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Association of low-level arsenic exposure in drinking water with cardiovascular disease: A systematic review and risk assessment

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ABSTRACT

The U.S. Environmental Protection Agency (EPA) is developing an integrated assessment of non-cancer and cancer risk assessment of inorganic arsenic (iAs). Cardiovascular disease (CVD) in association with iAs exposure has been examined in a number of studies and provides a basis for evaluating a reference dose (RfD) for assessing potential non-cancer health risks of arsenic exposure. In this systematic review of low-level iAs exposure (i.e., <100–150 μg/L arsenic water concentration) and CVD in human populations, 13 cohort and case–control studies from the United States, Taiwan, Bangladesh, and China were identified and critically examined for evidence for derivation of a RfD. Eight cross-sectional and ecological studies from the United States were also examined for additional information. Prospective cohort data from Bangladesh provided the strongest evidence for determining the point of departure in establishing a candidate RfD based on a combined endpoint of mortality from "ischemic heart disease and other heart diseases." This study as well as the overall literature supported a no-observed-adverse-effect level of 100 μg/L for arsenic in water, which was equivalent to an iAs dose of 0.009 mg/kg-day (based on population-specific water consumption rates and dietary iAs intake). The study population was likely sensitive to arsenic toxicity because of nutritional deficiencies affecting arsenic methylation and one-carbon metabolism, as well as increasing CVD risk. Evidence is less clear on the interaction of CVD risk factors in the United States (e.g., diabetes, obesity, and hypertension) with arsenic at low doses. Potential uncertainty factors up to 3 resulted in a RfD for CVD in the range of 0.003–0.009 mg/kg-day. Although caution should be exercised in extrapolating these results to the U.S. general population, these doses allow a margin of exposure that is 10–30 times the current RfD derived by EPA (based on skin lesions in Southwest Taiwan). These findings suggest that the current EPA RfD is protective of CVD.

1. Introduction

Although health risk assessments of arsenic (As) typically focus on cancer, several recent studies have examined non-cancer health outcomes in association with environmental arsenic exposure, primarily in drinking water (e.g., Argos et al., 2011; Chen et al., 2010, 2011, 2013a,b; Guha Mazumder et al., 2012; Parvez et al., 2013). The mode of action of arsenic toxicity may also involve a continuum of non-cancer effects leading to tumor formation with sufficient dose and duration (Cohen et al., 2013). These recent studies provide an improved scientific basis for re-evaluating the U.S. Environmental Protection Agency's (EPA) chronic oral reference dose (RfD) for assessing the non-cancer health risks associated with arsenic exposure (EPA, 1993). EPA is currently conducting an integrated assessment of non-cancer and cancer toxicity endpoints for inorganic arsenic (iAs) with review and input from the National Academy of Sciences (NAS). The NAS Inorganic

Abbreviations: As, arsenic; BHMT, betaine homocysteine methyltransferase; BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; DMA, dimethylarsenic acid; DHF, dihydrofolate; DMG, dimethylglycine; dUMP, deoxyuridine monophosphate; EPA, U.S. Environmental Protection Agency; HEALS, Health effects of arsenic longitudinal study; HR, hazard ratio; iAs, inorganic arsenic; IMT, intimal–medial thickness; LOAEL, lowest-observed-adverse-effect level; MMA, monomethylarsonic acid; MS, methionine synthase; MT, methyltransferase; MTHFR, methylenetetrahydrofolate reductase; NAS, National Academy of Sciences; NE, northeast; NHANES, National Health and Nutrition Examination Survey; NOAEL, no-observed-adverse-effect level; OR, odds ratio; PAD, peripheral artery disease; POD, point of departure; *p*-H, *p*-value for heterogeneity; QRA, quantitative risk assessment; RfD, reference dose; RR, relative ration; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; SD, standard deviation; SW, southwest; THF, tetrahydrofolate; TS, thymidylate synthase.

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Arsenic Committee recommended ischemic heart disease (Tier 1) and hypertension and stroke (Tier III) among the health outcomes for consideration (NRC, 2013).

The relationship between arsenic and cardiovascular disease (CVD) effects has been studied in populations exposed to elevated arsenic levels in drinking water (e.g., Chen et al., 2011) and in patients receiving high doses of arsenic trioxide as a chemotherapy drug for specific leukemia sub-types (Mathews et al., 2011). With an increasing number of studies on CVD mortality (primarily) and incidence (secondarily) that include estimates of risk at lower chronic arsenic exposure levels (i.e., <100–150 μg/L arsenic in drinking water), patterns are beginning to emerge regarding doses for which elevations in CVD risk are more likely, or where the magnitude of association is minimal if present at all.

This study presents a systematic review of the epidemiologic evidence on the relationship between arsenic exposure and CVD in studies that include the lower end of the exposure range and CVD. The evidence from these studies was critically examined to evaluate a possible no-adverse-effect level and implications for a non-cancer RfD specific to CVD.

