Studies Not Included in US EPA IRIS (2005, 2010) and SAB (2007) Reference Lists*

1.	Au WW, Giri AK, Ruchirawat M. Challenge assay: A functional biomarker for exposure-induced DNA repair deficiency and for risk of cancer. Int J Hyg Environ Health. 2010 Jan;213(1):32-9. Epub 2009 Oct 8. A variety of biomarkers have been used to monitor exposed populations to determine potential health hazards from their exposure to environmental toxic agents. However, the majority of these biomarkers have been focused onto the identification of biological damage from the exposure. Therefore, there is a need to develop functional biomarkers that can identify exposure-induced functional deficiencies. More importantly, these deficiencies should be positioned along pathways that are responsible for the development of specific diseases. One of such pathways belongs to the extensive and complex DNA-repair machinery. The machinery thus becomes a large target for damage from environmental toxic agents. The hypothesis is that damage to any component of a repair pathway will interfere with the pathway-specific repair activities. Therefore, when cells from exposed populations are challenged with a DNA-damaging agent in vitro, the in vivo exposure-induced repair deficiency will be dramatically amplified and the deficiency will be detectable in a challenge assay as increased chromosome aberrations, micronuclei or un-repaired DNA strand breaks. The challenge assay has been used in different laboratories to show that a variety of exposed populations (with exposure to air pollutants, arsenic, benzene, butadiene, cigarette smoke, incense smoke, lead, mercury, pesticides, uranium or xylene but not to low concentrations of air pollutants or butadiene) expressed abnormal challenge response. The predicted health consequences of some of these studies have also been validated. Therefore, the challenge assay is a useful functional biomarker for population studies. Details of the challenge assay and its application will be presented in this review. Copyright 2009 Elsevier GmbH. All rights reserved.	2010
2.	Cai BZ, Meng FY, Zhu SL, Zhao J, Liu JQ, Liu CJ, Chen N, Ye ML, Li ZY, Ai J, Lu YJ, Yang BF. Arsenic trioxide induces the apoptosis in bone marrow mesenchymal stem cells by intracellular calcium signal and caspase-3 pathways. Toxicol Lett. 2010 Mar 15;193(2):173-8. Epub 2010 Jan 14. It was previously reported that excessive arsenic trioxide would produce cardiovascular toxicity. Bone marrow mesenchymal stem cells (BMSCs) have been shown to play a supporting role in cardiovascular functions. The increasing apoptosis of BMSCs commonly would promote the development of cardiovascular diseases. Thus we hypothesize that arsenic trioxide caused apoptosis in BMSCs, which provided a better understanding of arsenic toxicity in hearts. The present study was designed to investigate the proapoptotic effects of arsenic trioxide on BMSCs and explore the mechanism underlying arsenic trioxide-induced BMSCs apoptosis. We demonstrate that arsenic trioxide significantly inhibited survival ratios of BMSCs in a concentration-dependent and time-dependent manner. The Annexin V/PI staining and terminal deoxynucleotidyl transferasemediated dUTP nick-end labelling (TUNEL) assay also showed that arsenic trioxide markedly induced the apoptosis of BMSCs. The caspase-3	2010

* US EPA Science Advisory Board. June 28, 2007. "Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: A Report of the US EPA Science Advisory Board." Report to US EPA. EPA-SAB-07-008. 88p.

US EPA. July 2005. "Toxicological Review of Ingested Inorganic Arsenic (Draft)." 106p.

US EPA. February 2010. "Toxicological Review of Inorganic Arsenic in Support of Summary Information on the Integrated Risk Information System (IRIS) (Draft)." EPA/635/R-10/001. 575p.

	activity was obviously enhanced in the presence of arsenic trioxide in a concentration-dependent manner in BMSCs. Additionally, arsenic trioxide caused the increase of intracellular free calcium ([Ca(2+)](i)) in rat BMSCs. BAPTA pretreatment may attenuate the apoptosis of BMSCs induced by arsenic trioxide. Taken together, arsenic trioxide could inhibit the proliferation and induce the apoptosis of BMSCs by modulating intracellular [Ca(2+)](i), and activating the caspase-3 activity. Copyright 2010 Elsevier Ireland Ltd. All rights reserved.	
3.	Calatayud M, Gimeno J, Vélez D, Devesa V, Montoro R. Characterization of the intestinal absorption of arsenate, monomethylarsonic acid, and dimethylarsinic acid using the Caco-2 cell line. Chem Res Toxicol. 2010 Mar 15;23(3):547-56. Many toxicological studies have been conducted with arsenic species in target organ cell lines. However, although epithelial gastrointestinal cells constitute the first barrier to the absorption of contaminants, studies using intestinal cells are scarce. The present study examines absorption through the intestinal epithelium of the pentavalent arsenic species most commonly found in foods [arsenate, As(V); monomethylarsonic acid, MMA(V); and dimethylarsinic acid, DMA(V)], using the Caco-2 cell line as a model. Different concentrations (1.3-667.6 microM) and culture conditions (media, pH, addition of phosphates, and treatment with ethylenediaminetetraacetic acid) were evaluated to characterize such transport. The apparent permeabilities indicate that the methylated species show low absorption, whereas As(V) is a compound with moderate absorption. The kinetic study shows only a saturable component for MMA(V) transport in the range of concentrations assayed. The existence of paracellular transport was shown for all of the species, with greater significance in the case of the methylated forms. As(V) absorption was inhibited by 10 mM phosphate, and a phosphate transporter therefore could take part in intestinal absorption. Acidification of the medium (pH 5.5) resulted in a marked increase in As(V) and DMA(V) permeability (4-8 times, respectively) but not in MMA(V) permeability. This makes it necessary to consider the possible existence of absorption in the proximal intestine and even in the stomach, where the environment is acidic; alternatively, an H(+)-dependent transporter may be involved. The results obtained constitute the basis for future research on the mechanisms involved in the intestinal absorption of arsenic and its species, a decisive step in relation to their toxic action.	2010
4.	Cao L, Zhou XD, Sens MA, Garrett SH, Zheng Y, Dunlevy JR, Sens DA, Somji S. Keratin 6 expression correlates to areas of squamous differentiation in multiple independent isolates of As(+3)-induced bladder cancer. J Appl Toxicol. 2010 Feb 22. [Epub ahead of print] This laboratory has shown that arsenite (As(+3)) exposure can cause the malignant transformation of the UROtsa human urothelial cell line. This single isolate formed subcutaneous tumors with a histology similar to human urothelial cell carcinoma. The tumors also displayed areas of squamous differentiation of the urothelial cells, an infrequent but known component of human bladder cancer. In the present study, five additional independent isolates of As(+3)-transformed urothelial cells were isolated and each was shown to produce subcutaneous urothelial cell tumors with a characteristic histology very similar to those described in the initial report. That there were underlying phenotypic differences in the six independent isolates was demonstrated when they were assessed for their ability to form tumors within the peritoneal cavity. It was shown that two isolates could form hundreds of small peritoneal tumor nodules, one isolate a moderate number of tumor nodules, and three isolates no or only one tumor nodule. The peritoneal tumors were also characterized for their degree of squamous differentiation of the urothelial cells and, while areas of squamous differentiation could be found, such differentiation was substantially reduced compared to subcutaneous tumors. Immunostaining for keratin 6 was tested as a potential marker for malignant urothelial cells that had undergone squamous differentiation. Keratin 6 was shown to consistently stain only cells having some evidence of squamous differentiation. Keratin 16 was	2010

