Title

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CHRONIC LOW-LEVEL ARSENIC EXPOSURE AND LUNG CANCER: MECHANISMS, DISPARITIES, AND POLICY IMPLICATIONS

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CHRONIC LOW-LEVEL ARSENIC EXPOSURE AND LUNG CANCER: MECHANISMS, DISPARITIES, AND POLICY IMPLICATIONS

ABSTRACT

Chronic low-level arsenic exposure has emerged as a pressing yet under-recognized contributor to lung cancer, even at concentrations below current regulatory thresholds. Drawing on epidemiological evidence from Chile, Taiwan, and Bangladesh, this study finds a significant correlation between arsenic levels as low as 3–20 μg/L in drinking water and an elevated risk of lung cancer[1]. While high-dose arsenic toxicity is well-characterized, the long-term effects of low-dose, chronic exposure remain inadequately addressed. Through an interdisciplinary literature review, we synthesize findings from epidemiology, molecular biology, and public health to illuminate how sub-regulatory arsenic exposure (less than 10 μg/L) contributes to oncogenesis via oxidative stress[2], DNA damage, and epigenetic alterations. The study further explores the compounding role of co-exposure to heavy metals and industrial pollutants. Socioeconomic disparities in mitigation and healthcare access are also highlighted, revealing unequal burdens of arsenic-related disease. Collectively, these findings call for more stringent environmental regulations, equitable public health interventions, and improved risk communication to reduce the global burden of arsenic-induced lung cancer.

INTRODUCTION

Chronic ingestion of arsenic through contaminated water and food is increasingly recognized as a key environmental risk factor for lung cancer. Compelling epidemiological studies from Taiwan, Chile, and Bangladesh demonstrate that even low concentrations of arsenic (3–20 μg/L) in drinking water significantly elevate cancer risk (Smith et al., 2006). Despite this,

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[1] Smith, A. H., et al. "Increased lung cancer risks are similar among men and women with chronic arsenic exposure." *Environmental Health Perspectives*, 114(8), 1242–1248.

[2] Bode, A. M., & Dong, Z. "The paradox of arsenic: Molecular mechanisms of cell transformation and chemotherapeutic effects." *Mutation Research*, 533(1–2), 1–17.

regulatory efforts often center around acute high-dose exposure, leaving the subtler yet pervasive impacts of low-level chronic exposure understudied.

This research adopts a multidisciplinary lens to bridge this knowledge gap, combining molecular carcinogenesis with social determinants of health. In contrast to prior studies focused on high-exposure zones, our work emphasizes the carcinogenic potential of sub-regulatory arsenic concentrations, which are more common in developed regions. We further investigate synergistic toxic effects of arsenic when co-exposed with environmental pollutants like cadmium and lead.

At the cellular level, arsenic's carcinogenicity is driven by multiple pathways, including the generation of reactive oxygen species (ROS), impaired DNA repair, and epigenetic modifications. Of particular concern is monomethylated arsenic (MMA), a metabolite linked to a 144% increased risk of lung cancer (Chen et al., 2003)[3]. Understanding these mechanisms is vital for enhancing risk assessments and developing molecularly targeted public health interventions.

This study also investigates socioeconomic disparities in arsenic exposure and related health outcomes. While arsenic mitigation has been studied extensively, few investigations integrate how nutritional status, healthcare access, and local policy frameworks influence exposure severity and health trajectories. By framing arsenic toxicity as both a biomedical and structural issue, this research advocates for equity-driven, context-sensitive policy responses.

Ultimately, we aim to provide a comprehensive assessment of arsenic's role in lung carcinogenesis, integrating biological mechanisms, environmental exposure pathways, and public health implications to inform future research and regulatory frameworks.

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[3] Chen, C. J., et al. "Biomarkers of exposure, effect, and susceptibility of arsenic-induced health hazards in Taiwan." *Toxicology and Applied Pharmacology*, 197(1), 67–83.