2. Methodology

2.1. Search strategy

A structured literature review was conducted in PubMed to identify epidemiologic studies published through March 1, 2014, that reported on the association between low-level arsenic exposure and CVD in adults. The search string referenced the exposure (arsenic) and the health outcomes of interest (cardio, cardiac, CVD, cardiovascular mortality, coronary artery disease, carotid artherosclerosis, carotid atherosclerosis, peripheral arterial disease, peripheral vascular disease, stroke, myocardial infarction, heart attack, ischemic heart disease, heart, blood pressure, cardiovascular function biomarker, microvascular disease, macrovascular disease, hypertension, blackfoot disease, cerebral infarction, and angina). All titles and abstracts were screened first, followed by a full-text review of relevant review articles, including meta-analyses, and published studies based on original data. Citations of relevant references were screened for additional studies that were not identified through the initial electronic search.

2.2. Inclusion criteria for overall assessment of dose–response at lower doses

Studies were included in the systematic review based on the following criteria: (1) epidemiologic evaluations comparing a population exposed to ingested arsenic that included lower exposure levels (e.g., generally <100–150 μg/L or equivalent biomarker levels) with a population that had much lower or minimal arsenic exposure (external or internal comparisons involving different dose groups were allowed if the study reported a referent group of minimal exposure); (2) publications in the English language; and (3) reported statistical associations between arsenic exposure and CVD outcomes with corresponding measures of variability (e.g., 95% confidence level (CI)). Studies with sufficient information to calculate relative risk (RR) estimates at lower arsenic exposure levels or measures of variability, or both, were also included. If more than one study examined the same cohort or study population and had the same outcome, data were extracted from the publication with the most comprehensive analysis or length of follow-up.

The primary study designs of interest for evaluating a potential causal dose–response relationship between arsenic exposure and CVD, and for the identification of a point of departure (POD) for an oral RfD applicable to U.S. populations, were observational cohort and case–control studies (Vlaanderen et al., 2008). However, since only one such study design was identified from the United States (Moon et al., 2013), ecologic and cross-sectional studies from the United States were considered secondarily. No restrictions on the number of study subjects were implemented. All studies not meeting these inclusion criteria, including studies that only reported descriptive statistics for the exposure-outcome relationship (e.g., means and standard deviation), were excluded. In total, 21 epidemiologic studies (12 case–control or cohort studies from Taiwan, Bangladesh, or China; 1 cohort study from the United States; and 8 cross-sectional or ecologic studies from the United States) met the inclusion criteria for evaluating the weight of evidence on low-level arsenic exposure and CVD incidence and mortality (Table 1).

2.3. Data extraction and key studies for development of an oral non-cancer RfD

All epidemiologic studies identified for the systematic review were evaluated based on the qualitative and quantitative information reported by the authors. Extracted data for the present study included information on the study design and location, distribution (i.e., means, medians) of arsenic water concentration or other exposure measures (e.g., urinary arsenic) as well as the categories of exposure analyzed, type of CVD outcome (s) evaluated, the fully-adjusted magnitude of association with corresponding 95% CI, and evidence of a dose–response trend. Two investigators (J.S.T and V.P.) independently performed data extraction. All discrepancies were discussed and resolved by unanimous agreement.

Key research for the derivation of a RfD at levels of exposure below 100–150 μg/L for arsenic in drinking water were studies with the strongest and most transparent methodology. Studies were also judged based on the quality of the reported evidence. Based on recommended criteria for evaluating epidemiologic studies for the purpose of performing a quantitative risk assessment (QRA) (Vlaanderen et al., 2008), all studies meeting inclusion criteria were first examined for quality of the study design, conduct, and reporting of analytical results: (1) case–control or cohort study design required; (2) exposure expressed on a ratio scale and specific for iAs; (3) detailed description of the statistical analysis presented (including testing of the proportional hazards assumption when using a Cox model regression for analysis); (4) detailed description of inclusion/exclusion criteria; (5) outcome assessment performed according to recognized standards (e.g., use of the International Classification of Diseases); and (6) consideration of relevant potential confounding factors.

Studies fulfilling these six recommended criteria were then evaluated using guidelines determining *a priori* for ideal minimum thresholds and for assessing reliable dose–response data for QRA: (1) response rate exceeding 70% or evidence that participants did not differ from non-participants; (2) loss-to-follow-up of ≤20% (Merril and Timmreck, 2006) or evidence that attrition bias did not affect the results; (3) length of follow-up greater than 5 years in cohort studies; (4) quality of the exposure measurement, assessment, and relevance for the risk of CVD development; (5) narrow exposure categories at low doses for defining the dose–response relationship; (6) blinded exposure and health outcome assessment; (7) low potential for information bias; and (8) insight into possible systematic error affecting the study results.

Studies that largely, but did not entirely, meet the first set of criteria because of less information in one category (e.g., less detail on inclusion/exclusion criteria) were also evaluated using the second tier of criteria to ensure no studies with possibly useful dose–response data were overlooked.