Insinuation of Toxic Metal on Smokers’ Lungs

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ABSTRACT

Heavy metals are major cause of environmental pollution and due to their toxicity, they persist long in atmosphere. Toxic metals or heavy metals have ability to accumulate in human body and cause various respiratory disorders. Heavy metals sometimes become highly toxic by reacting with different environmental elements. Tobacco smoking is one of the major concerns for the accumulation of toxic metals in smokers’ lungs and people residing with smokers (known as passive smokers) also being affected, especially children. ETS (environmental tobacco smoke) represents inhaling of tobacco and release heavy metals in ambient air involuntary. The development of children pulmonary function severely gets affected due to passive smoking. Every year millions of people die because of tobacco. Heavy metal content is present in the lung tissue of smoker and non-smokers, and which get mixed with the blood at time of gasses exchange in alveoli and circulate in the body. Therefore, tobacco smoking is considered one of the serious global health concern due to its carcinogenic effects on human body. This majorly happens because of the presence of toxic metals like Arsenic (As), Cadmium (Cd), Mercury (Hg), Lead (Pb), Chromium (Cr). The concentration of both Pb and Cd, are potent human carcinogen. This study presents important information regarding effect of heavy metals inhaled content in tobacco and its transference to cigarette smoke and their accumulation in smokers’ lung tissue.

Keywords: Heavy Metals, Metal Pollution, Pulmonary disorders, Tobacco, Carcinogens.

INTRODUCTION

Toxic metals are release in environment due to various anthropogenic activities. These activities have increased drastically in recent decade 1. Electronic waste, industrial smoke, and diesel soot playing prominent role in effecting the health of the people. People residing in developing countries are suffering from various respiratory disorders especially the population involved in smoking2. Metals occurs naturally among other environment pollutants and persist for long. Hence, human exposure to metals is inevitable, and some studies have reported gender differences in the toxicity of metals 1. High-dose heavy metals exposure, particularly arsenic, mercury, cadmium, and lead, may induce severe complications such as breading trouble, abdominal pain, and kidney dysfunction or Failure 3. Smoking and chewing tobacco kill millions of people around the world every year. The tobacco was determined to contain 11 toxic metals, the total metal content in cigarettes is present in its ashes 4. The metals content was also determined in the lung tissue of smokers and non-smokers. The number of heavy metals is said to be increased in the lungs of smokers as heavy metals are getting accumulated due to inhaling of polluted air and because of smoking 4. Several acute and chronic toxic effects of heavy metals affect different body organs. Gastrointestinal and kidney dysfunction, nervous system disorders, skin lesions, vascular damage, immune system dysfunction, birth defects, and cancer are examples of the complications of heavy metals toxic effects 2. Humans are exposed to these heavy metals every second by ingestion (drinking or eating) or inhalation polluted air (breathing). Most of the toxic heavy metals like lead, cadmium, antimony, mercury, arsenic, and thallium, are common in industrial operations and are substantial pollutants of the environment due to electronic waste burning (PCBs) 5. Thallium has a more severe effect than other heavy metals but is less abundant in nature 2; it is a cause of alopecia in humans. Followed by mercury and arsenic most abundant metals in biosphere and carcinogenic in nature if inhaled 7. The main objective of this review is to provide insight into the sources of heavy metals and their harmful effects on the humans with smoking habits.

