



TOXIC AND TRACE ELEMENTS IN TOBACCO

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CORRIGENDUM

Page 4, paragraph 4, line 4 "15 ug/g" should read "15ug/l".

Page 6, line 15 from the bottom should read as follows:
significant relationship with respect to sex in adults, etc.

Page 8, third paragraph, line 16 "renal cortex" should
read "lungs".

Page 9, first line "136" should read "0.6".

Page 15, paragraph 2, line 5 "0.04" should read "0.4".

Page 15, last paragraph, third line "(2)" should read "(7)".

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EXECUTIVE SUMMARY

Much is known about the harmful health effects of carbon monoxide, nicotine, tar, irritants and other noxious gases emitted from tobacco smoke, but not enough emphasis has been put on the harmful effects of heavy metals and other toxic elements present in tobacco smoke. Smoking influences the concentrations of several elements in some organs. Knowledge of the harmful health effects of heavy metals and other trace elements inhaled by the smokers is still incomplete. The present review summarizes evidence on important elements i.e. aluminium, arsenic, cadmium, chromium, copper, lead, manganese, mercury, nickel, polonium-210, selenium, and zinc. The following are the most salient findings:

Cadmium: Tobacco plants have a special ability to remove cadmium from the soil and concentrate it in leaves. About 16% of cadmium in cigarettes is found in ash, 15% in the filter after smoking, 17% in the butt, and more than 50% passes out in the smoke. Cadmium concentrations in blood, renal cortex, renal medulla, liver, lung, prostate, and fat tissue are significantly higher in smokers than in nonsmokers, while cadmium concentration in urine shows unclear relation to smoking. The biological half-life of cadmium in the lung is estimated to be 9.4 years. The placental cadmium concentration is higher in smoking mothers and have a significant correlation with cadmium concentration in cord blood. Cadmium accumulates in amniotic fluid and amniotic membranes. In both blood and milk cadmium concentrations increase with cigarette consumption.

Chromium: Urinary chromium levels are influenced by smoking depending upon the intensity of cigarette consumption.

Lead: Lead concentrations in blood are affected by smoking. The activity of delta-aminolevulinic acid dehydratase in blood shows clear negative correlation with amounts of cigarettes smoked. In children, parental smoking habits have a significant effect on lead concentrations in blood. Maternal smoking has a greater impact than paternal smoking.

Mercury: 10 to 20% of mercury in the cigarette is emitted through smoke. Mercury concentrations in blood, urine, hair, kidney, liver, and lung show no correlation with smoking.

Polonium: Po-210 concentration in lung is significantly higher in smokers and in ex-smokers than in nonsmokers. It is estimated that the critical bronchial regions of smokers' lung may be exposed to as much as 7×10^{-5} Sv (equivalent to 7 mrem) of radioactivity with each cigarette.

Zinc: About 70% of zinc in unsmoked tobacco is estimated to be in the smoke. Zinc concentrations in cord vein blood are influenced by mothers' smoking; there is a 5% decrease in plasma zinc, and a 12% decrease in cord vein erythrocyte zinc in infants of smokers. This may be related to low birth weight of newborns of smoking mothers.

1. INTRODUCTION

There has been a long history between human beings and tobacco. Tobacco plants are grown in nearly every country of the world. About 80 percent of world consumption of tobacco is through cigarette smoking.

The scientific literature is full with evidence on the harmful health effects of tobacco smoking, particularly in relation to cancer of the lungs and other sites, cardiovascular diseases, respiratory diseases and other adverse conditions. Not enough attention has been paid, however, to the important effects that heavy metals and other toxic elements inhaled through tobacco smoke may have on biochemical processes that occur in the body. Heavy metals, like almost all substance emitted from tobacco smoke are first trapped in the lungs and then pass into the blood stream. Once accumulated in the human body through smoking, heavy metals have long biological half-lives and chronic effects on human health may result in later years from prolonged intake of such toxic elements, some of which are powerful carcinogens. Several of them accumulate in bones and trigger disorders of mineral metabolism e.g. osteoporosis. Many papers on the mineral element concentrations of tobacco and tobacco smoke have been published by various authors, but in a scattered fashion.

The present paper reviews the literature on heavy metals and other toxic mineral elements present in tobacco leaves, cigarettes, and tobacco smoke in relation to their uptake by human tissues and organs, and to their harmful effects on human health.

More than 400 literature references published since 1966 have been scrutinized in the preparation of this paper. Evidence has been summarized relative to twelve most important elements; aluminium (Al), arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), lead (Pb), manganese (Mn), mercury (Hg), nickel (Ni), polonium-210 (Po), selenium (Se), and zinc (Zn). Barium, beryllium, cobalt, molybdenum, strontium, and vanadium are also important elements. However, no evidence was found suggesting a relationship between tobacco smoking, element concentration, and human health. Tin is a ubiquitous element and is supposed to be present in tobacco leaves as well. However, no report could be found on tin in relation to tobacco or tobacco smoke. Although Fe and Mg concentrations in tobacco leaves are relatively high, these metals are not considered in this paper as no harmful health effects are known at these concentrations.

It should also be kept in mind that the body burden of heavy metals increases in the case of occupational exposure, and tobacco smoking enhances the adverse effects of such exposures.

2. ANALYTICAL METHODS

Besides tobacco, the main sources of trace elements in cigarettes are also the wrapping paper and the filter. The analytical methods used in most of the studies were neutron activation (1-3, 5, 7-10), photon activation (4), and proton-induced X-ray emission (6). These methods allow simultaneous determination of up to 28 elements, for example Al, As, Ba, Br, Ca, Ce, Cl, Co, Cr, Cs, Eu, Fe, Hf, K, La, Mg, Mn, Na, Ni, Rb, Sb, Sc, Se, Sr, Th, Ti, V, and Zn. The concentration ranges of the main elements determined in twelve brands of commercially manufactured cigarettes from the United States are shown in Table 1.

