Epigenetic Phenomena of Arsenic and Histone Tail Modifications: Implications for Diet and Nutrition

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Abstract

Naturally occurring inorganic arsenic has been identified as the causal agent in human skin, lung, bladder, liver, and prostate cancers. Furthermore, arsenic exposure has also been associated with noncarcinogenic health outcomes, including cardiovascular disease, neurologic deficits, neurodevelopmental deficits in childhood, and hypertension. According to the Agency for Toxic Substances and Disease Registry, arsenic is considered number one on the substance priority list. However, the overall risks on human health may exceed the documented levels due to lack of a comprehensive consideration of exposure through diet and anthropogenic factors. Arsenic permeates through water and soil, and related health issues elicit global concerns for the mass public. The exact mechanism of arsenic toxicity is still not fully understood, although convincing evidence and recent advance in epigenetic research such as DNA methylation and histone

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V. B. Patel, V. R. Preedy (eds.), *Handbook of Nutrition, Diet, and Epigenetics*,
https://doi.org/10.1007/978-3-319-55530-0_17

posttranslational modifications have broadened our scope in understanding the mechanism of arsenic toxicity and carcinogenicity. This chapter will present the most recent literatures on the effect of arsenic on histone tail modifications as well as implications on food and diet.

Keywords

Inorganic arsenic · Histone tail modifications · Methylation · Acetylation · H3.1 · Stem-loop binding protein · Nutrition

List of Abbreviations

AcCOA	Acetyl coenzyme A
As	Arsenic
As (III)	Trivalent As
As (V)	Pentavalent As
As3MT1	Arsenic methyltransferase 1
BL-41	Human lung carcinoma cells
DMA5+	Dimethylarsinic acid
HACAT	Male-derived human keratinocytes
HAT	Histone acetyltransferase
HEK293	Female-derived human embryonic kidney cells
H(X)K(X)	Histone (X) Lysine (X)
iAs	Inorganic arsenic
K	Lysine
MMA5+	Monomethylarsonic acid
PBMC	Peripheral blood mononuclear cells
Ppb	Parts per billion
PTMs	Histone posttranslational modifications
R	Arginine
SAM	Cofactor S-Adenosyl methionine

Introduction

Arsenic (As) is a naturally occurring ubiquitous metalloid found in the Earth's crust, sediments rich in organic matter, as well as volcanic terranes. Corrosion of rocks and minerals coupled with anthropogenic sources of contamination such as application of arsenical pesticides, mining, and burning of fossil fuels exacerbates arsenic contamination in the groundwater. Areas of the world suffering most heavily include Bangladesh and West Bengal. In the 1960s and 1970s, international aids and governmental institutions initiated the digging of tube wells in effort to provide alternatives for people suffering from low-quality surface drinking water and related waterborne diseases. However, due to the lack of pretesting for underground impurities, the hundreds of thousands of tube wells providing arsenic-contaminated drinking water became the sources of one of the most devastating mass poisoning in human history. However, the extent of arsenic contamination is not localized to

these two particular regions. In fact, alarming levels found in the French Mediterranean coastal areas, the United States, China, Ghana, and Mexico illustrate the wide-ranging presence of this hazardous carcinogen around the globe. Beginning in the 1990s, arsenic elicited health concerns which began to gain recognition as a global public health issue; today a staggering amount of nearly 200 million people are exposed to unacceptable levels of this class one human carcinogen. Although the World Health Organization's recommended limit is 10 parts per billion (ppb), arsenic concentrations documented in approximately 70 countries can range anywhere from 0.5 to 5000 ppb (Shankar et al. 2014).

Metabolism

The various chemical forms and oxidation states of arsenic dictate its availability and toxicity. Inorganic arsenic is known to be more toxic and prevalent in terrestrial environments. Out of the four types of valence states, inorganic arsenic (iAs) chiefly exists as trivalent As (III) or pentavalent As (V). As the dominant form found in groundwater, the pernicious effect of As (III) is exacerbated by its intrinsically higher toxicity than As (V) as well as its uncharged state, which impedes the effective removal from water. Depending on the regional characteristics and type of human activities, the public can be exposed to arsenic either through ingestion, which is the main route of exposure due to pervasive contamination in drinking water and various foods, and/or inhalation. Once ingested, inorganic arsenic will go through two major steps of metabolism: biotransformation and methylation. Biotransformation refers to the reduction of As (V) to As (III). Methylation, which is also considered a detoxification mechanism, involves a two-step process in facilitating the excretion of methylate inorganic As (III) from the body via the kidneys. Arsenic methyltransferase 1 (As3MT1) catalyzes iAs into monomethylarsonic acid (MMA5+) and dimethylarsinic acid (DMA5+), respectively. The end products are more readily excreted from the body probably due to less protein binding from the reduction in overall charge caused by methylation. However, during the sequential methylation steps, MMA3+ and DMA3+ may form and remain in the tissues. Low levels of these reactive and cytotoxic intermediates can often be detected in people who are chronically exposed to arsenic-contaminated drinking water, and the methylated form of As is inherently more toxic to the body than the non-methylated form with DMA3+ being the most toxic species. It would be of interest to understand the role of AS3MT1 in human carcinogenesis and whether inhibition of this enzyme might be protective against As-induced cancer even though it increases the rate of As excretion.