	shown to follow the staining pattern of keratin 6. The isolates and tumor heterotransplants were all examined for keratin 6, 16 and 17 mRNA and protein expression. Copyright (c) 2010 John Wiley & Sons, Ltd.	
5.	Chandronitha C, Ananthi S, Ramakrishnan G, Lakshmisundaram R, Gayathri V, Vasanthi HR. Protective role of tannin-rich fraction of Camellia sinensis in tissue arsenic burden in Sprague Dawley rats. Hum Exp Toxicol. 2010 Feb 9. [Epub ahead of print] The protective effect of green tea (Camellia sinensis) was tested against arsenic-induced toxicity. However, the possible role of tannins in green tea in alleviating hepatic and renal oxidative injury has also been studied. Administration of sodium arsenite (100 mg/kg/day) for 28 days in Sprague Dawley female rats resulted in significant reduction of biochemical parameters such as delta-aminolevulinic acid dehydratase (ALAD), reduced glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD) and elevation of thiobarbituric acid reactive substances (TBARS) and the index of nitrite/nitrate (NOx) levels. The tissue arsenic burden was increased after arsenic exposure for a period of 28 days. Green tea crude fraction (GTC) co-treated with sodium arsenite for 28 days caused significant ($p < .01$) elevation of ALAD, GSH, GPx, SOD, and nitrate/nitrite levels and reduction of the TBARS level and tissue burden when compared to detannified green tea fraction (GTDT)-treated groups. The protective role of tannin-rich fraction of C. sinensis when compared to the detannified fraction was also confirmed by histological examinations. The greater activity of GTC than that of detannified green tea fraction correlates with the higher content of tannins in green tea. Overall, these results indicate that the tannin-rich green tea could have improved the defense mechanism against arsenic-induced oxidative stress and reduced the tissue arsenic burden.	2010
6.	Escudero-Lourdes C, Medeiros MK, Cárdenas-González MC, Wnek SM, Gandolfi JA. Low level exposure to monomethyl arsonous acid-induced the over-production of inflammation-related cytokines and the activation of cell signals associated with tumor progression in a urothelial cell model. Toxicol Appl Pharmacol. 2010 Apr 15;244(2):162-73. Epub 2010 Jan 4. Human bladder cancer has been associated with chronic exposure to arsenic. Chronic exposure of an immortalized non-tumorigenic urothelial cell line (UROtsa cells) to arsenicals has transformed these cells to a malignant phenotype, but the involved mechanisms are not fully understood. Chronic inflammation has been linked with cancer development mainly because many pro-inflammatory cytokines, growth factors as well as angiogenic chemokines have been found in tumors. In this study the chronology of inflammatory cytokines production was profiled in UROtsa cells chronically exposed to the toxic arsenic metabolite, monomethylarsonous acid [50 nM MMA(III)] to know the role of inflammation in cell transformation. Acute 50 nM MMA(III) exposure induced over-production of many pro-inflammatory cytokines as soon as 12 h after acute exposure. The same cytokines remain over-regulated after chronic exposure to 50 nM MMA(III), especially after 3 mo exposure. At 3 mo exposure the sustained production of cytokines like IL-1, IL-6, IL-8 and TNF is coincident with the appearance of characteristics associated with cell transformation seen in other arsenic-UROtsa studies. The sustained and increased activation of NFkappaB and c-Jun is also present along the transformation process and the phosphorylated proteins p38 MAPK and ERK 1/2 are increased also through the time line. Taken together these results support the notion that chronic inflammation is associated within MMA(III)-induced cell transformation and may act as a promoting factor in UROtsa cell transformation. Copyright 2009 Elsevier Inc. All rights reserved.	2010
7.	Fei DL, Li H, Kozul CD, Black KE, Singh S, Gosse JA, DiRenzo J, Martin KA, Wang B, Hamilton JW, Karagas MR, Robbins DJ. Activation of Hedgehog signaling by the environmental toxicant arsenic may contribute to the etiology of arsenic-induced tumors.	2010

	Cancer Res. 2010 Mar 1;70(5):1981-8. Epub 2010 Feb 23. Exposure to the environmental toxicant arsenic, through both contaminated water and food, contributes to significant health problems worldwide. In particular, arsenic exposure is thought to function as a carcinogen for lung, skin, and bladder cancer via mechanisms that remain largely unknown. More recently, the Hedgehog signaling pathway has also been implicated in the progression and maintenance of these same cancers. Based on these similarities, we tested the hypothesis that arsenic may act in part through activating Hedgehog signaling. Here, we show that arsenic is able to activate Hedgehog signaling in several primary and established tissue culture cells as well as in vivo. Arsenic activates Hedgehog signaling by decreasing the stability of the repressor form of GLI3, one of the transcription factors that ultimately regulate Hedgehog activity. We also show, using tumor samples from a cohort of bladder cancer patients, that high levels of arsenic exposure are associated with high levels of Hedgehog activity. Given the important role Hedgehog signaling plays in the maintenance and progression of a variety of tumors, including bladder cancer, these results suggest that arsenic exposure may in part promote cancer through the activation of Hedgehog signaling. Thus, we provide an important insight into the etiology of arsenic-induced human carcinogenesis, which may be relevant to millions of people exposed to high levels of arsenic worldwide.	
8.	Gunia S. Molecular interaction between arsenic hydrate microcrystals and the cell-surface endopeptidase CD10 (neprilysin) - A possible link to the development of renal and cutaneous malignancies upon occupational exposure to arsenic compounds? Med Hypotheses. 2010 Feb 5. [Epub ahead of print] Arsenic poisoning has become a worldwide public health concern since arsenic is recognized as a human carcinogen although the detailed mechanisms of carcinogenesis related to arsenic exposure are not completely understood at present. In particular, the skin and the kidneys are prone to neoplastic transformation upon occupational exposure of the human body to inorganic arsenic compounds. The cell-surface endopeptidase CD10 is variably expressed in cutaneous and renal malignancies, and due to this expression profile, might theoretically be implicated in arsenic-induced skin and renal neoplasias. From the functional point of view, CD10 conveys important anti-tumorigenic effects brought about by the inactivation of neuropeptide growth factors implicated in cancer progression. Placing the focus on the structural composition of arsenic hydrate microcrystals encountered in the cellular microenvironment, the present hypothesis suggests so far neglected molecular interactions between arsenic microcrystals and membrane-bound CD10 to be implicated in arsenic-induced carcinogenesis. Copyright © 2010 Elsevier Ltd. All rights reserved.	2010
9.	Habib GM. Arsenite causes down-regulation of Akt and c-Fos, cell cycle dysfunction and apoptosis in glutathione-deficient cells. J Cell Biochem. 2010 Mar 24. Arsenic is a well-known environmental toxicant but the mechanism by which it causes cytotoxicity is poorly understood. Arsenite induces apoptosis in glutathione (GSH)-deficient GCS-2 cells by causing cell cycle dysfunction and down-regulating critical signaling pathways. This study was designed to examine the effect of arsenite on redox-sensitive phosphatidylinositol 3-kinase (PI3K)/Akt, a signaling pathway involved in cell survival and growth, and transcription factor, activating protein-1 (AP-1). Arsenite significantly diminished Akt and c-Fos levels and caused accelerated degradation of these proteins by ubiquitnation. Arsenite also induced cell cycle arrest and apoptosis. The cell cycle arrest involved the down-regulation of cyclin A2, cyclin D1, cyclin E, cyclin dependent kinases (CDK) 2, CDK4, and CDK6. Apoptosis involved down-regulation of anti-apoptotic proteins Bcl-2, Bcl-xL, survivin, and inhibitor of apoptosis protein (IAP) and up-regulation of pro-apoptotic protein Bax. Taken together, our results suggest that a possible mechanism of arsenite-induced toxicity under	2010

	low/no GSH conditions, is to negatively regulate GCS-2 cell proliferation by attenuating Akt and AP-1 by ubiquitination and causing cell cycle dysfunction and apoptosis. J. Cell. Biochem. (c) 2010 Wiley-Liss, Inc.	
10.	Kato M, Takeda K, Hossain K, Thang ND, Kaneko Y, Kumasaka M, Yamanoshita O, Uemura N, Takahashi M, Ohgami N, Kawamoto Y. A redox-linked novel pathway for arsenic-mediated RET tyrosine kinase activation. J Cell Biochem. 2010 Mar 16. [Epub ahead of print] We examined the biochemical effects of arsenic on the activities of RET proto-oncogene (c-RET protein tyrosine kinases) and RET oncogene (RET-MEN2A and RET-PTC1 protein tyrosine kinases) products. Arsenic activated c-RET kinase with promotion of disulfide bond-mediated dimerization of c-RET protein. Arsenic further activated RET-MEN2A kinase, which was already 3- to 10-fold augmented by genetic mutation compared with c-RET kinase activity, with promotion of disulfide bond-mediated dimerization of RET-MEN2A protein (superactivation). Arsenic also increased extracellular domain-deleted RET-PTC1 kinase activity with promotion of disulfide bond-mediated dimerization of RET-PTC1 protein. Arsenic increased RET-PTC1 kinase activity with cysteine 365 (C365) replaced by alanine with promotion of dimer formation but not with cysteine 376 (C376) replaced by alanine. Our results suggest that arsenic-mediated regulation of RET kinase activity is dependent on conformational change of RET protein through modulation of a special cysteine sited at the intracellular domain in RET protein (relevant cysteine of C376 in RET-PTC1 protein). Moreover, arsenic enhanced the activity of immunoprecipitated RET protein with increase in thiol-dependent dimer formation. As arsenic (14.2 microM) was detected in the cells cultured with arsenic (100 microM), direct association between arsenic and RET in the cells might modulate dimer formation. Thus, we demonstrated a novel redox-linked mechanism of activation of arsenic-mediated RET proto-oncogene and oncogene products. J. Cell. Biochem. (c) 2010 Wiley-Liss, Inc.	2010
11.	Kligerman AD, Malik SI, Campbell JA. Cytogenetic insights into DNA damage and repair of lesions induced by a monomethylated trivalent arsenical. Mutat Res. 2010 Jan;695(1-2):2-8. Epub 2009 Sep 30. Arsenic is a human carcinogen, and only recently animal models have been developed that are useful in investigating its carcinogenic mode of action (MOA). However, how arsenic induces cancer is still an open question. In a previous paper, we proposed a model detailing how arsenic might induce DNA lesions leading to cytogenetic damage [A.D. Kligerman, A.H. Tennant, Toxicol. Appl. Pharmacol. 222 (2007) 281-288]. In this model we hypothesized that arsenic does not induce chromosome damage via DNA adduction but induces short-lasting lesions from the action of reactive oxygen species (ROS). These lesions cause single-strand breaks (SSB) that induce chromosome breakage when treatment is in late G(1)- or S-phase. However, if treatment is confined to the G(0)- or early G(1)-phase of the cell cycle, it is predicted that little or no cytogenetic damage will result at the subsequent metaphase. Here, we describe the results from testing this model using monomethylarsonous acid (MMA(III)) and cytosine arabinoside (araC), a DNA chain terminator, to extend the time that DNA lesions remain open during repair to allow the lesions to reach S-phase or interact to form DNA exchanges that would lead to exchange aberrations at metaphase. The results of our study only partially confirmed our hypothesis. Instead, the results indicated that the lesions induced by MMA(III) are quickly repaired through base excision repair, that there is little chance for araC to extend the life of the lesions, and thus the DNA damage induced by arsenicals that leads to chromosome aberrations is very short lived. Published by Elsevier B.V.	2010
12.	Li Y, Xu Y, Ling M, Yang Y, Wang S, Li Z, Zhou J, Wang X, Liu Q. Mot-2-mediated Crosstalk between NF-kappaB and p53 is Involved in Arsenite-induced Tumorigenesis of Human Embryo Lung Fibroblast Cells. Environ Health Perspect. 2010 Mar 2. [Epub ahead of	2010

