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Critical Review

Metals in Cigarette Smoke

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Summary

Metals are vital for a huge number of physiological processes in the human body, but can also destroy health when the concentration is not within the physiologically favourable range. Cigarette smoking interferes with the carefully controlled metal homeostasis of the human body. This review focuses on the consequences of metal delivery to the human body by cigarette smoking and discusses the body's responses. The metal content of tobacco plants, smoke, the circulation, and various organs is discussed. Finally, we link individual cigarette smoke contained metals to the genesis of human diseases.

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Keywords Cigarette smoke extract; smoking; tobacco; metal; cadmium; lead; nickel; zinc; aluminium; chromium; copper; mercury; selenium; vanadium; manganese.

INTRODUCTION

Plants have evolved mechanisms to gain access to essential elements from the soil. The ability of plants, like *Nicotiana tabacum* to accumulate metals is utilized by modern biotechnology to remove metal contaminations from soil. However, with respect to tobacco farming for cigarette production, this ability of *Nicotiana tabacum* becomes a health threatening problem. In fact, toxic metals such as aluminium, cadmium, chromium, copper, lead, mercury, nickel, and zinc are found in tobacco, cigarette paper, filters, and cigarette smoke. The role of these metals in the pathophysiology of diseases caused by cigarette smoking is poorly understood. There are emerging data suggesting that the alteration of metal homeostasis in the human body by cigarette smoking plays a crucial role in the genesis of a number of diseases. We have recently shown that metals in cigarette smoke are essential in the process leading to damage of the vascular endothelium (*1*). Dysfunction and disruption of the vascular endothelium is the primary event in the genesis of atherosclerosis, which is the leading cause of death in developed countries and accounts for a dramatically increasing number of deaths in developing countries too. Thus, the relevance of metals in the genesis of an additional group of important and deadly diseases could be pinpointed. In a model system designed to allow for a vascular biology physiologically relevant sampling of smoke constituents (*2*), we tested 12 different cigarette brands, and were able to detect a range of different metals in the liquid phase. Based on our results and data from the literature we will, in the following sections, discuss the concentrations of the relevant metals in cigarettes, cigarette smoke, in the circulation and organs, like lung, liver, kidney, and brain in smokers compared to non-smokers. Finally, we will discuss the health consequences of metal presence and deposition in these organs.

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ALUMINIUM

Aluminium is highly concentrated in cigarettes, with values ranging from 699 – 1200 μg/g (*3*). In non Al-exposed individuals, a mean plasma concentration of 4.2 μg/l was found, but these levels were not influenced by age or smoking habits (*4*). Although the mechanism is not known, various data provides evidence that Al is associated with Alzheimer's disease (AD) (*5, 6*). Trace metal homeostasis plays a big role in the normal functioning of the brain, and disturbances in it can exacerbate events associated with AD (*6*). There is no hint, however, that smoking is directly related with AD (*7, 8*). In addition, Al also plays a causal role in the development of microcytic anaemia and osteomalacia and can potentiate inflammatory and oxidative events (*6, 7*).

CADMIUM

Cadmium is the best studied metal from cigarette smoke, and smoking is the main source of cadmium intake by

humans. The content of cadmium in cigarettes and cigarette smoke was analysed in a number of studies. Although the Cd amounts varied, the average Cd content per cigarette lies between 0.5 and 1.5 μg per cigarette (*9, 10*). The different results may be the consequence of different analytical techniques, but are most likely due to differences between cigarette brands. In our own investigations, we found that cigarettes were fairly varied in their Cd content.

When the cigarette is smoked, Cd is transformed to cadmium oxide, which is then inhaled. Approximately 10% of the Cd is deposited in the lungs, and 20–50% is transferred to the circulation (*9, 10*). Mortada et al. (*11*) reported that the mean whole blood Cd content in smokers was 1.9 times higher that in non-smokers (2.67 $\pm$ 1.21 μg/l and 1.37 $\pm$ 0.45 μg/l respectively (mean $\pm$ SD), average age 30 years). Satarug et al. (*12*) reported that smokers have a 1.7 fold increase of serum Cd content compared to non-smokers (0.92 $\pm$ 0.83 μg/l and 0.55 $\pm$ 0.48 μg/l, average age 36 years). Barany et al. (*13*) reported that serum Cd values of young smokers was at least 3.1 fold increased in comparison to young non-smokers (0.61 $\pm$ 0.75 μg/l and below the lower limit of detection (LOD) 0.2 μg/l; average age 16 years). These data highlight the dramatic difference in serum cadmium levels between smokers and non-smokers at a young age, and that this difference is reduced but still present at older ages. Additionally, the accumulation of cadmium in the circulation with time can be seen.