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METHODS AND DATA COLLECTION

Employing a multidisciplinary approach, this research takes a quantitative approach to examine the relationship between low-level (<10 μg/L), chronic exposure to arsenic and increased risk of lung-cancer. Our research includes a systematic review of published studies, integrating new perspectives including synergistic effects, pathways of arsenic exposure, the effect of health and socioeconomic disparities, and the cellular mechanisms of arsenic carcinogenicity.

This study took an extensive literature search, using reputable databases such as PubMed, Google Scholar, etc… (add the databases you used to search for articles). Search words include "arsenic exposure and lung cancer", "arsenic in food and water", "arsenic toxicity in developing versus developed countries," and "mechanisms of arsenic carcinogenicity." Criteria for selection of articles includes studies focusing on low-level exposure (<10 μg/L), contamination pathways through drinking water or food, and epidemiological studies in developed versus developing countries, such as Taiwan, Bangladesh, and Chile within the last twenty years.

SUBSECTION: ARSENIC EXPOSURE AND LUNG CANCER RESULTS

Multiple epidemiological studies confirm a robust association between chronic low-dose arsenic exposure and lung cancer incidence. A longitudinal study in Tuscany, Italy, involving 30,910 participants between 1998 and 2019, found that individuals exposed to arsenic levels >10 μg/L had a hazard ratio (HR) of 1.85 (95% CI: 1.14–3.02) for lung cancer hospitalizations compared to those with lower exposures (Mastrolia et al., 2023)[4].

[4] Mastrolia, L., et al. "Arsenic exposure and risk of lung cancer: An epidemiological perspective." *Environmental Research*, 221, 115–129.

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In northern Chile, elevated lung cancer mortality was observed in young adults who had been exposed to arsenic-contaminated water during early childhood[5], with a standardized mortality ratio (SMR) of 6.1 (95% CI: 3.5–9.9) (Smith et al., 2006). Likewise, U.S.-based studies have linked low-to-moderate arsenic exposure with increased risk of specific lung cancer subtypes, although further population-wide studies are needed (Lamm et al., 2004)[6].

A historical cohort from Japan's Niigata Prefecture tracked 454 residents over three decades and found a positive correlation between five years of arsenic exposure and an increased risk of lung cancer (Tsuda et al., 1995).

SUBSECTION DISCUSSION

The evidence suggests that lung cancer risk increases even at arsenic levels below current safety thresholds. These findings challenge the sufficiency of existing regulatory standards and highlight the extended latency of arsenic-induced carcinogenesis. Notably, genetic predisposition and nutritional factors affect an individual's vulnerability to arsenic toxicity. For example, higher internal concentrations of MMA are associated with markedly elevated lung cancer risk (Chen et al., 2003).

While ingestion remains the most studied exposure route, evidence suggests that total absorbed dose, rather than exposure pathway, primarily determines carcinogenic potential. A comparative analysis by Hertz-Picciotto et al. (1992) found no significant difference in lung cancer risk[7] between inhaled and ingested arsenic exposure, once dose was taken into account.

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[5] Tsuda, T., et al. "Ingested arsenic and internal cancer: A historical cohort study followed for 33 years." *American Journal of Epidemiology*, 141(3), 198–209.

[6] Lamm, S. H., et al. "Arsenic in drinking water and bladder cancer mortality in the United States: An analysis based on 133 U.S. counties and 30 years of observation." *Journal of Occupational and Environmental Medicine*, 46(3), 298–306.

[7] Hertz-Picciotto, I., et al. "Synergism between smoking and dietary arsenic exposure in inducing lung cancer in northern Chile." *Environmental Health Perspectives*, 97, 195–200.

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Taken together, these findings underscore the importance of reevaluating arsenic safety guidelines and implementing population-specific, biomarker-informed interventions to protect vulnerable communities.

