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An insight of environmental contamination of arsenic on animal health

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ABSTRACT

The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic. Exposure to arsenic is mainly via intake of food and drinking water, food being the most important source in most populations. Although adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues and is even increasing in some areas. Long-term exposure to arsenic in drinking-water is mainly related to increased risks of skin cancer, but also some other cancers, as well as other skin lesions such as hyperkeratosis and pigmentation changes. Therefore, measures should be taken to reduce arsenic exposure in the general population in order to minimize the risk of adverse health effects. Animal are being exposed to arsenic through contaminated drinking water, feedstuff, grasses, vegetables and different leaves. Arsenic has been the most common causes of inorganic chemical poisoning in farm animals. Although, sub-chronic and chronic exposure of arsenic do not generally reveal external signs or symptoms in farm animals but arsenic (or metabolites) concentrations in blood, hair, hoofs and urine are remained high in animals of arsenic contaminated zones. So it is assumed that concentration of arsenic in blood, urine, hair or milk have been used as biomarkers of arsenic exposure in field animals.

1. Introduction

Arsenic (As) is an environmental chemical element of high concern for human health [18,20]. Environmental exposure to arsenic imposes a big health issue worldwide. Since the middle of the 19th century, production of heavy metals increased steeply for more than 100 years, with concomitant emissions to the environment [11,47]. Chronic arsenic poisoning, or arsenicosis, is typically defined by the classical dermal stigmata, together with internal disorders in the presence of known arsenic exposure. Groundwater contaminated with arsenic is the major source of both human and animal exposure to arsenic. Chronic exposure to arsenic can cause skin, lung and bladder cancers [22]. A small but measurable increase in the incidence of bladder cancer was associated with exposure to concentration as low as 10 ppm of inorganic arsenic [7]. Epidemiological studies suggested a strong correlation between chronic arsenic exposure and various noncancer human diseases, such as hyperkeratosis, atherosclerosis, diabetes, and chronic obstructive pulmonary diseases [32]. In arsenic affected areas, livestock are also exposed to toxic levels of arsenic very similar to human beings. Other than drinking water, feed materials are also considered as a source of arsenic for animal in arsenic contaminated areas. A large number of animals maintained by arsenic affected peoples are provided with arsenic contaminated drinking water, grasses, feedstuffs, vegetables and rice plants. The ingested high amount of arsenic may be retained in the blood, urine, faeces, hair and tissues of animal that is consumed by human beings directly or indirectly. Once cattle are affected, environmental contamination of arsenic occurs through domestic and agricultural use of cow dung [35]. Animals are exposed to arsenic in arsenic contaminated zone. In my review I emphasize the deleterious effect of arsenic on animal health.

2. Occurrence, exposure, effects and significance

Arsenic is an environmental toxicant with wide distribution in rock, soil, water and air. Arsenic compound is classified into two viz. inorganic arsenic and organic arsenic. Inorganic arsenic is generally abundant in groundwater used for drinking in several countries all

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over the world (e.g. Bangladesh, Chile and China), whereas organic arsenic compounds (such as arsenobetaine) are primarily found in fish, which thus may give rise to human exposure [47]. It is a great environmental contaminant in the Bengal delta basin and is responsible for causing carcinogenicity to millions of people and animals [18,22]. Emissions of heavy metals to the environment occur through wide range of processes and pathways, including to the air to surface waters and to the soil [18]. Atmospheric emissions tend to be of greatest concern in terms of human health, both because of the quantities involved and the widespread dispersion and potential for exposure that often ensues [41]. People may be exposed to potentially harmful chemical, physical and biological agents in air, food, water or soil. However, exposure of arsenic does not result only from the presence of a harmful agent in the environment but the key word in the definition of exposure is contact [3,38]. Soil is being contaminated with arsenic though irrigated water and rice, vegetables, plants are thereby contaminated with arsenic through its uptake to the toxic level [9,10]. 25(twenty) million people of 50 (Fifty) districts involving nearly 85% of the total area of Bangladesh have arsenic in ground water [6]. Arsenic contamination in drinking water has been documented in Nepal, Myanmar, China, Inner Mongolia, Thailand, Vietnam and Japan, South America, Chile, Bolivia, Central northern Mexico, Peru and Argentina, Democratic Republic, and Cambodia [20]. Both human and animal beings are expelled to drink arsenic contaminated water in that particular zone of West Bengal, India. The concentration of arsenic in drinking water exceeds the permissible limit i.e. 0.05 mg/L [35,47].