Cadmium not only accumulates in the circulation but also in the kidneys, mainly in the kidney cortex, where metallothioneins chelate Cd and immobilize it. A number of studies have shown that this accumulation of Cd in kidneys causes tubular dysfunction and renal end stage failure, but there is also evidence that the amount of cadmium delivered by smoking is to small to cause kidney failure (*11, 12, 14*). Further, Cd has been shown to reduce bone mineral density (osteoporosis) and to cause osteomalacia, the combination of which is called itai itai (ouch-ouch) disease (*9, 14*). Cd has been linked to the genesis of cancers of the breast, prostate, colon, rectum, kidney and the lung (*9, 14*), but the existing data do not clearly support the hypothesis that the amount of Cd contained in cigarette smoke is sufficient to cause cancers. Additionally, cigarette smoke delivered Cd has been shown to reduce birth weight, and although the placenta seems to protect the foetus from maternal Cd, child Cd burden increases soon after birth via breast milk (*15*). Finally, Cd is under suspicion to cause cataract, emphysema, hypertension, and cardiovascular disease (*16–18*).

CHROMIUM

Chromium can exist in several oxidation states, although only the trivalent, Cr (III), and the hexavalent, Cr (VI), forms are common in the natural environment.

Based on reports, Chromium levels in mainstream cigarette smoke ranges from 0.0002–0.5 μg per cigarette (*19*). It is known that Cr accumulates in tissue, especially in the lung. Concentrations of about 4.3 mg/kg (dry weight) are found in smokers compared to 1.3 mg/kg in non smokers, increasing with age and smoking time (*20*).

Hexavalent Chromium (VI) is recognized by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen. Chromium (VI) compounds, mostly hydroxyl radicals, induce DNA-damage (single strand breaks) (*21*) and have potential cell transforming effects (*22*). Other, non cancerous, effects of Cr on the respiratory tract include ulceration, chronic rhinitis and pharyngitis, impaired lung function and emphysema (International Chromium Development Association, ICDA, Paris, 1997). Interestingly, there is evidence that the respiratory tract has developed considerable defence mechanisms towards Cr (VI) (*23*), which is reduced to the non carcinogenic (?) form of Cr (III) (*24*).

COPPER

The Cu content in tobacco leaves was reported to be 156 μg/g. Serum concentrations in youngsters are about 0.95 mg/l (*25*), in adults 1.10 mg/l (*25, 26*), and 1.31 mg/l in smokers (more than 10 cigarettes/day) (*27*), although the differences did not reach significance. However, Lapenna et al. described a significant correlation between plasma levels of Cu and lipid peroxidation in smokers (*28*). Since free Cu^{2+} is a potent catalyst in the so-called Fenton reaction in which radicals are produced, these observations might indicate that Cu is increased and 'functional' in smokers.

LEAD

Smoking is not the main source of Pb uptake by humans, but the contribution of smoking to the total Pb load in humans has become increasingly relevant. The reason for this is the reduction of Pb emissions originating from petrol, which have been reduced in recent decades by the introduction of unleaded petrol. Approximately 50% of total Pb taken up by humans originates from petrol, but Pb ingestion via food is also important (*14*).

The Pb content of a cigarette is around 1.2 μg, and about 6% passes over to mainstream smoke, which is inhaled by smokers (*27*). Mortada et al. (*11*) report blood Pb levels (mean $\pm$ SD) in non-smokers of 101.6 $\pm$ 30.9 μg/l and in smokers of 143.7 $\pm$ 33.8, whereas Satarug et al. (*12*) report Pb serum levels of 4.2 $\pm$ 5.4 μg/l in non-smokers and 9.0 $\pm$ 12 in smokers. The dramatic difference between blood and serum Pb concentrations is due to the fact that Pb in the circulation is mainly bound to erythrocytes (*14*). Pb is eliminated from the body via urine, but this occurs slowly and accumulation in the skeleton is observed. Although the blood brain barrier is relatively impermeable for Pb, especially children are at a high risk to accumulate the neurotoxic Pb in the brain and central nervous system, resulting in mental retardation and other

neurological disorders (*29*). In addition, children from parents who smoke accumulate high levels of blood lead via passive smoking. These facts are just one further example that stresses the urgent need to protect children form active as well as passive smoking.

Other possible health consequences of lead accumulation are hypertension and peripheral arterial diseases (*18*), as well as cataract (*17*).

MANGANESE

Manganese is an essential element in food, but also a potent neurotoxin. Airborne Mn passes the closely regulated homeostatic control mechanism through the hepatic portal system. Mn concentrations in tobacco range from 155–400 μg/g. The serum concentration ranges between 0.19 and 5.69 μg/l, but no relation to socioeconomic status, tobacco or alcohol consumption has been found (*30, 31*). High concentrations of Manganese cause psychiatric syndromes (hallucinations, emotional lability), first described in 1800 as Manganese Madness. Today it is known as Parkinson-like syndrome (*32*). Mn, together with other metals like copper is associated with Parkinson Disease (PD) (*33*), but there is an inverse correlation between smoking and PD (*34*).

MERCURY

In contrast to occupational exposure, food consumption, (especially fish) and amalgam tooth fillings (*14*), smoking plays only a minor role as a source for Hg uptake by humans. Suzuki et al. (*35*) reported that only 5–7 ng of mercury per cigarette are transferred into the smoke, and a number of studies failed to describe a significant correlation between the smoking status and blood or serum Hg levels. However, in one study smoking-mediated Hg delivery was reported to increase the number of sister chromatid exchanges (*36*).