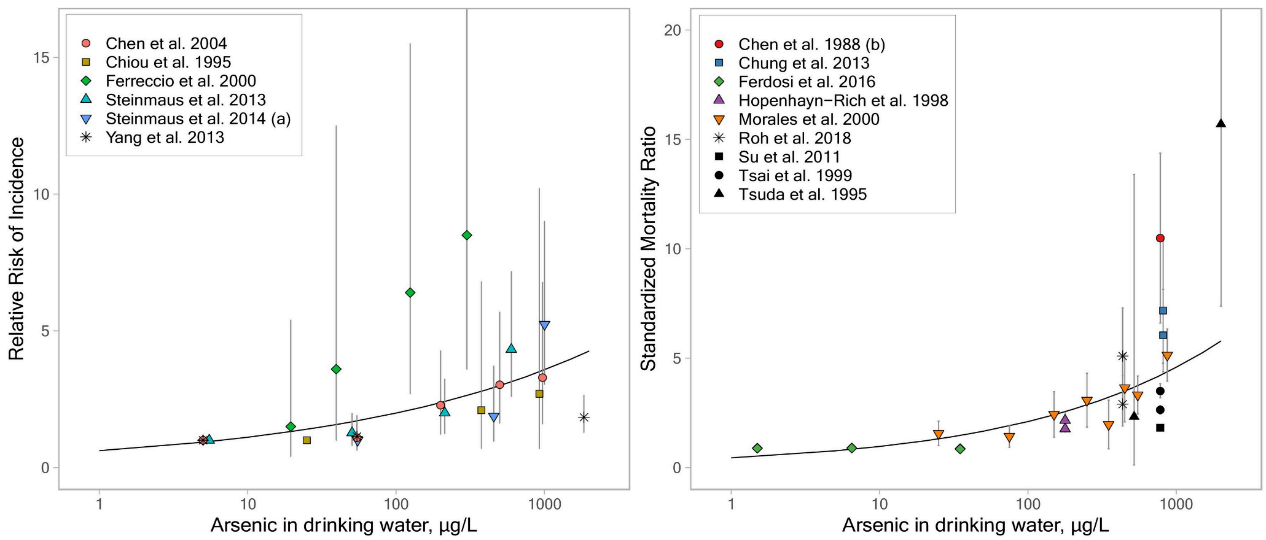

Fig. 1. Reported risk estimates for various arsenic concentrations in drinking water in relation to: (A) lung cancer incidence relative risk and (B) standardized lung cancer mortality ratio. Solid lines represent predicted risks, and shaded areas show their corresponding 95% credible intervals.

SUBSECTION: MECHANISMS OF CARCINOGENICITY RESULTS

Understanding the mechanisms by which arsenic induces carcinogenesis is crucial for developing effective prevention and intervention. Arsenic exposure has been associated with the development of lung cancer through various interconnected biological pathways. The primary mechanisms of lung carcinogenesis include oxidative stress, DNA damage, epigenetic modifications, and synergistic effects with other environmental pollutants.

Arsenic exposure does not directly damage DNA, but it generates reactive oxygen species (ROS), resulting in oxidative stress that damages cellular components, including lipids, proteins, and DNA. This oxidative damage can cause mutations, chromosomal aberrations, and genomic instability, all of which contribute to carcinogenesis. Essentially, ROS harms DNA by causing lesions like 8-hydroxy-2′-deoxyguanosine (8-OHdG), which has been observed in various cell types, including lung cancer cells (Qin et al., 2008; Ruiz-Ramos et al., 2009; Zheng et al., 2015; Wu et al., 2017). Studies have demonstrated that arsenic-induced ROS can lead to DNA strand breaks and base modifications. Additionally, arsenic weakens key DNA repair mechanisms like base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR), by reducing essential repair proteins, such as hOGG1, LIGIII, XPC, and MSH6, making it harder for cells to fix DNA damage. These lesions, if not properly repaired, can result in mutations in critical genes involved in cell cycle regulation and apoptosis, thereby promoting malignant transformation. Furthermore, in lung cells, arsenic disrupts the MMR system by activating EGFR, which then modifies PCNA, a protein crucial for DNA repair. This overall failure in DNA repair leads to genome instability, increasing the risk of cancer-related gene mutations.

