Environmental Research 147 (2016) 537–555

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

Inorganic arsenic and respiratory health, from early life exposure to sex-specific effects: A systematic review

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ARTICLE INFO

Article history:
Received 17 July 2015
Received in revised form
4 February 2016
Accepted 5 February 2016
Available online 15 February 2016

Keywords:
Arsenic
Drinking water
Lung diseases
Systematic review
Epidemiology

ABSTRACT

This systematic review synthesizes the diverse body of epidemiologic research accrued on inorganic arsenic exposure and respiratory health effects. Twenty-nine articles were identified that examined the relationship between inorganic arsenic exposure and respiratory outcomes (i.e. lung function, symptoms, acute respiratory infections, chronic non-malignant lung diseases, and non-malignant lung disease mortality). There was strong evidence of a general association between arsenic and non-malignant respiratory illness, including consistent evidence on lung function impairment, acute respiratory tract infections, respiratory symptoms, and non-malignant lung disease mortality. Overall, early life exposure (i.e. *in utero* and/or early-childhood) had a marked effect throughout the lifespan. This review also identified some research gaps, including limited evidence at lower levels of exposure (water arsenic <100 μg/L), mixed evidence of sex differences, and some uncertainty on arsenic and any single non-malignant respiratory disease or pathological process. Common limitations, including potential publication bias; non-comparability of outcome measures across included articles; incomplete exposure histories; and limited confounder control attenuated the cumulative strength of the evidence as it relates to US populations. This systematic review provides a comprehensive assessment of the epidemiologic evidence and should be used to guide future research on arsenic's detrimental effects on respiratory health.

1. Introduction

The World Health Organization (WHO) lists inorganic arsenic (InAs) as one of 10 chemicals of major public health concern (World Health Organization, 2010b). Arsenic is a naturally occurring yet life-threatening toxicant to which millions are inadvertently exposed annually (World Health Organization, 2010a). Arsenic contaminates the groundwater (wAs) of many countries, including Bangladesh, Chile, China, India, Mexico, Central Europe, and the United States, at levels which exceed the WHO standard of 10 μg/L (World Health Organization, 2010a).

The International Agency for Research on Cancer classifies InAs and arsenic compounds as group 1 lung carcinogens, meaning there is sufficient evidence to conclude that InAs exposure from inhalation and ingestion causes lung cancer in humans (International Agency for Research on Cancer, 2009). Presently, InAs is the only group 1 lung carcinogen known to be active by both inhalation and ingestion (Smith et al., 2009). Compared to the body of research on InAs and lung cancer, however, the body of research on InAs and non-malignant lung disease is less cohesive and more difficult to characterize.

One of the first studies on InAs exposure and respiratory health dates back to the 1970s in Chile. In 1958 the city of Antofagasta started supplementing its main water supply (wAs levels around 90 μg/L) with river water (wAs levels near 1000 μg/L) to accommodate the city's growing population (Smith et al., 2006; Borgoño et al., 1977; Zaldivar, 1980). By 1971 a water treatment plant had been installed and wAs levels were gradually returned to pre-1958 levels. However, during the intervening period before the water was treated, lasting from 1958 to 1970, all residents of Antofagasta, Chile consumed very high levels of InAs (wAs > 800 μg/L) in their drinking water (Borgoño et al., 1977). In Borgoño et al. (1977), which occurred several years after peak exposure, children with arsenical skin lesions had a greater prevalence of bronchopulmonary disease history and chronic cough compared to children who did not have arsenical lesions. Although symptoms and functional disabilities associated with non-malignant lung disease generally appear in late adulthood, the Antofagasta study began shedding light on an important result – that developing lungs are particularly vulnerable early in life and that InAs exposure *in utero* and during childhood can have life-long consequences.

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http://dx.doi.org/10.1016/j.envres.2016.02.009

Table 1
Eligibility criteria and objectives created *a priori* using adapted PICOS format.

Topic	Question	Exclude if…
Participants	Are the study participants human?	Not human
Exposure	Does the article have a relevant exposure measurement?	No measure of exposure (or occupationally/ ATO chemotherapy exposed)
Comparisons	Does the article have a control or referent group?	No reference group (i.e. *case study or case report*)
Outcome	Does the article have a relevant outcome (i.e. *lung function, respiratory symptoms, acute respiratory infections, chronic non-malignant lung disease, and non-malignant respiratory mortality*)?	Not relevant
Study design	Does the article report primary data?	No primary data

There is only one review article on InAs and non-malignant lung disease, published almost a decade ago (Guha Mazumder, 2007), but no systematic reviews or meta-analyses have summarized the evidence on this body of research. Instead of focusing on a singular aspect of non-malignant lung disease, this systematic review holistically describes the relationship between InAs and non-malignant lung disease, and also groups respiratory health diseases into easily interpretable categories, including lung function, respiratory symptoms, acute respiratory tract infections, chronic non-malignant lung diseases and non-malignant lung disease mortality. We define respiratory health quite broadly but because this outcome is inherently heterogeneous, encompassing numerous phenotypes among people of different ages and various disease trajectories, there may be additional non-malignant lung disease outcomes which we have unintentionally neglected in this review.

