Arsenite Cocarcinogenesis: An Animal Model Derived from Genetic Toxicology Studies

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Although epidemiologic evidence shows an association between inorganic arsenic in drinking water and increased risk of skin, lung, and bladder cancers, no animal model for arsenic carcinogenesis has been successful. This lack has hindered mechanistic studies of arsenic carcinogenesis. Previously, we and others found that low concentrations (≤ 5 μm) of arsenite (the likely environmental carcinogen), which are not mutagenic, can enhance the mutagenicity of other agents, including ultraviolet radiation (UVR) and alkylating agents. This enhancing effect appears to result from inhibition of DNA repair by arsenite, but not via inhibition of DNA repair enzymes. Rather, low concentrations of arsenite disrupt p53 function and upregulate cyclin D1. Failure to find an animal model for arsenic carcinogenesis might be because arsenite is not a carcinogen per se but acts as an enhancing agent (cocarcinogen) with a genotoxic partner. We tested this hypothesis with solar UVR in hairless but immunocompetent Skh1 mice. Mice were given 10 mg/L sodium arsenite in drinking water (or not) and irradiated with 1.7 KJ/m^2 solar UVR 3 times weekly. As expected, no tumors appeared in any organs in control mice or in mice given arsenite alone. After 26 weeks irradiated mice given arsenite had a 2.4-fold increase in skin tumor yield compared with mice given UVR alone. The tumors were mostly squamous cell carcinomas, and those occurring in mice given UVR plus arsenite were much larger and more invasive. These results are consistent with the hypothesis that arsenic acts as a cocarcinogen with a second (genotoxic) agent by inhibiting DNA repair and/or enhancing positive growth signaling. Skin cancers in populations drinking water containing arsenic may be caused by the enhancement by arsenic compounds of carcinogenesis induced by UVR (or other environmental agents). It is possible that lung and bladder cancers associated with arsenic in drinking water may also require a carcinogenic partner. *Key words:* **arsenic, carcinogenesis, cocarcinogen, DNA repair, genotoxicity, proliferation, ultraviolet light.** *Environ Health Perspect* **110(suppl 5):749–752 (2002).**
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Arsenic as a Human Carcinogen

Chronic arsenic exposure is of concern mainly because of its carcinogenic effects. Evidence for arsenic as a human carcinogen comes from studies of lung cancer in ore smelters, and of skin, lung, and bladder cancers in people exposed to drinking water containing arsenic or exposed therapeutically to Fowler's solution (potassium arsenite). The increase in cancer risk observed in epidemiologic studies is attributed mainly to the presence of inorganic trivalent arsenic (*1,2*).

Arsenic is the most extensively studied of the metals and metalloids found in drinking water. The association between skin cancer and arsenic ingestion in drinking water was seen in studies in Taiwan, Chile, Argentina, and Mexico (*3–7*). Bates et al. (*8*) reviewed studies on arsenic ingestion and internal cancers and found that many studies were uninformative because of low statistical power or potential bias either in collection or analysis of data. However, all studies in the Taiwan area found an association with increased lung cancer risk (*9*). Analysis of a Japanese population exposed to arsenic in drinking water also found an association with increased lung cancer risk, but in addition found evidence of strong synergy between smoking and arsenic ingestion (*10*). Similar results were seen in a Taiwan population (*11*) where there was no increased risk in nonsmokers but a risk ratio of 2.45 in smokers in the arsenic-endemic area. In a recent review, Hertz-Piccioto (*12*) calculates that the synergistic excess fraction of lung cancer (i.e., the proportion of cases among those with two exposures that would not have occurred had only one of the exposures been present) ranges from 30 to 54% for smoking and industrial exposure to arsenic.