NICKEL

Nickel has been shown to cause a number of different forms of cancer, especially of the respiratory tract. The main mechanism responsible for this activity is that Ni is mutagenic (*37*) and has been reported to induce sister chromatide exchanges. In addition, there is evidence that Ni affects heart development in unborn mice (*38*). As for a number of other metals in cigarette smoke, the question about Ni is whether the amount of Ni transferred from the smoke to the lung and then to the circulation is high enough to cause disease. The amount of Ni in the tobacco plant lies between 0.64 and 1.15 μg/g, and varies highly in cigarettes between 0.078 μg and 5 μg (*27*). Serum concentrations of Ni have been analysed, but data shows that smoking is not an important source for Ni.

SELENIUM

Although tobacco plants and cigarette smoke contain Se, smoking has been shown to reduce blood Se levels (*39*). Interestingly, Se has been reported to function as a protective agent for cancers and heart disease. The mechanisms underlying serum Se reduction are not clear, but may be similar to that described for serum Zn reduction by cigarette smoking (see below).

VANADIUM

The general toxicity of V is low. Food is the major source of exposure to V for the general population.

The cigarette V concentration ranges between 0.49–5.33 μg/g (average: 1.11 μg/cigarette). About 60% of the vanadium remains in the ash, 8.3% in the cigarette filter and 31.3% in the smoke (*40*). In contrast to the gastrointestinal tract, the lungs absorb soluble Vanadium well. The excretion of the metal by the kidney is rapid (half life 20–40 h). V has been shown to have insulin-like properties in both animal and human studies (*41*). The serum concentration of non-V-exposed non smokers is 0.8 μg/l (*42*), but the effects of smoking on serum V levels have to our knowledge not been studied. Vanadium is known to provoke local irritation of the eyes and the upper respiratory tract (like rhinitis, cough, conjunctivitis, chest pain) (*43*). It is also suspected to cause neurobehavioral impairments, which affect attention and visuospatial abilities (*42*).

ZINC

Although zinc is present in cigarettes (average 24 μg/g) and about 70% is transferred to the smoke (*27*), Zn serum concentrations in the average population have not been found to be affected by the smoking status (e.g., a study by Galan et al. (*44*) with 3128 participants; 13.3% smokers). However, there is evidence that under special circumstances, like pregnancy, mononuclear cells and maybe also other cell types have a reduced Zn content (*27*). Reduced Zn levels have been shown to constitute a pro-carcinogenic factor (*45*) as well as affecting immune system function (*46*). The mechanism by which cigarette smoking reduces Zn levels is thought to result from an increased blood Cd concentration, which induces the expression of metallothioneins, which bind Cd but also Zn.

CONCLUSIONS

One of the most important conclusions of our review on the occurrence and relevance of different cigarette smoke constituent metals on human health is that a lot more work is needed to gain a clear insight into the function and relevance of the individual metals. Nevertheless, it can be stated that

Table 1
Overview on metals (and selenium) in cigarette smoke and contribution to the genesis human diseases

Metal	Present in Cigarettes/smoke:	Levels in the circulation affected by smoking:	Relevant for diseases:	Diseases caused:
Al	Yes	No	–	–
Cd	Yes	Increased	Yes	Renal end stage failure, osteoporosis, others.
Cr	Yes	Increased	Yes	Mutagenic/cancers
Cu	Yes	?	?	Oxidative stress
Mn	Yes	No	–	–
Ni	Yes	No	–	–
Pb	Yes	Increased	Yes	Neurological disorders (children!)
Se	Yes	Decreased	Yes	Cancers, cardiovascular diseases
Hg	Yes?	No	–	–
V	Yes	?	No	–
Zn	Yes	Generally: No special circumstances: Decreased	?	Immune dysfunction; cancerogenic

metals contained in cigarette smoke play crucial roles in the pathophysiologies of nearly all smoking caused diseases; cancers, chronic obstructive pulmonary diseases, cardiovascular diseases, retinal degeneration, neurological disorders, renal dysfunction, degeneration of bone, immune dysfunction, and problems during embryonic development. Basically, cigarette smoke metals and Se in the amount as delivered by cigarette smoking, could be grouped (see Table 1) into: non-hazardous for human health (Al, Mn, Ni, Hg, V), hazardous because of accumulation in the circulation/other organs (Cd, Cr, Pb), hazardous because of indirect down-regulation (Se), and not clear (Cu, Zn). The down-regulation of some elements (Se, Zn?) is of particular interest, because it highlights that: (i) metals compete with each other for acceptor sites, and that (ii) via the same or similar mechanisms toxic metals can also interfere with cations of high physiological relevance (e.g., Ca and Pb).

Finally, it should be mentioned that relevant cigarette smoke contained metals are catalysts and thereby can accelerate physiological processes, leading to oxidative stress (e.g., copper in the Fenton reaction), and consequently to damage and inflammation, that again causes cardiovascular diseases, cancers, degenerative diseases, and aging.

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