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REVIEW
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# INTERACTIONS OF ESSENTIAL AND/OR TOXIC METALS AND METALLOID REGARDING INTERINDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY TO VARIOUS TOXICANTS AND CHRONIC DISEASES IN MAN

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The review is a synthesis of the most recent evidence for the important role of the interactions of essential and/or toxic metals and metalloids regarding human health and diseases. Information is presented on the mechanisms of interaction between various metals and/or metalloids (including the influence of pH, exposure duration, and other exposure variables such as various life-style factors in man), possible differences in the susceptibility to adverse health effects between man and other mammals, and the role of metals and metalloids in oxidative stress-mediated diseases, antioxidant defence system, adaptive response and genetic repair processes. With regard to generally large interindividual differences in the susceptibility to various toxicants in humans, further epidemiological research in the quantitative contribution of interaction between lead, cadmium, copper, zinc and selenium, based on biological monitoring, is recommended. Interaction of these elements may explain individual susceptibility to various chronic diseases, even those showing transgenerational characteristics (such as significantly lowered sperm count and fertilizing capacity of men over the last five decades, known to have occurred in the general population world-wide).

*Key terms:*
adaptive response, antioxidant defence system, cadmium, copper, free radicals, genetic repair, lead, oxidative stress, selenium, zinc

Essential metals and metalloids (e.g. Zn, Cu, Fe, Ca, Mg, Co, Cr(III), Mo, Ni, Mn, K, Na and Se) are known to be beneficial for the health and longevity of man and other mammals, because their deficiency causes impaired function and damage to the organism, although each can be toxic if by any means it is overly accumulated in the organism (1-8). In the past there has been more concern about the health effects of »too little« rather than »too much«, as one tends to

regard an essential element as having only beneficial effects. Recent epidemiological studies have shown that many of the essential metals are interactive, and that the metabolism of some essential metals can alter the metabolism of other metals even at low to moderate exposure levels, particularly when exposure is long-term. For example, the gastrointestinal absorption rates of Cu, Fe and Zn are interrelated so that an increase or decrease of one alters the absorption or metabolic requirement of the other (8). Variation in exposure levels of some essential metals, and an essential metalloid such as Se, may alter their respective relative amount necessary for the optimum activity of enzymes requiring these elements as co-factors (8–10). Increased interest in the toxicity of essential elements (7, 8) has evolved because evidence is emerging that subtle deviations from, or even within the range of their »normal values« in human biological specimens, can affect vital cognitive and immune functions, which has great importance for public health. However, possible interaction of exposure to other metals and metalloids has on the whole been ignored when reporting such »normal values« in humans, and an ongoing international project (»TRACY«) is attempting to establish reliable *reference values* for a particular metal or metalloid in human biological specimens. This has also prompted governmental regulatory agencies, such as the U.S. Environmental Protection Agency, to set environmental standards for several essential elements in the same way as for toxic elements such as Pb, Cd, Hg and As.

Among the essential elements, Zn and Se appear to be particularly important because of the wide range of their beneficial effects in man, and the fact that relatively large variation in the Zn and Se exposure levels is usually found among the general population. For example, it is known that Zn is required for optimum activity of over 200 enzymes (including those for genetic repair), nutritional and/or conditioned Zn-deficiency is regarded a major public health problem throughout the world, and Zn-deficiency is common for patients in a period of stress, trauma or inflammation, although such risk of Zn-deficiency is frequently overlooked (1, 11–13). The major beneficial effects of Se relate to its high antioxidant capacity in preventing formation of free radicals or as a radical scavenger, its role in antioxidant defence system as the essential component for optimum activity of the enzyme glutathione peroxidase, its capability of binding several toxic metals and metalloids and thus making them unavailable to act adversely, and by its ability to prevent and/or suppress the development of chronic diseases such as cancer, atherosclerosis etc. (1, 3, 9, 10). It is also known that the average Se levels in blood or serum of the general populations widely differ between, and quite often within, different countries (2, 14).

Toxic metals and metalloids (e.g. Pb, Cd, Hg, Al, Tl, Cr(VI), Ag, Ba, Be, Bi, Sn, Ge, Sb, Te and As) can also be interactive between each other, and with certain essential elements (1–6). Their toxicity is regarded to be mainly because they substitute the essential elements in various enzymes and/or change enzyme steric conformation, thus affecting enzyme activity. However, in most cases the exact mechanism(s) of interaction(s) of essential and/or toxic metals and metalloids is not known and, in particular, their *quantitative* interrelationship(s)

to the corresponding health effect(s) in man remains to be established. Namely, evidence is accumulating that such *dose-response relationships* may considerably differ between humans and other mammals, and particularly between primates and rodents. The effects of certain metals and metalloids, and the contribution of their interaction(s) in either increasing or decreasing individual susceptibility to adverse health effects, are known to be *specific* for a particular chemical form, i.e. »speciation« of the metal or metalloid. For example, compounds of the trivalent chromium, Cr(III), are essential while those of the hexavalent chromium, Cr(VI), are highly toxic; organometal compounds of Hg, Pb and Sn are considerably more toxic than inorganic, while the reverse is the case for As compounds.