Health Effects

Depending on the chemical form, oxidation state, amount, and length of exposure, arsenic can elicit a wide range of acute and chronic health concerns. As a class I human carcinogen, arsenic has long been reported to cause cancers of the lung,

urinary bladder, kidney, skin, and prostate. Approximately 100 million people are chronically exposed to arsenic in drinking water at levels higher than 50 ppb (Moon et al. 2012). As Chen et al. reported in 2011, arsenic exposure via drinking water at levels between 10 and 300 ppb could induce inimical ramifications including neurological complications, respiratory, hepatic and renal dysfunctions, skin lesions, diabetes, cardiovascular diseases, etc. One of the most distinguishable manifestations of arsenic exposure is skin abnormality. Generally, skin lesions such as melanosis, keratosis, and black foot disease may develop 5–10 years after chronic arsenic exposure. Furthermore the ability of arsenic to readily cross the blood-brain barrier makes the brain especially vulnerable to its toxic effects. Exposed populations may experience difficulties in learning and maintaining concentration. Although the pituitary gland is especially susceptible, arsenic has the ability to deposit in all parts of the brain, thus negatively impacting brain development, learning, and even sustained concentration (Sanchez-Pena et al. 2010).

Epigenetics

The exact mechanism of arsenic toxicity is still not fully understood, although convincing evidence supporting the role of genotoxicity and cytotoxicity has long been studied. Since arsenic lacks the characteristics of a traditional mutagen, recent advances in elucidating the mechanism of arsenic toxicity have shifted toward epigenetic modifications, including DNA methylation and histone posttranslational modifications (PTMs). Epigenetics is broadly defined as the heritable and sometimes reversible change in gene expression and function in the absence of any change in the DNA sequence (Bitto et al. 2014). In order for gene expression to occur, DNA must unravel and become accessible to transcriptional factors. The accessibility of the DNA may be influenced by various mechanisms; histone methylation and acetylation are instrumental in impinging the chromatin structure. Histone methylation is an important tool in distinguishing genes that are or are not transcribed. Lysine (K) and arginine (R) are the only two residues capable of being methylated although lysine methylation is most commonly observed for H3 and H4. Both lysine and arginine are positively charged and retain hydrophobic/basic features. While arginine can only be mono- and di-methylated, lysine can be mono-, di-, and trimethylated. Methylation of lysines or arginines does not alter the positive charge of the amino acid, while acetylation of lysines neutralizes the positive charge.

Although most literature emphasizes the effect of arsenic on DNA methylation, a growing body of evidence is pointing toward understanding arsenic's ability to induce alterations in histone methylation both in vivo and in vitro. In order for the massive amount of DNA (the length of a car) to fit inside a nucleus which is typically 6 um in diameter, the DNA must be tightly compressed into structures called chromatin. The basic unit of a chromatin is the nucleosome, which consists of 147 base pairs of double-stranded DNA circled 1.65 times around an octamer of alkaline proteins called histones (Luger et al. 1997). Histones are composed of five major groups: H1, H2A, H2B, H3, and H4. Two copies of each of the four canonical

histones are required to make up the octamer core, while H1 stabilizes and serves as the linkage between nucleosomes and is involved in the higher-order chromatin structures. Besides the globular core, N-terminal tails that protrude from the nucleosome can have up to 60 different residues, each of which can be readily modified through methylation, acetylation, biotinylation, ubiquitination, phosphorylation, etc. Although globular core modifications have also been identified through mass spectrometry, the N-terminal tail alterations, especially methylation and acetylation, have been more comprehensively studied. Similar to DNA methylation, cofactor S-adenosyl methionine (SAM) acts as the methyl donor. Histone methyltransferases specific for lysine and arginine serve to replace each of the hydrogen on the NH2, NH2+, or NH3 groups with a methyl group. The methylation state (mono-, di-, or tri-) on each residue will prompt different responses for the chromatin structure and the recruitment of transcriptional modifiers (Bannister and Kouzarides 2011). Interestingly, current studies based on the epigenetic effects of arsenic have only reported on the methylation of lysine residues on H3K4, H3K9, H3K27, and H3K36, yet results have been largely inconsistent; see Table 1 (Howe and Gamble 2016).

