พิษสารตะกั่ว : ทัศนใหม่บนปัญหาเก่า

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Hazards with Lead : A New Look at an old Problem

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บทความนี้ได้รวบรวมอันตรายที่เกิดจากพิษสารตะกั่ว ซึ่งปนเปื้อนอยู่ทั่วทุกหนทุกแห่งทั้งในบรรยากาศ อาหาร น้ำดื่ม และสภาพแวดล้อมในการทำงาน หลักฐานทางวิทยาศาสตร์ได้ระบุชัดเจนว่าเด็กเป็นผู้ที่เสี่ยงต่ออันตรายอันเนื่องมาจากพิษสารตะกั่วมากที่สุดเนื่องจากส่งผลกระทบต่อสมอง พฤติกรรมและการเรียนรู้ของเด็กโดยตรง การเกิดพิษอันเนื่องมาจากสารตะกั่วนั้นมีกลไกที่ค่อนข้างสลับซับซ้อน ในปัจจุบันอาจกล่าวได้ว่าสภาพแวดล้อมที่ปลอดสารตะกั่วนั้นพบได้น้อยมากทำให้สารตะกั่วสามารถดูดซึมเข้าสู่ร่างกายได้ทุกขณะไม่ว่าจะโดยการกินหรือผ่านเข้าทางผิวหนังโดยตรง การตรวจพบสารตะกั่วตกค้างในมนุษย์ไม่ว่าจะเป็นที่เส้นผม เลือดหรือเนื้อเยื่ออื่นๆ ของร่างกายย่อมแสดงให้เห็นว่าประชากรโลกเคยสัมผัสกับสารตะกั่วมาบ้างไม่มากก็น้อย แต่สารตะกั่วที่ตรวจพบในเนื้อเยื่อไม่ได้บ่งบอกว่าผู้ป่วยได้รับสารตะกั่วชนิดใด ได้มาอย่างไร หรือจำเป็นต้องแสดงอาการอันเนื่องมาจากพิษสารตะกั่วหรือไม่ พบว่าคนส่วนใหญ่จะไม่แสดงอาการผิดปกติใดๆ แม้ว่าจะตรวจพบสารตะกั่วตกค้างในร่างกาย

หน่วยงานระดับชาติและองค์กรระหว่างประเทศตระหนักถึงปัญหาเหล่านี้ดีและพยายามอย่างยิ่งที่จะควบคุมปริมาณสารตะกั่วในน้ำมัน อาหาร กากผลิตจากโรงงาน น้ำดื่มและแม้กระทั่งเครื่องสำอาง WHO ได้กำหนดค่าต่ำสุดของการตกค้างของสารตะกั่วในสารอาหารที่ยังจัดว่าอยู่ในเกณฑ์ปลอดภัยไว้ไม่เกิน 3 ppm ส่วนประเทศสหรัฐอเมริกากำหนดปริมาณสารตะกั่วตกค้างในน้ำดื่มของเด็กนักเรียนว่าจะต้องมีปริมาณน้อยกว่า 0.2 mg. Pb./litre การควบคุมปริมาณสารตะกั่วตกค้างในอาหารนั้นค่อนข้างยุ่งยากเนื่องจากต้องคำนึงถึงการควบคุมในส่วนของห่วงโซ่อาหารทั้งหมด และยังไม่กระจ่างว่าปริมาณสารตะกั่วในผลผลิตที่เจริญเติบโตในสภาพแวดล้อมที่มีสารตะกั่วเจือปนเป็นจำนวนมากจะมีผลอย่างไรต่อร่างกายมนุษย์ จากการศึกษาทดลองพบว่าสารตะกั่วจะมีผลเสียต่อผนังเซลล์ ไมโตคอนเดรีย และโปรตีนภายในนิวเคลียสทำให้เกิดการเปลี่ยนแปลงอย่างถาวรโดยเฉพาะในเซลล์ที่ไวต่อการกระตุ้น ที่สำคัญได้แก่ผลกระทบต่อการสังเคราะห์ฮีม การทำงานของระบบภูมิคุ้มกัน และการทำงานของไต แต่ที่นับว่าร้ายแรงที่สุดคือผลกระทบต่อสมองในเด็กที่กำลังเจริญเติบโต การศึกษาจึงควรมุ่งเน้นไปที่การหาวิธีการที่ช่วยค้นหาผู้ป่วยพิษตะกั่วระยะต้น