Among the toxic elements, Pb and Cd appear to be particularly important because of the wide range of their adverse effects in man, the fact that they are pervasive in the human environment, and are both known to accumulate in the human body over a lifetime, including pre-natal life (especially Pb). The biological half-lives of Pb and Cd in the human body (i.e. the time for clearance of half the body burden of the metal following cessation of exposure) are estimated to be about 10–20 years, whereas data regarding various target organs are particularly scarce and inconclusive (1–3). It is known, however, that Pb is mostly accumulated in the bones, whereas Cd is mostly accumulated in the renal cortex. Although the storage of Pb in bones (up to 95% of the body burden of Pb) has long been considered to be a sequestration or removal of Pb from its active sites in soft tissues, recent data have shown that Pb can be mobilized from bones under certain stresses and physiological changes (15). Apart from numerous sources of occupational exposure to each of the metals, the most important non-occupational sources are: food (especially seafood from metal polluted areas), water (Pb mostly from Pb pipes in contact with soft and acidic water), air (especially Pb from petrol in dense traffic areas), smoking habits (Cd and to a lesser extent Pb from tobacco) and alcohol consumption (Pb-contaminated alcoholic beverages). There is also some evidence of the possible effect of Pb and alcohol interaction in man, i.e. an ethanol-induced increase in the biologically active fraction of Pb accumulated in the organism (16, 17).

Recent epidemiological studies have indicated possible toxicokinetic interaction between Cd and Zn (18), and Pb and Zn (19), resulting in relative Zn-deficiency even at low to moderate exposure levels of Cd or Pb. Such observations are important because they may help to explain the conflicting results of epidemiological studies on the various adverse health effects of Pb and/or Cd. Namely, it is known that human exposures to Pb and Cd, occupational or environmental, quite often involve considerable exposure to Zn (and vice versa), which may act as an antagonist and thus mask the Pb- and/or Cd-related effects. Moreover, interactions of Pb and/or Cd with Zn have the potential for explaining the development of certain diseases showing transgenerational characteristics, such as considerably lowered sperm count and fertilizing capacity in men (20, 21) which is known to have occurred in the general population world-wide over the last five decades (22).

## Mechanisms of interaction of various metals and metalloids and possible differences in susceptibility to adverse health effects between man and other mammals

Various metals and metalloids can interact by influencing each other's absorption rate, distribution in the organism, biotransformation and/or excretion rate (where »biotransformation« refers to their formation of conjugates or complexes with various compounds in the organism and/or changes in their valency or oxidation state). This is mostly due to the competition for the same binding site(s) in various enzymes (and thus affecting enzyme activity), various proteins involved in their transport and distribution (especially metallothionein, which binds many metals and metalloids and the synthesis of which can be induced by certain metals, e.g. Zn and Cd but not Pb), and various tissues (especially cell membranes and organ barriers), thus affecting their function (1–6). Metals and metalloids generally have high affinity for binding to the sulfhydryl or »thio-« (-SH) groups, and also to other ligands such as the phosphate-, amino-, or carboxy- groups (3, 4). A consequence of the induced biosynthesis of metallothionein (MT), i.e. a low molecular weight protein containing many -SH groups and protecting against toxicity of several metals and metalloids, is an increase in tissue content of elements other than the inducing agent. For example, following MT induction by orally administered Cd in rat, the renal concentrations of MT-bound Zn, Cu and Hg can increase in parallel with Cd, although the renal toxicity of Hg can thus be lowered (4). Similarly, formation of compounds or complexes among metals and metalloids can reduce the biological availability of the elements involved, which can explain the protective effect of Se against the toxicity of Hg, and possibly also As, Cd, Pb, Bi, Co, Cu, Pt, W, Ge, Sb, Ag, Tl and Te (1–4).

Recent evidence shows that the effects of acute exposure may widely differ from those of chronic exposure to a particular metal or metalloid. For example, animal experiments using acute simultaneous exposure to Se with a toxic metal, i.e. Hg, Cd, or Pb, usually show increased tissue deposition of a toxic metal compared to exposure to the metal alone (conceivably due to formation of biologically inert metal-Se complex), as opposed to chronic exposure situation (which corresponded to normal or slightly increased human exposure to these elements) when Se decreased, rather than increased, toxic metal retention and tissue deposition (4, 23). Such differences are important because the large majority of information about interactions of metals and metalloids relates to animal experiments at high doses and/or relatively short-term exposures, and is not applicable to human exposure situations.

If various metals and metalloids were present in equimolar concentrations (which is applicable to laboratory conditions only), elements with small atomic radius and high valency state would have particularly great affinity for binding sites in biota, although none as great as the hydrogen ion ($H^+$) and thus the role and vital importance of the tissue pH is clear (4). Apart from pH, the relative ionic concentrations of metals and metalloids are highly important for the outcome of their binding to bioligands. However, regardless of the type of biological

mechanism involved, the intensity of most interactions may be influenced by the concentration and other exposure variables, among which the exposure duration and the life-style factors such as dietary habits, smoking, alcohol, use of medications, and occupational and/or environmental exposure to other chemicals, play a highly important role (4, 24).

In general, the mechanisms of interaction between different chemicals and/or other factors can be roughly divided regarding two basic consequences of interaction: (A) the quantity of the chemical in a target organ, i.e. at the site(s) of its effect in the organism, is changed - *toxicokinetic interactions*, or (B) the intensity of a specific response corresponding to the quantity of the chemical in a target organ, e.g. enzyme activity or adverse health effect, is changed - *toxicodynamic interactions*. However, both toxicokinetic and toxicodynamic interactions (i.e. A and/or B) may influence individual susceptibility to a particular chemical, resulting in a change in the speed or sequence between initial reaction and final adverse health effect. The influence of several concomitant factors can result in either: (a) *additive effects* - when the intensity of the combined effect is equal to the sum of the effects produced by each factor separately, (b) *synergistic effects* - when the intensity of the combined effect is greater than the sum of the effects produced by each factor separately, or (c) *antagonistic effects* - when the intensity of the combined effect is smaller than the sum of the effects produced by each factor separately (24).

