Arsenic exposure and skin cancer: Mechanisms, clinical evidence and public health implications (Review)

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Abstract. Skin is among the most frequent sites of cancer diagnosis, and the global incidence of skin cancer continues to rise despite extensive public health initiatives and preventive strategies. Arsenic, a ubiquitous environmental metalloid classified as a Group 1 carcinogen, remains an important concern due to widespread exposure through contaminated drinking water, food sources and occupational contact. Arsenic-associated skin carcinogenesis involves complex, interdependent molecular processes and has been linked to the disruption of redox signalling, altered DNA damage signalling and repair responses as well as epigenetic reprogramming. In keratinocytes, arsenic perturbs redox and stress-response pathways and may disrupt genome maintenance and cellular stress signalling in experimental systems. Arsenic may also alter microRNA networks and affect telomere and mitochondrial homeostasis, although the contribution of these processes to malignant transformation remains context-dependent; in melanoma, the carcinogenic mechanisms of arsenic are less well characterized. Clinically, arsenic is recognized as a carcinogen in non-melanoma skin cancer (NMSC) and evidence from high-exposure endemic regions, together with occupational cohorts, suggest a dose-responsive association. For melanoma, clinical evidence is more heterogeneous and subject to substantial potential confounding, although some studies suggest modest risk elevation in high-exposure or occupational settings. Collectively, convergent mechanistic, experimental and epidemiological data support arsenic as an independent carcinogen, particularly in NMSC. These findings underscore the need for heightened clinical vigilance, particularly in exposed populations, and call for renewed public health strategies and regulatory frameworks to mitigate the persistent global burden of arsenic-associated skin cancer.

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1. Introduction

The global cancer burden is projected to climb from 19.3 million incident cases in 2020 to 28.4 million by 2040 (1). The International Agency for Research on Cancer (IARC) attributes a portion of malignancies to chronic exposure to environmental toxicants, especially redox-active trace elements released by mining, smelting, intensive agriculture, food consumption and fossil-fuel combustion (2,3). In Caucasian populations, the skin is the most common site for cancer diagnosis, and incidence continues to climb worldwide despite extensive educational and preventive efforts (4-6). Skin cancer includes both malignant melanocytic neoplasms and keratinocyte-derived tumours; within the latter group, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most important clinical entities (4,7). Although solar ultraviolet radiation (UVR) remains the canonical driver, a growing body of mechanistic and epidemiological evidence implicates heavy metals, and, pre-eminently, arsenic, in cutaneous carcinogenesis (8-10).

Arsenic, a metalloid, stands as a notable carcinogen due to its widespread exposure through contaminated drinking water and in occupational settings, as well as its multifaceted mechanisms of action in cutaneous cells (11,12). Chronic

arsenic exposure is associated with a spectrum of skin lesions, ranging from hyperkeratosis and hyperpigmentation to SCC and BCC (13). Mechanistic studies have implicated altered redox regulation, dysregulated DNA damage signalling and epigenetic reprogramming in arsenic-associated carcinogenesis (14-17). Experimental co-exposure models using solar/solar-simulated UVR (typically UVA-dominant with a UVB component) show that drinking-water arsenite (AsIII) acts as a co-carcinogen in SKH-1 mice. However, population evidence for interaction is mixed and may depend on exposure range and cancer subtype, and the relevance of these models to human arsenic-associated skin cancer remains uncertain, since arsenic-related non-melanoma skin cancer (NMSC) also arises in sun-protected sites (18-21).

The present review aims to consolidate the current understanding of the role of arsenic in cutaneous carcinogenesis. To the best our knowledge, no prior review has provided an integrative synthesis of molecular mechanisms with epidemiological evidence addressing arsenic-induced skin cancer.

2. Arsenic exposure, biotransformation and toxicity

Environmental mobilization and biotransformation. Arsenic is a semi-metallic element that crystallises in a covalently bound lattice whose restricted electron mobility confers brittleness despite its metallic lustre (22). Naturally occurring arsenic is chiefly encountered as sulphide or sulphosalt minerals, including arsenopyrite, realgar, orpiment and enargite, distributed throughout ore bodies (23). Mining-independent lithogenic sources, principally arsenopyrite, realgar, orpiment and related sulphosalts, constitute the dominant geogenic reservoir from which arsenic is mobilised into soil and aquifer matrices. These mineralogical origins frame the paradoxical status of the element as a non-essential yet redox-active xenobiotic capable of wide-ranging biochemical disruption (23,24).

Human uptake is governed by chemical speciation and solubility, with water-borne arsenicals generally exhibiting greater gastrointestinal bioavailability than food-bound counterparts or poorly soluble soil sulphides (23). Notably, more than three-quarters of an oral dose is recovered as inorganic As^{3+}/As^{5+} or their mono- and dimethylated derivatives, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), respectively (25). Although inhalation of arsenic trioxide particulates remains critical in occupational contexts such as non-ferrous smelting, community-level risk is overwhelmingly driven by ingestion of contaminated drinking water (24). Dermal absorption is minor relative to these routes. Passive transmembrane diffusion predominates in humans and mice, whereas carrier-mediated transport has been reported in rats, hinting at species-specific differences in epithelial handling (25).

Ingested arsenicals undergo a sequence of redox interconversion, enzymatic methylation via the one-carbon metabolic network and subsequent renal elimination (26-28) (Fig. 1). Arsenate (AsV) can be transported by sodium/phosphate cotransporters such as NaPi-IIb (encoded by *SLC34A2*), whereas AsIII can be transported by aquaglyceroporins, including AQP9 (29,30). After passage to the portal blood, both species are taken up by hepatocytes whose cytosol contains millimolar glutathione (GSH) and high activities of glutaredoxin and thioredoxin. AsV can be enzymatically reduced to AsIII in mammalian systems, providing a substrate for methylation (28,31). The resulting AsIII is the substrate for the cytosolic arsenic(+3) methyltransferase (AS3MT), which transfers a methyl group from S-adenosyl-L-methionine (SAM) to generate monomethylarsonous acid (MMAIII) and S-adenosyl-L-homocysteine (32). MMAIII constitutes a branch point; it can oxidize non-enzymatically to pentavalent MMA (MMAV) or it can re-enter AS3MT for a second methyl transfer, yielding dimethylarsinous acid (DMAIII) (31,33). DMAIII can likewise oxidize to pentavalent DMA (DMAV); MMAV and DMAV are major methylated end products detected in human urine (31,33).

Although the major methylated end products of inorganic arsenic biotransformation in humans are well established, the enzymatic sequence by which reduction, methyl transfer and oxidation are coupled remains debated, and multiple mechanistic models have been advanced (31). A widely used Challenger-type redox-cycling scheme describes the oxidative methylation of trivalent arsenicals alternating with the reduction of pentavalent intermediates, yielding the sequential appearance of mono- and dimethylated species and predicting trivalent methylated intermediates in the pathway (26,27). Consistent with this, Thomas *et al* (26) summarised evidence that methylated arsenicals containing arsenic in the trivalent oxidation state have been identified as intermediates and detected in human cells cultured with inorganic arsenic and in the urine of chronically exposed individuals, as well as highlighted their heightened biological reactivity relative to inorganic trivalent arsenic. However, in comparative reviews of AS3MT function, this redox-cycling model does not, in its basic form, identify the methyl donor or the source of reducing equivalents, leaving key biochemical steps incompletely specified (27). By contrast, the sulfhydryl/thiol-complex model advanced by Hayakawa *et al* (34) proposes that thiol-containing complexes of trivalent arsenicals, particularly GSH conjugates, are obligatory substrates for sequential methyl transfer reactions (27,34). In support of this concept, Hayakawa *et al* (34) reported that arsenic triglutathione (ATG) can form non-enzymatically from iAs(III) in the presence of millimolar GSH, that recombinant human Cyt19/AS3MT catalysed methyl transfer only when ATG was present and that monomethylarsonic diglutathione (MADG) served as a substrate for further methylation to dimethylarsinic glutathione (DMAG), whereas MMA(III) was not methylated under their conditions. A limitation of the thiol-complex model is the chemical lability of proposed GSH-conjugated intermediates. Specifically, Hayakawa *et al* (34) noted that MADG and DMAG were unstable at lower GSH concentrations, undergoing hydrolysis and oxidation to MMA(V) and DMA(V), complicating the interpretation and detection of intermediates in biological matrices. Notably, comparisons emphasise that neither model alone is fully satisfactory, and that further structural/functional understanding of AS3MT and its interaction with cellular reductants is required to reconcile these frameworks (27,34).

