

**HEAVY METALS: TOXICITY AND CARCINOGENICITY**

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**Summary**

Heavy metals represent both essential components for the maintenance of normal biological functions, and toxic agents with damaging consequences when present in inappropriate amounts. In this review, we will consider the factors affecting metal toxicity and the principal chelating agents used for the treatment of metal intoxications.

**Keywords:** Heavy metals / Carcinogenicity / Toxicity / Chelating agents

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### Introduction

Toxic metal, defined "heavy metals," are elements and metal compounds that negatively affect people's health. Although there is no clear definition of what a heavy metal is, density is in most cases taken to be the defining factor. Heavy metals are thus commonly defined as those having a specific density of more than 5 g/cm<sup>3</sup>, they principally exist as cations and some may have different oxidation states and high tendency to form complex compounds. The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic (arsenic is a metalloid, but is usually classified as a heavy metal).<sup>1</sup>

Heavy metals are considered among the most dangerous and damaging polluting substances. They may be found in food, water and air, and, if assumed in high amounts they may alter biological functions and cause damage.<sup>1</sup>

However, in very small amounts, many of these are necessary to support life, in larger amounts, they can become toxic. They may build up in biological systems and become a significant health hazard.<sup>2</sup>

Since metals are widely distributed in environmental matrices. Humans are exposed to them by either anthropogenic activities or inadvertently by necessity.

### Toxicity and carcinogenicity

Toxic metals generally interfere with a number physiological processes, including central nervous system (CNS), haematopoietic, hepatic and renal functions. Given their specific interactions with cells, tissues and organs, metals can induce several toxic effects, that may be either local or systemic. Toxic effects can be acute or chronic. For example, acute intoxications by lead are rare, given its high capacity of accumulating in bone and erythrocytes, instead chronic intoxications (Saturnism) is more common.<sup>3</sup>

Some metals (e.g., Hg, Au, Pt, Be, Cr, Ni) may induce hypersensitivity reactions (Type I, Type II, Type III or Type IV)<sup>4</sup> and most metals may function as carcinogens or co-carcinogens.<sup>5</sup> Some carcinogenic metals are typically mutagens and teratogenic.<sup>6</sup>

In assessing the toxicity of metals need to consider several factors. It is important the half life, characteristic of each metal (e.g. for mercury is 60-70 days,<sup>7</sup> for cadmium is of 10-20 years<sup>8</sup> and for lead is 10 years<sup>9</sup>). Moreover, some metal can have, depending on the tissue, different half life: for Pb it corresponds to a few weeks in soft tissue, however, it is of 20 years in bone tissue.

It is important also chemical forms (elemental, organic or inorganic) and binding capability of the metal. In fact, the chemical form can strongly alter the pharmacokinetic properties of the metal, including its absorption, distribution and ability to reach the cellular and intracellular targets.<sup>10</sup>

In reality, the chemical form strongly affects route of exposure and bioavailability, as well as the toxicity profile. Organic forms of metals are usually highly lipophilic and, thus, easily cross biological membranes (e.g., gastro-intestinal wall, placenta, blood-brain barrier).

Accordingly, the organic forms of mercury (methylmercury, ethylmercury and phenylmercury), can cross the blood-brain barrier and to accumulate in lipophilic tissue giving neurotoxicity. In adult, the major toxic effects of organic forms are on the central nervous system, where loss of neuronal cells may occur in specific anatomical regions. Signs and symptoms include paresthesia, cerebellar ataxia, dysarthria, constriction of the visual fields and loss of hearing.<sup>11</sup>

Then, all organic chemical forms of mercury can cross the placenta and for this reason this metal is considered teratogenic.<sup>6</sup>

Compared to organic forms, inorganic salts of metals, usually hydrophilic, lead different toxic effects. In the case of the vapours of atomic Hg and inorganic salts (HgO, HgS and Hg<sub>2</sub>Cl<sub>2</sub>), they mainly cause renal toxicity.<sup>7a, 12</sup>

It is essential to underline that toxic effects of metals are often tissue-specific, and this is in most cases due to the presence of specific proteins that selectively bind metals (*Metallothionein*, MT).<sup>13</sup> In the case of cadmium, in the liver it can bind to glutathione (GSH) and be excreted through the bile or it may bind to metallothionein, thus forming a complex (Cd-MT) that represents a form of metal accumulation.<sup>14</sup>

In virtue of physical–chemical similarities, non essential metals (metals that do not play any role in physiological functions) many of which are toxic, may compete with essential metals (metals that are indispensable for several biological processes), thus disrupting homeostatic ionic equilibrium. For example, lead can substitute for iron in the ferrochelatase structure, thus disrupting iron incorporation into haemoglobin. Inhibition of ferrochelatase by lead represents one of the mechanisms implicated in the development of anaemia.<sup>15</sup>

Heavy metals often possess high affinity for thiolic, aminic, phosphoric and carboxylic groups of organic compounds showing a high tendency to combine with reactive sites of the biological molecules, including proteins and nucleic acids. Inactivation of sulfhydryl groups or displacement of essential metals may cause disruption of basic metabolic processes such as replication, transcription and repair of DNA.