The quantity of a particular toxic chemical or characteristic metabolite at the site(s) of its effect in the human organism can be more or less well assessed by biological monitoring (2, 6), i.e. by choosing the correct biological specimen and optimal timing of specimen sampling, taking into account specific biological half-lives for a particular chemical in both the critical organ and the applied biological specimen. However, reliable information concerning other possible factors that might influence individual susceptibility in man is generally lacking, and consequently the majority of knowledge regarding the influence of various factors is based on experimental animal data (24).

It should be stressed that relatively large differences exist between man and other mammals in the intensity of response to an equivalent level and/or duration of exposure to many toxic chemicals, including several metals and metalloids (1). For example, man appears to be considerably more sensitive to the adverse health effects of methyl-Hg and inorganic Pb, and to differ in Se metabolism, compared to the rat (commonly used in experimental animal studies). Moreover, it has been concluded that markers of toxicity of essential elements identified in experimental models must be validated in human subjects, and that human studies should be used as a basis for the evaluation of adverse health effects (8, 10). Some of these inter-species differences can be attributed to the fact that the transportation, distribution and biotransformation pathways of various chemicals are greatly dependent on subtle changes in the tissue pH and the oxido-redox equilibrium in the organism (as are the activities of various enzymes), and that the oxido-redox system of man differs considerably from that of the rat. This is obviously the case regarding important antioxidants such as vitamin C and

glutathione (GSH), which are essential for maintaining oxido-redox equilibrium and which have a protective role against the overproduction and adverse effects of the oxygen- or xenobiotic-derived free radicals which are involved in a variety of pathological conditions. Namely, man is incapable of auto-synthesizing vitamin C, contrary to the rat and most other mammals; the level as well as the turnover rate of erythrocyte GSH in man is considerably lower than that in the rat; the levels of vitamin C and protein -SH content in the respiratory tract lining fluids are also lower in man compared to either the rat or guinea pig (25); man is also deficient in some of the protective antioxidant enzymes compared to the rat and other mammals, e.g. glutathione peroxidase is considered to be poorly active particularly in human sperms (26). These examples illustrate the potentially greater vulnerability to oxidative stress in man (which can be manifested in particularly sensitive cells, e.g. apparently greater vulnerability of the human sperm to toxic influences than that of the rat), which can result in different response or greater susceptibility to the influence of various factors in man compared to other mammals (24).

Although human exposures to metals quite often, if not typically, involve multiple elements, very few studies of human subjects have attempted to investigate how different metals may interact in inducing health effects. The changes in susceptibility to adverse health effects due to interaction of various metals and/or metalloids have been studied mainly in experimental animals (mostly in the rat), and predominantly relate to combinations of only two different elements, high doses and short-term exposures. Relevant clinical and epidemiological studies are lacking, particularly when considering the possibly greater intensity of response or the variety of adverse health effects in man compared to other mammals. However, in man there is a variety of possible multiple interactions of both essential and/or toxic metals and metalloids (24), as these are involved in the possible influence of age (e.g. a lifetime body accumulation of environmental Pb and Cd), sex (e.g. a common Fe-deficiency in women), dietary habits (e.g. increased dietary intake of toxic metals and metalloids and/or deficient dietary intake of essential metals and metalloids), smoking habit and alcohol consumption (e.g. additional exposure to Cd, Pb and other toxic metals), and use of medications (e.g. a single dose of an Al-containing antacid can result in a 50-fold increase in the average daily intake of Al through food). The possibility of various additive, synergistic or antagonistic effects of exposure to various metals and metalloids can be illustrated by basic examples related to the main toxic elements (see table), apart from which *further* interactions may occur because essential elements can also influence one another (e.g. the well known antagonistic effect of Cu on the gastrointestinal absorption rate as well as the metabolism of Zn, and vice versa). These interactions may have a relevant role in the development of several chronic diseases which are mediated through the action of free radicals and oxidative stress. However, growing evidence of species differences between humans and animals in metal metabolism and mechanisms of metal toxicity makes human studies all the more valuable for health risk assessment purposes.

Table. *Basic effects of possible multiple interactions concerning the main toxic and/or essential metals and metalloids**