	print] Background: Inactivation of p53 is involved in arsenite-induced tumorigenesis; the molecular mechanisms, however, remain poorly understood. Objective: To investigate the molecular mechanisms underlying the inactivation of p53 and neoplastic transformation of human embryo lung fibroblast (HELF) cells induced by arsenite. Methods: Anchorage-independent growth assays were performed, and tumorigenicity in intact animals was assessed to confirm arsenite-induced neoplastic transformation. The levels and functions of p53, NF-kappaB (a key transcriptional regulator), and mot-2 (a p53 inhibitor) and their relationships in arsenite-induced transformed HELF cells were determined by 2-DE, RT-PCR, Western blot, immunofluorescence, and co-immunoprecipitation assays. Results: Exposure of HELF cells to low levels of arsenite increased their proliferation rate and anchorage-independent growth, and disrupted normal contact inhibition. When introduced into nude mice, transformed cells were tumorigenic. Proteomic analysis was used to identify proteins with altered expression between untreated and arsenite-exposed cells. There was decreased expression of NKRF (an inhibitor of NF-kappaB-mediated gene transcription), increased expression of mot-2, and increased activation of NF-kappaB. Changes in cells exposed to 1.0 muM arsenite were more marked than changes in cells exposed to 0.5 or 2.0 muM arsenite. Inactivation of NF-kappaB prevented malignant transformation induced by 1.0 muM arsenite. Moreover, a mechanism was identified whereby NF-kappaB regulated p53. Specifically, activation of NF-kappaB up-regulated mot-2 expression, which preventsed nuclear translocation of p53 and switched the binding preference of the p53 and NF-kappaB co-activator CBP from p53 to NF-kappaB. Conclusions: Mot-2-mediated crosstalk between NF-kappaB and p53 appears to be involved in arsenite-induced tumorigenesis of HELF cells.	
13.	Manimaran A, Sarkar SN, Sankar P. Influence of repeated preexposure to arsenic on acetaminophen-induced oxidative stress in liver of male rats. Food Chem Toxicol. 2010 Feb;48(2):605-10. Epub 2009 Nov 22. We evaluated whether repeated arsenic preexposure can increase acetaminophen-induced hepatic oxidative stress. Rats were exposed to arsenic (25 ppm; rat equivalent concentration of maximum groundwater contamination level) via drinking water for 28 days. Next day, they were given single oral administration of acetaminophen (420 or 1000 mg/kg b.w.). Hepatotoxicity was evaluated by assessing serum biomarkers, cytochrome-P450 (CYP) content, CYP3A4- and CYP2E1-dependent enzymes, lipid peroxidation and antioxidants. Arsenic or acetaminophen increased serum ALT and AST activities and depleted CYP. Arsenic decreased, but acetaminophen increased CYP-dependent enzyme activities. These agents independently increased lipid peroxidation and decreased antioxidants. Arsenic did not alter the effects of acetaminophen on serum biomarkers, caused further CYP depletion and decreased acetaminophen-mediated induction of drug-metabolizing enzymes. Arsenic enhanced the lower dose of acetaminophen-mediated lipid peroxidation and glutathione depletion with no further alterations in enzymatic antioxidants. However, arsenic attenuated the higher dose-mediated lipid peroxidation and glutathione depletion with improvement in glutathione peroxidase and glutathione reductase activities, further decrease in catalase and no alterations in superoxide dismutase and glutathione-S-transferase activities. Results show that arsenic preexposure increased the susceptibility of rats to hepatic oxidative stress induced by the lower dose of acetaminophen, but reduced the oxidative stress induced by the higher dose. Copyright 2009 Elsevier Ltd. All rights reserved.	2010
14.	Meliker JR, Slotnick MJ, Avruskin GA, Schottenfeld D, Jacquez GM, Wilson ML, Goovaerts P, Franzblau A, Nriagu JO. Lifetime exposure to arsenic in drinking water and bladder cancer: a population-based case-control study in Michigan, USA. Cancer Causes Control. 2010 Jan 19. [Epub ahead of print]	2010

	OBJECTIVE: Arsenic in drinking water has been linked with the risk of urinary bladder cancer, but the dose-response relationships for arsenic exposures below 100 mug/L remain equivocal. We conducted a population-based case-control study in southeastern Michigan, USA, where approximately 230,000 people were exposed to arsenic concentrations between 10 and 100 mug/L. METHODS: This study included 411 bladder cancer cases diagnosed between 2000 and 2004, and 566 controls recruited during the same period. Individual lifetime exposure profiles were reconstructed, and residential water source histories, water consumption practices, and water arsenic measurements or modeled estimates were determined at all residences. Arsenic exposure was estimated for 99% of participants' person-years. RESULTS: Overall, an increase in bladder cancer risk was not found for time-weighted average lifetime arsenic exposure >10 mug/L when compared with a reference group exposed to <1 mug/L (odds ratio (OR) = 1.10; 95% confidence interval (CI): 0.65, 1.86). Among ever-smokers, risks from arsenic exposure >10 mug/L were similarly not elevated when compared to the reference group (OR = 0.94; 95% CI: 0.50, 1.78). CONCLUSIONS: We did not find persuasive evidence of an association between low-level arsenic exposure and bladder cancer. Selecting the appropriate exposure metric needs to be thoughtfully considered when investigating risk from low-level arsenic exposure.	
15.	Peng Z, Geh E, Chen L, Meng Q, Fan Y, Sartor M, Shertzer HG, Liu ZG, Puga A, Xia Y. I{kappa}B kinase {beta} regulates redox homeostasis by controlling the constitutive levels of glutathione. Mol Pharmacol. 2010 Feb 16. [Epub ahead of print] Cytokine-activated IkappaB kinase beta (IKKbeta) is a key mediator of immune and inflammatory responses, but recent studies suggest that IKKbeta is also required for tissue homeostasis in physio-pathological processes. Here we report a novel role for IKKbeta in maintenance of constitutive levels of the redox scavenger glutathione (GSH). Inactivation of IKKbeta by genetic or pharmacological means results in low cellular GSH content and marked reduction of redox potential. Similar to Ikkbeta (-/-) cells, Tnfr1(-/-) and p65(-/-) cells are also GSH deficient. As a consequence, cells deficient in IKKbeta signaling are extremely susceptible to toxicity caused by environmental and pharmacological agents, including oxidants, genotoxic agents, microtubule toxins and arsenic. GSH biosynthesis depends on the activity of the rate limiting enzyme glutamate-cysteine ligase (GCL), consisting of a catalytic (GCLC) and a modifier (GCLM) subunit. We find that loss of IKKbeta signaling significantly reduces basal NF-kappaB activity and decreases binding of NF-kappaB to the promoters of Gclc and Gclm, leading to reduction of GCLC and GCLM expression. Conversely, overexpression of GCLC and GCLM in IKKbeta-null cells partially restores GSH content and prevents stress-induced cytotoxicity. We suggest that maintenance of GSH is a novel physiological role of the IKKbeta-NF-kappaB signaling cascade to prevent oxidative damage and preserve the functional integrity of the cells.	2010
16.	Rana T, Bera AK, Das S, Pan D, Bandyopadhyay S, Bhattacharya D, De S, Das SK. Supplementation of ascorbic acid prevents oxidative damages in arsenic-loaded hepatic tissue of rat: An ex vivo study. Hum Exp Toxicol. 2010 Mar 18. [Epub ahead of print] Oxidative stress due to arsenic toxicity and ameliorative potentiality of <scp>l</scp>-ascorbic acid was evaluated in an ex vivo system of rat hepatic tissue. The study revealed that arsenic increased the activity of superoxide dismutase (SOD) and catalase (CAT) and the level of lipid peroxidation (LPO), protein carbonyl (PC) and nitric oxide (NO) at 1 hour, 1.5 hours and 2 hours of incubation. Co-treatment with <scp>l</scp>-ascorbic acid was found effective to normalize the activity of SOD and CAT and the production of LPO, PC and NO in hepatic tissue. This ex vivo study suggested that ascorbic acid is helpful to ameliorate arsenic-induced oxidative stress. This may be one of the alternative screening systems to study the efficacy of	2010