Most metals may function as carcinogens or co-carcinogens producing a cascade of biochemical events (Fig.1).<sup>5b</sup>

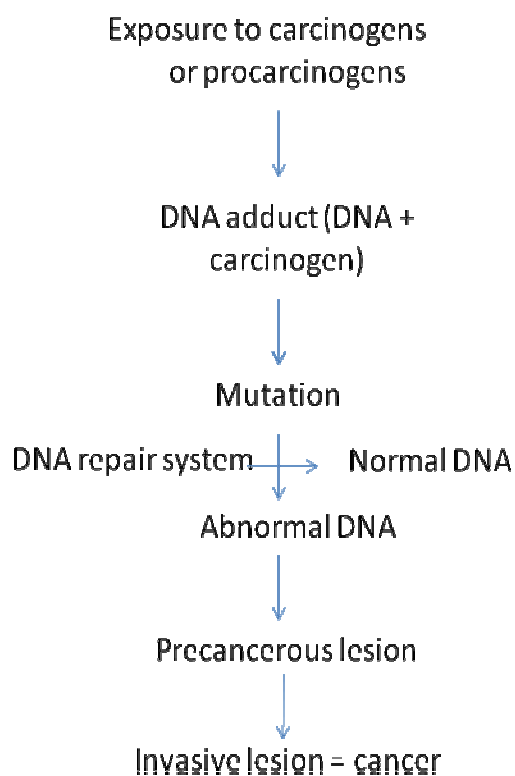


Fig.1: Schematic model of chemical carcinogenesis.

Based on epidemiological evidence, nickel, chromium and arsenic are classified as human carcinogens as well as cadmium, berillium and lead are potentially carcinogenic in humans.<sup>5a</sup> By contrast, the cancerogenicity of cobalt, iron, manganese, platinum, titanium and zinc has also been confirmed in animal studies and at very high doses.<sup>16</sup>

The exact mechanism of genotoxic action of metals is not completely understood but, usually, the cancerogenic potency increases with increasing electronegativity (range from 1.2 and 1.9) and decreasing solubility (the scarcely soluble compounds are more potent carcinogens than soluble salts).<sup>17-18</sup>

For example several mechanism have been proposed to explain arsenic carcinogenicity.<sup>5a</sup> The carcinogenic mode of action involves cytotoxicity followed by regenerative cell proliferation. The cytotoxicity is due to formation of a reactive metabolite, most likely dimethylarsinous acid (DMAIII), which causes oxidative damage and/or binds with critical urothelial sulfhydryl groups.<sup>5a</sup>

### Inactivation

Very important is the study of ways of elimination and inactivation of metals to prevent the deleterious effects. To limit absorption after a toxicant ingestion it is essential to performe a gastric lavage. Alternatively, various human metal intoxications can be efficiently treated by administration of chelating agents. These are chemical compounds able to bind the metal with a higher affinity as compared to endogenous ions, and to form a hydrophilic complex that can be easily eliminated.<sup>19</sup>

The main chelating agents used to treat metal intoxications are dimercaprol (BAL) and BAL-glucoside,<sup>20</sup> ethylene diamine tetraacetic acid (EDTA),<sup>21</sup> dimercaptosuccinic acid (DMSA) and dimercaptopropionic sulfonate (DMPS),<sup>22</sup> D-penicillamine,<sup>23</sup> and deferoxamine.<sup>24</sup>

Although chelating agents are useful for the detoxification of heavy metals they have many side effects (for BAL: hypertension, tachycardia, thrombocytopaenia, nephrotoxicity, for EDTA: renal system toxicity, for DMSA and DPMS: gastrointestinal discomfort, for D-penicillamine: glomerulonephritis and hypersensitive allergic reactions ect).

Therefore is desirable to identify new compounds specifically used for the treatment of poisoning from toxic metals more tolerable by the human body.

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