| | |
|---|---|
| Al | – decreases the absorption rate of Ca and impairs the metabolism of Ca; deficient dietary Ca increases the absorption rate of Al<br>– impairs phosphate metabolism<br>– data on interactions with Fe, Zn and Cu are equivocal (i.e. the possible role of another metal as a mediator) |
| As | – affects the distribution of Cu (an increase of Cu in the kidney, and a decrease of Cu in the liver, serum and urine)<br>– impairs the metabolism of Fe (an increase of Fe in the liver with concomitant decrease in hematocrit)<br>– Zn decreases the absorption rate of inorganic As and decreases the toxicity of As<br>– Se decreases the toxicity of As and vice versa |
| Cd | – decreases the absorption rate of Ca and impairs the metabolism of Ca; deficient dietary Ca increases the absorption rate of Cd<br>– impairs the phosphate metabolism, i.e. increases urinary excretion of phosphates<br>– impairs the metabolism of Fe; deficient dietary Fe increases the absorption rate of Cd<br>– affects the distribution of Zn; Zn decreases the toxicity of Cd, whereas its influence on the absorption rate of Cd is equivocal<br>– Se decreases the toxicity of Cd<br>– Mn decreases the toxicity of Cd at low-level exposure to Cd<br>– data on the interaction with Cu are equivocal (i.e. the possible role of Zn, or another metal, as a mediator)<br>– high dietary levels of Pb, Ni, Sr, Mg or Cr(III) can decrease the absorption rate of Cd |
| Hg | – affects the distribution of Cu (an increase of Cu in the liver)<br>– Zn decreases the absorption rate of inorganic Hg and decreases the toxicity of Hg<br>– Se decreases the toxicity of Hg<br>– Cd increases the concentration of Hg in the kidney, but at the same time decreases the toxicity of Hg in the kidney (the influence of the Cd-induced metallothionein synthesis) |
| Pb | – impairs the metabolism of Ca; deficient dietary Ca increases the absorption rate of inorganic Pb and increases the toxicity of Pb<br>– impairs the metabolism of Fe; deficient dietary Fe increases the toxicity of Pb, whereas its influence on the absorption rate of Pb is equivocal<br>– impairs the metabolism of Zn and increases urinary excretion of Zn; deficient dietary Zn increases the absorption rate of inorganic Pb and increases the toxicity of Pb<br>– Se decreases the toxicity of Pb<br>– data on interactions with Cu and Mg are equivocal (i.e. the possible role of Zn, or another metal, as a mediator) |

* Data are mostly related to experimental studies in the rat, whereas relevant human data, particularly regarding quantitative dose-response relationships, are generally lacking (1–6, 24).

## The role of metals and metalloids in oxidative stress-mediated diseases and the antioxidant defence system of man

There is rapidly growing evidence of the role of the oxygen- or xenobiotic-derived *free radicals* and other *reactive oxygen species* (ROS) as mediators in tissue injury and development of *oxidative stress*, implicated in the pathogenesis of

over 100 human diseases (26–28). For example, oxidative stress is found to be related to inflammation in general, radiation disease, cancer, atherosclerosis, myocardial infarction, ageing, reperfusion injury, rheumatoid arthritis, diabetes, male infertility, and immunological disorders including human acquired immunodeficiency syndrome, i.e. it is speculated that ROS may propagate human immunodeficiency virus (HIV) infection. As several recent reviews deal with these subjects (25–33), only very basic information will be presented here, with particular emphasis to recent evidence implicating the role for both essential and/or toxic metals and metalloids in this respect (34–42).

A *free radical* is any chemical species capable of independent existence (hence the term »free«) that contains unpaired electron that is alone in an orbital, which renders such species highly reactive to form complexes, conjugates or covalent adducts with various compounds in the organism. A superscript dot (•) is conventionally used to denote free radical species, e.g. the simplest free radical known is a hydrogen atom ($H^{\bullet}$), the gases nitric oxide ($NO^{\bullet}$) and nitrogen dioxide ($NO_2^{\bullet}$) are free radicals, whereas ozone ($O_3$) and hydrogen peroxide ($H_2O_2$) are not free radicals but can oxidize many biological molecules directly and, in addition, can produce free radicals (28). In man and other aerobic organisms a four-electron reduction of molecular oxygen ($O_2$) to water, i.e. chemical process requiring donation of four electrons, is known to be the major source of the energy necessary for their functioning. However, during this process the partially reduced and reactive oxygen species can be produced to a certain extent under a variety of circumstances that are associated with disease in humans. The one-, two-, and three-electron reduction products are superoxide radical ($O_2^{-\bullet}$), $H_2O_2$, and hydroxyl radical ($OH^{\bullet}$), respectively. It is now well established that all aerobic cells produce, enzymatically or non-enzymatically, a continuous flux of $O_2^{-\bullet}$, $H_2O_2$, and possibly $OH^{\bullet}$, which is the most highly reactive oxygen radical known. The best known sources of electrons for the reduction of $H_2O_2$ to $OH^{\bullet}$ are transition metal cations, particularly the ferrous ion, $Fe^{2+}$, and the cuprous ion, $Cu^{+}$, when they undergo oxidation to $Fe^{3+}$ and $Cu^{2+}$. The other potential source of $OH^{\bullet}$ in biological systems is the radiolysis of water by ionizing radiation, which does not require participation of a transition metal cation. It should be mentioned that, apart from the oxygen-centered radicals such as $O_2^{-\bullet}$, $OH^{\bullet}$ and the peroxyl ($ROO^{\bullet}$) or alkoxyl ($RO^{\bullet}$) radicals of organic compounds (which are the most common type found as oxygen is most prevalent in biological systems), the sulfur-, carbon-, nitrogen- and phosphorus-centered radicals may also occur in biological systems and are important in initiating and/or propagating various types of injury (26–28).

*Reactive oxygen species* (ROS) is a collective term that includes not only oxygen radicals ($O_2^{-\bullet}$, $OH^{\bullet}$, $ROO^{\bullet}$ and $RO^{\bullet}$) but also some reactive derivatives of oxygen that do not contain unpaired electrons, e.g. $H_2O_2$, singlet oxygen, and hypochlorous acid (HOCl). It is well established that ROS (especially $O_2^{-\bullet}$ and $H_2O_2$) are continuously produced in man by radiolysis, photolysis, thermal degradation of organic substances, and oxido-redox reactions catalyzed by a number of metals and metalloids (26–28, 41). The rate of ROS production is known to increase at increased partial pressure of oxygen ($pO_2$), which can explain the pulmonary injury of $O_2$ toxicity and the phenomenon of reperfusion

injury (27). An increase in ROS is also known to be present in active sportsmen and other intensive physical exercise situations. It is also well known that inflammatory cells produce ROS (during the process of phagocytosis), and that the cell and tissue injury associated with acute or chronic inflammation is attributable, at least in part, to the toxicity of ROS. On the other hand, ROS production by phagocytes ($O_2^{-\bullet}$, HOCl and $H_2O_2$) is known to play an important role in the killing of several bacterial and fungal strains, thus protecting the organism. It should be stressed, however, that increased ROS are found to be related to UV light and ionizing irradiation, the metabolism of many drugs and other xenobiotics, and may explain the adverse health effects of environmental pollutants such as: ozone, oxides of nitrogen, tobacco smoke, several halogenated hydrocarbons (e.g. carbon tetrachloride and bromobenzene), paraquat (a herbicide), several alkylating agents, and several metals and metalloids (28, 30, 41).

