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# Interactions by Carcinogenic Metal Compounds with DNA Repair Processes

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## 1. Introduction

Some metal compounds, including arsenic, beryllium, cadmium, chromium and nickel have long been recognized as human and animal carcinogens, while for other as antimony, cobalt, lead and vanadium their carcinogenic action are probable or possible. Except chromium (VI), carcinogenic metals are only weak mutagens in mammalian cells and often inactive in bacterial assays. Since the mutagenicity in bacterial assays indicates reactivity with DNA, metals are thought to exert genotoxicity mainly by indirect mechanisms. The four main, partly overlapping, DNA repair pathways operating in mammalian cells are base excision, mismatch, nucleotide excision and recombinational repair; each of repair pathways is involved in the removal of the specific DNA lesions. In addition, many carcinogenic metal compounds at low concentrations have been identified as inhibitors of the repair of DNA damage caused by other xenobiotics or endogenous factor. Furthermore, DNA is not only damaged by environmental mutagens including UV-light and polycyclic aromatic hydrocarbons, but also by reactive oxygen species generated from the same metallic elements. Failure to repair DNA damage can result in the accumulation of damaged DNA, mutation and carcinogenesis.

## 2. Mechanism of action

The potential target of metallic elements on DNA repair proteins are the zinc finger structures in their DNA binding motifs. Within these structures, zinc is complexed to four cysteines and/or histidines, folding different structural domains mediating DNA-protein as well as protein-protein interactions. It is estimated that about 1% of all mammalian genes encode zinc finger proteins, which are involved in many processes maintaining genomic integrity (Mackay & Crossley, 1998). The zinc ions do not participate in interactions conveyed by zinc finger domains, but are necessary for their function since they maintain their three-dimensional structures. In the case of transcription factors and DNA repair proteins, the absence of metal ions lead to loss in DNA-binding capacity. The functions of individual zinc finger include recognition of structures and sequences of nucleic acids and proteins. The majority of identified zinc finger may be classified as transcription factors. Another well known function of various zinc finger motifs, is the assembly of multiprotein

complexes having structural or enzymatic functions. The main zinc finger proteins involved are the bacterial formamidopyrimidine-DNA glycosylase (fpg), the xeroderma pigmentosum A (XPA) protein, the poly(ADP-ribose) polymerase (PARP) and tumor suppression protein p53. The studies about of metal ions interaction indicated that apparently similar zinc finger domains may have different reactivity and suggested to draw a sort of list of possible mechanisms of zinc finger damage (Hartwig, 2001). Among these mechanisms, the most important are isostructural substitution, substitution with altered geometry, mixed complex formation, and catalysis of thiol oxidation. Many studies showed that different concentrations are needed to observe an inhibition and wide differences were observed for example when comparing the results obtained with Fpg and XPA (Witkiewicz-Kucharczyk & Bal., 2006). Regarding XPA, arsenic and lead did not decrease its binding to a UV-irradiated oligonucleotide, whereas cadmium, cobalt and nickel interfere with its DNA binding ability. A simultaneous treatment with zinc largely prevented this inhibition (Asmuß et al., 2000). Structural investigations by different spectroscopic methods revealed a tetrahedrally co-ordination of all three metal ions with no major distortion of XPA while for cadmium an increased Cd-S bond length was observed. Poly(ADP-ribosyl)ation of various proteins is one of the earliest nuclear events following DNA strand break induction. Yager & Wiencke (1997) and Hartwig et al., (2002) demonstrated an inhibition of H<sub>2</sub>O<sub>2</sub>-induced PARP activity in intact cells by nickel, cobalt, cadmium and very low concentration of arsenic in HeLa cells, while no effect was observed with lead. One other zinc-dependent protein with great impact on the processing of DNA damage and genomic stability is the p53 suppressor protein. Zinc has been shown to be required for proper folding in wild type conformation, and exposure to either isolate p53 protein or human breast cancer cells to cadmium resulted in disruption of native p53 conformation and inhibition of DNA binding (Meplan et al., 1999). Witkiewicz-Kucharczyk & Bal (2006) assessed the different metal binding properties of zinc finger and reported that cobalt is practically isostructural with zinc in zinc finger peptides and proteins, regardless of the number of cysteine residues involved. However, there is a strong, although quantitative variable thermodynamic preference for zinc over cobalt in tetrahedral environments provided by zinc finger. This effect is due to the ligand field stabilization effect, modulated by entropic contributions (Lachenmann et al., 2004). The substitution of nickel into zinc finger can also be achieved, but it results in distortions of the binding geometry and alterations of the peptide fold. A distorted tetrahedral coordination was found for cysteine<sub>2</sub>-Histidine<sub>2</sub> zinc fingers (Posewitz & Wilcox, 1995), while a nearly square planar arrangement of donors was demonstrated in a cysteine<sub>4</sub> environment (Bal et al., 2003). Also the efficacy of cadmium binding is related to the number of coordinated thiolates (Krizek et al., 1993). Zinc seems to be preferred in the cysteine<sub>2</sub>-histidine<sub>2</sub> environment, the affinities of zinc and cadmium may be comparable for cysteine<sub>3</sub>-histidine, and cadmium is strongly preferred in cysteine<sub>4</sub> zinc finger peptides (Kopera et al., 2004). This preference is due to the high enthalpy of the cadmium-S bond. The cadmium ion fits into tetrahedral environments with little strain, however, it is significantly larger than zinc and cobalt ions, which results in local distortions of zinc finger geometries (Buchko et al., 2000). Finally lead, element with high affinities to thiolates, can replace zinc in zinc finger domains and disrupt their fold. Arsenic too is known to have a high affinity to -SH groups and it is demonstrated by arsenic-mediated repair inhibition not related with a direct mechanism of one or more specific repair proteins, but rather with changes in gene expression and/or signal transduction (Asmuß et al., 2000). Finally redox regulation has been *in vitro* and *in vivo* demonstrated in several DNA-binding zinc finger

proteins. The metal ions can oxidize the essential cysteines and/or other residues in zinc finger structures interfering in metal binding domain. Taken together, the above mentioned mechanisms indicate that DNA repair, zinc homeostasis, oxidative assault and the redox status of the cell are all interconnected (Fig 1). The toxic/carcinogenic metals with sufficiently high affinities to thiols may interfere at all stages of zinc homeostasis and signaling, but specific ways of their actions can only be understood in appropriately complicated experimental designs. Yet each zinc finger protein exerts its own structural function toward metallic compounds but no general prediction about this phenomenon appear to be possible.