Key Words : ตะกั่ว มลภาวะสิ่งแวดล้อม ห่วงโซ่อาหาร สุขภาพ สมดุลย์โลหะหนักในร่างกาย

Summary

The present review focusses upon the hazards associated with lead as a contaminant in the air, food, drinking water and in the working environment. Children are at greatest risk of lead poisoning and neurological, behavioural, and cognitative problems are well documented. Lead is a complex toxicological problem. It is absorbed into the body through ingestion, digestion and through contact with the skin. Very few environments are lead-free and most people show some lead in their hair, blood or other body tissues as evidence of exposure to lead or lead compounds at some time. However, evidence of lead in tissues in not a reliable guide either to the type or period of exposure, or the presence of lead-related toxic changes. Lead toxicity is frequently asymptomatic.

National and international authonries have attempted to control environmental lead pollution through placing restrictions on lead in petrol, food, factory emissions, drinking water and cosmetics. The recommended maximum "safe" lead level in food is given as 3 ppm

(World Health Organisation). In the United States, school Drinking water lead recommendations are for <0.2 mg.Pb./litre. Control of lead in food is complicated by lead entering food chains. The metal accumulates in plants grown in contaminated area Lead is a cumulative poison with no knows functional role in the human body. Experimental studies have shown that it acts on cell membranes, mitochondria and nuclear proteins to evoke irreversible changes in sensitive cells. Impairment is haem synthesis as a consequence of interaction with trace metals (Fe, Zn, Ca, Cu, Mg), immunological dysfunction, and renal damage are common features of lead toxicity in humans and exprimental animals. Greatest concern relates to the influence of lead on the brain in young children. Studies are urgently required to assist in the identification of early manifestations of lead toxicity.

Key words : lead, environmental contamination, food chains, human health, metal ion balances in the body.

Introduction

Lead is a major environmental problem in many parts of the world and over the past 50 years has been the subject of more than 4000 scientific reports, epidemiological studies and reviews by expert working parties. My own intererest in the action and interaction of metals in biological systems, together with the recent report of lead in the hair of paint shop workers and radiator mechanics in the region of Khon Kaen[1], has prompted me to write the present subject review.

Although lead has been known to the human race for many centuries, its toxic properties have only been recognised for about 60 years. In 1942, Sollemann[2] noted that chronic lead poisoning was quite a common disease with characteristic symptoms including the "lead line" at the margin of the gums, marasmus and anaemia, muscle pain and neurological damage. At that time, it was assumed that these symptoms would regress if a patient avoided lead contamination. We now know that lead is a cumulative poison and is stored in the body (particularly in bone).

Lead is commonly found in plant life growing near old mining sites, and in the proximity to major roads where it is contaminated by petrol fumes. Many papers that I have consulted discusss problems associated with lead entering human food chains. There seems to be overwhelming evidence to show that the major part of lead found in the human body is derived from the diet or drinking water. In Great Britain, it is probable that the longterm average dietary intake of lead for adults is in the range 70-150 μg/day[3]. The British Department of Health and Social Security working party met in 1974, 1978 and 1980 to review the influence of lead on the human population, but with particular emphasis on the influence of lead in petrol on the health and well being of children.

Humans and animals are exposed to lead contamination in their food and water, and in the air they breath. As a consequence, the metal may enter the body through gastroinstestinal absorption, inhalation or by percutaneous absorption. The U.S Department of Health and Human Services[4] noted that lead acetate is absorbed by the human body 1.5 times more rapidly that any other lead compound. Organolead compounds are considerably more toxic than inorganic substances.

In clinical and epidemiological studies, evidence of lead in the hair and/or blood irrefutable evidence that a person has inhaled, consumed or otherwise been in contact with lead in inorganic or organic form at some time, it is not a reliable guide either to the period of lead exposure, or to the presence of lead-related toxicity. Frequently, lead poisoning is asymptomatic or accompanied by subtle changes that are not readily appreciated. Many inconsistencies are seen in the literature relating to analytical procedures, clinical observations and toxicologiocal interpretations.