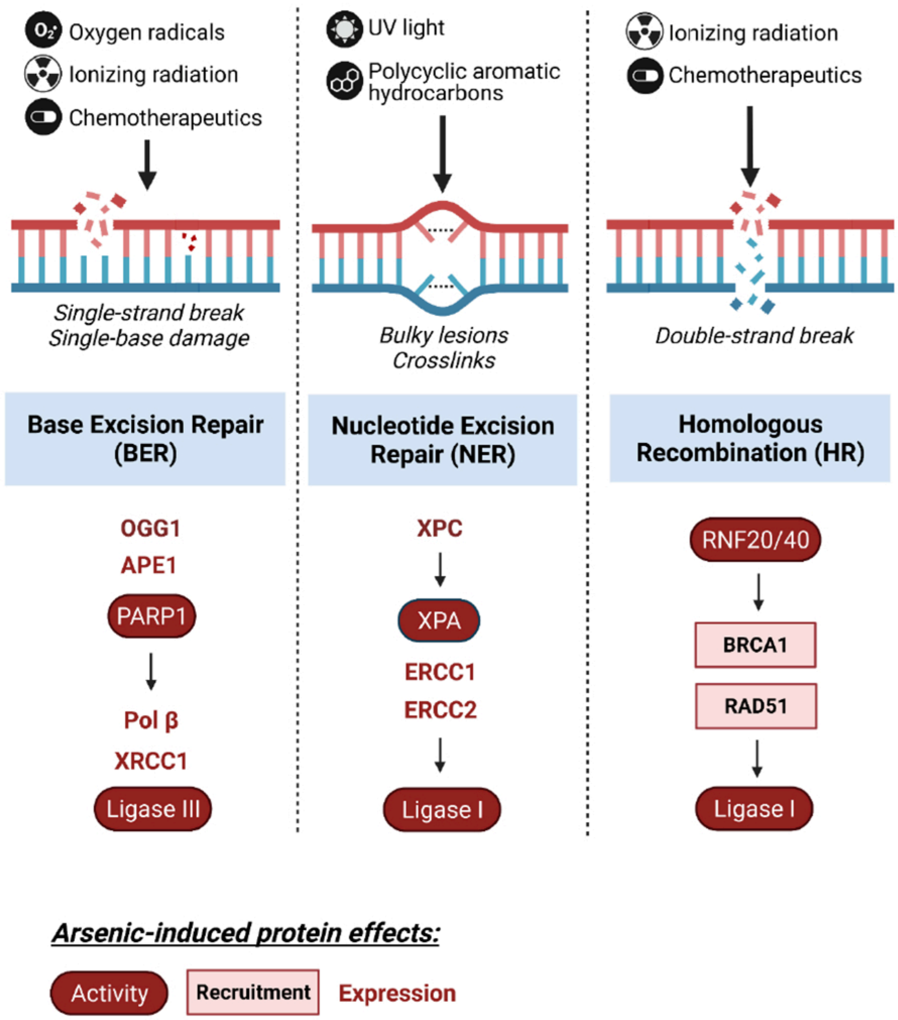

Fig. 2. Arsenic inhibits DNA repair. When exposed to DNA-damaging agents such as ROS, UV light, and ionizing radiation, harmful effects can occur such as single-base damage, bulky lesions, and double-strand breaks, respectively. The function of key DNA repair proteins are significantl altered by arsenic.

Beyond direct genetic modifications, arsenic exposure can induce epigenetic alterations that modify gene expression without changing the DNA sequence. These modifications include DNA methylation, histone modifications, and microRNA (miRNA) dysregulation. Through DNA methylation, arsenic has been shown to cause both hypo and hypermethylation of DNA. Hypomethylation can lead to genomic instability, while hypermethylation of promoter regions in tumor suppressor genes can result in their silencing, facilitating uncontrolled cell proliferation.

