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Cancer risk from heavy metals: mechanisms, evidence and toxicity pathways

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Introduction

This review discusses the risks of heavy metals induce malignancies, and reports the separate effects of nonradioactive and radioactive metals. We have used the term cancer as commonly used in literature to refer to all forms of malignancy. Heavy metals are pervasive environmental toxicants with recognized impacts on human carcinogenesis. Several metals including cadmium (Cd), nickel (Ni), and hexavalent chromium (Cr(VI)) are classified as Group 1 human carcinogens by the International Agency for Research on Cancer (IARC) (1). Others, including arsenic (As), beryllium (Be), and lead (Pb), are probable or possible carcinogens. Mechanistically, non-radioactive heavy metals promote cancer through chemical and biochemical mechanisms, whereas radioactive metals cause cancer primarily through ionizing radiation–induced DNA damage. These two pathways have distinct molecular patterns but converge on genomic instability with resulting malignant transformation.

Non-radioactive heavy metals: cancer through chemical mechanisms

Major metals with established carcinogenicity

Metals with strong epidemiologic and mechanistic evidence include: Cadmium (Cd), Nickel (Ni), Chromium (CrVI), Arsenic (As), Beryllium (Be), and Lead (Pb) (weak human data, strong mechanistic data).[1–6] Many others likely have similar potential but lack extensive study.

Key mechanisms of carcinogenesis

DNA damage and genomic instability

The patterns of Non-radioactive metals causing DNA damage are as follows:

Mechanisms:

- Oxidative DNA damage
- Abasic sites and strand breaks
- DNA–protein cross-linking
- Chromosomal aberrations and aneuploidy

Cadmium inhibits DNA repair rather than generating Reactive Oxygen species (ROS) directly:

- Suppresses Nucleotide Excision Repair (NER), Base Excision Repair (BER), and mismatch repair.
- Causes accumulation of unrepaired DNA lesions

Nickel induces chromatin condensation, impairing gene expression & repair.

Cr(VI) enters cells, is reduced, and generates ROS-mediated DNA damage.

- DNA double-strand breaks
- DNA adducts

Epigenetic dysregulation

Heavy metals alter:

- DNA methylation
- Histone modification
- miRNA expression

Nickel causes hypermethylation of tumor suppressor genes, silencing p16, RASSF. Cadmium and arsenic cause global DNA hypomethylation, with the net effect of causing genomic instability.

Oxidative stress and redox imbalance

Most metals generate ROS or deplete antioxidant defenses.

Effects include:

- Oxidative DNA damage (8-oxo-dG)
- Lipid peroxidation
- Protein oxidation
- Pro-inflammatory signaling

Cr(VI) and As are strong ROS inducers.

Cadmium inhibits antioxidant enzymes, indirectly causing ROS accumulation.

Inflammation and immune modulation

Chronic inflammation promotes tumorigenesis.

Mechanisms:

- NF-κB activation
- IL-6, TNF-α upregulation
- COX-2 induction

- Fusion outcomes that result in proliferation, angiogenesis, and alteration of survival and apoptosis. Fusion outcomes are the result of two or more biological events becoming fused together to form another entity, such as gene fusion or cellular fusion.

Endocrine disruption

Some metals act as metalloestrogens.

Cadmium mimics estrogen binding to ER-α, stimulating breast carcinogenesis.

Organ systems and cancer types for select metals

Cadmium

Cancers: lung, prostate, breast, kidney.[2]

Sources:cigarette smoke. mining/smelting, contaminated food (rice, grains).[2]

Nickel

Cancers: nasal/paranasal sinus, lung.[3,5]

Mechanisms dominated by epigenetic silencing.[3,5]

Chromium (Cr(VI))

Cancers: lung (strongest), nasal.[4,5]

Mechanism: intracellular reduction to Cr(III) + ROS + DNA crosslinks.[4,5]

Arsenic

Cancers: skin. lung, bladder.