*Oxidative stress* has been recently defined as a disturbance in the prooxidant-antioxidant balance in favour of the former, *leading to potential damage* (27). The continuous exposure of aerobic organisms to oxidant stress is the »price« they pay for their greatly enhanced energy production capacity compared to anaerobic organisms. In order to survive this constant bombardment by ROS, all aerobic organisms have developed a number of antioxidative defences. The absence of such antioxidant defence systems in anaerobic organisms is the reason why they die when exposed to $O_2$. However, even in aerobic organisms these antioxidative defences are not perfect, and the free radical theory of ageing is based on the premise that a small amount of injury occurs daily, culminating in changes characteristic of ageing (27). Because proteins, lipids, carbohydrates, and nucleic acids (DNA and RNA) are susceptible to oxidation, there is a wide variety of mechanisms whereby ROS can harm cells and tissues. ROS may damage tissues through peroxidation of cell lipids, DNA strand breakage (either single- or double-strand breakage), alteration of amino acids in either structural or functional proteins, or alterations of cellular metabolism. Certain membrane functions may also be disturbed, e.g. oxidation of membrane -SH groups alters a variety of functions such as $K^+$ pumping capacity or amino acid transport ability. Oxidant-induced membrane lipid peroxidation causes disruption of membrane integrity, increases permeability to ions leading to severe deregulation (e.g. a rise in cytosolic $Ca^{2+}$ appears to promote cytotoxicity of oxidants) which, as well as chromosomal breakage, are major mechanisms leading ultimately to growth inhibition and cell death. Oxidants can cause permanent structural damage to DNA as well as transient changes in gene expression, and can alter the expression of growth- and differentiation-related genes. Single-strand breaks in DNA are shown to accumulate in a variety of mammalian cells upon exposure to ROS generated by the number of different mechanisms, and are also shown to depend on the source of ferric ion, $Fe^{3+}$. Such DNA damage can be prevented by Fe-chelation, by lowering pH, by increasing chemical antioxidants as well as by radical scavengers (30). In general, oxidants are cytostatic and cytotoxic (causing growth inhibition and cell killing), although under exceptional circumstances they can promote growth and facilitate mutation of cancer-related genes (31). Cells are also exposed to ROS generated by inflammatory reactions,

metabolism of xenobiotics, and influence of irradiation. When the delicate balance between oxidant burden and antioxidant defence is overwhelmed, *oxidative stress* ensues (27, 31, 32). Mechanistically, oxidative stress may contribute to initiation and/or propagation of disease process.

Mammalian cells normally contain many antioxidants, some of which are non-enzymatic and can act in preventing formation of free radicals or as radical scavengers, and others that enzymatically transform ROS into less reactive chemical species (31, 32). *Non-enzymatic antioxidants* can be roughly divided into: (a) those of low molecular weight, such as vitamin C, vitamin E, beta-carotene (the provitamin A), glutathione, and uric acid, and (b) those of larger molecular weight, such as lactoferrin, albumin, ceruloplasmin, transferrin, and metallothionein. It is well known that several of these compounds act protectively by binding heavy metals (essential and/or toxic), making them unavailable for production of free radicals or participation in lipid peroxidation. Among the *enzymatic antioxidants*, superoxide dismutases (SOD), glutathione peroxidases (GPx), and catalase (CAT) play a central role. It should be stressed that certain essential metals, or metalloid, are a constitutive part of the active site in these antioxidant enzymes, i.e. Cu and Zn, Mn, or Fe in SOD (Cu,Zn-SOD, Mn-SOD, Fe-SOD), Fe in CAT, and Se in GPx. Most of these antioxidative defences are indicative of the role of metals in human evolution and the role of evolution in the toxicology of metals (42), as interference with the normal function of the essential metal (or metalloid) results in a toxic outcome. It may be no coincidence that the protective mechanisms for $O_2$ are also used to protect against a number of toxic metals. It should also be mentioned that the activity of any enzyme, as well as the affinity of any metal or metalloid for binding to various compounds in the organism, greatly depends on subtle changes in the tissue pH (4, 41), and that the most important system for pH regulation in man and other mammals (i.e. the buffer system $HCO_3^-/H_2CO_3$ and elimination of $H_2CO_3$ by its conversion into $CO_2 + H_2O$) is dependent of the Zn-containing enzyme, carbonate acid anhydrase.