Impact on human health. Chronic exposure to inorganic arsenic initiates a coordinated, multisystem injury cascade (35,36). Chronic arsenic exposure is associated with characteristic cutaneous findings, including palmoplantar

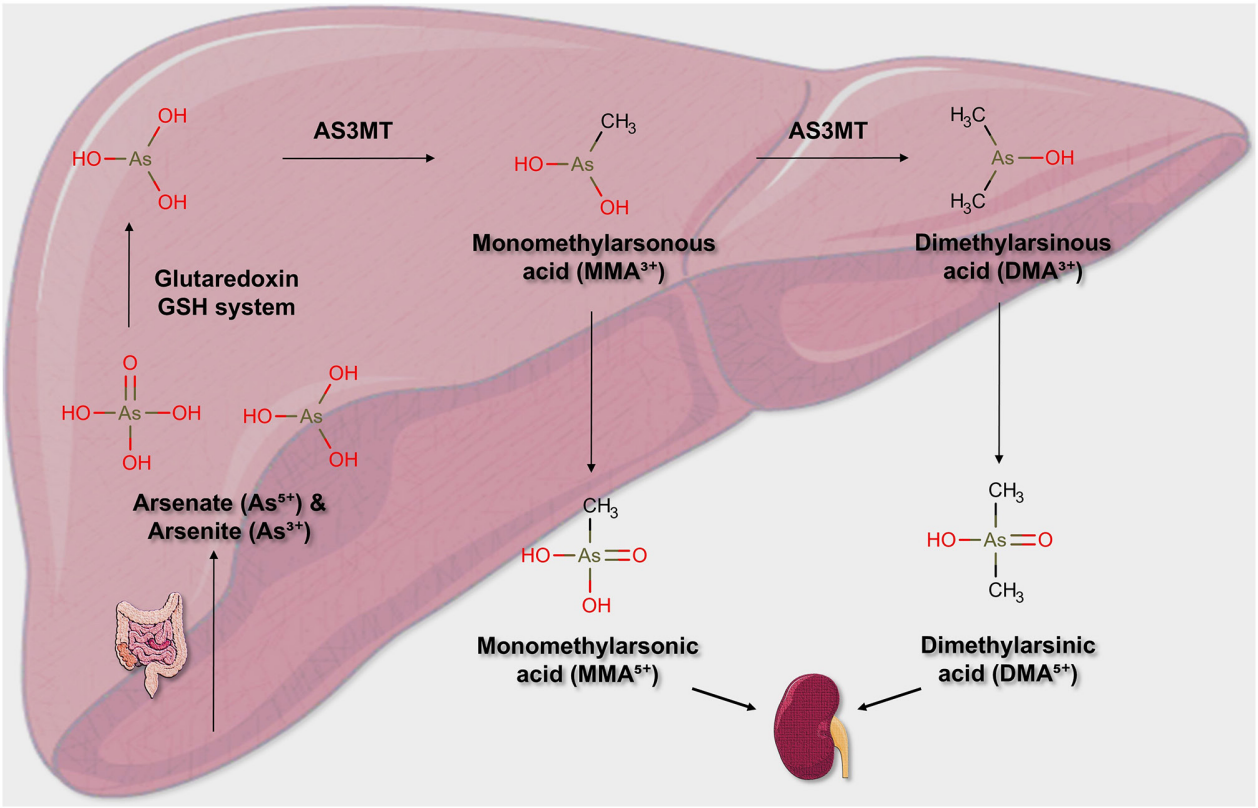

Figure 1. Biotransformation pathways of arsenic. GSH, glutathione; AS3MT, cytosolic arsenic(+3) methyltransferase.

hyperkeratosis, raindrop-like pigmentary changes, Bowen's disease and keratinocyte cancer types such as SCC and BCC (37,38). Arsenic exposure has been associated with increased atherosclerotic cardiovascular disease risk, including ischemic heart disease, and obliterative peripheral vascular disease underpins the classical 'Blackfoot' gangrenous vasculopathy (39,40). In the renal cortex, the metal concentrates in the proximal tubular epithelium, collapsing mitochondrial bioenergetics and eliciting a necro-inflammatory loss of reabsorptive capacity, a lesion that predicts chronic kidney disease in exposed communities (41). Neurotoxic sequelae span painful stocking-glove sensory neuropathy in adults to measurable decrements in child neurodevelopment, reflecting axonal bioenergetic failure and disrupted neurogenesis (42-44). In addition, early-life dietary exposures, particularly from rice-based and other baby food products, constitute a significant vector for inorganic arsenic exposure. Rice cereals and related baby foods have been repeatedly documented to contain elevated arsenic concentrations, with surveys reporting detection in a large portion of commercially available products and, in some rice cereals, concentrations exceeding established guidance levels (45). Hepatocytes, already burdened as the primary site of arsenic biotransformation, manifest steatosis, stellate-cell activation and progressive fibrotic remodelling that can culminate in macronodular cirrhosis (46). At the endocrine level, nano-to micromolar AsIII blunts glucose-stimulated insulin secretion, injures β-cell mitochondria and hastens both type 1 and type 2 diabetic phenotypes *in vivo* (47,48). Hematopoietic progenitors are likewise vulnerable, with chronic drinking-water exposure suppressing erythroid differentiation (49,50). Parallel impairments in macrophage lysosomal biogenesis and T-cell cytokine polarization compromise host defence and vaccine responsiveness, underscoring the emerging profile of arsenic as a human immunotoxicant (51-53). Finally, across the skin, lungs, bladder and liver, the mechanistic impact of arsenic converges to create a potent human carcinogen (54) (Fig. 2).

Clinical evidence estimates a potentially lethal acute oral dose of inorganic arsenic/arsenic trioxide in the 100-300 mg range (36,55). Chronic exposures of a lower magnitude precipitate dermatological hallmarks, hyperpigmentation, diffuse or punctate keratoses and NMSC (56). Gastrointestinal manifestations diverge temporally: fulminant diarrhoea typifies acute poisoning, whereas protracted exposure yields intermittent vomiting and enteropathy (36). Toxicodynamic heterogeneity arises from physicochemical variables (such as solubility and oxidation state), exposure metrics (such as dose frequency and duration) and host factors (12,57). Thus, seafood containing predominantly arsenobetaine may exceed total-arsenic guidelines yet confer minimal risk, whereas trace concentrations of soluble oxyanions in drinking water convey a disproportionate hazard (58).

Molecular mechanisms of arsenic toxicity. Arsenic affects >200 enzymes, notably those mediating DNA replication/repair and ATP metabolism, in part by substituting phosphate in high-energy intermediates (24,36). Intracellular reduction of As^{5+} to the more membrane-permeant As^{3+} constitutes a bioactivation step; trivalent AsIII preferentially complexes with vicinal dithiols in lipoic-acid-containing enzymes such as pyruvate dehydrogenase, impairing mitochondrial acetyl-CoA production and compromising oxidative phosphorylation (59). Covalent binding to GSH and cysteine-rich

