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REVIEW ARTICLE

ARSENICOSIS: A REVIEW OF ITS TOXICOLOGY AND DERMATOLOGICAL MANIFESTATIONS

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ABSTRACT

Arsenicosis is an adverse health condition due to prolong ingestion of arsenic contaminated water. It is most prevalent in Bangladesh. More than 67 million people in Bangladesh are exposed to 0.05 mg/ liter or above of arsenic in their drinking water and it is now considering a biggest crisis in health and social sector in the modern world. Arsenicosis affects almost all the vital system of the body. Skin involvement is the earliest and commonest feature. Major dermatological manifestations are melanosis, keratosis and skin malignancies. Diagnosis is usually done by history, clinical feature and laboratory analysis. In this article, author describes the extent of arsenic sis in Bangladesh and emphasizes dermatological manifestations of the disease.

INTRODUCTION

Arsenicosis is a multisystem disorder due to prolong exposure of arsenic mainly by drinking water. Chronic toxicity due to ingestion of arsenic contaminated ground water has become a major health problem in Bangladesh. It is now identified in many countries. It is showed that arsenicosis can affect any country irrespective of geographical or economical situation. The symptoms and signs caused by long-term elevated exposure to arsenic differ between individuals, population groups and geographical areas. There are no internationally recognized criteria for the diagnosis and management of arsenicosis. The purpose of this paper is to review toxicology of this disorder and its relateddermatological features in context to Bangladesh.

Toxicology

Arsenic is a natural component of the Earth's crust. It is found everywhere including atmosphere, soil, rock, water, organism, plant etc. Natural concentrations of arsenic in rock are 1.5-2.0 mg, in contaminated soil up to 500mg/kg and in natural water is 0.1-0.4microgram/L. Arsenic is also emitted into the atmosphere by high-temperature processes such as coal-fired power generation plants, burning vegetation and volcanic action.

Arsenic can combine with both metals and non-metal to form mainly following 2 types of compounds:

- Inorganic Arsenic, Trivalent, e.g. arsenates, Pentavalent, e.g. arsenates
- Organic Arsenic, Mono- methyl arsonic acid (MMA), Di-methyl arsinic acid (DMA) etc.

The organic forms are comparatively non-toxic and mostly present in sea foods. Inorganic forms are toxic to human health and present in almost everywhere including air, water, soil and food. After ingestion, arsenic is absorbed from the gastrointestinal tract; following absorption, arsenic undergoes metabolism through repeated reduction and oxidative methylation. It is widely accepted that methylated metabolites of inorganic arsenic are less reactive and less genotoxic; metabolism is regarded as a bio-inactivation mechanism. Following metabolism, arsenic is rapidly cleared from blood, and only 0.1% of the arsenic remains in the plasma 24 hours after dosing. Urine is the most common route of elimination. As much as 45% to 75% of the dose is excreted in the urine within a few days to a week (Gomez-Caminero, 2001 and Vahter, 1980). The trivalent state of arsenic, As^{3+}, is widely distributed by virtue of its binding with sulfhydryl groups in keratin filament and has a tendency to accumulate in the skin, hair, nails, and mucosae of the oral cavity, esophagus, stomach, and the small intestine (Lindgren, 1982). On the other hand, arsenate (As^{5+}) is the predominant form deposited in the skeleton because of its ability to replace phosphate in the apatite crystal in bones; as a result of this it is retained there for a longer time (Lindgren, 1982). Within 30 hours of ingestion, arsenic deposits in the hair. Daily consumption of water with greater than 50 micrograms per liter of arsenics, usually lead to health problems.

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Some people may be affected by lower levels of arsenic than others. Young children, the elderly, people with long-term illnesses, and unborn babies are at greatest risk of being affected. If the exposure is of a large concentration then the progression of the arsenic poisoning event would lead to seizures, electrolyte disturbances and systemic shock and even death. Trivalent arsenic is believed to be a carcinogen that induces chromosomal abnormalities. However, the exact molecular mechanism of arsenic induced carcinogenesis is less understood (A Field Guide for Detection, 2002). It has been shown to induce sister chromatid exchanges, chromosomal aberrations, and also DNA-protein crosslinks in lymphocytes and in fibroblasts (Jha, 1992), to explain this genotoxicity, several mechanisms have been put forward, one of which emphasizes the role of reactive oxygen species in inducing the chromatid exchange (Nordenson, 1991). The other theory highlights the role of arsenic in impairing the DNA repair process. DNA excision repair of thymine dimer in human fibroblast is inhibited by inorganic arsenic (Okui, 1986) As^{+3} is found to inhibit DNA ligase (Li, 1989), and tubulin polymerization. It has also been shown that arsenic alters the activity of tumor suppressor gene p53 by DNA methylation.

