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Review

Health Effects Associated with Inhalation of Airborne Arsenic Arising from Mining Operations

Rachael Martin [1,*], Kim Dowling [1], Dora Pearce [1,2], James Sillitoe [3] and Singarayer Florentine [1]

[1] Faculty of Science, Federation University Australia, University Drive, Mt Helen, VIC 3350, Australia; E-Mails: k.dowling@federation.edu.au (K.D.); dpearce@unimelb.edu.au (D.P.); s.florentine@federation.edu.au (S.F.)

[2] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Level 3, 207 Bouverie Street, Melbourne, VIC 3010, Australia

[3] Research and Innovation, Federation University Australia, University Drive, Mt Helen, VIC 3350, Australia; E-Mail: j.sillitoe@federation.edu.au

* Author to whom correspondence should be addressed; E-Mail: r.martin@federation.edu.au; Tel.: +61-353-276-402; Fax: +61-353-279-017.

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Abstract: Arsenic in dust and aerosol generated by mining, mineral processing and metallurgical extraction industries, is a serious threat to human populations throughout the world. Major sources of contamination include smelting operations, coal combustion, hard rock mining, as well as their associated waste products, including fly ash, mine wastes and tailings. The number of uncontained arsenic-rich mine waste sites throughout the world is of growing concern, as is the number of people at risk of exposure. Inhalation exposures to arsenic-bearing dusts and aerosol, in both occupational and environmental settings, have been definitively linked to increased systemic uptake, as well as carcinogenic and non-carcinogenic health outcomes. It is therefore becoming increasingly important to identify human populations and sensitive sub-populations at risk of exposure, and to better understand the modes of action for pulmonary arsenic toxicity and carcinogenesis. In this paper we explore the contribution of smelting, coal combustion, hard rock mining and their associated waste products to atmospheric arsenic. We also report on the current understanding of the health effects of inhaled arsenic, citing results from various toxicological, biomedical and epidemiological studies. This review is particularly aimed at

those researchers engaged in the distinct, but complementary areas of arsenic research within the multidisciplinary field of medical geology.

Keywords: aerosol; arsenic; coal; dust; epidemiology; cancer; mining; smelting; tailings

1. Introduction

Arsenic is the 20th most abundant element in the earth's crust and may be released into the atmosphere as a result of natural processes and anthropogenic activities [1]. Environmental arsenic is released via chemical and physical weathering processes, biological activity and volcanic emissions, while anthropogenic sources include mining, metal smelting and burning of coal. Annual global arsenic emissions are estimated to be 24,000 t [2], with around 60% originating from copper smelting and coal combustion alone [3]. In some urban and highly industrialized areas, less than 2% of the atmospheric arsenic inputs originate from natural sources [3].

Emissions of arsenic-bearing particulate matter (PM) are of particular concern for human populations living in proximity to an emission source. Arsenic and inorganic arsenic compounds are classified as Group 1 carcinogens and are associated with cancers of the lung, bladder, kidney, skin, liver and prostate [2]. It should be noted that within the general population, inhalation is only considered a minor exposure pathway for inorganic arsenic compounds, and ingestion is considered the primary exposure pathway [2]. However, populations living in the vicinity of an arsenic emission source have an increased risk of additional exposure through inhalation of arsenic-contaminated particulates [4–9].

Despite their substantial contribution to global atmospheric arsenic species, mining operations play an understudied role in the generation of contaminated dust and aerosols [10]. To identify some of the emerging issues associated with arsenic in particulate matter this review presents key findings from a range of distinct but complimentary areas of research within the multidisciplinary field of medical geology, including geochemistry, toxicology, biomedicine and epidemiology. We will discuss two key themes: (i) the origin, occurrence and current monitoring of mining-related arsenic in the atmosphere; and (ii) the current understanding of the health effects of inhaled arsenic, citing results from various toxicological, biomedical and epidemiological studies.

2. Mining Operations as a Source of Airborne Arsenic

For brevity, the term "mining operations" is utilized throughout this paper to include all mining and mining-related activities including extraction, mechanical and high temperature processing, transportation, and storage of mine waste products. To compare or describe the impacts of different types of mining operations, specific mining terms are used.

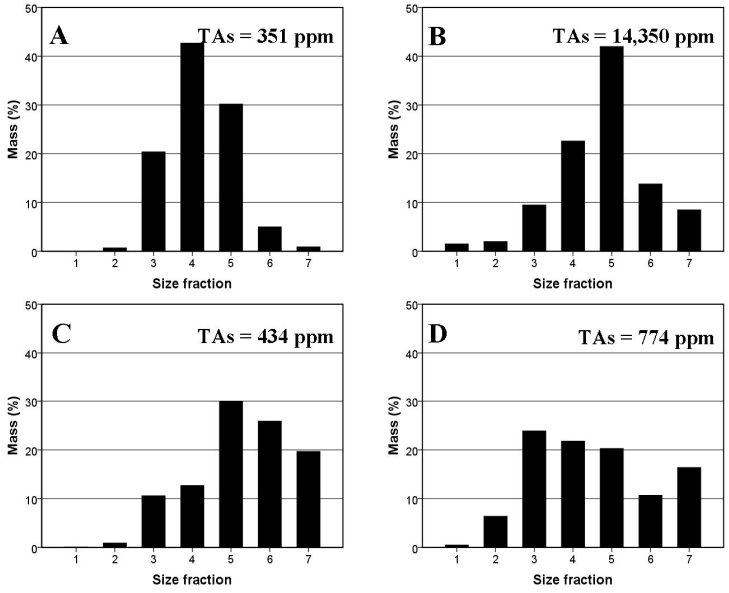
2.1. Generation of Dust and Aerosol: An Overview

Mining operations release arsenic into the atmosphere via wind-borne dispersal of arsenic-laden particulates [11], with dust being the dominant transport medium for these emissions [3]. Active mining operations produce and/or mobilize dust to varying degrees in all stages of the mining process:

during the removal of overburden; in all aspects of the handling of ore, including its extraction, transportation and further processing; as part of waste disposal operations; and as a result of wind erosion of exposed areas [12–15]. Mining operations associated with an opencut coal mining operation in India, for example, generate 9.4 t of dust per day [16]. Active and abandoned mine tailings, mine sites and processing facilities also represent important sources of dust [17–22].

To demonstrate the potential for mine tailings to generate dust emissions, Figure 1 compares the total mass distribution (%) by particle size fraction of four different types of arsenic-bearing gold mine tailings in an historical mining region in regional Victoria, Australia. Comparable with the findings of a Californian-based study [21], our data suggest that mine tailings in this locality may contain up to 45% dust (particles ≤ 100 μm), as recorded in the fine-grained battery sand (Figure 1C). Future analysis may reveal the relationship between total arsenic concentration and particle size in these mine tailings samples.

Figure 1. Percentage mass distribution by particle size fraction for historical mine tailings including: (**A**) coarse battery sand; (**B**) red calcine sand; (**C**) fine battery sand; (**D**) composite coarse/fine battery sand. Size fractions Size fractions 1: >2000 μm; 2: 1000–2000 μm; 3: 500–1000 μm; 4: 250–500 μm; 5: 100–250 μm; 6: 53–100 μm; 7: ≤53 μm. Total arsenic (TAs) concentration (ppm) of each mine waste sample is also shown. (Our results obtained using a modified sieving method protocol described by Kim *et al.* [21]).



While most mining operations generate coarse dust, high temperature processes, such as smelting and coal combustion, are typically associated with fine particulates, accumulation-mode particulates, and vapors [10]. Coarse particles (≥2.5 μm diameter) are produced by mechanical processes such as the crushing and grinding of ore, and may be resuspended via wind erosion and mechanical disturbance [10,23]. Fine (≤2.5 μm) and accumulation mode particles (0.1–2.5 μm) are produced during smelting and combustion through the condensation of high temperature vapors, diffusion and coagulation [10,23].

Coarse and fine particulates have widely varying atmospheric residence times, and as a result, widely varying distributions. Arsenic associated with the fine fraction may remain in the atmosphere between seven [24] and up to 10 days (reviewed in Matschullat [3]), and can travel long distances [25].

Coarse particulates have a much shorter atmospheric residence time, typically minutes to hours due to a larger settling velocity [10]. Particle segregation of mine waste can occur during airborne transport, thereby reducing the size of the individual particles deposited [17]. In addition to mining operation type, atmospheric contaminant concentrations are also influenced by the distance and position of a sampling site in relation to the source, the height of the source (e.g., chimney or tailings pile), the type of dust suppression or flue gas cleaning, the exit velocity of the flue gas, and the prevailing wind speed [26] as well as changes in industrial technologies [27].

2.2. Origin, Production and Release of Particulate Arsenic

It is widely accepted that global atmospheric arsenic fluxes are dominated by mining-related industries involving high temperature processing [3]. An estimated 60% of global anthropogenically-generated atmospheric arsenic is attributed to copper smelting and coal combustion, with annual outputs of 12,080 and 6240 t respectively [3]. While it is well-documented that mine tailings represent major sources of arsenic-contaminated dust throughout the world [10,19,28,29], the contribution by these sources to total global atmospheric arsenic fluxes is yet to be assessed [3]. The occurrence of arsenic-bearing phases in unprocessed ore and the generation of particulate arsenic by different types of mining processes will be reviewed in the following sub-sections.

2.2.1. Smelting Operations

Gold, copper, lead and zinc ores typically contain arsenic-bearing minerals such as pyrite (FeS_2), galena (PbS), chalcopyrite ($CuFeS_2$) and the dominant arsenic-bearing mineral, arsenopyrite (FeAsS), which contains approximately 46% arsenic by weight [2]. The high temperature purification of arsenic-bearing ores during smelting and roasting volatilizes arsenic [30,31], and the resultant vapors may contain up to 95% arsenic [32]. Arsenic in close proximity to smelters and roasters is typically arsenic trioxide in particulate form [33,34], and depending on the feed material and extraction process, flue dusts can contain up to 30% arsenic trioxide [35,36]. Fugitive emissions of particulate arsenic may occur at various stages of high temperature processing, as well as during the transport and storage of ores, concentrates and waste heaps [37].

Although high efficiency control devices are often employed in smelters to reduce emissions, the quantity of total arsenic emitted from a single smelting operation can be substantially high. For example, around 300 t of arsenic are emitted annually from the Copper Smelter Complex Bor, in eastern Serbia [38]. Furthermore, uncontained smelter flue dusts represent an important potential source of airborne arsenic, compared with other secondary smelter by-products [39]. Over a period of 20 years, a copper smelter in Japan produced an estimated 9000 t of arsenic-rich flue dust (19.5 wt % of As) which is currently stockpiled at an undisclosed location in Japan [32]. Stockpiled by-products of the smelting process with high arsenic content present ongoing sources for redistribution.

2.2.2. Coal Combustion

Coal is a complex mixture of organic and inorganic compounds formed over millions of years from successive layers of fallen vegetation. Coal contains detectable levels of the vast majority of elements in the periodic table, including arsenic and other potentially toxic and environmentally sensitive

elements [40,41]. Although much of the arsenic in coal is associated with the inorganic or mineral fraction (such as pyrite and other sulphide minerals), a significant portion is associated with organic matter [42,43]. Arsenic concentrations in coal typically range between 1–10 and 1500 $mg \cdot kg^{-1}$, but concentrations as high as 32,000 $mg \cdot kg^{-1}$ have been reported in some super-enriched coal samples (reviewed in Kang *et al.* [42]). Arsenic in coal occurs in three non-exclusive distinct forms: arsenical pyrite, arsenopyrite and arsenate species [44,45].

During coal combustion, arsenic readily oxidizes to form arsenic oxide vapor [44] which combines with calcium oxide and condenses on the surface of fly ash particles in the form of calcium arsenate [46–48]. The inverse correlation between arsenic concentration and particle size which has been observed demonstrates that volatilized arsenic preferentially adsorbs or condenses on the finer particles [31]. Furthermore, higher combustion temperatures result in higher concentrations of particulate arsenic. For example, an increase in total arsenic concentration in PM_1 (particulate matter <1 μm) from 0.07 to 0.25 $mg \cdot m^{-3}$ at respective temperatures of 1100 and 1400 °C was reported in one study [48].

