Published in final edited form as:

Environ Toxicol. 2019 February ; 34(2): 188–202. doi:10.1002/tox.22673.

State of the science review of the health effects of inorganic arsenic: perspectives for future research

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Abstract

Human exposure to inorganic arsenic (*i*As) is a global health issue. Although there is strong evidence for *i*As-induced toxicity at higher levels of exposure, many epidemiological studies evaluating its effects at low exposure levels have reported mixed or inconclusive results. To highlight the current state of the science on *i*As exposure and health effects, identify the gaps in scientific knowledge, and recommend critical areas for future research, we comprehensively reviewed the literature and evaluated the scientific knowledge on human exposure to arsenic, mechanisms of action, systemic and carcinogenic effects, risk characterization, and regulatory guidelines. We identified areas where additional research is needed. These priority areas include: a) further development of animal models of *i*As carcinogenesis to identify molecular events and effects of *i*As on cancer initiation, promotion and progression; b) characterization of underlying mechanisms of *i*As toxicity including identification of exposure, susceptibility and/or effect biomarkers; c) assessment of gender-specific susceptibilities and other modifying factors that affect arsenic metabolism; d) sufficiently powered epidemiological studies to ascertain relationship between *i*As exposure and reproductive and developmental effects; e) evaluation of genetic and epigenetic determinants of *i*As-induced effects in children; and g) epidemiological studies of people chronically exposed to low concentrations of *i*As. This information will provide new insights on *i*As toxicity/carcinogenicity and further advance the understanding of its spectrum of adverse health effects.

Keywords

arsenic; adverse health effects; mechanisms of action; knowledge gaps; future research directions

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CONFLICT OF INTEREST

All authors declare no competing and/or financial conflict of interest. They have read the paper, and agreed the work to be submitted to the Environmental Toxicology journal.

1. INTRODUCTION

Arsenic is found naturally in trace quantities in nearly all environmental compartments. The periodic table of elements lists its atomic number and atomic weight as 33 and 74.92 respectively as. This element also has an electronic configuration of [Ar] $3d^{10}$ $4s^2$ $4p^3$, and a density of 5.727 g/cm^3. From a public health point of view, arsenic and arsenic-containing compounds are divided into three groups that include the elemental, inorganic, and organic forms. The magnitude of its toxic effects has been linked to its chemical species as well as to its dose and length of exposure. [1,2] We have recently reported on the list of major arsenicals of public health concern.[3]

Several hundreds of million individuals are chronically exposed worldwide, mainly in Bangladesh, Chile, India, Mexico, Taiwan, United States of America and Uruguay where the groundwater supply contains high amounts of arsenic above WHO recommended limits of 10 μg/L.[4,5] Arsenic exerts its toxicity on multiple organ systems including auditory, cardiovascular, developmental, hematologic, hepatic, nervous, renal and respiratory systems. It has also been associated with many types of cancer (skin, lung, liver, and bladder). [5,6,7,8,9,10,12] However, the scientific evidence for many of these findings is weak and often contradictory. Here we present a comprehensive review that highlights the current state of the science with respect to *i*As exposure and health effects, identifies the gaps in scientific knowledge, and recommends critical areas for future research.

2. ARSENIC BIOTRANSFORMATION AND TOXICITY

In humans, methylation is the major biotransformation pathway for *i*As (Figure 1). The primary metabolism of *i*As [As (+3) and As (+5)] leads to the formation of monomethylarsonic acid [MMA (+5)] which undergoes a secondary methylation to produce dimethylarsinic acid [DMA (+5)].[11] The reduction of pentavalent forms of *i*As [As (+5)] to arsenites [As(+3)] is catalysed by glutathione arsenate reductase, and the methylation of arsenates to trivalent forms is achieved by the action of *S*-adenosyl methionine that transfers the methyl group.[13,14] Arsenic 3-methyl transferase catalyzes *i*As methylation, and its activity varies greatly in different species including humans.[15] The degree of methylation is assessed by determining the fractions of As (+3)/MMA and MMA/DMA. High levels of methylation have been characterized by a low ratio of MMA/DMA while low levels of methylation are associated with a low ratio of As(+3)/MMA.[16,17]

Although methylation was previously taught as a mechanism to reduce toxicity,[18] it may be a bioactivation process if the metabolites contain arsenic with three oxidative states. [19] Both MMA (+3) and DMA (+3) have been shown to cause enzyme inhibition, cell toxicity, and genotoxicity at high level of exposure. In addition, DMA (+3) induces the activation of oncogenes and produces bladder cancer in rats, suggesting that it may also be carcinogenic in humans.[20] It has been estimated that after *i*As ingestion, the species excreted in urine include over 60% DMA and relatively equal amount of *i*As and MMA. Because of inter-individual variability in arsenic methylation capacity, there exists a significant variability in the magnitude of toxic manifestations that may be explained by the variability in genetic susceptibility factors.[21,22] Many studies on arsenic biotransformation have reported strong

positive associations between low levels of secondary methylation and increased incidence and prevalence of arsenic-induced disorders.[4,23] Also, methylated thioarsenicals have recently been identified as a new group of arsenic metabolites in biological systems.[24]

In addition to the methylation capacity[25], human susceptibility to arsenic toxicity is significantly modulated by many other intrinsic and extrinsic factors that may increase its health risks. Men have lower rates of secondary methylation than women, leading to higher MMA/DMA ratios in males.[26,27] Hence, male individuals may be more susceptible.

Differential methylation and excretion rates of arsenic are also found in human populations.[28,29] Hence genetic susceptibility factors are key modulators of arsenic toxicity.[30] Other epidemiological studies conducted in Bangladesh have reported that dietary intake of nutrients influence the toxicity of arsenic by modulating its metabolism.[31] Also, folic acid consumption increases the biotransformation of *i*As leading to excretion of DMA in urine, and the reduction of MMA concentration in the blood.[32,33] A more recent study pointed out that a low MMA/DMA ratio resulting from As metabolism is associated with elevated risk of overall metabolic syndrome that contribute to the risk of diabetes.[34]

3. MECHANISMS INVOLVED IN ARSENIC TUMORIGENESIS

Many biochemical mechanisms have been proposed for *i*As as a human carcinogen.[35] These mechanisms of action include induction of oxidative damage,[36] activation of mitosis, and induction of genotoxic damage,[37] interference with the methyl transfer to DNA,[38] decrease of DNA repair mechanisms; perturbation of signalling cascades[30,40], disruption of transcriptional and translational activities, histone perturbations 41, differential microRNA expression [42], cytotoxicity and regenerative hyperplasia resulting from *i*AS interaction with protein sulfhydryls, [43] and changes in genes and proteins expression.[44,45] In its recent position paper, the Society of Toxicology has emphasized the need for using model systems that mimic diversity in human populations to identify biomarkers and disease endpoints at low levels of iAS exposure.[46]