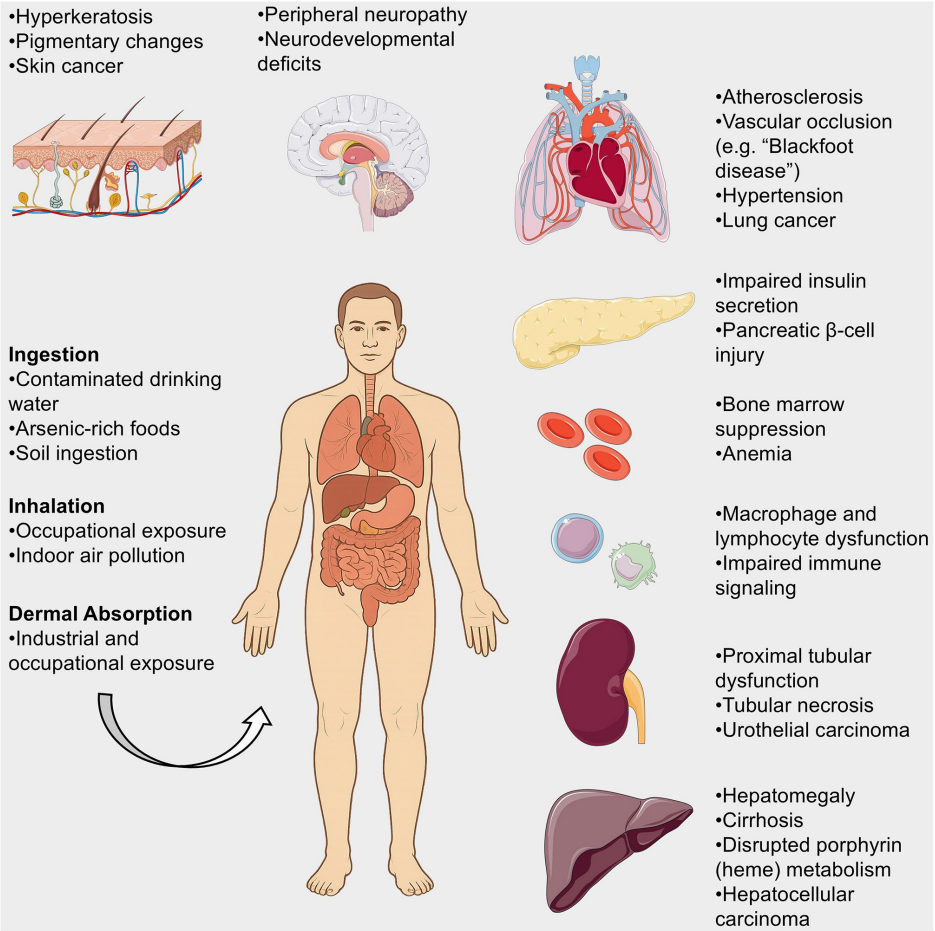

Figure 2. Multisystem clinical manifestations of chronic inorganic arsenic exposure.

motifs in thioredoxin reductase further disrupts redox homeostasis (59). Concomitantly, arsenic exposure is associated with increased cellular reactive oxygen species (ROS) and reactive nitrogen species (such as $O_2^{\bullet -}$, H_2O_2, NO• and peroxyl species), generated predominantly via indirect mechanisms such as mitochondrial electron-transport perturbation and disruption of thiol redox buffering (60-64). The resultant oxidative milieu precipitates lipid peroxidation, protein carbonylation and DNA strand damage (24,36).

Neurotoxicity is a recognised adverse outcome of inorganic arsenic exposure. In neuronal cell models, inorganic arsenic can increase oxidative stress and impair mitochondrial function, contributing to apoptotic signalling. These *in vitro* effects are typically observed at micromolar concentrations, which exceed concentrations reported in a number of environmentally exposed populations, and therefore require careful dose-contextualisation (65-67). The resulting redox disequilibrium accelerates membrane-lipid peroxidation and causes accumulation of 8-hydroxy-2'-deoxyguanosine adducts in neuronal DNA (68,69). Oxidative stress has been reported to act upstream of a MAPK switch in which p38 and the neuron-restricted isoform of JNK3 are selectively phosphorylated; pharmacological blockade of either kinase rescues rat cerebellar neurons from AsIII-induced apoptosis and preserves axonal integrity, establishing the relationship between p38/JNK3 and cytoskeletal disintegration and axonal degeneration (69,70). Concurrently, sustained ROS generation can promote mitochondrial permeability-transition pore opening, precipitating cytochrome c efflux, caspase-9 activation and apoptosis in neural stem cells and PC12 neurons (71,72) (Fig. 3). In hepatic tissue, AsIII exposure has been associated with mitochondrial dysfunction, including cytochrome c release, caspase-9 activation and mitochondrial swelling, with oxidative stress acting as a contributing mediator of cell injury and death (73). *In vivo*, rural women chronically exposed to low-level arsenic exhibited elevated circulating TNF-α, IL-6, IL-8 and IL-12 with concomitantly decreased IL-10 levels, alongside increased 8-hydroxy-2'-deoxyguanosine adducts in airway epithelial DNA (74).

Beyond external dose metrics, intrinsic factors modulate vulnerability. Solubility and oxidation state govern intrinsic toxicity, but frequency, duration, age, sex, nutrition and genetic polymorphisms affecting methyltransferase enzymes collectively dictate clinical outcome (12,57). Populations reliant on high-bioavailability water sources manifest more severe sequelae than those ingesting comparably dosed staple foods wherein arsenic is predominantly protein-bound and poorly absorbed (58).

3. Arsenic and carcinogenesis

The inclusion of arsenic in Group 1 of the IARC monograph series reflects strong epidemiological links to skin, lung, bladder, liver and renal cancer (11). Arsenic commands

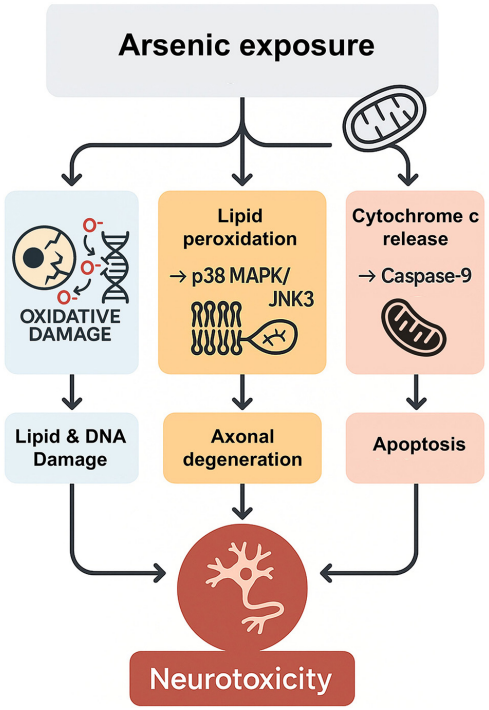

Figure 3. Pathways of arsenic-induced neurotoxicity. Arsenic exposure can perturb cellular redox homeostasis increasing oxidative stress and contributing to lipid and DNA damage. Lipid peroxidation can engage stress-activated kinase signalling (p38 MAPK/JNK3), promoting axonal degeneration. In parallel, mitochondrial dysfunction can promote cytochrome c release with downstream caspase-9 activation and apoptosis.

considerable public health attention due to concentrations in both groundwater and treated drinking water frequently surpassing the U.S. Environmental Protection Agency (EPA) enforceable maximum contaminant level of 10 μg l^{-1}, thereby signalling a tangible toxicological hazard (75). Nation-wide surveys further indicate that roughly 7% of U.S. domestic wells yield water with arsenic levels exceeding this regulatory threshold (76). In clinical investigations, evidence supports an association between prolonged arsenic exposure and increased cancer risk, with risk generally rising with exposure level and duration (77).

Sarkar *et al* (78) reported that patients diagnosed with colorectal carcinoma displayed a mean serum arsenic concentration significantly higher than that observed in healthy controls. Additional serum analyses in bladder-cancer cohorts reveal arsenic concentrations that are higher than those measured in matched healthy individuals (79). Marked heterogeneity in tissue-specific arsenic concentrations has also been observed, likely reflecting cancer-type-dependent metal accumulation driven by the unique biological attributes of distinct cell populations (76,80,81).

The oncogenic impact of inorganic arsenic is multifactorial, with oxidative stress, indirect DNA damage, global and gene-specific epigenetic reprogramming and inhibition of DNA repair machineries converging to facilitate malignant transformation (82-84) (Fig. 4). Although inorganic arsenic is not generally considered a classical direct-acting mutagen, substantial evidence supports indirect genotoxicity, including interference with DNA damage response/repair and chromosomal alterations (85-88).