Table 1 Arsenic's effect on histone methylation in different tissues

Methylation marker	Direction of change	Specific residue	Type of tissue	References
H3K4	Increase	H3K4me2, H3K4me3	A549 cells, steel workers, RWPE1 cells, female Bangladeshi adults	Zhou et al. (2008, 2009) and Chervona et al. (2012)
	Decrease	H3K4me3	Male Bangladeshi adults	Chervona et al. (2012)
H3K9	Increase	H3K9me2, H3K9me3	A549 cells, male and female Bangladeshi adults, Jurkat and CCRF-CEM	Zhou et al. (2008, 2009), Chervona et al. (2012), and Pournara et al. (2016)
	Decrease	H3K9me3	CD4+ cells from Argentinian women	Pournara et al. (2016)
H3K27	Increase	H3K27me3	PMBC of Bangladeshi women, female-derived mouse embryonic fibroblasts	Chervonat et al. (2012) and Kim et al. (2012)
	Decrease	H3K27me3	A549 cells, PBMC of Bangladeshi men	Zhou et al. (2008) and Chervona et al. (2012)
H3K36	Increase	H3K36me2, H3K27me3	PBMCs of Bangladeshi men, A549 cells, lymphocytes of Chinese adults	Howe et al. (2016), Zhou et al. (2008), and Ma et al. (2016)
	Decrease	H3K36me2, H3K27me3 among men	A549 cells, male Bangladeshi adults, HEK293T and HaCaT	Chervona et al. (2012), Ma et al. (2016), and Zhou et al. (2008)

The table summarizes the inconsistencies found in histone methylation after treatment with arsenic. Different tissues induce different posttranslational modifications

H3K4 and H3K36 are associated with transcriptional activation (Bannister and Kouzarides 2011; Wagner and Carpenter 2012). As (III) increased global levels of H3K4me2 in A549 cells and H3K4me3 in RWPE1 cells (Zhou et al. 2008, 2009). A positive correlation between arsenic and H3K4me3 was found in peripheral blood mononuclear cells (PBMC) of Bangladeshi adult women (Chervona et al. 2012). Due to their role in DNA repair, dysregulation in H3K36me2 and H3K36me3 has been implicated in several cancer types (Jha et al. 2014; Kuo et al. 2011; Pfister et al. 2015). Arsenic (III) led to an increase in H3K36me3 in both A549 cells and lymphocytic cells from Chinese adult participants (Zhou et al. 2008; Ma et al. 2016). In contrast to H3K4 and H3K36, H3K9 and H3K27 are typically associated with transcriptional repression, although all four are important for genomic stability (Rivera et al. 2015; Yuan et al. 2011). In A549 cells, As (III) boosted H3K9me2 and H3K9me3 levels. Similarly positive correlations in H3K9me2 and H3K9me3 were detected in the PBMC of adult Bangladeshi participants and CD4+ cells from acute lymphoblastic leukemia patients, respectively (Chervona et al. 2012; Pournara et al. 2016). As for H3K27, two studies involving adult females and in vitro female mouse embryonic fibroblasts showed increase in H3K27me3 after As (III) treatment (Chervona et al. 2012; Kim et al. 2012).

Despite seemingly sufficient evidence supporting the above findings, there are also plenty of studies suggesting the opposite. Specifically, two studies have reported that arsenic differentially influences the level of H3K4me3 based on sex (Chervona et al. 2012; Tyler et al. 2015). Although, as pointed out earlier, female participants showed positive correlation between H3K4me3 and As (III), male participants showed the exact opposite (Chervona et al. 2012). Similarly for H3K9 methylation, despite increase in H3K9me2 and H3K9me3 found in in vivo and in vitro data, a study based on Argentinian women showed an inverse association between H3K9me3 and urinary arsenic (Howe and Gamble 2016; Pournara et al. 2016). Another epidemiology study based in China also observed negative association between urinary As and H3K9me2 in lymphocytic cells (Ma et al. 2016). Interestingly, the level of H3K9me2 seems to change in response to the duration of exposure. The same study by Ma et al. (2016) assessed the response in male-derived human keratinocytes (HaCat) and female-derived human embryonic kidney cells (HEK293) and found that after initial reduction in H3K9me2, both cell lines showed elevation after 8–12 h. This may be an important insight into the discrepancies between in vitro and epidemiological findings. Additionally, the differential effect of arsenic based on sex is also shown in H3K27me3. In contrast to the female participants and female-derived mouse embryonic fibroblasts, H3K27me3 was reduced in A549 cells and male participants in the same study group (Chervona et al. 2012; Zhou et al. 2008). In another study using HepG2 cells, H3K27me3 levels stayed constant after As (III) treatment (Ramirez et al. 2008). Lastly, like the other three posttranslational modifications, H3K36 methylation also demonstrated controversial results. Unlike the positive correlation found in A549 cells and Chinese adult lymphocytes, H3K36me3 levels decreased in a dose-dependent manner in HEK293 and HaCat cells (Ma et al. 2016; Zhou et al. 2008).