It has also been pointed out that arsenic metabolism is epigenetically dysregulated by human microbiome and liver enzymes.[47] However, chromosomal aberrations, free radicals production, and alteration of transcription factors are the only three mechanisms of arsenic tumorigenesis that have been widely characterized.[48] Other potential modes of arsenic carcinogenesis, including the alteration in DNA repair, DNA methylation, gene amplification, p53 expression, and progression of carcinogenesis, are not well elucidated. Hence, arsenic carcinogenesis remains a subject of great scientific debate. Data generated from mechanistic studies indicate that arsenic may also promote or stimulate cancer progression, and/or act as a co-carcinogen. Figure 2 presents an overview of various modes of action of *i*As.[3]

3.1. Induction of Reactive Oxygen Species and Oxidative Stress

*i*As at high concentrations induces oxidative stress (OS) in biologic systems. OS is considered as one of the key processes involved in skin carcinogenesis resulting from *i*AS exposure.[36] Several investigations have shown that arsenic stimulates the formation of pro-

oxidant molecules in many cell lines[49,50], resulting in the repression of enzymatic biomarkers such as glutathione [51], and other known anti-oxidant enzymes.[52] Signalling molecules (e.g., MAPK, NF-κB, etc.) can also be activated in response to arsenic-induced OS.[53] It has been pointed out that the activator protein 1 (AP-1) activity influences the differential effect between low (mitogenic) and high (pro-inflammatory) doses of exposure.[44,54]

3.2. Induction of Mutagenicity and Genotoxicity

Arsenic elicits a low level of mutagenicity in bacterial assays. Bioassays conducted with *Escherichia coli* showed inconsistent results.[55] In mammalian assays, arsenic has also shown a weak level of mutagenicity. Although few studies have reported that arsenicals induce mutations in L51784ytK± mouse lymphoma cells, such findings have not been duplicated elsewhere.[56] However, in co-culture of human-hamster cells, arsenic trioxide induces a positive mutagenicity.[57] Arsenicals also elicit potent clastogenic effects.[58,59] They induce significant changes in number and structure of chromatids and chromosomes.[60,61,62] At low doses they are found to induce loss or gain of one chromosome, as well as exchange of sister chromatids.[63] iAs carcinogenicity has also been associated with alteration of cell cycle proteins, alteration of DNA repair leading to free radicals production and genotoxicity[50], and alteration of aberrant cytokeratin expression.[64] *i*As also promotes tumorigenesis by inducing cell proliferation through modulation of specific signal transduction pathways.[65]

3.3. Modulation of Keratin Expression

In endemic areas, arsenic exposure causes hyperkeratosis and squamous cell carcinoma. These dermatologic effects are associated with alterations in cytokeratin (CK) expression.[66] Hence, CK expression has been used as a biomarker of arsenic-related skin carcinogenicity and biochemical changes in epithelial structures (Markey et al., 1991). Studies have also shown that the transcription of many keratin genes such as CK1, CK8, CK 10, CK13 and CK18, is significantly increased in arsenic-treated HaCaT cells exposed to arsenic.[67]

3.4. Aberrations of Gene Expression

*i*As induces aberrations of gene expression in many biologic systems. Using high throughput technologies, specific target genes associated with arsenic toxicity/carcinogenicity in cells of various organs and tissues have been identified. Clewell et al.[68] examined *i*As modulation of gene expression in mice. From microarray experiments, they observed a decrease in gene expression at 1 week followed by an upregulation of gene expression at 12 weeks. They also found that gene expression correlated with cytotoxicity at the early time point and regenerative proliferation at the later. Using an *in vitro* approach, Efremenko et al.[69] tested the effects of two arsenite compounds (mixture of As (+3) compounds, and As_2O_3) on gene expression in lung cells. They reported from their genomic and cell signalling pathways analysis that arsenic concentrations below 0.1μM are not toxic to human cells.

In a specific group of a cohort of arsenic-exposed people in Bangladesh, several important single nucleotide polymorphisms (SNPs) located near the 10q24.32 region of the were identified in the arsenic 3 methyl transferase gene (AS3MT) gene that were highly linked to dermatologic disorders and correlated with urinary *i*As metabolite profile.[22] A similar

As3MT transcription study conducted in residents of an arsenic-endemic region in India reported a significant increase of cytogenetic damage in lymphocytes. It was concluded that G>A transition in the C10 or f32 region is a key process involved in arsenic toxicity and susceptibility.[70]

3.5. Dysregulation of Cellular Immune Function

Immunosuppression has been highly associated with *i*As arsenic tumorigenicity. This carcinogen disrupts the bioactivity of cellular immune system causing a reduction of CD4+ cells in epidermal keratinocytes, and inducing skin carcinogenesis.[71,72] Using ATO as a test compound and HaCaT keratinocytes as a test system, Udensi et al.[34] pointed out that low concentrations of arsenic modulate gene expression in the immune system. While many biomarkers such as cytokines are up-regulated, other signalling molecules are down-regulated. There is also scientific evidence indicating that the activation of specific cytokines enhances carcinogenesis.[73]

3.6. Alteration of Protein Structure

Arsenic reduces mitochondrial enzymes' activity and uncouples oxidative phosphorylation leading to the impairment of cellular respiration.[3] *iAs* toxicity has been associated with the high degree of interaction between arsenites and sulfhydryl (SH) components of proteins, and the replacement of phosphorus by arsenates.[74,55] Its interaction with the SH groups inhibits the activity of important enzymes, and subsequently decreases fatty acids catabolism.[55] By binding to SH-groups of proteins and vicinal cysteines, and by interfering with the disulfite bonds, arsenic alters the conformation of protein structure[45] and the number of proteins.[75]

3.7. Induction of Cell Proliferation

In human keratinocytes, *i*As has been shown to induce an up-regulation of growth factors, cycling proteins, ERK signalling, and other mitogenic markers.[40] *i*As also exerts a hormesis-like dual effect in various cell lines; leading to the differential toxicity observed between low and high exposure doses.[12,54]

3.8. Dysregulation of Epigenetic Mechanisms

DNA methylation, histone modification and microRNA expression have been identified as the prominent epigenetic mechanisms of *i*As toxicity.[76,77,78,79,80,81] *i*As alteration of epigenetic mechanisms has also been linked to an up-regulation of cancer-related genes, as well as a down-regulation of programmed cell death.[82,83] Mass and Wang[84] examined the role cytosine methylation plays in arsenic-induced lung cancer. Both sodium arsenite and sodium arsenate produced a dose-dependent hypermethylation of DNA. A plausible, unified hypothesis for arsenic tumorigenicity may therefore be related to its interaction with DNA. Van-Breda et al.[85] identified target genes that may be involved in lung tumorigenesis as a result of arsenic interaction of DNA.