Lead in the Human Environment

Lead acetate and lead phosphate are major sources of environmental lead contamination[4], but the majonity of clinical and epidemiological reports refer to "lead" in general terms.

DeMichele[5] noted thats at the levels to which people may be exposed in their workplace and in the general environment, "lead is a toxic element in most of its chemical forms, whether it is inhaled, ingested or absorbed through the skin". The level of toxicity related inevitably to the amount of lead absorbed into the body and the sensitivity of the tissues exposed.

Accurate figures for human lead exposure in different parts of the world are difficult to assess, and those that are available vary greatly. In the United States, estimates over the period 1972-1974 suggest that

132,000-180,000 workers were exposed occupationally to lead acetate or lead phosphate. Airborn emissions of lead were believed to be 46.9 million pounds each year. People in towns and cities in North America were presumed to inhale 500-10,000 ng.Pb/m^3 in 1980. The average lead concentration in the American diet is 200 ng/g (0.2 ppm)[6]. The natural concentration of lead in seawater and fish-meat (tuna) was given as 0.0005 and 0.03 ng/g respectively[7]. At that time, the Environmental Protection Agency (EPA) recommended maximum permissible exposure levels of 15 ng. Pb/m^3 [8]. The maximum "safe" intake level recommended by the World Health Organisation is equivalent to 300 ng/g or 0.3 ppm in the adult diet[9].

The principle industrial and commercial used of lead are listed in **Table I**. Where it may be possible to regulate the concentrations of lead compounds in petrol, dyes, paints and water resistent products, cosmetics and pharmaceutical preparations (astringents), it is exceedingly difficult to control the amount of lead leaching into drinking water from lead pipes, or the accumulation of lead in food plants grown on lead contaminated soil. Lead emissions in factory fumes or smelter effluent are further well publicised forms of human exposure, but regulations are in force in many contries now to control lead in work places. Piccinini et al[10] reported finding higher levels in the hair of children whose parents were exposed to lead occupationally. These authors presumed that lead was carried home on dirty working clothes. Other reports illustrate that human lead toxicity exhibits marked geographic and socioeconomic variations (11-14).

Lead contamination is a commonly reported cause of poisoning in cattle, sheep and wildlife in many parts of the world[15-18]. One report, note lead concentrations of 50 ppm in the milk of cattle grazing in the vicinity of an old lead mine. Calves and other farm animals are known to ingest lead in paint, wood preservatives, insulating materials and discarded batteries.

Lead in Human Food Chains

In their general conclusions, the DHSS Working Party [3] on lead and human health reported that people in Great Britain derive most of their body lead burden from food, especially from canned foods or vegetables contaminated by lead from the soil. Farm animals fed on lead-rich pastures contain high levels of lead in milk and meat. Blood lead in sheep grazing in the region of the Nile delta in Egypt were reported to be 0.062-0.83µg/ml[19]. Although there is little doubt that lead like other toxic minerals enters human food chains, the full extent of the problem is unclear. Water contamina-

Table I

Source of Lead	Compounds	Human Exposure
Industry-		
chemical syntheses	raw metal, acetate and misc.	inhalation, ingestion &
soldering, canning	compounds	dermal absorption
batteries		
gold cyanidation		
metal coatings		
Paints, waterproofing	acetate, kphosphate	ingestion and dermal absorption
Pigments (pottery, glass)	acetate	dermal absorption
Pharmaceutical	acetate	dermal use of astringents, poultices and antiseptics
Plastics, styrene	phosphate	dermal absorption, ingestion
Cosmetics	acetate	dermal absorption in hair dyes
Petrol	acetate	inhalation, dermal contact.

tion is a major source of lead and is highlighted in many publications. Whereas Murphy[20] noted that the ultimate goal by the U.S Environmental Protection Agency (EPA) is removal of lead from drinking water[8], the wide use of lead piping makes this aspiration difficult to achieve. In Great Britain, the estimated cost of removing lead from drinking water could be £8 billion However, lead concentrations in the drinking water in many cities are now legally controlled, and miximum permitted limits reviewed regularly. To this end, the EPA has developed an action level of 0.015 ml/litre for lead in drinking water, that authorities must meet. For schools, the EPA recommends lead levels of 0.020 mg/litre in a 250 ml water sample. It is clear that the amount of lead absorbed into the body from drinking water or other source will depend greatly on the age of the individual, his/her ethinic or social class and the composition of the diet[21]. There are conflicting reports of lead uptake by food in the cooking process[22]. The relationship between lead in food and levels present in human hair and/or blood is unclear and reports available are confusing