Arsenic causes hyperpigmentation keratosis, weakness, anaemia, burning sensation of eyes, solid swelling of legs, liver fibrosis, chronic lung disease, gangrene of toes, neuropathy, and skin cancer and other clinical manifestations. Except abdominal pain, the prevalence of all other clinical manifestations tested (e.g., pigmentation, keratosis, hepatomegaly, weakness, nausea, lung disease and neuropathy) were found to be significantly higher in arsenic exposed people (water arsenic>0.05 mg/L) compared to control population (water As level<0.05 mg/L) [17,18]. 6 (Six) million people of seventy-nine blocks of nine district viz. Malda, Murshidabad, Nadia, North and South 24 Parganas, Bardhaman, Hoogly, Howrah and Kolkata in West Bengal, India are affected with the arsenic related health hazards where arsenic concentration exceeds 50μg/lit) [20,35,47]. Bangladesh is one of the worst cases of environmental toxicity. In addition, among 42 heifers 29 died from arsenic poisoning in South America, after an arsenical soil and the grass sample contained 2262 ppm as dry weight [29]. In those areas, over a 44 day period, 4 of 5 affected calves in a 170 herd of beef cattle died after exhibiting clinical signs of lethargy, ataxia, anorexia, and diarrhoea. [14] revealed that histopathological examination of tissues and toxicological analysis of a suspicious powder discovered in the pasture confirmed arsenic trioxide toxicosis.

Arsenic is contaminated in food chain though drinking water, food, meat, milk and egg. The ingestion of bovine milk is one of the most important pathways of exposure to chemicals and the accumulation of persistent organic chemicals in tissues in the agricultural food chain. It was shown that arsenic concentrations in all water samples were over the suggested level for cattle intoxication and ranged from 0.23 to 2.54 mg/L [38]. Besides, the total arsenic concentrations from cow's milk ranged from 0.9 to 27.4 ng/g at Francisco I, Maderond Matamoras countries [41]. In Northen Scotland, the level of arsenic in the blood (19 μg/kg) is at least two orders of magnitude higher than the level of blood in unexposed area [15]. In chronic experimental study, arsenic (ppm) burden in blood, liver, kidney were estimated as 3.49 ± 0.10, 5.45 ± 0.35 and 4.87 ± 0.17 in chronic arsenic (10 ppm) intoxicated rat after 12 weeks [30]. [4] revealed that the concentration of arsenic in blood of acute and subacute arsenic toxicity in goat ranges from 0.13 ± 0.01 to 4.95 ± 0.03 mg% and 0.12 ± 0.02 to 1.32 ± 0.27 mg% respectively in West Bengal, India. Arsenic is deposited in liver, kidney and spleen and most of it is excreted via urine (if salt is not readily absorbed) and much of it is eliminated via faeces [43]. Animals are able to tolerate low levels of arsenic and the normal level in cattle tissues was less than 0.5 ppm. The kidneys are a primary route of excretion whereas liver is the target for arsenic deposition. [42] reported that urine samples contained 0.15–16.4 mg/kg in an outbreak of arsenical poisoning in cattle in Mexico. An estimation of arsenic content in hair samples and the value went as much as 5–10 mg/kg while animals not exposed to arsenic (normal) should contain less than 0.5 mg/kg [40]. The maximum concentration of arsenic in tissue reaches about 8 hrs after ingestion and the animals that survive for 2–3 days may have levels as low as 3 mg/kg [40].