Clastogens are agents that cause structural chromosomal aberrations, and arsenic has long been recognised to produce chromosomal alterations *in vitro* and in exposed populations. The U.S. National Research Council (NRC) concluded that chromosomal alterations rather than point mutations are more likely to be involved in arsenic carcinogenicity and that these aberrations could arise via direct or indirect interaction with DNA, with indirect mechanisms considered much more likely (86). The NRC further noted that human *in vivo* cytogenetic data indicate that the predominant effect is clastogenesis rather than aberrant chromosomal segregation, and summarised the most plausible general mode of action as induction of structural and numerical chromosomal abnormalities without acting directly with DNA (86). In human keratinocytes, chronic low-dose inorganic arsenic suppresses DNA damage response signalling (reduced ATM Ser1981 phosphorylation and checkpoint kinase 2 activation), is accompanied by reduced RAD50 expression and is associated with increased double-strand break accumulation. Accordingly, the genotoxicity of arsenic is best framed as predominantly indirect, arising from redox imbalance/oxidative stress signalling and interference with DNA-damage signalling/repair, which together promote single- and double-strand DNA breaks and downstream chromosomal instability (67,86).

Consistent with this paradigm, inorganic arsenic does not readily form stable bonds with DNA directly and is therefore not expected to act as a classical genotoxicant; its genotoxicity emerges through indirect mechanisms. The biotransformation of AsIII to methylated arsenicals, particularly dimethylarsinic species, may amplify oxidative stress signalling and DNA strand breakage under certain exposure conditions. Although increased intracellular ROS has been reported in some experimental systems, these findings vary by arsenical species, concentration, exposure duration and cell type, and should therefore be interpreted cautiously in relation to human exposure scenarios (24,87,88).

Oxidative DNA damage and genotoxicity. Oxidative stress associated with arsenic exposure is thought to arise largely through indirect mechanisms, including impaired antioxidant defences and mitochondrial dysfunction (87-89). Although mutational consequences have been reported in some experimental systems, the relevance of specific oxidative signatures and mutation spectra to human arsenic-associated skin carcinogenesis remains uncertain (90,91). Beyond the nuclear genome, oxidative stress compromises mitochondrial DNA integrity, a process mechanistically linked to aberrant bioenergetics, evasion of apoptosis and altered differentiation (92). Oxidative stress associated with arsenic exposure intersects with the DNA-damage response at multiple nodes. Experimental models demonstrate sustained double-strand breaks and impaired recruitment of repair factors, culminating in chromosome mis-segregation and aneuploidy (93). A predilection for centromeric instability manifests as dicentric chromosomes, lagging chromatids and micronuclei formation, lesions that correlate with increased cancer incidence (94). Genomic instability is reinforced by end-to-end chromosomal fusions, aberrant sister-chromatid separation and telomere dysfunction (95). Overall, the available evidence is more consistent with predominantly indirect effects of arsenic on

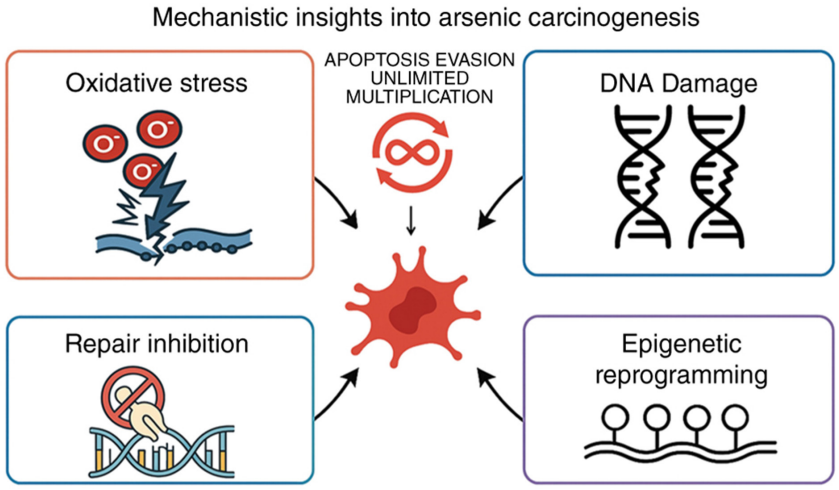

Figure 4. Oncogenic mechanisms of arsenic. Arsenic exposure has been associated with oxidative stress, DNA damage and genomic instability, impaired DNA repair capacity and epigenetic reprogramming. These pathways can contribute to apoptosis resistance and sustained proliferative signalling.

genomic integrity, mediated through redox perturbation, dysregulated DNA damage signalling and chromosomal instability, rather than through classical DNA-adduct formation.

Epigenetic dysregulation. Epigenetic dysregulation is an important component of arsenic-associated carcinogenesis. The earliest documentation of arsenic-induced global epigenetic perturbation dates to the 1980s (96). Genome-wide profiling has mapped thousands of loci exhibiting altered promoter methylation following occupational or environmental exposure, affirming the breadth of the epigenomic footprint of arsenic (97). A key limitation across the literature is that experimental systems span wide concentration ranges, and some *in vitro* paradigms use arsenicals at levels that induce marked oxidative stress or growth inhibition; under such conditions, epigenetic readouts may reflect secondary stress responses and/or selection of resistant subclones, rather than primary reprogramming.

At low, non-cytotoxic exposure levels, arsenic promotes both hyper- and hypomethylation. The directionality appears context-dependent, reflecting genomic context and chromatin state, with gene-specific hypermethylation co-existing alongside global hypomethylation in the same cell (93,98). Since methylation readouts can be distorted by overt cellular stress, findings from high *in vitro* concentrations should be interpreted cautiously. Central to this duality is the metabolic coupling between arsenic methylation and the SAM one-carbon pool. SAM acts as a co-substrate for arsenic methyltransferase, yet intracellular SAM concentrations (~80 μM) are typically sufficient to buffer moderate arsenic loads, arguing against wholesale SAM depletion at environmentally relevant exposures. Nonetheless, SAM utilisation for arsenic detoxification has been implicated in DNA hypomethylation when drinking-water As exceeds 500 μg l^{-1} (93,99). Thus, the influence of arsenic on methyl-donor availability may be threshold dependent, with marked effects emerging only at high-level exposures.

Consistent with an epigenetic mechanism, promoter hypermethylation of canonical tumour suppressors has been reported *in vitro* and *in vivo*. Arsenic exposure elicits dense methylation of *TP53* and *CDKN2A*, while chronic As(V) ingestion induces hypermethylation of *Cdkn2a* and *Rassf1a* in murine lung tissue (100,101). Beyond promoter methylation, arsenic also intersects p53 checkpoint control through homeodomain-interacting protein kinase-2 (*HIPK2*), a stress-responsive kinase that phosphorylates p53 on Ser46 to license its pro-apoptotic transcriptional program after genotoxic injury. In epidermis, HIPK2 integrates canonical UV-ATR signalling, and genetic or functional attenuation of HIPK2 suppresses p53-Ser46 signalling and favours survival of UV-damaged keratinocytes; conversely, loss of *Hipk2* in mice accelerates two-stage chemical skin carcinogenesis, underscoring a tumour-suppressive role in cutaneous epithelium (102-104). Sodium arsenite stabilizes HIPK2 protein (and HIPK1) and activates a HIPK2-CREB pathway, indicating that arsenic exposure can rewire HIPK2 output toward transcriptional programs beyond p53. While these experiments were not performed in keratinocytes, they establish biochemical tractability of HIPK2 to arsenic (104).

Conversely, hypomethylation of repetitive elements such as long interspersed nuclear element-1 (LINE-1) is a frequently reported feature of arsenic exposure (105). LINE-1 hypomethylation correlates with genomic instability and has been linked to diverse pathologies, including colon cancer and β-thalassaemia (93). Epidemiological studies have reported arsenic-specific demethylation at LINE-1 loci across multiple cohorts (106,107). Overall, due to the strong influence of age on DNA methylation, age-matching in animal experiments and age-adjustment in human studies are important to reduce confounding when interpreting arsenic-associated methylation differences.

Beyond DNA methylation, arsenic provokes wide-ranging alterations in histone post-translational modifications (PTMs). Mass-spectrometry-based chromatin dissections reveal global shifts in histone acetylation, methylation and phosphorylation patterns after sub-micromolar AsIII exposure (108,109). Mechanistically, arsenic activates nuclear mitogen- and stress-activated protein kinase 1, which simultaneously demethylates H3K9 and phosphorylates H3S10, thereby upregulating immediate-early proto-oncogenes such as *FOS* and *JUN* (110-112). Arsenic also remodels the histone-variant

landscape, increasing levels of histone H2B type 1-K, type 1-C, type 1-D and type 1-B proteins and inducing polyadenylation of canonical histone H3.1 through degradation of stem-loop binding protein (113,114). The resulting stabilisation of poly(A)+ H3.1 transcripts outside the S phase drives genomic instability, mitotic arrest and malignant transformation (93). Together, these findings support a broad effect of arsenic on chromatin organization, although the relevance of specific changes to human skin carcinogenesis has yet to be concretely established.

