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Review

# Arsenic ototoxicity

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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.

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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

(AAS) is the most commonly used method for measuring arsenic in the body and samples can be prepared in different ways: (Valentine et al., 1979; Foa et al., 1984; Curatola et al., 1978; Agahian et al., 1990; Mushak et al., 1977) Chromatography technique can be used (Pinto et al., 1976) and Neutron activation analysis (INAA) can be used to detect arsenic in liquids and soft tissues (Landsberger and Simsons, 1987). However, there is no standard method. The total arsenic measurement methods used by several authors are summarized in the Table 1.

Different biologic measurement methods reflect different time frames of exposure. For instance, urinary arsenic reflects acute exposure, and arsenic in the nails reflects exposure over several months (Marchiset-Ferlay et al., 2012).

## 5. Arsenic toxicity

Arsenic exposure affects all body systems: cardiovascular, nervous, hepatobiliary, gastrointestinal, renal, dermatologic and respiratory systems (Tchounwou et al., 2003). It is known that arsenic also has carcinogenic effects. In regions with high levels of arsenic, mortality rates for cancers of bladder, kidney, skin, and liver are higher (Chappell et al., 1997).

### 5.1. Mechanisms of toxicity and carcinogenicity

The major mechanism of arsenic related toxicity is oxidative stress (Shi et al., 2004). Oxidative stress can cause deterioration of cellular signaling pathways and affect multiple systems. As a result of the accumulation of free radicals; cell death, abnormal gene expressions, and degradation of DNA, lipids, and proteins are seen. The methylated form of arsenic inhibits DNA repair processes (Mass et al., 2001). Trivalent arsenicals can inhibit more than 200 enzymes by binding thiol or sulfhydryl groups to proteins. Pentavalent arsenicals can interchange with phosphate, which happens on many pathways (Hughes, 2002). Possible carcinogenic mechanisms following arsenic exposure are progression of carcinogenesis, altered DNA repair, p53 suppression, altered DNA methylation patterns and gene amplifications (Miller et al., 2002).

Also, arsenic induced remission in acute promyelocytic leukemia because of its apoptosis effect in malignant cells (Diaz et al., 2005).

### 5.2. Arsenic ototoxicity

In the literature, studies on both humans and animals reveal the ototoxicity of arsenic.

#### 5.2.1. Effects in animals and in vivo studies

One of the studies on arsenic ototoxicity in animals is that of Anniko, who investigated the acute effect of atoxyl (organic arsenical drug) on guinea-pig cochlea. In this study Reissner's membrane degeneration, mitochondria and cytoplasm injury in the cells were detected (Anniko, 1976a). In another study by Anniko, investigating the chronic effects of arsenic, microvilli loss and depressions in epithelial cell of the stria vascularis were detected (Anniko, 1976b).

Arsenic deposition was detected in the nervous system of rats (Garcia-Chavez et al., 2006). In neurotoxicity studies, after rats had been exposed to arsenic, there was decreased neurofilament light subunit (NF-L) in the sciatic nerve (Vahidnia et al., 2006). Also it is shown that arsenic affects one of the major components of neurons, tau protein (MAP-tau), a member of the microtubule protein family, which is predominantly associated with phosphorylation of microtubules of the axons. Giasson et al. demonstrated hyperphosphorylation of tau-proteins in Chinese hamster ovary (CHO) cells *in vitro* following treatment with arsenite (Giasson et al., 2002). These studies on neurotoxicity indicate that arsenic may be involved in the cascade leading to deregulation of tau function associated with neurodegeneration. In a study on the effect of arsenic on cultured rat astroglia, decreased cell viability and increased DNA damage were detected (Jin et al., 2004).

Arsenic increases the toxic effect of lead and cadmium in brain cells of the cerebellum and cortex, and has a synergistic toxic effect on these metals (Gu et al., 2009). In another study on rats using arsenic, cadmium and lead, the total neurotoxicity caused by these three heavy metals were found to be higher than expected or theoretically predicted (Rai et al., 2010).