3. Chronic arsenic toxicity and animal health

Arsenic (As) is found in the natural environment, being present in soil, groundwater and plants. Epidemiological evidences indicated that it is also a carcinogen in both human and animal beings [47]. Areas of our planet with a significant presence of inorganic arsenic have been identified, particularly in Asia and other non-European countries. In Europe, the levels of arsenic in the environment are rather low, with the exception of some areas with particular geological formation or industrial process [18,21]. Contamination of arsenic in drinking water is a major health problem throughout the world. Inorganic arsenic has a pronounced acute toxicity in human and experimental animals [33]. Human exposure to arsenic in drinking water has been associated with cancers (lung, bladder and skin), chronic diseases of skin, heart, lungs, nervous system and diabetic effects [1,49]. Arsenic can enter the food chain, causing widespread distribution throughout the plant and animal kingdom [16,18,20].

The clinical characteristic of acute arsenic poisoning includes intense abdominal discomfort, vomiting and diarrhoea followed by rapid circulatory collapse in animals. Death may occur within a few days and sometimes in less than one hour [47]. [6] reported that Irritant chemicals like arsenic, lead, copper, thallium, phenol etc. cause gastritis in monogastric animals with dysentery, toxamia and nervous signs. The chronic form of arsenic toxicity in cattle includes particular fibrosis producing stiffness and asymmetrical enlargement of hocks or other joints of the limbs [46] if feed levels greater than 250 ppm are fed for several weeks. [40] reported that toxicity leads to incoordination with ataxia and posterior paresis but alertness and appetite remain normal. Acute and subacute arsenic toxicity in experimentally induced goat were characterised by increased heart rate, respiration rate, absence of ruminal motility, diarrhoea, drooling of saliva, stiff gait, paresis of hindquarter, lameness, tremor, convulsion, coffee coloured urine congested mucous membrane, paresis of limb and death, whereas chronic arsenic exposure causes reduced body weight, coffee coloured urine, congested mucous membrane and polyuria [4]. Arsenic and its metabolites are readily excreted in urine and bile; while in contrast, very little arsenic is excreted in breast milk [18,22]. However, the absorption of ingested inorganic arsenic varies, depending on the solubility of the arsenical compounds (the more water soluble the compound, the greater its absorption), the presence of other food constituents and nutrients in the gastrointestinal tract, and on the food matrix itself [12]. The transport of inorganic arsenic in edible tissues of mammals and birds is generally low, and, thus, foods derived from these tissues contribute only insignificantly to the possible intoxication of human. The inorganic and organic compounds of arsenic have

different bioavailability [5]. There are also significant differences in bioavailability among the various organic compounds of arsenic.

The organic arsenic compounds have been used as feed additives to control diseases and increase body weight (BW) in pigs and poultry since the mid 1940's and are still used today in various countries [18]. Furthermore, arsenic readily passes through the placenta in mammals, including humans, resulting in similar exposure levels in both the foetus and the mother [5,13,47]. Specifically, the maximum content of arsenic in complete feed has been set by the European Union at 2 mg/kg feed (with 12% moisture) for all animal species and 10 mg/kg for fish and fur animals [5,12]. In the bloodstream, arsenic is distributed between the plasma and the erythrocytes, in which it is bound to the globin of hemoglobin. The relative amounts in each compartment depend on the valency and dose of arsenic administered, as well as the species of animal [5,21]. The concentration of arsenic decreases rapidly in various tissues of the body, after ingestion ends. However, several weeks later, arsenic is translocated to hair and skin because of the high concentration of sulfur-containing proteins in these tissues. The US NRC [33] reported that in cattle the maximum tolerable dose of arsenic is 50 and 100 mg/kg diet for inorganic and organic arsenic compounds [31], respectively, and in goats is 30 mg/kg diet [5,31]. The organic compounds of pentavalent arsenic are absorbed in a significant extent from the gastrointestinal tract of rodents, swine and humans (>40%, 17–33% and 75–80% of ingested dose, respectively), while the organic compounds of trivalent arsenic are generally poorly absorbed [5,22]. The toxic dose for oral sodium arsenite (NaAsO2) is 6.5 mg/kg BW in horses, 7.5 mg/kg BW in cattle, 11 mg/kg BW in sheep, and 2 mg/kg BW in pigs, while for arsenic trioxide (As_2O_3) is 7.5–11 mg/kg BW in pigs and 33–55 mg/kg BW in horses, cattle and sheep [5,31]. In contrast to inorganic arsenic, in pigs treated with 100 mg arsanilic acid/kg of diet for 6 weeks, only a reduction in food intake was noticed, whereas administration of 1 g arsanilic acid/kg of diet resulted in clinical signs of toxicity [5,47].