Histone acetylation is one of the most extensively studied posttranslational modifications. The negatively charged DNA is tightly bound to the positively charged histone side chain. And upon acetylation, histone acetyltransferase (HAT) transfers an acetyl group from acetyl coenzyme A (AcCOA) to a lysine residue thereby removing the positive charge, loosens bound DNA, and stimulates the accessibility of the promoter region. Unlike histone methylation, less histone acetylation modifications are observed after arsenic treatment. The two most prominent examples are H4K16 acetylation (H4K16ac) and H3K9 acetylation (H3K9ac); see Table 2. Not only is H4K16ac critical for the compact state of higher-order chromatin structure, but this PTM also plays important roles in the interaction between chromatin fibers and nonhistone proteins, DNA damage response, gene expression, and cell cycle control (Chen et al. 2015; Shogren-Knaak et al. 2006). Due to its extensive functions in maintaining genomic stability, dysregulation in H4K16ac is implicated in many cancers (Shogren-Knaak et al. 2006). The effect of arsenic on H4K16ac and H3K9ac levels is analogous to the inconsistencies found in histone methylation. H4K16ac has been shown to be stagnant in female-derived human embryonic kidney and UROTsa cells, elevated in human neonatal keratinocytes, and reduced in another set of studies using UROTsa cells (Herbert et al. 2014; Rahman et al. 2015; Shogren-Knaak et al. 2006). H3K9ac is vital for immune response and recruitment of nucleotide excision repair (NER) factors for DNA repair. Findings on H3K9ac level after arsenic exposure are similarly dispersed as the H4K16ac results. In HepG2, Jurkat, and CCRF-CEM cells, As (III) triggered increase in this PTM (Pournara et al. 2016; Ramirez et al. 2008). On the other hand, H3K9ac was decreased in UROTsa and human embryonic kidney cells, as well as in PMBCs of

Table 2 Arsenic's effect on histone acetylation in different tissues

Acetylation marker	Direction of change	Type of tissue	References
H4K16	No change	Female-derived human embryonic kidney cells	Rahman et al. (2015)
	Increase	Used primary human neonatal keratinocytes	Herbert et al. (2014)
	Decrease	UROTsa cells	Chervona et al. (2012) and Rahman et al. (2015)
H3K9	No change	Lymphocytes from Chinese adults, CD4+ and CD8+ cells from Argentinian women	Ma et al. (2016) and Pournara et al. (2016)
	Increase	HepG2 cells, Jurkat and CCRF-CEM cells	Ramirez et al. (2008) and Pournara et al. (2016)
	Decrease	UROTsa cells from female human ureter, PBMCs of Bangladeshi adults	Rahman et al. (2015) aand Chervona et al. (2012)

The table summarizes the inconsistencies found in histone acetylation after treatment with arsenic. Different tissues induce different posttranslational modifications

adult participants from Bangladesh (Chervona et al. 2012; Rahman et al. 2015). Furthermore, epidemiological studies in both China and Argentina showed no significant correlation between with H3K9ac and As in lymphocytes and immune cells (Howe and Gamble 2016; Ma et al. 2016; Pournara et al. 2016).

The discrepancies found in the canonical histone posttranslational modifications may be attributed by several factors. First, the content and dosage for the studies are varied. Although As (III) can be generated from both As2O3 and NaAsO2, As2O3 may be more toxic. Furthermore, as shown in the H3K9me2 example, PTM levels drastically changed direction after 8–12 h of exposure. In other words, short-term in vitro data may not be an accurate reflection of chronically exposed patients. Second, the degree of arsenic metabolism may differ between cell lines. Differences in methodology such as use of different cell lines, treatment sources, and exposure times all contribute to the lack of consistency among the featured studies. Third, not only are the sources of treatment for in vitro and epidemiological studies different, exposure pathways are also limited to inhalation and drinking water. However, an important aspect of arsenic exposure comes from everyday diet. The method of ingestion may greatly affect the outcome in histone PTMs due to differences in metabolic mechanisms. The lack of consistency in experimental design undermines the precision of the research results and hinders direct comparisons between the studies. On the other hand, the use of different cell lines, participants, dosage, total treatment time, and route of exposure provides us with an array of information which is an important basis for deepening our understanding of arsenic-induced histone posttranslational modifications.