	antioxidant and hepatoprotective agent.	
17.	Reznikova TV, Phillips MA, Patterson TJ, Rice RH. Opposing actions of insulin and arsenite converge on PKCdelta to alter keratinocyte proliferative potential and differentiation. Mol Carcinog. 2010 Apr;49(4):398-409. When cultured human keratinocytes reach confluence, they undergo a program of changes replicating features of differentiation in vivo, including exit from the proliferative pool, increased cell size, and expression of specialized differentiation marker proteins. Previously, we showed that insulin is required for some of these steps and that arsenite, a human carcinogen in skin and other epithelia, opposes the differentiation process. In present work, we show that insulin signaling, probably through the IGF-I receptor, is required for the increase in cell size accompanying differentiation and that this is opposed by arsenite. We further examine the impact of insulin and arsenite on PKCdelta, a known key regulator of keratinocyte differentiation, and show that insulin increases the amount, tyrosine phosphorylation, and membrane localization of PKCdelta. All these effects are prevented by exposure of cells to arsenite or to inhibitors of downstream effectors of insulin (phosphotidylinositol 3-kinase and mammalian target of rapamycin). Retrovirally mediated expression of activated PKCdelta resulted in increased loss of proliferative potential after confluence and greatly increased formation of cross-linked envelopes, a marker of keratinocyte terminal differentiation. These effects were prevented by removal of insulin, but not by arsenite addition. We further demonstrate a role for src family kinases in regulation of PKCdelta. Finally, inhibiting epidermal growth factor receptor kinase activity diminished the ability of arsenite to prevent cell enlargement and to suppress insulin-dependent PKCdelta amount and tyrosine 311 phosphorylation. Thus suppression of PKCdelta signaling is a critical feature of arsenite action in preventing keratinocyte differentiation and maintaining proliferative capability.	2010
18.	Salazar AM, Miller HL, McNeely SC, Sordo M, Ostrosky-Wegman P, States JC. Suppression of p53 and p21CIP1/WAF1 reduces arsenite-induced aneuploidy. Chem Res Toxicol. 2010 Feb 15;23(2):357-64. Aneuploidy and extensive chromosomal rearrangements are common in human tumors. The role of DNA damage response proteins p53 and p21(CIP1/WAF1) in aneugenesis and clastogenesis was investigated in telomerase immortalized diploid human fibroblasts using siRNA suppression of p53 and p21(CIP1/WAF1). Cells were exposed to the environmental carcinogen sodium arsenite (15 and 20 microM), and the induction of micronuclei (MN) was evaluated in binucleated cells using the cytokinesis-block assay. To determine whether MN resulted from missegregation of chromosomes or from chromosomal fragments, we used a fluorescent in situ hybridization with a centromeric DNA probe. Micronuclei were predominantly of clastogenic origin in control cells regardless of p53 or p21(CIP1/WAF1) expression. MN with centromere signals in cells transfected with NSC siRNA or Mock increased 30% after arsenite exposure, indicating that arsenite induced aneuploidy in the tGM24 cells. Although suppression of p53 increased the fraction of arsenite-treated cells with MN, it caused a decrease in the fraction with centromeric DNA. Suppression of p21(CIP1/WAF1) like p53 suppression decreased the fraction of MN with centromeric DNA. Our results suggest that cells lacking normal p53 function cannot become aneuploid because they die by mitotic arrest-associated apoptosis, whereas cells with normal p53 function that are able to exit from mitotic arrest can become aneuploid. Furthermore, our current results support this role for p21(CIP1/WAF1) since suppression of p21(CIP1/WAF1) caused a decrease in aneuploidy induced by arsenite, suggesting that p21(CIP1/WAF1) plays a role in mitotic exit.	2010
19.	Schwartz MS, Benci JL, Selote DS, Sharma AK, Chen AG, Dang H, Fares H, Vatamaniuk OK. Detoxification of multiple heavy metals by a half-molecule ABC transporter, HMT-1, and coelomocytes of Caenorhabditis elegans. PLoS One. 2010 Mar 5;5(3):e9564.	2010

	BACKGROUND: Developing methods for protecting organisms in metal-polluted environments is contingent upon our understanding of cellular detoxification mechanisms. In this regard, half-molecule ATP-binding cassette (ABC) transporters of the HMT-1 subfamily are required for cadmium (Cd) detoxification. HMTs have conserved structural architecture that distinguishes them from other ABC transporters and allows the identification of homologs in genomes of different species including humans. We recently discovered that HMT-1 from the simple, unicellular organism, Schizosaccharomyces pombe, SpHMT1, acts independently of phytochelatin synthase (PCS) and detoxifies Cd, but not other heavy metals. Whether HMTs from multicellular organisms confer tolerance only to Cd or also to other heavy metals is not known. METHODOLOGY/PRINCIPAL FINDINGS: Using molecular genetics approaches and functional in vivo assays we showed that HMT-1 from a multicellular organism, Caenorhabditis elegans, functions distinctly from its S. pombe counterpart in that in addition to Cd it confers tolerance to arsenic (As) and copper (Cu) while acting independently of pcs-1. Further investigation of hmt-1 and pcs-1 revealed that these genes are expressed in different cell types, supporting the notion that hmt-1 and pcs-1 operate in distinct detoxification pathways. Interestingly, pcs-1 and hmt-1 are co-expressed in highly endocytic C. elegans cells with unknown function, the coelomocytes. By analyzing heavy metal and oxidative stress sensitivities of the coelomocyte-deficient C. elegans strain we discovered that coelomocytes are essential mainly for detoxification of heavy metals, but not of oxidative stress, a by-product of heavy metal toxicity. CONCLUSIONS/SIGNIFICANCE: We established that HMT-1 from the multicellular organism confers tolerance to multiple heavy metals and is expressed in liver-like cells, the coelomocytes, as well as head neurons and intestinal cells, which are cell types that are affected by heavy metal poisoning in humans. We also showed that coelomocytes are involved in detoxification of heavy metals. Therefore, the HMT-1-dependent detoxification pathway and coelomocytes of C. elegans emerge as novel models for studies of heavy metal-promoted diseases.	
20.	Singh S, Rana SV. Ascorbic acid improves mitochondrial function in liver of arsenic-treated rat. Toxicol Ind Health. 2010 Mar 31. [Epub ahead of print] Arsenic is an ubiquitous and well-documented carcinogenic metalloid. The most common source of arsenic is drinking water. The mechanism of arsenic toxicity in a cell has historically been centered around its inhibitory effects on cellular respiration and mitochondrial injury. Ascorbic acid, a low molecular weight, water-soluble antioxidant, improves the reduced glutathione (GSH) status by recycling oxidized glutathione. Ascorbic acid can improve mitochondrial function by improving the thiol status; thereby preventing reactive oxygen species-mediated damage to liver as well as kidney. Ascorbic acid has been shown to protect membrane and other cellular compartments by regenerating vitamin E. Therefore, ascorbic acid seems to be a suitable protective factor against arsenic toxicity. Present reports describe the effect of ascorbic acid on oxidative phosphorylation, adenosine triphosphatase (ATPase), succinic dehydrogenase, caspase-3 and apoptosis in the liver of rats treated with arsenic trioxide (As(III)). Ultrastructural changes in the mitochondria have also been reported. We show that cotreatments with ascorbic acid and As(III) improve mitochondrial structure and function. We attribute these improvements mainly to antioxidative role of ascorbic acid. Apoptosis was restricted due to caspase-3 inhibition. Ascorbic acid could protect DNA from the attack of reactive oxygen species generated by As(III). Consequently its events led to improved ADP:O ratio, normalized ATPase activity and restored the activity of succinic dehydrogenase. Overall, results support the protective role of ascorbic acid against As(III)-induced liver injury.	2010
21.	Sinha D, Roy S, Roy M. Antioxidant potential of tea reduces arsenite induced oxidative stress in Swiss albino mice. Food Chem Toxicol. 2010 Apr;48(4):1032-9. Epub 2010 Jan 21.	2010