Cadmium concentrations in tobacco, filter, and smoke were determined either by a calorimetric method (11), by stripping voltametry (12, 13), or by atomic absorption spectrometry (14). Lead concentrations were mainly measured by atomic absorption spectrometry (14, 15). Mercury was usually determined by radiochemical neutron activation analysis (RNAA). More recently, instrumental neutron activation analysis (INAA) has been made possible by using a high-resolution Ge(Li) gamma-ray detector (16).

Most studies on element concentrations of biological materials reviewed in this paper used atomic absorption spectrometry (AAS). Indeed, because of its high sensitivity and specificity, and because of the small sample volume required, AAS is very often used (17-20) even for those elements which could be determined by NAA. An additional big advantage of AAS is that it does not require a nuclear reactor as NAA does. Recently, a new analytical methodology, inductively coupled plasma-atomic emission spectrometry (ICP-AES) or ICP-mass spectrometry have also been used. These techniques allow simultaneous multi-element determination.

Regarding polonium determination, the radioactive nuclide Po-210 is usually isolated radiochemically from cigarettes, and its concentration is then analyzed by measuring its alpha activity (21).

Element concentration varies among brands and even within the same brand (2). In the tobacco plant, element concentrations vary between the young top, the middle, and the old leaves of the same stalk (4).

Footnote: In this review the following symbols are used: mBq (milliBecquerel) and pCi (picoCurie) as units of radioactivity; Sv (Sievert) and mrem (milliroentgen-equivalent-man) as units of radiation exposure; ug (microgram); umol (micromole); IU (International Unit as enzyme activity); ng (nanogram); r (correlation coefficient), p (probability), NS (Not Significant) in statistical analyses. The number after +/- is the standard deviation of the mean value.

3. TRANSFER OF ELEMENTS FROM TOBACCO TO SMOKE

It is important to consider the transfer of elements from cigarette tobacco to smoke and to smoke condensate. Cigarette filters are manufactured with the aim to remove undesirable volatile combustion products without deteriorating the smoking flavour. There are several reports on element concentrations in filters before and after smoking (7, 8), and on the comparison of element concentrations in cigarette tobacco with those in smoke (3, 5-7, 9). Sidestream smoke differs from mainstream smoke in composition and particle size (22). Smaller particle size of sidestream smoke suggest that this type of smoke may reach more distant alveolar spaces than mainstream smoke.

Environmental smoke pollution consists of sidestream smoke, escaped mainstream smoke, and exhaled smoke. Passive smokers are therefore exposed to toxic substances including heavy metals and trace elements. Several studies have indicated that passive smoking may cause cancer in nonsmokers. It is also known that some heavy metals implicate cardiovascular diseases (23, 24). Churg and Wiggs (25) analyzed the exogenous mineral particle concentration, size, type, and distribution in male cigarette smokers. They found a significant correlation between amount of cigarette smoking and particle concentration in the upper lobe of the lungs, but not in the lower lobe. Particle size was not related to the amount of smoking.

Further mobilization of elements to the lungs of the smokers may occur depending on the initial concentrations of the elements in tobacco and wrapping paper, the method of smoking, the efficiency of the filter to block the volatile combustion products, and the combustion temperature. Better understanding of these processes would be of great importance to the smokers' health.

4. BIOCHEMICAL EFFECTS OF TOXIC AND TRACE ELEMENTS

Aluminium: Aluminium concentration in tobacco is relatively high as shown in Table 1. Buratti et al. (26) investigated Al levels in urine, plasma and erythrocytes of 97 healthy, non-occupationally exposed men, and found ~~<15 ug/g~~ in urine, <8 ug/l in plasma, and <5 ug/l in erythrocytes in 95% of the subjects. They also stated that none of these levels was influenced by smoking status, cigarette consumption, or age. However, Al is interesting because of recent informations on its higher levels in brain of patients with Alzheimer's disease. The likelihood that smoking may be associated with Alzheimer's disease was also reported (27).

Arsenic: As shown in Table 1, As concentration in tobacco is low. Usually the results were below the detection limit. There have been a few reports on As concentrations in blood, plasma and organs in non-occupationally exposed subjects.

<15 ug/l

Vahter and Lind (28) reported that the median concentration of inorganic arsenic was 8 ug/g creatinine in urine in the general Swedish population. They also found that this value was independent of place of residence, sex, smoking and consumption of beer and wine. As to organic As, median concentration was 12 ug/g creatinine, and this value increased with consumption of some kinds of seafoods but was not influenced by smoking. On the other hand, Andren et al. (29) reported an association between As levels in urine of children and parental smoking habits. The mean As value in urine of children of non-smoking parents was 4.2 ug/g creatinine, in children with one parent who smoked it was 5.5, and in children with two parents who smoked it was 13 ug/g creatinine, respectively. No significant differences were found in As levels in liver, renal cortex, lung and hair among smokers and nonsmokers (30), nor were differences found in As levels in semen from smokers and nonsmokers (31).

Cadmium: Cadmium is highly toxic, and is one of the most important elements when the adverse effects of smoking on human health are considered. Cadmium concentrations in blood, urine, and organs of occupationally unexposed non-smokers are very low. Tobacco plants have a special ability to remove cadmium from the soil and concentrate it in leaves. Bache et al. (12) demonstrated that tobacco plants absorb unusually high concentrations of cadmium from soil. Cadmium levels in tobacco leaves range from 0.77 to 7.02 ug/g (32). These are very high levels compared to that in food which is normally below 0.05 ug/g. Commercial cigarette tobacco contains cadmium at levels of 0.5 to 3.5 ug/g, the concentrations being independent of the producing country or curing process (11, 14, 32, 33).