Ultraviolet radiation (UVR) from sunlight is the most prominent carcinogen in our natural environment and the most important cause of skin cancers (*13*). For reasons that become evident below, we hypothesize that just as tobacco smoke synergizes with arsenic in causing lung cancer, so too does UVR synergize with arsenic in causing skin cancer. This is not meant to rule out possible synergy with other causes of skin cancer, such as ionizing radiation, cigarette smoke, other environmental polycyclic aromatic hydrocarbons, and papillomavirus (*14–17*).

Problems in Finding an Animal Model for Arsenic Carcinogenesis

Because of the lack of a good animal model, arsenic compounds are the only compounds that the International Agency for Research on Cancer (IARC) considers to have sufficient evidence for human carcinogenicity but inadequate evidence for animal carcinogenicity (*18*). The review of arsenic carcinogenicity by IARC (*1*) lists four different species (mouse, rat, dog, rabbit) given various arsenic compounds by different routes of exposure. There was no consistent demonstration of arsenic carcinogenicity in these studies. A few reports of arsenic-induced carcinogenesis exist. When rats were treated by intratracheal instillation with a vineyard pesticide containing calcium arsenate, 10 of 25 rats died. Of the 15 surviving rats, 9 developed lung carcinoma. However, most of the tumors were very small and could only be detected microscopically, and parts of the lung were severely damaged (*19*). Similar results were observed in hamsters (*20*). Pershagen et al. (*21*) applied carrier dust (charcoal carbon) for longer lung retention of arsenic trioxide and other chemicals to mimic the situation encountered in smelter workroom air, with some success. Despite these positive results, it must be kept in mind that very toxic doses of arsenic compounds were required for tumor induction. All published reports attempting to induce tumors with arsenic in drinking water have given negative results (*22*).

Because arsenite is not significantly mutagenic in bacterial or mammalian cells at concentrations giving high levels of survival (see below), it is sometimes assumed that arsenite must be a tumor promoter. There is little evidence for this view, as negative results have

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been obtained in bioassays testing arsenite for promotional activity (*23,24*). Arsenic compounds were also not carcinogenic to animals when tested at reasonable doses as initiators in two-stage carcinogenesis assays (*1,22*).

Molecular and Genetic Toxicology of Low-Level Arsenite

Unlike many carcinogens, arsenite is not a mutagen except weakly at high (toxic) concentrations in *Escherichia coli* or Chinese hamster V79 cells (*25,26*). Attempts have been made to find genetic markers more likely to detect large deletions. In transgenic G12 cells assayed at the *E. coli gpt* locus, which can detect clastogens causing deletions (*27*), and in mouse lymphoma cells, which can tolerate deletions at the TK locus, weak effects are also seen at toxic doses (*28,29*). This is also true in A_L cells (CHO-K1 cells containing a single copy of human chromosome 11), which can suffer deletions (*30*).

Arsenite does, however, induce chromosome aberrations, aneuploidys, and micronuclei (a marker of chromosome damage) in cultured cells (*31*). Micronuclei are found in the bone marrow of mice treated with arsenite (*2*) and in exfoliated bladder cells from exposed humans (*32*). Arsenite caused gene amplification at the *dhfr* locus in SV40-transformed human keratinocytes but failed to cause amplification of the SV40 sequences (*33*). This finding suggests that arsenite does not induce signaling typical of DNA-damaging agents (which induce SV40 amplification in this system), but rather might affect checkpoint pathways such as those involving p53, whose disruption leads to cellular gene amplification (*34*).

Arsenite can induce transformation to a more malignant phenotype in Syrian hamster embryo cells, BALB/3T3 mouse embryo cells, and 10T1/2 mouse embryo cells (*31,35,36*). Arsenite also caused anchorage-independent growth, a marker of transformation, but no focus formation or immortality in diploid human fibroblasts (*37*). We have found that human osteosarcoma cells can be transformed to anchorage independence by exposure to low concentrations of arsenite for 8 weeks but not for 2 weeks (*35*). The mechanism of arsenite's ability to transform cells is not known.