4. Molecular targets of arsenic toxicity

Growing evidences revealed that trivalent form of arsenic is more toxic than pentavalent form [28]. Arsenic is able to suppress replication of DNA with altered repair of enzymes [27,36] (see Table 1). It causes inhibition of enzymatic activity in mitochondrial with inhibition of dehydrogenase and stimulation of mitochondrial adenosine triphosphatase activity by the uncoupling of oxidative phosphorylation and impairment of tissue respiration triggering cytotoxicity [37]. Interestingly, it reacts with thiol groups (- SH) resulting affection of the conversion of lipoic acid to acetyl lipoic acid and in turn acetyl CoA [44]. The dangerous effect of arsenic is to alter mitochondrial membrane potential with alteration of ATP formation during glycolysis and induction of apoptosis in various cells [34,36]. It also has genotixic effect in mammalian cells with elevation of peroxynitrite anions. It causes oxidative-DNA damaged based on iron release from ferritin with production of reactive oxygen species (ROS) [8,25]. It has also clastogenic effect in several cell types [16,45]. Another mechanism of arsenic toxicity is the methylation of inorganic arsenic [39]. Documentary evidences suggest that reactive oxygen species (ROS) are key players in the induction of oxidative stress in cells and exposure to arsenic generates nitric oxide (NO) and superoxide anions(O2-) which are subsequently converted to more damaging species such as hydroxyl radical (OH) [16,34]. With the reaction and interaction of these reactive species with target molecules, oxidative stress, lipid peroxidation, DNA damage and the activation of signaling cascades associated with tumor promotion and/or progresssion occurs [24,34]. He also reported that the uncoupling of oxidative phosphorylation decreeses cellular respiration and increases free radical producion leading to hepatotoxicity and porphyrinuria which are commonly associated with acute exposure to arsenic [16,24].

5. Arsenic in food chain through water-soil-plant-animal-man continuum

General population exposure to arsenic is mainly via intake of food and drinking water. Food is the most important source, but in some areas, arsenic in drinking water is a significant source of exposure to inorganic arsenic [5]. Arsenic contamination in groundwater has become an additional concern vis-à-vis its use for irrigation purposes and its subsequent entry into the food-chain through various food crops and fodders [19]. Consequently, the potential adverse effects of arsenic to animal and human health are determined by the amount of inorganic arsenic present in food subsequently. [23] revealed that cooked rice with discarded water had significantly lower concentration of arsenic compared to raw rice whereas raw rice had higher concentration of arsenic compared to raw vegetables. Drinking water may contain significant amounts of inorganic arsenic, while significant source of arsenic in the diet of human and animals have been identified to fish and other marine organisms, as well as their products [2]. Then, all the inorganic and organic arsenic compounds accumulate to various tissues (higher to lower concentration: kidneys > lungs > urinary bladder > skin > blood > liver) [5,18,22] (Fig. 1). Zhao et al. [50] reported that excessive accumulation of As, particularly inorganic arsenic (As(i)), in rice (Oryza sativa) poses a potential health risk to populations with high rice consumption.