3.9. Modulation of Signal Transduction

Arsenic alters cell cycle regulation by interfering with signal transduction.[86] *i*As alters the interaction of transcription factors with DNA.87, and up-regulates many signalling pathways.[40,87] Arsenic species and cell types also influence the degree of interference with signalling pathways.[88] As a potent stimulator of mitogenic activity and angiogenesis, NF-κB ranks among the biomarkers of *i*As tumorigenicity.[70] Arsenic activation of the MAPK pathway up-regulates AP-1 and its transcription molecules.[89]Also, the activation and translocation of protein kinase c are required for arsenic-induced signal transduction through interaction with MAPK.[90] Phillips et al. reported that AsIII maintains epidermal growth factor receptor signaling by attenuation of bone morphogenetic protein 6 induction of dual specificity phosphatases 2 and 14.[91]

3.10. Induction of Co-carcinogenicity

In mice *i*As alone does not induce cancer but rather acts as a co-carcinogen to promote UV radiation-induced tumorigenesis.[92] Although *i*As is considered a weak mutagen, it can promote the toxicity and tumorigenicity of other carcinogenic agents to which humans are exposed.[93] However, many studies on arsenic co-carcinogenicity have not been reproduced in other laboratories.

3.11. Modulation of miRNAs Expression

MicroRNAs (miRNAs) are small RNAs which regulate gene expression and protein translation. They regulate gene expression by acting as oncogenes or tumor suppressors, thereby impacting cell proliferation, carcinogenesis, or apoptosis. They function by interacting with target mRNA, suppressing mRNA level and repressing protein translation.[94,95] The role of miRNAs on *i*As-induced toxicity in Jurkat T cells was examined by applying transcriptomics and bioinformatics tools to reconstruct arsenic-relevant molecular pathways and miRNA regulatory networks.[96] Thirty six miRNAs were dysregulated, 25% of which were validated by RT-PCR. The computational analysis of molecular networks pointed to an involvement of *i*As in cell cycle progression, and blockage of apoptosis.

On the other hand, Ghaffari et al.[76] assessed the role of miRNAs in NB4 cells apoptosis caused by arsenic trioxide (ATO). They found that over 40 miRNAs were upregulated, while fewer than 4 were downregulated. They also discovered that a large proportion of these upregulated miRNAs acted as tumor suppressors to activate the apoptosis pathway. In a more recent study designed to examine the role of miRNAs in ATO-induced QT prolongation, Shan et al.[95] discovered that ATO significantly upregulated the muscle-specific miRNA-1 and miRNA-133, as well as their transactivator serum response factor.

3.12. Induction of Apoptosis

Several studies have demonstrated the role of apoptosis in the effectiveness of ATO as a chemotherapeutic drug against acute promyelocytic leukemia. Its therapeutic potential is linked to genotoxic, cytotoxic and apoptotic effects.[96,97] ATO modulates the intrinsic pathway of programmed cell death, through specific genotoxic and apoptotic signalling mechanisms.[98] It activates Bax translocation from the cytoplasm into the nucleus, causing mitochondrial membrane depolarization, cytochrome C release, and caspases activation.

[99,100] It also induces phosphatidylserine externalization and nucleosomal DNA fragmentation.[101] Other reports have pointed out that ATO causes programmed death of cells associated with other cancers.[102,103,104] Despite its toxic effects, arsenic may also be involved in cell repair mechanism. For instance Ding et al. reported that arsenite supresses UV radiation -induced Poly(ADP-ribose) polymerase-1 (PARP-1) participating in repair mechanism of oxidative DNA damage in human keratinocytes.[105]

4. EPIDEMIOLOGY OF ARSENIC TOXICITY

Arsenic is a systemic toxicant that produces a multitude of adverse effects on almost all the organ systems in humans at high doses. Both acute and chronic health effects have been investigated, and their types and magnitude vary greatly depending on the dose and species of arsenic, as well as on specific intrinsic and extrinsic factors.[106,104] The clinical and pathological manifestations of arsenicosis have been widely reported,[3,8,9,107] and include black foot disease in Taiwan, atherosclerosis,[108] cerebral infarction, hypertension, diabetes mellitus,[109] skin pathologies, liver and lung fibrosis, hearing loss, and neurologic damage in children. [110] However, many of these clinical endpoints do not show a strong scientific evidence. Hence further studies are needed to improve the scientific knowledge.

4.1. Systemic Effects

4.1.1 Dermatologic Effects—Many forms of skin lesions, including hyperpigmentation, hypopigmentation, keratosis and Bowen's disease, constitute the most common signs and symptoms of arsenicosis.[111,112] These clinical signs of toxicity are the most sensitive indicators of arsenicosis that have been observed in patients.[113] The same study also pointed out that the male population suffered more from dermatological lesions than the female population. This gender difference could be because men are more likely to be more excessively exposed to sun light than women.[114] Among the clinical symptoms of arsenic toxicity, skin lesions are considered as a major biomarker of acute toxicity.[110]

4.1.2 Cardiovascular Effects—Increased rates of high blood pressure and cardiovascular disease (CVD) mortality have been linked to chronic arsenic intake.21 High incidence of hypertension has been reported in residents of a rural area of Bangladesh who consumed arsenic-contaminated groundwater during their entire life.112 The risk of dying from arsenic-induced CVD has been documented in Chile,[115] and Japan.[116] Although there is a strong evidence of arsenic-induced cardiotoxicity,[117] many epidemiological studies reporting potential associations relate to highly exposed populations. The scientific evidence of causal association with low level exposure is inconclusive.[118] From a recent investigation, Sidhu et al.[119] concluded that the available evidence does not show a robust mechanism of action of *i*As in CVD incidence, nor does it show a linear dose–response relationship; indicating that this relationship has a threshold.

4.1.3 Reproductive and Developmental Effects—iAs causes deleterious effects on human reproduction. Both teratogenic and developmental toxicities have been characterized. [120,121] However, because of the potential confounding factors and recall bias associated with both ecological and retrospective study designs, it has been pointed out that stronger study

designs would increase the statistical power and produce stronger results. Although a statistically significant association with birth defects was observed in a research on Bangladeshi women, other assessment endpoints did not show any significant associations.[122] Based on the low amount of teratogenic outcomes, the authors pointed out that the reported link to birth defects may be a statistical error. Hence it is recommended that further studies be done with a larger sample size to increase statistical power and strengthen the scientific evidence.