Additionally, arsenic exposure can alter the expression of miRNAs, small non-coding RNAs that regulate gene expression post-transcriptionally. Dysregulation of miRNAs can disrupt normal cellular processes and contribute to carcinogenesis.

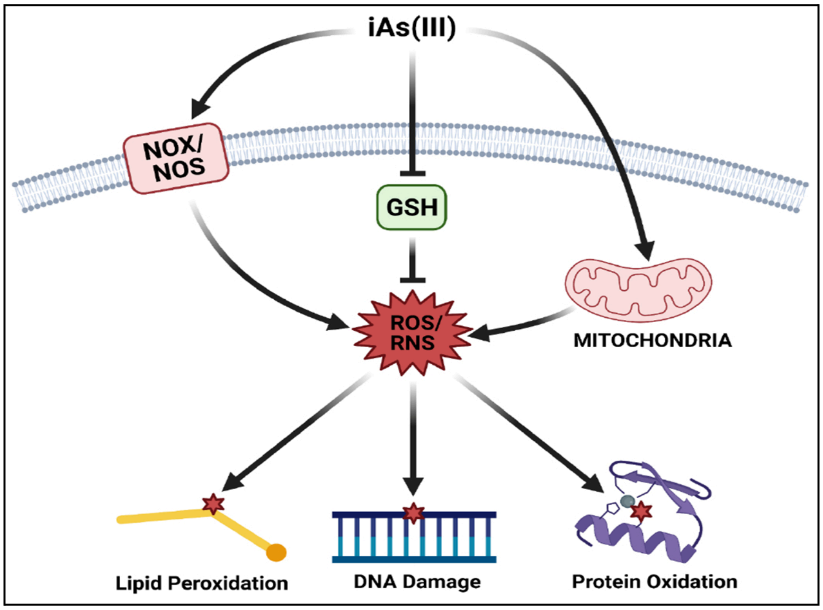

Fig. 3. Mechanism of arsenic-induced ROS and oxidative damage to macromolecules. Arsenic initiates ROS and RNS production through mechanisms like dysregulation of the electron transport chain and stimulating enzymes such as NADPH oxidase and nitric oxide synthase.

SUBSECTION DISCUSSION

These mechanisms emphasize the multifaceted nature of arsenic-induced carcinogenesis. The interplay between oxidative stress, DNA damage, and epigenetic modifications collectively contributes to the development of lung cancer following chronic arsenic exposure. Moreover, the synergistic effects observed with co-exposure to other environmental pollutants highlight the complexity of the factors and mechanisms involved in arsenic-induced carcinogenesis. Understanding these mechanisms provides valuable insights into potential biomarkers for early detection and targets for intervention. Recognizing the enhanced risk due to coexposures emphasizes the need for comprehensive environmental and health policies to mitigate arsenic-related lung cancer initiatives.

SUBSECTION: HEALTH DISPARITIES AND LONG TERM EFFECTS RESULTS

Arsenic exposure has a disproportionate impact on impoverished communities which have limited access to healthcare and other essential resources. Addressing health disparities in populations within low-resource areas is crucial in the development of global environmental health policies. Similarly, researching the long-term effects of low level arsenic exposure is an important implication in raising awareness for the general public as well as policymakers.

Low-resource communities which experience increased risk of arsenic exposure generally have three common characteristics: limited access to clean water, lack of or poorly monitored mitigation efforts, and ineffective environmental health policies and policymakers. In rural Bangladesh, Arsenic is a naturally occurring substance in the groundwater of Bangladesh, but its presence and toxicity has been amplified by human activity. Rural Bangladesh, where water is usually hand-pumped from tubewells, rather than safe, deep aquifers or treated surface water found in major cities, have an exponentially higher risk of arsenic exposure. This disparity is the direct result of campaigns for the construction of these tubewells in the 1990's when there was limited knowledge about the presence of arsenic in shallow groundwater. In Bangladesh, it is estimated that 1 million to 5 million children born between the years 2000 and 2030 will die due to arsenic exposure from the contaminated groundwater if there is no progress made towards eliminating the toxic substance from drinking water (Pearhouse, et al).