Historical Background

Arsenic is known to human since 400-500 B.C. for its therapeutic use in Greece and Rome. Hippocrates recommended arsenic for treatment of skin ulcer & boil. In Indian sub-continent during the period of Buddha, it had been used for the treatment of many diseases. Alchemiste Geber-discovered arsenic oxide in 9^{th}century. The poison was transformed into a medicine in the 1700s, when Thomas Fowler developed a solution of arsenic trioxide in potassium bicarbonate (1%w/v) for the treatment of asthma, chorea, eczema, pemphigus, and psoriasis (Fowler′s, 2008). It was also used empirically for the treatment of a variety of diseases, including leprosy, syphilis, and yaws (Anonymous Arsenic, 2008). In 1822 as was identified as possible carcinogen. Interestingly enough, the dilemma of its effects and side effects is still going on; in spite of health crisis due to arsenic poisoning, in many countries, arsenic trioxide (trisenox) has been used in the treatment of patients with acute promyelocytic leukemia (Waxman, 2001), in modern time and has even obtained the FDA approval in September 2000 [(14)]for use in the condition. It is colorless, odourless, and tastelessand these characteristic contributed much to use it as a poison of choice.Arsenic poisoning, accidental or deliberate has been implicated in the illness or death of a number of people throughout the history.Recent forensic evidence uncovered the evidences of arsenic poisoning as a cause of death of following prominent people: Francesco I de Medici, Grand duke of Tuscany (1541-1587), Eric VII of Sweden(1533-1577), George III of Great Britain (1738-1820), Theodor Ursinus (1749-1800), Napoleon Bonaparte (1769-1821) (Arsenic poisoning, 2008).

Arsenicosis Case Definition

WHO working group defined Arsenicosis as "a chronic condition arising from prolonged ingestion of arsenic above safe dose for at least six months, usually manifested by characteristic skin lesions of melanosis and or keratosis with or without involvement of internal organs" (http://apps.searo.who.int/PDS_DOCS/B0301.pdf). The WHO Guideline value for arsenic in drinking water is set at 10 ppb. This is the drinking water standard adopted in many industrialized countries. However many developing countries have kept the limit at 50 ppb for practical reasons.

Arsenicosis in Bangladesh

"*Bangladesh is in the midst of a mass poisoning in history, dangerous level of arsenic have been found in the ground water, entering millions of people sip by sip as they drink from over 4 million tube wells."* New York Times: 10.11.1998.

Prior to the 1970s, Bangladesh had one of the highest infant mortality rates due to ineffective water purification sewage system. Millions of wells were constructed then to provide drinking water. In result, infant mortality and diarrheal diseases were reduced by 50%.But among 8.4 million wells, approximately 1 in 4 of these wells is now contaminated with arsenic. So far ground water contamination by arsenic is detected in 62 districts out of 64 and about 38200 arsenicosis patients were identified across the country (Bangladesh Arsenic Mitigation Water Supply Project, 2005). Arsenicosis was first reported in ChapaiNawabgonj district in year 1993. Now, it is estimated that between 35 to 77 million Bangladeshi or 28 to 62% of the total population of 125 million are now at risk of chronic arsenic poisoning (Bangladesh Arsenic Mitigation Water Supply Project, 2019). It is described in world media as the largest known mass poisoning in history (New York, 1998) Times.

Global Scenario of Arsenic Contamination

Arsenic contamination of groundwater is widespread and there are a number of regions where arsenic contamination of drinking-water is significant. It is now recognized that at least 140 million people in 50 countries have been drinking water containing arsenic at levels above the WHO provisional guideline value of 10 µg/L (Brammer, 2009). In 1917, chronic arsenicism (Arsenicosis) through ground water was first identified in Cordoba of Argentina (Bell Ville Disease). High concentrations of arsenic in drinking-water are found in various parts of the world including Argentina, Bangladesh, Chile, China, Hungary, India (West Bengal), Mexico, Nepal, Pakistan, Thailand, USA, and Viet Nam. It may be mentioned thatin USA, and many other countries safe level of arsenic is below 0.01mg/l (Smedley, 2002).