Besides inducing posttranslational histone modifications, arsenic has recently been shown to alter the expression of histone genes themselves. There are three distinct groups of histone genes: replication dependent, replication independent, and those that encode tissue-specific isotypes (Lanzotti et al. 2002; Marzluff 2005). Replication-dependent histone genes encode for canonical histones and are the only genes that form a stem-loop structure at the 3′ end instead of with a poly (A) tail (Dominski and Marzluff 1999). The stem loop consists of 26 highly conserved nucleotides and serves as the binding site for the stem-loop binding protein (SLBP). SLBP engages in pre-mRNA processing and accompanies mature histone mRNA to the cytoplasm to ensure efficient translation (Marzluff 2005; Whitfield et al. 2004). In consideration to its many important roles, the loss of SLPB would nonetheless invoke serious consequences such as abnormal processing of canonical histone mRNAs. Aberrant levels of histone gene expression induced by arsenic were first identified in PBMCs; in this study, 8% of all altered histone genes were canonical histones (Brocato et al. 2014). Brocato et al. specifically looked at the changes in H3.1 gene expression. As predicted, in both human lung carcinoma cells (BL-41) and PMBCs, 1uM of arsenic exposure prompted a double-fold increase in poly-adenylated H3.1 mRNA level (Brocato et al. 2014, 2015). Previous studies have suggested that the loss of stem-loop binding protein may contribute to the poly-adenylation of canonical histones (Brocato et al. 2015; Lanzotti et al. 2002). A sample pathway is presented in Fig. 1. This hypothesis was confirmed when arsenic-induced SLBP reduction due to promoter repression resulted in increased

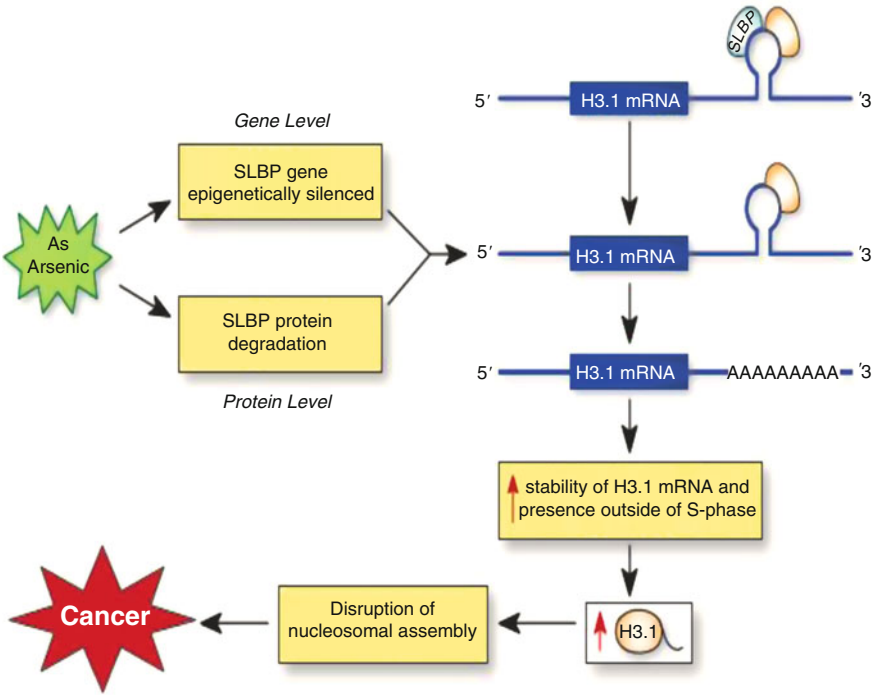

Fig. 1 Arsenic-induced depletion of SLBP and subsequent aberrant polyadenylation of H3.1 mRNA and its effects (Source comes from Brocato et al. 2015. The pathway illustrates the potential mechanism of arsenic-induced SLBP reduction and subsequent polyadenylation of H3.1 mRNA)

expression of polyadenylated H3.1 mRNA (Brocato et al. 2014). Because poly (A) tail provides stability and prolonged half-life, the initial increase in canonical histone genes may be due to increased histone mRNA stability through replacing the stem-loop structure with a poly (A) tail. More importantly, studies are finding that polyadenylation of H3.1 mRNA may be a potential mechanism for arsenic carcinogenesis as H3.1-transfected cells showed significant increase in colony formation/anchorage-independent growth, hence cell transformation (Brocato et al. 2014). Despite convincing evidence of arsenic-induced SLBP reduction and subsequent increase in H3.1 mRNA polyadenylation, the exact mechanism still requires further examination.

