, most commonly oxygen, silicon, and fluorine. According to ATSDR (Agency for Toxic Substances and Disease Registry (ATSDR), 2008), several are the uses of Al such as beverage cans, pots, pans, but also foils, airplanes, siding and roofing. In addition, powdered Al metal is often used in explosives and fireworks,

Box 3
Key points of Cd effects on colon cells.

Key points	References
• Cd is a carcinogenic heavy metal which has several employments in industry. Cd is mainly absorbed through inhalation and ingestion, although absorption through skin is also possible.	(ATSDR, 2012; Nordberg and Costa, 2021)
• In CRC cells, Cd seems to have a dual effect: higher doses of Cd induce toxic and apoptotic responses within the cells, while lower doses activate cellular survival responses and stimulate proliferation.	[(Kwon et al., 2013; Hajrezaie et al., 2015; Lu et al., 2015)
• Understanding the dose-dependent effects of Cd on colon epithelial cells could lead to potential therapeutic interventions for CRC prevention and treatment.	/

while Al compounds could be used in many applications such as alums in water-treatment and alumina in abrasives and furnace linings (Krewski et al., 2007a). Al is found in consumer products including drugs as antacids, astringents, buffered aspirin, vaccines, but also food additives, antiperspirants, and cosmetics (Sanajou et al., 2021; Shah et al., 2017; Bonfiglio et al., 2023a).

High environmental levels of the metal are generally associated to mining and processing of Al ores or the production of metal, alloys, and compounds but also from coal-fired power plants and incinerators. It could accumulate within air, as particles, but also in water and soil. As for other metals, exposure to the Al may occur mainly through skin and diet absorption (Tietz et al., 2019), while in the case of occupational exposure, during the refining of the primary metal and in secondary industries, the main route is represented by inhalation of dust and fumes containing Al. Within the body, Al elimination route follows primarily the kidneys, even if a little part of this metal is eliminated through the bile (Krewski et al., 2007b). Moreover, Al tends to accumulate mainly in lung and bone, but also in muscle, liver and brain, and its tissue concentration increases with age. As other toxic metals, Al increases ROS levels within the cells. Indeed, by disrupting homeostasis of metals such as magnesium (Mg), Ca, and Fe, Al triggers ROS production and target SOD and aconitase, so the following oxidative damage could be considered a possible mechanism for the onset of Al toxicity (Kumar et al., 2009).

Concerning the possible correlation between Al and CRC, the epidemiological study on trace elements within healthy and cancerous biopsies found no significative difference in Al concentration, although it was higher in cancer tissues compared to normal ones (Sohrabi et al., 2018). However, even if there's a lack in epidemiological results linking Al and cancer transformation in colon, some interesting evidence came from the bench. In an in vitro and in vivo study conducted by Pineton de Chambrun et al. (2014) demonstrated a possible correlation between Al and exacerbated inflammation and damage in colitis. Through three colitis mice models, the authors observed that oral administration of Al intoxication worsened intestinal inflammation. Specifically, the Al treatment led to increased intensity and duration of macroscopic and histologic inflammation, elevated colonic myeloperoxidase activity, and in chronic colitis models, it induced increased expression of inflammatory cytokines, such as IL-1b, IL-17a, and Nlrp3, along with decreased epithelial cell renewal compared to control animals.

In a later study, the evaluation of Al cytotoxicity and RNA expression patterns on HT-29 colon cancer cells has been performed (Djouina et al., 2016). By morphological and molecular investigations, the authors found that 100-200 μg/ml Al can alter cell cycle, inducing G1/S arrest, nuclear fragmentation and chromatin condensation which are hallmarks of apoptosis, and higher concentrations are able to increase production of ROS. Moreover, transcriptomic analysis of HT-29 cells exposed to noncytotoxic dosage of Al (100 mg/ml for 24 h), showed that this element is able to modify expression of several genes involved in cancer progression. In a study published in 2022, the effect of Al was evaluated on human biopsies isolated from patients with Crohn's disease and control subjects, as well as on Caco-2 colon cancer cells (Djouina et al., 2022). The findings of this study revealed that treatment with 100 μg/ml of Al citrate induced cytokine secretion in the colons of patients with Crohn's disease but not in healthy individuals. Moreover, confocal microscopy showed that Al was localized in the cytoplasm and nucleus of Caco-2 cells exposed to 100 μg/ml of Al citrate for 15 days. This exposure also led to an increased expression of inflammatory markers, such as NLRP3 and IL1β. Additionally, the study found a correlation between Al internalization and genetic polymorphism of ABCB1 or SLC26A3 transporters. These genetic variations may be responsible for increased colon susceptibility to Al-induced inflammation, suggesting that alterations in the detoxifying response might contribute to the development of inflammatory bowel disease (IBD) as well as CRC.

