Biomonitoring Exposure to Metal Compounds with Carcinogenic Properties

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Several metals such as arsenic, beryllium, chromium and nickel are carcinogenic to man when they occur in certain well-defined physicochemical forms. The carcinogenic potential of these metals is linked to their mutagenic properties. The determination of the metal or possibly of its metabolites in biological media and the cytogenetic examination of somatic cells are two methods that can currently be used to monitor exposure of populations at risk. Due to the use of inappropriate methodology, the value of the positive cytogenetic results published so far appears questionable. By contrast, the concentrations of metals in blood, urine, or other biological materials can be determined with accurate and precise methods. Although it does not permit a direct assessment of the carcinogenic risk, this approach is currently the most suitable for monitoring exposed populations.

Carcinogenicity and Mutagenicity of Metal Salts

There is clear evidence that arsenic, beryllium, chromium, and nickel, when present in certain well defined physicochemical forms, represent a carcinogenic hazard to man. Earlier observations of cadmium carcinogenicity were not sustained by the recent updates of cohorts. To varying degrees, the epidemiological findings have been duplicated by positive results in laboratory animals but, if we except the case of arsenic, metal carcinogenesis is not a problem of environmental contamination at trace levels but is relevant to occupational medicine (1).

From the results of the several hundreds short-term tests performed to assess the carcinogenic properties of metal salts on the basis of mutagenicity (2), it can be concluded that there is a clear relationship between the carcinogenic potential of a metal compound and its genotoxicity. It is evident, however, that a number of assays such as the Ames' test on Salmonella typhimurium are not appropriate for assessing the carcinogenicity of metals (3). It is mainly on the basis of negative results obtained with this assay that it was inferred that metal carcinogens act by nongenotoxic mechanisms. Recently, however, it has been shown that some mutagenic substances do not induce significant reversion in the Ames test, although they produce forward mutations in mammalian somatic cells or in some bacteria, i.e., resistance to antibiotics or other detectable mutations that can be positively selected.

As far as mechanisms are concerned, forward mutations may be caused by unrepaired or unrepairable insertions, deletions, rearrangements, or point mutations that are not detectable in the Ames test. In that respect, it is of interest to point out that the fluctuation assay is a more sensitive technique than the plate incorporation assay. This illustrates the importance of choosing a method appropriate for highly toxic substances. These assays have also demonstrated that the response obtained depends on the ability of the metal to penetrate the cell and to interact with DNA, the chemical speciation, the physical properties (oxidation state, e.g., Cr(VI) and Cr(III), As(V), and As(III); charge, solubility, crystal form, properties of ligands, complex stereochemistry) and the possible interactions with other xenobiotics are, in that respect, critical. Metals such as Ni(II) or Cd(II) may be precipitated as insoluble phosphate salts due to orthophosphate ions present in the normal bacteriological culture medium and, for this reason, may not be detected as mutagenic. Some of the variation observed in the results of the bioassays of different metal salts could, therefore, be due to differences in bioavailability rather than in genotoxic potential (4).

The relation observed between the carcinogenicity of some metal compounds and their genotoxic potential does not exclude the possibility of additional mechanisms. Development of tumors is a multistep process in which initiation must usually be followed by various factors promoting growth of the transformed cells. Beside their general cytotoxic action causing denaturation of macromolecules, several metals may alter the fidelity of tran-
scription by DNA polymerase (5), produce apurinic intermediates (6), or compete with an essential metal needed to stabilize the structure of a biomolecule. B-DNA, the classical Watson-Crick double helix, contains 10 residues per turn, whereas Z-DNA, a left-handed double form of DNA, contains about 12 residues per turn (7). Some metal salts such as Ni(II) have been shown to induce conformational transition of B-DNA to Z-DNA, which is more sensitive for the induction of mutations by some chemicals (8). Several compounds, such as inorganic soluble arsenic salts can inhibit the repair of DNA damage (9). Other mechanisms could also play a role, such as blocking of cell-to-cell communication, stimulation of lipid peroxidation (10), solid-state carcinogenesis (11), inflammation and chronic mitogenesis increasing the probability of converting endogenous DNA damage into mutations (12), increasing intracellular radicals, interacting with detoxification mechanisms, catalyzing redox reactions, interfering with respiratory chains, increasing DNA alkylation by ubiquitous carcinogens affecting spindle apparatus, or destroying cellular homeostasis (13).

