Agenda Item 2.2  Health Research on Arsenic Poisoning (Scientific Debate)

AN OVERVIEW

GAPS IN HEALTH RESEARCH ON ARSENIC POISONING
# Content

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1. INTRODUCTION

Arsenic is a toxic chemical that can exist as inorganic or organic forms. Inorganic arsenic also exhibits two main species namely III and V. Inorganic As (III) and As (V) are appreciably more toxic than many organ arsenicals.

Humans may be exposed to inorganic arsenic from all four environmental matrices of air, water, soil and food. It is estimated that in North America at least 25% of the daily intake of arsenic from meats, poultry, dairy products, cereals and tea are in the inorganic form. An important source of inorganic arsenic in our region is from ingestion of contaminated water in Bangladesh, India, Myanmar, Nepal and Thailand. Estimates for the number of persons exposed to arsenic contaminated water above the WHO guideline values of 10ug/L vary depending on the country, the survey method and testing method. However, it is believed that that in Bangladesh alone about 25 million of subjects and in West Bengal about another 5 million subjects and close to a quarter million from Thailand are at risk. In these three countries about a quarter million subjects are already showing signs of the disease. Although arsenic contamination of ground water has been reported from Nepal and Myanmar, the extent of the contamination or the number of subjects showing the disease have not been systematically characterized. Details are covered in the accompanying document, “Arsenic contamination in ground water affecting some countries of the South-East Asia Region” (SEA/RC54/8).

Organic arsenic forms are predominantly found in fruit, vegetables, seaweed, marine fish and shellfish. For example, fish and shellfish can bioaccumulate arsenobetaine and arsenocholine, organoarsenicals compounds not known to be toxic to human health.

The clinical manifestation of arsenic toxicity depends on the duration, dose of arsenic, route of exposure and predisposing host factors. Typically, chronic exposure over 14 days, with doses between 0.005 to 0.09-mg/Kg-body weight/day resulted in arsenic diseases. The two clinical end-points of chronic exposure are cancers and non-cancers. Cancers of the lungs, bladder, kidney and skins have been consistently observed in subjects drinking arsenic-contaminated water. The evidence linking arsenic to cardiovascular disease is inconclusive and that due to diabetes and negative reproductive outcomes are suggestive. A consistent hallmark of chronic manifestation is dermal changes known as hyperkeratosis.

2. CRITICAL EPIDEMIOLOGICAL ASSESSMENT OF ARSENIC POISONING

The regional office undertook a meta-analysis was undertaken to assess epidemiological association of arsenic with dermal lesions. A total of 18 studies from Bangladesh, 16 from India and 23 from elsewhere were systematically reviewed for coherency of observation using set criteria of exposure and outcome measurements. The results show that between 16% and 21% of the exposed subjects develop the dermal lesions. This observation is open to interpretation: First, since these subjects were not from an inception cohorts they will have different duration of exposure and thus they will reach the disease end-points at different times. Hence they cannot be accounted in the average figure at a single point in time. It may also be argued that this wide variation is due to errors in measuring both the exposure and the outcome. It may be equally argued that among those who develop the disease there are co-factors affect bioavailability of arsenic differentially leading to varied toxicity.

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1 List of publications used in the meta-analysis is given at item 3 of “Suggested Further Readings”
response. Thus, there is an underlying need for research in these areas to delineate if one or several of these possibilities are involved in the genesis of arsenicosis.

3. GAPS IN EXISTING KNOWLEDGE ON ARSENIC TOXICITY AND NEEDS FOR ADDRESSING FURTHER ISSUES

A review of the current data shows five main areas of uncertainty in our understanding of arsenic toxicity: 1) in the measurement of exposure to arsenic because of lack of validity of testing kits, 2) in measuring the outcome of exposure to arsenic due to lack of objective criteria for defining a clinical cases, 3) in estimating the prevalence of arsenicosis due to uncertainty in measuring the exposure and the outcome, 4) about the health outcomes of low-dose exposure to arsenic and the role of cofactors in modifying the onset and prognosis of arsenicosis, and, 5) about arsenic removal technologies.

All these uncertainties are inter-linked and will propagate together to compound the errors in measurement. If a case is not clearly defined, it will be misclassified leading to erroneous counts. By the same token, if exposure to arsenic is not accurately measured the exposure status will be misclassified. Both these errors will lead to biased estimates of true prevalence, making it difficult to assess the true impact of any intervention measures. For convenience, these issues are elaborated under the headings of risk assessment and risk management below.

3.1 Risk Assessment

While risk assessment is a three-step process consisting of hazard identification, dose response assessment and exposure assessment, the first requirement for all these processes is valid laboratory assays for measuring exposure to arsenic.

Valid laboratory assays must distinguish between forms and species of arsenic including markers of exposures under field conditions. All currently used field kits in our Region must be validated for sensitivity and specificity against the “gold standard” test. Countries in the region must establish a policy for the import and testing of test kits.