6. Remedy for arsenicosis

Previously arsenic was used as a medicine and has its poisonous effect since humans first became interested in chemistry [5] (WHO, 2001). The poisonous effect of arsenic is dose and duration dependent manner. Arsenic is rapidly distributed through blood stream and eliminated via kidneys as methylated arsenic metabolites [48,31]. Concentration of arsenic in environment is judged by analyzing the content in hair and nails as arsenic tends to accumulate in these tissues for a prolong time. It is also obvious that high dose of arsenic in drinking water may be a predisposing factor in arsenic toxicities in both human and animal beings exposed to arsenic contaminated area. Several methodological studies have been done to combat the toxic effect of arsenic on both human and animal beings. [48,31] stated that the symptoms and signs of arsenic poisoning may be reduced if the quality of drinking water improved. Numerous studies suggested that improvement of water quality, the rate of improvement in the symptoms and signs of arsenic poisoning in both animal and human beings may increase with a decrease in arsenic level in the drinking water source [48,31,26]. Thus, it may be essential for the control of the disease to improve water quality in areas of endemic arsenic toxicosis (WHO, 2001).

6.1. WHO'S [47] recommendation

[1] Arsenic is being exposed in environment via natural, industrial or from administered acute poisoning. [2] Animals are less sensitive than human being. [3] Chronic exposure leads to dermatosis when animal or human being are exposed to arsenic contaminated drinking water for long time. [4] Arsenic enters into the body through contaminated food and drinking water. [5] Generally weak and malnutritious people are prone to arsenicosis. [6] Melanosis with keratosis in palm is common symptoms of skin

Table 1
Molecular targets of Inorganic and organic arsenic with biological outcomes during arsenic toxicity (Adapted from Miller [27] with modifications).

Affected Cellular Process	Mechanism of action	Biological effects
Oxidative stress	Reactive Oxygen Species	Sulfhydryl-containing proteins
	redox-sensitive signaling	NO, S-nitrosothiols, AP-1, NF-kappaB, p53, p21 ras
	Generation of free radicals	loss of antioxidant defence
	Fenton-type reactions	Protein oxidation
	Reduction of SOD and catalase	Lipid peroxidation
	enzyme activities	Diminution of intracellular glutathione level
	Intracellular thiol homeostasis	erythrocytic damage
	Metal-induced signal transduction pathways	Activation of NF-kappaB
	Mitogen-activated protein MAP-kinases,	Cellular stress
	extracellular regulated kinase (ERK),	Production of nitric oxide
	c-jun terminal kinase (JNK), and p38	
	Phosphorylation of ERK	Heat shock proteins synthesis and cell transformation
		APL fusion protein, PML-RARalpha degradation
	Expression of dominant-negative Erk2	Cell transformation
	Overexpression of dominant-negative JNK1	NF-κB activation
Carcinogenesis	Clastogenesis	Chromosomal translocation
		chromosomal mutagenicity
		micronuclei, chromosomal aberrations,
		sister chromatid exchanges
	Signaling pathways responsible for cell growth	Sister chromatid exchange and chromosomal breakage
	Genotoxic pathways	Tumor promotion
		hypermethylation of cytosine
	Mitotic damages	induction of aneuploidy and single strand breaks in DNA
	p53-mediated mechanisms	DNA to form a variety of adducts
	DNA damage	Changes of cellular integrity
		calcium-mediated production of peroxynitrite,
		hypochlorus acid production of metallothioneins
	Activator protein 1 (AP-1), mitogen-Activated	Transactivation of AP-1
	protein (MAP) kinases and protein kinase C (PKC)	
	DNA-protein cross-links	MAP kinase Erk kinase (MEK)1 inhibitor, or
		overexpression of dominant-negative PKCα
		Granulocyte macrophage colony stimulating factor
		(GM-CSF), transforming growth factor alpha
		(TGF-alpha) and proinflammatory cytokine
		tumor necrosis factor alpha (TNF-alpha)
	Suppresion of p53 gene	c-myc overexpression and apoptosis
	Alteration of DNA repair processes	Transcription of the hTERT gene
		cytokine production of different oncogenes
	Mitogen-activated protein kinases	Elevated expression of cyclin D1, p53-dependent
	(MAP-kinases) pathway	p21 expression
	DNA repair	Reduced activity of isolated poly(ADP-ribosyl)ation
		Diminished gene expression of xeroderma pigmentosum
		group (XPC) and Xeroderma Pigmentosum Complementation
		Group (XPE) and a reduced XPC protein level
	Unfolding of the zinc-binding structure	Micronucleated polychromatic erythrocytes in bone
Apoptosis	Intracellular glutathione and hydrogen peroxide (H2O2)	Signal transduction pathways
	Mitochondrial membrane potential	Cell death, cell shrinkage, membrane blebbing, chromatin
		condensation, and nuclear fragmentation
	Vascular endothelial growth factor (VEGF),	Cytochrome *c* release and activation of the caspase cascade
	activating of caspases with p53 overexpression	
		Release of soluble intermembrane proteins, which
		cause DNA fragmentation
		Inhibition of glutathione peroxidase (GPx) activity
		Cytochrome *c* release and activation of the caspase cascade
	Increased *bax* expression	Down-regulation of bcl-2 family members sensitizing
		cells toward apoptosis
	Inhibition of NFκB activity	Interferes with intracellular adhesion molecule and vascular
		cell adhesion molecule up-regulation, inhibiting IL-6
		secretion resulting from adhesion of MM cells to bone
		marrow stroma
	Inhibits GTP-induced polymerization of tubulin	Cytoskeletal protein damage
	Altered nuclear distribution of PML	PML is recruited onto matrix-bound nuclear
		bodies (NB), for degradation
Antiproliferative activity	Inhibition of STAT3 activity	Transcription inhibition of IL-6-responsive genes
	Growth arrest in the G_1 phase of the cell cycle	Enhancement of cyclin dependent protein kinase
		inhibitors (CDKI) p21 and p27
	Induction of differentiation	Induced expression of cell surface maturation
	c-Jun NH2-terminal kinases., de-polarization of	markers (CD11b)
	mitochondrial membrane, generation of	Induction Cell proliferation
	cytochrome c, activation of caspases	cell growth and cell cycle arrest
Angiogenesis inhibition	Inhibition of vascular endothelial growth factor	Diminished vascular endothelial growth factor
		expression inhibits Endothelial cell proliferation
		in a dose- and time-dependent manner