Nandi et al. (11) reported the mean Cd concentrations in four cigarette brands as being 22.7 (18.5-28.0) ug per pack of 20 cigarettes, 3.6 (2.6-4.2) ug in the ash from 20 cigarette, and 3.3 (2.4-4.4) ug in 20 filters. Mussalo-Rauhamaa et al. (14) reported on analyses of cadmium contents in cigarette tobacco from 1920 to 1984. The mean Cd content was 1.7 ug/g.

An important point is that large part of the cadmium content of cigarette tobacco passes into the smoke. Nandi et al. (11) observed that the cadmium content of the ash of smoked cigarettes is relatively constant, i.e. 16% on average of that present in the unsmoked cigarette. The filters after smoking contained a further 15%. These results indicate that during cigarette smoking, most of the cadmium present in tobacco, in this case 69%, passes into the smoke. Schenker (32) found 15.9% in the ash, 14.6% in the butt, 17% in smoke inhaled by the smoker, and 52.4% in the smoke that develops at the burning end of the

cigarette. This is plausible since the temperature at the lit end of a cigarette exceeds the boiling-point of cadmium (767 C). Mussalo-Rauhamaa (14) found that an average of 2.0% Cd passes into mainstream smoke, and about 20-50% Cd remains in the ashes and butts of smoked cigarettes. This indicates that a large amount passes to sidestream smoke. Bache et al. (12) reported that tobacco contains 1.87 ug/g of Cd on average, and the concentration of Cd in mainstream particulate fractions was 147.4 ng/cigarette. Bache et al. (13) compared Cd concentrations in mainstream smoke particulates from filter-tipped and unfiltered cigarettes, and found 110.8 +/- 7.0 ng per filter-tipped and 153.0 +/- 136.0 ng per non-filter cigarette.

Schenker (32) estimated the weekly Cd intake in humans: of the 284 ug Cd ingested in food including water, only 6% is resorbed. From inhaled air, 25% of Cd is deposited in the lungs and 70% of this is resorbed. From smoking, 50 % is deposited and 70% of it is resorbed. Smoking 40 cigarettes/day provides twice as much cadmium as food. By comparison, cadmium uptake from air is insignificant. On the other hand, based on 24-hour fecal sample analyses collected daily from 225 farmers Reddy and Dorn (34) estimated that the smoking-related increase in daily Cd intake was about 1 ug over that of non-smokers.

There have been many reports on the uptake of cadmium from smoking, and cadmium concentrations in blood, urine, milk, and organs. Cadmium concentrations in blood in relation to smoking habits are summarized in Table 2. In all studies, blood Cd concentrations increased with increased smoking (24, 35-40). The same tendency was also observed in other reports (42-46). In some reports (37, 41, 47) blood Cd levels do not show any significant ^{relationship with} respect to sex in adults nor in children, but do show a highly significant influence of age. However, no variation with age was noted by Grasic et al. (39), nor with sex by Elinder et al. (48). It is known that alcohol drinking modifies blood Cd concentrations (39). There have been a few reports concerning urinary Cd concentration. Wibowo et al. (44) found significant correlation between increasing Cd concentrations in urine and age, but an unclear effect of smoking on Cd excretion in urine. Abe et al. (49) studied 1200 females of various ages and reported that Cd contents in urine increased from 0.88 ug/l in the 20-30 year old women to reach a maximum of 1.78 ug/l in the 50-60 years and gradually decreased to 1.31 ug/l in the 80+ old ladies.

Smoking among women (more than 8 cigarettes/day) did not induce an increase in Cd contents in urine (49). Angerer et al. (41) measured urinary Cd concentrations in 35 men and 19 women and

found mean values of 2.67 ug/l in men and 2.34 ug/l in women. When subdivided among non-smokers (n=25), ex-smokers (n=14) and smokers (n=14), the mean values were respectively 2.47, 2.78, and 2.47 ug/l, and not significantly different. Significant differences in Cd levels were instead found in renal cortex, renal medulla, lung, prostate, and muscle from the same subjects depending on whether they were nonsmokers, ex-smokers, or smokers (see below).

According to Mussalo-Rauhamaa et al. (14) the number of years of smoking and the number of cigarettes smoked per day were predictive of the effect of smoking on Cd content in fat tissue of male smokers; mean Cd content was four times (10.1 ng/g) higher in smokers than in nonsmokers (2.5 ng/g).

There are some reports on the effect of smoking on Cd concentration in kidneys obtained at autopsy. As shown in Table 3, nonsmokers had the lowest average cadmium concentrations; light smokers had concentrations 15-20% higher; heavy smokers (more than 25 cigarettes/day) had concentrations 15-20% higher than light smokers. The cadmium concentrations in both the cortex and the medulla were consistently higher in smokers compared with nonsmokers across all age groups (50). The same authors (50) reported that cadmium concentration in kidney varied with age and smoking habit, but not with sex. At the age 50-60, Cd contents in cortex was at its maximum with a geometric mean of 19 ug/g. The age-related maximum was parallel to the cadmium contents in urine (49).

Summer et al. (51) reported high cadmium concentration in the renal cortex of smokers, ranging from 5 to 99 ug/g. In smokers (more than 20 cigarettes/day), the mean concentration in renal cortex (33.3 ug/g on average) was twice that in nonsmokers.

In the study by Angerer et al. mentioned above (41), the mean Cd concentrations in kidney cortex were 10.4, 23.5, and 42.5 ug/g wet weight among nonsmokers, ex-smokers, and smokers respectively, while the concentrations in medulla were 1.9, 9.1, and 14.5 ug/g.

Zhuang et al. (30) found that Cd concentrations in renal cortex were related to the life-long smoking habits of the autopsied subjects. Namely: 70 ug/g dry weight in nonsmokers, 111 ug/g in light smokers (5-20 cigarettes/day) and 192 ug/g in heavy smokers (> 20 cigarettes/day).

Blanusa et al. (52) reported analogous results: Cd concentrations in renal cortex were 225 ug/g dry weight in smokers and 74 ug/g dry weight in nonsmokers. They found no major morphological differences in the kidneys and no association with age.