Heavy Metal Toxicity

Arsenic is odourless and tasteless. Inorganic arsenic is a known carcinogen and can cause cancer of the skin, lungs, liver, and bladder 8. Arsenic is one of the most important heavy metals causing disquiet from both ecological and individual health 9. Arsenic is a protoplasmic poison since it affects primarily the sulfhydryl group of cells causing malfunctioning of cell respiration, cell enzymes and...
mitosis\(^9,^{10}\). According to the WHO, the major concern for public health is heavy metal that is Cadmium\(^5,^{6}\), and Cadmium is the only metal which can get accumulated in tobacco plant naturally (Nicotiana tabacum)\(^7\). This leads to “hyper-accumulation” to very high cadmium concentrations especially in the leaf part of the tobacco plant\(^5\). The balance of the oxidant–antioxidant system and induce inflammatory responses can be disturbed in various organs due to poisoning. Exposure to Pb can produce alteration in physiological functions of the body and is associated with many diseases\(^9,^{13},^{15}\). It has been reported that Pb gets easily absorbed in the lungs of the children because of passive smoking\(^12\). Each year, between 25,000–30,000 tons of Cd is released into the environment because of many activities, both natural and man-made. However, the main sources through which Cd makes its way into the human body are agricultural produce (food), and smoke produced by the combustion of tobacco\(^14\). It was observed in a study that one cigarette generally contains approximately 1–2 mg of Cd, and half of this amount enters the lungs by way of smoking and becomes part of the systemic circulation\(^18\). Cadmium has many applications, e.g., in batteries, pigments, plastics and metal coatings and is widely used in electroplating\(^19\). Cr (VI) and Cr (III) are the most stable forms and only their relation to human exposure is of high interest\(^20\). Occupational sources of chromium include protective metal coatings, metal alloys, magnetic tapes, paint pigments, rubber, cement, paper, wood preservatives, leather tanning and metal plating\(^17\).

Table 1: Showing effects of increased Pb levels in human blood\(^11\)

<table>
<thead>
<tr>
<th>Source</th>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>Pb levels</td>
<td>Pb ions diffuse across blood-brain barrier</td>
</tr>
<tr>
<td>Organ</td>
<td>Pb levels</td>
<td>Pb enters cell through calcium channel and binds with calmodulin (CaM)</td>
</tr>
<tr>
<td>System</td>
<td>Pb levels</td>
<td>Pb ions diffuse across blood-brain barrier and enters brain</td>
</tr>
</tbody>
</table>

Schroeder et al.\(^{16}\) (1970) reported that cigarettes contained 390 g/kg of Cr, but there has been no significant report published on the amount of chromium inhaled through smoking.

Table 2: Types of Mercury Toxicity SADER\(^21\)

<table>
<thead>
<tr>
<th>Source</th>
<th>Inorganic mercury</th>
<th>Methyl mercury</th>
<th>Elemental mercury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sources</td>
<td>Biological oxidation of mercury, dimethylation of mercury by intestinal microflora</td>
<td>Pesticides, fish, poultry</td>
<td>Fossil fuels, dental amalgams, old latex paint, incinerators, thermometers</td>
</tr>
<tr>
<td>Absorption</td>
<td>75–85% of vapor absorbed</td>
<td>95–100% absorbed in intestinal tract</td>
<td>7–15% of ingested dose absorbed and 2–3% dermal dose absorbed in animals</td>
</tr>
<tr>
<td>Distribution</td>
<td>Distributed throughout the body, lipophilic, readily crosses blood-brain barrier and placental barrier, accumulates in brain and kidney</td>
<td>Does not cross blood-brain or placental barrier, present in brain neonates, accumulates in kidney</td>
<td>Distributed throughout the body, lipophilic, readily crosses blood-brain barrier as well as placental barrier, accumulates in kidney and brain</td>
</tr>
<tr>
<td>Excretion</td>
<td>90% excreted in bile, feces, 10% in urine</td>
<td>Sweat, saliva, urine and feces</td>
<td>Sweating, urination, feces, and saliva</td>
</tr>
<tr>
<td>Reason for toxicity</td>
<td>Oxidation to inorganic mercury, generation of free radical; binding to thiol in enzymes and structural proteins</td>
<td>Binding to thiol in enzymes and structural proteins</td>
<td>Oxidation to inorganic mercury, generation of free radical, binding to thiol in enzymes and structural proteins</td>
</tr>
</tbody>
</table>

Tobacco Toxicity

Tobacco is processed from the leaves of plants in the genus Nicotiana\(^12\). Smoking negatively impacts on health across the life-course and dramatically reduces both quality of life and life expectancy\(^19\). The negative impacts of tobacco smoking include, among others, increased rates of cardiovascular-related death (e.g., ischemic heart disease and stroke)\(^14\). Nowadays, about 12% of all deaths among adults aged 30 years and over are attributed to tobacco\(^19\). It is estimated that globally tobacco kills around 6 million people each year: five million from direct tobacco smoking while 600,000 deaths are attributable to second-hand smoke effects\(^21\). On current smoking trends, the annual death toll from tobacco is expected to rise to around 10 million people by 2030\(^{32}\). Direct tobacco smoking and involuntary smoking (exposure to second-hand smoke) have been classified by the International Agency for Research on Cancer (IARC) as agents considered carcinogenic to humans (classified as group 1 exposure circumstances)\(^16\). Tobacco smoke can be an important source of known toxic compounds such as nitrosamines, polycyclic aromatic hydrocarbons (PAHs), pesticides, heterocyclic and aromatic amines, and metals\(^17\).