Recent evidence strongly supports the view that a balance between several antioxidants is essential for protection against *oxidative stress* (28, 30, 31), which may explain why attempts of therapy by increasing a single antioxidant have been ineffective (27, 33, 34). Vitamin C is an important antioxidant not only because it scavenges neutrophil oxidants but also because it may reduce vitamin E, thus restoring the antioxidant capacity of this important lipid antioxidant (which plays a key role in protecting the integrity of biomembranes by controlling lipid peroxidation). The decreased levels of vitamin C and vitamin E seen in cigarette smokers appear to be mainly caused by their increased utilization in the lung subsequent to their oxidation by oxidants contained in cigarette smoke (25). It should be mentioned that vitamin C is regarded an outstanding antioxidant which can also act as a prooxidant if accompanied by an excess of $Fe^{3+}$. Glutathione (GSH) and other compounds containing -SH groups are capable of scavenging $OH^{\bullet}$, $H_2O_2$, HOCl and other oxidative products of phagocytes. Decreased GSH levels were noted in bronhoalveolar lavage fluids in several diverse lung diseases (25), and systemic GSH deficiency was found in HIV-seropositive individuals (43). Alterations in intracellular Ca homeostasis with a rise in the cytosolic concentration

of $Ca^{2+}$ is known to accompany depletion of both GSH and protein -SH groups. Several observations indicate that changes in protein -SH are linked to a loss of viability of the cell (30), e.g. addition of dithiothreitol (a reagent containing -SH groups) prevents an increase in $Ca^{2+}$, loss of protein -SH groups, and loss of viability. Similarly, addition of vitamin E maintains -SH levels concomitantly with protection against cell killing. In other words, current evidence suggests that the loss of protein -SH groups in both the plasma membrane and endoplasmic reticulum disrupts the function of proteins critical to the regulation of Ca homeostasis (30).

Recent studies have also shown that the balance between several antioxidant enzymes, rather than the activity of a single component, determines the degree of protection against oxidants (31). For example, SOD and CAT may mutually protect each other from inactivation by active oxygen; the balance between SOD and CAT plays a crucial role for the overall vulnerability of the genome to a mixture of $O_2^{-\bullet}$ and $H_2O_2$; the efficacy of protection against ischaemia-reperfusion injury is better by the conjugates of Cu,Zn-SOD and CAT than Cu,Zn-SOD alone. Moreover, evidence is emerging that overexpression of SOD can sensitize, rather than protect cells from oxidative stress. It has been shown that small deviations from the physiologic activity ratios of CAT/SOD or GPx/SOD have a dramatic effect on the resistance of cells to oxidant-induced damage and cell killing, that high levels of either Cu,Zn-SOD, Mn-SOD or Fe-SOD are toxic (i.e. sensitize to cell growth inhibition and killing) whereas elevated levels of CAT or GPx protects from growth inhibition and killing, and that GPx strongly protects from toxicity of $O_2^{-\bullet}$ plus $H_2O_2$ up to a threshold dose, beyond which cell killing was just as efficient as for excess SOD levels alone (31).

The aforementioned facts are illustrative of the highly relevant role of both essential and/or toxic metals and metalloids in human health and disease. It is clear, however, that *oxidative stress* can ensue because of either an overproduction of ROS, a deficient or impaired antioxidant defence system, or both. Not only can many toxic metals and metalloids increase ROS production, but also certain essential metals (e.g. Fe and Cu); some can produce GSH-deficiency (e.g. Cu, Hg, As, Pb and Cd, even at relatively low levels if exposure is long-term) whereas others have antioxidant properties by acting protectively to GSH and other -SH groups (e.g. Se and Zn); some can induce synthesis of metallothionein (e.g. Cd and Zn) which acts protectively against toxicity of several metals and metalloids (e.g. Cd, Hg, Pb and As); some are the constitutive part essential for optimum activity of antioxidant enzymes (e.g. Zn, Cu, Mn, Fe and Se). Therefore, not only the direct effects of toxic metals and metalloids, the indirect effects of toxicokinetic interaction(s) between them and essential elements, which can result in relative deficiency of the latter, but also their role in initiating and/or propagating the adverse health effects of other environmental and occupational pollutants or life-style factors in man through mechanisms involving *oxidative stress*, have a great potential for explaining the development of numerous diseases as well as the large interindividual differences in susceptibility to various toxicants in man.

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## The role of metals and metalloids in adaptive response and genetic repair processes regarding interindividual differences in susceptibility to various toxicants in man

*Adaptive response* refers to the ability of the cell or organism to increase its resistance to the damaging effects of a toxic agent when first pre-exposed to a lower dose of the same agent, or certain other agent (in the latter case the term *cross-resistance* is usually used). Many different types of damaging agents, including alkylating agents, heat stress, oxidant stress, radiation, and heavy metals have been reported to induce an adaptive response. For example, it has been shown that exercise training, which involves an oxidative stress, leads to a reduction in the amount of lipid peroxidation produced during acute exercise. Similarly, cross-resistance of oxidatively stressed cells to other toxic agents, including γ- and X irradiation, heat shock, aldehydes, heavy metals, alkylating agents, and heme, has also been reported (29).

It is important to realize that cells have *two* primary lines of defence against oxidative stress. The first consists of the aforementioned non-enzymatic and enzymatic antioxidant system involved in preventing oxidative damage to the cell. The second line of defence consists of repair enzymes which remove and/or repair oxidatively damaged macromolecules (28, 29), e.g. DNA repair often involves DNA nucleases and glycosylases. It has been found that the mechanism of adaptive response for many toxicants, and of cross-resistance among them, often includes the induction of synthesis of DNA repair enzymes and/or induced synthesis of protective proteins separate from the system of DNA repair (29). For example, exposure to heat is characterized by the induced synthesis of so-called »heat shock proteins«, known to protect cells against subsequent toxic levels of heat and certain other stresses. It is important to note that heat shock, as well as inflammation, has been reported to increase intracellular oxidative damage. A number of other toxic agents also induce similar type of protective proteins in very rapid fashion, and it appears that the induction of »heat shock proteins« is a global response to stress that can explain the underlying mechanism behind the cross-resistance for many toxicants (29). Similarly, it is well known that Cd induces the synthesis of metallothionein which binds Cd and many other metals and metalloids, thus preventing them to increase cellular lipid peroxidation and/or to decrease the availability of other essential -SH groups. It appears that the Cd-induced adaptive response, and related cross-resistance for several toxic metals and metalloids, acts primarily through an oxidative stress mechanism, since it has been shown that pre-exposure to Cd also protected cells against oxidative damage (29).