Cd levels in lung at necropsy were determined by Paakko et al. on Finnish subjects (53). It was found to be higher (3.0 ug/g dry wt) in smokers than in ex-smokers (1.1 ug/g) and nonsmokers (0.4 ug/g). Lung Cd levels were significantly and positively correlated with total smoking time and pack-years and, in ex-smokers, negatively correlated with length of time since stopping smoking (53). These authors calculated at 9.4 years the biological half-life of Cd in human lung, and estimated that it would take ex-smokers with a history of 31.9 pack-years about 23.6 years for the lung Cd level to decrease to the level of never-smokers.

Angener et al. (41) also found higher Cd concentrations in lungs of German subjects in relation to smoking. Cd levels were 0.05 +/- 0.03 ug/g in nonsmokers, 0.22 +/- 0.24 ug/g in ex-smokers, and 0.22 +/- 0.20 ug/g in smokers.

Zhuang et al. (30) found that Cd concentrations in ~~renal cortex~~ ^{lungs} were 1.07 ug/g wet weight in Chinese nonsmokers, and 2.15 - 2.30 in smokers. The values reported in the latter three references (53, 41, 30) vary widely. Most likely the discrepancies are due to ethnic differences and age of subjects.

Liver Cd concentration was reported as 1.5 ug/g wet weight in biopsy samples of smokers and 1.2 in ex-smokers (41), regardless of sex. Unfortunately, no data were given for nonsmokers. In prostate, Cd concentration was 57.8 ng/g in nonsmokers, 102.3 in ex-smokers and 148.8 in smokers. In muscle, it was 51.7 ng/g in nonsmokers, 53.7 in ex-smokers, and 60.8 in smokers.

The effect of cadmium intake through smoking on pregnant women, foetus and infants has been studied. Blood cadmium levels increased in control non-pregnant smokers but not in the pregnant ones, although the number of cigarettes smoked per day did not differ between the groups (54). Smokers had higher placental Cd level than nonsmokers (55).

Another study showed that cadmium concentrations in maternal blood (1.1 ug/l) and amniotic fluid (1.0 ug/l) were significantly higher ($p < 0.001$) than in umbilical cord blood (0.4 ug/l). The highest cadmium concentration (35.1 ng/g) was found in amniotic membranes (56). Schiele et al. (57) studied the correlation between maternal smoking and blood Cd levels in newborns. Levels in newborns of smokers (0.4 ug/l) and those of nonsmokers (0.3 ug/l) were not significantly different. These results suggest the existence of a placental barrier for cadmium. These authors found a significant relationship between smoking habits and maternal blood Cd concentrations: the median value in nonsmokers was

0.6

1.36 ug/l and that in smokers 1.1 ug/l. Blood Cd levels in mothers and offsprings were not influenced by the age of the mothers (57). On the other hand, other authors failed to see any significant difference between Cd levels in cord blood and those found in maternal blood (58). Smokers did not have significantly higher Cd levels in amniotic fluid or in serum, which suggest instead an ineffective placental barrier against this element (58).

Kunhert et al. (59) investigated the association between placental Cd, placental Zn, placental Cd/Zn ratio, age, parity, and smoking status in smoking and nonsmoking pregnant women. Low infant birth weights were observed more frequently in older female smokers.

Radish et al. (36) determined cadmium concentration in mature milk and in blood from 15 nonsmokers and 56 smokers during the nursing period. In both blood and milk Cd concentrations increased with cigarette consumption. The median value of cadmium concentration in blood was 0.54 ug/l and that in milk was 0.07 ug/l in nonsmokers. These values rose to 1.54 ug/l and 0.16 ug/l in women smoking more than 20 cigarettes per day.

It is known that smoking is contraindicated in hypertensive subjects. Vivoli et al (23) pointed out that Cd concentrations and Cd/Zn ratio were significantly higher in hypertensive than in normotensive patients. Kromhout et al (24) found that blood Cd was strongly and positively related to cigarette smoking (24). Several other authors reported on Cd in relation to cardiovascular diseases and/or hypertension, and smoking (93-98).

Chromium: In healthy, occupationally non-exposed subjects in two regions of Italy (n=548: 357 males and 191 females) the total urinary chromium concentrations were higher in males than in females (0.62 ug/l vs 0.54 ug/l) in the first region, as well as in the second one (0.55 ug/l vs 0.51 ug/l), with no significant regional differences: the mean values for both sexes together were 0.59 +/- 0.26 in the first region and 0.52 +/- 0.31 in the second (60). The smoking habits seem to influence urinary Cr levels as shown in Table 4.

Paakko et al. (61) determined Cr contents in lung tissue of 45 Finnish subjects without malignant diseases or occupational exposure to heavy metals. The Cr concentrations (mean +/- SD ug/g dry weight) were 1.3 +/- 0.9 in nonsmokers, 4.3 +/- 3.3 in smokers, and 4.8 +/- 4.0 in ex-smokers, respectively. The pulmonary Cr content increased with age and smoking time, and no decreasing tendency was observed after smoking stopped. It must be borne in mind that the biological effects of Cr depend largely upon its chemical speciation: in its hexavalent form chromium is toxic and carcinogenic, but in its trivalent form it is physiologically essential in sugar (99) and lipid metabolism (100).

Copper: Copper is an essential element. Its normal level in the blood is relatively high, in the order of mg/l. Copper content of tobacco was reported to be 15.6 ug/g, that is 6.5 times that of Pb and 9.2 times that of Cd (14). Kromhout et al. (24) investigated 152 elderly Dutch men and found that men smoking 10 or more cigarettes/day had significantly higher serum copper levels than the nonsmokers. The mean values of serum Cu concentrations were 1.14 mg/l in nonsmokers, 1.21 mg/l in smokers of less than 10 cigarettes/day, and 1.31 mg/l in smokers of more than 10 cigarettes/day. Serum copper was thus positively related to cigarette smoking and inversely to high density lipoprotein cholesterol (24).