Toxic metals play important role in accumulation in human body due to tobacco smoking as it contains toxic compounds\(^8,^9\). Effectively, various toxic compounds are presents in tobacco smoking which while smoking transfer into blood at time of exchange of gases.\(^8,^{20},^{21}\). The extent of
which a metal transfer from tobacco to cigarette smoke varies greatly depending on several factors such as the metal properties, metal content in the tobacco, design of cigarette, length of rod and type of filter used.\textsuperscript{7, 8, 17}

Anaemia may develop with Pb poisoning via the inhibition of ferro chelatase and aminolaevulinic acid dehydratase (ALAD), the two of many enzymes involved in heme biosynthesis.\textsuperscript{19} Exposure to Pb can produce alteration in physiological functions of the body and is associated with many diseases.\textsuperscript{25, 26} Pb accumulation in human body is highly toxic which causes adverse effects on the neurological dysfunctions, biological disruptions, and cognitive disabilities functions in the bodies. The international level-of-concern for Pb poisoning is 10 μg/dl in the blood.\textsuperscript{27, 19} In recent years, adulteration of opium with heavy metal (Pb) has been considered a threat to human life.\textsuperscript{18} The increasing order of metal content depending on their toxicity is Tl > As > Hg > Cd > Pb > Cr > Al > Mn > Ba > Zn > Ni. Various cigarette brands were analysed for metals contents.

Table 3: Cut-offs for blood metal levels

<table>
<thead>
<tr>
<th>Metal</th>
<th>Cut-off (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony</td>
<td>2</td>
</tr>
<tr>
<td>Arsenic</td>
<td>3.12</td>
</tr>
<tr>
<td>Barium</td>
<td>77.6</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.15</td>
</tr>
<tr>
<td>Cesium</td>
<td>10</td>
</tr>
<tr>
<td>Chromium</td>
<td>1.86</td>
</tr>
<tr>
<td>Cobalt</td>
<td>0.63</td>
</tr>
<tr>
<td>Copper</td>
<td>1495</td>
</tr>
<tr>
<td>Lead</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Manganese</td>
<td>18.3</td>
</tr>
<tr>
<td>Nickel</td>
<td>2.62</td>
</tr>
<tr>
<td>Selenium</td>
<td>201</td>
</tr>
<tr>
<td>Zinc</td>
<td>5234</td>
</tr>
</tbody>
</table>

Table 4: Hypothetical Mechanisms of Metal Toxicity

<table>
<thead>
<tr>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
</tr>
<tr>
<td>Proteins</td>
</tr>
<tr>
<td>DNA</td>
</tr>
</tbody>
</table>

Overview of Effect of Tobacco on Lungs of Smoker & Passive Smokers

Lung diseases caused by smoking include COPD, which includes emphysema and chronic bronchitis.\textsuperscript{31, 32} Cigarette smoking causes most cases of lung cancer.\textsuperscript{13, 2} If you have asthma, tobacco smoke can trigger an attack or make an attack worse.\textsuperscript{31, 32} Smokers are 12 to 13 times more likely to die from COPD than non-smokers.\textsuperscript{31, 32} Smoking can cause lung disease by damaging your airways and the small air sacs (alveoli) found in your lungs.\textsuperscript{32}

Cigarette smoking is an important worldwide health problem, and it has been reported that 1.7 million Thai youths currently smoke.\textsuperscript{30} In previous studies, cigarette smoking was found to influence the lung function of the adolescent boys and girls.\textsuperscript{13, 14} The number of cigarettes was the best measure of exposure to husbands’ smoking, while exposure at workplace was more strongly related to the duration of exposure.\textsuperscript{8}

Table 4: Hypothetical Mechanisms of Metal Toxicity

Figure 1: Health Consequences Causally Linked to Exposure to Passive Smoking Smoke