Solid by-products of the combustion process, including fly ash and bottom ash, are major sinks for arsenic. An estimated 90% to 100% of arsenic is captured in coal combustion by-products [49], with a preferential enrichment (up to 80%) for the fly ash component (reviewed in Yudovich and Ketris [50]). Removal efficiencies of arsenic by particulate control systems such as cyclones, electrostatic precipitators, wet scrubbers and fabric filters range between 43% and 99%, depending on the control device used [51]. An early study by Ondov *et al.* [52] reported that arsenic penetration through electrostatic precipitators (ESP) and wet scrubbers may be as high as 8.8% and 7.5%, respectively. Despite the widespread use of ESPs in Europe, a reported 575 t of arsenic were emitted from the combustion of coal during 1990 [35]. Similarly, in China around 550 t of arsenic were emitted from coal-fired power plants during 2007 [51]. Arsenic emissions arising from coal burning industries are an ongoing issue of global significance.

2.2.3. Mine Tailings

Fugitive dust emissions from mine wastes and mechanical processes associated with the hard rock mining industry such as crushing of sulphide ore and concentrates, and mechanical disturbance and wind erosion of uncontained mine tailings [10,53] are also associated with elevated levels of arsenic [17–19,54]. This is not surprising given that mine wastes and tailings are often characterized by extremely high arsenic concentrations. Concentrations in tailings ranging between 2250 and 21,400 $mg \cdot kg^{-1}$ have been detected in the Zimapan mining district in Mexico [55], and in some historical gold mine waste disposal areas in Victoria, Australia, concentrations of up to 15,000 $mg \cdot kg^{-1}$ have been recorded [56]. The preferential enrichment of arsenic in the finer size fraction in mine tailings [21,57] suggests that re-suspended dusts are characterized by higher arsenic content than the material from which it is suspended.

2.3. A Global Issue

The magnitude of the problems associated with arsenic contamination from mining operations is a serious ongoing issue in many localities throughout the world, and there are no indications of abatement. If the projected increase in global copper production over the next 20 years is correct [58], it could be reasonably expected that smelter emissions, and the generation of flue dust and other

associated waste products, will also increase [39]. Furthermore, despite an overall increase in the number of coal plant retirements in some localities [59], the global demand for coal is predicted to rise at a rate of 1.3% per year, from 147 quadrillion Btu in 2010 to 180 quadrillion Btu in 2020 and 220 quadrillion Btu in 2040 [60]. Expansion of coal consumption reflects substantial increases in China and India [60]. In India, arsenic-contaminated fly ash from coal combustion processes occupies more than 65,000 acres, rendering the surrounding land unsuitable for agriculture [61].

Although not increasing substantially, the number of abandoned mines worldwide runs into millions [62], and their impact is likely to increase due to population growth and urban expansion. In the United States of America, 80% of an estimated 46,000 known abandoned mine sites require further investigation and/or remediation [63]. In Australia, there are more than 50,000 registered abandoned mines ranging from isolated minor surface works to more extensive and complex sites [64,65] In Mexico, the area affected by mining activities is estimated to be over 21.7 million hectares [66]. Each year in China the mining industry produces wastes that occupy an additional 2000 ha [67], and around 4000 Mt of tailings are stockpiled on land that is urgently needed for other purposes [68].

Given the widespread geographical distribution of arsenic-rich mine wastes and the global reliance on smelting and coal combustion for various products and services, the systematic characterization and ongoing monitoring of particulate arsenic generated by mining operations are becoming increasingly important for reliably determining the impacts on human health and the environment [45].

3. Monitoring and Assessment

A number of monitoring and assessment studies have been undertaken for different purposes: (i) to identify the dominant emissions sources of arsenic; (ii) to predict the potential contribution of an identified arsenic emission source to the atmosphere; and (iii) to identify the airborne arsenic species (Table 1). For monitoring and reporting purposes, atmospheric total arsenic concentrations are often compared with the annual mean target value of 6 $ng \cdot m^{-3}$, as set by current European Union air quality standards [69]. According to the World Health Organization (WHO) [70], the excess lifetime risk of contracting lung cancer if continuously exposed to 6.6 $ng \cdot m^{-3}$ is 1:100,000.

The different methodologies used to collect PM from mining operations are reflected in the contrasting size fractions and reporting units listed in Table 1. Air monitoring programs use various types of sampling equipment to collect PM, and the arsenic content of the PM is typically reported in terms of $ng \cdot m^{-3}$. Measurement of total suspended particulates (TSP) was the United States of America standard for atmospheric aerosol until the discovery of the relationship between particle size and lung deposition of inhaled particles [71].

The smaller the particle, the deeper it will travel into the respiratory tract (RT) and PM_{10} (particulate matter $\leq$10 μm) represents the upper limit for tracheobronchial and alveolar deposition in the human lung [72]. To meet the new PM_{10} health-based standard (adopted by the USA, Europe and elsewhere during the mid to late 1980s), collection devices such as the cascade impactor and multiple orifice uniform deposit impactor (MOUDI) have been used in various atmospheric monitoring studies [10,18,54]. These sampling systems are designed to collect a pre-selected suite of aerodynamically-fractionated samples which enables a systematic investigation into the arsenic content of particulates of interest to health. The relationship between particle size and human exposure will be reviewed in detail in Section 4.

Particulate arsenic may also be measured in size-fractionated mine waste samples generated through dry sieving bulk samples [21,57]. Similar to the cascade impactor mentioned above, this method facilitates a systematic characterization of collected mine waste samples but reports the concentrations in terms of $\mu g \cdot g^{-1}$. While this technique cannot provide a quantitative assessment of atmospheric arsenic at a particular location, the data may be useful for predicting potential particulate arsenic emissions from the source.

Atmospheric arsenic concentrations vary between localities and the type of emission source (Table 1). The following sub-sections examine the contribution of each emission source to atmospheric arsenic levels in various localities throughout the world.

3.1. Smelting

Much of the atmospheric arsenic research and monitoring published to date has focused on emissions from smelting operations. This reflects the dominant contribution by smelter emissions to global anthropogenic atmospheric arsenic inputs. As reviewed in Matschulatt [3], copper and zinc smelting activities contribute of 12,800 and 2210 t of arsenic respectively into the atmosphere per year, whereas steel production contributes a comparatively lower annual quantity of 60 t per annum. It should also be noted that in some industrial localities, smelting and other processes associated with the manufacturing of ceramic materials represent important sources of arsenic in the atmosphere [27]. Smelting operations produce the greatest localized air and soil arsenic concentrations while coal combustion distributes arsenic to the air in substantially lower concentrations over a wider area [73].

In the vast majority of case studies summarized in Table 1, concentrations exceeded, and in some cases, greatly exceeded, the annual WHO-prescribed target value [70]. In one extreme case, an average concentration of 330 $ng \cdot m^{-3}$ was reported in TSP collected approximately 1 km from a complex lead-copper smelter in Belgium [4]. Similarly, a maximum arsenic concentration of 572.3 $ng \cdot m^{-3}$ (mean, 93.9 $ng \cdot m^{-3}$) was recorded in TSP collected in the vicinity of a smelter in Walsall, UK, during an air monitoring program conducted between 1972 and 1989 [26]. Interestingly, a declining trend in atmospheric arsenic levels was reported at all of the UK monitoring locations, except the Walsall smelter site [26]. The authors postulated that widespread industrial switching from coal combustion to oil and gas as a domestic energy source for space heating was the probable cause for the overall decline in atmospheric arsenic in the UK [26]. Similar results were recorded in an industrial area in Spain, whereby reductions in atmospheric arsenic concentrations were significantly associated with decreases in industrial activities, specifically the production of ceramic materials [27].

Although the quantification of arsenic in TSP provides one measurement of arsenic contamination in the atmosphere, this measurement may underestimate the respiratory health risks to nearby communities due to the inverse relationship between particle size and arsenic content. After the introduction of particle size-selective criteria, various studies have measured and compared arsenic content in the PM_{10} and $PM_{2.5}$ fractions collected in the vicinity of smelting operations (Table 1). Data from these studies suggest a general trend for preferential enrichment in $PM_{2.5}$ [74–76]. For example, an air monitoring study conducted approximately 3.5 km from the Huelva copper smelter in southwestern Spain found that 85% of the total arsenic concentration in the PM_{10} size fraction was concentrated in $PM_{2.5}$ [77]. Similar studies conducted in the same locality yielded comparable results [74,75]. In contrast to these findings, one study reported that $PM_{2.5}$ collected in the vicinity of a

copper smelter in Tacoma, WA, USA, contained only 37% of the total arsenic in the PM_{10} fraction (calculated from Polissar *et al.* [78]). These results highlight the importance of site-specific investigations during health-based risk assessments.

The greatest atmospheric arsenic levels generated by smelting operations occur in close proximity to the smelter, and decrease with increasing distance from the source [4,76,77]. Multiple reports suggest that the maximum concentrations are typically found within 1 km of the smelter site [4,78–81]. Furthermore, declines in concentrations have been observed over a relatively short distances. For example, atmospheric arsenic levels at a distance of 1 and 2.5 km from a complex copper-lead smelter in Belgium were 330 and 75 $ng \cdot m^{-3}$, respectively [4]. These results were supported by a complementary soil-based study that documented an exponential decline in soil arsenic and heavy metal concentrations within 1 km of a lead smelter in the Czech Republic, followed by a less-steep decrease between 1 and 6 km [37].

Meteorological variables, particularly surface wind circulation, play a critical role in determining the transport and spatial distribution of the pollution plume from smelting operations [82]. Contrary to the general trend between concentration and distance from the emission source, Serbula *et al.* [81] reported average arsenic levels of 131.4, 51.3 and 93.7 $ng \cdot m^{-3}$ at respective increasing distances of 0.8 (town park), 1.9 (institute) and 2.5 km (Jugopetrol) from a copper smelter in Bor, eastern Serbia. Compared with the mid-distance sampling location (institute), the farthest sampling location (Jugopetrol, which is downwind from the pollution source) experienced high-frequency exposure to the emissions as a result of dominant WNW and NW winds. To further highlight the impact of prevailing wind direction, the maximum concentration reported at Jugopetrol was equal to the maximum recorded at the sampling location closest to the smelter (Table 1). Similar relationships between atmospheric arsenic (and other metals), and surface wind characteristics in the vicinity of copper smelters have been documented [74,83]. In addition to wind direction, wind speed plays an important role in determining particulate arsenic distribution from smelting operations. The greatest concentrations of arsenic (and other metallic elements) emitted from the copper smelter in Bor occurred during calm conditions (wind speed less than 0.5 m/s) [38]. Low wind speeds inhibit the dispersal of local pollution away from the emission source and can therefore lead to very high localized concentrations of atmospheric pollutants [38].

3.2. Coal Combustion

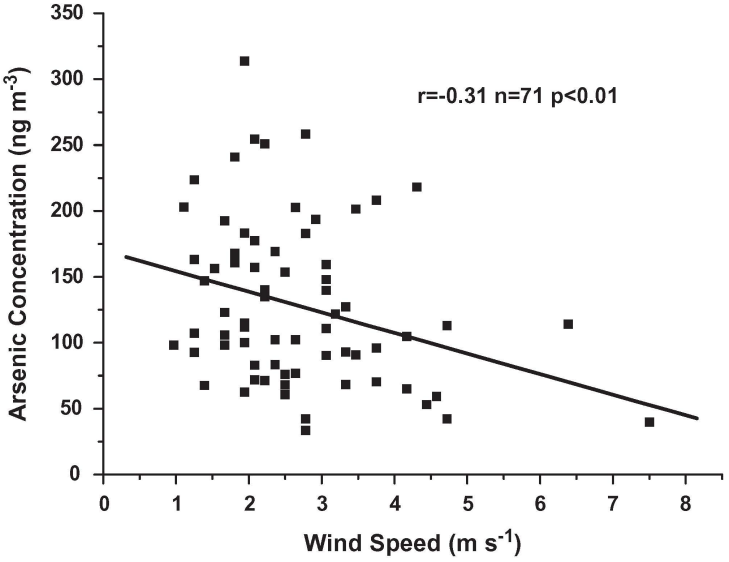
Global coal combustion contributes an estimated 6240 t of arsenic to the atmosphere each year, equating to approximately half the contribution from copper smelting [3]. Atmospheric arsenic concentrations in coal combustion emissions are generally lower and typically distributed over a wider area. As a possible result of these two factors, coal combustion as a source of atmospheric arsenic has received less attention in the literature compared with copper/zinc/lead smelting.

Much of the research into coal combustion as a source of atmospheric arsenic has been undertaken in China (Table 1), and a recent review article listed this source as one of the key contributors to atmospheric arsenic in this country [84]. The mean atmospheric arsenic concentration for 32 localities across China was 51 ± 67 $ng \cdot m^{-3}$ (range, 0.03–200 $ng \cdot m^{-3}$). However, in heavily industrialized areas such as around Beijing, concentrations may be substantially greater [9].