Skin Manifestations

Arsenicosis can cause a numbers of adverse condition in health, including dermal lesions, peripheral neuropathy, skin cancer, bladder and lung cancers and peripheral vascular disease (Tseng, 1968; Zaldivar, 1980; Valentine, 1982; Cebrian, 1983; Khan, 2003; Mandal, 2004). Increased risks of above mentioned skin disorder have been reported to be associated with ingestion of drinking-water at concentrations ≤50 µg arsenic/litre (A Field Guide for Detection, Management and Surveillance of Arsenicosis Cases, 2005). Usually dermatological manifestations start to appear after minimum exposure periods of approximately 5 years.It may be 80% of them with urinary excretion of arsenic value between 1-3 mg/l (Rahman, 2001). In one large-scale study, 3695

(20.6%) of 18,000 persons in Bangladesh and 8500 (9.8%) of 86,000 persons in West Bengal living in arsenic-affected districts were found to show dermatological features of arsenicosis (Rahman, 2001), Pigmentary changes (melanosis) and hyperkeratosis are the predominant cutaneous effects; though at times, Bowen's disease or skin cancers may arise too. Epidemiological studies in different regions of the world have consistently demonstrated a strong association between long-term inorganic arsenic ingestion and skin lesions, typically in the form of hyperkeratosis, hyperpigmentation or hypopigmentation.

causes of blackfoot disease were not considered). There are also considerable evidences from other studiesin different countries. A similar exposure–response pattern was observed in a study in Bangladesh, where prevalence of keratosis was used as a surrogate for arsenic exposure (USNRC, 1999 and USNRC, 2001).

'Dermatological lesions are classified or described in different studies. An unique description by Deoraj Caussy is shown in Table 1. Another description or classification of arsenical skin lesions by Guha Majumdar is shown in Table 2.

Table 1. Classification of skin lesions in arsenicosis (Courtesy) DeorajCaussy, New Delhi, 2005

CHARACTERISTIC CUTANEOUS LESION OF ARSENICOSIS

MELANOSES

MELANOSIS
Palm of a man suffering from melanosis

Fine-freckled or spotted pattern on trunk and extremities (rain-drop pigmentation)

Diffused or generalized hyper pigmentation

Rounded hypo-pigmented or de-pigmented macules on a normal or hyper-pigmented background (leukomelanosis)

Localized or patchy pigmentation generally on the body

Pigmentation of mucous membranes (e.g. oral mucosa), usually in combination with other changes listed above (less common)

KERATOSES

Characterized by thickening of the skin and appearance of papules or nodules that can both be further sub-categorized as follows:

MILD
Slight thickening, or minute papules (less than 2 mm) of palms and soles, often associated with a grit-like texture, that may be primarily detectable by palpation

MODERATE
Multiple, raised keratosis (>2 to 5 mm), appearing

Table 2. Classification of skin lesions in arsenicosis

Grade-I	Mild	a. Diffuse melanosis. b. Suspicious spotty depigmentation/ pigmentation over trunk/limbs c. Mild diffuse thickening of soles and palms.
Grade-II	Moderate	a. Definite spotty pigmentation /depigmentation on the trunk and limbs, bilaterally distributed. b. Severe diffuse thickening (with/without wart like nodules of the palms and soles).
Grade-III	Severe	a. Definite spotty pigmentation/depigmentation as above with few blotchy pigmented/depigmented macular patches over trunks or limbs b. Pigmentation involving the undersurface of tongue and/or buccal mucosa. c. Larger nodules over thickened palms and soles. Diffuse verrucous lesions of the soles with cracks and fissures and keratotic horns over palms/soles.