Human Lead Absorption from Food and Environmental Sources

Lead must be absorbed into the human body and sufficient present in susceptible tissues to be toxic. Although hair lead is commonly used as an index of lead absorption, it may not accurately reflect blood concentrations or the amount stored in bone, teeth or other tissues[23]. Recent researches suggest that ingested lead accumulates in tooth anamel and is a potential cause of dental decay[24]. In a study conducted in South Wales by the Medical Research Council Laboratory,[13], blood lead levels in children and adults exposed to 2.8 mg/Pb/liter in tap water averaged <0.35 µmol./litre. No toxic sings were recorded in any individual. In contrast, in the Omaha study conducted 1971-1977 blood lead in 1232 children exposed to air lead of 0.02-1.69 µg/m^3 was expected to increase to 22.7 ± 8.3 µg/dl (Lead enters the body mainly through gastrointestinal absorption. Isotope studies using radiolabelled lead showed that approximately 10% of the lead ingested is absorbed, but the variations seen were large [26,27]. In part, this variability in absorption may be due to the composition of the diet and the presence of other metal ions. Calcium, zinc, copper and magnesium in the diet are known to impair lead uptake by campeting for receptor proteins in the gut mucosa[28]. Compared to the laboratory rat, the human absorbes ten times the amount of lead from its intestine[29].

All lead compounds, with the possible exception of silicate, are absorbed at mucus membranes and possibly by other exposed tissues. Uptake depends upon their solubility. Lead compounds administed in the diet may dissolve in the hydrochloric acid of the stomach. Interstinal flora may also metabolise lead compounds to a form that is more readily absorbed.

Airborne lead is absorbed through the mucosae of the nose and respiratory tract. The use of lead as a petrol additive is of particular concern in urban communities where atmospheres are polluted by uncombusted tetraethyl lead[30,31]. Being fat soluble, organo lead compounds are very readily absorbed into the body, and through the blood-brain barier. Greatest risk occurs near major roads where concentrations of 6-9 µg/m^3 were recorded in the 1980 DHSS working party report[3]. Sollemann[2] assumed that only about 12% of the lead in the air inhaled near factory sites was actually absorbed, but with the improved methodology available nowadays, this estimate may be low.

Uptake of lead by the skin has been of increasing concern recently in view of the practice of using lead acetate in hair dyes. Although lead acetate is not regarded as a typical water soluble dye, concern has arisen that it may be toxic if absorbed in sufficient amounts over a long period[32]. These authors studied 9 volunteers who sued a hair dye containing 2% lead acetate according to manufacturers instructions over a 90 day period. Hair lead levels increased from <6-14 ppm to 27-446 ppm. with no obvious toxic sequalae. Elsewhere, Cohen and Roe[33] estimated that approximately 0.5% of the lead present in the body was absorbed from hair dyes, and that the risks of dying hair with lead acetate were small.

Percutaneous uptake of inorganic lead is reduced by the presence of anionic ligands in epidermal cells, but the use of organo lead compounds in petrol (lead naphthoate, lead oleate etc.) presents a more serious risk, as these are more readily absorbed[34,35]. Tetraethyl lead is absorbed more readily than other compounds including acetate, phosphate, oleate and orthoarsenate. The influx of five major lead compounds into the hu-

man skin has been given as-

tetrabutyl lead	-	20	μg/cm²/hour
lead olete	-	4.2	μg/cm²/hour
lead linoleate	-	1.0	μg/cm²/hour
lead naphthoate	-	1.0	μg/cm²/hour
lead acetate	-	0.16	μg/cm²/hour
lead oxide	-	0.03	μg/cm²/hour

Cytotoxicity of Lead

Lead has no know biochemical or physiological role in mammalian cells or tissues and is potentially toxic. It has a strong affinity for sulphydryl groups, the aminogroup of lysine, the carboxyl group of glutamic and aspartic acids, and the hydroxyl group of tyrosine. Lead also binds to proteins (including many enzymes), modifying their structure, and hence impairing their availability for metabolic processes.