Another study performed on HT-29 human colon cancer cells demonstrated that exposure to cytotoxic doses of Al(4 μM) can impair several cell functions (Yu et al., 2019). Metabolomics and gene expression analysis revealed that Al induced modifications in the TCA cycle, glycolysis, gluconeogenesis, GSH metabolism, as well as increased levels of ROS and oxidative damage.

Consistent with the aforementioned studies, Jeong et al. (2020a) further demonstrated the oxidative and pro-inflammatory role of Al in colon epithelial cells. Treatment of HT-29 cells with increasing concentrations of $AlCl_3$ (0–16 mM) for 24 h led to a dose- and time-dependent increase in ROS and oxidative stress. This was associated with the activation of the ERK-NF-kB pathway, resulting in a reduction of epithelial barrier integrity through down-regulation of mRNA levels of tight junction molecules, such as occludins and claudins, and up-regulation of MMP-9 and MLCK. Furthermore, $AlCl_3$ treatment up-regulated pro-inflammatory cytokines TNF-a, IL-1b, and IL-6.

In a in vivo investigation (Jeong et al., 2020b), C57BL6 mice exposed to oral administration of $AlCl_3$ (5–50 mg/kg body weight) for 13 weeks exhibited pathological alterations, Myeloperoxidase (MPO) activation, and increased inflammatory cytokines (TNF-a, IL-6, and IL-1b) in the colon. These findings collectively suggest that Al may play a significant role in inflammation of colon epithelial cells and could be associated with various colon diseases, ranging from IBDs to cancer (Fig. 3).

However, it is worth noting that a quantitative mass spectrometry environmental and toxicological study on human colon adenomatous polyp tissues, compared to non-polypotic biopsies, did not find any differences concerning Al deposition in early-stage tumorigenic tissue and their normal counterparts (Alimonti et al., 2008). This implies that the relationship between Al and colon diseases may be complex and requires further investigation to fully understand its implications in different pathological conditions.

