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Review

Biomonitoring of humans exposed to arsenic, chromium, nickel, vanadium, and complex mixtures of metals by using the micronucleus test in lymphocytes

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ABSTRACT

Various metals have demonstrated genotoxic and carcinogenic potential via different mechanisms. Until now, biomonitoring and epidemiological studies have been carried out to assess the genotoxic risk to exposed human populations. In this sense, the use of the micronucleus assay in peripheral blood lymphocytes has proven to be a useful tool to determine increased levels of DNA damage, as a surrogate biomarker of cancer risk. Here we review those biomonitoring studies focused on people exposed to arsenic, chromium, nickel, vanadium and complex mixtures of metals. Only those studies that used the frequency of micronuclei in binucleated (BNMN) cells have been taken into consideration, although the inclusion of other biomarkers of exposure and genotoxicity are also reflected and discussed. Regarding arsenic, most of the occupational and environmental biomonitoring studies find an increase in BNMN among the exposed individuals. Thus, it seems conclusive that arsenic exposure increases the risk of exposed human populations. However, a lack of correlation between the level of exposure and the increase in BNMN is also common, and a limited number of studies evaluated the genotype as a risk modulator. As for chromium, a BNMN increase in occupationally exposed subjects and a correlation between level of exposure and effect is found consistently in the available literature. However, the quality score of the studies is only medium-low. On the other hand, the studies evaluating nickel and vanadium are scarce and lacks a correct characterization of the individual exposure, which difficult the building of clear conclusions. Finally, several studies with medium-high quality scores evaluated a more realistic scenario of exposure which takes into account a mixture of metals. Among them, those which correctly characterized and measured the exposure were able to find association with the level of BNMN. Also, several genes associated with DNA damage repair such as *OGG1* and *XRCC1* were found to influence the exposure effect.

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1. Introduction

Heavy elements are widely distributed in the Earth's crust. They comprise a defined group of elements that include transition metals and some metalloids. Soil erosions by wind and water dissolution are natural mechanisms involved in the environment resulting in the occurrence of heavy elements in air and water matrices. Other natural phenomena, such as volcanic eruptions, can also contribute to the presence of metals in the environment [1]. Nevertheless, anthropogenic activities, such as mining and smelting, act as primary sources of metal spread by polluting wide areas, thus acting as important sources of human exposure [2]. For this reason, areas covering mining, foundries and smelters, as well as other metal-based industrial operations, are considered highly polluted zones. Workers involved in such activities or people living in surrounding areas are considered to be highly metal-exposed human groups [3,4].

Metals are of great importance in our daily life, and mankind as we know it would not have evolved if not for their existence. Their frequent use makes their omnipresence and a constant source of human exposure. This close relationship between humans and metals suggests that several metals are biologically considered essential nutrients, necessary for the correct functioning of various biochemical and physiological processes [5]. Cobalt, copper, chromium, iron, magnesium, manganese, molybdenum, nickel, selenium and zinc belong to the group of essential metals, but their presence in the body below or above certain concentrations can also lead to disease states [6]. In fact, for most metals, exposure has been linked to the induction of adverse health effects as well as to different human pathologies. From bacteria to humans, metal exposure has been associated with cell damage located in different organelles and membranes, with the proven capability of reaching the nucleus and interacting with DNA [7]. From this point of view, different metal compounds are considered genotoxic and carcinogenic [8–11].

The genotoxic and carcinogenic potential of metals is mainly dependent on their state of oxidation, as it affects their uptake, intracellular transport, distribution and bioavailability [12]. A general pattern of the genotoxic/carcinogenic mode of action of metals comprises the following steps: (1) Induction of oxidative stress and damage to cellular components, including DNA; (2) interference with DNA repair systems, resulting in genomic instability and (3) interruption of cell growth and proliferation via signalling pathways and deregulation of oncogenes or tumour suppressor genes [12,13].

Many studies have been conducted on human populations exposed to metals to determine the induction of biomarkers of genotoxicity. Unfortunately, in many cases, the exposure consists of complex mixtures of metals, making it difficult to assign the observed effects to one particular metal compound. This is true in the case of exposure to air pollution particles, for instance, where part of their genotoxic effects can be attributed to their metal contents [14]. A similar situation occurs in smelting operations, where metals other than the predominant one can be found at considerable concentrations in the area [15,16]

In addition to the epidemiological studies aiming to determine the carcinogenic risk associated with metal exposure, the biomonitoring of human populations exposed to potential xenobiotic agents gives us valuable information regarding exposure biomarkers and biomarkers of effect [17]. Among the biomarkers of effect, those used to detect DNA damage – primary or fixed at the gene or chromosome level – are of prime importance. Some of these biomarkers are considered surrogate biomarkers of cancer risk, particularly the frequency of micronuclei in peripheral blood lymphocytes (PBL) [18].

The micronucleus (MN) assay is regarded as a sensitive and simplistic method to perform. A MN is formed as a result of chromosomal breakage due to misrepair of DNA lesions or loss of chromosomal segregation due to mitotic errors [18]. The possible causative factors in MN formation are induction of oxidative stress, exposure to clastogens or aneugens, genetic defects in cell cycle checkpoints or DNA repair genes, deficiency of essential cofactors in DNA metabolism and chromosomal segregation [19–24]. Evaluation of MN frequency in PBL using the cytokinesis blocked micronucleus (CBMN) assay has been widely employed to measure chromosomal or genetic damage in human populations resulting

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