Observations of skin lesions following low chronic exposure have suggested that these characteristic dermal changes are sensitive indications of the toxic effects of inorganic arsenic (IPCS, 2001). These effects have been demonstrated in many studies using different study designs. Exposure–response relationships and high risks have been observed for each of these end-points. The effects have been most thoroughly studied in Taiwan (Tseng, 1977). In this large study.a population of 40 421 was divided into three groups based on the arsenic content of their well water (high, >0.60 mg/l; medium, 0.30–0.59 mg/l; and low, <0.29 mg/l) 31) (Tseng, 1977). There was a clear dose–response relationship between exposure to arsenic and the frequency of dermal lesions, “blackfoot disease” (a peripheral vascular disorder and pigmentation) and skin cancer. However, in this study, there were several methodological weaknesses which complicate the interpretation of the results. In addition, the possibility of other

Fig. 1. Melanosis

Followings are the major dermatologial manifestations

Melanosis*:* The earliest and the commonest cutaneous sign is melanosis (Saha, 2003 and Milton, 2003). In a study, conducted in the arsenic-prevalent area of Bangladesh, 100% of the patients of arsenocolsisshowed pigmentary changes (Milton, 2003). Prolonged ingestion of arsenic results in pigmentation, most intense on the trunk (Fig. 1), which can be diffused (Tay, 1974; Saha, 1995) of localized, particularly affecting skin folds (DeorajCaussy, 2005 and Tay, 1974). Fine freckles of spotted.

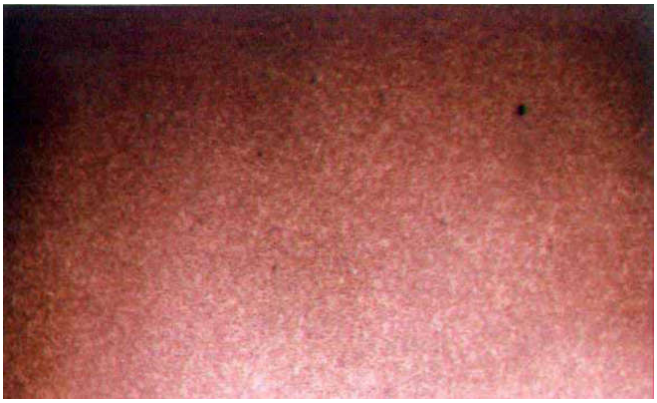

Fig. 2 Rain drop pigmentation

pigmentary changes are also seen, known as *'rain-drop pigmentation'* (DeorajCaussy, 2005 and Tay, 1974) [Fig. 2]Sometimes macular areas of depigmentation may appear on normal skin or hyperpigmented background producing the distinctiveappearanceof 'leucomelanosis (DeorajCaussy , 2005 and Saha, 1995) [Fig.3]

Fig. 3. Leukomelanosis

Blotchy pigmentation may also involve mucous membranes such as the undersurface of the tongue or buccal mucosa (DeorajCaussy, 2005' Tay, 1974 and Saha, 1995).

Keratosis*:*Arsenical hyperkeratosis appears predominantly on the palms and soles, and it has been found that keratosis on the soles is the most sensitive marker for the detection of arsenicosis at an early stage (Kadono, 2002). Keratoses are graded as mild, [Fig.4] moderate, or severe depending on the extent and severity (Deoraj Caussy, 2005).

Fig. 4. Mild Keratosis

In the mild vatiety of keratosis, the involved skin has anhardened texture with papules less than 2 mm in size [Fig.4] that can be best felt by palpation. In the *moderate* variety, the lesions usually advance to form raised, punctate,keratosis, 2-5 mm in.[Fig.5] When the keratosis becomes *severe,* it may form keratotic elevations more than 5 mm in size and sometimes become confluent and diffuse [Fig. 6] and sometimes result in cracks and fissures too (Saha, 2006; Milton, 2003) [Fig.7]

Fig. 5. Moderate Keratosis

Fig. 6. Severe Keratosis

Fig. 7. Severe Keratosis with crack and fissure

Though palms and soles are primarily affected by hyperkeratosis, dorsa of the extremities and trunk may also be affected by it. It is interesting that palmar keratosis usually appear earlier than arsenic-related cancers of bladder and lung; thus it can act as an early marker of carcinogenicity (Cuzick, 1984)