Biomonitoring People Exposed to Carcinogenic Metals

Methods currently available for the biological monitoring of populations exposed to mutagenic or carcinogenic chemicals evaluate the exposure to genotoxic compounds by measuring their concentration in body fluids, by estimating the amount of compound bound to target macromolecules (DNA), or by detecting various genotoxicity end points or early signs of neoplasia. The majority of these tests are, however, under development, and only three may be considered for routine biomonitoring: determination of the chemical or its metabolites in biological media, determination of the mutagenic activity in biological media, and cytogenetic observations on somatic cells. Mutagenic activity is generally detected by the Ames' test performed on urine. Because this test has been found to be inappropriate to detect the mutagenicity of metal compounds, the monitoring of people exposed to metal salts is generally restricted to the determination of the chemical in biological media and to cytogenetic analysis on peripheral blood lymphocytes.

Arsenic

Humans may be exposed to different arsenic compounds which markedly differ in their chemical and toxicological properties. In industry and in areas where drinking water is contaminated by arsenic, humans are exposed to inorganic arsenic, which may cause cancers of the respiratory tract (by inhalation) or the skin (by ingestion). In the humans, inorganic arsenic is methylated into two metabolites that are more readily excreted in urine: monomethylylarsonic acid (MMA) and dimethylylarsonic acid [DMA or cacodylic acid (14,15)]. High amounts of arsenic may also be absorbed through the consumption of fish and other marine organisms. Seafood, however, contains essentially organic derivatives of arsenic (e.g., arsenobetaine), which display a negligible toxicity and are rapidly excreted without further biotransformation.

Determination of Arsenic and Its Metabolites. The biological method currently used for monitoring arsenic exposure in industry relies on the determination of urinary arsenic with a speciation between organic and inorganic arsenic, MMA and DMA, to avoid the interference of arsenic from seafood. The total urinary excretion of inorganic arsenic and its metabolites is normally below 10 µg/g creatinine (16). The determination of total arsenic concentration in urine (without speciation) can be considered for monitoring exposure to inorganic arsenic only if the subject has been instructed to refrain from eating seafood 2 or 3 days before urine collection. The arsenic level in blood does not seem to be a reliable indicator of chronic arsenic exposure (17).

Because of their high content in sulfhydryl groups (keratin), nails and hair can accumulate inorganic arsenic but not or only to a small extent can these tissues accumulate the methylated metabolites of arsenic or arsenic from marine origin. In contrast to urinary or bloodborne arsenic, which reflects mainly recent exposure, hair and nails allow integration of the arsenic exposure over their period of growth. The concentration of arsenic in hair or nails is normally below 1–2 ppm (16). A segmental analysis of these materials may even provide information on the sequence of exposure episodes. The problem of hair or nail analysis is, however, to differentiate endogenous arsenic from arsenic adhering to the external surface (18).

Cytogenetic Observations on Somatic Cells. Arsenicals have been shown to be powerful clastogens in experiments performed in vitro on different mammalian cell types, and slightly positive results have been obtained in vivo in laboratory animals. In humans, no clear evidence of clastogenicity has been produced so far, despite the numerous cytogenetic studies carried out on highly exposed populations. The latter included patients treated with arsenic, wine growers contaminated by arsenic-containing pesticides, and workers exposed to airborne arsenic at the Rönnåker copper smelter in Northern Sweden (19–22).