	Environmental arsenic (As) is a potent human carcinogen and groundwater As contamination is a major health concern in West Bengal, India. Oxidative stress has been one of the prime factors in As-induced carcinogenicity. Generation of reactive oxygen species (ROS), beyond the body's endogenous antioxidant balance cause a severe imbalance of the cellular antioxidant defence mechanism. Tea, a popular beverage has excellent chemopreventive and antioxidant properties. In this study it was investigated whether these flavonoids could ameliorate the arsenite (As III) induced oxidative stress in Swiss albino mice. Bio-monitoring with comet assay elicited that the increase in genotoxicity caused by As III was counteracted by both black tea and green tea. Elevated levels of lipid peroxides and protein carbonyl by As III were effectively reduced with green as well as black tea. They also exhibited protective action against the As III induced depletion of antioxidants like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and glutathione (GSH) in mice liver tissue. Thus the tea polyphenols by virtue of their antioxidant potential may be used as an effective agent to reduce the As III induced oxidative stress in Swiss albino mice. 2010 Elsevier Ltd. All rights reserved.	
22.	Suzuki, S., Arnold, L.L., Pennington, K.L., Chen,B., Naranmandura, H., Le, X.C., and Cohen, S.M. Dietary administration of sodium arsenite to rats: Relations between dose and urinary concentrations of methylated and thio-metabolites and effects on the rat urinary bladder epithelium. Toxicol Appl Pharmacol. 2010 Apr 15;244(2):99-105. Epub 2010 Jan 4. Based on epidemiological data, chronic exposure to high levels of inorganic arsenic in drinking water is carcinogenic to humans, inducing skin, urinary bladder and lung tumors. In vivo, inorganic arsenic is metabolized to organic methylated arsenicals including the highly toxic dimethylarsinous acid (DMA(III)) and monomethylarsonous acid (MMA(III)). Short-term treatment of rats with 100 microg/g trivalent arsenic (As(III)) as sodium arsenite in the diet or in drinking water induced cytotoxicity and necrosis of the urothelial superficial layer, with increased cell proliferation and hyperplasia. The objectives of this study were to determine if these arsenic-induced urothelial effects are dose responsive, the dose of arsenic at which urothelial effects are not detected, and the urinary concentrations of the arsenical metabolites. We treated female F344 rats for 5 weeks with sodium arsenite at dietary doses of 0, 1, 10, 25, 50, and 100 ppm. Cytotoxicity, cell proliferation and hyperplasia of urothelial superficial cells were increased in a dose-responsive manner, with maximum effects found at 50 ppm As(III). There were no effects at 1 ppm As(III). The main urinary arsenical in As(III)-treated rats was the organic arsenical dimethylarsinic acid (DMA(V)). The thio-metabolites dimethylmonothioarsinic acid (DMMTA(V)) and monomethylmonothioarsinic acid (MMMTA(V)) were also found in the urine of As(III)-treated rats. The LC(50) concentrations of DMMTA(V) for rat and human urothelial cells in vitro were similar to trivalent oxygen-containing arsenicals. These data suggest that dietary As(III)-induced urothelial cytotoxicity and proliferation are dose responsive, and the urothelial effects have a threshold corresponding to the urinary excretion of measurable reactive metabolites.	2010
23.	Tiwari H, Rao MV. Curcumin supplementation protects from genotoxic effects of arsenic and fluoride. Food Chem Toxicol. 2010 Feb 17. [Epub ahead of print] The present study was aimed to evaluate curcumin as a potential natural antioxidant to mitigate the genotoxic effects of arsenic (As) and fluoride (F) in human peripheral blood lymphocytes. The study was divided into nine groups consisting of negative control, positive control treated with ethyl methane sulphonate (EMS; 1.93mM) and curcumin control with only curcumin (1.7muM) in blood culture. As (1.4muM) and F (34muM) were added alone as well as in combination, to the cultures, with and without curcumin. Cultures were analysed for chromosomal aberrations (both structural and numerical) and primary DNA damage via comet	2010

	assay as the genotoxic parameters after an exposure duration of 24h. Results revealed that curcumin efficiently ameliorates the toxic effect of As and F by reducing the frequency of structural aberrations (>60%), hypoploidy (>50%) and primary DNA damage. In conclusion, curcumin mitigates the genotoxic effects of the two well known water contaminants (As and F) effectively and efficiently at the given concentration in vitro. Copyright © 2010 Elsevier Ltd. All rights reserved.	
24.	Tokar EJ, Diwan BA, Waalkes MP. Arsenic exposure transforms human epithelial stem/progenitor cells into a cancer stem-like phenotype. Environ Health Perspect. 2010 Jan;118(1):108-15. BACKGROUND: Inorganic arsenic is a ubiquitous environmental carcinogen affecting millions of people worldwide. Evolving theory predicts that normal stem cells (NSCs) are transformed into cancer stem cells (CSCs) that then drive oncogenesis. In humans, arsenic is carcinogenic in the urogenital system (UGS), including the bladder and potentially the prostate, whereas in mice arsenic induces multi-organ UGS cancers, indicating that UGS NSCs may represent targets for carcino-genic initiation. However, proof of emergence of CSCs induced by arsenic in a stem cell population is not available. METHODS: We continuously exposed the human prostate epithelial stem/progenitor cell line WPE-stem to an environmentally relevant level of arsenic (5 microM) in vitro and determined the acquired cancer phenotype. RESULTS: WPE-stem cells rapidly acquired a malignant CSC-like phenotype by 18 weeks of exposure, becoming highly invasive, losing contact inhibition, and hyper-secreting matrix metalloproteinase-9. When hetero-transplanted, these cells (designated As-CSC) formed highly pleomorphic, aggressive tumors with immature epithelial- and mesenchymal-like cells, suggesting a highly pluripotent cell of origin. Consistent with tumor-derived CSCs, As-CSCs formed abundant free-floating spheres enriched in CSC-like cells, as confirmed by molecular analysis and the fact that only these floating cells formed xeno-graft tumors. An early loss of NSC self-renewal gene expression (p63, ABCG2, BMI-1, SHH, OCT-4, NOTCH-1) during arsenite exposure was sub-sequently reversed as the tumor suppressor gene PTEN was progressively suppressed and the CSC-like phenotype acquired. CONCLUSIONS: Arsenite transforms prostate epithelial stem/progenitor cells into CSC-like cells, indicating that it can produce CSCs from a model NSC population.	2010
25.	Wen W, Ding J, Sun W, Wu K, Ning B, Gong W, He G, Huang S, Ding X, Yin P, Chen L, Liu Q, Xie W, Wang H. Suppression of cyclin D1 by hypoxia-inducible factor-1 via direct mechanism inhibits the proliferation and 5-fluorouracil-induced apoptosis of A549 cells. Cancer Res. 2010 Mar 1;70(5):2010-9. Epub 2010 Feb 23. Hypoxia-inducible factor (HIF) and cyclin D1 are both key mediators of cell growth and proliferation in normal and cancer cells. However, the interrelation between HIF and cyclin D1 remains unclear. In the present study, we observed the inverse correlation between cyclin D1 and HIF-1 in hypoxia condition. Overexpression of the dominant negative mutant of HIF-1alpha (DN-HIF) significantly enhanced cyclin D1 expression upon hypoxia or arsenite exposure, suggesting the negative regulation of cyclin D1 by HIF-1. Furthermore, we found that the impairment of HIF-1 increased cyclin D1 expression in A549 pulmonary cancer cells, which in turn promoted G1-S cell cycle transition and cell proliferation. Cyclin D1 expression was increased in s.c. xenograft of DN-HIF stably transfected A549 cells in nude mice compared with that of control cells. Chromatin immunoprecipitation assay revealed that HIF-1 was able to directly bind to the promoter region of cyclin D1, which indicates that the negative regulation of cyclin D1 by HIF-1 is through a direct mechanism. Inhibition of histone deacetylase (HDAC) by pretreatment of cells with trichostatin A or specific knockdown of HDAC7 by its shRNA antagonized the suppression of cyclin D1 by HIF-1, suggesting that HDAC7 is required for HIF-1-mediated cyclin D1 downregulation. Moreover, we found that 5-	2010

	fluorouracil-triggered apoptosis of DN-HIF-transfected A549 cells was reduced by sicyclin D1 (cyclin D1-specific interference RNA) introduction, suggesting that clinical observation of HIF-1 overexpression-associated chemoresistance might be, at least partially, due to the negative regulation of cyclin D1.	
26.	Whitfield JB, Dy V, McQuilty R, Zhu G, Heath AC, Montgomery GW, Martin NG. Genetic Effects on Toxic and Essential Elements in Humans: Arsenic, Cadmium, Copper, Lead, Mercury, Selenium and Zinc in Erythrocytes. Environ Health Perspect. 2010 Jan 5. [Epub ahead of print] Background and Objectives. Excess of toxic trace elements or deficiency of essential ones has been implicated in many common diseases or public health problems, but little is known about causes of variation between people living within similar environments. We have examined effects of personal and socioeconomic characteristics on concentrations of As, Cd, Cu, Hg, Pb, Se and Zn in erythrocytes, and tested for genetic effects using data from twin pairs. Methods. We used blood samples from 2926 adult twins living in Australia (1925 women, 1001 men, aged 30-92 years), and determined element concentrations in erythrocytes by ICP-MS. We assessed associations between element concentrations and personal and socioeconomic characteristics, and the sources of genetic and environmental variation and covariation in element concentrations. We evaluated the chromosomal locations of genes affecting these characteristics by linkage analysis in 501 dizygotic twin pairs. Results. Concentrations of Cu, Se and Zn, and of As and Hg, showed substantial correlations and the latter is mainly due to common genetic effects. Genetic linkage analysis showed significant linkage for Pb (chromosome 3, near SLC4A7) and suggestive linkage for Cd (chromosomes 2, 18, 20 and X), Hg (chromosome 5), Se (chromosomes 4 and 8), and Zn (chromosome 2, near SLC11A1). Conclusions. Although environmental exposure is a pre-condition for accumulation of toxic elements, individual characteristics and genetic factors are also important. Identification of the contributory genetic polymorphisms will improve our understanding of trace and toxic element uptake and distribution mechanisms.	2010
27.	Wilhelm CS, Kelsey KT, Butler R, Plaza S, Gagne L, Zens MS, Andrew AS, Morris S, Nelson HH, Schned AR, Karagas MR, Marsit CJ. Implications of LINE1 methylation for bladder cancer risk in women. Clin Cancer Res. 2010 Mar 1;16(5):1682-9. Epub 2010 Feb 23. PURPOSE: Epigenetic alterations including changes to cellular DNA methylation levels contribute to carcinogenesis and may serve as powerful biomarkers of the disease. This investigation sought to determine whether hypomethylation at the long interspersed nuclear elements (LINE1), reflective of the level of global DNA methylation, in peripheral blood-derived DNA is associated with increased risk of bladder cancer. EXPERIMENTAL DESIGN: LINE1 methylation was measured from blood-derived DNA obtained from participants of a population-based incident case-control study of bladder cancer in New Hampshire. Bisulfite-modified DNA was pyrosequenced to determine LINE1 methylation status; a total of 285 cases and 465 controls were evaluated for methylation. RESULTS: Being in the lowest LINE1 methylation decile was associated with a 1.8-fold increased risk of bladder cancer [95% confidence interval (95% CI), 1.12-2.90] in models controlling for gender, age, and smoking, and the association was stronger in women than in men (odds ratio, 2.48; 95% CI, 1.19-5.17 in women; and odds ratio, 1.47; 95% CI, 0.79-2.74 in men). Among controls, women were more likely to have lower LINE1 methylation than men (P = 0.04), and levels of arsenic in the 90th percentile were associated with reduced LINE1 methylation (P = 0.04). CONCLUSIONS: LINE1 hypomethylation may be an important biomarker of bladder cancer risk, especially among women.	2010
28.	Xue J, Zartarian V, Wang SW, Liu SV, Georgopoulos P. Probabilistic Modeling of Dietary Arsenic Exposure and Dose and Evaluation with 20032004 NHANES Data. Environ Health	2010