Given that high temperature processes are typically associated with fine and accumulation-mode particles, arsenic levels in PM_{10} and $PM_{2.5}$ are frequently reported [85–88]. Comparable average PM_{10} arsenic concentrations were recorded in Beijing (58.3 $ng \cdot m^{-3}$) and nearby Taiyuan (43.36 $ng \cdot m^{-3}$) whereas the average $PM_{2.5}$ concentration in Ji'nan (40 $ng \cdot m^{-3}$) was almost double that of Beijing (23.08 $ng \cdot m^{-3}$ Table 1). These values greatly exceed the recommended target value of 6 $ng \cdot m^{-3}$.

Wind conditions appear to play an important role in the dispersal of atmospheric arsenic emitted by coal combustion sources [9]. Consistent with the trend found in the vicinity of smelting operations, one study [9] reported a statistically significant negative correlation between atmospheric arsenic concentration and wind speed in Beijing, China ($R = -0.31$, $p < 0.01$; Figure 2).

Figure 2. Relationship between total atmospheric arsenic concentration and wind speed in Beijing, China, for the period February 2009 to March 2011. Reprinted from Yang *et al.* [9] with permission from Elsevier.



3.3. Mine Tailings

Research into mine tailings as a source of atmospheric arsenic has gained momentum in the last decade. Mine tailings have the potential to generate high levels of dust with extremely high atmospheric arsenic concentrations, particularly in arid and semi-arid environments [10]. The Rosh Pinah lead and zinc mine and ore processing plant in Namibia reported a maximum arsenic concentration of 9140 $ng \cdot m^{-3}$ (median, 4970 $ng \cdot m^{-3}$) in wind-blown dust from tailings that cover more than 60 ha and are more than 20 m high [89]. Comparable with the trend observed around smelting operations, the impact of mine tailings on atmospheric arsenic levels are typically greatest at the source [11,17,18,54]. At the Rosh Pinah mine and ore processing plant atmospheric arsenic levels decreased from 4970 $ng \cdot m^{-3}$ at the tailings dam to 60 $ng \cdot m^{-3}$ at a distance of 2.5 km from the mine [89]. This relationship is most likely a result of the short atmospheric residence time of coarse particles (≥2.5 μm) typically found in mine tailings [10].

Arsenic enrichment in the finer fractions of size-fractionated mine tailings has been reported [19,21,57]. Although these findings are not reflective of actual atmospheric arsenic emissions from a particular source, the finer size fractions are more susceptible to wind-borne transport and are most likely to be re-suspended by wind or mechanical disturbance. Kim *et al.* [21] examined the distribution of arsenic

concentration as a function of particle size in mine tailings samples collected from two different localities in the Randsburg historic mining district in south-central California, USA. Although there were distinct differences in the arsenic distributions amongst the wastes, there were obvious inverse relationships between grain size and arsenic concentration. The high arsenic content recorded in the dust size fraction of each sample (range, 356–8210 ppm) illustrates the potential of their corresponding sources to generate potentially hazardous emissions [21].

The effects of seasonality on particulate arsenic emissions from mine tailings have also been investigated. Meteorological factors associated with different seasons, especially rainfall and temperature, have been shown to have a dramatic impact on arsenic mobility through the air [54,90]. During the dry summer months in the City of Lavrion, Greece, concentrations of arsenic in PM_{10} increased dramatically (more than 6 times) compared with concentrations during late winter [54,90]. Similarly, a study in Aznalcazar, southwest Spain, found that sporadic rainfall and low convective atmospheric dynamics during the late winter were associated with relatively low re-suspension of PM from heavy metal mining wastes [54]. During summer, the combination of intensive convective circulation and low rainfall facilitates surface drying leading to enhanced re-suspension of PM. Low rainfall and decreased humidity lead to increased atmospheric particulates, and therefore, increased atmospheric arsenic concentration [90].

3.4. Arsenic Speciation in Particulate Matter

Environmental arsenic exists in four oxidation states including As(V), As(III), As(0) and As(-III) [91,92]. The most common forms of arsenic in the environment include the trivalent (arsenite) and pentavalent (arsenate) species [93], and they are often found occurring together [94,95]. Under oxidizing conditions, such as in surface soils and water, arsenic typically occurs in the pentavalent form [92], whereas in sufficiently reducing environments, or in the presence of a reducing agent, arsenite is the dominant form [94,96]. It is widely recognized that arsenite species have greater mobility in the environment [97] and are reported to be 25 to 60 times more toxic than the corresponding pentavalent forms [98]. Since the oxidation state of arsenic in soil, water, and other environmental matrices is one of the key factors governing toxicity, speciation analysis is of interest in human exposure studies.

Speciation analysis has been used widely for the identification and quantification of arsenic species in bulk samples of surface soils and mine wastes [94,95,99,100]. However, comparatively less work has been conducted in relation to arsenic speciation in atmospheric PM generated by mining operations [9,18,44,74–76,83]. Research conducted to date indicates that both arsenate and arsenite may co-exist in smelter, coal combustion and gold roaster emissions [9,44,45,74–76,83,94] although reported levels for the trivalent species are generally much lower than those for the arsenates (Table 1). For example, arsenate and arsenite concentrations in coal combustion emissions in China were 67 and 4.7 $ng \cdot m^{-3}$, respectively [9]. Similarly, Oliveira *et al.* [83] reported respective arsenate and arsenite concentrations of 10.4 and 1.2 $ng \cdot m^{-3}$ in copper smelter emissions in Spain. The presence of arsenite in smelter emissions may result from the reduction of arsenate by aerosol sulphur dioxide S(IV) complexes during transport of the emission plume [101].

Airborne monitoring programs combined with speciation analysis demonstrate clearly that airborne arsenic is a serious and ongoing issue in mining communities and heavily industrialized areas throughout the world.

Table 1. Summary of the average, minimum and maximum total arsenic (TAs) concentrations recorded in particulate matter (PM) from various mining operations, including smelting, coal combustion and mine waste. Values for TAs are expressed as nanogram per cubic meter ($ng \cdot m^{-3}$) unless otherwise specified. Where applicable, all units of distance measurement have been converted to metric system.

Source	Location	Size Fraction (Time Period)	Distance (km)	TAs (Min–Max)	As(III) (Min–Max)	As(V) (Min–Max)	Ref.
Pb-Cu smelter	Belgium	TSP (May–September 1978)	<1	330			[4]
			2.5	75			
Cu smelter	Tacoma, WA, USA	$PM_{2.5–10}$ (January 1985–Febrary 1986)	0.8	153.9 ± 269.4			[78]
		$PM_{2.5}$ (January 1985–Febrary 1986)		90.2 ± 170.7			
		$PM_{2.5–10}$ (January 1985–Febrary 1986)	10	3.7 ± 9.6			
		$PM_{2.5}$ (January 1985–Febrary 1986)		4.4 ± 3.6			
Cu smelter	Walsall, UK	TSP	<1	93.9 ± 89.7 (10.6–572.3)			[26]
Cu smelter	Quillota, Central Chile	PM_{10} (December 1999–November 2000)	≤40	32.5 ± 33.7 (1.7–196)			[102]
Cu smelter	Huelva, southwest Spain	TSP (January–December 2000)	2	12.3 ± 1.6 (3.0–33.8)	1.2 ± 0.3 (0.3–1.8)	10.4 ± 1.8 (2.1–30.6)	[83]
Cu smelter	Huelva, southwest Spain	PM_{10} (2001)	2	7.7 (1.6–29.4)	1.2 (0.6–2.2)	6.5 (0.01–25.7)	[75]
		PM_{10} (2002)		9.9 (1.3–79.8)	2.1 (0.4–3.4)	7.8 (0.01–56.2)	
Cu smelter	Huelva, southwest Spain	$PM_{2.5}$ (2001)	2	6.4 (0.8–30.2)	0.9 (0.01–1.6)	5.0 (0.01–25.3)	[74]
		$PM_{2.5}$ (2002)		7.9 (1.0–56.6)	1.4 (0.1–2.7)	6.6 (0.01–56.2)	
Cu smelter	Huelva, southwest Spain	PM_{10} (2004)	3.5	4.67 (max: 22.4)			[77]
		$PM_{2.5}$ (2004)	3.5	3.04 (max: 19.0)			
		PM_{10} (2005)	3.5	10.6 (max: 62.1)			
		$PM_{2.5}$ (2005)	3.5	9.18 (max: 60.3)			
Cu mining and smelter complex	Bor, eastern Serbia	PM_{10} (15–year average; 1994–2008)	0.8	131.4 (<2–669)			[81]
			1.9	51.3 (<2–356)			
			2.5	93.7 (<2–670)			
Cu mining and smelter complex	Bor, eastern Serbia	PM_{10} (24 March–1 April 2009)	0.65	32.97 ± 53.63 (2.4–149)			[38]
Ferromanganese plant	Dunkirk, France	PM_{10} (January 2003–March 2005)	2	5.1 ± 5.4 (0.5–35.1)			[103]
Cu smelter	Huelva, southwest Spain	$PM_{2.5}$ (16–22 October 2009)	5	2.1 ± 4.2 (0–20)			[82]

Table 1. *Cont.*

Source	Location	Size Fraction (Time Period)	Distance (km)	TAs (Min–Max)	As(III) (Min–Max)	As(V) (Min–Max)	Ref.
Complex Cu smelter	Tsumeb, Namibia	PM_{10} (2010–2011)	Smelter boundary	310			[80]
			Low exposure site	190			
Coal combustion	Beijing, China	PM_{10} (2001 and 2006)	12 sites across city	58.3 ± 60			[86]
Coal combustion	Beijing, China	TSP (February 2009–March 2011)	n.a.	130 ± 60 (30–310)	4.7 ± 3.6 (0.73–20)	67 ± 35 (14–250)	[9]
Coal combustion	Beijing, China	$PM_{2.5}$ (December 2012–January 2013)	n.a.	23.08			[85]
Coal combustion	Taiyuan, China	PM_{10} (2–16 March 2004)	n.a.	43.36 ± 27.61 (11.98–82.55)			[87]
Coal combustion	Ji'nan, eastern China	$PM_{2.5}$ (17–28 September 2010)	5	40 ± 40			[88]
Coal mine (raw coal)	Southwest Virginia, USA	PM_{10} (7 August 2008)	0.3	0.958			[12]
			1.6	0.735			
Gold mine tailings	Rodalquilar, southeastern Spain	PM_{10}	n.a.	1581 ppm			[19]
		Mechanically re-suspended in lab, n=2		1368 ppm			
Pb-Zn mine	Rosh Pinah, Namibia	TSP	0	4970 (2800–9140)			[89]
		Tailings dam	0	280 (130–920)			
		Ore treatment plant	1.5	30 (30–70)			
			2.5	60 (20–80)			
Cu-Pb-Zn mine tailings	Aznalcazar, South Spain	TSP (20 May–27 December 1998)	0	221 (4.9–2681)			[54]
			0.5	69 (2–921)			
Historical Ag-Pb mine tailings	City of Lavrion, Greece	PM_{10} Overall average	1	520 (1–3031)			[90]
		Winter		115 (1–791)			
		Summer		909 (121–3031)			
Abandoned Au mine tailings	Nova Scotia, Canada	>16 µm (2004)	0	8200		Present but not quantified	[18]
		16–8 µm (2004)		2020			
		8–4 µm (2004)		631			
		4–2 µm (2004)		337			
		2–1 µm (2004)		58.3			
		1–0.5 µm (2004)		13.3			