4.1.4 Neurological Effects—Many studies assessing the neurotoxicity of arsenic have focused on the assessment of its acute and subchronic toxicities on the brain, and other neurologic parts,[2] as well as on the examination of its neurodevelopmental endpoints.[123] Wasserman et al.[124] investigated whether a decrease in arsenic exposure can improve the intellectual ability of children. They assessed specific intelligence-related endpoints, and also analyzed both blood and urinary biomarkers at baseline and 2 years after the change of groundwater source. They found that urinary arsenic (UAs) and creatinine (Cr) concentrations were significantly reduced and negatively associated with all intelligence assessment indices except processing speed. Also, a reduction of UAs/Cr by 100 ppm increased the brain function by 0.91 point. Although many studies show that *i*As alters many intelligence markers, other epidemiological investigations have shown a negative relationship with cognitive function of young people.[125] However, the influence of other factors such as co-exposure to multiple neurotoxicants, inaccurate measures of biomarkers of effect, susceptibility and effect, social-cultural influences, and/or other potential risk/uncertainty factors, weaken the strength of association.[126] Therefore, additional well-designed epidemiological investigations are necessary to ascertain the neurodevelopmental outcomes resulting from chronic *i*As exposure.

4.1.5 Respiratory Effects—Respiratory effects other than lung cancer have been associated with arsenic poisoning.[109] The risk of these effects has been reported in many areas of arsenicosis. A group of specific signs and symptoms associated with chronic inhalation of arsenic has been reported from a clinical study of copper smelter workers.[127] Also, an epidemiological study of ninety four individuals with skin lesions in Bangladesh reported that chronic arsenic ingestion was linked to chronic bronchitis, and the risk for male individuals was larger than the incidence rate in females.[128] Recently, Recio-Vegas et al.[129] carried out research on paediatric health and concluded that arsenic decreases the forced vital capacity in these children. Another study suggested that exposure to arsenic in drinking water during early childhood may increase mortality of lung cancer and bronchiectasis in young adults.[130]

4.1.6 Hepatotoxic Effects—Arsenic exposure induces many hepatotoxic effects including hepatomegaly, portal fibrosis and cirrhosis.[131] In their evaluation of the magnitude of hepatotoxic lesions associated with chronic *i*As exposure, Mazumder128 found that hepatomegaly was prevalent in 76.6% of patients, and its incidence correlated well with the dose level. In a similar research done in Northeastern Taiwan, Hsu et al.[132] reported strong positive correlations between arsenic exposure and prevalence of chronic hepatitis or cirrhosis in residents who were not infected by the viruses of hepatitis B and hepatitis C. A

previous study on individuals consuming arsenic contaminated water from groundwater in three towns of Lagunera, Mexico, implicated arsenic in the incidence of cholestasis.[133]

4.1.7. Hematologic Effects and Diabetes—Arsenic exposure induces many hematological abnormalities.[2] In a previous study conducted on residents of an arsenicosis area of Mexico, Hernandez-Zavala et al.[134] found that arsenic exposure modulates porphyrin metabolism leading to high amounts of both total and coproporphyrin III isomer in urine. From an ecological investigation designed to examine the causes of death in several residential areas of Taiwan, Tsai et al.[135] found that diabetes mellitus was the primary risk factor associated with the mortality of many blackfoot-disease patients. Studies conducted in other arsenicosis endemic areas have also reported a high incidence of diabetes in long-time residents.[136]

4.1.8 Renal Effects—The capillaries, tubules and glomeruli constitute the primary sites of arsenic toxicity to the kidneys.[137,138] Arsenic-induced capillary damage leads to the dilation of glomerular arterioles and hematuria, while proximal tubules damage leads to abnormal amount of proteins in the urine, and impairment of energy production.[139] From a Taiwanese study examining the impact of arsenic exposure on the kidneys, Chen et al.[140] reported that the rate of abnormal beta 2 microglobulin (β2MG) increased dose-dependently with the urinary arsenic (U-As) concentrations. The risk of tubular and glomerular dysfunction was associated with the risk of abnormal β2MG (> 0.154 mg/L). Renal dysfunction rates significantly increased when the U-As rose above 75 μg/g creatinine. Peters et al.[141] studied the potential association of arsenic biotransformation with urinary creatinine and renal performance, and concluded that arsenic exposure only had a marginal inverse association with the estimated glomerular filtration rate. However, increases in several biomarkers of arsenic-induced renal dysfunction including NAG, beta 2-microglobulin and micro albumin,[142] RBP,[143] and alpha 1-microglobulin[144] have been reported. Zheng et al.[145] highlighted many investigations that reported potential association of arsenic with assessment endpoints such as albuminuria, proteinuria and mortality from chronic kidney disease (CKD). Zheng et al.[146] tested the association of *i*As exposure with CKD, and found that its methylation products were correlated to CKD. However, further research is needed to ascertain whether arsenic is a prominent cause of CKD.

4.1.9 Gastrointestinal Effects—Acute arsenic exposure causes multiple gastrointestinal disorders including burning sensations, painful swallowing, thirst, diarrhoea and stomach ache.[136,147,148] High arsenic exposure as in cases of suicidal attempts and intoxication can lead to diarrhoea and gastroenteritis, as well as circulatory collapse and kidney damage.[149] Also, the rupture of blood vessels may lead to a major loss of body fluid and proteins. While several clinical manifestations of arsenic toxicity have been associated with acute exposure,[150]low concentrations may not be toxic to the gastrointestinal tract or may produce only moderate effects.[137]

4.2 Carcinogenic Effects

Population-based studies have shown that iAs induces multiple neoplasms such as bladder and kidney,[151] liver,6 prostate and lung,[148] and especially skin[109] cancers. *i*As-induced

kidney tumors arise from the kidney pelvis urothelium and are essentially related to the urinary bladder tumors.[103] Some of these tumors, such as myeloma, prostate, bladder, and peripheral lymphocytes show very weak and inconsistent evidence of carcinogenicity when exposure is low.[118,152] Hence, *i*As modes of action as well as its possible carcinogenic effects at low exposures are not clearly understood. From an experimental study, Waalkes at al.[153] reported that in utero *i*As exposure causes tumors in CD1 male mice. The conclusion of this study has been questioned by Cohen et al.[154,155] because of the relatively high incidence of spontaneous cancer in CD1 mice, poor survival of the low-dose group, and lack of a dose-response relationship. While a recent re-evaluation by Druwe and Burgoon[156] states that the original findings of Waalkes et al.[153] are supported, methodological limitations and other issues still remain and the interpretation of the Waalkes study is unclear.[154,155]