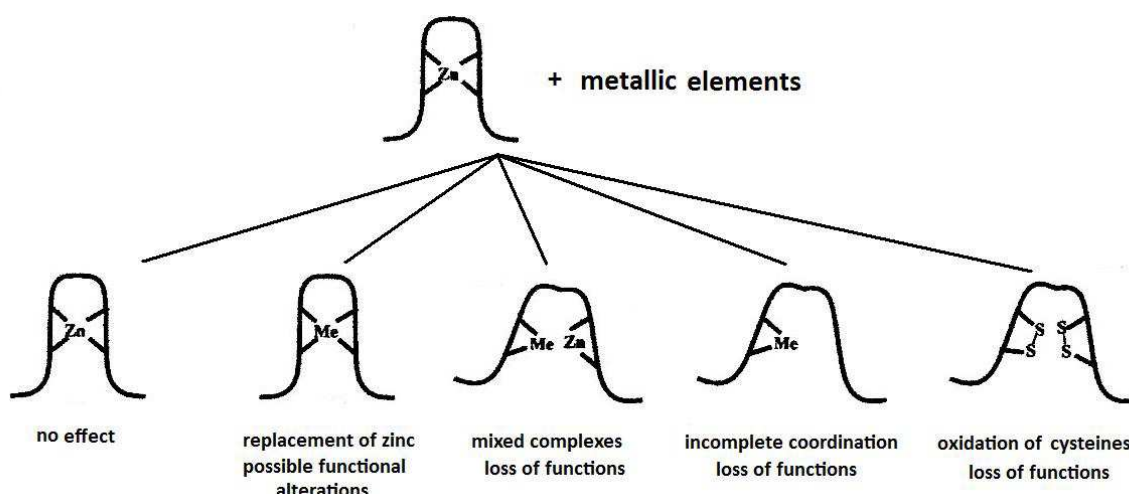


Fig. 1. Schematic representation of potential interactions of metallic elements with zinc-binding structures in transcription factors and DNA repair protein (modified from Hartwig et al., 2001).

### 3. Arsenic

Different mechanism of action have been suggested for arsenic carcinogenicity including the induction of oxidative stress, induction of genetic damage, altered DNA methylation patterns, enhanced cell proliferation, inhibition of the tumor suppressor protein p53, DNA repair alteration and recently biomethylation (Aposhian & Aposhian 2006). A possible molecular mechanism for arsenic toxicity may lie in its ability to react with thiols, for example, in zinc binding structures of transcription factors, cell cycle control and DNA repair proteins (Kitchin & Wallace, 2008). Nucleotide excision repair (NER) in particular is strongly inhibited by arsenic. NER is capable of removing a wide variety of bulky, DNA helix distorting lesions, caused, e.g., by UV-irradiation or environmental mutagens. Arsenic is known to enhance the persistence of bulky DNA lesions and consequently the mutagenicity induced by UV and benzo[a]pyrene (Hartmann & Speit 1996; Gebel, 2001). Since bulky lesion formation is the possible responsible for their carcinogenicity, genetic integrity depends largely on NER efficiency. Many studies have shown that inorganic arsenic inhibits repair of bulky DNA adducts induced by UV-irradiation (Hartwig et al., 1997; Danaee et al., 2004) or benzo[a]pyrene in cultured cells and laboratory animals (Schwerdtle et al., 2003; Shen et al., 2008); additionally arsenite has been shown to down-regulate expression of some NER genes in cultured human cells (Hamadeh et al., 2005). In

humans, arsenic exposure via drinking water was correlated with a dose relationship dependent to decreased expression of some NER genes and reduced repair of lesions in lymphocytes (Andrew et al., 2006). Human lymphoblastoid cells were pre-exposed to arsenite (As(III)) alone and in combination with UV, the pre-treatment with As(III) specifically inhibited the repair of UV-induced pyrimidine dimer-related DNA damage and leads to enhanced UV mutagenesis. Hartwig et al (1997) investigated the effects of arsenite in removal of benzo[a]pyrene-induced DNA damage. When damaged DNA is replicated prior to repair, these adducts can lead to mutations and cancer. This study was carried out in A549 human lung cancer cells; in absence of arsenite, about 45% of benzo[a]pyrene diol-epoxide-DNA adducts were repaired within 6–8 h, in presence of arsenite, there was a significant increase of adduct formation. Additionally, the repair capacity towards the stable lesions was decreased in a concentration-dependent shape reaching about 25% of the control at 75  $\mu$ M, a still slightly cytotoxic effect for this cell line (Schwerdtle et al., 2003b). Similar results have been obtained *in vivo*. Thus, in rats the frequency of benzo[a]pyrene-induced DNA adducts quantified by  $^{32}$ P post-labeling was drastically reduced in the presence of arsenite (Tran et al., 2002). Interesting was the evidence in the human study, arsenic exposure was associated with decreased expression of excision repair cross-complement 1 (ERCC1) in isolated human lymphocytes at the mRNA and protein levels. The mRNA levels of ERCC1 expression were positively associated with water arsenic concentration and nail arsenic concentration and significantly correlated with the amount of OGG1, a base pair excision repair gene (Mo et al., 2009). More detailed studies have been undertaken to assess the potential effects of the trivalent and pentavalent methylated metabolites on DNA repair processes. In humans and many other mammals, inorganic arsenic is converted into trivalent and pentavalent methylated metabolites, monomethylarsonous (MMA(III)) and dimethylarsinous (DMA(III)) acid, monomethylarsonic (MMA(V)) and dimethylarsinic (DMA(V)) acid. Biomethylation has long been thought to be a sort of detoxification process, yet nowadays it is reasonable to conclude that some adverse health effects seen in humans chronically exposed to inorganic arsenic are in fact caused by these metabolites. When considering MMA(III) and DMA(III) been demonstrated in some investigations as toxic, or even more toxic, compared to inorganic arsenic with an increase in benzo[a]pyrene diol-epoxide-DNA adducts formation and repair inhibition for MMA(III), at much lower concentrations than arsenite (Schwerdtle et al., 2003). Repair inhibition was also observed at 5  $\mu$ M DMA(III), but no effect on adduct generation was evident. Nevertheless, the cytotoxicity of the trivalent metabolites was also higher as compared to arsenite (Hartwig et al., 2003). Moreover, significant but less repair inhibition was mediated by 250 and 500  $\mu$ M of DMA(V) or MMA(V). Altogether, the results demonstrate that arsenite as well as the methylated metabolites interfere with cellular repair systems; the strongest effects with respect to inhibitory concentration were found for the trivalent metabolites (Schwerdtle et al., 2003b). Shen et al. (2009) investigated the difference manifested by DMA(III) compared to other trivalent arsenic species on the formation of benzo[a]pyrene diol-epoxide-DNA adducts. At concentrations comparable to those used in the study by Schwerdtle et al. (2003) they found that each of the three trivalent arsenic species were able to enhance the formation of benzo[a]pyrene diol-epoxide-DNA adducts with the potency in a decreasing order of MMA(III) > DMA(III) > As(III), well related with their cytotoxicity. Similar to As(III), DMA(III) the modulation of reduced glutathione (GSH) or total glutathione S-transferase (GST) activity could not account for its enhanced effect on DNA adduct formation. Additionally, similar effects elicited by the trivalent arsenic species were