Table 1. *Cont.*

Source	Location	Size Fraction (Time Period)	Distance (km)	TAs (Min–Max)	As(III) (Min–Max)	As(V) (Min–Max)	Ref.
Former Au mine tailings	Yellowknife, Canada	TSP (July–September 2004)	<1	19 (1–76)			[104]
		PM_{10} (July–September 2004)		6 (1–15)			
Different mine waste types	Butte, Montana, USA	PM_{10} Mine waste type 1	n.a.	406 ppm			[57]
		PM_{10} Mine waste type 2		467 ppm			
		PM_{10} Mine waste type 3		469 ppm			
		PM_{10} Mine waste type 4		769 ppm			
Ag-Au mine tailings	Descarga mine tailings site, USA	>2830 µm	n.a.	203 ppm			[21]
		2830–1700 µm		452 ppm			
		1700–1000 µm		976 ppm			
		1000–500 µm		1870 ppm			
		500–250 µm		2650 ppm			
		250–125 µm		3790 ppm			
		125–75 µm		3650 ppm			
		75–45 µm		4720 ppm			
		45–32 µm		7060 ppm			
		32–20 µm		8210 ppm			
Pb-Zn mine waste	Oklahoma, USA	PM2.5 (July–September 2005)	<1	0.64 ± 0.48			[11]
			5	0.62 ± 0.32			
			18	0.56 ± 0.33			
Cu-Au-Ag mine waste	Rio Tinto mines, Spain	Total bulk deposition (March 2009–February 2010/March 2010–February 2011)	0	4.4/2.1 $mg \cdot m^{-2}$			[17]
			0.5	0.7/0.5 $mg \cdot m^{-2}$			
			1.5	0.7/1.0 $mg \cdot m^{-2}$			
Smelter & coal combustion	China (various localities)	Average of PM10, PM2.5 TSP and dust		51.0 ± 67			[84]
Smelter & other industries	Aspropyrgyros Greece	TSP (December 2004–June 2006)	n.a.	3.4 ± 0.3	<0.2	3.2 ± 0.4	[76]
		PM_{10}–$PM_{2.5}$ (December 2004–June 2006)		1.9 ± 0.3	<0.2	1.7 ± 0.4	
		$PM_{2.5}$ (December 2004–June 2006)		1.1 ± 0.3	<0.2	1.0 ± 0.4	

4. Human Exposure

Communities living in the vicinity of mining operations may be exposed to airborne arsenic-contaminated particulates and be at risk of health deterioration though absorption after dermal and eye contact, or by ingestion after inhalation [28]. However, arsenic absorption through the skin following dermal and eye contact is a minor contributor compared with ingestion and inhalation exposures [25] and will not be further discussed here. Furthermore, incidental ingestion of arsenic-contaminated particulates, usually as a result of contaminated food or water supplies, has been the most thoroughly investigated pathway, and its significant range of adverse effects have been well documented following acute, intermediate and chronic exposures [25], negating the need for further detailed review here.

For the general population, ingestion is typically considered the primary exposure pathway to arsenic, and inhalation of arsenic bearing PM has been considered to be a minor exposure route [2]. The relatively neglected topic of inhalation exposure with consequent issues linked to airborne PM containing arsenic species from proximate mining industries needs to be addressed. For example, exposure assessments of communities living in the vicinity of smelting and coal combustion operations suggest that inhalation may play a similar, if not more important role than ingestion, in the overall exposure to airborne particulate arsenic [4,105–107]. In addition, it has been shown that children are particularly susceptible to inhalation exposure due to: (i) their increased likelihood of coming into contact with dust [78]; and (ii) children inhale a greater volume of air than adults relative to their size [108].

Therefore, in the following sections we will consider some of the ways in which inhaled arsenic-contaminated particulates generated by mining operations may lead to systemic absorption, toxicity, and arsenic-related disease endpoints. In order to understand how arsenic becomes mobile (or bioavailable) and exerts its toxic effects in the human body, we will begin with a discussion on the fate of inhaled particles in the RT with particular emphasis on the role that particle size plays in determining the ultimate absorption or defense mechanisms.

4.1. Deposition Location and Particle Clearance from the Respiratory Tract (RT)

The location and manner in which PM is deposited in the RT are critical for understanding how the arsenic-bearing particles might react with different lung constituents. When PM is inhaled, a proportion of the particles are retained while the remainder are expelled via exhalation. Retained particles are deposited in different regions of the RT according to their size [109–111] and as a general rule, the smaller the particle the deeper it will penetrate into the RT and the longer it will be retained (Table 2; [72,112]). To protect the body against foreign materials, the human respiratory system has developed a range of physiological lines of defense [113,114]. We will review the deposition location of inhaled particles as a function of particle size, the methods of clearance from each location, and pathways for absorption. When referring to the different "deposition regions", we use the morphometric model described by the International Commission on Radiological Protection [115]. This model divides the human RT into three major anatomical regions: (i) the extra-thoracic; (ii) the tracheobronchial, and; (iii) the alveolar, which are modeled deposition locations for the inhalable, thoracic and respirable particulate size fractions, respectively [116].

Table 2. Deposition of PM_{10} in different regions of the human respiratory tract [115,116] as a function of particle size (data from Newman [72]), including the estimated retention time of the particle size in each deposition location (data from Bailey [112]).

Anatomical Region (Corresponding Particulate Size Fraction)	PM Size (μm)	Deposition Location	Retention Time
Extra-thoracic (Inhalable)	7–10	Nasal passage	1 day; small fraction may be retained for longer
	5–7	Pharynx	Few minutes
Tracheobronchial (Thoracic)	3–5	Trachea	Few minutes
	2–3	Bronchi	Hours to weeks
	1.0–2.5	Terminal bronchioles	Hours to weeks
Alveolar (Respirable)	0.5–1.0	Alveoli	50 to 7000 days

4.1.1. Extra-Thoracic Region (Inhalable Particulate Fraction)

The inhalable particulate fraction (particles up to 10 μm in size) consists of particles that can be deposited into the extra-thoracic region and become trapped in the nasal cavity [109], mouth [116] and pharynx [117]. The vast majority of particles deposited in the extra-thoracic region are removed via a combination of nose-blowing, sneezing and mucociliary transport to the gastrointestinal (GI) tract [117]. Nose-blowing clears from 0.5% to 50% of particles from the front of the nose, while the remainder is slowly cleared into the GI tract [117]. Particles in the pharynx may reach the GI tract within one hour following deposition [117], and a very small proportion (around 0.05%) may be absorbed directly via the pharynx epithelium and cleared into the blood or lymphatic system [117]. Ingestion is therefore the dominant exposure pathway to particles deposited in the extra-thoracic region.

4.1.2. Tracheobronchial Region (Thoracic Particulate Fraction)

The thoracic particulate fraction is comprised of particles (1–5 μm in size) that penetrate the extra-thoracic region [116] and deposit in the tracheobronchial region. This region consists of the trachea, bronchi and terminal bronchioles [115]. Particles deposited here are of particular importance because lung carcinomas occur preferentially in the bronchial airways [110]. Particles trapped in the mucous produced by the bronchial epithelial cells are typically cleared by mucociliary transport into the throat, and then expectorated or swallowed [28,114,118]. While it is generally accepted that mucociliary transport is the principal clearance mechanism in the first 24 h [118], the rate of clearance depends upon on the clearance velocity of the mucous, particle shape, charge and surface geochemistry [119]. Furthermore, the ciliary movement is ineffective if the mucous is not of the correct viscosity due to illness or pharmacological action [109]. Other clearance mechanisms from the tracheobronchial region include coughing, absorption through airway epithelium into the blood or lymphatic system, and phagocytosis [113,118], and depending on the method of clearance, particles can be retained in the RT for weeks (Table 2; [112]). As described in sub-Section 4.2, the solubility of the particle plays an important role in determining which clearance mechanism is employed and the duration of the retention.

4.1.3. Alveolar Region (Respirable Particulate Fraction)

Airborne particles ≤1 μm can be deeply inhaled into the unciliated airways of the lung (the alveolar region) and absorbed directly into the pulmonary circulation system [113]. Alternatively, these particles may be phagocytosed and cleared by alveolar macrophages, and then either absorbed into regional lymph nodes via lymphatic vessels [120] or transported into the ciliated airways and cleared via mucociliary transport [121]. This latter process may take weeks to months to complete [122]. Alveolar macrophages are important cells of the immune system, exhibiting major phagocytic abilities and in response to inflammatory reactions, release reactive oxygen species (ROS). Under normal exposure conditions, the components of the inflammatory reaction interact synergistically with ROS to eliminate foreign material from the respiratory system [123].

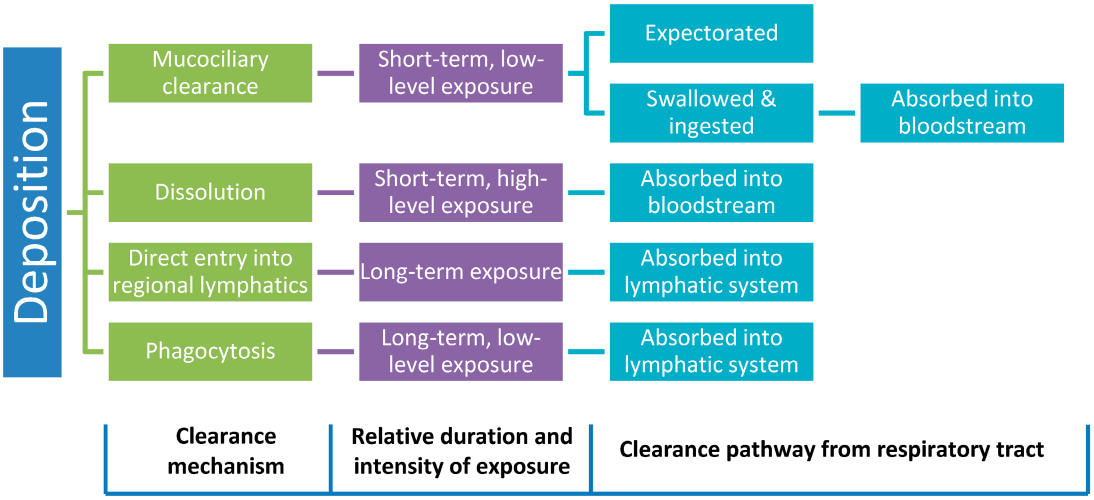
4.2. Effects of Exposure Duration and Solubility

Variation in the solubility of different arsenic compounds is important for exposure and risk assessment studies [57]. In the case of short-term inhalation exposure (minutes to hours), the number of particles in the RT decreases over time until all particles have been cleared via phagocytosis and/or mucociliary transport [124]. Deposited particles containing soluble arsenic compounds may expose nearby cells to a high concentration of arsenic [125], which rapidly declines as the dissolved arsenic is removed from the lungs [126] via absorptive mechanisms through the airway epithelium [127]. Lantz *et al.* [128] proposed that this exposure regime would reduce the time for interaction with pulmonary cells and tissue. Less soluble particles on the other hand that are retained in the lung expose the target tissue to arsenic for a longer period of time (up to weeks), as observed in rodents after intratracheal instillation of inorganic arsenic compounds of varying solubility [125,126,129,130].

In the case of long-term exposure (days to years), a steady state between deposition and clearance will be reached and the retained fraction will remain in the lungs for most of the exposure period [110]. Consequently, retention of particles containing soluble and slightly soluble arsenic compounds, especially those particles deposited in the alveolar region and sequestered in the lymph nodes, may expose cells to low doses of arsenic for a prolonged period of time. It is frequently reported that long-term, low-level exposures to arsenic may be predictive of toxic effects [126,131,132] and the pathogenesis of lung diseases, such as lung carcinoma [130].

Figure 3 illustrates that following inhalation, arsenic can follow different pathways leading to systemic absorption, and each pathway is highly dependent upon particle solubility and method of clearance. Systemic exposure to arsenic may occur as a result of ingestion following mucociliary clearance, by dissolution in the lung fluid, direct entry into lymph nodes, or by phagocytosis. Systemic exposure to arsenic following inhalation of arsenic-bearing particulates could therefore be considered as a multi-pathway process with differing durations and intensities of exposure.

Figure 3. Potential pathways leading to systemic absorption of inhaled arsenic, including clearance mechanisms and their associated durations and intensities of exposure. Adapted from Wang [120].



4.3. Pulmonary Bioavailability of Inhaled Arsenic

The bioavailable fraction of arsenic is considered to be an important determinant of toxicity and the associated disease response [133]. The term bioavailability may be interpreted in a number of different ways [134], however and for the purposes of this review paper, the terms bioavailability and bioaccessibility will be used in accordance with the definitions prescribed by Ng *et al.* [135]. Briefly, the portion of a contaminant that is absorbed into the body following exposure is referred to as the bioavailable fraction and is typically measured *in vivo* [135]. Bioaccessibility on the other hand refers to the soluble fraction of a compound following *in vitro* gastrointestinal or pulmonary extraction, and may be used as a surrogate for estimating the bioavailability of a contaminant [135].