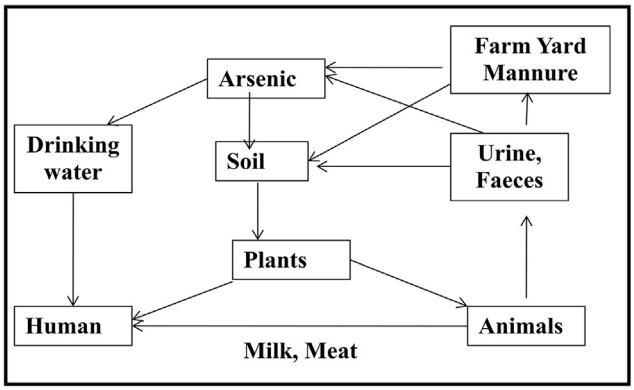

Fig. 1. Schematic diagram of arsenic contamination in both human being and livestock.

infection of chronic arsenicosis. Melanosis may be disappeared when medicine is applied but keratosis can not alter though further complication may be prevented. [7] Till now no medicine was found suitable once complication developed. [8] Arsenic free drinking water or environment or decrease in arsenic concentration level is only the solution of arsenicosis.

7. Conclusion

Chronic arsenicosis leads to increased risks of skin cancer with altered functions of organs with exhibition of skin lesions viz. hyperkeratosis and pigmentation. Lung cancer may be developed if arsenic is consumed through inhalation for a long time. Recent studies stated that chronic arsenic exposure causes damage of renal tubular with fractures of bones. It is obvious that livestock populations consume huge amount of arsenic through contaminated drinking water, rice plants and grasses per day. Faeces and urine of animals are important biomarker to contaminate water and agricultural land. . Although livestock populations share the same drinking water and the vegetation growing on the same soil as humans, reports on clinical arsenicosis in livestock are meager. Estimation of concentration of arsenic in different samples of animals is indicated for evaluation of arsenic exposure. Therefore, measures should be taken to reduce arsenic exposure in the general population in order to minimize the risk of adverse health effects with drinking of arsenic free water.

Conflict of interest

There are none.

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