The cytotoxicity of lead is a large subject and the information available incomplete and widely scattered. There is extensive evidence that cellular toxicity due to lead is mediated by the ability of the metal to interact with key trace metals such as zinc, calcium, magnesium, copper and iron, with inhibition of major metalloenzyme complexes. Evidence is available to show that in eliciting toxic processes, laed acts on cell membranes, cell organelles (especially) microsome and mitochondria), biosynthetic pathways and chromosomomes of susceptible cells. Lead may be toxic to any cell in the body but the following seem to be the most vulnerable-

erythroid cells of the bone marrow
polymorphonuclear leucocytes
brain and peripheral nervous system
renal tubular epithelium
hepatocytes.

The erythroid cells of the bone marrow are a principle target of lead toxicity and abundant evidence is available to show that lead impairs iron, zinc and copper metabolism in haematopoiesis, with affected patients developing anaemia[64]. Thus Baker *et al* [36] reported that 60% of 129 workers exposed to lead occupationally and showing blood haemoglobin of ≥ 9.3 lm.mol/litre had blood lead concentrations of 26 μg/dl. Much clinical and experimental evidence points to the ability of lead to inhibit δ-aminolevulinic acid dehydratase and ferrocheletase enzymes[37-40] and impair carrier protein activity (i.e. caeruloplasmin)[41]. However, experimental studies suggest that zinc can actually alleviate the toxic effects of lead by inhibiting its uptake from the intestine[42]. It may be presumed that if this is the case, zinc acts by blocking lead receptor proteins. A state of ionic competition exists[28].

Other evidence from the study of 129 Caucasian workers exposed to lead suggests that lead may also affect the sodium-potassium interchange (the so called sodium-potassium pump mechanism) at red blood cell membranes[43], but further study is neccessary to determine if red cell Na^+-K^+ co-transport activities are sensitive indicators of long term or recent exposures to lead.

Limited evidence is available to show that lead may impair immune responsiveness and the "processing" of antigenic materials by T-lymphocytes. Thus Fischbein *et al* [44] demonstrated that in individuals exposed to low level lead, the immune responsiveness of T-cells to mitogens was significantly depressed. Elsewhere, reduced chemotaxic and phagocytic activity has been reported in blood neutrophils in patients exposed occupationally to lead and showing significantly reduced urinary δ-amino-levulinic acid levels [45,46].

Lead is probably the most abundant nephrotoxic metal. The nephrotoxicity of lead is characterised by the presence of lead intranuclear inclusion bodies, karyomegaly and cytomegaly, and mitochondrial damage, particularly in the proximal renal tubule (which is susceptible to damage by other heavy metals) [47]. It is probable, that lead accesses renal cells by an endocytic process or by passive diffusion (especially for organolead compounds) [48]. Once inside the cell, lead binds initially to high-affinity proteins and then is taken up by the nucleus where it precipitates with the formation of characteristic inclusion bodies [49]. Experimental studies in rats have demonstrated that lead readily penetrates into kidney cells and may be isolated from all fractions of renal haomogenate [50]. When dogs were dosed orally with lead carbonate (50 mg.kg/day) degenerative changes were evident in proximal tubules of the inner cortex and all enzymes including acid and alkaline phosphatases, dehydrogenases and glucosae-6-phosphatase were greatly reduced [51]. Liver cell damage also illustrated the propensity of lead or lead metabolites to impair cell physiology and respiration.

In view of the putative role of lead as an environ-

mental carcinogen[4], a number of in vitro studies have been conducted to evaluate its mutagenicity and clastogenicity. Thus Chinese hamster ovary cells and human fibroblasts have been exposed to lead chromate in culture and shown a reduced survival after 24 hours treatment[52]. At concentrations of 0.4-8.0 μg/cm^2, the authors noted a dose related increase in metaphase damage, human fibroblasts showing greater sensitivity. However, Winder and Bonin (53) examining the genotoxicity of lead compounds in a range of laboratory assays reported contradicitory findings and considered that lead was not unequivocally established as a cause of the genetical defects observed in persons exposed to lead occupationally. Further work is required urgently.