In order to assess the relative risk of inhalation exposure to metal-laden particles of various origins, simulated lung fluids (SLF) such as Gamble's solution and artificial lysosomal fluids (ALF) have been used in various studies [136–139]. Gamble's solution is an electrolyte fluid similar in composition to that of interstitial fluid with a pH near 7.4, and aims to mimic the aqueous component of the lung [140]. ALF is analogous to the fluid produced by macrophages during phagocytosis [141] and has a pH of around 4.5 [137]. Biological fluid pH is an important parameter governing the solubility of arsenic and other metals. For example, arsenic solubility measured as a percentage of the total arsenic concentration of mine waste, was reported as 36.6% in simulated stomach fluid (pH 1.2) and 0.4% in SLF (pH 7.5) [57], suggesting that an acid medium is required for arsenic dissolution. When determining pulmonary arsenic bioaccessibility, it may therefore be prudent to also investigate the behavior of arsenic in the more acidic ALF solution.

A limited number of studies aimed at comparing the bioaccessibility of other metallic compounds in SLF and ALF solutions reported significantly higher dissolution rates of potentially toxic metals in ALF [137,139]. Conversely, Plumlee *et al.* [142] found that SLF (near-neutral pH) was effective in leaching arsenic from dust samples collected from a dry lake, and the oral and inhalation bioaccessible arsenic fractions found in these particular dust samples were comparable. While it is important to note

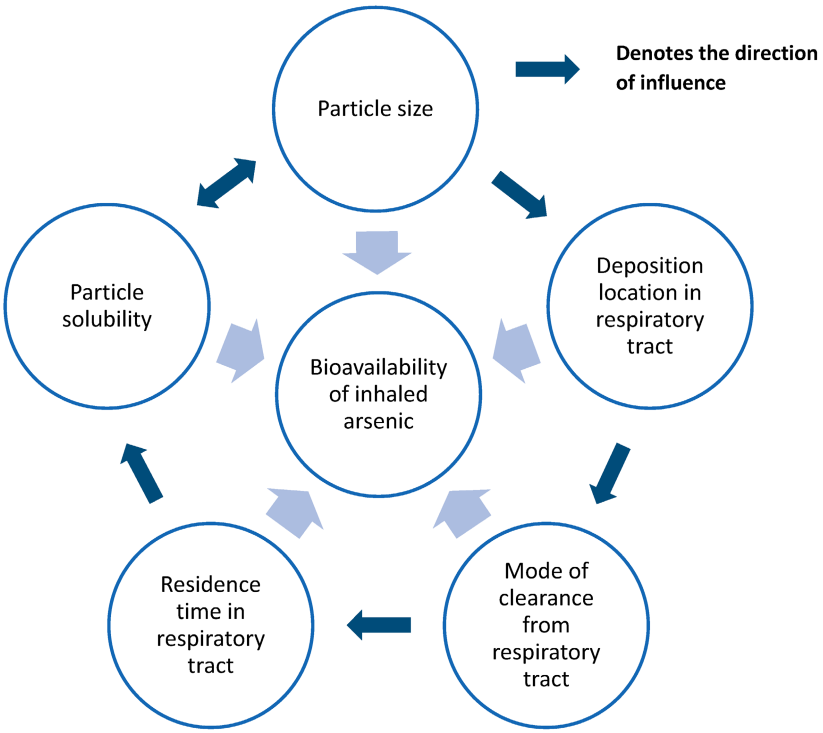
that the contrasting results between these studies highlight the importance of site-specific bioaccessibility assessments, they also indicate that certain arsenic species are relatively mobile at near-neutral conditions. Furthermore, the differences may also be attributed to the contrasting dissolution times used in each study: the mine waste and the dry lake dust samples underwent dissolution times of around 2 h [57] and 24 h [142], respectively. Given that fine particles may be retained in the RT for prolonged periods of time (Table 2), incubation duration is a particularly important parameter in bioaccessibility studies.

Pulmonary bioaccessibility tests may be more reliable predictors of bioavailability than the widely-used aqueous solubility tests, since Rhoads and Sanders [125] reported that arsenic, and other metals with low aqueous solubility, were highly soluble in the lungs of rats. A more recent study observed that SLF was more effective than deionized water at leaching arsenic in the ≤20 µm size fraction of soil impacted by fire, with leachate concentrations of 19 and 2 µg/L, respectively [143].

4.4. Summary

A summary of some of the key factors governing bioavailability of inhaled arsenic-bearing particles is proposed (Figure 4). Particle size governs the deposition location of inhaled particulates in the RT. Knowledge of the location and solubility of deposited particles is important for predicting the methods of clearance from and retention time in the RT, and therefore the types of lung fluids with which the particles may interact. Contact with pulmonary fluids can then release arsenic from inhalable arsenic-bearing particulates. Since the retention of arsenic in the body is predictive of toxicity and the pathogenesis of disease [126,131,132], the long-term pulmonary bioavailability of arsenic represents important consideration in the health risk assessment of populations living in mining-affected regions.

Figure 4. Diagrammatic representation of the interactions between key factors governing the pulmonary bioavailability of arsenic.



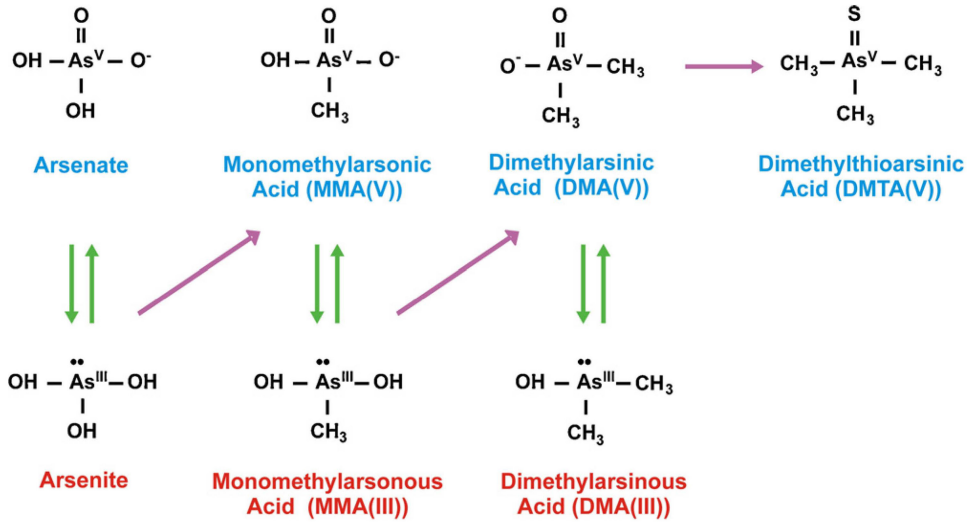
5. Importance of Metabolic Transformation in Arsenic Toxicity

5.1. Arsenic Biomethylation

The role of metabolism in arsenic toxicity has been the subject of several detailed reviews [144–149] therefore the following discussion will provide an overview of the key concepts only. Methylation is the major metabolic pathway for ingested inorganic arsenic in most mammals, and occurs via alternating reduction of pentavalent arsenic to the trivalent state, followed by oxidative addition of a methyl group [146,150–153]. Biotransformation of inorganic arsenicals occurs primarily in the liver with an estimated 70% [154] of metabolites readily excreted in urine [147,155–157]. The remaining portion deposits differentially in other target organs and tissues including the kidneys and the lungs, as well as keratinized tissues such as skin, nails, and hair [158–161].

In terms of clearly understanding arsenic biochemistry and toxicology, arsenic methylation presents a complex problem because the metabolic sequence (Figure 5) yields at least six distinct products, each with its own unique toxicology: arsenite, monomethylarsonic acid (MMA^V), monomethylarsonous acid (MMA^{III}), dimethylarsinic acid (DMA^V), dimethylarsinous acid (DMA^{III}) and dimethylthiolarsinic acid ($DMTA^V$) [146,162,163]. Various studies have demonstrated that the unstable trivalent intermediary products, MMA^{III} and DMA^{III}, are highly reactive and substantially more toxic than the inorganic and pentavalent compounds [149,152,162,164,165]. Arsenic methylation is therefore widely considered to be a bioactivation pathway rather than a detoxification process [144], with the resulting toxicity closely linked to the methylation status and valence state of the metabolites [166]. Therefore, understanding the arsenic biomethylation pathway is critical to elucidating its subsequent action as a toxin and carcinogen [167].

Figure 5. Metabolic pathway of inorganic arsenic. Reprinted from Chilakpati [168] with permission from Elsevier.



5.2. Oxidative Stress as a Mode of Action for Arsenic Carcinogenesis

Although several modes of action for arsenic carcinogenesis have been presented in the literature including oxidative stress, suppressed DNA repair, altered methylation patterns, genotoxicity and cell

proliferation [144], the oxidative stress theory has been intensively investigated and is supported by a substantial mass evidence [168–171]. Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS), or free radicals, and antioxidant defense mechanisms [172]. Free radicals are characterized by the presence of unpaired electrons and the associated reactivity can lead to tissue injury [173].

The first oxidative stress theory for arsenic proposed that a minor metabolite of DMA^V, dimethylarsine (a trivalent arsenic compound), is produced via a process of reduction *in vivo* [170], possibly following a reaction between DMA^{III} and specific coenzymes important for cellular respiration [174]. Dimethylarsine is estimated to be around 100 times more toxic than DMA^{III} which is a potent genotoxin in its own right [174]. Dimethylarsine can react with molecular oxygen forming the dimethylarsenic ($(CH_3)_2As$) radical, and the superoxide anion O_2^- [175]. Through the addition of another molecule of oxygen, the dimethylarsenic radical forms the dimethylarsenic peroxyl ($(CH_3)_2AsOO$) radical. Finally, the hydroxyl radical ($HO^{\cdot}$) can be produced via reaction with cellular iron and other transition metals [170,175].

Although an excessive production of ROS, such as superoxide anion and hydroxyl radical, is commonly associated with impaired cellular functions, DNA damage and carcinogenesis [144,175,176], the dimethylarsenic and/or dimethylarsenic peroxyl radicals were found to play a crucial role in lung-specific DNA damage, tumorigenesis [169–171,174,177] and general arsenic-induced toxicity [178]. The generation of oxidative stress as a potential mode of action of arsenic for its disease endpoints is an ongoing area of research and the associated complexities have been comprehensively reviewed [145,158,175,179].

5.3. The Human Lung as a Target Organ for Arsenic Toxicity

Remarkably, arsenic is the only reported human lung carcinogen for which there is sufficient evidence of pulmonary carcinogenicity as a result of both inhalation and ingestion exposures [25,180]. Smith *et al.* [181] reported that the relative risk of lung cancer following inhalation and ingestion of arsenic was independent of the exposure pathway. Distinguishing between the different routes of exposure is complicated not only by the arsenic transformations that take place in the body, but also the common target organs following the different exposure pathways [163]. The high variability in pulmonary solubility observed for different arsenic compounds [126,129,130] also represents a confounding factor.

For systemically absorbed arsenic, via inhalation or ingestion, research suggests that the pulmonary system may function as a target tissue for toxicity based on the observation that dimethylarsine is excreted as a gas from the circulation via the lungs [170,177]. High partial pressures of molecular oxygen in the lungs may promote dimethylarsenic and dimethylarsenic peroxyl radical formation as dimethylarsine is excreted and passed through to the respiratory system [144,158,175].

Less soluble arsenic compounds can be retained in the lung as observed in humans [182] and rodents [126,129,130]. According to Styblo *et al.* [152], human lung epithelial cells have very low arsenic methylation capacity *in vitro*, which may translate to a lower capacity to convert inorganic arsenic methylate arsenicals *in vivo*. A reduced capacity to methylate arsenicals could be associated with an increased risk of toxicity due to prolonged retention of inorganic arsenic in the lung [183]. In

support of these observations, various *in vivo* studies have reported that arsenic toxicity is closely linked with a prolonged retention of inorganic arsenic in the lungs of rodents [129,130]. Further studies to examine the direct effects of inorganic arsenic compounds on pulmonary cells in order to elucidate the carcinogenic mode of action of retained arsenic-bearing particulates are suggested.

5.4. Direct Effects of Arsenic on Pulmonary Cells

Some of the key effects of arsenic exposure on a range of different pulmonary cell lines are summarized in Table 3. Since the dose response of arsenic can be substantially different in animal models compared with *in vivo* human exposure [184], this section will primarily focus on studies involving pulmonary cell lines, specifically human bronchial epithelial (HBE) cells derived from human lung epithelium [168], alveolar macrophage (AM) cells, which are typically harvested from animals [185], and human pulmonary fibroblast (HPF) cells. HBE and AM cells represent the first lines of defense against foreign particles [185], while HPF cells are important for regeneration and repair of chemically or mechanically damaged tissues [186]. As discussed by Dodmane *et al.* [165], although the effects of *in vitro* arsenic exposure are likely to reflect the *in vivo* effects, a cautionary approach should be adopted when interpreting the data due to the variability of effects observed amongst experimental systems.