Skin Cancers: Usually three types of skin cancers are observed: Bowen's disease; basal cell carcinoma and squamous cell carcinoma. In Japan, a study showed that Bowen's disease develop after 10 years, invasive squamous cell carcinoma develop after 20 years and internal malignancy particularly pulmonary malignancy develop after 30 years of arsenic exposure (Miki, 1982). It has been suggested that human papilloma virus (HPV) infection could constitute an additional risk factor for the development of non-melanoma skin cancer in humans chronically exposed to as (Rosales-Castillo, 2004). There are also published reports of Merkel cell carcinoma, (Lien, 1999) sometimes arising in association with Bowen's disease (Tsuruta, 1998 and Ohnishi, 1997) in patients with arsenicosis. There is also a study which has demonstrated an increased risk of melanoma in persons with elevated toenail arsenic concentrations, (Beane Freeman, 2004) raising the issue relating to the role of arsenic in the development of melanoma. Skin cancer in arsenicosiscan arise in the hyperkeratotic areas, [Fig.8] as well as appear on non-keratotic areas of the trunk, extremities, [Fig-9] or head (Yeh, 1973 and Sommers, 1953).

Fig. 8. Sumons cell carcinoma

Fig. 9. Sumons cell carcinoma

Skin is thought to be perhaps the most sensitive site for arsenic-induced malignancies 51). The lesions are frequently multiple and involve covered areas of the body; unlike non-arsenical skin cancer, which usually presents as a single lesion and which occurs frequently on the exposed parts of the body (Tseng, 1977 and Zaldivar, 1981).

Histopathological feature

There is a paucity of reports regarding the types and patterns of histopathological changes in skin lesions of chronic arsenicosis. A study from Bangladesh (Dhar, 1997). documented that hyperkeratosis, parakeratosis, acanthosis, papillomatosis, hypergranulosis, and dysplastic changes to be the most important and constant findings. However, basal pigmentation and dermal changes were found to be inconstant features. In another study, hyperkeratotic lesions of 70 patients witharsenicosis were compared with 20 controls (Sikder, 2004). Significant findings included hyperkeratosis (100%), parakeratosis (97%), acanthosis (95.7%), and papillomatosis (74%). The results were found to be significantly more ($P < 0.001$) in the patients than in controls. Basal cell pigmentation was found in 42.8% ($P > 0.05$) and dysplasia and malignant changes in 7% ($P > 0.1$). There is no study about the histopathology of arsenic related pigmentary lesions. A study on the neoplastic manifestations of arsenicosis revealed pre-cancerous skin lesions in 6.6% and cancerous lesions in 0.8% of the patients (Ahmad, 1998).

Conclusion

Arsenicosis is a health crisis for millions of people of Bangladesh and part of India. The extent and magnitude of the problem is really high. The risks of this disease not only confined in this region but many others countries may experience the same in future. Current knowledge and technology are not good enough to address the burning problem of arsenicosis. Clinicians, scientists and health personnel, irrespective of any country, region or nationality, should be more oriented and co-ordinatedin the fight against the curse of arsenicosis.

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REFERENCE

A Field Guide for Detection, Management and Surveillance of Arsenicosis Cases. WORLD HEALTH ORGANIZATION Regional Office for South-East Asia.Edited by DeorajCaussy, New Delhi, 2005.

Ahmad SA, Sayed MHS, Khan MH, et al . Arsenicosis: neoplastic manifestation. *J Prevent Soc Med* 1998;17:110-5.

Anonymous Arsenic: Victoria King discovers the history of the infamous element. History magazineAvailable from: http://www.history-magazine.com/arsenic.html. . [last accessed 2008 Apr 2].

Arsenic poisoning. Available from: http://en.wikipedia.org/wiki/Arsenic_poisoning. [last accessed on 2008 Apr 2].

Arsenic Pollution: A GlobalSynthesis.Ravenscroft P, Brammer H, Richards K. Wiley-Blackwell; 2009.

Bangladesh Arsenic Mitigation Water Supply Project, Data Book 2004 Decem; 5: Dhaka, Bangladesh.

Beane Freeman LE, Dennis LK, Lynch CF, Thorne PS, Just CL.Toenail arsenic content and cutaneous melanoma in Iowa. *Am J Epidemiol.,* 2004;160:679-87.

Cebrian ME et al. 1983. Chronic arsenic poisoning in the north of Mexico. Human Toxicology, 2:121– 133.