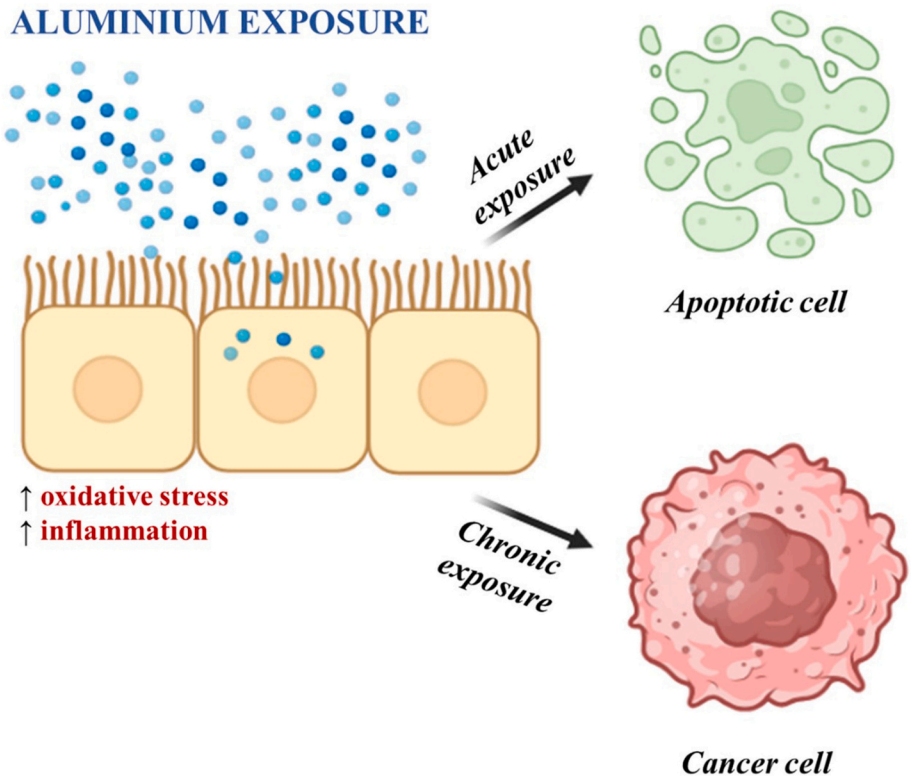

Fig. 3. Effects of aluminium on colon cells. The image depicts the effects of aluminium on colon cells. Acute exposure to aluminium can induce cell death through apoptosis. This acute exposure can lead to significant cell loss and tissue damage. On the other hand, chronic exposure to low doses of aluminium is associated with several pathological mechanisms. Specifically, low-level aluminium exposure triggers an increase in reactive oxygen species (ROS) within colon cells, resulting in oxidative stress. Prolonged ROS accumulation can initiate chronic inflammation involving immune cells, which, in turn, can damage healthy colon cells. Over the long term, chronic inflammation and cellular damage may contribute to genomic instability, increasing the risk of mutations and the potential development of tumor cells in the colon. The progressive formation of tumor cells could be linked to the cumulative effect of chronic aluminium exposure, suggesting a possible connection between prolonged exposure to this metal and the development of related conditions, such as colon cancer.
Fig. 3 has been created by using BioRender.

2.4.1. Discussion and perspectives

While the evidence points towards Al's potential pro-inflammatory and oxidative roles in colon epithelial cells, it is essential to acknowledge that the relationship between Al and colon diseases may not be straightforward. The lack of significant differences in Al deposition in early-stage tumorigenic colon tissues compared to healthy tissues warrants further investigation.

In light of these findings, future perspectives should focus on unravelling the precise molecular mechanisms by which Al induces inflammation and oxidative damage in the colon. Moreover, more comprehensive studies involving human cohorts and animal models could provide a clearer understanding of Al's role in various colon diseases and its implications for public health. Key concepts about the effect of Al in CRC are listed in Box 4.

2.5. Other metals: Cu, Hg and As

Cu is a noble metal found in transcription factors and in a variety of

Box 4
Key points of Al effects on colon cells.

Key points	References
• Al is a widely distributed metal and has several usages. Exposure to the Al may occur mainly through skin and diet absorption, while in the case of occupational exposure, the main route is represented by inhalation of dust and fumes containing Al.	(Agency for Toxic Substances and Disease Registry (ATSDR), 2008; Tietz et al., 2019)
• On colon epithelial cells, Al acts as pro-inflammatory and oxidative metal mainly in cancer or pathological inflammatory conditions, as evidenced by both in vitro and in vivo studies	(Pineton de Chambrun et al., 2014; Jeong et al., 2020a)
• Further studies based on human cohorts and animal models are required to clearly determine the role of Al in colon diseases and its implications for public health.	/

human enzymes. This is an essential trace element, and its deficiency impairs vital physiological functions as it is involved in heme synthesis and iron absorption (*LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]*, 2012). However, when exposed to living cells in excessive amounts, Cu can exert cytotoxic effects (Carcinogenic of Group 3 by IARC classification). The cytotoxicity of Cu is primarily attributed to its ability to generate ROS, causing oxidative stress and damaging cellular components such as lipids, proteins, and DNA. Furthermore, Cu ions can disrupt essential enzymatic functions and interfere with cellular signaling pathways, leading to cellular dysfunction and apoptosis (programmed cell death) (Barceloux, 1999b).

A study conducted in the Middle East showed how environmental pollution could play a role in the development of CRC. Fifty patients with confirmed diagnosis of CRC were enrolled, and through flame atomic absorption spectroscopy (FAAS) it was found that Cu concentrations in tumor tissues were higher than in control ones (Sohrabi et al., 2018). According to this, a study conducted in Poland showed that in a cohort of 187 patients with a diagnosis of CRC, average blood copper levels were higher than matched healthy counterparts (Baszuk et al., 2021). These evidences suggest a possible putative association between elevated Cu concentration and increased risk of CRC.