Arsenite enhances the mutagenicity of ultraviolet C light (UVC) (*28*), which causes DNA lesions repairable by nucleotide excision repair, as well as *N*-methyl-*N*-nitrosourea (MNU) (*26*), which causes DNA adducts repairable by base excision repair, in V79 cells. This suggests that arsenite might inhibit a late step in DNA repair shared by both DNA repair pathways. (V79 cells lack O^6-methylguanine DNA methyltransferase, so all premutagenic MNU adducts would be subject to base excision repair.) An assay for DNA strand breaks or gaps showed that in cells treated with MNU plus arsenite, breaks remained open 3 hr after MNU treatment, whereas in the absence of arsenite, the breaks had closed by that time (*26*). This suggested that either the polymerase or the ligase step of base excision repair had been blocked by arsenite.

In subsequent experiments nuclear extracts of cells treated with arsenite decreased nuclear ligase activity, particularly of the enzyme now called DNA ligase III (previously called DNA ligase II) (*38*). Treatment of cells with MNU resulted in a robust activation of DNA ligase III activity after 3 hr, the mechanism of which is still unknown. This activation was blocked by cotreatment of cells with arsenite, and in fact a 50% inhibition of ligase activity was seen even in control cells. However, when arsenite was added to nuclear extract from untreated cells, inhibition occurred only at concentrations of arsenite 1,000-fold higher than those seen after cellular exposure to arsenite, indicating that arsenite does not directly inhibit DNA ligase activity (*38*). This was recently confirmed using purified DNA ligase III (*39*). Further support was found in experiments using single-cell alkaline electrophoresis (comet assay). Treatment of cells with arsenite inhibited DNA strand break rejoining, which was also attributed primarily to inhibition of DNA ligase III by using a ligase III–specific substrate (*40*). In addition, DNA polymerases α and β are not sensitive to inhibition by arsenite. DNA polymerase β, in fact, is stimulated by arsenite concentrations up to at least 12 mM, and DNA polymerase α requires >1 mM arsenite for inhibition (*39,41*). Our hypothesis was that arsenite downregulates control of DNA repair rather than inhibiting DNA repair enzymes.

In a test of this hypothesis, we recently showed that in cells treated with arsenite and ionizing radiation, the p53-dependent increase in p21 expression, normally a block to cell cycle progression after DNA damage, is deficient (*42*). This is expected to lead to faulty DNA repair. In addition, we and others have found that low (nontoxic) exposure to arsenite enhances positive growth signaling (*24,42–46*). We suggest that the

Table 1. Tumors appearing in mice given UVR alone or UVR plus arsenite.

Mouse	Tumor number	Tumor type					
		SCC(HI)	SCC(MI)	KIN	Fib	Pap	Hyp
UVR alone							
1	4	1	2		1		
2	4	1	3				
3	2	1	1				
4	4	2	1			1	
5	2		1			1	
6	2	1	1				
7	6	1	2	3			
8	3	1	2				
9	5	2	2	1			
10	2	1	1				
11	6	2	3	1			
12	5		3	2			
13	2		2				
14	3	1	1	1			
15	3		1	2			
Total (%)	53	14 (26.4)	26 (49.1)	10 (18.9)	1 (1.9)	2 (3.8)	0 (0)
UVR plus arsenite							
1	9	5	2	2			
2	3	2	1				
3	3	1	1				1
4	6	5	1				
5	19	10	3	3	1	1	1
6	6	4	1			1	
7	8	3	3	2			
8	5	2	2	1			
9	15	9	5			1	
10	12	7	3	2			
11	3	1	1				1
12	9	2	4	2		1	
13	8	4	4				
14	12	5	4	2			1
15	9	4	3	2			
Total (%)	127	64 (50.4)	38 (29.9)	16 (12.6)	1 (0.79)	4 (3.1)	4 (3.1)

Abbreviations: Fib, fibrosarcoma; Hyp, hyperplasia; KIN, keratinocytic intraepidermal neoplasia; Pap, papilloma; SCC(HI), squamous cell carcinoma (highly invasive); SCC(MI), squamous cell carcinoma (minimally invasive).

absence of normal p53 functioning and increased positive growth signaling in the presence of DNA damage both contribute to defective DNA repair and account for the comutagenic effects of arsenite.