Most of these studies have been performed on lymphocytes cultured for 72 hr. The number of cells examined was small (generally 100), and gaps contributed greatly to the increase of structural aberrations. In the smelters, the yield of structural aberrations was significantly increased compared to the controls, but the correlation between the frequency of aberrations and arsenic exposure was rather poor except for chromosome-type aberrations. Because in smelters the workers were generally exposed to a mixture of possible mutagens, the authors suggested that the role of arsenic was only to inhibit the repair of damage produced by other environmental agents (19–22). Observations on patients treated with arsenic could clarify the situation because doses are still higher and fewer possibilities of interference with other mutagenic agents exist. Petres et al. (23) and Nordenson et al. (24) reported a significant increase of aberrations in these persons, but this was not confirmed by Burgdorf et al. (26), in spite of
the fact that some patients received, in addition to arsenic, local irradiation doses as high as 50 Gy.

A similar contradiction appears in the ability of arsenic to increase the yield of sister chromatid exchanges (SCEs) in vivo in human peripheral blood lymphocytes: Burgdorf et al. (25) found a 3-fold increase of SCEs in six patients treated with arsenic, whereas the SCE rate was normal in both arsenic-treated and untreated patients examined by Nordenson et al. (24). It should be recalled that an increase of SCEs has been obtained in vitro with all the arsenic salts tested up to now (26).

Beryllium

Numerous epidemiological studies suggest an increase of respiratory cancers among persons occupationally exposed to beryllium. The carcinogenic activity of beryllium, whether administered in the form of the metal, alloys, or other organometallic compounds, has been confirmed in a number of experiments on laboratory animals.

**Determination of Beryllium.** Data on the toxicokinetics of beryllium in humans are insufficient to propose a reliable method for the biomonitoring of this metal. Beryllium can be measured in blood and urine, but it is not known to what extent the concentration of beryllium in these fluids relates to recent or past exposure. Observations on newly exposed workers suggest that beryllium in urine may be a reflection of the current exposure (27), but it has also been reported that the urinary excretion of beryllium may remain elevated several years after the end of exposure (28,29). In persons nonoccupationally exposed, the mean concentration of beryllium in urine and blood is around 1 μg/L (27).

**Cytogenetic Observations on Somatic Cells.** As far as we know, no cytogenetic study has been reported on workers exposed to beryllium.

Cadmium

Cadmium is efficiently retained by humans: it accumulates with a biological half-life of 10–30 years. The highest cadmium concentrations are found in the kidneys, which can account for more than 50% of the cadmium body burden at environmental exposure levels (16).

The carcinogenicity of cadmium for human is currently a much debated question. Earlier suspicion that exposure to cadmium compounds, primarily cadmium oxide, could be a factor in prostatic cancer, genito-urinary cancers, and gastric cancer has not been sustained by updates of the cohorts (30). The case for implicating cadmium in the induction of lung cancer has also been greatly weakened by a reappraisal of the data taking into account the possible confounding with exposure to arsenic (30).

**Determination of Cadmium.** The cadmium body burden may be directly estimated by a neutron activation technique (31). This noninvasive method which has been used to assess the critical level of cadmium in the human renal cortex (32,33), but it is not suitable to a routine application. The biomonitoring of populations exposed to cadmium in the work or general environment relies on determining the metal in blood and urine. The concentration of cadmium in urine is mainly a reflection of the cadmium body burden. In the general population exposed to cadmium via contaminated diet or by tobacco smoking, the urinary excretion of cadmium increases on the average with age to a maximal value reached between 50 and 60 years of age. In workers occupationally exposed to cadmium, the urinary excretion of the metal also increases with the duration of exposure in parallel with the body burden. There are, however, two situations in which urinary cadmium no more reliably mirrors the body burden: a) when the cadmium binding capacity of the organism is saturated, which may occur after acute or prolonged exposure to high levels of cadmium, and b) when the ability of proximal tubule cell to reabsorb cadmium and to store it is compromised by the occurrence of renal lesions (34). In the absence of occupational exposure, the concentrations of cadmium in blood and urine are normally below 5 μg/L and 2 μg/g creatinine, respectively (Table 1).