Nutrition

Despite natural occurrences in groundwater, advancement in technology and the increase in the usage of arsenic containing drugs, fertilizers, insecticides, herbicides, etc., fuel the increase in human exposure to this detrimental carcinogen. In addition to drinking water, exposure to vast amount of inorganic arsenic also occurs through

Table 3 Arsenic concentration in contaminated soil, water, and food crops

Country	Soil ($mgkg^{-1}$)	Groundwater (μgL^{-1})	Rice ($mgkg^{-1}$)	Vegetables ($mgkg^{-1}$)	References
Bangladesh	5.64–29.5	290–710	0.02–3.40	0.09–2.03	Das et al. (2002)
India	5.9–9.7	320–640	0.33–0.45	NA	Bhattacharya et al. (2010)
China	129	329	1.09	2.38	Liu et al. (2010)
Nepal	6.1–16.7	ND-1014	0.18	0.33	Dahal et al. (2008)
Taiwan	7.92–12.7	13.8–881	NA	0.01–0.15	Kar et al. (2013)
Limits	20[a]	100[b]	1[c]	1[c]	Bhattacharya et al. (2010)

Source comes from Fayiga et al. (2016). Amount of arsenic found in each four different categories. The limits for each category are set by:
[a]European Union limit for agricultural soil
[b]FAO limit for irrigation water
[c]WHO limit for food crops

food contamination, which is especially prominent in grains, rice, and vegetables. Contaminated groundwater used to irrigate crops and soil will pollute the topsoil, which will eventually lead to the accumulation of significant amounts of arsenic in cultivated vegetables and crops (Fayiga and Saha 2016). One of the most efficient accumulators of arsenic is rice. Rice serves as a staple food for approximately half the world's population, mainly in Southeast Asia, Latin America, and sub-Saharan Africa (Azam et al. 2016). According to an investigation carried out by FAO, the average consumption of rice in China, India, and the United States is approximately 212 g/day, 195 g/day, and 25 g/day, respectively (FAO 2010). As the second most commonly cultivated crop, extensive arsenic contamination may elicit massive public health issues. Table 3 from Fayiga and Saha documents countries that use arsenic-contaminated irrigation water above the FAO limit. Not only does arsenic-contaminated water reduce plant growth and yield, but also accumulation of the carcinogenic compound poses devastating threat to the food consumers, which include both humans and animals. Figure 2 illustrates the increasing emphasis on arsenic and nutrition based on the escalating number of publications throughout the years.

Another anthropogenic source of arsenic contamination comes from arsenic-based drugs such as roxarsone and nitarsone, which release unnecessary sources of inorganic arsenic, MMA, and DMA (Nigra et al. 2016). These drugs have been deliberately and consistently fed to chicken and turkey in the United States for decades in effort to improve weight gain and meat pigmentation and prevent diseases such as histomoniasis and coccidiosis (Abraham et al. 2013; Chapman and Johnson 2002). In fact, 88% of chickens on the market had been treated with roxarsone back in 2010 (Nachman et al. 2012). A study in 2013 reported that based on the average poultry consumption in the United States, the consumers would be receiving a 1.44^10–6 mg/kg daily dose of iAs, which would consequently result in 124 excess bladder and lung cancer cases (Nachman et al. 2013). After