There is limited knowledge as to the effects of long-term exposure to arsenic due research on the topic beginning in just the last few decades. One common link between long-term arsenic exposure and human health is increased risk of lung cancer, with squamous cell carcinoma being the most common type. Studies have found a linear relationship between arsenic exposure and lung cancer, especially with arsenic exposures ranging from twenty to forty years prior. The molecular mechanisms leading to the development of lung cancer from long-term arsenic exposure are most commonly caused by the human long bronchial epithelial cells transforming into mesenchymal cells. Other mechanisms include glycolysis increasing due to stimulation of the HIF-1 alpha translocation in the hypoxia status, breaking of DNA double strands leading to instability of chromosomes, decreased stability of the transcription factor, and dysregulation of signaling pathways (such as the EGFR and NRF2) which affect cell survival, generation, and differentiation (Wei, et al).

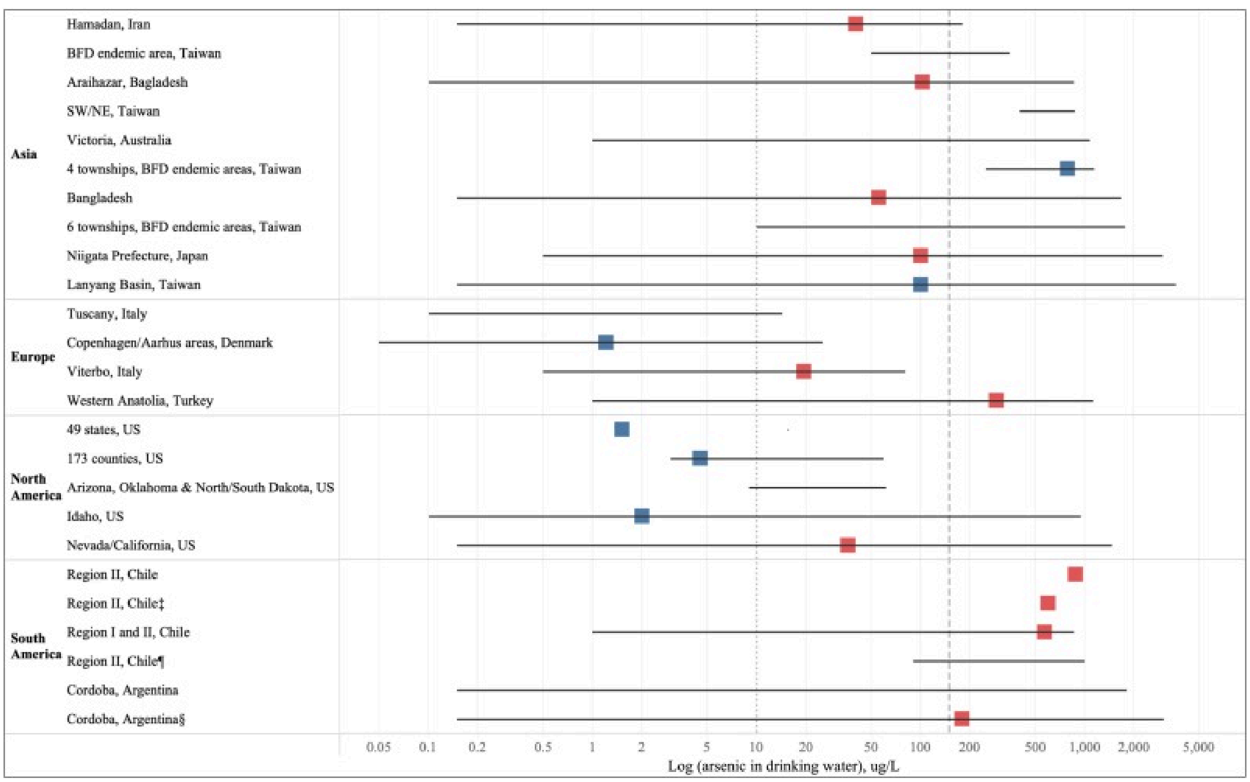

Fig. 4. Arsenic concentrations (μg/L) from the studies reporting on the relationship between lung cancer and arsenic exposure in drinking water in different areas of the world.