Blanusa et al. (52) did not find any correlation between Cu concentrations in human kidney-cortex and smoking; Cu concentrations in kidney cortex were also insignificantly related to smoking: 12.5 +/- 3.5 ug/g dry weight in nonsmokers and 13.4 +/- 3.6 ug/g dry weight in smokers.

Lead: The mean content of lead in filter-tipped cigarettes produced between 1960 and 1980 was 2.4 ug/g, and an average of 5.8% of it passed to mainstream smoke (14).

The Pb concentration of 10 different brands of Japanese tobacco was 1.28 ug/cigarette (range: 0.96 - 2.00) (62). Vivoli et al. (15) determined lead contents in 23 brands of cigarettes including 8 imported and 15 Italian domestic brands, and found 0.6 to 2.00 ug Pb/cigarette.

Regarding blood lead levels and smoking, Grasmic et al. (39) investigated 6437 French people. Men have significantly higher average levels than women. The lead levels in both sexes show a general tendency to increase with age. A comparison of the blood lead values according to smoking habits shows higher geometric means in current smokers and in former smokers than in nonsmokers. Blood lead level increases with increasing cigarette consumption in women, but not in men (39). This is shown in Table 5.1 which has been prepared from the results reported by Grasmick et al. (39).

Quinn and Delves also observed that blood Pb concentration in British adults rose with increasing levels of cigarette smoking (63). Watanabe et al. (62) investigated more than 2500 Japanese farmers and reported that the mean blood lead levels in male were 37.9 ug/l in nonsmokers, 36.4 ug/l in smokers of 1 to 10 cigarettes/day, and 50.3 ug/l in smokers of 11 to 20 cigarettes/day, and then plateaued regardless of higher cigarette consumption levels. These Pb levels are less than half as high as those reported by Grasmick et al. (39).

However, both investigations (39, 62) showed the same tendency of blood lead levels to increase with increasing cigarette consumption. This increase may be further pronounced in the case of alcohol consumption.

Kromhout et al. (24) reported that blood lead was influenced by smoking and was related to blood pressure, the relation being stronger for systolic than for diastolic pressure.

Table 5.2 shows the results of blood lead level and smoking reported by many investigators (24, 35, 64-67). The majority of the studies showed an increase in blood Pb levels with smoking.

Vivoli et al. (15) investigated the effect of smoking on erythrocyte 5-aminolevulinic acid dehydratase, which is the second enzyme in the porphyrine biosynthetic pathway, and is known as the most sensitive indicator for lead burden to the body. They found a negative correlation between the activity of this enzyme in blood and cigarette consumption. The mean values of enzyme activity units were 117.5 in nonsmokers, 88.8 in smokers consuming fewer than 20 cigarettes per day, and 74.1 in smokers consuming more than 20 cigarettes a day.

Zielhuis et al. (68) also observed that the changes of lead levels and erythrocyte 5-aminolevulinic acid dehydratase activity in adult non-occupationally exposed females are in relation to direct and indirect effects of smoking.

These results strongly suggest an effect of lead contained in cigarettes on the human body. Other metals do not exert such effect as shown by the fact that Cd, Hg, As, Mg and Zn at the concentrations found in cigarettes or in smoke never inhibit erythrocyte 5-aminolevulinic acid dehydratase activity (69).

Korpela et al. (56) showed that mean lead concentration 21 maternal (40.4 ug/l) and umbilical cord (37.1 ug/l) blood were similar and correlated significantly with each other ($r=0.77$). Lead concentration in amniotic fluid (59.6 ug/l) was significantly higher ($p<0.001$) than in maternal or umbilical cord blood. Like Cd (see above) lead also accumulates in amniotic fluid and amniotic membranes.

Ernhart et al. (70) investigated the role of lead as a behavioral teratogen at low exposure level in 162 mother-infant pairs in which 80% of the mothers reported having smoked during pregnancy. The correlation coefficient for maternal and cord blood lead was 0.80. Three scales: the NBAS (Brazelton Neonatal Behaviour Assessment) Abnormal Reflexes, the G/R (Graham/Rosenblith) Neurological Soft Sign, and the G/R Muscle Tonus, out of 10 were related minimally to either cord or maternal blood lead after regression analysis.

Passive smoking plays an important role in child exposure to lead. Andren et al. (29) investigated 127 children in relation to their living area and their parents' smoking habits. The geometric mean of blood Pb concentrations was 34.6 ug/l, and this value did not differ between children living in a village close to a Pb-emitting glassworks and children living in a non-exposed reference area. No other environmental and dietary factors were related to blood Pb levels in children, except parental smoking. In children of nonsmoking parents Pb blood level was 30 ug/l on average, in children with one parent who smoked it was 39 ug/l (37 ug/l if the father was smoking and 47 ug/l if the mother was smoking), and in children with both parents smoking it was 47 ug/l.

Willers et al. (71) studied 133 children living in a town with a lead smelter. Here again, there was a significant association between high Pb blood levels of the children and parental smoking at home. The children whose parents did not smoke at home had lower Pb blood levels (35.2 ug/l) than those with one smoking parent (38.5 if the father smoked and 43.0 ug/l if the mother smoked) and, of course, than those with both parents smoking (43.3 ug/l). There was a clear dose-response relationship with maternal smoking: 35.2 ug/l in children of nonsmoking mothers, 41.7 in children whose mothers smoked 1 to 7 cigarettes per day, 41.7 if the mothers smoked 8 to 15 cigarettes per day, and 45.6 ug/l in children whose mothers smoked more than 15 cigarettes per day. Sherlock et al. (72) also observed higher blood lead concentration in children whose one or both parents smoked, but the difference was not significant at the 5% level.