demonstrated to be highly time-dependent. Nollen et al. (2009) investigated the gene expression, total protein level and localization of proteins during NER and comparing inorganic arsenite and MMA(III). Arsenite and MMA(III) strongly decreased expression and protein level of the main initiator of global genome NER, i.e. Xeroderma pigmentosum complementation group C (XPC). This led to diminished association of XPC to sites of local UVC damage, resulting in decreased recruitment of further NER proteins. These data demonstrate that in human skin fibroblasts arsenite and MMA(III) more interacts with XPC expression, resulting in decreased XPC protein level and diminished assembly of the NER. The observed stronger impact on XPC by MMA(III) may explain the more potent NER inhibition by MMA(III) as compared to arsenite (Schwerdtle et al., 2003; Shen et al., 2008). Finally, these data provide further evidence that in the case of DNA repair inhibition the biomethylation of arsenic increases inorganic arsenic induced genotoxicity and probably contributes to its carcinogenicity. With respect to DNA repair inhibition, several studies point to an interaction of arsenic with various DNA repair pathways, which may in turn decrease genomic integrity. The effect of arsenic on the extent of poly(ADP-ribosyl)ation has been investigated previously in two studies with controversial conclusion. Yager & Wiencke (1997) observed a decreased amount of poly(ADP-ribose) in human T-cell lymphoma-derived at arsenite concentrations above 5  $\mu$ M. In contrast, an increase of poly(ADP-ribosyl)ation reaction was reported at higher concentrations in CHO-K1 cells (Lynn et al., 1998). Hartwig et al., 2003b investigated the effects of arsenite on poly(ADP-ribosyl)ation stimulated by  $H_2O_2$  in intact cells by applying an anti-poly(ADP-ribose) monoclonal antibody. The experiments demonstrated a clear reduction of poly(ADP-ribosyl)ation level just evident at the extremely low and non-cytotoxic concentration of 10nM arsenite and reaching about 40% of residual activity at 0.5  $\mu$ M arsenite. There was an increase in induced DNA single strand break formation by arsenite in agreement with the assumed role of poly(ADP-ribosyl)ation in DNA strand break repair (Hartwig et al., 2003b). Also the effect of the arsenicals on the activity of the isolated formamidopyrimidine glycosylase (Fpg) was examined. Fpg is a glycosylase initiating base excision repair in *Escherichia coli*: it recognizes and removes a lot of DNA base modification including 7,8-dihydro-8-oxoguanine (8-oxoguanine). Even though Fpg is a bacterial repair protein, the recent discovery of human homologues suggests its relevance for mammalian cells too (Hazra et al., 2003). After 30 min preincubation MMA(III) and DMA(III) inhibited Fpg activity in dose-dependent shape, yielding 48 and 15% of the Fpg activity at 1 mM, respectively. In contrast, arsenite and the pentavalent metabolites did not show any effects on Fpg activity up to 10mM (Schwerdtle et al., 2003b). Finally, we describe the effects of arsenic compounds on the zinc finger structure of XPA. Different arsenicals promote the release of zinc from a peptide consisting of 37 amino acids representing the zinc finger domain of the human XPA protein (XPAzf). All trivalent arsenic compounds induced zinc release from XPAzf, starting at low micromolar concentrations, with MMA(III) and DMA(III) more active than arsenite. In contrast, MMA(V) and DMA(V) showed no or only slight effects up to 10mM (Schwerdtle et al., 2003b). Moreover there are some evidence about the influence of arsenic on BER, the predominant repair pathway for DNA lesions caused by reactive oxygen species (ROS) (Liu et al., 2001). Some studies have shown that low doses of arsenic can also cause an hormetic response in DNA polymerase  $\beta$  (Pol  $\beta$ ), as well as telomerase activity (Zhang et al., 2003; Snow et al. 2005). DNA polymerase  $\beta$  is not only responsible for the incorporation of nucleotides in BER, but also excises the 5'-deoxyribose-5-phosphate (dRP) moiety prior to completion of repair (Wilson, 1998). Sykora et al. (2008) investigated the regulation of DNA