Transcriptomic and non-coding RNA alterations. Splicing regulation emerges as an additional target of arsenic toxicity. Genome-wide analyses have identified widespread exon-usage changes in arsenic-exposed human cells, implicating aberrant alternative splicing in tumour initiation (115). Given that 95% of multiexon human genes are subject to alternative splicing under physiological conditions, even subtle perturbations can reconfigure proteomic diversity (98). Dysregulated splicing has established roles in angiogenesis, epithelial-mesenchymal transition and other oncogenic processes (116-118). Arsenic-mediated changes in polymerase II kinetics, together with DNA methylation and histone PTMs, likely influence exon recognition. Notably, the epigenetic silencing of *PARP1* or CCCTC-binding factor in arsenic-treated cells demonstrably alters splice-site choice, highlighting a functional intersection between chromatin architecture and splicing fidelity (93,119).

Non-coding RNA (ncRNA) circuitry is likewise perturbed. Only ~2% of the human transcriptome encodes protein, leaving a vast landscape of regulatory ncRNAs susceptible to environmental modulation (93,120). Arsenic exposure provokes broad microRNA (miRNA) dysregulation, with one investigation documenting aberrant expression of 36 miRNAs and earlier work describing global miRNA shifts (121-123). Since miRNAs govern mRNA stability and translation, their disruption may reinforce arsenic-induced epigenetic and transcriptomic re-wiring.

Despite substantial progress, important knowledge gaps remain regarding dose-response thresholds at environmentally relevant exposures, the translation of experimental findings to human cutaneous carcinogenesis and tissue-specific susceptibility. The relative contributions of epigenetic dysregulation, altered splicing and non-coding RNA perturbation to malignant transformation also remain incompletely defined. Integrating multi-omics profiling with precise exposure assessment in well-characterised human cohorts will be essential for the development of validated biomarkers and evidence-based mitigation strategies.

4. Mechanistic pathways in arsenic-induced skin cancer

Arsenic-induced carcinogenesis in the skin encompasses complex and multifaceted mechanistic pathways, characterized by notable molecular heterogeneity across both melanoma and NMSC (Fig. 5). Experimental studies have implicated redox perturbation, altered DNA damage signalling and changes in repair responses in arsenic-exposed cells. Evidence of AsIII interaction with zinc-finger motifs in solution or cell-free systems does not, by itself, establish loss of repair protein function *in vivo*; accordingly, the described DNA-repair effects are context-dependent cellular observations rather than definitive *in vivo* mechanisms (20,124-127). Beyond genotoxic stress, arsenic modulates transcriptional and post-transcriptional programmes. miRNA-mediated immunological dysfunction, telomere attrition and promoter hypomethylation interlaced with focal hypermethylation at tumour-suppressor loci, as revealed by epigenome-wide analyses, have been implicated in skin cancer susceptibility (14-16,128).

Arsenic-UVR interactions have been explored in experimental and epidemiological studies, with some reports suggesting that co-exposure may modify tumour-related outcomes, yet the clinical relevance of these findings remains uncertain. The occurrence of arsenic-associated NMSC in sun-protected sites indicates that UVR interaction is not required to explain arsenic-induced skin carcinogenesis. Complementing these pathways is the concept of co-carcinogenesis. Carcinogenicity is not restricted to directly mutagenic insults; tumour promotion can also proceed through agents that intensify the mutational output of a second, primary genotoxin (129-131). Since arsenic-associated cutaneous carcinogenesis is not restricted to UV-exposed settings, UVR co-mutagenesis is best interpreted as a potential modifier mechanism that may operate in specific contexts rather than a universal requirement. Mechanistic insight into this synergy has been limited, with hypotheses spanning oxidative stress, inhibition of DNA repair proteins and epigenetic dysregulation (20,83,126,127).

In melanoma, the precise carcinogenic mechanisms of arsenic remain less delineated but likely involve overlapping pathways identified in NMSC. Reports suggest that combined arsenic-UVR exposure may accelerate melanoma formation and increase mutational loads in murine models (20,132,133). Arsenic promotes genomic instability, perturbs apoptosis and interferes with MAPK and PI3K pathways, augments angiogenesis and, in the presence of platelets, enhances tumour-cell extravasation (133-136). Collectively these effects provide a plausible mechanistic framework linking arsenic with melanoma pathogenesis; however mechanistic claims are largely drawn from experimental models and should be interpreted cautiously when extrapolating across species and exposure scenarios.

Experimental and mechanistic evidence of arsenic-UVR synergy. Genomic profiling of N/TERT-1 keratinocytes demonstrated that 1 μM AsIII alone induced no measurable increment in single-base substitutions (SBS) relative to vehicle controls (20,137). However, when the identical arsenic dose is accompanied by exposure to a physiologically spectrum-matched solar simulator, the aggregate SBS + doublet base substitution (DBS) load nearly doubles vs. UVR alone. The mutation pattern is compatible with altered cellular handling of UVR-induced damage, but does not by itself establish a specific repair defect or define the dominant mechanism in human disease (20,126,127). It should be highlighted that the translational relevance of micromolar *in vitro* AsIII exposures to typical drinking-water-associated internal doses remains uncertain and warrants cautious interpretation.

Mechanistically, arsenic has been shown to delay repair of UVR-induced cyclobutane pyrimidine dimers in keratinocytes, with proposed pathways including perturbation of redox and signalling processes that secondarily impair repair capacity, and disruption of zinc-dependent protein motifs has