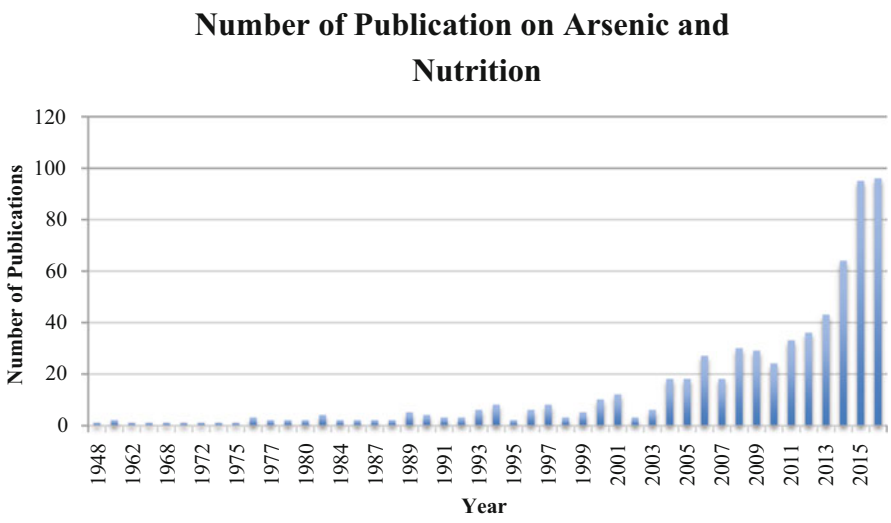

Fig. 2 Increasing number of publications on arsenic and nutrition. The graph is generated based on key word searches on PubMed between 1848 and 2016. The graph illustrates increasing importance placed on arsenic and nutrition over the years

concluding that increase of iAs in poultry was directly induced by feed additives, the FDA subsequently eliminated marketing support for the use of roxarsone and nitarsone in 2013 and 2015, respectively. However, due to decades of chronic arsenic exposure, the extent of the public health issue remain unknown as studies have shown that cancer risks remain elevated years after the exposure was eliminated.

Besides rice and poultry, arsenic tarnishes a wide array of foods such as fish, milk, eggs, fruits, vegetables, etc.; see Fig. 3. Although results are somewhat inconsistent, studies have suggested that selenium, vitamins, tea, Zn, etc., may reduce the damaging health effects of arsenic (Yu et al. 2016). On the other hand, unhealthy diets such as high sugar and high fat have been shown to exacerbate the effect of arsenic exposure. One study exposed pregnant mice to arsenic-contaminated drinking water. After giving birth, a subset of offspring continued to receive the As treatment, while high-sugar and high-fat foods were provided for all mice throughout the experiment (Ditzel et al. 2016). Overall, mice that were exposed to arsenic-contaminated drinking water before and after birth demonstrated more adverse outcomes, as illustrated by insulin resistance, obesity, and high triglycerides in blood compared to the other groups. This study not only illustrated the synergistic effect of arsenic and other food sources, which prompts alarming attention regarding lifestyle factors for those already exposed, but also indicated that neonatal exposure to arsenic may lead to health consequences later on. The prevalence of arsenic in drinking water coupled with prevailing risk through everyday diet further complicates public health outlook for those exposed to arsenic.