5.4.1. Pulmonary Cytotoxicity of Arsenic

Cytotoxicity assays, and the measurement of representative parameters associated with cell pathology, are widely used to quantitatively assess the *in vitro* potency of a toxicant in the whole animal. Clear dose-response relationships between arsenic concentration and cytoxicity have been established in HBE cells [165,168,187–189], HPF cells [189–191] and AM cells [185]. Figure 6 shows a notable decrease in HPF and HBE cell survival, in a time- and concentration-dependent manner, following 24 and 120 h treatments with sodium arsenite [189]. Relative cell survival rates indicate that sodium arsenite is more cytotoxic to HPF than HBE cells (Figure 6; [189]). A similar study found that arsenic trioxide was also toxic to HPF cells, however greater concentrations were required to produce similar effects [190]. The differential cytotoxicities observed between these two trivalent arsenic compounds can be attributed to the fact that arsenic trioxide has a lower solubility in the lung than sodium arsenite [126].

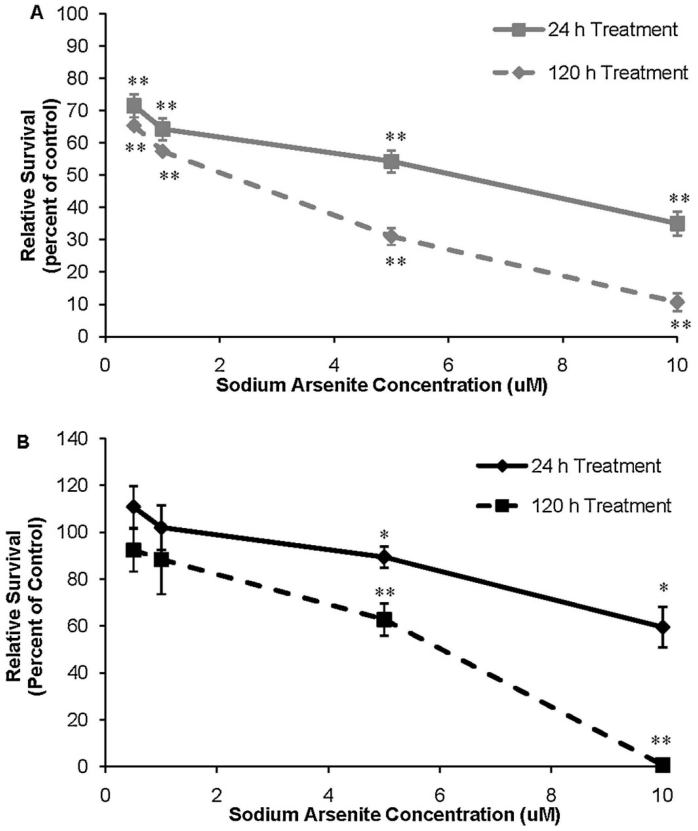
Consistent with other lines of evidence presented in previous sections, recent studies confirm that methylated arsenicals are more cytotoxic to pulmonary cells than the inorganic trivalent forms [165,168,188]. For example, the respective median lethal concentrations (LC50) of As^{III}, DMA^{III} and MMA^{III} in HBE cells were reported as 5.8, 1.4 and 1.0 μM, after a 72 h exposure period [165]. $DMTA^{V}$, exhibited a similar cytotoxicity potency to DMA^{III} [168]. While little is known about the pulmonary toxic effects of $DMTA^{V}$, gene expression analysis has shown that cells exposed to $DMTA^{V}$ and DMA^{III} share a relatively high number of differentially expressed genes (DEGs) following exposure to minimally cytotoxic arsenic concentrations, indicating the existence of associated similarities in the cellular mechanism of cytotoxicity of these two arsenicals at lower concentrations [168].

A systematic assessment of the cytotoxic effects and cellular uptake of As^{III}, MMA^{III}, DMA^{III}, MMA^{V}, DMA^{V} and thiodimethylarsinic acid (thio-DMA^{V}, $[(CH_3)_2As(S)OH]$) on human alveolar

epithelial cells has been undertaken in complementary studies [187,188]. Thio-DMA^V is a human arsenic metabolite of inorganic arsenic and is formed immediately when $DMTA^V$ is added to aqueous solution [187]. Cytotoxicity was quantified by measuring reductions in cell number, cell volume and colony formation following a 24 h exposure period [187,188]. In terms of these cytotoxicity endpoints, the cytotoxic order of extracellular arsenic concentrations was reported as DMA^{III} > MMA^{III} > thio-DMA^V ≥ As^{III} ≥ MMA^V ~ DMA^V [187]. Taking into consideration the bioavailability of each arsenic species, as measured by cellular uptake, the cytotoxic order was reported to change to thio-DMA^V ~ As^{III} ~ MMA^{III} > DMA^{III} ≥ MMA^V ~ DMA^V [187]. Cellular uptake of thio-DMA^V was strongly correlated with cytotoxicity endpoints, including cell number (correlation coefficient, −0.986) and colony forming ability (correlation coefficient, −0.998) [187].

Differences in arsenic-induced cytotoxicity endpoints reported in the literature may be attributed to variability in a number of experimental parameters: (i) the arsenic species or compound; (ii) the cell exposure duration; (ii) the cell systems used in each study; and (iii) the methods for assessing cytotoxicity endpoints.

Figure 6. Cytotoxicity of sodium arsenite in: (**A**) human lung fibroblast cells, and (**B**) human lung epithelial cells, following 24 and 12 h treatments. Reprinted from Xie *et al.* [189] with permission from Elsevier.



5.4.2. Effects of Arsenic-Induced Reactive Oxygen Species (ROS) Production on Human Bronchial Epithelial (HBE) Cells and Human Fibroblast (HF) Cells

Although ROS are widely recognized for their beneficial and growth-promoting effects on cells, overproduction can lead to toxic effects [192] including damage to cellular DNA and protein [144].

Studies show that HBE and HPF cells generate elevated ROS levels in a dose-dependent manner in the presence of arsenic [191,193]. Moreover, chronically exposed arsenic-transformed HBE cells constitutively generate cellular ROS (probably hydrogen peroxide) in the absence of further arsenic exposure [193]. Constitutive generation of ROS was found to be necessary for activating certain signaling pathways that regulate cell survival and cell proliferation [193].

Enhanced arsenic-induced ROS generation and accumulation have been associated with dose-dependent responses in rates of cell proliferation and colony formation in HBE cells [193–196] as well as anti-apoptotic signaling [195]. Increased cell proliferation is a distinguishing characteristic of cancer cells and is crucial for tumor formation, while apoptosis plays an important role in killing abnormal cells so that they cannot form tumors [193]. One study reported that increased cell proliferation of arsenic-exposed cells was mediated by anti-apoptotic-signaling induced by cyclooxygenase, COX-2 [197], an enzyme associated with inflammation and other pathogenesis [198]. Enhanced ROS levels play an important role in mediating COX-2 production in airway epithelial cells [199].

ROS production has also been linked with gene expression changes in HBE cells consistent with several of the proposed mechanisms for arsenic carcinogenesis [144] including oxidative stress, DNA damage and a weakened tumor-suppression response [165,168,195]. Suckle *et al.* [195] assessed the malignant potential of *in vitro* arsenic-transformed cells by injecting them into mice. The *in vivo* study identified phenotypic characteristics consistent with malignant lung epithelial cells [195], and whole genome expression profiling identified potential mitochondrial oxidative stress and increased metabolic energy output, which is indicative of increased mitochondrial energy production [195]. Importantly, chronic arsenic exposure may therefore target mitochondrial function leading to enhanced ROS generation and cancer-related gene signaling [195]. Antioxidants that target mitochondrial function could play a role in ameliorating some of the effects of arsenic in chronically-exposed populations [200].

Zhao *et al.* [201] recently discovered that long-term exposure to arsenic altered cellular energy metabolism through the induction of aerobic glycolysis (the Warburg effect), as observed in arsenite-treated HBE and other human cell lines cells. The Warburg effect is a metabolically supportive phenotype for the increased energy demands associated with the growth, proliferation and invasion of cancer cells (see the review by Vander Heiden *et al.* [202]). Unlike normal cells which produce lactate under anaerobic conditions only, the Warburg effect states that cancer cells generate large quantities of lactate regardless of oxygen availability [202]. This study was potentially the first to link an environmental toxicant with the induction of the Warburg effect, and thus this discovery may assist in identifying the role of arsenic toxicity in other diseases associated with disrupted energy metabolism, such as diabetes and atherosclerosis [201].

5.4.3. Arsenic-Induced Suppression of Alveolar Macrophage (AM) Function

Alveolar macrophages (AM) serve as the front line of cellular defence against foreign material by clearing the air spaces of any infectious, toxic or allergenic particles that have penetrated mechanical defences, such as the nasal passages and mucociliary transport system [203]. Under normal conditions, ROS are secreted by alveolar macrophages in response to phagocytosis or stimulation with specific agents, and play a key role in efficiently killing invading pathogens [204]. Various detrimental

effects of arsenic on these important cell functions have been observed (Table 3). For example, Palmieri *et al.* [185] noted concentration-dependent reductions in AM viability and size following exposure to sodium arsenite concentrations of 2 and 2.5 μM, respectively, and a notable increase in apoptosis after 5 μM. In the presence of the lower sodium arsenite concentrations (<2 μM), AM cells maintained the ability to regulate cell homeostasis whereas higher doses (≥5 μM), reduced cell viability to 50% [185]. Increasing cell culture time generally played a key role in amplifying the observed adverse effects, particularly during exposure to the higher (5 and 10 μM) sodium arsenite concentrations [185].

Contrary to the commonly-observed response by arsenic-exposed HBE and HPF cells, AM cells typically exhibit a dose-dependent reduction in ROS production in the presence of arsenic [128,185,205–208]. Soluble trivalent arsenic was notably more potent at inhibiting ROS production than the corresponding pentavalent form, with superoxide inhibition occurring at respective concentrations of 0.1 and 1 μg/mL [208]. In contrast, the slightly soluble trivalent and pentavalent forms showed similar patterns in ROS production with inhibition occurring at a concentration of 10 μg/mL arsenic [128,207]. Gercken *et al.* [205] postulated that the depression of O_2^- (superoxide anion) production by arsenic-exposed AM may be linked with high concentrations of arsenic on the particle surface. Both the studies by Lantz *et al.* [128,208] observed that a 24 h period of arsenic exposure was required to suppress ROS production.

Suppression of ROS production, or a reduction in AM function as demonstrated by others [128,185,205,207,208], may therefore inhibit phagocytosis: an important clearance mechanism of foreign particles, such as dust and bacteria, from the lung. Suboptimal phagocytosis by AM cells has been associated with a decreased ability to clear dead or dying cells from the respiratory system thereby leading to pathological inflammation [209] as well as an increased susceptibility to pulmonary infection such as pneumonia, in respiratory health-compromised individuals [210].

5.4.4. Arsenic-Induced Inhibition of the Wound Healing Response in Human Bronchial Epithelial (HBE) Cells

As the respiratory epithelium is frequently injured by inhaled pollutants or micro-organisms, the epithelial wound repair response plays a critical role in the maintenance of epithelial barrier integrity [211]. Concentration-dependent arsenic-induced inhibition of wound healing in mechanically-wounded HBE cells has been demonstrated (Table 3). In the absence of arsenic, the wounded area of an epithelial monolayer of HBE cells was largely repaired (approximately 80%) by migrating cells after a period of 4 h [212]. In the presence of 30 and 60 ppb arsenic however, the amounts of wound closure were 48% and 24%, respectively [212]. The highest concentration (290 ppb) resulted in the expansion of the wound area in the first hour, followed by 16.5% healing at 4 h [212]. Further analyses indicated that overexpression of matrix metalloproteinase (MMP-9), an enzyme important for human respiratory healing and wound closure [213], leads to dysregulated wound repair in the presence of arsenic and reductions in cellular migration [212].