Fulton et al. (73) investigated the influence of blood lead on the ability at attainment of 855 boys and girls, 6 to 9 years old. The effect of blood lead concentrations was small compared with other factors, but the number of cigarettes smoked by parents was negatively correlated with the British Ability Scales (BAS) combined scores. This indicates that low levels of lead exposure have a potentially small but harmful effect on a child's performance on BAS tests.

Although elevated mean blood Pb levels in children were found to be associated with elevated soil Pb levels (92), Pb from tobacco smoke can be an additional cause of indoor air pollution for children.

Manganese: As shown in Table 1, Mn concentration in cigarette tobacco ranges from 155 to 400 ug/g. Leaf Mn concentrations increase with increasing Mn application rates in soil, but decrease with increasing soil pH (74). Little data is available on Mn levels in human materials from subjects without occupational or other exposure to the metal. Only two reports were found in the literature. Pleban and Pearson (75) determined Mn concentration in whole blood from 60 healthy subjects, and found it to be 9.03 +/- 2.25 ug/l.

Mn concentration in serum from 20 healthy subjects was 1.82 ± 0.64 ug/l. Serum levels reported by Adamska-Dyniewska et al. (76) in 80 healthy non-exposed subjects were 3.9 ± 1.8 ug/l. In both reports no significant correlation between Mn levels and smoking status was observed.

Mercury: Hg concentrations in tobacco leaf, wrapping paper, and whole cigarette were analyzed by Suzuki et al. (17). Only inorganic Hg was found. There are indications that Japanese cigarettes may contain as much as 60 ng Hg per stick, versus only 30 ng in foreign brands. One cigarette may release 5 to 7 ng Hg into smoke (17).

Hg serves no biological function and its presence in organs reflects contact of the organism with its environment. According to a report by Zander et al. (18), the mean Hg level in urine in human subjects was 0.75 ug/l (age 1 - 79 years). Subjects older than 18 years had significantly higher Hg levels in urine than younger subjects. The effect of age is substantially more pronounced in females than in males. Females also have, on average, higher urinary Hg levels than males. Smoking does not affect urinary mercury excretion.

Boitean et al. (19) reported that the average Hg concentration in hair was 1.06 ug/g with no significant differences between males and females. Smoking does not appear to influence Hg concentration in hair.

Bonithon-Kopp et al. (52) investigated blood Hg concentrations in 417 pregnant women and 417 matched controls and found no variations associated with smoking in either group.

Zhuang et al. (30) reported Hg concentrations of 0.62 ± 0.46 ug/g dry weight in renal cortex, 0.37 ± 0.26 in liver, and 0.10 ± 0.04 in lung with no influence of the smoking habits of the subjects.

In an investigation of 56 mother-neonate pairs, the geometric means of Hg concentrations were 5.2 ug/g (2.9 - 93.3) in maternal blood and 4.3 ng/g (2.4 - 75.30) in umbilical cord blood. There was no statistical difference in Hg concentrations on either side of the placenta (20). These results suggest that human placenta is not an effective barrier to toxic metal intake by the fetus. Smoking did not exert any significant effect on Hg levels in both maternal and cord blood (19). As Wulf et al. showed (47), however, the effects of smoking on blood Hg concentration were more clearly visible

when the sister chromatid exchange (SCE) test was used as an index: for every 10 g of tobacco smoked per day the SCE per cell was 0.7 times higher as compared to nonsmokers.

Nickel: Nickel has been determined in cigarette tobacco, in smoke, wrapping paper, filters, and ash (1, 6-9, 12). Variations that exist in nickel concentrations are due to differences in cigarette brands and on countries of production. Tobacco plants tend to strongly absorb nickel (as well as cadmium, see above) from soil and deposit it in leaves (12).

According to Bache et al. (12), nickel contents were 0.64 ug/g in soil-grown tobacco and 1.15 ug/g in sludge-grown tobacco. When these different types of tobacco were machine-smoked the average quantities of nickel found in mainstream particulate fractions were 72.6 ng per cigarette produced from soil-grown tobacco and 78.5 ng per cigarette produced from sludge-grown tobacco. Hallak could not detect nickel in cigarette tobacco nor in smoke, but found 0.1 ug in the wrapping paper of a cigarette in each of the 5 brands tested (6).

Iskander (9) analyzed four foreign brands and found 2.78 to 4.84 ug Ni per cigarette, 3.14 to 4.61 ug in the ash from each cigarette, and 0.5 to 2 ug in the wrapping paper from each cigarette. In Egyptian cigarettes the same author (7) found the values: 5.46 ug/g in cigarette tobacco, 27.8 ug/g in ash and 4 ug/g in wrapping paper. Nickel concentrations in filters were not much different before and after smoking: 0.4 to 1 ug per filter depending upon the brands in foreign cigarettes (8), and 5 ug/g of filter in Egyptian cigarettes (7).

Nickel forms a toxic carbonyl compound. Because of the high carbon monoxide level of tobacco smoke, nickel carbonyl thus produced is considered a potential carcinogen.

Polonium: Several investigators have provided evidence of the presence of Po-210 in tobacco and tobacco smoke. Po-210 in tobacco plants is derived from the soil and/or the air as a result of radioactive decay of Pb-210 or Ra-226, or from Rn-222 daughters.

Furnica and Toader (21) found a variable Po-210 content oscillating between 1.48 mBq/g (0.04 pCi/g) and 10.7 mBq/g (0.29 pCi/g) or 4.18×10^{-18} to 3.10×10^{-17} grams of Po per gram of tobacco depending upon the cigarette blend. Radford and Hunt analyzed 4 brands of American cigarettes and found Po-210 levels of 15.9 mBq (0.43 pCi) in a whole cigarette, 1.4 mBq (0.038 pCi) in the ash of a whole cigarette, and 4.4 mBq (0.12 pCi) in the butt (77).