Arsenic as a Cocarcinogen

Based on our understanding of the genetic toxicology of arsenic, we have developed a new mouse model for arsenic carcinogenesis that combines a nontoxic concentration of sodium arsenite in drinking water with a low (nonerythemic) dose of solar ultraviolet radiation (UVR) (*36*). Skh1 (hairless but immunocompetent) mice given 10 mg/L arsenite (equivalent to ~5,770 ppb arsenic) in drinking water for 26 weeks had a 2.4-fold increase in yield of tumors after 1.7 KJ/m^2 solar UVR 3 times weekly compared with mice given UVR alone (Table 1). The tumors on mice receiving arsenite plus UVR were more highly invasive than those receiving UVR alone ($p < 0.01$ by Fisher's exact test). This concentration of arsenite had no effect on weight gain, appearance, health, or activity of the mice. As expected, no tumors appeared in any organs of mice given arsenite alone. Tumors appeared only in mice that had received UVR, and only on the exposed area (backs) of the mice. The tumors were mostly squamous cell carcinomas; those occurring in mice given UVR plus arsenite appeared earlier (Figure 1) and were much larger than in mice given UVR alone (*35,36*).

Mutations of the tumor suppressor *p53* gene are the most frequent genetic abnormality seen in human cancers and occur in up to 90% of squamous cell carcinomas (depending on the study) (*47,48*). P53 protein inhibits cellular progression through the cell cycle in response to DNA damage. If damaged DNA were to be replicated, it could be mutated or lost because of chromosome breaks. Evidence suggests that *p53* mutations are an early event in skin cancer (*47*). Transgenic mice null for *p53* are at increased risk of chemical carcinogen–induced skin tumors (*49*). Arsenite in drinking water may have an effect similar to *p53* mutation by preventing normal *p53* function.

This is the first demonstration that low concentrations of arsenite can enhance the onset and growth of malignant skin tumors induced by a genotoxic carcinogen in mice (*36*). It should be noted that the concentration of sodium arsenite used in the drinking water corresponds to approximately 5,770 µg/L arsenic. This is >100 times the currently allowable level in drinking water in the United States. It is about 4.4 times higher than the highest concentration (1,300 µg/L) found in Nevada drinking water (*32*) and only 1.7 times higher than the highest concentrations (3,400 µg/L) found in drinking water in the West Bengal region of India (*50*). It is of great importance to perform dose–response experiments on the cocarcinogenic effects of arsenite in drinking water to establish the shape of the dose–response curve and to determine whether a threshold exists.

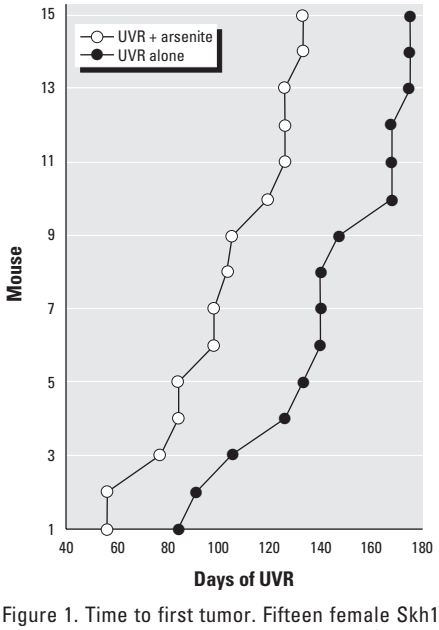

Figure 1. Time to first tumor. Fifteen female Skh1 mice were each treated with solar UVR (mostly UVB) alone or solar UVR plus arsenite in drinking water according to the protocol in Rossman et al. (*36*). Results are expressed as the time after start of irradiation when the first tumor appeared.

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