	Perspect. 2010 Mar;118(3):345-50. Background: Dietary exposure from food to toxic inorganic arsenic (iAs) in the general U.S. population has not been well studied.Objectives: The goal of this research was to quantify dietary As exposure and analyze the major contributors to total As (tAs) and iAs. Another objective was to compare model predictions with observed data.Methods: Probabilistic exposure modeling for dietary As was conducted with the Stochastic Human Exposure and Dose SimulationDietary (SHEDS-Dietary) model, based on data from the National Health and Nutrition Examination Survey. The dose modeling was conducted by combining the SHEDS-Dietary model with the MENTOR-3P (Modeling ENvironment for TOtal Risk with Physiologically Based Pharmacokinetic Modeling for Populations) system. Model evaluation was conducted via comparing exposure and dose-modeling predictions against duplicate diet data and biomarker measurements, respectively, for the same individuals.Results: The mean modeled tAs exposure from food is 0.38 microg/kg/day, which is approximately 14 times higher than the mean As exposures from the drinking water. The mean iAs exposure from food is 0.05 microg/kg/day (1.96 microg/day), which is approximately two times higher than the mean iAs exposures from the drinking water. The modeled exposure and dose estimates matched well with the duplicate diet data and measured As biomarkers. The major food contributors to iAs exposure were the following: vegetables (24%); fruit juices and fruits (18%); rice (17%); beer and wine (12%); and flour, corn, and wheat (11%). Approximately 10% of tAs exposure from foods is the toxic iAs form.Conclusions: The general U.S. population may be exposed to tAs and iAs more from eating some foods than from drinking water. In addition, this model evaluation effort provides more confidence in the exposure assessment tools used. Editor's SummaryEfforts to regulate arsenic (As) intake have focused on water contaminated with inorganic As (iAs), which is substantially more toxic than organic As. Recent studies have suggested that dietary iAs intakes may be higher than intake via As-contaminated water in some populations, but estimates of dietary intakes are complicated by variation in dietary patterns and iAs content of foods. Xue et al. (p. 345) used a probabilistic approach to estimate As intake and identify major dietary sources of total As and iAs for the general U.S. population. Food consumption data from the National Health and Nutrition Examination Survey (NHANES 2003-2004) were analyzed using the Stochastic Human Exposure and Dose Simulation-Dietary (SHEDS-Dietary) model to estimate intakes, and the MENTOR-3P (Modeling Environment for Total Risk with Physiologically Based Pharmacokinetic Modeling for Populations) system was used to predict urinary As excretion levels based on those intakes. Model predictions were then compared with urinary As biomarker data from the same NHANES participants to assess model performance. The authors report that the estimated mean iAs intake from food was double the estimated mean intake of iAs from drinking water; that major dietary sources of iAs were vegetables, fruit juices and fruits, rice, beer and wine, flour, corn, and wheat; and that model estimates were consistent with observations based on duplicate diet and urinary As biomarker data.	
29.	Banerjee P, Bhattacharyya SS, Pathak S, Boujedaini N, Belon P, Khuda-Bukhsh AR. Evidences of Protective Potentials of Microdoses of Ultra-high Diluted Arsenic Trioxide in Mice Receiving Repeated Injections of Arsenic Trioxide. Evid Based Complement Alternat Med. 2009 Feb 25. [Epub ahead of print] The present study was undertaken to examine if microdoses of ultra-high diluted arsenic trioxide (a potentized homeopathic remedy, Arsenicum Album 200C, diluted 10(-400) times) have hepatoprotective potentials in mice subjected to repeated injections of arsenic trioxide. Arsenic intoxicated mice were divided into: (i) those receiving Arsenicum Album-200C daily, (ii) those receiving the same dose of diluted succussed alcohol (Alc 200C) and (iii) another group receiving neither drug nor succussed alcohol. Two other control groups were also	2009

	maintained: one fed normal diet only and the other receiving normal diet and Alc-200C. Toxicity biomarkers like aspartate and alanine aminotransferases, glutathione reductase, catalase, succinate dehydrogenase, superoxide dismutase and reduced glutathione contents were periodically assayed keeping the observer 'blinded'. Additionally, electron microscopic studies and gelatin zymography for matrix metalloproteinases of liver tissues were made at day 90 and 120. Blood glucose, hemoglobin, estradiol and testosterone contents were also studied. Compared to controls, Arsenicum Album-200C fed mice showed positive modulations of all parameters studied, thereby providing evidence of protective potentials of the homeopathic drug against chronic arsenic poisoning.	
30.	Bourdonnay E, Morzadec C, Sparfel L, Galibert MD, Jouneau S, Martin-Chouly C, Fardel O, Vernhet L. Global effects of inorganic arsenic on gene expression profile in human macrophages. Mol Immunol. 2009 Feb;46(4):649-56. Epub 2009 Jan 6. Inorganic arsenic, a major environmental contaminant, exerts immunosuppressive effects towards human cells. We previously demonstrated that relevant environmental concentrations of inorganic arsenic altered morphology and functions of human primary macrophages, suggesting interference with macrophage differentiation program. The goal of this study was to determine global effect of low concentrations of arsenic trioxide (As(2)O(3)) on gene expression profile in human primary macrophages, in order to identify molecular targets of inorganic arsenic, especially those relevant of macrophage differentiation process. Using a pan-genomic microarray, we demonstrate that exposure of human blood monocyte-derived macrophages to 1microM As(2)O(3) for 72h, a non-cytototoxic concentration, results in up-regulation of 32 genes and repression of 91 genes. Among these genes, 26 are specifically related to differentiation program of human macrophages. Particularly, we validated that As(2)O(3) strongly alters expression of MMP9, MMP12, CCL22, SPON2 and CXCL2 genes, which contribute to major macrophagic functions. Most of these metalloid effects were reversed when As(2)O(3)-treated macrophages were next cultured in arsenic-free medium. We also show that As(2)O(3) similarly regulates expression of this macrophagic gene subset in human alveolar macrophages, the phenotype of which closely resembles that of blood monocyte-derived macrophage. In conclusion, our study demonstrates that environmentally relevant concentrations of As(2)O(3) impair expression of macrophage-specific genes, which fully supports interference of metalloid with differentiation program of human macrophages.	2009
31.	Chen CH, Chiou HY, Hsueh YM, Chen CJ, Yu HJ, Pu YS. Clinicopathological characteristics and survival outcome of arsenic related bladder cancer in taiwan. J Urol. 2009 Feb;181(2):547-52; discussion 553. Epub 2008 Dec 13. PURPOSE: We compared clinicopathological characteristics and outcomes in patients with bladder cancer who were exposed to graded arsenic levels in drinking water. MATERIALS AND METHODS: From 1993 through 2006, 977 patients with bladder cancer in Taiwan were studied retrospectively. Patients were from 3 areas, including the core zone (arsenic related blackfoot disease endemic area with a well water arsenic level of 350 to 1,100 ng/ml), zone 1 (a well water arsenic level of 350 ng/ml or greater but not a blackfoot disease endemic area) and zone 2 (a well water arsenic level of less than 350 ng/ml). Clinicopathological characteristics and survival outcome were compared among the groups. RESULTS: Of these patients 81 (8.3%), 246 (25.2%) and 650 (66.5%) lived in the core zone, and zones 1 and 2, respectively. More high grade and high stage tumors were observed in core zone patients than in those in zones 1 and 2, including high grade in 48.7% vs 41.4% and 39.2% of patients, advanced disease in 39.5% vs 31.0% and 18.5% and nodal metastasis in 8.6% vs 3.3% and 3.4%, respectively. Median overall and cancer specific survival in core zone patients was significantly shorter than in patients in zones 1 and 2, including 69 vs 119 and 113-month	2009