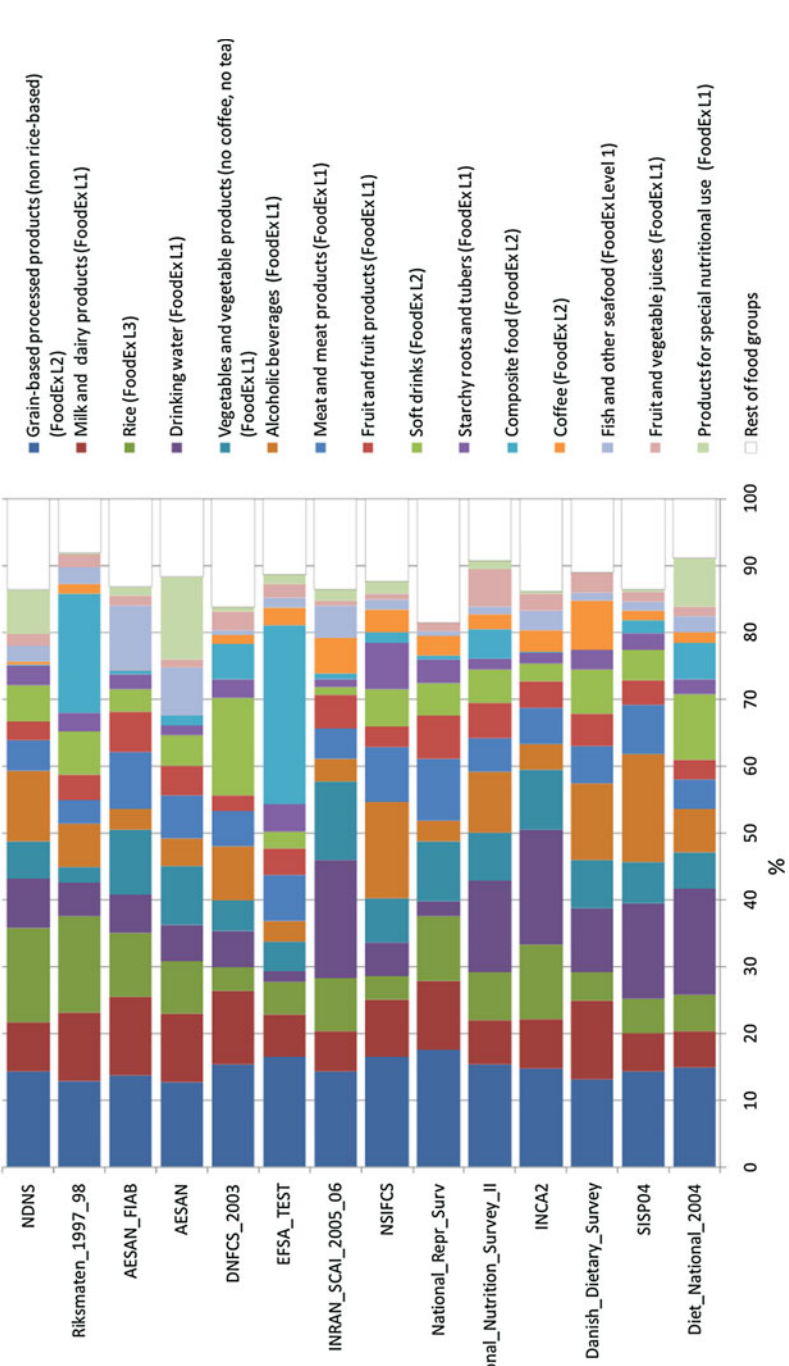

Fig. 3 Percent of dietary iAs in each type of food for adults in Europe. The source is from EFSA (2014). The table illustrates the percent of iAs in various food groups for adult Europeans. The *left* of the graph depicts the study used to collect the data

Conclusion

More than 200 million people are exposed to arsenic either through drinking water, inhalation, or diet. As a class I human carcinogen, exposure to arsenic has been documented to cause neurodevelopmental deficits; cardiovascular disease; human skin, lung, and bladder cancers; etc. Although the exact mechanism of arsenic toxicity and carcinogenicity is still unclear, evidence supporting the role of histone posttranslational modification and histone gene expression reviewed in this chapter provides new insights for our understanding and further investigation. Due to the pervasive presence of arsenic in food and water, policy makers as well as individuals must actively seek preventative ways of reducing chronic exposure. Responsible agencies such as the FDA, lawmakers, and food producers must engage in rigorous monitoring of arsenic contamination and enforce the removal from the market if standards are violated. Physicians and medical professionals should inform the public of potential sources of arsenic and recommend safe substitutions, especially for pregnant women and infants. And most importantly, individuals must take up the responsibility of educating themselves regarding the source in effort to avoid and reduce exposure and further contamination.

Dictionary of Terms

- **Canonical histones** – Most common histones found in the nucleus; H3 is an example of canonical histone.
- **Histone methyltransferase** – An enzyme that carries a methyl group from SAM to a histone lysine or arginine reside.
- **Histomoniasis** – Also called blackhead disease. It is a parasitic disease found in birds.
- **Coccidiosis** – Parasitic infection in the intestinal tract of animals, commonly seen in turkeys.
- **Anthropogenic activity** – Most commonly refers to environmental issues related to human activity such as the use of pesticides, herbicides, etc.
- **Histone N-terminal tail** – N-terminus is the beginning of a protein or peptide and terminated with –NH2. The histone N-terminal tail is the location of posttranslational modifications.

Key Facts of Arsenic Exposure and Application

- Albertus Magnus was the first person to isolate arsenic in 1250.
- Arsenic is a class I human carcinogen, categorized by the International Agency for Cancer Research.
- Inorganic As (III) is the most toxic form for human exposure.
- Set by the US Environmental Protection Agency, the maximum As concentration in drinking water is 10 parts per billion.

- Degree of As toxicity is based on individual metabolic rate/ability.
- Inorganic arsenic can be found in various food sources such as fish, milk, eggs, fruits, and vegetables but mainly in rice and poultry.
- Arsenic can be used in a variety of areas including medicine, alloys, and pesticides.

Summary Points

- Around 200 million people worldwide are exposed to arsenic either through inhalation, drinking water, and/or food.
- Besides DNA methylation which has been extensively studied, arsenic has been shown to effectively alter histone tail modifications such as histone methylation and acetylation.
- Canonical histone gene expression may be directly altered by arsenic exposure.
- Studies have shown that after arsenic exposure, total canonical histone gene expression can go up by twofold. H3.1 is one of these canonical histones.
- Arsenic may degrade stem-loop binding protein as a mechanism of inducing polyadenylated histone H3.1 mRNA.
- Key regulators, lawmakers, food producers, medical professionals, as well as the public must rigorously monitor arsenic contamination in food and enforce the removal from the market if standards are violated.

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