polymerase  $\beta$  (Pol  $\beta$ ) and AP endonuclease (APE1), in response to low but physiologically relevant doses of arsenic. Lung fibroblasts and keratinocytes were exposed to As(III), and mRNA, protein levels and BER activity were assessed. Both Pol  $\beta$  and APE1 mRNA exhibited significant dose-dependent down regulation at doses of As(III) above 1  $\mu$ M. However, at lower doses Pol  $\beta$  mRNA and protein levels, and consequently, BER activity were significantly increased. In contrast, APE1 protein levels were only marginally increased by low doses of As(III) and there was no correlation between APE1 and overall BER activity. Enzyme supplementation of nuclear extracts confirmed that Pol  $\beta$  was rate limiting. These changes in BER are related to the overall protective against sunlight UV-induced toxicity at low doses of As(III) while at high doses there is a synergistic toxicity action. The results provide evidence that changes in BER due to low doses of arsenic could contribute to a non-linear, threshold dose response for arsenic carcinogenesis. The primary function of APE1 in BER is to act as an endonuclease responsible for the excision of apurinic/aprimidinic (AP) sites. However, APE1 is also a redox factor responsible for signal transduction in response to oxidative stress (Hsieh et al., 2001). Arsenic has the potential to affect both the endonuclease and the functions of APE1, through its increase in ROS levels and inhibition of DNA repair (Hamadeh et al., 2002).

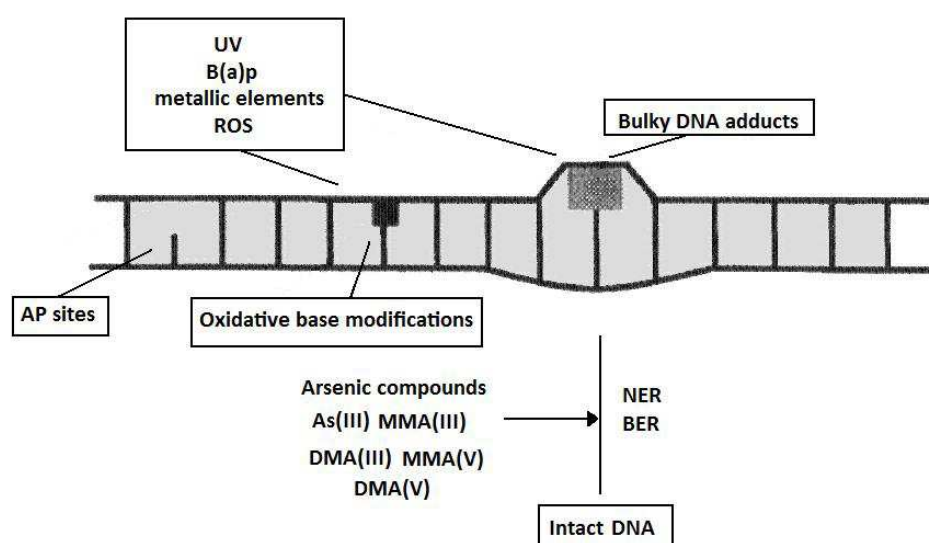


Fig. 2. Schematic outline of DNA repair inhibition by arsenite and its methylated metabolites(modified from Hartwig et al., 2003).

#### 4. Beryllium

Beryllium does not directly damage the DNA but it can lead to morphological cell transformation and inhibition of DNA repair synthesis. However, the effects observed on DNA repair are not specific for beryllium since similar findings are reported for other metallic compounds. A possible hypothesis is that the mechanism of genotoxicity is unlikely to be a non-threshold mechanism. A practical threshold can be postulated for beryllium since both direct DNA repair enzyme inhibition or DNA/protein expression-mediated effects do definitely require more than one ion to inhibit all DNA repair enzyme molecules (Strupp, 2011a). Dylevøi (1990), using four strains of *E. coli* with different DNA repairing capacities, established that beryllium efficacy in the DNA repair test depended

on pH of medium and ions concentration. The DNA of rat primary hepatocytes was treated by incubation with 2-acetylaminofluorene, a known DNA damaging agent, and co-incubated with beryllium metal extracts (Strupp, 2011b). They observed that, the DNA repair synthesis were reduced by co-incubation with beryllium metal extract. However, it should be noted that this effect was observed only when the concurrent DNA damage was massive (>80% cells in repair), while no effects were observed in cells with lower DNA damage. These findings deserve however further investigations about their relevance in vivo.

## 5. Cadmium

Several reports suggested that cadmium genotoxicity is not direct but rather mediated by reactive oxygen free radicals and resulting oxidative stress. In spite of being a weak genotoxic chemical, cadmium exhibits remarkable potential to inhibit DNA damage repair, and this has been identified as a major mechanism for its carcinogenicity (Giaginis et al., 2006). Cadmium is comutagenic and increases the mutagenicity of UV radiation, alkylation and oxidation in mammalian cells. These effects may be explained by cadmium inhibition on several types of DNA repair: base excision repair, nucleotide excision repair, mismatch repair and the elimination of the premutagenic DNA precursor 8-oxodGTP. Regarding base excision repair, low concentrations of cadmium which did not generate oxidative damage as such, inhibited the repair of oxidative DNA damage in mammalian cells (Dally & Hartwig 1997; Fatur et al. 2003). Exposure of human cells to sub-lethal concentrations of cadmium leads to a time and concentration dependent decrease in hOGG1 activity, i.e. of the main DNA glycosylase activity responsible for the initiation of the base excision repair of 8-oxoguanine, an abundant and mutagenic form of oxidized guanine. The study of Bravard et al. (2010) confirms that part of the inhibitory effect of low dose cadmium on the cellular 8-oxoguanine DNA glycosylase activity can be attributed to an already described reduced hOGG1 transcription (Youn et al., 2005). This moderate inhibitory effect of cadmium on hOGG1 mRNA levels cannot explain the dramatic decrease observed in the levels and activity of hOGG1 protein. Indeed, inhibition of the ectopically expressed hOGG1-GFP in cells exposed to the metal confirmed the post-transcriptional effect of cadmium on hOGG1 protein and activity levels. A different response of the second enzyme in the cellular BER pathway has been described. Bravard et al (2010) found that in vivo treatment of human cells with cadmium has no effect on the APE1 activity, suggesting that in their experimental conditions most cadmium is complexed within the cells and therefore the intracellular concentrations of free cadmium do not reach the levels required for the inhibition of APE1. These results, taken together with the indirect inhibition of hOGG1 by oxidation, support the hypothesis that the effects on the BER pathway are in the consequence of the cellular redox imbalance rather than the direct interaction with proteins. Candelas et al. (2010) showed that cadmium inhibits the repair of uracil (U) in DNA, resulting both from mis-incorporation and cytosine (C) deamination. These lesions, as those on AP sites, are common in any cell, and must constantly be repaired to avoid mutagenic events. The necessity to continuously repair these lesions is underscored by the high levels of expression of UNG2 and APE1 (Cappelli et al., 2001). This genotoxic consequence of cadmium exposure might participate in the deregulation of physiological cellular processes by altering the pattern of gene expression on the one hand (U), and increasing the mutation rate on the other hand (on