	overall survival and for the 75th percentile of cancer specific survival 34.5 vs 119 and 113 months, respectively. On multivariate analysis with adjustment for tumor grade and stage the zonal difference was not a significant factor for overall or cancer specific survival. CONCLUSIONS: Patients with arsenic related bladder cancer may have decreased overall and cancer specific survival because they have more unfavorable tumor phenotypes than patients in other areas in Taiwan.	
32.	Chen CL, Chiou HY, Hsu LI, Hsueh YM, Wu MM, Chen CJ. Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern Taiwan. Environ Res. 2009 Sep 5. [Epub ahead of print] Our previous study combining two arseniasis-endemic areas in Taiwan confirmed a dose-response association of lung cancer and arsenic exposure. We conducted current analysis to elucidate the dose-response relationship in lower exposure level, and to evaluate whether the association differs in different histological types. In addition, whether specific characteristics of well water consumptions increased lung cancer risk was examined in order to establish a complete risk profile for arsenic exposure. A total of 8086 residents in northeastern Taiwan were followed for 11 years and 6888 participants remained in the final analysis because 1198 residents with unknown arsenic concentration were excluded. The 178 incident lung cancers were ascertained through linkage with the national cancer registry profiles in Taiwan. All analyses were performed by Cox's proportional hazards regression models. We found a significant dose-response trend (P=0.001) of lung cancer risk associated with increasing arsenic concentration. There was no apparent increased risk at concentrations between 10 and 100mug/L, but concentrations between 100 and 300mug/L showed evidence of excess risk (RR 1.54, 0.97-2.46). The relative risk was 2.25 (95% CI: 1.43, 3.55) for exposure to >/=300mug/L when compared to <10mug/L. The significant dose-response trends and the synergistic effect of arsenic exposure and cigarette smoking can be found in squamous and small cell carcinomas, but not in adenocarcinoma. Despite lacking statistical precision, when duration is accounted for, all levels of exposure including low concentration were in the direction of increased risk of lung cancer, and these associations tended to increase with longer durations of exposure. This study provides additional evidence linking arsenic to lung cancer, and the indications that arsenic may play a more important role in certain histological type may help with further research in carcinogenic effect of inorganic arsenic on lung cancer.	2009
33.	Chowdhury NJ, Misbahuddin M, Rahman MS. Corn extracts lower tissue arsenic level in rat. Bangladesh Med Res Counc Bull. 2009 Apr;35(1):21-5. This study was carried out to see whether corn extracts could reduce the accumulation of arsenic in different tissues of rat. Exposure to arsenic (700 microg/rat/day) orally for 15 days led to significant accumulation of arsenic and significant reduction in the concentration of reduced glutathione (GSH) in different tissues. While water, salt, ethanol and alkali extracts of corn were co-administered at a dose of 0.5 mL/rat/day orally by stomach tube during last 8 days, arsenic concentration decreased significantly in all tissues and reduced glutathione (GSH) concentration increased significantly in tissues except heart and skin. Among the extracts, water extract produced maximum reduction of arsenic (69.07% in liver, 64.98% in kidney, 63.47% in lung, 57.55% in heart and 69.30% in skin) and elevation of reduced glutathione level in all tissues (17.03% in liver, 46.73% in lung, 32.67% in heart and 55.38% in skin) except kidney, in which maximum elevation of reduced glutathione was attained by ethanol extract (23.14%). This study suggests that corn extracts might protect rats from accumulation of arsenic in different tissues and oxidative stress, which is reflected by the increasing reduced glutathione concentration in those tissues.	2009
34.	Colin P, Koenig P, Ouzzane A, Berthon N, Villers A, Biserte J, Rouprêt M. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. BJU	2009

	Int. 2009 Nov;104(10):1436-40. Epub 2009 Aug 18. Primary cancers of the ureter and renal pelvis are rare tumours, > 90% of which are transitional cell carcinomas. Only approximately 5% of urothelial tumours arise in the upper urinary tract (UUT). Many environmental factors contribute to the development of these cancers. Some are similar to bladder cancer-associated factors (tobacco, occupational exposure), while others are more specific to carcinogenesis of the UUT (phenacetine, Balkan endemic nephropathy [BEN], Chinese herb nephropathy or association with Blackfoot disease [BFD]). This review discusses the environmental factors involved in UUT carcinoma. Tobacco and occupational exposure remain the principal exogenous risk factors for developing these tumours. Conversely, carcinogenesis of UUT tumours resulting from phenacetine consumption has almost disappeared. Although the incidence of BEN is also on the decline, roles for aristolochic acid and the consumption of Chinese herbs in the physiopathology and induction of this nephropathy, respectively, have proposed. In Taiwan, the association of this tumour type with BFD and arsenic exposure remains unclear to date. As some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, there is variability in interindividual susceptibility to the development of UUT carcinoma when exposed to the aforementioned risk factors Cytosolic sulfotransferases (SULTs) catalyse the detoxification of many environmental chemicals but also in the bioactivation of dietary and other mutagens. Polymorphism of the SULT gene, is thought to confer susceptibility to upper tract tumours.	
35.	Fatmi Z, Azam I, Ahmed F, Kazi A, Gill AB, Kadir MM, Ahmed M, Ara N, Janjua NZ; Core Group for Arsenic Mitigation in Pakistan. Health burden of skin lesions at low arsenic exposure through groundwater in Pakistan. Is river the source? Environ Res. 2009 Jul;109(5):575-81. Epub 2009 May 5. A significant proportion of groundwater in south Asia is contaminated with arsenic. Pakistan has low levels of arsenic in groundwater compared with China, Bangladesh and India. A representative multi-stage cluster survey conducted among 3874 persons > or = 15 years of age to determine the prevalence of arsenic skin lesions, its relation with arsenic levels and cumulative arsenic dose in drinking water in a rural district (population: 1.82 million) in Pakistan. Spot-urine arsenic levels were compared among individuals with and without arsenic skin lesions. In addition, the relation of age, body mass index, smoking status with arsenic skin lesions was determined. The geographical distribution of the skin lesions and arsenic-contaminated wells in the district were ascertained using global positioning system. The total arsenic, inorganic and organic forms, in water and spot-urine samples were determined by atomic absorption spectrophotometry. The prevalence of skin lesions of arsenic was estimated for complex survey design, using surveyfreq and surveylogistic options of SAS 9.1 software.The prevalence of definitive cases i.e. hyperkeratosis of both palms and soles, was 3.4 per 1000 and suspected cases i.e. any sign of arsenic skin lesions (melanosis and/or keratosis), were 13.0 per 1000 among > or = 15-year-old persons in the district. Cumulative arsenic exposure (dose) was calculated from levels of arsenic in water and duration of use of current drinking water source. Prevalence of skin lesions increases with cumulative arsenic exposure (dose) in drinking water and arsenic levels in urine. Skin lesions were 2.5-fold among individuals with BMI <18.5 kg/m2. Geographically, more arsenic-contaminated wells and skin lesions were alongside Indus River, suggests a strong link between arsenic contamination of groundwater with proximity to river.This is the first reported epidemiological and clinical evidence of arsenic skin lesions due to groundwater in Pakistan. Further investigations and focal mitigation measures for arsenic may be carried out alongside Indus River.	2009
36.	Gallogly MM, Starke DW, Mieyal JJ. Mechanistic and kinetic details of catalysis of thiol-disulfide exchange by glutaredoxins and potential mechanisms of regulation. Antioxid Redox Signal. 2009 May;11(5):1059-81.	2009

	Glutaredoxins are small, heat-stable proteins that exhibit a characteristic thioredoxin fold and a CXXC/S active-site motif. A variety of glutathione (GSH)-dependent catalytic activities have been attributed to the glutaredoxins, including reduction of ribonucleotide reductase, arsenate, and dehydroascorbate; assembly of iron sulfur cluster complexes; and protein glutathionylation and deglutathionylation. Catalysis of reversible protein glutathionylation by glutaredoxins has been implicated in regulation of redox signal transduction and sulfhydryl homeostasis in numerous contexts in health and disease. This forum review is presented in two parts. Part I is focused primarily on the mechanism of the deglutathionylation reaction catalyzed by prototypical dithiol glutaredoxins, especially human Grx1 and Grx2. Grx-catalyzed protein deglutathionylation proceeds by a nucleophilic, double-displacement mechanism in which rate enhancement is attributed to special reactivity of the low pK(a) cysteine at its active site, and to increased nucleophilicity of the second substrate, GSH. Glutaredoxins (and Grx domains) have been identified in most organisms, and many exhibit deglutathionylation or other activities or both. Further characterization according to glutathionyl selectivity, physiological substrates, and intracellular roles may lead to subclassification of this family of enzymes. Part II presents potential mechanisms for in vivo regulation of Grx activity, providing avenues for future studies.	
37.	Jin Y, Zhao F, Zhong Y, Yu X, Sun D, Liao Y, Lv X, Li G, Sun G. Effects of exogenous GSH and methionine on methylation of inorganic arsenic in mice exposed to arsenite through drinking water. Environ Toxicol. 2009 May 15. [Epub ahead of print] We hypothesized that chronic exposure to arsenic would deplete the reduced glutathione (GSH) and methionine in vivo, thereby impair the methylation capacity of inorganic arsenic (iAs) ingested. Our experiment was designed to explore the effects of exogenous GSH and methionine on arsenic methylation in mice exposed to arsenite via drinking water. Levels of iAs, monomethylarsenic acid (MMAs), and dimethylarsenic acid (DMAs) in the liver and blood were determined by the method of hydride generation coupled with atomic absorption spectrophotometry. Compared with mice exposed to arsenite alone, administration of GSH or methionine increased the secondary methylation index in the liver and primary methylation index in the blood, which resulted in the consequent increase of DMAs percent and decrease of iAs percent in the blood. Moreover, administration of GSH resulted in the increase of DMAs percent in the liver and total arsenic in the blood. Increase of total arsenic in the blood was mainly due to the increase of DMAs. Findings from the present study suggested that administration of GSH or methionine might potentiate the methylation capacity of arsenic in both liver and extrahepatic tissues, which may facilitate the excretion of arsenic and decrease arsenic related toxicities in the body. (c) 2009 Wiley Periodicals, Inc. Environ Toxicol, 2009.	2009
38.	Kumar A, Adak P, Gurian PL, Lockwood JR. Arsenic exposure in US public and domestic drinking water supplies: A comparative risk assessment. J Expo Sci Environ Epidemiol. 2009 Apr 29. [Epub ahead of print] Although approximately 35 million people in the US obtain drinking water from domestic wells, few studies have investigated the risk of arsenic exposure from this source. In this paper arsenic concentrations were modeled for public and domestic wells using a dataset from the US Geological Survey (USGS). Excess lifetime and annual risks for lung and bladder cancer were calculated based on the carcinogenic potency and average arsenic concentrations in public and domestic water supplies. Monte Carlo uncertainty analysis was used to estimate the degree of confidence in these estimations. Results indicated that domestic well users accounted for 12% of the US population, but 23% of overall arsenic exposure from drinking water. Assuming that the new and more restrictive arsenic maximum contaminant limit (MCL) is implemented for public water supplies, it is anticipated that the proportion of people experiencing excess annual	2009