Regulation of MMP-9 and migration of airway epithelial cells are linked with ATP-dependent Ca^{2+} signalling [213]. Tightly coordinated Ca^{2+} transport and activity are vital during early wound healing processes; therefore Ca^{2+} is commonly used as an immediate damage indicator [214]. Furthermore,

general interference with airway ATP signalling has been linked with chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) [215]. To investigate whether arsenic disrupts Ca^{2+} signalling in mechanically-wounded HBE cells, Ca^{2+} concentrations were monitored following acute (24 h) and chronic (4–5 weeks) exposure with micromolar and nanomolar concentrations of sodium arsenite [216,217]. Significant and dose-dependent reductions in Ca^{2+} propagation in wounded cells compared to controls were observed (Figure 7; [216,217]). Arsenic-induced suppression of the wound healing response as a result of both acute and chronic exposures (well below levels typically associated with inhalation where arsenic has been linked with disease presentation) may ultimately result in a reduced ability of the lung epithelium to effectively and sufficiently close a barrier breach [212,216,217].

Figure 7. Wound healing assay of 16HBE14o- cells exposed chronically (4–5 weeks) to 0, 130, or 335 nM sodium-arsenite: (**A**) Representative images of initial wounding (left column), 30 min post-wounding (middle column), and 1 h post-wounding (right column). White scale bar represents 50 μM; (**B**) Quantification of percent wound closure over time at 30 and 60 min post-wounding. "*" indicates significant difference from untreated controls by a one-way ANOVA ($p < 0.05$). Reprinted with permission from Sherwood *et al.* [217].

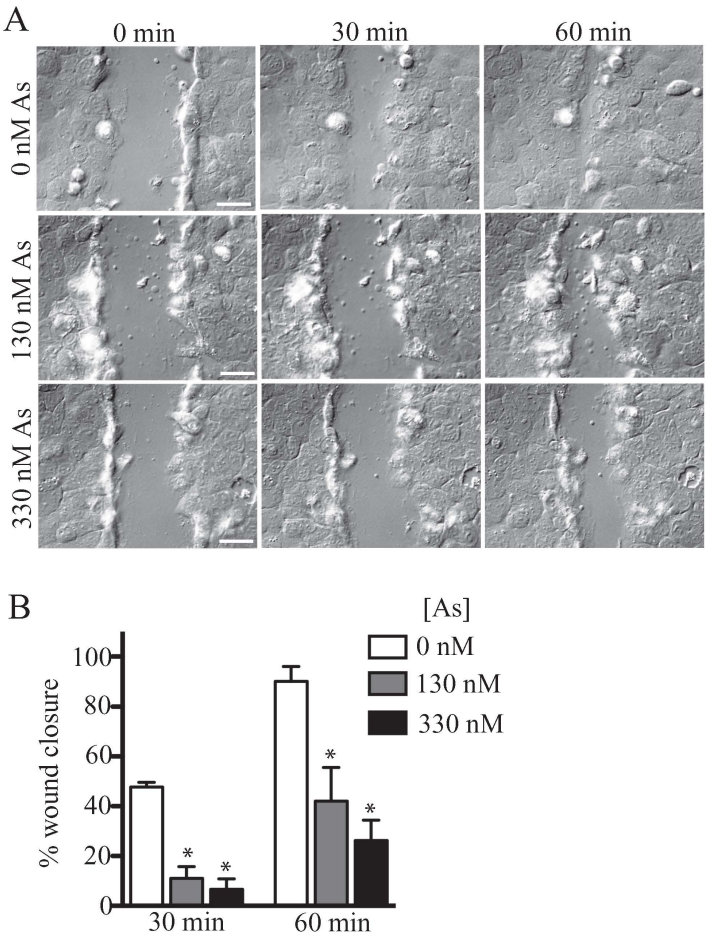


Table 3. Direct effects of arsenic exposure on human bronchial epithelial (HBE) cells, human pulmonary fibroblast (HPF) cells, and pulmonary alveolar macrophage (AM) cells. All experiments were conducted *in vitro*, unless otherwise specified. Specific cell lines are listed in accordance with the abbreviations used in each study.

As Compound	Dose	Cell Line	Pathological Effects	Potential Human Effects	Ref.
Human bronchial (or alveolar epithelial) cells					
Na-arsenite	0.5–10 μM for 24 and 120 h	NHBE	Dose-dependent reduction in cell survival; chromosomal aberrations suggestive of DNA double strand breaks	Lung cancer	[189]
Na-arsenite, MMA^{III}, DMA^{III}	Variable for 3 days	HBE	MMA^{III} & DMA^{III} were more cytotoxic; dose-dependent alteration of inflammatory response at low concentrations; alterations in oxidative stress and DNA damage repair at increasing concentrations	Pulmonary diseases linked with inflammation and increased bronchial cell proliferation	[165]
Na-arsenite	0–4 μM for 2 weeks	HBEp	Concentration-dependent increase in cellular lactate production; lactate produced via aerobic glycolysis (the Warburg effect)	Growth, proliferation and invasion of cancer cells	[201]
As-trioxide	2.5 μM for 6 months	BEAS-2B *In vivo* (Nu/nu mice) *In silico* Signalling pathway analysis	Time-dependent cell proliferation; cells exhibited a cancer-like phenotype Tumour formation; time-dependent increase in tumour volume; cells exhibited a malignant and metastatic phenotype ROS generation; DNA damage; chronic inflammation; dysregulation of pro- and anti-cancer gene signalling, anti-apoptosis and invasive signalling	Lung cancer	[195]
Na-arsenite	130 and 330 nM for 4–5 weeks and 0.8 and 3.9 for 24 h	16HBE14o-cells (wounded)	Dose-dependent reduction in the wound healing response (Ca^{2+} signalling), leading to inhibition of wound repair	Chronic lung disease, e.g., bronchiectasis	[216,217]
Na-arsenite MMA^{III}, DMA^{III}, MMA^{V}, DMA^{V}, $DMTA^{V}$	Various (μM) for 24 h	A549	DMA^{III} and MMA^{III} showed pronounced cellular uptake; differential cellular endpoints related to DNA repair	Arsenic-induced diseases	[187,188]
Na-arsenite	0.25–5 μM for 26 weeks	BEAS-2B	ROS-induced cell proliferation and colony formation; constitutive generation of ROS (probably H_2O_2); degree of effects were concentration-dependent	Primary lung tumour formation	[193]
Na-arsenite	20 nM, 200 nM, 2 μM and 20 μM for 12, 24 and 48 h	BEAS-2B	Enhanced cell growth and proliferation; up-regulation of protein, Cyclin D1, is commonly over-expressed in cancer cells	Development/progression of lung carcinogenesis	[196]
Arsenite, MMA^{III}, DMA^{III}, $DMTA^{V}$	Variable concentrations for 24 h	BEAS-2B	Arsenite was least cytotoxic; methylated forms shared similar cytotoxicities; dose-dependent increase in number of differentially expressed genes linked to carcinogenicity; minimally cytotoxic arsenic levels induced oxidative stress	Lung cancer	[168]

Table 3. *Cont.*

As Compound	Dose	Cell Line	Pathological Effects	Potential Human Effects	Ref.
Na-arsenite	30, 60, 290 ppb for 24 h	16HBE14o- (wounded)	Dose-dependent inhibition of the wound healing response	Compromised lung function	[212]
Na-arsenite	5–40 μM for 6–48 h	BEAS-2B	Overexpression of COX-2; apoptotic disruption; cell proliferation	Accumulation of genetically damaged cells leading to malignancy	[197]
Human pulmonary fibroblast cells					
Na-arsenite	0.5–10 μM for 24 and 120 h	HPF	Dose-dependent reduction in cell survival; concentration-dependent increase in chromosome damage such as DNA double strand breaks.	Lung cancer	[189]
As-trioxide	1–50 μM for 24 h	HPF	Dose-dependent reduction in cell survival between 10 and 50 μM As-trioxide		[190]
As-trioxide	1–50 μM for 0–180 h	NHBF	Dose-dependent increase in ROS (O_2^-) levels; cell growth inhibition and cell death		[191]
Alveolar macrophage cells (harvested from animals)					
Na-arsenite	1.25–10 μM for 24–96 h	Mouse AM	Dose-dependent reduction in macrophage viability and volume; time-dependent increase in apoptotic cell at higher arsenic concentrations; decrease in ROS (O_2^-) generation at low concentrations	Immunological disorders; decreased capacity to respond to toxicants	[185]
As-trioxide & Ca-arsenate (slightly soluble)	0.1–300 μg/mL for 24 h	Rat AM	Dose-dependent reduction of ROS (O_2^-) after 24 h; similar pattern for both arsenicals (around 10 μg/mL)	Alteration in AM function; compromised host defence	[128]
Na-arsenite & Na-arsenate (soluble forms)	0.1–300 μg/mL for 24 h	Rat AM	Dose-dependent reduction of ROS (O_2^-) after 24 h; As^{III} more potent than As^{V}; differential immune response between the two species	Compromised defence against infection and altered immune surveillance	[208]
Arsenic (fly ash)	50–230 ppm for 24 h	Rabbit AM	Concentration-dependent inhibition of ROS (H_2O_2 and O_2^-) production	Suppression of AM function	[206]
As-trioxide	0.1–1000 μM for 24 h	Rabbit AM	Concentration-dependent inhibition of ROS (H_2O_2 and O_2^-) production	Increased susceptibility to bacterial infections	[207]
As-trioxide (fly ash)	Industrially-relevant levels for 24 h	Rabbit AM	Suppressed ROS (O_2^-) production	Suppression of AM function	[205]

6. Epidemiological and Exposure Monitoring

Epidemiological studies provide an important link between health effects and air pollution exposure, because they provide an accurate representation of the health records and environmental conditions pertaining to a well-defined population [218]. In this regard epidemiological studies of industrially-exposed cohorts conducted during the mid-1900s have provided strong evidence of a causative role for airborne arsenic in respiratory cancer mortality. This has resulted in a diverse but important body of historical epidemiological evidence accrued on the health risks and disease outcomes associated with known, high level occupational inhalation exposures [219–221].

However, with increasing concerns regarding the effects of peripheral exposure to potential carcinogens, there is increasing attention directed at the health of communities living in the vicinity of smelting and mining operations and uncontained mine wastes and tailings. Notwithstanding the common source of the concerns, it has been observed that there are important differences between the situations of occupationally- and environmentally-exposed cohorts. Occupational studies usually differ methodologically from the environmental investigations in that there is a contained area of contamination and a restricted population who are exposed to high levels of airborne material. Whereas studies of environmental exposure in communities living in arsenic-affected areas usually start at birth, and the exposure itself may not be recognized for many years and may be intermittent, thereby rendering epidemiological studies more difficult to design and interpret, particularly since they are observational only. For these reasons, we report separately on the findings for each exposure type, since they will address different aspects of the effects of airborne particulate matter on health.

6.1. Known Occupational Exposures

An industrial hygiene study conducted between 1943 and 1965 at the Anaconda copper smelter in Montana, USA, recorded extremely high levels of airborne arsenic (≥5000 $\mu g \cdot m^{-3}$), particularly in and around the ore roasting furnace, materials crushing plant and the arsenic refinery departments [222]. Similar conditions were reported at the Ronnskar smelter in Sweden [220]. Airborne arsenic concentrations in excess of 20,000 $\mu g \cdot m^{-3}$ were not uncommon at these two smelting operations [220,222]. Lower values for airborne arsenic were typically found in areas such as the administration departments, electrical and machine workshops, outdoor environment, building department and general office area [220,222]. Significantly, airborne arsenic concentrations reported at the latter two locations are 8- and 2000-fold greater than the current target value of 6 $ng \cdot m^{-3}$ proposed by EU regulations.

Symptoms of severe arsenic exposure among smelter workers observed during the 1920s included a notable rise in the rate of sick days due to various acute and chronic respiratory disorders [223]. Arsenic trioxide-laden dust (generated as a by-product of the copper smelting process) deposited in the nose and respiratory airways forms arsenous acid on contact with moisture, resulting in necrosis of the mucous membranes [223]. Diseases reported among smelter workers during the early 1930s were bronchitis, tracheitis, ulcers, laryngitis, rhinitis, perforation of the nasal septum, atrophy of the mucus membranes in the respiratory passages and occupational arsenical dermatitis (unpublished works by Inghe and Bursell [224], translated in Gerhardsson *et al.* [225]). Emphysema and ischemic heart disease were also noted [219]. Despite the prevalence of these non-malignant respiratory disorders,

meta-analysis of the available epidemiological data did not detect any statistically significant excesses in mortality among smelter workers compared to the control cases [219,221].