To date, an increasing number of studies have focused on cuproptosis, a new form of programmed cell death caused by excess intracellular Cu (Kirshner et al., 2008; Tsvetkov et al., 2019). Few investigations have focused on Cu-induced proliferation instead, which is an important process in tumor growth (Blockhuys et al., 2017). Cuproplasia, defined as copper-dependent cell growth and proliferation, is a newly recognized form of regulated copper-dependent cell proliferation (Ge et al., 2022), his term encompasses both neoplasia and hyperplasia, describes both primary and secondary effects of Cu via signaling pathways, and includes enzymatic and non-enzymatic copper-modulated activities. In this scenario, some approaches have been applied to assess patients' Cu status, such as measuring cuproenzyme activity and detecting routine blood counts because Cu depletion is reflected in a decreased count of white blood cells.

Zhang et al. (2023) identified a cuproplasia-related gene expression signature in CRC by informatic analysis. Also, survival data suggests that cuproplasia related genes could be a robust prognostic indicator and predictive factors for the benefits of immunotherapy in CRC patients. Of note, in an in vitro study it was demonstrated that copper-nanoparticles were able to induce apoptosis and oxidative stress in SW480 human colon cancer cells. Specifically, authors observed that CuNPs lead to increased expression of Bax and p53, and decreased expression of Bcl-2 thus inducing the apoptotic process. These data open interesting new perspective in the use of toxic element, in specific concentrations, to inhibit cancer progression.

Hg is a highly toxic heavy metal known for its severe cytotoxic effects on living organisms (Carcinogenic of Group 2 by IARC classification) (Yang et al., 2020). The cytotoxicity of Hg arises from its ability to interact with cellular components, disrupting vital processes and leading to cellular damage (Rupa et al., 2023). Hg can enter cells and generate ROS, causing oxidative stress and damaging crucial cellular structures, such as membranes, proteins, and DNA (Renu et al., 2021; Teschke, 2022). Additionally, Hg can inhibit enzymes and interfere with cellular signaling pathways, resulting in cellular dysfunction and apoptosis (Skalny et al., 2022; Hossain et al., 2021). The central nervous system is particularly vulnerable to Hg toxicity, and chronic exposure can lead to neurological disorders and cognitive impairments (Santos-Sacramento et al., 2021; Paduraru et al., 2022). Furthermore, Hg can accumulate in the food chain, posing a threat to wildlife and humans who consume contaminated fish or other seafood (McNutt, 2013). Given its potential for widespread environmental contamination and detrimental health effects, stringent measures are necessary to minimize exposure and manage Hg pollution effectively. The possible association between Hg intake and CRC risk has been investigated in Korea (Kim et al., 2020). Specifically, a case-control study with 2769 participants (923 cases and 1846 controls) was conducted in order to establish the dietary Hg intake and its association with CRC occurrence. Results of this epidemiological investigations showed that high intake of Hg are associated with an elevated risk of overall CRC.

Few data are currently available about the possible role of As in CRC. The toxic effects of inorganic As (Carcinogenic of Group 1 by IARC classification) on target organs have been studied extensively (Nurchi et al., 2020; Bolt, 2013), but there is little information about the toxicity of this form of As in the gastrointestinal tract, although food and drinking water are the main ways for exposure to this toxic element. In vitro studies have shown that acute exposure to inorganic As, particularly the trivalent form and the trivalent metabolites derived from it, generates oxidative stress and a proinflammatory response, and a redistribution of the proteins that form tight junctions, which are responsible for maintaining the structure of the intestinal epithelium (Calatayud et al., 2013; Calatayud et al., 2014). Chiocchetti et al. (2019) performed a long term exposure experiment in which no tumoral intestinal cell were treated with As(III) for 6 months. The results of this study showed that As(III)-treated cells were hyperproliferative, grew in low-serum media and were able to form free-floating spheres after 2 weeks of treatment thus suggesting a possible role of As in CRC carcinogenesis. Similar data were obtained by exposing female Swiss mice to As trioxide (As2O3) (Moulahoum et al., 2017). Results showed that As trioxide administration accelerated 1,2-dimethylhydrazine-induced colon carcinogenesis. Aberrant crypt foci distribution was found to be predominant in the distal part of the colons of treated mice. Moreover, histological analysis showed that As trioxide treatment induced cell death (apoptosis/necrosis) and induction of mitochondrial swelling, leading to the acceleration of the carcinogenesis process mostly in the distal colons.