With regard to genetic repair, many data show the central role of cell ability to repair DNA as the decisive determinant of the final outcome of tissue injury, since DNA repair can be either activated or inhibited by various toxicants among which metals and metalloids play a highly relevant role (29, 35, 39, 40). The

level of the individual capacity to repair DNA damage may explain the delicate difference of genotoxicity versus direct chemical toxicity, as well as some of interindividual differences in susceptibility to a particular toxicant in man (44). For example, direct genotoxic effects of Pb and Cd (such as increased rate of DNA single-strand breaks, DNA-protein cross-links, chromosomal aberrations, etc.) in mammalian cells in culture are known to be rather weak and occur only with highly toxic levels of the metal, particularly in the case of Pb. On the other hand, both Pb and Cd at low, non-toxic levels can enhance the genotoxicity of other DNA damaging agents (such as UV light, X-rays and certain chemicals) and thus act as co-mutagens, predominantly by interfering with DNA repair processes (39). The indirect genotoxic effects of Pb and Cd can be mediated through their interaction with Zn (i.e. *toxicokinetic interaction* resulting in relative Zn-deficiency in man when exposure to Pb or Cd is long-term and/or *toxicodynamic interaction* by their inhibition of the Zn-dependent enzyme(s) activity). Namely, it is known that Zn is the essential component for optimum activity of enzymes involved in the synthesis and repair of DNA and RNA (39), while RNA determines protein synthesis. Naturally, this may affect the final outcome of tissue injury from other toxicants, shown to be determined by whether or not sustainable tissue repair response accompanies the injury (45). It is likely that in circumstances with excess Zn (including cell culture experiments) genotoxic effects of Pb and Cd will not occur, which may explain the conflicting results of epidemiologic studies in particular (because human exposure to Pb, Cd, and Zn are often combined with each other). However, possible adverse effects of interaction of Pb and/or Cd with Zn (35, 39) include: disordered Zn-finger proteins which play a crucial role in cell development and differentiation; DNA damage related to impaired function of the Zn-dependent DNA and RNA polymerases; decreased capacity of intracellular and/or extracellular metallothioneins (MT) for storage and supply of Zn (which is regarded as the main purpose of intracellular MT). In addition, both Pb and Cd may contribute to the genotoxic effects of other agents through their well-known capability to decrease GSH level, thus decreasing antioxidant defences, as well as their interference with the metabolism of Ca, Fe and Cu, each of which may contribute to *oxidative stress* and related effects on DNA replication and repair.

It is well known that in the human population large interindividual differences exist in susceptibility to pollutant toxicity, including genotoxicity, so it is important to pay more attention to identifying the factors underlying interindividual variability in susceptibility (44). In humans, as opposed to animals, genetic variability among individuals is immense. For example, approximately 20,000 polymorphic proteins are found, and some of these proteins will inevitably influence individual susceptibility to toxicant exposure. It has also been shown that for a given level of genotoxin exposure, interindividual variation in DNA adduct binding (a type of direct toxicant-induced damage to DNA) may vary up to 10-fold. The individual risk of developing cancer is determined not only by exposure but by the ability to cope with the genotoxic burden (44). However, exposure to more than one

toxic agent is common in real life, considering occupational and/or environmental exposure and influences of life-style factors such as dietary habits, smoking, alcohol and use of medications (24, 46). There is considerable evidence that competition between various enzymes for shunting the same substrate into divergent metabolic pathways can lead to dramatic changes in toxicity (47). Interactions between xenobiotics based on enzyme inhibition or enzyme induction can be very profound, e.g. those related to the cytochrome P450 enzymes which play a central role in the metabolism of xenobiotics (24, 47).

It is important to realize that activities of enzymes, in a general sense, may change by altering either the enzyme *amount* (i.e. induction/repression), enzyme *specific activity* (i.e. activation/inhibition), or both. In this respect, enzyme activity changes by various metals and metalloids and interactions among them are particularly important, since this can affect the prevention and repair of damage by other toxicants.

## Conclusions and recommendations

Recent evidence indicates a highly relevant role for both essential and/or toxic metals and metalloids in oxidative stress-mediated diseases, antioxidant defence system, adaptive response, genetic repair processes, and related interindividual differences in susceptibility to various toxicants in man. Further research in the contribution of certain metals and metalloids in initiating, propagating, or preventing the development of a wide variety of chronic diseases in man should primarily relate to epidemiologic studies of *dose-response relationships,* based on biological monitoring, by considering interactions between various metals and metalloids, i.e. the quantitative interrelationship of several elements (combined *dose*, assessed by analyzing particular elements in human biological specimens) to a particular health effect (*response*). The role of interaction(s) between Pb, Cd, Cu, Zn and Se could be particularly important, as they are pervasive in the human environment, can affect each other's absorption rate and metabolism, and have recently been shown to be involved in several mechanisms important for the final outcome of the adverse health effects of various toxicants. Interaction of these elements may elucidate a large part of the interindividual differences in susceptibility to various chronic diseases, even those showing transgenerational characteristics (such as significantly lowered sperm count and fertilizing capacity of men over the last five decades, known to have occurred in the general population world-wide).