4.2.1 Arsenic and Skin Cancer—Higher incidence and prevalence rates of skin cancers, as well as intra-epidermal carcinomas have been linked to acute arsenic exposure.[156] A variety of skin lesions are often considered as sensitive biomarkers of susceptibility and effect and may co-exist in many regions where arsenicosis is prevalent.[156,157] The skin is a target organ of arsenic poisoning but not considered as the primary route of exposure.[158] The gastro intestinal tract and the lungs are the major routes of As exposure but it is distributed primarily to the liver, kidney, lung, spleen, aorta, and skin.[158,159,160] Human skin diseases associated with arsenic exposure include; intraepidermal carcinomas (Bowen disease), squamous cell carcinomas (SCC), basal cell carcinomas (BCC), and Merkel cell carcinoma (MCC), hyperkeratosis and hyperpigmentation.[161,162,163]

4.2.2 Arsenic and Liver Cancer—As indicated earlier arsenic exposure causes a multitude of hepatotoxic effects that are characterized by significant alterations in the architecture and functions of the liver.[164,165] Besides systemic effects, increased risk of hepatocellular carcinoma has been found in many endemic areas of arsenicosis. However, it has been pointed out that the observed risk may be mediated through a combination of arsenic and other underlying environmental and genetic risk factors of liver cancer.[166] In other reports, angiosarcoma has also been associated with to *i*As toxicity.[167]

4.2.3 Arsenic and Kidney Cancer—Data of many epidemiological studies on arsenic and renal cancer do not support a strong association, although a few investigations on employees of a smelter plant in Tacoma, Washington, USA have reported significant increases in the incidences of renal, lung, gastrointestinal, and hemato-lymphatic malignancies.[168,169] In a recent experimental study investigating the role of Raf kinase inhibitor protein (RKIP) in arsenic-induced liver and kidney cancers, Tsao et al.[170] discovered that the arsenic amounts and RKIP translation in the liver and kidneys were inversely correlated. They concluded that the decrease of RKIP expression in both organs may be considered as a biomarker of arsenic-induced carcinogenesis.

4.2.4 Arsenic and Urinary Bladder Cancer—Scientific evidence from epidemiological investigations shows a causal relationship between high *i*As intake and bladder cancer. In a recent epidemiological research in Maine, New Hampshire, and

Vermont (USA), Baris et al.[171] pointed out that bladder cancer rate was positively linked to arsenic doses. Positive associations have also been reported with regard to cancer of the urinary system.[172] However, an integration of scientific data from both experimental investigations and epidemiological studies indicates that arsenic exposure at concentrations less than 100 μg/L has minimal effect on bladder cancer risk. Using the mode of action data to assess the magnitude of bladder cancer in response to *i*As exposure, Gentry et al.[173] reported that exposure to low *i*As concentrations is highly unlikely to induce carcinogenic or systemic effects in the bladder tissue. Establishing the safe levels of exposure to *i*As represents a major challenge to the scientific community. Additional mode of action research is necessary to determine the threshold or maximum dose of *i*As that would not induce other cancer types.

4.2.5 Arsenic and Lung Cancer—Research on industrial studies on workers points to arsenic association with lung cancer risk.[174] It is probable that *i*As acts in conjunction with other related risk factors such as radiation, asbestos, radon, nickel, chromates, as well as genetic and nutritional factors.[108] Many population-based studies on populations consuming high iAs concentrations have reported higher risk of lung neoplasm.[175] However, similar investigations on people subjected to low arsenic amounts have yielded mixed results, with some showing no increase in cancer incidence,[176,177] and others showing a significant increase in cancer risk.[178] Efremenko et al.[67] reported from their genomic and cell signalling pathways analysis that biological responses are not likely to occur at arsenic concentrations below 0.1μM. More recently, Lynch et al.[151] conducted an evaluation of epidemiological investigations carried out in various regions of the world and found a weak association between *i*As and cancer promotion. They estimated that *i*As-induced cancer risk is much lower than observed bladder and lung cancer incidences; suggesting that human exposure to low iAs levels will not produce an increase in cancer incidence.

4.2.6 Arsenic and Gastrointestinal Cancer—There are no compelling reports linking arsenic exposure to the increased cancer incidence of the gastrointestinal tract. The potential association is not clear because most observations on cancer incidence and cancer mortality rates have been made from occupational studies where participants were co-exposed to arsenic and other risk/confounding factors.[179]

4.2.7 Arsenic and Brain Cancer—In a recent review, Escudero-Lourdes[180] reported that oxidative stress and activation of pro-inflammatory responses mediated by cytokines and related factors play a key role in *i*As-induced cognitive impairment. However, limited research has examined iAs role in brain tumorigenesis. Although Navas-Acien et al.[181] found that arsenic may enhance the risks of gliomas and meningiomas in Swedish populations, the heterogeneous exposures to multiple pollutants prevent attribution to arsenic.

5. HEALTH RISK CHARACTERIZATION AND REGULATORY GUIDELINES

Global public health research has shown that *i*As induces several types of systemic pathologies as well as carcinogenic effects.[3,8,9] The association with *i*As exposure is strong for dermatologic and many internal cancers.[2,3,7,182] *i*As is a carcinogen that is classified in

Group 1 [6,182] or Group A.[109,183,184] For non-cancer effects, 3×10^{-4} mg/kg/day has been established as a safe oral dose that is unlikely to cause any lifetime deleterious effects, considering the critical biomarkers of dermatologic effects.[7,109,185,186] Similarly, a specific criterion range has been estimated for neurobehavioral effects in children.[123] Also a cancer potency factor has also been established based on skin cancer.[184]

As presented on Table 1, many regulatory and advisory agencies have developed guidelines that set standards or criteria to limit the levels of exposure to arsenic in various environmental media.[109,183,184,185,186,187,188,189,190] A reevaluation of these environmental health standards is being carried out by EPA, examining both carcinogenic and non-cancer health effects.[7] Recent reports have underscored the critical need for integrating scientific data from recent or ongoing experimental investigations and epidemiological studies to minimize uncertainties in the estimation of dose-response relationships regarding the cancer risk associated with low level of *i*As exposure.[191]