Absorption and Distribution of Lead in the Body

Evidence of lead exposure is accumulating in human populations throughout the world and many epidemiological, occupational and experimental studies conducted to understand mechanisms of lead uptake, metabolism and deposition (54). Much of the body lead burden derives from the diet and is absorbed into the blood stream before being deposited in the liver, kidney, brain and other tissues. Children are especially vulnerable to lead poisoning but animal experiments have proved useful in demonstration uptake and distribution of the metal and the influence of age[55]. Lead acetate fed at 2% in diet to pregnant rats led to reduced size and post-natal growth of the offspring with evidence of paralysis developing after three weeks. Lead was identified in the mother's milk and in the blood, brain, liver and kidneys of the infants. Tissue lead concentations in infants increased until about 5 weeks post-natally and then declined.

Bone is well known as a major resevoir for lead in human adults and children[56,57]. The metal is probably not strongly bound and may be released back into the circulation to be toxic in susceptible tissues. High levels of bone lead have been shown in children who died of lead-related encephalopathy[58]., Experimental studies in isolated murine ostecolasts suggests that the regulation of lead uptake and release from/by bone is in part regulated by calciotropic hormones, circulating calcium levels, phosphate and magnesium ions, and maybe other factors[57]. Factors controlling lead uptake by the human are imperfectly known. Whereas with zinc, uptake of the metal from the gastrointestinal tract or the skin seems to be regulated by the concentration present in the circulation, in the case of lead, the total body content of lead does not affect lead uptake[5]. There is no obvious "feedback" mechanism in the human (and probably animal) body to limit lead absorption. Metal uptake from food, air or by percutaneous absorption can be expected to displace calcium from bone and impair iron metabolism. Some lead will be eliminated via the skin, hair and sweat, but the amount found in these tissues may not be an accurate guide as to the total body lead content.

Lead as a cause of Reproductive Disorder and Deformities in the Unborn Child

In 1975, the Swedish Council for Environmental Information[59] launched a three years project to evaluate the potential teratogenic risks associated with exposure to environmental chemicals including lead. They noted that lead exposure in pregnant women is an unequivocal cause of spontaneous abortion, stillbirth and premature delivery but, despite numerous experimental studies in experimental animals which have shown structural and behavioural fetal abnormalities[60,61]. The committee concluded that "lead is not a teratogen in man in the classical sense". Recurrent postnatal exposure is an established cause of long lasting central nervous system defects including metal retardation, siezure disorders and behavioural aberration, particularly at blood lead concentrations of 80-100 μg.Pb,/dl.[59].

The Way Forward

Lead exposure is a potential hazard to exposed populations, with children at serious risk of developing brain damage. However, a recent report in the journal *Science of the total Environment*[62] questioned the long accepted view that lead is as injurious to the human body as is widely publicised. Workers showing blood lead concentrations of 1.8 μmol/litre and given neuropsychological tests failed to show neurological impairment. Nevertheless, governments in many countries are compelled to reduce lead in the environment and in food and water. Baker[36] called for the establishment of permissible blood lead not exceeding 60 μg/dl. However, Russell-Jones (30) noted that if a neu-

rotoxin capable of producing encephalopathy or even death at blood levels of around 80 µg/dl were continually released into the atmosphere so as to produce a mean concentration in urban of 15-20 µg/dl, it would be remarkable if this did not produce widespread neurological problems in younger members of the community. Even so, some member countries of the OECD have blocked attempts to reduce environmental lead, or eliminate the use of lead in petrol and paint. It is hoped that in due course, those countries producing lead, will adopt a "voluntary action" plan to eliminate environmental contamination [63].

Regulators have the opportunity of restricting the use of lead in petrol, engineering practice and in medical and cosmetic products. To this end, the Environmental Protection Agency (U.S.A) has developed an action level of 0.015 mg/l (in 1 ml samples) that water purveyors must meet to be in compliance with Federal Regulations [8,20]. However, because there is much ambiguity as to the implications of lead in hair, blood or other tissues, in terms of human health and irreversible tissue damage; scientists and clinicians should research further into laboratory tests for diagnosis of early neurological and/or biochemical changes which will eventually present in terms of frank neurological damage with behavioural and cognitative impairment

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