#### 5.2.2. Observations in human

The ototoxicity of arsenic was also supported with human studies. Sensorineural hearing loss was reported in individuals exposed to arsenic. In a study conducted in Inner Mongolia, a region in China rich in arsenic, there was statistically significantly more hearing loss cases in an arsenic affected village, compared with an unaffected village (Guo et al., 2007). In a study by Bencko and Symon, in which they confirmed elevated arsenic levels in blood, urine and hair samples, they detected hearing loss at 125 Hz, 250 Hz and 8000 Hz in children aged 10 years old who lived in an area polluted with arsenic (Bencko et al., 1977). Contrary to expectations, during an investigation of public schools near a copper smelter, six children with high urinary arsenic levels had no hearing loss in a pure tone audiometry test (Milham, 1977). In a national population-based study on individuals above the age of 50, urinary concentrations of environmental chemicals were measured and hearing loss was assessed using questionnaires (Shiue, 2013). It was found that urinary arsenic concentrations of acid and 2, 4, 5-trichlorophenol concentrations were significantly associated with hearing disorders. In a survey of 2535 adolescents in the United States, lead and mercury levels in the blood, urinary cadmium levels, and urinary arsenic levels were analysed, and the adjusted odds ratios were calculated using multivariate logistic regression analysis for hearing loss. In cases showing high blood levels of lead, there was an increased odds of high-frequency hearing loss; and in cases of high blood levels of cadmium, increased odds of low-frequency hearing loss were detected. However there was no overall association determined between quartiles

of blood mercury or urinary arsenic levels and hearing loss (Shargorodsky et al., 2011).

In one of the studies assessing occupational exposure, investigating the isolated effect of arsenic on hearing in mine workers with blood arsenic levels and hearing thresholds of 0.5, 1, 2, 3, 4, and 6 kHz frequencies, hearing thresholds were increased for each frequency in the group consisting of mine workers who had been exposed to chronic levels of arsenic and had high blood levels of arsenic, compared with mine workers who hadn't been exposed to arsenic (Kesici et al., 2016). However, in this current study a correlation was not detected between arsenic levels and hearing thresholds and this result was attributed to blood arsenic levels reflecting short-term exposure. In a similar study on gold miners, Saunders et al. measured fingernail metal levels, Békésy-type pure-tone thresholds and distortion product otoacoustic emission (DPOAE) levels of 59 subjects (Saunders et al., 2013). Widespread hearing loss was evident, but no relationship between heavy metal levels and auditory test results could be identified, although they did find a significant relationship between arsenic concentrations and DPOAE amplitude at 2 kHz in the low frequency group.

In a study by Chuang et al. on factory workers, blood levels of selenium, lead, manganese, and arsenic were measured but arsenic could not be identified as a cause for hearing loss in multiple linear regressions analysis. In this study it was identified that selenium has a protective effect on auditory function and lead causes significant increases in hearing thresholds (Chuang et al., 2007). In a study on workers investigating blood levels of manganese, copper, zinc, arsenic, cadmium and lead, and hearing thresholds, this was the result: Lead was the only metal found in the blood, which is significantly correlated with hearing loss, following adjustment for age and noise level, using the logistic regression model analysis (Hwang et al., 2009).

In studies on humans, because of co-exposure to other heavy metals, it is hard to investigate the isolated effect of arsenic in terms of ototoxicity. Therefore all possible heavy metals were examined and an adjustment analysis was applied by using logistic regression model analysis in the studies, and this situation causes an important limitation in human toxicity studies. It can be said that arsenic have ototoxic effect but further studies investigating isolated ototoxic effect of arsenic are needed. Furthermore, until now, pure tone audiometry was used in studies on the effect of arsenic on the hearing system. For a more detailed analysis on the effect of arsenic on the hearing system and for it to be better understood, the use of electrophysiologic measurements such as electrocochleography, otoacoustic emissions, and evoked response audiometry is required.

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