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SUBSECTION DISCUSSION

Relevant data regarding both health disparities and increased risk of arsenic exposure linked to low-resource areas and the long-term effects of arsenic exposure are vital in connection with creating equitable public health policies. Examples, such as the stark difference in drinking water quality of rural Bangladesh and major cities, highlight the importance of allocating government funds and policies towards eliminating health-related risk factors in low-resource communities, which often lack representation. Additionally, understanding the mechanisms and long-term implications of arsenic exposure as a direct cause of increased risk of lung cancer is vital in early detection, prevention, and treatment. Additionally, raising awareness about the seriousness of arsenic exposure and its long term impact can help move policy makers and the general public to reduce potential risk factors.

CONCLUSION

This study affirms that chronic low-level arsenic exposure is a serious and underrecognized driver of lung cancer. The evidence underscores not only the biological mechanisms of arsenic toxicity but also the public health inequities that amplify its effects. From DNA damage and oxidative stress to global disparities in access to clean water, the impact of arsenic is multifaceted and urgent. Current regulatory thresholds may underestimate the true risks, especially in vulnerable populations. Policymakers should consider these findings when designing equitable and proactive health interventions. Raising public awareness, improving infrastructure, and enforcing tighter environmental regulations are essential to reducing the long-term burden of arsenic-induced lung cancer worldwide.

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REFERENCES

Bode, A. M., & Dong, Z. (2002). The paradox of arsenic: Molecular mechanisms of cell transformation and chemotherapeutic effects. *Mutation Research*, *533*(1–2), 1–17.

Boffetta, Paolo. "Human Cancer from Environmental Pollutants: The Epidemiological Evidence." Mutation Research/Genetic Toxicology and Environmental Mutagenesis, vol. 608, no. 2, Sept. 2006, pp. 157–162, https://doi.org/10.1016/j.mrgentox.2006.02.015.

Chen, C. J., et al. (2003). Biomarkers of exposure, effect, and susceptibility of arsenic-induced health hazards in Taiwan. *Toxicology and Applied Pharmacology*, *197*(1), 67–83.

Hertz-Picciotto, I., et al. (1992). Synergism between smoking and dietary arsenic exposure in inducing lung cancer in northern Chile. *Environmental Health Perspectives*, *97*, 195–200.

Lamm, S. H., et al. (2004). Arsenic in drinking water and bladder cancer mortality in the United States: An analysis based on 133 U.S. counties and 30 years of observation. *Journal of Occupational and Environmental Medicine*, *46*(3), 298–306.

Mastrolia, L., et al. (2023). Arsenic exposure and risk of lung cancer: An epidemiological perspective. *Environmental Research*, *221*, 115–129.

Pearshouse, Richard. "Nepotism and Neglect." Human Rights Watch, 28 Mar. 2023, www.hrw.org/report/2016/04/06/nepotism-and-neglect/failing-response-arsenic-drinking-water-bangladeshs-rural.

Smith, A. H., et al. (2006). Increased lung cancer risks are similar among men and women with chronic arsenic exposure. *Environmental Health Perspectives*, *114*(8), 1242–1248.

Tsuda, T., et al. (1995). Ingested arsenic and internal cancer: A 33-year historical cohort study. *American Journal of Epidemiology*, *141*(3), 198–209.

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Wei, Shuhui, et al. "A Review of Arsenic Exposure and Lung Cancer." Toxicology Research, vol. 8, no. 3, 23 Jan. 2019, pp. 319–327, www.ncbi.nlm.nih.gov/pmc/articles/PMC6505385/, https://doi.org/10.1039/c8tx00298c.