6. PERSPECTIVES FOR FUTURE RESEARCH

Recently, the Society of Toxicology has expressed the urgent need for further research on arsenic as a toxicant of major concern (SOT, 2017)[46]. From our evaluation of published studies on the critical issues related to *i*As toxicity and the major challenges facing regulatory agencies in preventing or reducing its adverse health outcomes, we are proposing the following areas of future research focus:

6.1. Further development of animal models of arsenic carcinogenesis

Published research has demonstrated that several important molecular mechanisms are involved in *i*As-induced carcinogenesis. These mechanisms include: production of ROS and oxidative damage, alteration of DNA structure, chromosomal aberrations, stimulation of mitogenesis, interference with DNA function, hypomethylation of DNA, perturbation of signalling cascades, disruption of transcriptional and translational activities, post-translational histone modifications, differential microRNA expression, and changes in genes and protein expression. While several of these modes of action of arsenic tumorigenicity have been well elucidated in many *in vitro* studies using various cell lines, some of the underlying mechanisms that drive the malignant transformation are not clearly understood, because of the inexistence of an appropriate animal test system. Further development of animal models of arsenic carcinogenesis is strongly encouraged to assist with the assessment and understanding of the molecular events and biochemical processes that drive the initiation, promotion and progression of human cancers.

6.2. Characterization of the underlying mechanisms of iAs toxicity and carcinogenicity

Scientific evidence shows that *i*As disrupts important biologic functions through interaction with and damage to key cellular components. Hence, further characterization of the underlying mechanisms and molecular targets of arsenic toxicity and carcinogenicity including the identification specific biomarkers of exposure, susceptibility and/or effect will certainly contribute to the global efforts to combat arsenic toxicity.

6.3. Evaluation of combined effects of iAs and other potential carcinogens

Current scientific evidence from mechanistic investigations suggests that arsenic is a known human carcinogen that may also promote or progress tumorigenesis by interacting with other carcinogenic agents. Considering the likelihood for multiple chemical exposures in arsenicosis areas, additional research is necessary to characterize the outcomes of arsenic interactions with other potential carcinogens (e.g. biotoxins, pesticides, UV, other toxic metals).

6.4. Characterization of gender-specific susceptibility markers and other factors

The scientific evidence from epidemiological studies shows that the biotransformation rate has a major influence on arsenic tumorigenicity. Population-based investigations show that the male populations have a lower methylation capacity, which could make them more susceptible to arsenic toxicity than females. Research conducted in arsenicosis endemic areas has found higher prevalence rates of truncal hyperpigmentation, palmar-plantar keratosis, and chronic bronchitis in male individuals compared to female populations. Hence, additional studies are needed to characterize gender-specific markers and other factors that influence the biotransformation process.

6.5. Characterization of other potential modifying factors involved in iAs toxicity

Research has suggested that the magnitude of toxic manifestations is influenced by arsenic species and dose, and individual characteristics such as age, gender, nutritional status, genetic factors, and lifestyle. Further research on potential modifying factors such as nutritional status (folate, methionine, selenium and other essential elements), genetic polymorphisms, and/or the presence of other diseases that may affect arsenic metabolism should be conducted. Therefore, determining the biologic or biochemical basis for the potential differences in susceptibility among various population subgroups is a worthy research endeavour.

6.6. Determination of the role played by genetic susceptibility and changes in gene expression in arsenic toxicity

The application of novel omics technologies has led to the recent developments in genetic and molecular epidemiology. Although there remain some research gaps to be filled, these scientific advances are increasing our knowledge on the specific mechanisms involved in arsenic tumorigenicity. The use of high throughput technologies has led to the characterization of specific target genes modulated by iAs tumorigenicity. The intra-species variability in *i*As methylation leads to the observed differences in toxic manifestations among individuals. Also, few studies on arsenic biotransformation and related manifestations of toxicity have identified several genome-wide SNPs that show a significant association of arsenic methylation capacity and skin lesions. However, many genome-wide association studies are statistically underpowered and do not also account for individual differences in arsenic exposure. Therefore, additional genetic variations studies that involve sufficiently large numbers of participants are needed to clearly determine the role played by genetic susceptibility and changes in gene expression on arsenic toxicity. These studies should also consider other important factors such as *i*As dose and exposure duration, as well

as the nutritional status, and the demographic, sociocultural and economic profiles of participants in the context of socio-economic and environmental determinants of *i*As-induced diseases.

6.7. Sufficiently powered epidemiological studies involving large numbers/ populations of women living in arsenicosis endemic areas

Scientific evidence from epidemiological studies conducted in arsenicosis endemic areas has demonstrated mixed results. While some studies have reported a negative impact on reproduction outcomes, other investigations have found that the teratogenic outcomes were similar between exposed and unexposed populations. Based on the fact that many of these investigations are limited by the low number of participants, it is recommended that additional epidemiological studies be done on large numbers/populations of women living in arsenicosis endemic areas to ascertain the specific reproductive and developmental impacts of arsenic toxicity.

6.8. Evaluation of both genetic and epigenetic mechanisms in iAs-induced teratogenic, developmental, and carcinogenic effects in children

Very limited scientific data are available on the genetic and epigenetic mechanisms by which arsenic induces teratogenic, developmental, and carcinogenic effects in children who may be exposed to higher doses of arsenic through in-utero exposure, water and food consumption, and/or hand-to-mouth ingestion of contaminated soils. Hence, further genetic and epigenetic studies are needed to evaluate the impacts of *i*As on fertility, gestation, and offspring.

6.9. Assessment of types/species and concentrations of arsenic in food products

While drinking water supply from arsenic-contaminated groundwater has long been the primary source of human exposure and public health concern, recent studies have pointed out a substantial risk of arsenic-induced health impacts through consumption of various dietary staples such as cereals and juices that may contain appreciable amounts of *i*As. Additional research is needed to assess the chemical forms and levels of arsenic in foodstuffs, as well as to characterize both individual and population exposures. A holistic approach that considers all potential exposure sources, as well as the exposure pathways, frequencies and durations, should be applied. Also, the risk estimation should be based on the integration of actual dose resulting from combined exposure sources, and other modifying factors.

6.10. Epidemiological investigations of people in low iAs-contaminated regions

Characteristic skin lesions involved (hyperpigmentation, hypopigmentation/depigmentation, keratosis and Bowen’s disease) constitute the most sensitive and common signs and symptoms of arsenicosis that can be used as biomarkers of high *i*As exposure. Although there is a strong evidence of arsenic-induced systemic and carcinogenic effects at higher levels of exposure, many epidemiological studies evaluating such pathologic outcomes at low levels of *i*As exposure have reported mixed results; with some showing a significant association, and others showing no association. The potential weaknesses in study designs combined with differences in dose, nutritional status, gender, age and genetic variations may

explain the inconsistencies in the research findings. Therefore, additional investigations are required to elucidate and determine the strength of association, as well as to generate new scientific data that can be used to reduce uncertainties in the characterization of health risks of low levels of *i*As exposure. It is essential that the scientific quality and strength of population-based studies be enhanced by improvements in the strategic areas of research approach including study design, statistical power, and health risk assessment.