Cuzick J, Harris R, Mortimer PS. Palmar keratoses and cancers of the bladder and lung. Lancet 1984;1:530-3.

Dhar RK, Biswas BK, Samanta G, et al. Groundwater arsenic calamity in Bangladesh. CurrSci 1997;73:48-59.

Fowler′s solution. Drugstore museumAvailable from: http://drugstoremuseum.com/sections/levelinfo2.php?level_id=145d%22vel=2%20. [last accessed on 2008 Apr 2].

Gomez-Caminero A, Howe P, Hughes M, Kenyon E, Lewis DR, Moore M, *et al*. Kinetics and metabolism in laboratory animals and human. Arsenic and arsenic compound. Environmental health criteria 224.International programme on chemical safety. Geneva: *World Health Organization*; 2001. p. 112-67.

Guha Mazumdar, D N., 2001. Clinical aspects of Chronic Arsenic Toxicity. Journal of the Association of Physicians of India, 49, 650-55.

GuhaMazumder DN, Das Gupta J, Santra A, Pal A, Ghose A, Sarkar S, Chattopadhaya N, Chakraborti D. Non-cancer effects of chronic arsenicosis with special reference to liver damage. In: CO Abernathy, RL Calderon, WR Chappell, editors. Arsenic:Exposure and Health Effects. London: Chapman and Hall; 1997. p. 112-23.

http://apps.searo.who.int/PDS_DOCS/B0301.pdf

http://www.who.int/mediacentre/factsheets/fs372/en/

http://www.who.int/topics/arsenic/en/

IPCS 2001. Arsenic and arsenic compounds. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 224).

Jha AN, Noditi M, Nilsson R, Natarajan AT. Genotoxic effects ofsodium arsenite on human cells. *Mutat Res* 1992; 284:215-21.

Kadono T, Inaoka T, Murayama N, Ushijima K, Nagano M, Nakamura S, et al . Skin manifestations of arsenicosis in two villages in Bangladesh. *Int J Dermatol* 2002;41:841-6.

Khan MM, Sakauchi F, Sonoda T, Washio M, Mori M. Magnitude of arsenic toxicity in tube-well drinking water in Bangladesh and its adverse effects on human health including cancer: evidence from a review of the literature. *Asian Pac J Cancer Prev* 2003;4:7-14.

Li JH, Rossman TG. Inhibition of DNA ligase activity by arsenite: a possible mechanism of its comutagenesis. *MolToxicol* 1989;2:1-9.

Lien HC, Tsai TF, Lee YY, Hsiao CH. Merkel cell carcinoma and chronic arsenicism. *J Am AcadDermatol* 1999;41:641-3.

Lindgren A, Vahter M, Dencker L. Autoradiographic studies on the distribution of arsenic in mice and hamsters administered ^{74}As-arsenite or arsenate. *Acta Pharm Toxicol (Copenh)* 1982; 51:253-65.

Lu FJ., 1990. Blackfoot disease: arsenic or humic acid? Lancet, 336(8707):115–116.

Mandal, N.K., Biswas, R. 2004. A study on arsenical dermatosis in rural community of West Bengal. *Indian J Public Health* 2004;48:30-3.

Mass MJ, Wang L. Arsenic alters cytosine methylation patterns of the promoter of the tumor suppressor gene p53 in human lung cells: a model for a mechanism of carcinogenesis. *Mutat Res* 1997;386:263-77.

Miki Y et al; Cutaneous and Pulmonary Cancers Associated With Bowen's Disease; J Am Acad Dermatol; 1982, 6 : 26.

Milton AH, Hasan Z, Rahman A, Rahman M. Non-cancer effects of chronic arsenicosis in Bangladesh: preliminary results.J Environ Sci Health A Tox Hazard Subst Environ Eng 2003;38:301-5.

New York Times 10.11.1998.

Nordenson I, Beckman L. Is the genotoxic effect of arsenic mediated by oxygen free radicals? Hum Hered 1991;41:71-3.

Ohnishi Y, Murakami S, Ohtsuka H, Miyauchi S, Shinmori H, Hashimoto K. Merkel cell carcinoma and multiple Bowen′s disease: incidental association or possible relationship to inorganic arsenic exposure? J Dermatol 1997;24:310-6.