Exposure to cadmium can also be monitored by measuring the urinary excretion of metallothionein. The concentration of metallothionein in urine goes hand in hand

| Table 1. Biological methods for monitoring exposure to metals with established or suspected carcinogenicity (16). |
|--------|----------------|----------------|-----------------|----------------|
| Metal | Biological parameter | Biological material | Normal value | Tentative maximum permissible value | Remarks |
| Arsenic | Total As | Urine | < 40 μg creatinine | | Interference from fish consumption |
| | Total As | Hair | < 1 μg/g | | |
| | Inorganic As and its metabolites | Urine | < 20 μg/g creatinine | < 50 μg/g creatinine (TLV: 50 μg/m³) | |
| Beryllium | Be | Urine | < 2 μg/g creatinine | | Nonsmokers |
| Cadmium | Cd | Urine | < 2 μg/g creatinine | 5 μg/g creatinine | |
| | Cd | Blood | < 0.2 μg/100 mL | 0.5 μg/100 mL | |
| Chromium (soluble compounds) | Cr | Urine | < 5 μg/g creatinine | 30 μg/g creatinine | |
| Nickel (soluble compounds) | Ni | Urine | < 2 μg/g creatinine | 30 μg/g creatinine | |
| | Ni | Plasma | < 0.05 μg/100 mL | 1 μg/100 mL | |

TLV, threshold limit value.
with that of cadmium, regardless the status of renal function and the intensity of cadmium exposure. The advantage of metallothionein is that it is not influenced by the external contamination—a problem frequently encountered when monitoring trace metals in biological fluids (35).

Increased levels of cadmium have been reported in hair samples from persons occupationally exposed to cadmium or living in the vicinity of cadmium industries (36,37). The difficulty with hair analysis is to distinguish endogenous cadmium from external contamination. Furthermore, it is unlikely that the concentration of cadmium in hair is related with that in the main target organs (kidney or lung).

During exposure to cadmium, the blood cadmium concentration is mainly an indicator of the intake over the last few months (i.e., of the recent exposure) (31). In persons with previous high exposure (e.g., retired workers) the concentration of cadmium in blood may be predominantly influenced by the body burden if the amount of cadmium released from storage sites exceeds that currently absorbed.

**Cytogenetic Observations on Somatic Cells.** The majority of the assays performed in vitro and in vivo to evaluate the clastogenic properties of cadmium salts in mammalian cells yielded negative results (38), and this was confirmed by Bui et al. (39) on Itai-Itai patients and male workers from an alkaline battery factory and by O’Riordan et al. (40) on a population employed in the manufacture of cadmium pigments. In both studies none of the individuals had received radiotherapy or drugs known to produce chromosome damage. The cadmium blood level at the time of the cytogenetic observations were 1.95 µg/100 mL versus 0.2 µg/100 mL in the controls in the group studied by O’Riordan et al. (40) and, in the study of Bui et al. (39), ranged from 24.7 to 61.0 ng/g and from 15.5 to 28.8 ng/g for the industrial workers and the Itai-Itai patients, respectively.

Positive results were reported by several authors who studied workers exposed to cadmium in zinc smelting plants (41–44) or Japanese Itai-Itai patients (45,46). In the studies on industrial workers, the cadmium content of blood did not differ greatly from the values reported by O’Riordan et al. (40), and no correlation was found with the degree of exposure. Furthermore, it should be pointed out that persons working in such industries are exposed to a mixture of different metals. Itai-Itai disease represents a particularly severe manifestation of chronic cadmium poisoning and was observed in several hundreds of middle-aged women in a Japanese village near Toyama. This intoxication resulted from the ingestion of rice irrigated with water contaminated with cadmium, originating from a zinc mine. In addition to possible synergism, the increase in the yield of structural aberrations could also result from the fact that most of the patients received heavy radiodiagnostic exposures and various drugs.

**Chromium**

The behavior of chromium in the organism is greatly influenced by its oxidation state. The hexavalent chromium (e.g., chromate) can readily cross cell membranes and is well absorbed by inhalation or the oral route, whereas the trivalent ion hardly moves across cell membranes and is poorly absorbed. Inside the cell, hexavalent chromium is reduced to trivalent chromium. The Cr\(^{3+}\) ion trapped intracellularly can then react with target molecules and in particular with DNA (47). Since the first cases of lung cancers among workers in chromate-producing industry reported around the 1930s, several epidemiological surveys confirmed the existence of an increased risk of lung cancer in chromate-production workers and, to a lesser extent, in workers from the chrome-pigment industry. Experiments on laboratory animals showed that the carcinogenicity of chromium depends on the oxidative state and the solubility of the compounds. The most active compounds seem to be the less water-soluble hexavalent derivatives (e.g., CaCrO\(_4\), ZnCrO\(_4\)).