The first cases of lung cancer that were traced to the work environment occurred at a Swedish smelter in the 1960s whereby a five-fold increase in lung cancer mortality compared with controls was observed [226]. Occupational health investigations at other smelting operations, as well as comprehensive reassessments and meta-analyses of previously reported data, demonstrated strong links between airborne arsenic exposure and respiratory cancer [220–222,227,228]. Lubin *et al.* [221] reported a statistically significant trend between the excess relative risk of respiratory cancer and cumulative exposure to airborne arsenic amongst a cohort of 8014 copper smelter workers in Montana, United States. Over a 50 year period, 446 deaths due to respiratory cancers were observed, comprising 428 lung cancers and 14 cancers of the larynx. No other cause of death was found to be associated with arsenic exposure, with the possible exception of COPD [221].

In addition to smelting, other studies have demonstrated a link between lung cancer and arsenic exposure at hard rock mining operations [228]. One of the most comprehensively investigated cases relates to four tin mines and three associated smelting operations in southern China, where underground miners were exposed to respirable concentrations of arsenic ranging between 0.1 and 38.3 $\mu g \cdot m^{-3}$ [229]. Chen and Chen [229] reported that the rates of lung cancer were strongly associated with cumulative dust exposure, arsenic exposure and duration of exposure. While the magnitude of risk from mining (odds ratio (OR), 8.8) was only slightly less than for smelting (OR, 12.3), exposure to both mining and smelting increased the risk to 22.0 [228]. The potential additive carcinogenic effects of inhaled crystalline silica, cigarette smoking and exposure to radon could not be ruled out [228].

To examine the distribution of arsenic in the body following long-term exposure, researchers collected and analysed tissues from deceased workers from the Ronnskar smelter in Sweden, and from various controls, and correlated these with the cause of death [225]. Post-mortem investigations discovered elevated levels of arsenic and seven other metals of concern in the lung, liver and kidneys of the deceased workers [182,225]. Median arsenic concentrations of 35 and 50 $\mu g \cdot kg^{-1}$ reported in lung tissue of the deceased smelter workers were six to seven times greater than the control cases [182,225], providing some evidence of a causative role for arsenic in respiratory cancer mortality among the exposed population [182]. Although the arsenic content diminished in liver tissue, a longer biological half-life of arsenic was observed in the lung [182]. Similar findings have been reported in animal studies [126]. An extended biological half-life and retention of arsenic in lung tissue may have implications for the development of respiratory disease. Lung cancer risk in a cohort of 107 Chinese tin miners was more dependent on the duration of arsenic exposure than then intensity [228]. Conversely, exposure intensity was more important in determining the lung cancer risk than duration in smelter workers [220,222], indicating a need for comparative studies with consistent exposure and outcome criteria.

Due to the use of exposure reduction measures by mining and mining-related industries, the number of published studies relating to rates of lung cancer and mortality in mining and mining-related industries has declined in recent years. However, occupational inhalation exposure to airborne arsenic remains a serious health issue in some localities. A recent study reported that copper smelter workers in northeastern China were exposed to airborne arsenic values that were up to 57% above the short-term exposure threshold limit value of 20 $\mu g \cdot m^{-3}$ [230]. Seven of the 38 copper smelter workers

selected for investigation had arsenic-related skin disorders including hyperkeratosis and/or hyper-pigmentation, as well as elevated urinary arsenic levels [230]. Urinary arsenic speciation analysis revealed that higher occupational exposures and skin damage cases were associated with a decreased capacity for arsenic methylation [230]. Similar results have been reported elsewhere [231]. These findings support the premise that suppressed methylation capacity results in an increased risk of arsenic toxicity due to the retention of arsenic in the body [183].

6.2. Inadvertent Environmental Exposures

It has been found that a number of populations around the world live in the vicinity of active or abandoned mining operations [28], and there exists overwhelming epidemiological evidence suggesting that there is an increased risk of arsenic exposure for these communities [4–9,78,107,232]. These studies show that children are particularly susceptible to inhalation exposure since they respire a greater relative volume of air with respect to their size, and may therefore be exposed to correspondingly higher levels of airborne contaminants than adults. Children also have an increased likelihood of coming into contact with soil and dust through playing in dirt contaminated with arsenic residues [78,233,234]. As a consequence, many human exposure monitoring studies have focussed on measuring arsenic exposure in child populations [4,7,107,233,235,236].

Measurement of arsenic in human nails, hair, urine and blood concentrations are commonly used for determining arsenic uptake in humans [78,105,232,235,236]. Blood and urine arsenic levels provide a reliable short-term measure of arsenic exposure because arsenic is readily excreted from the bloodstream via the kidneys [25]. Analysis of arsenic deposited in the toenails and hair provides useful indicators when the measurement of long-term, low-level arsenic exposure is required [234–238]. It has also been shown that analysis of the arsenic content of particles that have adhered to the hands of children can also be used as an indicator of potential exposure [4].

It is important to note that although such biological markers of arsenic exposure as those reported above are useful for predicting the degree of risk, elucidating the exact pathway to environmental uptake of arsenic in localities where multiple exposure pathways exist is not straightforward [233]. As previously mentioned in this review, airborne arsenic-contaminated particulates generated by mining operations often may be small enough to be inhaled, and have the potential to directly reach the tracheobronchial and/or alveolar regions of the RT of populations living within the reach of the industrial plume or raised dust material [19,54]. However, particles that have been deposited on the ground or other surfaces may be either ingested due to physical contact, or resuspended as dust, and then inhaled [19,105]. Many studies therefore report the existence of multiple possible pathways for human exposure to arsenic-bearing particulates in the vicinity of mining operations which contributes to the complexity of epidemiological studies of this issue [4,7,105,233,238] A recent study reported that the ingestion and inhalation exposure pathways contributed equally to the arsenic-associated carcinogenic and non-carcinogenic risks in such populations [105].

From the work reported in the above investigations, it is clear that human arsenic exposure is governed by a number of variables. There are important inverse relationships which have been frequently reported between the concentration of airborne arsenic levels and the distance from the source, and between biological arsenic levels and the distance of the home, playground or school

environment from metal smelters and other mining operations [4,7,107,233]. Buchet *et al.* [4] reported airborne arsenic concentrations of 330 and 75 $ng \cdot m^{-3}$, and dust concentrations of 1710 and 66 $\mu g \cdot g^{-1}$ at distances of 1 and 2.5 km from a lead smelter in Belgium, which are consistent with this inverse relationship. Correspondingly, the average arsenic concentration on the hands of children living within the 1 km zone was ten times greater than those children living further away [4]. Similarly, Hwang *et al.* [233] found that the urine arsenic content of children living near an extensively contaminated former copper smelter in Montana were significantly inversely correlated with distance from the smelter site.

As cautioned by Frost *et al.* [6], the assumption of a simple inverse relationship between arsenic uptake and distance from the emission source may oversimplify this phenomenon, since seasonality and wind direction are also important variables influencing exposure [9,107,231]. Milham and Strong [107] demonstrated that fluctuations in urine arsenic levels among children living near a copper smelter were closely associated with changes in prevailing wind direction. In this study, the urine arsenic concentrations of children living downwind of the smelter decreased simultaneously with shifts in wind direction [107]. Another study of children living near a former copper smelter site reported elevated biological arsenic levels during the summer, a time when seasonal factors enhance the mobilisation of dust from uncontained mine wastes, such as tailings and flue dust [233].

Carcinogenic and non-carcinogenic risks associated with inhalation exposure to atmospheric arsenic emitted by coal combustion have recently been estimated in exposed Chinese populations [9,105]. Because it has been observed that the average effective diameter of arsenic-containing aerosols from combustion processes is 1 μm [3], there exists a high potential for deposition in the terminal bronchioles and alveoli of exposed populations. Consequently, it has been estimated that more than two million residents in Beijing have an increased risk of developing cancer as a result of probable exposure to atmospheric arsenic, generated principally from coal combustion [9]. Recent measures of daily total inorganic arsenic inhalation exposure values for Beijing residents (0.3–0.8 $\mu g \cdot day^{-1}$) showed that they were 10 times greater than those in the United States (40–90 $ng \cdot day^{-1}$). These studies indicated that daily intakes of arsenite and arsenate in Beijing were 0.01–0.03 and 0.16–0.44 $\mu g \cdot day^{-1}$ by inhalation, respectively. Based on these exposures and the known effects of both arsenite and arsenate as carcinogens, an estimated excess cancer risk of $(4.2 \pm 2.0) \times 10^{-4}$ was predicted for the city's population [9]. In a similar study, Cao *et al.* [105] reported a median carcinogenic risk posed by arsenic inhalation of 2.91×10^{-3} in a community living near the largest coal refinery plant in a town of Shanxi Province, China.

6.3. Impacts of Climate Change

The effects of climate change are predicted to have an impact on mine waste chemistry and mobility. The predicted rise in global temperature is expected to increase the rate of mine waste weathering by a factor of approximately 1.3 by the year 2100 [239]. Prolonged weathering of mine waste materials will lead to the formation of a greater abundance of soluble salts [67]. Moreover, the anticipated increase in extreme weather conditions are likely to lead to a greater frequency and intensity of dust storms, as already observed in localities such as Asia, Africa, and Australia [240,241]

which in combination with the weathering, is likely to result in an increase in the occurrence and bioavailability of airborne arsenic.

7. Conclusions and Research Priorities

The potential health effects of exposure to airborne arsenic-bearing particulates generated by current and/or past mining operations are widely recognized as a growing issue of significant global importance. Investigations surveyed in this review, taken from disparate but complimentary lines of inquiry, strongly support a causative role for inhalation exposure of inorganic arsenic species in the aetiology of lung cancer and other respiratory health disorders, suggesting that a strong focus on this exposure modality is crucial for the long-term health of affected populations.

This review has highlighted the need to conclusively elucidate the exact mechanisms of arsenic-induced toxicity from exposure to PM in order to facilitate the prediction and diagnosis of adverse health consequences, and thereby enable adequate risk assessments to be undertaken.

Recent developments in various complimentary areas of research within the overarching field of medical geology including geochemistry, biomedicine, toxicology and epidemiology, have identified a number of factors that play a key role in understanding these varied phenomena. These include: (i) the effects of differing environmental variables leading to exposure; (ii) the influence of particulate characteristics on the initial deposition location in the RT; (iii) the differing toxicity levels of particulate-borne arsenicals, their species and their metabolites, and (iv) the complex pathogenesis of arsenic-induced lung disease.

While it is clear that absorbed arsenic exerts cytotoxic and genotoxic effects on pulmonary cells following both acute and chronic exposures, important species- and dose-dependent differences in toxicities between the two exposure regimes have been observed. It is also clear that particle size plays a major role in governing the deposition location, solubility, methods of clearance and retention time of arsenic-bearing species in the RT, and hence has a direct effect on the range of arsenic metabolites released to the body. Current research indicates that the exposure to arsenic and of these metabolites is predictive of the pathogenesis of lung disease, which leads to the conclusion that the long-term pulmonary bioavailability of arsenic in PM requires serious consideration in health risk assessments. Development of a series of standardized lung bioavailability assays that assess both short- and long-term exposures would be beneficial, particularly when drawing comparisons between studies.

The potential for human exposure to airborne arsenic will inevitably increase in the future due to several key factors. Increases in global copper production and coal use, with which arsenic species are intimately related, are indicators of increasing global wealth and population. With increasing wealth and population, consequent increases in urbanization will inevitably lead to encroachment on and disturbance of existing contaminated sites. In addition, it is predicted that climate change will have a considerable impact on mine waste chemistry and mobility, effectively amplifying every other risk factor, and increasing the urgency in gaining a greater understanding of all aspects of arsenic in our environment.

It is strongly recommended that future research prioritizes identifying human populations and sensitive sub-populations at risk of exposure, as well as developing long-term, cost-effective methods to adequately contain or reduce airborne emissions from known sources.

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Author Contributions

All authors contributed substantially to the work presented in this manuscript. As principal researcher, Rachael Martin made a substantial contribution to this work which was undertaken in association with her PhD program. Kim Dowling provided critical analyses and commentary during the development of this manuscript, ensuring that the reviewed literature was accurately interpreted. Dora Pearce provided extensive commentary on the epidemiology and other health-related sections of this manuscript, ensuring that all findings related to health outcomes were accurately represented. With an extensive background in the field of chemistry, James Sillitoe has made substantial contributions to this paper, particularly regarding the technical aspects. Singarayer Florentine assisted with the development of the underpinning theory and conceptual framework for this manuscript, as well as assisting with major re-drafting and editing.

Conflicts of Interest

The authors declare no conflict of interest.

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