It was shown due to smoker misclassification is very unlikely to be responsible for the increased health risks which is being recently observed in the epidemiological studies on humans on ETS.\textsuperscript{21} Few studies have shown, longitudinal and cross-sectional in environment tobacco smoke is playing pivotal role in various lung disorders and compared with significant relation with drug response and dose.\textsuperscript{10, 11} Acute exposure to environment tobacco smoking results in decrease of lung volumes and blood flows which also affected gaseous exchange, effecting whole system.\textsuperscript{12} Non-smoking individuals with long-term ETS-exposure have an increased risk of lung cancer. Hackshaw et al. reviewed 37 epidemiological studies on the risk of lung cancer in non-smoking persons (4626 cases).\textsuperscript{35} It was found that lifetime risk of lung cancer in non-smoking persons who lived with a smoker was 24% (95% CI 13% to 20%). Carcinogens related to tobacco smoking also detected in the blood of the ETS
exposed to passive smoker providing clear evidence of the ETS association. A dose-response relationship between the non-smoker’s risk of lung cancer and cumulative exposure to ETS was also demonstrated in this review.

**Mechanism of Epigenetics Due to Heavy Metals**

Epigenetic alterations can be promoted in heavy metals with help of methylation and modification of DNA and Histones respectively. Some heavy metals are capable of DNA methylations and histones modifications such as As, Hg, Chr, and Pb. On the other hand, only Cd and As are reported to mediate expression of noncoding RNAs, another molecular mechanism of epigenetic regulation. The exact mechanism of epigenetic changes due to heavy metals exposure is not fully determined. It seems that increased expression of protooncogenes and silencing of tumour suppressor genes via intracellular ROS production are the underlying causes. Expressions of some tumour suppressors gene are inhibited by the process of Methylation in DNA which leads to convert protooncogene to oncogene. As a result, changes in gene expression result in the alteration of the cellular division process and facilitation of malignant transformation of cells. Epigenetic dysregulations in human bronchial epithelial cells were reported following Cr6+ exposure. Some studies found increased levels of histone H3 methylation marks (H3K9me2 and H3K27me3) and histone methyltransferases (HMTases) reports suggested Cr-induced methylation of the p16 gene, a tumour suppressor gene, in the same cell line. Similarly, various genetic and epigenetic changes may attribute to the Hg, Pb, Cd and As toxic and they show high carcinogenic effects. DNA methylation as well as specific histone modification marks are associated with exposure to Cd and As.

**CONCLUSION**

In this review we reviewed the effects of some heavy metals, i.e., arsenic, lead, mercury, cadmium, chromium, on humans in form of tobacco smoking. We concluded that because of tobacco smoking 1 any form like cigarettes, hukkah, sheesha, inhaling of tobacco is responsible for accumulation of heavy metals in body. Controlling the activity of smoking plays crucial role because there are maximum chances that complication will be severe in future and there will adverse and more harmful effects can be imposed to human body by toxic and hazardous metals. Smoking especially in front of children if one of the major reasons for their improper growth and development. Observing the interventions and the exposure probably for decreasing more extra vulnerability to toxic metals in ecosystems and prevent humans to get affected in devastating ways and it can become significant step towards controlling pollution of heavy metals. Extensive steps have been taken by various national and international co-operatives to reduce toxicity of heavy metals in environment. Smoking has a multidimensional impact on lung such as respiratory disorders, breathing problems, pulmonary disorders. It remains the most prominent causative reason for developing the disease and carries a definitive prognostic and predictive value. Adenocarcinoma is more common in never smokers and females even children are getting exposed because of passive smoking. There are various for molecular profiling of never smokers where carcinogenesis stays presumptive but still if someone near then is smoker can be a reason for getting affected. Thus, Heavy metals can disrupt various cellular events including growth, proliferation, differentiation, damage-repairing processes, and apoptosis by disturbing the cell signalling pathways or kinase cascades. Some toxic or heavy metals including Hg, Pb, Cd, and As causes genomic instability. Collectively, these types of studies may substantially improve the understanding of the significance of heavy metal effect in smoking-related lung diseases and the corresponding potential diagnosis, monitoring, or treatment.

**REFERENCES**


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