**Determination of Chromium.** Absorbed chromium is rapidly eliminated in urine with biological half-times ranging from 15 to 41 hr (48). The concentration of chromium in urine is a reliable index of the recent exposure to soluble, hexavalent chromium salts. In the presence of poorly soluble chromium compounds, significant amounts of chromium may be deposited in the respiratory tract without necessarily producing elevated levels in urine or plasma.

It is well established that chromium accumulates in human lung with age, whereas it decreases in other organs [e.g., kidney (49)]. The concentration of chromium in lung tissue, normally lower than 1 ppm (wet weight), may reach very high values in occupationally exposed persons. For instance, values ranging from 58 to 1400 ppm have been reported in chromium-refining or plating workers (50). The chromium concentration in lung tissue may thus serve as a quantitative indicator of the previous exposure. The concentration in lung tissue is an important criterion for establishing a causal link between bronchial carcinoma and occupational exposure to certain chromium compounds.

Because there is a marked difference between trivalent and hexavalent chromium compounds in their ability to cross cellular membranes, the determination of chromium in erythrocytes has been proposed to specifically evaluate the exposure to hexavalent forms of chromium which are the most hazardous for man (47,48). This method also presents the advantage of integrating the chromium exposure over the life span of erythrocytes (about 100 days).

**Cytogenetic Observations on Somatic Cells.** Hexavalent chromium has been shown to display clastogenic properties in vitro in mammalian cells and in vivo in laboratory animals, whereas trivalent chromium appeared generally inactive (51). The positive results reported by Bigaliev et al. (52) and Azhajev (53) on workers engaged in chrome production has not been confirmed, however, by Huszafel-Pursialnen et al. (54) and Littorin et al. (55) for stainless-steel manual metal arc welders exposed to fumes containing chromium (III) and nickel. In the study of Littorin et al. (55), the mean exposure time was 19 years, the air chromium level averaged 81 µg/m\(^3\) at the time of exposure, and the urinary chromium was 47 µmole/mole
creatinine, but, in spite of the high level of exposure, the yields of structural chromosome aberrations and of micronuclei or sister chromatid exchanges were not significantly different from the values found in the matched controls. In the three studies, structural chromosome aberrations were observed after a culture time of 72 hr, and the number of cells examined was relatively low. It is of interest to point out that a chromosomal study reported recently by Sbrana et al. (56) showed only a weak increase in aberrant cells of workers directly exposed to chromite, which was nonsignificant using different statistical methods.

Nickel

The carcinogenicity of nickel is well documented. Experimental studies in laboratory animals indicate that nickel compounds insoluble in water display high carcinogenic potential, whereas the majority of soluble nickel salts seem to be devoid of carcinogenic properties. A marked increase in cancers of the lung and the nasal sinuses has been observed in workers at nickel refineries.

Once absorbed, nickel is rapidly eliminated with an urinary elimination half-time ranging from 17 to 53 hr (57,58). Observations in retired workers indicate, however, the existence of nickel storage deposits with longer elimination half-times (58). Like chromium, nickel accumulates in lung with age (49).

Determination of Nickel. For soluble nickel compounds (e.g., NiCl2, NiSO4) the concentrations of nickel in urine or plasma reflect the amount of nickel absorbed during the preceding days (i.e., recent exposure) and are usually related to the airborne concentrations of the metal. In adults without occupational exposure, the levels of nickel in urine and in plasma are usually below 2 μg/g creatinine and 0.05 μg/100 mL, respectively (Table 1).