A unique feature with arsenic is cancer promotion occurs without mutagenesis, via epigenetic + stem cell pathways.[6]

Explanation why many metals are carcinogenic

Many heavy metals interfere with:

- DNA repair pathways
- Cell cycle regulation
- Apoptosis
- Immune clearance
- Metabolic signaling

It is reasonable to assume that as these properties are shared by many metals, additional metals beyond those described above that alreadyare classified as carcinogens, likely have similar risk profiles.

Radioactive metals: malignancy induced by ionizing radiation

Radioactive metals emit alpha, beta, or gamma radiation, causing direct DNA damage, including:

- Double-strand breaks
- Base modifications
- Chromosomal fragmentation
- Telomere erosion

These lesions are highly mutagenic and difficult to repair.

Common radioative metals: Uranium (U). Thorium (Th). Radium (Ra). Polonium (Po), Plutonium (Pu).

Mechanisms of carcinogenesis

Direct DNA damage

Ionizing radiation creates the following: double-strand breaks, clustered DNA lesions, mutations in oncogenes/tumor suppressor.

Bystander Effects

Irradiated cells release signals that damage neighboring cells which result in: oxidative stress, apoptosis signaling, epigenetic changes

The result of neighboring or bystander cell injury is that malignancy occurs beyond the field of direct radiation exposure. This effect is also observed in medical imaging where x-rays (eg: CT) or gamma rays (eg: nuclear medicine, PET) are employed

Persistent Genomic Instability

Radiation creates long-term chromosomal instability, even in progeny cells.This is a key feature of radiation-induced carcinogenesis.

Cancer types associated with radioactive metals

Radioactive metals are at high risk to cause: lung cancer (inhalation), leukemia, thyroid, breast, gastrointestinal, bone cancer (radium incorporation).liver cancers (thorium, plutonium).[7] The timeline for induction of malignancies ranges from 2 years for blood cell line tumors (leukemia) to 20 years for solid organ tumors (liver).[7]

Individuals at highest risk for these malignancies are presently uranium miners and the result of nuclear accidents. An interesting and tragic historical group were radium dial workers.

Additional considerations

Synergy: Combined exposure of metals (e.g., Cd + As) produces synergistic mutagenesis, not merely additive. An important effect of two synergistic events that serve as a two hit mechanism is smoking with Cd exposure, which has been estimated as 100× lung cancer risk amplification.

Cancer preventive therapy unique to heavy metals: A recent book has described optimized therapy for removing heavy metals through chelation.[8] It is not unreasonable to consider that early recognition and removal of heavy metals through optomized chelation may serve to prevent the development of cancer, as cancer is generally a late outcome from toxicity.

Summery

Heavy metals create cancer risk through two mechanistically distinct pathways for nonradioctive metals (chemical toxicity) and ionizing radiation damage (radioactive metals). Chemical toxicity from non-radioactive metals result in: DNA damage, impaired repair, epigenetic dysregulation, oxidative stress, chronic inflammation, and endocrine disruption. Ionizing radiation from radioactive metals result in: direct DNA breaks, bystander effects, and persistent genomic instability. Although not the focus of this review these are the same events that occur with medical imagine that are based on x-rays (CT) and gamma rays (nuclear medicine, PET).

There are metals with clear association with malignancy induction (Cd, Ni, Cr(VI), As, Be), however it is most likely that the list is

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much longer than that described by AIRC classiification. This reflects that most metals cause: disruption of DNA repair enzymes, increase ROS, alter methylation, bind protein thiols, alter protein folding, impair apoptosis, and induce chronic inflammation.[6] It is reasonable therefore to consider that chronic exposure of many metals pose a risk for carcinogenesis (Table 1).

Table 1 Comparison of nonradioactive and radioactive metal patterns of injury.

Property	Non-radioactive metals	Radioactive metals
Metals	Cd, Ni, Cr, As	U, Th, Ra, Pu
Mode	Chemical	Physical (ionizing radiation)
DNA Damage	ROS, adducts, repair inhibition	Direct breaks, clusters
Epigenetics	Strong	Strong
Inflammation	Strong	Moderate
Mutagenicity	Indirect	Direct

Both patterns result in genomic instability and malignancy.

Acknowledgement

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Conflict of interest

None declared.

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