Mammalian antioxidant system consists of multiple interacting and interdependent components. Antioxidant composition varies between different animal species, e.g. humans are inherently deficient in key antioxidants such as vitamin C, GSH and the related activity of GPx (because GSH is the necessary

substrate for activity of GPx enzymes). These facts must be born in mind when considering the results of experimental animal studies for assessment of human health risk of exposure to oxidants as well as metals and metalloids.

It is known that Cu and Zn antagonisticly influence each other's absorption rate and metabolism. For example, a decrease in activity of Cu,Zn-SOD can be caused by Zn-supplementation as well as by Cu-deficiency. Thus, a balance between Cu and Zn is essential for optimum activity of this antioxidant enzyme which removes $O_2^{-\bullet}$ by greatly accelerating its conversion to $H_2O_2$. However, if $H_2O_2$ is not detoxified by $H_2O_2$-metabolizing enzymes such as CAT and GPx, it can react with $Fe^{2+}$ or $Cu^{+}$ to generate a much more potent oxidizing species such as $OH^{\bullet}$. This is important in view of the fact that the genome is one of the most vulnerable targets for oxidants (which cause permanent structural damage to the DNA as well as transient changes in gene expression). Thus, although SOD is important, an excess of SOD in relation to CAT and/or GPx (the latter, i.e. GPx, is generally regarded as the most important $H_2O_2$-removing enzyme in human cells) can be deleterious. This example indicates that the requirements of Cu, Zn, and Se are interrelated (because Se is required for optimum GPx activity), i.e. an increase or decrease of one determines the necessary body level for optimum function of the others.

Increased exposure to Pb, Cd, and Cu may additively or synergisticly contribute to: development of Zn-deficiency, inhibition of the Zn-dependent enzyme(s) activity, a decrease in GSH and biological availability of other essential -SH groups, and a decrease in the capacity of metallothionein for storage and supply of intracellular Zn. This is important in view of the fact that Zn is required for the synthesis and repair of DNA and RNA, related protein synthesis and tissue repair response. Thus, the Zn requirement for its optimum essential functions may be considerably greater when the body Pb, Cd and Cu levels are increased.

Increased exposure to Pb, Cd, and other toxic metals and metalloids may additively or synergisticly decrease the bioavailability of the body Se stores to GPx and other Se-dependent enzymes. Namely, their formation of conjugates or complexes with Se can decrease the bioavailability of the elements involved (assuming Se as well). On the other hand, an increase in Se may prevent their adverse effects, including a decrease in GSH and other essential -SH groups. Thus, the requirement of Se for optimum GPx activity and its other essential functions may be considerably greater when the body Pb and Cd levels are increased.

The aforementioned examples should be regarded as »the tip of the iceberg« concerning the possible biological consequences of interaction of various metals and metalloids, even at relatively low levels if exposure is long-term. Therefore, simultaneous analysis of several relevant elements in human biological specimens, particularly Pb, Cd, Cu, Zn and Se, is considered essential for evaluation of individual health risk and/or specific therapy with regard to oxidative stress and certain metals and metalloids.

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*Sažetak*

## INTERAKCIJE ESENCIJALNIH I/ILI TOKSIČNIH METALA I METALOIDA S OBZIROM NA INTERINDIVIDUALNE RAZLIKE U OSJETLJIVOSTI NA RAZLIČITE TOKSIČNE AGENSE I KRONIČNE BOLESTI U ČOVJEKA

Rad sjedinjuje najnovija saznanja o važnoj ulozi interakcija esencijalnih i/ili toksičnih metala i metaloida s obzirom na čovjekovo zdravlje i bolesti. Prikazani su podaci o mehanizmima interakcije između različitih metala i/ili metaloida (uključujući utjecaj pH, trajanja izloženosti te ostalih varijabli izloženosti kao što su različiti činioci čovjekova stila života), mogućim razlikama u osjetljivosti na štetne zdravstvene učinke između čovjeka i ostalih sisavaca te o ulozi metala i metaloida u oksidativnim stresom posredovanim bolestima, antioksidativnom obrambenom sustavu, prilagodbenom učinku i procesima genetskog popravka. S obzirom na općenito velike interindividualne razlike u osjetljivosti na različite toksične agense i kronične bolesti u ljudi, preporučena su daljnja epidemiološka istraživanja kvantitativnog doprinosa interakcije između Pb, Cd, Cu, Zn i Se, zasnovana na biološkom nadziranju. Ti su elementi (uključujući njihove spojeve) široko rasprostranjeni u čovjekovoj okolini, sposobni su međusobno utjecati na iznos apsorpcije i metabolizam svakog od njih, a nedavno je pokazano da su uključeni u nekoliko mehanizama koji određuju konačan ishod štetnih zdravstvenih učinaka različitih toksičnih agensa. Interakcija tih elemenata mogla bi objasniti osobnu preosjetljivost na različite kronične bolesti u čovjeka, čak i one koje pokazuju transgeneracijsko obilježje (npr. značajno sniženje broja spermija i oplodne sposobnosti muškaraca u posljednjih pet desetljeća, opaženo u općoj populaciji diljem svijeta).

*Ključne riječi:*
antioksidativni obrambeni sustav, bakar, cink, genetski popravak, kadmij, oksidativni stres, olovo, prilagodbeni učinak, selen, slobodni radikali

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