AP site), thereby interfering with the normal control of cell growth and division. Moreover cadmium exposure inhibits and modifies some proteins of BER such as formamidopyrimidine glycosylase (Fpg): the substitution of a cysteine in the zinc finger localized in the C terminal of Fpg protein may inhibit the binding of the protein to DNA (O' Connor et al., 1993). With respect to nucleotide excision repair, cadmium interferes with the removal of thymine dimers after UV irradiation by inhibiting the first step of this repair pathway (Hartwig & Schwerdtle 2002; Fatur et al. 2003). Also both association and dissociation of essential NER proteins are disturbed in presence of cadmium. Because of decreased of XPC nuclear protein levels, a reduced XPC localization to UVC-induced DNA damage in cells was observed after incubation with a non cytotoxic concentration of CdCl<sub>2</sub>. Interestingly, the tumor suppressor protein p53 also contain a zinc binding domain, which is essential for DNA binding and p53 function in transcription mechanism. In this context, Meplan et al. (1999) demonstrated that cadmium chloride alters p53 conformation in MCF7 cells, inhibits its DNA binding and down regulates transcriptional activation of a reporter gene. As p53 has been shown to act as a transcription factor for two important NER genes XPC and P48 and cadmium induced p53 conformational change may also result in altered p53 NER downstream effects (Adimoolam & Ford 2002). Cadmium exposure inhibits the xeroderma pigmentosum A (XPA) protein. XPA contains a typical four-cysteine zinc finger, which is not directly involved in DNA binding of the protein. The DNA binding capacity of XPA is strongly reduced after intoxication with cadmium (Hartmann et al., 1998; Hartwig et al., 2002). Another aspect is that cadmium found in liver and kidney cortex is bound to metallothioneins (MT), small, cysteine-rich metal-binding proteins which are considered to be protective from cadmium toxicity (Klaassen et al., 1999; Nordberg 2009; Chang et al., 2009). Nevertheless, Hartwig et al 2002 demonstrated that the inhibitory cadmium effect for fpg proteins were comparable independent of whether CdCl<sub>2</sub> or MT-bound Cd(II) was applied. Thus, metal ions complexed to MT may still be available for toxic reactions. In a recent study Schwerdtle et al., (2010) compared genotoxic effects of particulate CdO and soluble CdCl<sub>2</sub> in cultured human cells and reported that both cadmium compounds inhibited the nucleotide excision repair of benzo[a]pyrene diol epoxide-induced bulky DNA adducts and UVC-induced photolesions in a dose-dependent shape at non-cytotoxic concentrations. This agreement with the similar carcinogenic effects of both water-soluble and water insoluble cadmium compound indicates that Cd<sup>2+</sup> is the most common species responsible for indirect genotoxicity of the element (Oldiges et al., 1989).

## 6. Chromium

Among the carcinogenic metal compounds, only chromium (VI) has been clearly defined mutagenic in bacterial and mammalian test systems and its carcinogenic activity is thought to be due to the induction of DNA damage generated by reactive intermediates arising in its intracellular reduction to chromium (III) (Klein, 1996). Cr(VI)-carcinogenesis may be initiated or promoted through several mechanistic processes including, the intracellular metabolic reduction of Cr(VI) producing chromium species capable of interacting with DNA to yield genotoxic and mutagenic effects, Cr(VI)-induced inflammatory/immunological responses, and alteration of survival signaling pathways. The intracellular reduction of Cr(VI) produces a broad spectrum of DNA lesions including binary DNA adducts, DNA interstrand crosslinks (ICLs), DNA-protein adducts, DNA double-strand breaks and

oxidized bases (Nickens et al., 2010). On the contrary the knowledge about the role of DNA repair system in this process is lacking. Several lesions generated by Cr(VI) reduction (i.e. oxidized bases) are substrates for base excision repair (BER). In BER, damaged (alkylated or oxidized) bases are recognized by specific DNA glycosylases and are excised, resulting in the formation of apurinic/ apyrimidinic (AP) sites. Interesting to note that chromium(VI) can be reduced in body fluids, which results in its detoxification, due to the poor ability of chromium(III) to cross cell membranes. Infact chromium(VI), when introduced by the oral route, is efficiently detoxified up reduction by saliva and gastric juice and sequestration by intestinal bacteria (De Flora, 2000). Administration of up to 20 mg chromium (VI), either in drinking water or by gavage, failed to produce any effect in the mouse bone marrow micronucleus assay or in the rat hepatocyte DNA rapair assay (Mirsalis et al., 1996). The results of studies carried out by O'Brien et al (2002; 2005) suggested that NER functions is essential in the protection of cells from Cr(VI) lethality and for the removal of Cr(III)-DNA adducts. Brooks et al., (2008) suggest that NER and BER are required for Cr(VI) genomic instability and postulate that, in the absence of excision repair, DNA damage is directed an error-free system of DNA repair or damage tolerance.