Poorly soluble nickel compounds (e.g., Ni3P2, NiO), like chromium compounds, may form deposits in the respiratory tract without necessarily increasing the nickel concentrations in urine or plasma. Under these conditions, the lack of elevated values in urine or plasma does not indicate the absence of health risk. The amount of nickel deposited in the upper respiratory tract may, however, be estimated by measuring the nickel concentration in the nasal mucosa. This may be useful, for instance, to confirm previous exposure in retired workers who have developed nasal carcinoma (58).

Cytogenetic Observations on Somatic Cells. Some observations have been made by Boysen et al. (59) and Waksvick et al. (60,61) on subjects working in nickel refineries at Falconbridge Nikkelverk, Kristiansand, Norway. In this plant the converter matte (50% Ni, 30% Cu, 20% S, and some trace metals) is refined through several processes, including crushing, roasting, smelting, and electrolysis. A total of 100 cells per person were analyzed for the presence of structural aberrations after 48 hr of culture. The plasma concentrations of nickel averaged 1–5.2 μg/L. The results revealed a drastic increase in the frequency of gaps among the workers, whereas there was only a slight enhancement of breaks. These positive findings were confirmed later (61) by observing an increase in gaps and breaks in retired workers with more than 25 years of nickel exposure. The yield of SCEs was not modified when compared to control values.

Conclusions

The results of the observations performed on peripheral blood lymphocytes of people professionally or accidentally exposed to heavy metals very often appear contradictory, and methodological features as well as the levels of intoxication cannot explain the differences obtained for people exposed under comparable conditions. Furthermore, the observations on peripheral blood lymphocytes frequently disagree with the properties revealed by the different heavy metals in the in vitro assays and in the experiments on laboratory animals.

Compared to powerful clastogenic agents such as ionizing radiation, metals have a limited ability to induce structural aberrations. The nature of the aberrations observed indicates that metal salts displaying clastogenic properties cannot be considered as S-independent agents because the most common aberrations are gaps and chromatid-type aberrations. Furthermore, the yield of aberrations is always low in spite of the fact that in vitro systems imply exposure to high concentrations of the salts and that in the in vivo experiments laboratory animals were treated with acute sublethal doses or submitted to chronic exposure for long periods of time. Except for cases with very high intoxication, it is therefore hard to believe that chronic exposures to low doses of weak clastogenic S-dependent agents could enhance the yield of structural chromosome aberrations detectable in a sample of 50–200 cells, representing only a very small fraction of the cell population which has been exposed.

The SCEs observed after culture of peripheral blood lymphocytes from persons exposed to chemicals are generally considered the result of damage produced in vivo to genetic material. Therefore, one cannot exclude the possibility that the level of exposure in the in vivo studies performed up to now was too low to induce such changes. The fact that some studies reported for the same people an increase of structural aberrations with the absence of any increase in SCEs may be interpreted as the evidence that these chromosome anomalies originate from other environmental agents.

Most people are exposed not to a single metal but to a mixture of environmental mutagenic agents. It is therefore extremely difficult to establish a causal relationship between a low increase in chromosome aberrations and one of the many components encountered in the environment because these agents may interfere with each other to produce synergistic or antagonistic effects. Therefore, the only conclusion that can be drawn from such studies is that the working conditions encountered in a given plant or workplace have or have not led to an increase in aberrations in the peripheral blood lymphocytes of exposed subjects. The value of such studies would be greatly improved by adopting a careful methodology, by analyzing a larger number of cells, and by using appropriate controls.
The determination of the metal in blood or urine currently appears the most suitable biological method for monitoring exposure to carcinogenic metals. The concentration of the metal in biological fluids or excreta can be measured with great accuracy and precision, and international programs for quality assurance are available. One must, however, realize that when determined in blood or urine, the concentration of the metal is usually an indication of recent exposure. Another limitation is that these methods provide no information on the interaction of the metal with DNA in target tissues. Only an indirect assessment of the probability of such an interaction can be envisaged by referring to the maximum permissible value established for the analyzed medium. But the latter are rarely derived from quantitative relationships between the measured concentration and the risk of carcinogenicity so that such an assessment may be tainted with much uncertainty.

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