Responding to a U.S. congressional mandate, the U.S. National Research Council convened a group of experts in 2012 to evaluate and guide the Environmental Protection Agency's (EPA) Integrated Risk Information System's (IRIS) toxicological assessment of InAs (National Research Council, 2014). The National Research Council recommended the EPA conduct systematic reviews on 18 health endpoints of concern, including non-malignant respiratory effects, to support the agency's assessment. Several published systematic reviews and meta-analyses have already synthesized the epidemiological evidence on the relation between InAs and other health consequences, including lung cancer (Celik et al., 2008), skin lesions and skin cancers (Karagas et al., March 2015), cardiovascular disease (Navas-Acien et al., 2005; Moon et al., 2012), hypertension (Abhyankar et al., 2012), adverse pregnancy outcomes (Quansah et al., 2015), chronic kidney disease (Zheng et al., 2014), urinary tract cancers (Saint-Jacques et al., 2014), and type-2 diabetes (Navas-Acien et al., 2006). A systematic review on InAs and respiratory health is greatly needed.

We implemented a systematic approach to identify, evaluate, and synthesize the epidemiologic evidence on this body of research to better understand the effects of InAs exposure on different parameters of non-malignant lung disease in InAs-affected populations. We also examined whether there are timing-, dose- and sex-specific effects.

2. Methods

2.1. Search selection

We implemented an extensive search strategy with guidance from a Reference Librarian at Columbia University Medical Center and in accordance with PRISMA guidelines (Moher et al., 2009):

- Systematic searches in two bibliographic databases:
  MEDLINE/PUBMED (http://www.ncbi.nlm.nih.gov/pubmed).
  EMBASE (http://www.elsevier.com/solutions/embase).
- Gray literature searches using Google Scholar and Web of Knowledge's Citation Network.
- Handsearches of the references of included publications.

For bibliographic databases, our search combined comprehensive English terms representing non-malignant respiratory health effects with terms for InAs exposure with the Boolean operator AND (see supplementary material for complete list of search terms). Before conducting a full search, we piloted our search and made slight modifications to meet the specific needs of each database search whenever necessary. We conducted two searches on each bibliographic database. We used both keywords and MeSH terms for PubMed, and similarly for EMBASE, we used keyword and EMTREE/exp terms. Searches were limited to English-language articles published before January 2016. Articles had to meet the following *a priori* criteria to be eligible for inclusion: (1) contained original human-based research published in a peer-reviewed journal; (2) had a control or referent group; and (3) included an indicator of InAs exposure studied in relation to any one or more of the following outcome categories listed in Table 1.

We downloaded our search results using Endnote and subsequently transferred the references to DistillerSR for title and abstract screening (http://distillercer.com/products/distillersr-systematic-review-software/). After removing exact article duplicates, TS screened all titles and abstracts (if available). JG and MP conducted a blinded independent random check on 20% of the initial search results, with 100% concordance between authors for included and excluded articles. Articles which met the initial screening stages underwent full-text review by all authors.

During the full-text review, we assessed whether multiple publications from the same study population contained duplicate data. We identified multiple publications of the same study ("study" meaning effort to collect primary data and "publication" meaning effort at analyzing the data) by examining author affiliation, study design, cohort name, enrollment criteria, and enrollment dates. When there were multiple publications reporting on the same study we described the relevant publications and noted potential overlap in the results section.

2.2. Data extraction

We created and piloted a data extraction form using DistillerSR. The piloted form was then modified to fit our needs. TS extracted information from each article and co-authors spot-checked data extraction.

For publications that examined either exposure or outcome categorically, we presented evidence from the highest category vs. the lowest category. We performed additional subgroup analyses on (1) critical periods of exposure (i.e. *in utero* and early life exposure); (2) sex differences; and (3) low level InAs exposure (wAs < 100 μg/L). We specified all subgroup analyses *a priori*. We deemed a meta-analysis inappropriate due to the heterogeneous nature of the available publications.