One of the principal goals of exposure assessment is to determine prevalence of arsenicosis in relation to arsenic from all environmental media including water, air, soil and food. Currently, there is a wide range of the projected number of arsenic-affected patients in Bangladesh, India and Thailand. This is partly due to relying on non-validated arsenic testing for conducting active case search in the proximity of a contaminated well and then generalizing the results to the whole population.

Bioavailability of arsenic refers to the fraction of arsenic from external sources that actually gets internalised to cause toxicity. Since both organic and inorganic arsenic may be present in the food chain, proper research is needed to distinguish these species of arsenic in the food chain. The results will have will have tremendous public health significance since potentially erroneous exposure assessment will result, if one only measures exposure in drinking water in instances where significant concurrent exposure by food consumption is prevalent.

3.2 Risk Characterization

Risk characterization is used to establish the magnitude of the risk for developing arsenicosis after long-term exposure to low-dose arsenic-contaminated water.
The bulk of the evidence linking arsenical dermatitis to arsenic exposure is derived from cross-sectional studies. While such studies provide the first line of evidence, the interpretation of the conclusion is limited by confounding due to exposures from occupation, dietary habits and patterns of traditional medicine use. Thus, the extent to which unexposed or exposed persons develop clinical dermatological conditions mimicking chronic arsenical dermatitis is not known; similarly, the extent to which exposed persons do not develop chronic arsenical dermatitis is not known. These limitations can only be overcome by case-control studies. By proper manipulation, the case-control study can also establish if dietary habit, occupation or local conditions modify the onset of arsenicosis.

### 3.3 Risk Management

Risk management can be used to set the norm, standards and guidelines for harmonizing protocol on case detection and management as well the technologies for providing arsenic-safe water.

The accurate detection of arsenic cases is the cornerstone for good case management and reporting. Until now, **no uniform case definition of arsenicosis has been developed** or validated regionally or internationally, with the consequences that there is a wide discrepancy of arsenicosis prevalence. A reliable estimate of occurrences of arsenicosis can only be made by using valid laboratory assays, harmonized case definition and sound epidemiological design such as cluster sampling. Formulation of criteria for classifying cases into the categories of **suspected**, **probable**, and **confirmed** has developed and need to be validated.

The **lack of currently available proven therapy for clinical management of chronic arsenic poisoning** has led to a number of unsubstantiated therapeutic measures being used for treating arsenicosis. Any drugs used for therapy should first be evaluated by independent clinical trials. More case-control studies are needed to identify if particular dietary habits are cofactors in the genesis of arsenicosis. State-of-the-art therapy for chronic arsenicosis based on evidence is required for the proper management of patients suffering from arsenicosis.

The prohibitive cost of arsenic removal technologies has prompted the search for alternative options. These include: confirmation and use of “green” tubewells, use of deeper aquifers, promotion of rain-water, consideration of piped schemes based on central supply of surface water treatment or using a packet of chemicals for household treatment.

Since the efficacy of these technologies varies, the different protocols need verification. Researchers, NGOs, and private sectors have developed numerous community and point-of-use arsenic removal technologies. Research is needed to empower the community and strengthen the national capacity to independently evaluate such technologies.

### 4. Conclusions and Points for Consideration by ACHR

From the foregoing it is clear, despite our progress in the area of arsenic, there still exist clear knowledge gaps and hence there are research priorities to be addressed both in the clinical knowledge and in the measurement of arsenic. The main areas for considerations are:
• Inaccurate assessment of arsenic exposure because of lack of valid testing kits.
• Inconsistent case-definition due to lack of objective criteria for defining a clinical case.
• Unreliable estimate of the true prevalence of arsenicosis due to inaccurate exposure measurement and inconsistent use of case-definition
• Improper management of arsenic patients due to lack of clear guidelines based on evidence
• Uncertainty of the health outcomes of low-dose exposure to arsenic or the potential role of nutritional and other cofactors in modifying the onset or prognosis of arsenicosis.

WHO SEARO has already taken steps towards achieving some of these goals by making designating arsenic poisoning a regional priority area and formulating a strategic plan. The main focus of our goals are responding to arsenic hazards through exposure assessment, risk determination and risk management; strengthening infrastructure and capacity building through human resource development. In order to provide the best evidence-base options in these goals addressing the above research gaps, the partnership of the research community is essential in creating a regional network for the exchange of ideas, methods and experience.

SUGGESTED FURTHER READINGS

(1) Arsenic in Drinking Water and Resulting Arsenic Toxicity in India and Bangladesh - Report of a Regional Consultation, New Delhi, India, 29 April - 1 May 1997 (SEA/EH/507)
(2) Arsenic Contamination in Groundwater Affecting Some Countries in the South-East Asia Region (SEA/RC54/8), 3 July 2001
(4) TSDR, Case Studies in Environmental Medicine, Arsenic Toxicity, U.S. Department of Health & Human Services, June 1990
(5) List of meta-analysis (please see the References on the next page)
REFERENCES