Solnicka and Bischof (78) analyzed 5 brands of Czech cigarettes and found that Po-210 and Pb-210 were present in roughly equal amounts. The amounts found approximated those reported in American, Austrian and Russian cigarettes. Zijlstra surveyed the literature for the presence of Po-210 in cigarette tobacco. Since Po-210 was detected in several tissues and biological fluids of smokers in higher concentrations than in biomaterial of nonsmokers, the authors concluded that Po-210 could be a causal factor in carcinogenesis (79).

Little et al. (80) found the following average concentrations of Po-210 in lung samples from current smokers and nonsmokers: 0.27 mBq/g (0.0074 pCi/g) in smokers, and 0.06 mBq/g (0.0016 pCi/g) in nonsmokers, in peripheral parenchyma; ^{0.4} ~~0.04~~ mBq/g (0.011 pCi/g) in smokers, and 0.22 mBq/g (0.006 pCi/g) in nonsmokers, in peribronchial lymph nodes.

Westin (81) pointed out that tobacco may be the largest single worldwide source of carcinogenic ionizing radiation, and estimated that critical bronchial regions of smokers' lungs may be exposed to as much as 7×10^{-5} Sv (equivalent to 7 mrem) with each cigarette, primarily from the relatively high concentrations of Po-210 present in tobacco smoke.

Marmorstein (82) postulated that the high lung cancer or adenocarcinoma incidence in the United States may be related to increased amounts of radioactive polonium and lead inhaled from modern cigarettes. He estimated that high concentrations of these radioactive metals may be due to widespread use of high-phosphate tobacco soil fertilizers in use since 1940 (82). An alpha-emitter, radioactive polonium is completely volatilized at cigarette combustion temperature; 50% transfers directly into mainstream smoke (77).

Tobacco smoke containing Po-210 combines with household dust, settles on surfaces and clothing, and contributes to household alpha-particle activity. This activity from tobacco smoke may confound estimation of household radon levels (91).

Selenium: The range of selenium concentrations in 12 American brands were 0.007 to 0.091 ug/g (1). They were 0.087 ug/g in tobacco, < 0.4 ug/g in wrapping paper and 0.09 ug/g in filter both before and after smoking.

(7) Iranian and Pakistani cigarette brands showed higher concentrations: 0.30 ug/g ash from Egyptian cigarette tobacco (2), and 2.28 ug/g in tobacco and 2.16 ug/g in wrapping paper from the Pakistani brands (5). Selenium levels in wrapping paper were less than in cigarette tobacco (83, 84), but higher than in other papers (84). The analysis of the cigarette ash and filter showed that 45% of selenium was retained in the ash (5). The remaining amount volatilized and was not absorbed by the filter.

Environmental selenium varies considerably around the world. The daily intake in a standard diet is 62 mg, and the calculated body burden of selenium is 13 to 20 mg (84). Kidneys have the highest concentration of selenium (84). Smoking habits do not influence the selenium level in serum, this level being 1.70 umol/l serum in controls and 1.60 umol/l in male smokers (85).

Similar results were obtained by Miyamoto et al. (86) although lung cancer patients had lower serum selenium (0.099 ug/ml) than family members (0.116 ug/ml) and controls (0.122 ug/ml). Maternal cigarette smoking may exert harmful effect on selenium metabolism in the developing fetus, especially on glutathion peroxidase, a Se-containing enzyme. The mean glutathion peroxidase activity in cord blood from infants of smoking mothers was significantly lower (22.1 IU/g Hb) than in those from nonsmoking mothers (24.1 IU/g Hb) (87).

Zinc: The zinc concentrations analyzed in 12 American brands range from 16.8 to 30.5 ug/g (1). Hallak (6) reported that zinc contents were 22.4 to 26.6 ug/ cigarette, 0.2 ug/ cigarette in wrapping paper, and 0.116 to 0.248 ug/cigarette in smoke in Jordanian cigarettes (6). Iskander (9) found zinc concentration in ash and wrapping paper which were comparable to the results by Hallak (6) except the Egyptian brand which contained 0.63 ug/cigarette.

However, the zinc contents reported by Iskander in cigarettes were in a wider range (18.4 to 34.8 ug/cigarette) than those of Hallak. Zinc concentrations in filters after smoking were higher than before smoking, with variations depending on brands (8). Ahmad et al. estimated that 70% of zinc is transferred to the smoke from the tobacco and wrapping paper (5). Zinc concentrations in smoke was 7.12 ug/ml, but it was 12.6 ug/g in tobacco and 0.31 ug/g in wrapping paper (3).

Zinc is an essential element for human health. The normal values are 0.9 - 1.0 ug/ml serum, 10 - 12 ug/ml in red blood cells, 150 - 650 ug/24 h urine, and 0.1 - 10 ug/ml milk. These values are unaffected by smoking. Kidney-cortex concentrations are, however, influenced by smoking: 234 ug/g dry weight in nonsmokers and 328 in smokers. The difference was significant (52). Serum zinc was inversely related to resting heart rate (24).

Polymorphonuclear (PMN) cell zinc content was found to be significantly lower in smoking mothers (1.00 +/- 0.04 umol Zn per 1x10 exp 10 PMN cells) than in nonsmoking mothers (1.16 +/- 0.06 umol). Mononuclear (MN) cell zinc content is also lower (1.47 umol Zn per 1x10 exp 10 MN cells) in smokers than in nonsmokers (2.64 umol Zn per 1x10 exp 10 MN cells). It is known that pregnant women who smoke and have low polymorphonuclear cell zinc content are at risk of delivering small-for-gestational-age infants (88).

Mean maternal plasma of smoking women zinc and albumin levels 24 to 48 hours after delivery were lower than in control nonsmokers (61).

Infants of smokers have 5 % less plasma Zn, 12 % less cord vein red blood cell Zn, and 13 % decrease in the activity of alkaline phosphatase (a Zn enzyme) as compared to infants born to nonsmoking women. There is a relationship between cord vein erythrocyte Zn and birth weight (55, 59, 89, 90).