## 7. Nickel

Epidemiological studies in exposed workers identified some species of nickel as carcinogenic for upper respiratory tract and lung (Polednak 1981; Roberts et al. 1984; Roberts et al. 1989). The carcinogenic potency depends largely on properties such as solubility and kind of salts, which influence its bioavailability. Water soluble nickel salts are taken up only slowly by cells, while particulate of nickel compounds are phagocytosed and, due to the low pH, gradually dissolved in lysosomes, yielding high concentrations of nickel ions in the nucleus (Costa et al., 2005). Using in vitro cells and animal models, nickel compounds have been found to generate various types of adverse effects, including chromosomal aberrations, DNA strand breaks, high reactive oxygen species production, impaired DNA repair, hypoxia-mimic stress, aberrant epigenetic changes, and signaling cascade activation (Lu et al., 2005). Nickel has been shown to interfere with the repair mechanisms involved in removing UV-, platinum-, mitomycin C, g-radiation- and benzo[a]pyrene-induced DNA damage (Dally et al., 1997; Hartmann et al., 1998; Schwerdtle et al., 2002). These comutagenic effects are explained by the inhibition of all major types of DNA repair processes. Potentially sensitive targets for the toxic action of nickel(II) are zinc finger structures present in several DNA repair enzymes, including the bacterial Fpg protein and the mammalian XPA protein, DNA ligase III and poly(ADP-ribose) polymerase (PARP). Some studies investigated the effects of nickel compounds on the repair of DNA and showed that both soluble and particulate nickel can inhibit repair of benzo[a]pyrene DNA adducts in human lung cells (Schwerdtle et al., 2002). Low doses of nickel chloride (1  $\mu\text{mol/L}$ ) inhibited repair of UV or N-Methyl-N-nitro-N'-nitrosoguanidine -induced DNA damage as indicated by accumulating strand breaks, and 1–5  $\mu\text{m}$  nickel chloride inhibited the formamidopyrimidine-DNA glycosylase (Fpg), 3-methyladenine-DNA glycosylase II (Alk A) and endonuclease III (Endo III) enzymes involved in DNA excision repair (Wozniak and Blaziak, 2004). The mechanisms of this action may include interactions with a specific structure containing zinc or the -SH groups of repair proteins. Because nickel compounds, such as NiS, Ni<sub>3</sub>S<sub>2</sub>, NiO (black and green), and soluble NiCl<sub>2</sub>, have been shown to be active inducers of reactive oxygen species (ROS) in Chinese hamster ovary cells, the involvement

of reactive oxygen species has been implicated in the inhibition of DNA repair (Lynn, 1997). Inhibition of glutathione synthesis or catalase activity increased the enhancing effect of nickel on the cytotoxicity of ultraviolet light. Inhibition of catalase and glutathione peroxidase activities also enhanced the retardation effect of nickel on the rejoining of DNA strand breaks accumulated by hydroxyurea plus cytosine-beta-D-arabinofuranoside in UV-irradiated cells. Lynn et al., (1997) showed that nickel, in the presence of  $H_2O_2$ , exhibited a synergistic inhibition on both DNA polymerization and ligation and caused protein fragmentation. In addition, glutathione could completely repair the inhibition by nickel or  $H_2O_2$  alone but only partially the inhibition by nickel when associated with  $H_2O_2$ . Therefore, nickel may bind to DNA-repair enzymes and generate oxygen-free radicals to cause protein degradation in situ. Schwerdtle et al., (2002) studied the effect of soluble and particulated nickel compounds on the formation and repair of stable benzo(a)pyrene DNA adducts in human lung cells. With respect to adduct formation, NiO, but not  $NiCl_2$ , reduced the generation of DNA lesions by ~30%. Regarding their repair in the absence of nickel compounds most lesions were removed within 24h; nevertheless, between 20 and 35% of induced adducts remained longer than 48h after treatment;  $NiCl_2$  (100 $\mu$ M) led to ~80% residual repair capacity; after 500 $\mu$ M the repair was reduced to ~36%. Also, even at the completely non-cytotoxic concentration of 0.5  $\mu$ g/cm<sup>2</sup> NiO, lesion removal was reduced to ~35% of control and to 15% at 2.0  $\mu$ g/cm<sup>2</sup>. Nevertheless, under the same experimental conditions, the extent of DNA strand breaks and oxidative DNA base modifications were increased only at highly cytotoxic concentrations of both compounds (Hartwig et al., 2002). Repair inhibition by nickel appears therefore to be independent from metal compounds, and the results do not provide an explanation for the marked differences in carcinogenic potencies between soluble and particulated nickel species. However when considering the carcinogenicity in human or in experimental animals the retentions times in the body have to be taken into account. Thus, analysis of nickel contents in rat lungs after inhalation of different nickel species, especially for NiO, an impaired clearance and up to 1000-fold higher and persistent nickel lung burdens have been shown when compared to water-soluble nickel sulphate (Dunnick et al., 1995). Therefore, exposure to particulate nickel compounds may give rise to continuous DNA repair impairment and thus the biological consequences may be far more severe. The overall data add further evidences that the inhibition of DNA repair processes is an important mechanism in nickel genotoxicity, especially, because these effects are observed at low, non-cytotoxic concentrations. Since oxidative DNA damage is continuously induced during aerobic metabolism, an impaired repair of these lesions might explain the carcinogenic action of nickel(II).

## **8. Interaction on DNA repair processes of metallic elements classified as a possible or probable human carcinogen**

### **8.1 Antimony**

Trivalent antimony is a known genotoxic agent and it is classified as a possible human carcinogen by the International Agency for Research on Cancer (1989) and as an animal carcinogen by the Deutsche Research Foundation (DFG 2008). The chemico-toxicological characteristics of antimony are similar to those of arsenic: their trivalent species are responsible for toxicological properties, and they have carcinogenic potential. In contrast to arsenic, however, informations about the toxicity of antimony and its possible mechanisms are limited. Tkahashi et al., (2002) investigated the effects of antimony