7. CONCLUSIONS

Inorganic arsenic is known to increase the risks of systemic and carcinogenic effects in humans. While a significant number of non-cancer end-points have been linked to both acute and chronic *i*As exposure, many human neoplasms have been linked to long term exposure. Although these adverse health effects have been well characterized under specific exposure conditions, there are several gaps in scientific knowledge that should be addressed. In this regard the following technical objectives are proposed to direct future research endeavors in arsenic toxicology: a) develop animal models of arsenic carcinogenesis to further elucidate its modes of action; b) characterize the underlying mechanisms of *i*As tumorigenicity; c) evaluate the combined action of *i*As and other human carcinogens, for example cisplatin; d) characterize gender-specific susceptibility markers and other factors that influence the biotransformation process; e) characterize the potential modifying factors such as nutritional constituents, genetic polymorphisms, and/or the presence of other diseases that may affect arsenic metabolism, for example cardiovascular diseases; f) determine the role played by genetic susceptibility and changes in gene expression in arsenic toxicity; g) conduct stronger epidemiological studies to ascertain the specific impacts of *i*As toxicity on the reproductive and developmental systems; h) evaluate both genetic and epigenetic mechanisms in *i*As-induced teratogenic, developmental, and carcinogenic effects in children; i) assess the types/species and amount of arsenic in foodstuffs that are consumed in arsenicosis endemic areas; and j) conduct further epidemiological investigations on people consuming low concentrations of arsenic, in order to determine the magnitude and strength of association, as well as to generate new scientific data that can be used to reduce uncertainties in the estimation of the strength of association regarding the health risks associated with low levels of *i*As exposure. Emerging evidence describing the molecular pathogenesis of various cancers due to arsenic exposure such as cutaneous, lungs, liver, kidney lesions may be helpful in developing novel therapeutic interventions for these diseases in arsenic-exposed human populations. Scientific data generated from the proposed investigations will provide new insights on *i*As toxicity/carcinogenicity and further advance the understanding of its overall spectrum of adverse health effects. By providing a scientific basis for informed decision-making on the cost-effective control/prevention of arsenicosis, these novel studies would have a significant public health impact.

ACKNOWLEDGEMENT

Research primarily supported by Electric Power Research Institute (EPRI Agreement # 10006564). Leverage from NIH/RCMI Grant # G12MD0007581 is also acknowledged. The authors thank Drs. Annette Rohr and Leonard Levin at EPRI for reviewing the final manuscript.

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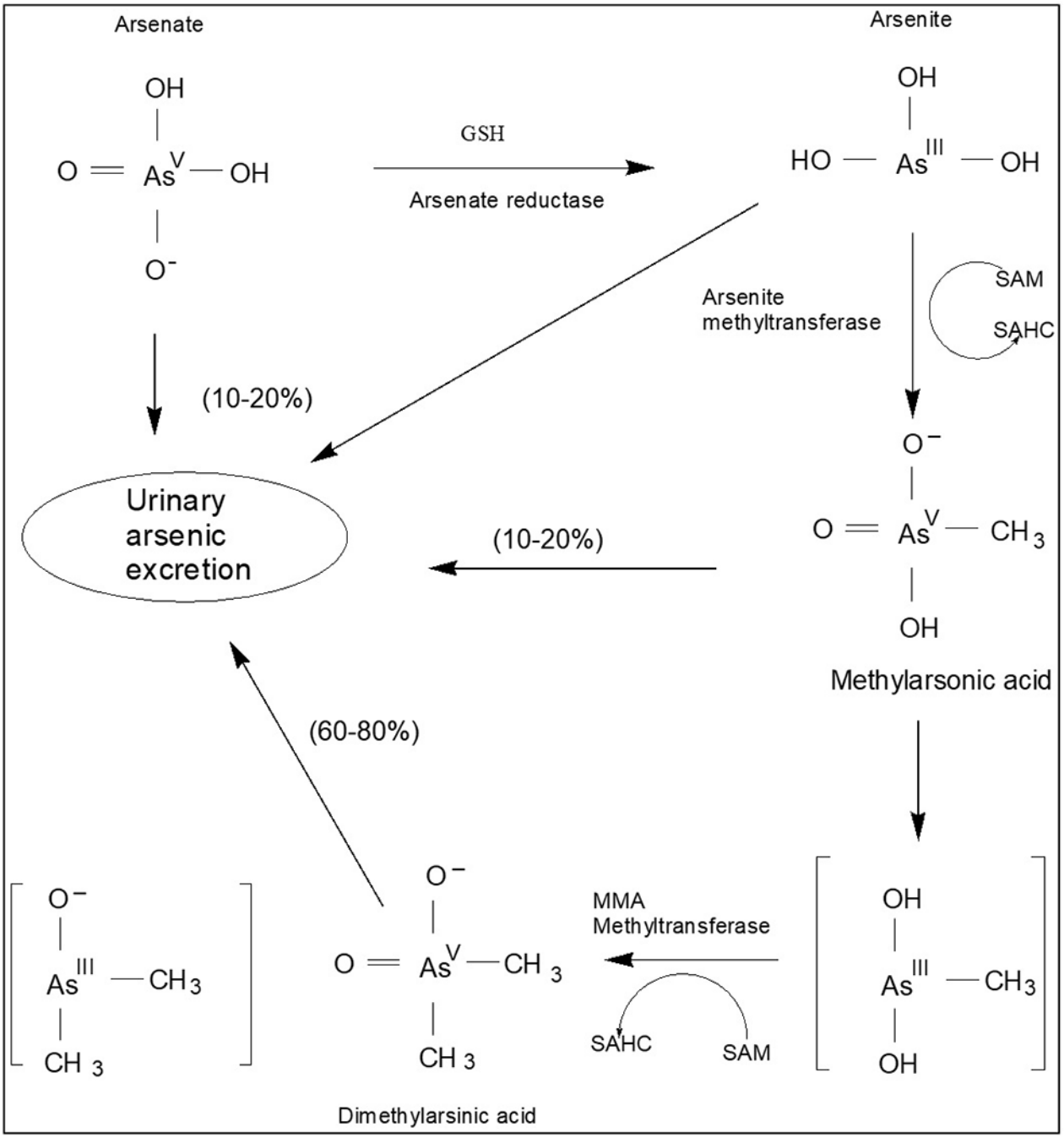