Although the mechanism of the association of smoking and intrauterine growth retardation is not known and there are other cause of Zn depletion in the fetus, there may also exist an interaction between cadmium inhaled by the mother with cigarette smoke and transfer of zinc to the fetus.

It is theorized that cadmium inhaled in cigarette smoke may stimulate synthesis of metallothionein that binds zinc in the intestine and placenta, thereby reducing intestinal absorption of zinc and its placental transfer.

Cd/Zn ratio was found to be positively related to birth weight. It is known that smoking during pregnancy increases the risk of small-for-date neonatal weight. Cadmium-zinc interaction may occur in the maternal-placental-fetal unit of pregnant smokers which may result in less favourable Zn status in the neonate (55, 59).

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Table 1. Concentration range for main trace and heavy elements in cigarette tobacco of 12 American brands

Element	Concentration range (ug/g)
Al	699-1200
As	<1
Ba	40.7-56.6
Ca	1.39-1.96(%)
Co	<0.01-0.94
Cr	<0.1-3.45
Fe	325-520
Mg	0.13-0.54(%)
Mn	155-400
Ni	<2-400
Se	<0.007-0.091
Sr	29.7-49.5
Zn	16.8-30.5

From: Iskander, F.Y., et al. (1986)
Analyst 111:107-109 (Ref. 1)

Table 2. Cadmium concentrations in blood and smoking habits

	nonsmoker	Smoking status (cigarettes/day)			Note	Reference Number
Mean	1.05	<10	>10		aged	24
SD	0.41	1.48	2.32		male	
n	53	0.79	1.00			
		58	40			
Mean ^a	0.41 ^a	<9	>10		Female	35
Range	<0.2-2.5	0.62 ^a	0.70 ^a			
n	84	<0.2-2.4	<0.2-4.4			
		61	77			
Median	0.54	<10	11-20	>20	Female	36
Range	0.2-1.5	0.97	1.13	1.54		
n	15	0.4-1.8	0.6-2.9	0.7-2.4		
Median	0.6	exsmoker	smoker		Male	37
Range	0.1-1.5	0.5	3.6			
n	30	0.3-1.6	0.2-13.2			
		3	27			
Median	0.5	0.5	2.7		Female	37
Range	0.1-2.0	0.2-1.1	0.1-12.7			
n	84	3	45			
Mean	1.1 (M+F)	<9	>20		total	38
		2.3 (M), 2.4 (F)	2.4 (M), 2.5 (F)		n=101	
Mean ^a	0.2	<10	11-12	>20	non-	39
Range	0.11-0.12	0.14	0.18	0.20	drinker	
n	301	0.13-0.16	0.16-0.19	0.16-0.24	male	
		108	121	28		
Mean ^a	0.11	0.14	0.16	0.23	non-	39
Range	0.11-0.12	0.14-0.15	0.15-0.18	0.19-0.27	drinker	
n	1133	322	153	21	female	
Mean	0.7		>20	>40	40-59	40
n	1469		>2.0	3.9	years old	
					men	
					total 6919	
Mean	2.1	exsmoker	smoker		male and	57
SD	1.0	2.8	4.2		female	
n	27	1.6	4.1			
		18	19			

a: geometric mean, unit:ug/l

Table 3. Cadmium concentrations in kidney and smoking habits

Smoking category	Number of subjects	Cortex	Medulla
Heavy smoker	175	19.1	9.7
Light smoker	159	16.2	8.3
Non-smoker	467	13.9	7.0
Not known	132	14.9	7.6
Overall	933	15.3	7.8

Geometric mean, ug/g

From: Scott, R. et al. (1987)
Human Toxicol. 6:111-119 (Ref. 50)

Table 4. Chromium concentrations in urine and smoking habits

Group	Number of subjects	Urinary chromium average + SD
Non smokers	115	0.46 + 0.28
Smokers (< 10 cigarettes per day)	25	0.51 + 0.16
Smokers (10-20 cigarettes per day)	22	0.67 + 0.46
Smokers (> 20 cigarettes per day)	25	0.66 + 0.33

From: Minoia et al.

Sci.Total Environ. 71:521-531, 1988 (Ref. 60)

Table 5.1 Lead concentrations in blood and smoking habits in non-alcohol drinkers

Sex	Non-smokers	Former smokers	Current smokers (>5 cig./day)	Tobacco effect
Male	10.3	10.8	11.7	
	9.9-10.7	10.3-11.2	11.2-12.2	P<0.001
	301	192	204	
Female	6.9	7.6	8.3	
	6.7-7.1	7.1-8.1	7.9-8.7	P<0.001
	1133	149	363	
Sex	1-10	11-20 (cigarette/day)	>20	Tobacco effect
Male	11.6	11.8	11.4	
	10.5-12.3	11.2-12.5	10.3-12.5	NS
	107	120	28	
Female	7.6	9.9	9.4	
	7.3-7.9	9.3-10.5	8.1-11.1	P<0.02
	320	150	20	

From: Grasmic et al. (1985). Sci. Total Environ.
41:207-217. (Ref. 39)

Table 5.2 Lead concentrations in blood and smoking habits

Sex (M/F)	Average ($\mu\text{g/l}$)	Number of subjects	Smoking status	Note	Reference Number
F	118 ^a	76	>10 cigarettes/day		
F	102 ^a	59	1-9		34
F	111 ^a	101	nonsmoking		
M	209	40	>10 cigarettes/day		
M	176	58	1-9		24
M	172	53	nonsmoking		
M	45	32	>20 cigarettes/day	Farmer	61
M	50	27	11-20		
M	36	9	1-10		
M	38	46	nonsmoking		
F	173 ^a	495	smoking		63
F	158 ^a	1127	nonsmoking		
M	294	29	smoking	Taxi-	64
M	274	20	nonsmoking	driver	
M+F	191	46	smoking		65
M+F	176	70	nonsmoking		

a: geometric mean

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