Okui T, Fujiwara Y. Inhibition of human excision DNA repair by inorganic arsenic and the co-mutagenic effect in V79 Chinese hamster cells. Mutat Res 1986;172:69-76.

Rahman MM, Chowdhury UK, Mukherjee SC, Mondal BK, Paul K, Lodh D, *et al* . Chronic arsenic toxicity in Bangladesh and West Bengal, India - a review and commentary. J ToxicolClinToxicol 2001;39:683-700.

Ramirez P, Eastmond DA, Laclette JP, Ostrosky-Wegman P. Disruption of microtubule assembly and spindle formation as a mechanism for the induction of aneuploid cells by sodium arsenite and vanadium pentoxide. Mutat Res 1997;386:291-8.

Rosales-Castillo JA, Acosta-Saavedra LC, Torres R, Ochoa-Fierro J, Borja-Aburto VH, Lopez-Carrillo L, et al . Arsenic exposure and human papillomavirus response in non-melanoma skin cancer Mexican patients: a pilot study. Int Arch Occup Environ Health 2004;77:418-23.

Saha KC. Chronic arsenical dermatoses from tube-well water in West Bengal during 1983-87. Ind J Dermatol 1995;40:1-12.

Saha KC. Diagnosis of arsenicosis. J Environ Sci Health A Tox Hazard Subst Environ Eng 2003;38:255-72.

Sikder MS, Rahman MH, Maidul AZ, Khan MS, Rahman MM.Study on the histopathology ofchronicArsenicosis.JPakistanAssocDerma2004;14:205–209.

Smedley, PL; Kinniburgh, DG (2002). "A review of the source, behaviour and distribution of arsenic in natural waters". Applied Geochemistry. 17 (5): 517–568

Sommers SC, Mcmanus RG. Multiple arsenical cancers of skin and internal organs. Cancer 1953;6:347-59.

Tay CH. Cutaneous manifestations of arsenic poisoning due to certain Chinese herbal medicine. Australas J Dermatol 1974;15:121-31.

Tseng WP (1977) Effects of dose–response relationship of skin cancer and blackfoot disease with arsenic. Environmental Health Perspectives, 19:109–119.

Tseng WP et al. (1968) Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. Journal of the National Cancer Institute, 40:453–463.

Tsuruta D, Hamada T, Mochida K, Nakagawa K, Kobayashi H, Ishii M. Merkel cell carcinoma, Bowen′s disease and chronic occupational arsenic poisoning. Br J Dermatol 1998; 139:291-4.

USNRC (1999) Arsenic in drinking water. Washington, DC, United States National Research Council, National Academy Press.

USNRC (2001) Arsenic in drinking water, 2001 update. Washington, DC, United States National Research Council, National Academy Press.

Vahter M, Norin H. Metabolism of ^{74} As-labeled trivalent and pentavalent inorganic arsenic in mice. *Environ Res* 1980;**21**:446-57.

Valentine JL et al. (1982) Arsenic effects on human nerve conduction. In: Gawthorne JM, Howell JM, White CL, eds. Proceedings of the 4th International Symposium on Trace Element Metabolism in Man and Animals, Perth, Western Australia, 11–15 May 1981. Berlin, Springer-Verlag, p. 409.

Waxman S, Kenneth C. Anderson. History of the Development of Arsenic Derivatives in Cancer Therapy. The Oncologist 2001;6:3-10.

WHO/SDE/WSH/03.04/75/Rev/1Arsenic in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality.

Yeh S. Skin cancer in chronic arsenicism. Hum Pathol 1973;4:469-85.

Yoshida T, Yamauchi H, Fan Sun G. Chronic health effects in people exposed to arsenic via the drinking water: dose-response relationships in review. ToxicolApplPharmacol 2004;198:243-52.

Zaldivar R, Ghai GL (1980) Clinical epidemiological studies on endemic chronic arsenic poisoning in children and adults, including observations on children with high- and low-intake of dietary arsenic. Zentralblatt fűr Bakteriologie und Hygiene, Abteilung I: Originale B, 170:409–421.

Zaldivar R, Prunes L, Ghai G. Arsenic dose in patients with cutaneous carcinomata and hepatic hemangio-enothelioma after environmental and occupational exposure. Arch Toxicol 1981;47:145-54.

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