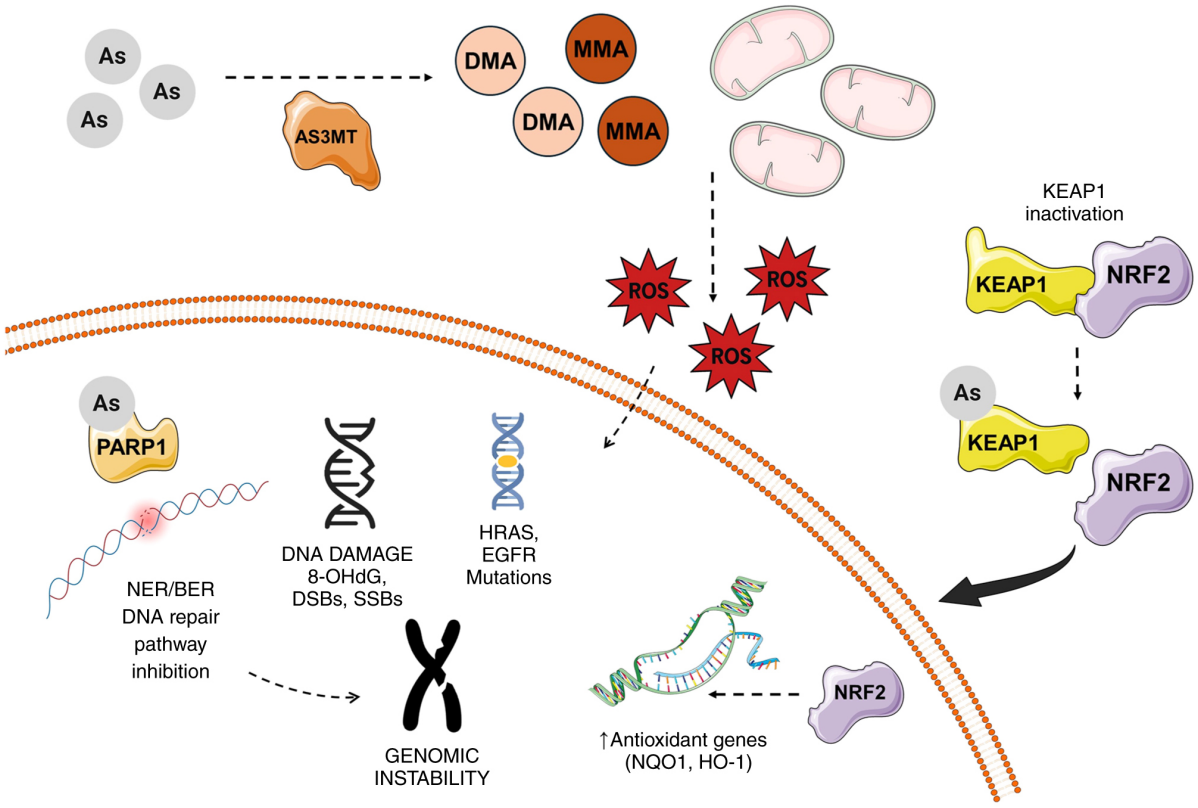

Figure 5. Mechanistic overview of the multifactorial actions of arsenic in keratinocytes. Inorganic arsenic is biotransformed by AS3MT into methylated arsenicals (MMA and DMA). In keratinocytes, arsenic exposure is linked to mitochondrial dysfunction and increased ROS. Oxidative stress is associated with DNA damage, including 8-OHdG adducts, SSBs and DSBs, and may contribute to oncogenic mutations in genes such as such as *HRAS* and *EGFR*. Arsenite can modify KEAP1, promoting NRF2 activation and induction of antioxidant genes (such as *NQO1* and *HO-1*). Arsenic can also inhibit PARP1-dependent signalling and is associated with reduced NER/BER DNA repair capacity, promoting genomic instability. AS3MT, arsenic(+3) methyltransferase; MMA, monomethylarsonic acid; DMA, dimethylarsinic acid; ROS, reactive oxygen species; SSBs, single-strand breaks; DSBs, double-strand breaks; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; KEAP1, Kelch-like ECH-associated protein 1; NRF2, nuclear factor erythroid 2-related factor 2; PARP1, poly (ADP-ribose) polymerase 1; NER, nucleotide-excision repair; BER, base-excision repair.

also been proposed in some contexts, but direct *in vivo* inhibition of specific factors (such as XPA) should not be assumed from biochemical findings alone (20,124,125,138). *In vivo* validation in SKH-1 hairless mice revealed a 1.3-fold increase in tumour multiplicity after 26 weeks of combined arsenic plus UVR exposure, alongside an ~6-fold escalation in both SBS and DBS events within harvested tumours; however, species differences in arsenic metabolism and disposition should be considered when extrapolating dose-response features from murine models to humans (20). Some evidence suggests that NMSC incidence in chronically exposed populations exceeds that predicted by arsenic or UVR alone (20,139). These findings support the view that arsenic can modulate UVR-associated carcinogenic responses in some experimental settings. At the same time, important uncertainties remain, including species differences in arsenic metabolism and disposition, exposure-level comparability and the fact that arsenic-associated NMSCs in humans also arise in sun-protected sites. Accordingly, UVR co-carcinogenicity should be regarded as a context-dependent experimental observation rather than an established mechanistic explanation for arsenic-associated skin cancer.

Genomic and transcriptomic landscape. NMSCs exhibit distinctive genetic and epigenetic perturbations upon chronic arsenic exposure (16,54). To interrogate tumour genomes emerging in this high-exposure context, Jasmine *et al* (16) analysed 32 histologically confirmed NMSCs (26 BCCs and 6 SCCs) together with 16 normal skin biopsies from HEALS/BEST participants using a 400-gene cancer panel. They catalogued 6,829 somatic mutations across tumours and 3,385 unique loci vs. 2,530 mutations (1,470 loci) in normal skin, revealing a substantial reservoir of UVR-signature C>T transitions even in clinically unremarkable epidermis (16,140,141). Despite a numerically higher median tumour-mutation burden in SCC (106 mut Mb^{-1}) relative to BCC (87 mut Mb^{-1}) and normal skin (82 mut Mb^{-1}), these differences did not attain statistical significance, underscoring the magnitude of UVR-imprinted mutations that accrues in chronically sun-exposed keratinocytes (16,140,141). Stringent subtraction of variants shared with normal skin delineated 1,611 NMSC-specific single-nucleotide variants, >600 of which map to cutaneous oncogene/tumour-suppressor registers in COSMIC or ClinVar (16). In BCC, high-frequency targets encompassed *PTCH1*, *NOTCH1*, *SYNE1*, *PKHD1* and *EP400*, whereas SCC samples were dominated by disruptive *TP53* lesions (16,142). These patterns mirror canonical driver spectra in Caucasian cohorts, with *PTCH1* and *SMO* mutations activating Hedgehog signalling in BCC and *TP53* inactivation stratifying high-risk SCCs, suggesting universality of these

pathogenic nodes even in an Asian, arsenic-burdened population (16,140,143-146).

Integration of RNA-sequencing data with mutational status has revealed that non-synonymous *PTCH1* alterations are accompanied by amplified Hedgehog-pathway and BCC transcriptional signatures, relative to *PTCH1*-wild-type BCC tumours (16). Analogous coupling has been observed for *NOTCH1*, *SYNE1* and *PKHD1*, whose mutations precipitate co-ordinated shifts in inflammatory circuits, including IL-17 and TGF-β signalling. In SCC, loss-of-function *TP53* variants re-wire p53-dependent cell-cycle and DNA-damage checkpoints, reinforcing the phenotypic dichotomy between the two major NMSC subtypes (16,142).

Stratification by urinary arsenic burden has uncovered a subtle antagonism whereby elevated exposure partially blunts the transcriptional consequences of oncogenic *PTCH1* or *NOTCH1* lesions, an effect postulated to reflect arsenic-mediated impairment of DNA-repair fidelity or epigenetic homeostasis, thereby superimposing non-genetic regulatory noise on mutation-driven expression programmes (16,54,142). Although the cohort size precluded firm genotype-phenotype correlations, these data imply that mutation-centric therapeutic stratification, such as smoothened antagonists for *PTCH1*-mutant BCC, must be contextualized by the broader exposome if precision oncology is to be realized in endemic regions (16,140,143,147). Likewise, transcriptomic fingerprints of aberrant IL-17 signalling nominate immune-modulatory regimens for molecularly annotated patient subsets, but prospective trials remain conspicuously absent (16,142,148).

Mitochondrial dysfunction. Arsenic has been reported to disrupt mitochondrial biogenesis and dynamics, processes important for cellular energy homeostasis and apoptosis. Since mitochondria are both major regulators of redox balance and sensitive targets of cellular stress, they may contribute to some downstream effects of arsenic exposure (149-152). In a West Bengal case-control study, promoter hypomethylation of *PPARGC1A* and *TFAM*, master regulators of mitochondrial biogenesis, correlated with urinary arsenic and with progression from premalignancy to carcinoma (152). Concomitant upregulation of *PPARGC1A*, *TFAM*, *NRF1* and *NFE2L2*, together with elevated mitochondrial-DNA copy number in malignant tissues, is consistent with a compensatory yet maladaptive mitochondrial biogenic burst (152). Experimental studies have linked arsenic exposure to mitochondrial oxidative stress, altered redox signalling and endoplasmic reticulum stress, changes that may compromise mitochondrial DNA integrity. Since mitochondrial DNA has more limited repair capacity than nuclear DNA, these effects could contribute to mitochondrial dysfunction under some exposure conditions (153-155). Dysregulated fusion-fission machinery further destabilises mitochondrial networks; expression of *OPA1*, *MFN1*/*MFN2* and *DNM1L* transcripts have been shown to be markedly altered across lesion stages (152,156-158). Collectively, these findings suggest that arsenic exposure may alter mitochondrial biogenesis, mtDNA copy number and organelle dynamics in keratinocytes, although the extent to which these changes are causal, adaptive or secondary likely depends on exposure context and disease stage (150,152,157,159-162).

Telomere dysregulation and alternative lengthening. Arsenic influences chromatin states at chromosome ends. Telomere attrition is a barrier to unlimited proliferation, and compromise of telomere integrity, whether by excessive shortening or by aberrant elongation, drives genomic instability and oncogenesis (163,164). Classically, tumour cells overcome the Hayflick limit via telomerase re-expression; a minority employ recombination-based alternative lengthening of telomeres (ALT). Both telomere attrition and aberrant elongation provoke genomic instability, and deviations in telomere length correlate with cancer and ageing (159,165-170). Chronic environmental carcinogens, including arsenic, perturb telomere homeostasis (15,171,172). Oxidative stress-mediated DNA damage and genomic instability have been implicated, and arsenic may promote epigenetic deregulation at telomeric and subtelomeric loci (15,95,108,150,173,174). Human studies offer conflicting reports, with some demonstrating telomere elongation and others demonstrating shortening after arsenic exposure (15,128,149,175-178).