2.5.1. Discussion and perspectives

Cu, Hg, and As, have distinctive cytotoxic effects on living cells and their potential implications for CRC development and environmental well-being. Further research and investigation into these toxicities are essential to develop effective strategies for minimizing exposure and mitigating their adverse effects on cellular health and overall well-being. Additionally, exploring the potential use of Cu nanoparticles in inhibiting cancer progression may pave the way for innovative therapeutic approaches. Overall, a comprehensive understanding of these toxic elements is crucial for safeguarding public health and promoting environmental sustainability.

3. Conclusions

This review sheds light on the hidden connection between toxic metal bioaccumulation and CRC, with a specific focus on Pb, Cr, Cd, Al, Cu, As, and Hg (Fig. 4). These toxic elements are ubiquitous in our environment due to industrial activities, pollution, and widespread use in various consumer products. Pb, Cr, Cd, Al, Cu, As, and Hg bioaccumulation in the human body over time can lead to chronic exposure, triggering a cascade of events that ultimately contribute to the development and progression of CRC. The mechanisms of toxicity for each metal vary, but they often involve oxidative stress, DNA damage, inhibition of crucial enzymes, disruption of cellular signaling pathways, and interference with essential biological processes.

Of particular concern is the intricate interplay of these toxic metals with genetic and molecular factors that can amplify their carcinogenic effects. Furthermore, recent studies highlight the emerging role of certain metals, such as copper, in promoting not only cytotoxicity but also cell proliferation, as seen in cuproplasia. These novel findings indicate that the impact of toxic metals on CRC is complex and multifaceted, requiring a deeper understanding to develop strategies of personalized medicine (Urbano et al., 2018; Schillaci et al., 2019a; Scimeca et al., 2021b; Schillaci et al., 2019b; Bonfiglio and Di Pietro, 2021; Amelio et al., 2020; Strafella et al., 2018; Ganini et al., 2021;

	82 Pb Lead Post-Transition Metal	24 Cr Chromium Transition Metal	48 Cd Cadmium Transition Metal	13 Al Aluminum Post-Transition Metal	29 Cu Copper Transition Metal	80 Hg Mercury Transition Metal	33 As Arsenic Metalloid
Biological functions	No physiological function	Glucose metabolism	No physiological function	No physiological function	No physiological function	No physiological function	No physiological function
Activated molecules and pathways	↑ROS	↑ROS-ATF6-PLK4 ↑RhoGDI ↑galectin, ↑c-Myc ↓p53 ↓RKIP	High dosage: ↑ROS ↑CASP3, ↑CASP7, ↑CASP9 Low dosage: p38-COX-2-PGE2 and the ROS-Akt pathway	↑TNF-a, ↑IL-1b, ↑IL-6, ↑IL-17a, Nlrp3 ERK-NF-kB pathway MPO	↑ROS ↑Bax, ↑p53, ↓Bcl-2	↓ROS	/
Impaired cellular processes	Oxidative stress Apoptosis	Disruption of cell cycle control Centrosome amplification Proliferation	Dual effect: - Apoptosis - Cell proliferation and migration	Reduction of epithelial barrier integrity Inflammation Oxidative stress	Curoptosis Curoplasia	Oxidative stress Cellular dysfunction Apoptosis	Carcinogenesis Aapoptosis Necrosis

Fig. 4. Biological functions influenced by bioaccumulation of toxic metals in colon cells. Image depicts the key biological functions influenced by the bioaccumulation of Pb, Cr, Cd, Al, Cu, Hg, and As in colon cells. The table also outlines the molecules and pathways activated by these metals and their impact on cellular processes. Understanding these effects is crucial for comprehending the potential health risks associated with exposure to these toxic metals and their contribution to colon-related disorders.

Cascella et al., 2018; Montanaro et al., 2021; Abruzzese et al., 2007; Scimeca et al., 2018d; Scimeca et al., 2018e; Scimeca et al., 2019b; Scimeca et al., 2018f; Scimeca et al., 2018g; Scimeca et al., 2019c). As set by the United Nations, the 2030 Agenda outlines a comprehensive framework to achieve sustainable development goals worldwide. Health and well-being are integral components of this agenda (Bonfiglio et al., 2023b), and efforts to combat the rising incidence of CRC must align with its objectives.