trichloride ( $\text{SbCl}_3$ ) and antimony potassium tartrate ( $\text{C}_4\text{H}_4\text{KO}_7\text{Sb}$ ) on the repair of DNA double strand breaks induced by  $\gamma$ -radiation. Antimony compounds inhibited repair of DNA double strand breaks in a dose dependent manner. Both in trichloride, 0.2 mM antimony significantly inhibited the rejoining of double strand breaks, while 0.4 mM was necessary in potassium antimony tartrate. The mean lethal doses ( $D_0$ ) for the treatment with antimony trichloride and antimony potassium tartrate, were approximately 0.21 and 0.12 mM, respectively. This indicates that the repair inhibition by antimony trichloride occurred in the dose range near  $D_0$ , but the antimony potassium tartrate inhibited the repair mechanism at doses where most cells lost their proliferating ability. This relationship is consistent with the general tendency of their respective toxicity: trivalent antimony compounds are less toxic than trivalent arsenic compounds, but more toxic than bismuth compounds (Leonard & Gerber, 1996; Huang et al., 1998). Grosskopf et al., (2010) show that trivalent antimony interferes with proteins involved in nucleotide excision repair and partly impairs this pathway, pointing to an indirect mechanism in the genotoxicity of trivalent antimony. After irradiation of human lung carcinoma cells with UVC, a higher number of cyclobutane pyrimidine dimers (CPD) remained in the presence of  $\text{SbCl}_3$ , whereas processing of the 6–4 photoproducts and benzo[a]pyrene diol epoxide (BPDE)-induced DNA adducts were not impaired. Nevertheless, cell viability was reduced more than in additive mode after combined treatment of  $\text{SbCl}_3$  with UVC as well as with BPDE. A decrease in gene expression and protein level of XPE was found and moreover, trivalent antimony was shown to interact with the zinc finger domain of XPA with concentration dependent release of zinc from peptide of this domain. Compared to the data on arsenite, antimony is more effective in zinc releasing from XPA, yielding 50% zinc release at 10 times lower concentration (Schwerdtle et al., 2003). Antimony might be able to interact with proteins involved in DNA repair, via their cysteine or histidine side chains. Complexes between antimony(III) and glutathione via sulphur binding site of the tripeptide have already been confirmed (Burford et al., 2005).

## 8.2 Cobalt

The carcinogenic potential of cobalt and its compounds was evaluated in 1991 by the International Agency for Research on Cancer (1991, 2006), the Commission concluded that cobalt and its compounds are possibly carcinogenic to humans (group 2B). Also the Deutsche Research Foundation (DFG 2008) has classified cobalt among the carcinogens of Category 2. Production of active oxygen species and inhibition of DNA repair appear to be the predominant mechanism of action in cobalt genotoxicity (Lison et al., 2001). Specifically by nucleotide excise repair pathway, in fact cobalt inhibits the removal of UV-induced cyclobutane pyrimidine dimers in mammalian cells but did not inhibit DNA strand rejoining after X-irradiation (Hartwig et al., 1991). Furthermore, by applying the nucleoid sedimentation assay in HeLa cells, Snyder et al (1989) demonstrated that cobalt causes an accumulation of DNA strand breaks after UV irradiation, indicating an impairment of the polymerization and/or the ligation step of nucleotide excision repair. Kasten et al. (1992) provided further evidence that cobalt at low non-cytotoxic concentration, inhibits both the incision and polymerization step of nucleotide excision repair in human fibroblasts. De Boeck et al., (1998) assessed the interference of cobalt compounds with the repair of primarily-induced DNA damage and showed that cobalt was able to cause persistence of methylmethanesulphonate-induced DNA lesions by interference its repair. In particular, cobalt inhibited the Xeroderma pigmentosum group A (XPA) protein, a zinc finger protein



involved in nucleotide excision repair (Asmuß et al. 2000) where it substituted for the zinc ion (Kopera et al. 2004). Cobalt at low, non-cytotoxic concentrations interferes with the incision step of UV-induced DNA repair, but the removal of lesions may not be uniformly affected (Kasten et al., 1997). This effect may be related to differences in processing these lesions. Regarding the effect of cobalt on the incision frequency, a potentially preferential inhibition of incisions at 6-4-photoproducts could be due to either the disruption of the highly effective damage recognition at the site of this lesion or to an enhanced inhibition of the global genome repair system, while the transcription-coupled repair is unaffected at low doses. In addition to the incision step, the polymerization is inhibited by cobalt as well, while the ligation of repair patches is not affected by this element. A possible mechanism of the interference of cobalt with DNA polymerases could be the competition with magnesium; in fact the inhibition of the polymerization step was completely reversed in the presence of magnesium ions (Kasten et al. 1992, 1997). Sirover and Loeb (1976) demonstrated a dose-dependent reduction of the catalytic activity as well as the fidelity of isolated DNA polymerases from different organisms after substitution of magnesium ions by cobalt. Taken together, the data indicate that cobalt belongs to a group of metal compounds which enhance the genotoxicity of direct mutagens.

### 8.3 Lead

The toxicity of lead and its compounds is well known for many centuries for anaemia, effects on nervous system and developmental disorders above all. Nevertheless, during the last years potential carcinogenic effects have been focused, leading to the classification of inorganic lead compounds as "Probably carcinogenic to humans" (Group 2A) by IARC (1987; 2006) and in the Group 2 by the Deutsche Research Foundation (DFG 2008). Although inorganic lead compounds exhibit only a weak mutagenic potential, they show more pronounced co-mutagenic activities in combination with DNA alkylating and oxidizing agents (Roy & Rossman, 1992; Hartwig et al., 1994). These effects were due to an interference with DNA repair processes, following an accumulation of DNA strand breaks, as shown in human HeLa cells after UV irradiation. Lead enhanced the frequencies of UV-induced mutations and sister chromatid exchanges at very low, nontoxic concentrations. Mutations as well as DNA strand breaks occurred only after long-term treatment at doses much higher than cytotoxic ones (Roy & Rossman, 1992). Considering the base excision repair, lead has been shown to inhibit the apurinic/apyrimidinic endonuclease (APE1) in micromolar concentration range both in an isolated enzymic test and in cells leading to an accumulation of apurinic sites in DNA and to an increase in methyl methanesulfonate-induced mutagenicity (McNeill et al. 2007). Current evidences suggest that inactivation of APE1 is mediated by a unique and specific interaction of metal with active site residues then disrupting the magnesium-dependent catalytic reaction. Furthermore, lead interferes with the repair of DNA double strand breaks via interaction with the stress response pathway induced by a phosphoinositol-3-kinase (PIKK) related kinase (Gastaldo et al. 2007). Due to its high affinity for sulfhydryl groups, a mechanism for lead interaction with proteins could be the displacement of zinc from zinc binding structures. In support of this assumption, in cell-free systems lead has been shown to reduce DNA binding of transcription factors (TFIIIA) and Sp1 (Huang et al. 2004). No impact was however described on the zinc-containing DNA repair proteins Fpg or XPA (Asmuß et al. 2000).

