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Review

# Arsenic ototoxicity

Gülin Gökçen Kesici

*Yenimahalle Education and Research Hospital, Department of Otolaryngology Head and Neck Surgery, Turkey*

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**Abstract**

High levels of arsenic are found in many parts of the world and more than 100 million people may have been exposed to it. There is growing evidence to indicate that arsenic has a deleterious effect on the auditory system. This paper provides the general information of arsenic and its ototoxic effects.



*Keywords:* Arsenic; Exposure assessment; Ototoxicity

**Contents**



High levels of arsenic are found in many parts of the world and it is thought that in excess of 100 million people may be exposed to it, some of them at chronic levels, making it a major public health problem. Soil, in mining areas or near smelters, may be contaminated with high levels of arsenic. The U.S. Environmental Protection Agency (EPA) has established the maximum contaminant level of arsenic in public drinking water to be set at ten parts per billion. The American Conference of Governmental Industrial Hygienists (ACGIH) determined the maximum contaminant level for arsenic in the air to be 10 μg/m$^3$. Natural levels of arsenic in the soil usually range from 1 to 40 mg/kg, but pesticide application or waste disposal can produce much higher values. (ATSDR, 2000).

Although extensive research has focused on investigating arsenic carcinogenicity, there is growing evidence to indicate that arsenic also has a deleterious effect on the auditory system. This paper will briefly describe the general information of arsenic and extend more detailed description to ototoxic effect of arsenic.

*E-mail address:* gulingokcenmd@gmail.com.

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Table 1
The total arsenic measurement methods used by several authors.

| Authors | Sample | Method | Preparation method |
|---|---|---|---|
| Valentine et al., 1979 | Blood and hair | HGAAS | Wet ash with nitric/perchloric acids; reduction with sodium borohydride |
| Foa et al., 1984 | Blood | HGAAS | Wet ash with nitric/perchloric acids; reduction with sodium borohydride |
| Curatola et al., 1978 | Hair | HGAAS | Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride |
| Agahian et al., 1990 | Nails | HGAAS | Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride |
| Mushak et al., 1977 | Soft tissue | GFAAS | Digestion with nitric/sulfuric acids; complexation with DDDC in potassium iodide; extraction with chloroform |
| Pinto et al., 1976 | Urine | Colorimetric photometry | Digestion with nitric and perchloric acid; reduction with tin chloride; generation arsine by addition of zinc; reaction with SDDC |
| Landsberger and Simsons, 1987 | Urine | NAA | Irradiate epithermally |

## 1. Arsenic compounds

Because arsenic has both metallic and nonmetallic properties, it is chemically classified as a metalloid. Metallic arsenic is a steel-gray solid material but in nature it is usually found in combination with other elements. When combined with oxygen, chlorine, and sulfur it is referred to as inorganic arsenic, but combined with carbon and hydrogen it is called organic arsenic. (ATSDR, 2000) Inorganic arsenic is more harmful than organic arsenic compounds. The main inorganic arsenic compounds found in water are specifically arsenite (AsIII) and arsenate (AsV). (Feldmann and Krupp, 2011) The molecular forms of arsenic compounds present in food are more variable and also non-toxic arsenic compounds have been detected in food. These compounds are generally known as organoarsenicals and are mostly found in marine food (especially fish) and constitute more than 85% of total arsenic concentrations. (Feldmann and Krupp, 2011) Another arsenic compound group is arsenic-containing ribofuranosides, known as arsenosugars. but there is insufficient information regarding their toxicity. (Feldmann and Krupp, 2011).

## 2. Arsenic exposure

Globally, a large number of people are chronically exposed to arsenic. Although arsenic is found naturally in the soil, air and water. It can also be detected in heavy metal ores such as copper and lead. Also coal and waste products often contain some arsenic. Exposure to arsenic occurs via oral, respiratory or dermal routes. In some mining areas, smelting sites and industrial zones, there are high levels of arsenic in the soil. High levels of arsenic can also be detected in some agricultural areas where pesticides are used and in regions where there are natural arsenic deposits. (Beamer et al., 2014; Menka et al., 2014) Furthermore, arsenic is found in water resources, particularly in groundwater in areas where the soil contains more arsenic. Most arsenic in food is found in seafood, rice/rice cereal, mushrooms, and poultry. The arsenic usually found in fish is less harmful organic forms of arsenic but some seaweeds may contain more harmful inorganic forms of arsenic. (ATSDR, 2000).

Another problem associated with arsenic exposure is the co-exposure of arsenic with other substances, such as lead, cadmium, fluoride, polyaromatic hydrocarbons, and pesticides. (Andrade et al., 2015; Estrada-Capetillo et al., 2014; Huang et al., 2013) Co-exposures may affect arsenic metabolism and can be synergistic or antagonistic. To understand the possible effects of co-exposure, randomized controlled animal studies and human studies analyzing data of groups such as miners in a multisystem way are required.

## 3. Metabolism of arsenic

Arsenic metabolism is complex and metabolites depend on the received arsenic compounds, administration route, and cell type used for the elimination of arsenic (Stice et al., 2016). During the metabolism of arsenic, those arsenic compounds are formed: methylated arsenicals such as DMAV (Dimethylarsinic acid), MMAV (Monomethylarsonic acid), DMAIII (Dimethylarsinous acid), and MMAIII (Monomethylarsonous acid) and As-glutathione (GSH) and a recently determined type of arsenicals, thiolated as compounds, including DMMTAV (Dimethylmonothioarsinic acid), DMDTAV (Dimethyldithioarsinic acid) and DMMTAV (Dimethylmonothioarsinic acid) conjugates. Although it has been established in which human tissues these metabolites are present, their role in toxicity has not yet been full clarified (Rehman and Naranmandura, 2012). However, certain metabolites are known to be more likely to cause some toxicity. For example, it is shown that MMA III and DMA III are more genotoxic, and DEMTAV is more cytotoxic (Mass et al., 2001; Kojima et al., 2005). Usually trivalent arsenicals are more toxic than pentavalent arsenicals(Styblo et al., 2000).

Besides their toxicity, some specific arsenic compounds are used in treatment of certain cancers (Antman, 2001). For example, arsenic trioxide ($As_2O_3$, ATO, Trisenox) has been used in treatment of acute promyelocytic leukemia (APL) (Liu et al., 2012).

## 4. Exposure assessments

As arsenic is found in multiple forms and diverse environments, assessing arsenic exposure is complex; there may be other metals in the same environment as the arsenic, such as cadmium and fluoride, or microorganisms might affect the arsenic metabolism. Atomic absorption spectrophotometry