Data here discussed emphasizes the importance of enhancing environmental monitoring and regulatory measures to limit the release of toxic metals into the environment. This entails promoting cleaner production processes, proper waste disposal, and the reduction of hazardous substances in consumer products. Additionally, public health initiatives should focus on raising awareness about the sources of toxic metal exposure and implementing measures to reduce human contact with these harmful substances.

Moreover, healthcare systems need to adopt preventive approaches that include routine screening for toxic metal exposure, especially in high-risk populations. Early detection of elevated metal levels can prompt timely interventions and lifestyle modifications to mitigate their carcinogenic effects. In this context, a recent study by Buonaurio et al. (2021) proposes a highly interesting strategy to investigate the potential effects of toxic metals in exposed workers. The authors found that even very low exposure to toxic elements such as Pb, Hg, and Cu can alter the physiological processes related to nucleic acid integrity. This innovative approach could potentially lead to the early detection of hazardous exposures, even at low doses of toxic elements.

In conclusion, integrating personalized medicine and genetic profiling into clinical practice may offer valuable insights into an individual's susceptibility to metal-induced carcinogenesis, allowing for tailored prevention and treatment strategies.

4. Future direction

It becomes evident that there is still much to explore and understand about the intricate relationship between toxic metals bioaccumulation and their involvement in CRC. Looking ahead, several promising directions warrant our attention especially those reported in the 2030 agenda:

Precision Risk Assessment: Future research should focus on refining risk assessment models for individuals exposed to toxic metals, considering factors such as genetic susceptibility and variations in metal metabolism. This will enable more precise identification of individuals at higher risk for colon cancer due to metal exposure.

Biomarkers and Early Detection: Investigating specific biomarkers associated with toxic metal exposure and their role in the early detection of CRC could revolutionize screening methods. Developing non-invasive tests that can detect metal-related changes in colon tissue or biomarkers in bodily fluids may lead to earlier diagnosis and intervention.

Mechanistic Insights: Deeper investigations into the molecular mechanisms through which toxic metals like Pb, Cr, Cd, Al, copper, As, and Hg contribute to CRC development are essential. Understanding these mechanisms at the cellular and molecular levels can open avenues for targeted therapies or preventive strategies.

Environmental Control and Regulation: Collaborative efforts between researchers, policymakers, and industries are necessary to reduce environmental exposures to toxic metals. Stricter regulations, sustainable industrial practices, and innovative pollution control measures should be a part of the 2030 agenda to mitigate metal exposure.

Global Awareness and Education: Public awareness campaigns and educational initiatives should be part of the 2030 agenda to inform individuals about potential risks associated with toxic metal exposure and the importance of reducing such exposures in daily life.

Interdisciplinary Collaboration: Encouraging collaboration between researchers from diverse fields, including oncology, environmental science, genetics, and epidemiology, can foster a holistic

understanding of the intricate relationship between toxic metals and CRC.

By incorporating these future directions into our research agenda, we can work towards reducing the burden of CRC associated with toxic metal bioaccumulation and ultimately contribute to improved public health outcomes in the years leading up to 2030 and beyond.

CRediT authorship contribution statement

Rita Bonfiglio: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Renata Sisto:** Writing – review & editing. **Stefano Casciardi:** Writing – review & editing. **Valeria Palumbo:** Methodology, Writing – review & editing. **Maria Paola Scioli:** Methodology, Writing – review & editing. **Alessia Palumbo:** Methodology, Writing – review & editing. **Donata Trivigno:** Methodology, Writing – review & editing. **Erica Giacobbi:** Methodology, Writing – review & editing. **Francesca Servadei:** Methodology, Writing – review & editing. **Gerry Melino:** Writing – review & editing. **Alessandro Mauriello:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Manuel Scimeca:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Manuel Scimeca reports financial support was provided by University of Rome Tor Vergata.

Data availability

No data was used for the research described in the article.

Acknowledgements

None.

Funding

This work has been supported by the BRIC2022 (INAIL) by MS and by "Diagnostica Avanzata" PNC-E3-2022-23683266 PNCHLS-DA to GM, AL, EC, MS, MA and by Associazione Italiana per la Ricerca contro il Cancro (AIRC) to GM (IG 2022 ID 27366; 2023–2027).

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