FIGURE 1:
Pathway of arsenic biotransformation in humans.[10]

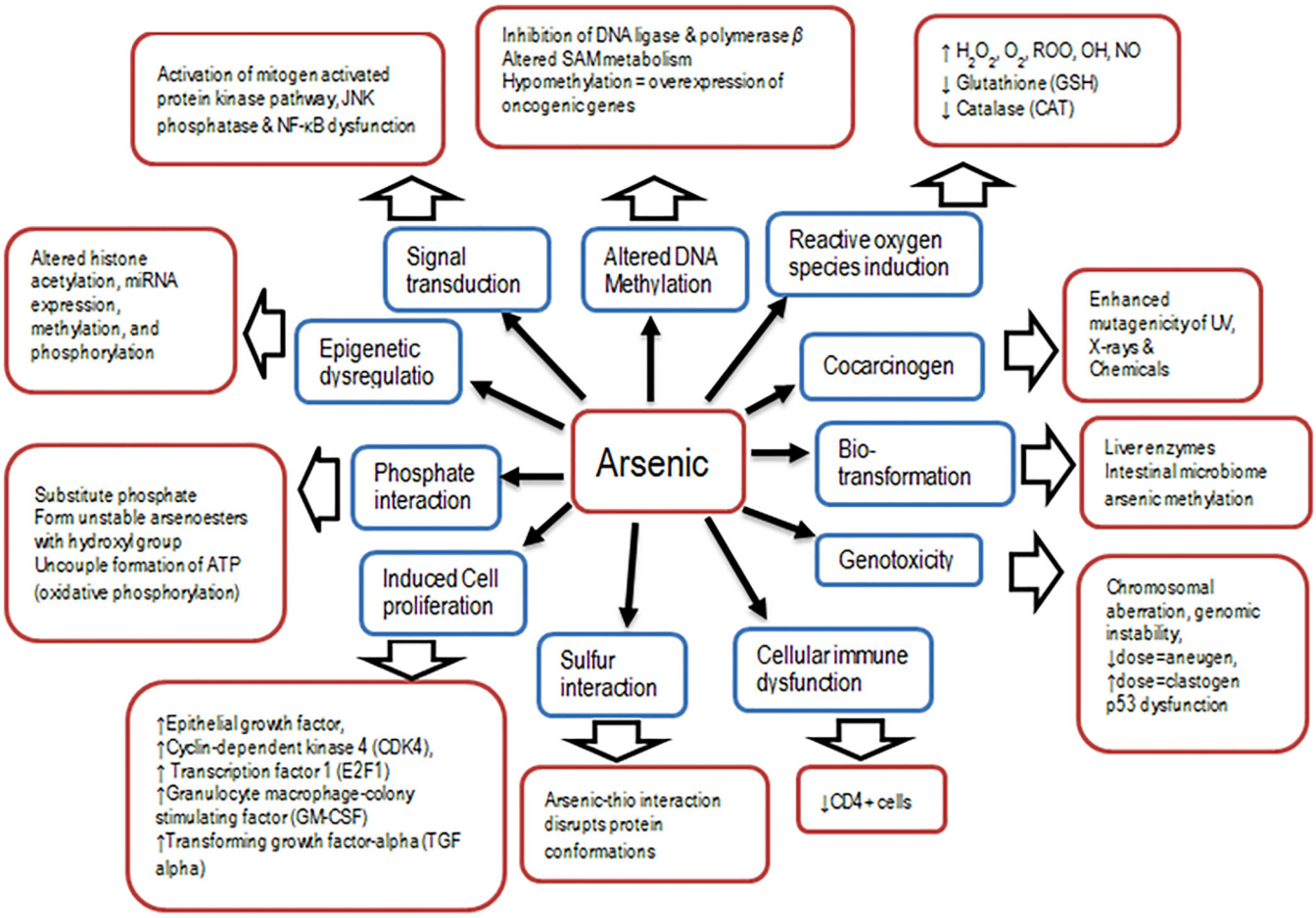

FIGURE 2:
Proposed mechanisms of action in arsenic carcinogenesis.[3]

Table 1:

National and international regulations and guidelines for the management of inorganic arsenic toxicity

Regulatory Agency	Exposure Medium	Standard/Criteria	Reference concentration/dose
United States Environmental Protection Agency (U.S. EPA)[183]	Drinking water	Maximum contaminant level	10 μg / L
	Drinking water	Maximum contaminant level goal	0 μg / L
	Food and drinking water	Reference dose for oral exposure	0.0003 mg/kg/day
	Drinking water	Cancer risk of 1 in 1,000,000 people	0.02 μg / L
	Food and drinking water	Cancer slope factor	1.5 per mg/kg/day
	Air	No current standard	N/A
	Air	Cancer risk of 1 in 1,000,000 people	0.0002 μg / m^3
	Air	Inhalation unit risk	0.0043 per μg / m^3
Agency for Toxic Substances and Disease Registry (ATSDR)[109]	Food and drinking water	Minimal risk level for oral exposure	0.005 mg/kg/day
	Food and drinking water	Minimal risk level for chronic exposure	0.0003 mg/kg/day
World Health Organization (WHO)[185]	Drinking water	Provisional drinking water guideline	10 μg / L
U.S. Food and Drug Administration (U.S. FDA)[186]	Apple juice	Provisional drinking water guideline	10 μg / L
	Eggs and uncooked edible tissues of chickens and turkeys	Tolerance /permissible level	0.5 ppm
	Certain uncooked edible byproducts of swine	Tolerance /permissible level	2 ppm
	Rice cereals for infants	Action/permissible level	100 μg / kg
National Institute for Occupational Safety and Health (NIOSH)[187]	Air / Workplace	Advisory for 15 minute ceiling limit based on classification of arsenic as a carcinogen	2 μg / m^3
American Conference of Governmental Industrial Hygienists (ACGIH)[188]	Air / Workplace	Threshold limit value –Time weighted average: TLV/TWA- 8 hour workday or 40 hour workweek	10 μg / m^3
	Urine	Inorganic arsenic plus methylated metabolites in urine at the end of work week	35 μg / L
Occupational Safety and Health Administration (OSHA)[189]	Air / Workplace	Permissible exposure limit / PEL over 8 hour day	10 μg / m^3
California Environmental Protection Agency(Cal. EPA)[190]	Air / Workplace	Acute inhalation reference exposure level	0.2 μg / m^3
	Air / Workplace	Chronic inhalation reference exposure level	μg / m^3