A pilot study of 40 tumour-adjacent-normal pairs (BCC or SCC) from individuals chronically exposed to arsenic revealed telomere elongation ≥2-fold in 85% of tumours, with positive correlation to urinary arsenic burden (15). These findings corroborate earlier skin-lesion data implicating arsenic in telomerase-independent telomere maintenance (15,179). DNA methylation profiling of four subtelomeric domains uncovered significant hypomethylation at 18p ($P<0.01$) but paradoxical hypermethylation at XpYp ($P<0.001$) (15). Overall, 65% of patients harboured methylation disturbances at more than two subtelomeric ends, consistent with a complex epigenetic landscape that may license ALT-type recombination (15,180-183). CpG methylation is recognised as a key regulator of subtelomeric recombination potential (15,184,185).

5. Arsenic and melanoma: Clinical and epidemiological evidence

While UVR remains the dominant established risk factor for cutaneous melanoma, mechanistic and epidemiological data suggest that arsenic may be a factor in cutaneous melanoma pathogenesis. Although its carcinogenicity for NMSC is well established, recent studies highlight the potential role of arsenic in melanoma pathogenesis, although the findings are heterogeneous.

Occupational arsenic exposure. Strong associative signals emerge from occupational cohorts in which arsenic exposure is both intense and well-characterised. In a hospital-based Italian case-control study, workers classified in the highest joint category of exposure intensity and probability exhibited a >3-fold elevation in melanoma risk [odds ratio (OR), 3.12; 95% confidence interval (CI), 1.10-8.86] (186). The effect appeared accentuated in women and in lighter phototypes, although small stratum-specific cell counts limited statistical confirmation (186). Similarly, the Agricultural Health Study linked inorganic-arsenic herbicide use to melanoma among licensed applicators (OR, 5.4; 95%, CI 1.3-22.9), with risk estimates >6.0 when lead-arsenate co-exposures accompanied fungicides such as benomyl or maneb/mancozeb (187). Earlier occupational assessments corroborate these observations:

A large interview-based series reported an overall OR of 4.1 for arsenic-exposed men, including a significant melanoma component (188). Collectively, these data underscore that specific arsenic formulations encountered in industrial or agricultural settings, particularly inorganic or metal-arsenical compounds, may convey substantial risk.

Environmental exposure. Early insights arose from biomarker-based work in Iowa, USA, where higher arsenic in toenails, a validated long-term integrator of exposure, was associated with a ~2-fold elevation in melanoma risk; among participants with a prior NMSC, the OR increased to nearly 7-fold, pointing to cumulative field cancerisation or shared susceptibility pathways (189). Two decades later, a geospatial analysis of historic goldfields in Victoria, Australia, confirmed that increasing natural log-transformed soil arsenic was accompanied by monotonic rises in smoothed standardised incidence ratios for melanoma of 0.05 per 2.7-fold change in men and women alike, with relative risks of 1.52 and 1.29, respectively, when contrasting the highest to the lowest quintile of exposure (190). Ecological limitations notwithstanding, these observations corroborate the relationship between geogenic arsenic reservoirs and melanoma occurrence. In the Buxar district, Bihar, India, where well water frequently exceeds 500 μg l^{-1}, 12 incident cancers were identified over 2 years, including melanoma; 1 illustrative patient presented with concurrent drinking-water arsenic of 534.2 μg l^{-1} and blood arsenic of 54.9 μg l^{-1}, underscoring a plausible exposure-response gradient (191). Bangladesh, the epicentre of the largest mass poisoning, similarly records melanoma as 1.15% of 960 arsenic-related skin tumours in a 12-year tertiary-care series, with all melanomas originating from the districts where water arsenic routinely exceeds 300 μg l^{-1} (192). Toenail and urine have emerged as complementary matrices, yet their interpretability differs. In South Korean patients, neither serum nor urinary total arsenic distinguished melanoma cases from controls, a result the authors attribute to the rapid renal clearance of arsenicals and the predominance of seafood-derived organic species in the Korean diet (193).

Conversely, a population-based case-control study in Iowa that integrated lifetime residential histories with satellite-derived UVR metrics found no association for either soil or groundwater arsenic, despite robust effects of adult UVR in men (21). Likewise, an extensive evaluation of National Health and Nutrition Examination Survey (NHANES) 2003-2016 data detected elevated odds of NMSC at higher urinary arsenic but not of melanoma (194). Comparable null findings were reproduced when NHANES was interrogated for the 2011-2016 cycles with additional adjustment for polycyclic aromatic hydrocarbons and multiple metals (195). In a New Mexico population-based study, the mean inorganic arsenic concentrations in current home drinking water were ~4 μg l^{-1} and were not associated with melanoma. Toenail arsenic was likewise unrelated to melanoma risk, and comet-assay analysis of blood samples showed no association between inorganic arsenic exposure and impaired DNA-repair capacity at the observed exposure levels (196).

A 2024 systematic meta-analysis yielded a pooled OR of 1.47 (95% CI, 1.01-2.13) for arsenic exposure and melanoma (133). Although subgroup restriction to US cohorts attenuated precision (OR, 1.40; 95%, CI 0.94-2.07), the directionality remained unchanged, and leave-one-out sensitivity analyses confirmed stability of the overall estimate (133). Overall, the epidemiological evidence for an association between arsenic exposure and melanoma remains mixed, with positive signals reported in some higher-exposure or biomarker-based studies, but insufficient consistency to support a definitive conclusion.

Effect modification and potential interactions. Arsenic has been reported to modify UVR-related effects in some non-melanoma experimental contexts, but whether a similar interaction is relevant to melanoma remains uncertain. In an Italian case-control study, risk elevation was more apparent among lighter phototypes, a phenotype intrinsically more UV-sensitive (186). Additionally, socioeconomic status (SES) further complicates the landscape: NHANES participants of higher SES are more likely to receive melanoma screening and simultaneously less likely to rely on private wells with elevated arsenic (194). By contrast, poverty may amplify exposure while restricting screening, explaining the disproportionate burden observed in disadvantaged goldfield communities and arsenic-contaminated districts of Bangladesh, where malnutrition-induced immunosuppression could potentiate oncogenesis (190,192,197).

Limitations of current evidence. Despite converging lines of evidence, notable gaps persist. Numerous occupational studies remain underpowered, rely on retrospective exposure assessment or lack biomarker verification (186,187). Environmental studies often contend with low-contrast exposure gradients, leading to non-differential misclassification and the dilution of effect estimates (21). Exposure misclassification remains a pervasive barrier: Urinary arsenic reflects recent intake, total arsenic conflates organic and inorganic species and water or soil measures ignore dietary sources. Toenail arsenic offers a longer window but is susceptible to hygiene and cosmetic practices (193). Few investigations deploy speciation or integrate cumulative dose metrics. Selection bias is plausible in clinical series from heavily contaminated regions where health-care access is limited (192). Additionally, confounding by socioeconomic status, healthcare access and sun-seeking behaviour complicates interpretation (194). Statistical power is constrained by the comparative rarity of melanoma relative to NMSCs in high-exposure settings, hence wide CIs even for robust point estimates (187,191). Finally, even in studies adjusting for proxies of sun exposure, residual confounding by intermittent UV intensity, sunburn history and sun-seeking behaviour may persist.

6. Arsenic and NMSC: Clinical and epidemiological evidence

In cutaneous SCC and BCC, UVR remains the dominant etiological driver, but clinical and epidemiological evidence accumulated over the past half-century highlights arsenic as a prominent environmental and occupational carcinogen for keratinocyte-derived skin neoplasms. Clinical datasets reveal that chronic arsenic exposure exerts an independent influence on keratinocyte carcinogenesis (198-200).