### 8.4 Vanadium

The International Agency for Research on Cancer has classified vanadium pentoxide ( $V_2O_5$ ) as a possible carcinogen (Group 2B) (2006) while the Deutsche Research Foundation included vanadium among the carcinogens of Category 2 (DFG, 2008). The genotoxicity of vanadium compounds is explained by mechanisms of induction of oxidative stress, inhibition of DNA repair and interference with the activity of protein phosphatases and kinases. Only few studies have been carried out about the genotoxic action of vanadium compounds; Ivancsits et al. (2002) tested the impact of vanadate(V) on DNA repair kinetics of UV and bleomycin treated human fibroblasts. They observed a significant increase of DNA migration in the alkaline comet assay accompanied by persistent double-stranded breaks after exposure to vanadate in combination with UV-light or bleomycin, as compared to vanadate treatment alone. This indicates that vanadate may act as an indirect genotoxic agent by converting repairable single-stranded breaks into non-repairable double-stranded breaks. This effect was confirmed by the strong differences between lymphocytes of workers exposed to vanadium pentoxide after bleomycin treatment and controls. Bleomycin-induced DNA migration was higher in the exposed group (25%), whereas the repair of bleomycin-induced lesions was reduced (Erlich et al., 2008).

## 9. Conclusion

The carcinogenic action of some metallic elements includes different mechanism such as induction of oxidative stress, inhibition of DNA repair, activation of mitogenic signalling, and epigenetic modification of gene expression. Nevertheless, each metallic elements and also each metal species exert characteristic interactions, and even though similar cellular pathways are affected, the underlying mechanisms are quite different. A relevant factor in metal carcinogenesis is the bioavailability of different metal species and the capacity to penetrate the cell barrier. The DNA does not appear to be the primary binding site for carcinogenic metal ions. This suggests that an inhibition of DNA repair processes may be a predominant mechanism in metal-induced genotoxicity. In addition, most carcinogenic metal compounds have been shown to increase the cytotoxicity, mutagenicity, and clastogenicity in mammalian cells when combined with different types of DNA-damaging agents (UV-light and/or alkylating agents). For most metal compounds, interactions with proteins appear to be more relevant for carcinogenicity as compared to direct DNA damage, and several targets have been identified, such as DNA repair, tumor suppressor and signal transduction proteins. Since metal ions can bind in principle to many electron rich centers in proteins the existence of particularly metal-sensitive protein structures may be suggested. The zinc finger proteins have been identified as potential molecular targets for toxic metal compounds and are involved not only in DNA binding but also in protein-protein interactions. Thus, there is an increasing evidence for zinc binding as structures very sensitive for toxic metal compounds. Significant factors appear to be not only the physicochemical properties but also accessibility and the protein microenvironment. The efficient repair of DNA lesions induced by endogenous processes and by environmental factors are an important prerequisite to maintain DNA integrity; if repair is not efficient, cells may accumulate DNA damage, leading to increased probabilities of genes instability and alteration in cellular cycle control and thus to tumor formation. The study and elaboration of metallic elements carcinogenicity should be conducted in parallel with dose-response studies in order to have a real idea of exposures especially when considering the possibility of co-exposures to other carcinogenic organic.

## 10. Abbreviations

APE1: Apurinic/apyrimidinic endonuclease  
 As(III): Arsenite  
 BER: Base excision repair  
 BPDE: Benzo[a]pyrene diol epoxide  
 CPD: Cyclobutane pyrimidine dimers  
 DFG: Deutsche Forschungsgemeinschaft, German Research Foundation  
 DMA(III): Dimethylarsinous acid  
 DMA(V): Dimethylarsinic acid  
 dRP: 5'-deoxyribose-5-phosphate  
 ERCC1: Excision repair cross-complement 1  
 Fpg: Formamidopyrimidine-DNA glycosylase  
 GSH: Reduced glutathione  
 GST: Total glutathione S-transferase  
 IARC: International Agency for Research on Cancer  
 MMA(III): Monomethylarsonous acid  
 MMA(V): Monomethylarsonic acid  
 MMR: Mismatch repair  
 MT: Metallothioneins  
 NER: Nucleotide excision repair  
 PARP: Poly(ADP-ribose) polymerase  
 Pol  $\beta$ : Polymerase  $\beta$   
 ROS: Reactive oxygen species  
 XPA: Xeroderma pigmentosum A  
 XPAzf: Zinc finger domain of the human XPA protein  
 XPC: Xeroderma pigmentosum complementation group C

## 11. References

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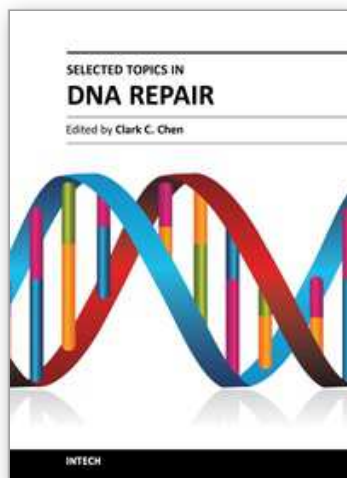
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This book is intended for students and scientists working in the field of DNA repair, focusing on a number of topics ranging from DNA damaging agents and mechanistic insights to methods in DNA repair and insights into therapeutic strategies. These topics demonstrate how scientific ideas are developed, tested, dialogued, and matured as it is meant to discuss key concepts in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

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