High exposure endemic regions. A prominent large-scale demonstration of the cutaneous carcinogenicity of arsenic derives from the nationwide retrospective survey of 1979-2007, which analysed >24,000 pathologically confirmed keratinocytic tumours across arseniasis-endemic and reference regions (200). Residents of Blackfoot disease endemic areas exhibited age-stratified incidence rates 4- to six-fold higher for SCC and three- to four-fold higher for BCC than counterparts elsewhere in Taiwan, with standardised-morbidity ratios (SMRs) peaking at 5.89 for SCC (1988) and 6.75 for BCC (1993). Notably, both SMRs declined only two decades after artesian-well use ceased, reinforcing a latency of 20-30 years for invasive NMSC following arsenic exposure (200) Notably, tumours in the Blackfoot disease endemic areas exhibited an anatomical distribution skewed towards sun-protected sites, supporting an important role for systemic arsenic exposure that is not readily explained by UV exposure alone (200). A complementary portrait emerges from Bangladesh, where >75 million inhabitants have historically consumed water containing >50 μg l^{-1} arsenic. In a 12-year tertiary-care series of cutaneous malignancies, BCC (58.65%) and SCC (40%), two-thirds of patients originated from districts with water arsenic concentrations >300 μg l^{-1} (192). More recent data from the Buxar district, Bihar, India, identified multiple cutaneous neoplasms in residents whose hand-pump water harboured arsenic concentrations as high as 534.2 μg l^{-1}, corroborating earlier observations (191).

Low level exposure in developed countries. An analysis of well-water datasets from Wisconsin revealed that individuals ingesting 1-9.9 μg l^{-1}, concentrations compliant with EPA limits, experienced a near-doubling of self-reported NMSC relative to those exposed to <1 μg l^{-1} (OR, 1.81; 95% CI, 1.10-3.14) (201,202). Although reliant on self-report, the study adjusted for age, sex and smoking, thus mitigating, though not eliminating, information bias. A New Hampshire case-control study utilising urinary arsenic metabolites confirmed a significant SCC risk increment per unit exposure (OR, 1.37; 95% CI, 1.04-1.80), with MMA and DMA displaying equivalent effect estimates (202,203). Ecological studies in Oregon originally failed to detect associations, yet methodological constraints, including community-level exposure assignment, limited water sampling and absence of cumulative metrics, may render null findings uninterpretable (202,204). In the largest nationally representative dataset, analysis of 14,716 adults disclosed a marginally significant positive trend between total urinary arsenic and physician-diagnosed NMSC (OR, 2.37; 95% CI, 0.98-5.75 in the third exposure quantile) (195). Although the cross-sectional design and self-report introduce misclassification, the finding corroborates earlier case-control results and emphasizes measurable risk even within typical U.S. exposure ranges. These data emphasize that current drinking-water guidelines may fail to protect susceptible populations (202,205). Private wells, largely exempt from federal monitoring, constitute a persistent reservoir of underappreciated risk and justify targeted screening initiatives (202,206).

Occupational exposure. The workplace represents a historically important setting for arsenic exposure assessment, but fewer investigations have isolated the occupational contribution of arsenic to NMSC, in part due to co-exposures, UVR, polycyclic aromatic hydrocarbons and pesticides confounding attribution. Systematic appraisal of occupational studies reveals modest and often non-significant elevation in BCC and SCC risk across agricultural and industrial cohorts; however, statistical significance was achieved among gardening and groundskeeping personnel (84,207-209). This heterogeneity arises partly from inadequate quantification of arsenic species, lack of adjustment for recreational sun exposure and confounders such as smoking. Some clinical studies have been interpreted as consistent with a possible interaction between arsenic exposure and UV-related risk, although the evidence remains limited. A case-control study in Romania demonstrated heightened NMSC risk exclusively among women simultaneously exposed to occupational sunlight and arsenic (84,210). Experimental models have reported altered DNA damage responses and increased oxidative stress in UV-irradiated keratinocytes exposed to arsenic (83,84,211). Clinically, arsenic-related BCC and SCC frequently arise on sun-protected sites, indicating that arsenic-associated carcinogenesis cannot be explained solely by canonical UV-driven mechanisms. This distribution is more consistent with systemic carcinogenic effects of arsenic, while the contribution of specific DNA repair pathways remains unresolved (212).

7. Conclusions

Accumulating epidemiological, clinical and mechanistic evidence positions arsenic as an environmental carcinogen in skin cancer, exerting its pathogenic effects through complex, interwoven molecular pathways. The available epidemiological, clinical and mechanistic evidence supports a role for chronic arsenic exposure in NMSC. High-incidence clusters in endemic regions, consistent risk elevations under low-dose exposure and tumour localization in sun-protected sites indicate that UV-centred explanations are insufficient to explain the full pattern of arsenic-associated skin cancer. Evidence from occupational and environmental exposures underscores a prolonged latency and is consistent with disruption of cellular homeostasis, DNA damage signalling and repair responses. For cutaneous melanoma, the epidemiological evidence is heterogeneous; several studies suggest increased risk in higher-exposure contexts and possible effect modification by host susceptibility or UVR, but residual confounding by UV-related behaviours and differential surveillance cannot be excluded. The weight of evidence remains insufficiently uniform to warrant definitive causal attribution at contemporary background exposures. Rigorous longitudinal investigations integrating refined exposure assessment, genotypic and phenotypic susceptibility markers and arsenic metabolism signatures are imperative to ascertain the precise contribution of arsenic to the global melanoma burden.

Mechanistically, current evidence supports roles for epigenetic dysregulation, altered DNA damage signalling and repair responses, and broader disturbances in cellular homeostasis. Clinically, these findings suggest that current approaches to skin cancer risk assessment may not fully capture arsenic-associated disease patterns. In

arsenic-burdened populations, conventional photodamage algorithms may underestimate risk; dermatological surveillance may therefore be extended to ostensibly low-risk, sun-protected skin and commence before the typical age at presentation. At the preventive level, translating candidate biomarkers into practice requires a clearer evidentiary path than is typically provided by mechanistic plausibility alone. Exposure assessment can be supported by speciated urinary arsenic metabolites, with attention to dietary confounding, and by longer-window matrices such as toenails. Early biological effect signals in arsenic-related cutaneous disease include oxidative DNA damage, exemplified by increased 8-hydroxy-2'-deoxyguanosine in arsenic-associated lesions, and global methylation indices such as LINE-1. Progression toward clinical use should follow BEST/FDA conventions, establishing analytical validity, prospective clinical validity and demonstrable clinical utility in risk-stratified surveillance and prevention (20,152,213-217). From a public-health and policy perspective, the data reviewed here raise questions about whether current regulatory thresholds, derived largely from internal cancer endpoints, fully capture skin cancer risk. Even sub-tens-of-μg l^{-1} arsenic concentrations within or below prevailing drinking-water standards have been associated with increased NMSC incidence in some industrialized settings, and private wells remain an unregulated reservoir of risk. Therefore, regulatory frameworks should transition from single-agent limits to exposure context standards that incorporate a broader exposure context and population-level modifiers of vulnerability, including genetic and socioeconomic factors. Pragmatically, point-of-use filtration and periodic speciation-based monitoring should be prioritized in high-incidence clusters, coupled with education on the dermatologic manifestations of chronic arsenism.

Notwithstanding these advances, critical knowledge gaps persist. Epidemiologically, low-level, chronic exposures in temperate climates yield heterogeneous risk estimates, a reflection of inadequate long-term biomarkers and confounding by metal mixtures, socioeconomic status and healthcare access. Most of the epidemiological evidence relies on retrospective or cross-sectional designs with imperfect exposure surrogates; most mechanistic data derive from immortalized keratinocyte lines or murine models that only approximate human cutaneous physiology, and the latency inherent in human carcinogenesis means contemporary cancer burdens reflect historic exposures that may no longer be measurable. Nonetheless, the coherence across molecular, cellular, animal and population levels supports a contributory role for chronic arsenic exposure in cutaneous carcinogenesis, while important uncertainties remain regarding exposure thresholds, mechanism and cancer subtype specificity.

Overall, the literature supports arsenic as a clinically and public-health-relevant environmental carcinogen in skin disease. The role of arsenic as an environmental carcinogen necessitates revised regulatory perspectives and enhanced public-health vigilance. Concerted interdisciplinary efforts, spanning molecular biology, epidemiology, clinical oncology and environmental policy, are essential to mitigate arsenic-driven skin cancer burden, especially given climate-mediated alterations in UVR exposure and persistent global reliance on arsenic-contaminated water sources.

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Competing interests

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