	fatalities from drinking water from domestic wells will increase to 29% unless corresponding efforts are made to reduce exposures among domestic well users. Differences between public and domestic wells were not consistent across the nation. Public wells tend to tap deeper aquifers than domestic wells, and as a result local arsenic-depth trends can contribute to differences between public and domestic wells. Domestic wells and public wells in the western US have the highest arsenic levels with excess fatality risks estimated to be in the range of 1 per 9300 to 1 per 6600 in these regions. Uncertainty distributions of excess fatalities were developed and resultant uncertainties were propagated in arsenic exposure and potency factor. Uncertainty in the carcinogenic potency of arsenic was the dominant source of uncertainty in most regions, but for domestic wells in the New England and Southeast regions uncertainty in arsenic exposure was dominant, indicating that additional data on arsenic concentrations in these areas would substantially improve regional risk estimates.Journal of Exposure Science and Environmental Epidemiology advance online publication, 29 April 2009; doi:10.1038/jes.2009.24.	
39.	Li JX, Shen YQ, Cai BZ, Zhao J, Bai X, Lu YJ, Li XQ. Arsenic trioxide induces the apoptosis in vascular smooth muscle cells via increasing intracellular calcium and ROS formation. Mol Biol Rep. 2010 Mar;37(3):1569-76. Epub 2009 May 13. The present study was designed to investigate whether arsenic trioxide induced the apoptosis in rat mesenteric arterial smooth muscle cells (SMCs), which provides new insights into mechanisms of arsenic-related vascular diseases. Here, we found that arsenic trioxide significantly decreased the viability of SMCs in a dose-dependent manner. In addition, higher level of arsenic trioxide directly caused cellular necrosis. The Hoechst and AO/EB staining demonstrated that apoptotic morphological change was presented in SMCs exposed to arsenic trioxide. The TUNEL assay displayed that more positive apoptotic signal appeared in SMCs treated with arsenic trioxide. The following result showed that ROS formation was markedly increased in arsenic trioxide-treated SMCs. Pretreatment with N-acetylcysteine, an anti-oxidant reagent, obviously attenuated the enhancement of ROS production and the reduction of cell viability induced by arsenic trioxide in SMCs. Arsenic trioxide also enhanced free intracellular Ca(2+) level in SMCs. BAPTA also significantly prevented the increased intracellular Ca(2+) and decreased cell viability induced by arsenic trioxide in SMCs. These results suggested that arsenic trioxide obviously induced apoptosis in SMCs, and its mechanism was partially associated with intracellular ROS formation and free Ca(2+) increasing.	2009
40.	Li Z, Piao F, Liu S, Wang Y, Qu S. Subchronic exposure to arsenic trioxide-induced oxidative DNA damage in kidney tissue of mice. Exp Toxicol Pathol. 2009 Aug 10. [Epub ahead of print] To evaluate the oxidative DNA damage in kidney tissue of mice exposed to arsenic trioxide (As) subchronically, expression of 8-hydroxy-2-deoxyguanosine (8-OHdG) and pathologic changes were observed. Forty mice were randomly divided into 4 groups of 10 each (5 mice of each sex). Group 1 received drinking water alone (control). Groups 2, 3 and 4 received 1, 2 and 4mg/L arsenic trioxide, respectively. Arsenic trioxide was given through drinking water for 60 days. The expression of 8-OHdG in the kidney tissue of mice was analyzed observed in these 4 groups. The groups treated with As showed pathologic changes in the kidney tissue and significant increase in the level of 8-OHdG expression ($P<0.01$). Moreover, the dose-dependent increase between As exposure and renal damages were observed. Especially, its immunoactivity was strong in the proximal convoluted tubule and Bowman's capsule. These results suggest that chronic exposure to As induces damages to kidney tissue, and especially the epithelial cells of proximal convoluted tubule and the podocytes of the Bowman's capsule may be more sensitive to As-induced nephrotoxicity.	2009

41.	Majumdar S, Chanda S, Ganguli B, Mazumder DN, Lahiri S, Dasgupta UB. Arsenic exposure induces genomic hypermethylation. Environ Toxicol. 2009 May 12. [Epub ahead of print] Gene-specific hypermethylation has previously been detected in Arsenic exposed persons. To monitor the level of whole genome methylation in persons exposed to different levels of Arsenic via drinking water, DNA was extracted from peripheral blood mononuclear cells of 64 persons. Uptake of methyl group from (3)H labeled S-Adenosyl Methionine after incubation of DNA with SssI methylase was measured. Results showed statistically significant (P = 0.0004) decrease in uptake of (3)H methyl group in the persons exposed to 250-500 mug/L arsenic, indicating genomic hypermethylation. (c) 2009 Wiley Periodicals, Inc. Environ Toxicol, 2009.	2009
42.	Mazumder DN, Majumdar KK, Santra SC, Kol H, Vicheth C. Occurrence of arsenicosis in a rural village of Cambodia. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2009 Apr;44(5):480-7. Ninety-seven subjects belonging to 40 families in a village in Cambodia were examined in a health camp where all the cases with skin disease assembled. These people had evidences of chronic arsenic exposure from reports of testing of water samples and of hair and/or nail studied. Seventy cases were diagnosed to be suffering from arsenicosis (Clinically and laboratory confirmed according to WHO criteria) as all these cases had evidences of pigmentation and/or keratosis characteristic of arsenicosis and history of exposure of arsenic contaminated water and/or elevated level of arsenic in hair and/or in nail. Highest number of cases belonged to age group of 31 to 45 yrs, both the sexes are more or less affected equally. Evidence of both pigmentation and keratosis were found in 60 cases (85.7%) while only pigmentation and only keratosis was found in 6 (8.5%) and 4 (5.7%) cases respectively. It was interesting to find 37.04% of children below the age of 16 years had skin lesions of arsenicosis. The youngest child having definite evidence of keratosis and pigmentation was aged 8 years, though two children aged 4 and 5 yrs had feature of redness and mild thickening of the palms. The minimum and maximum arsenic values detected in the nails were 1.06 and 69.48 mg/Kg respectively and the minimum and maximum arsenic values in hair were 0.92 and 25.6 mg/Kg respectively. No correlation was observed between arsenic concentration in drinking water and arsenic level in nail and hair. This is the first report of clinical and laboratory confirmed cases of arsenicosis in Cambodia.	2009
43.	Nollen M, Ebert F, Moser J, Mullenders LH, Hartwig A, Schwerdtle T. Impact of arsenic on nucleotide excision repair: XPC function, protein level, and gene expression. Mol Nutr Food Res. 2009 May;53(5):572-82. The ubiquitous occurrence of the human carcinogen arsenic results in multiple exposure possibilities to humans. The human diet, especially drinking water, is the primary source of inorganic arsenic intake in the general population. The ingested arsenic is metabolized to methylated derivatives; some of these metabolites are today considered to be more toxic than the inorganic species. Various modes of action have been proposed to contribute to arsenic carcinogenicity; inhibition of nucleotide excision repair (NER), removing DNA helix distorting DNA adducts induced by environmental mutagens, is likely to be of primary importance. Here, we report that arsenite and its metabolite monomethylarsonous acid (MMA(III)) strongly decreased expression and protein level of Xeroderma pigmentosum complementation group C (XPC), which is believed to be the principle initiator of global genome NER. This led to diminished association of XPC to sites of local UVC damage, resulting in decreased recruitment of further NER proteins. Additionally Xeroderma pigmentosum complementation group E protein (XPE) expression was reduced, which encodes for another important NER protein and similarly to XPC is regulated by the activity of the transcription factor p53. In summary, our data demonstrate that in human skin fibroblasts arsenite and even more	2009

	pronounced MMA(III) interact with XPC expression, resulting in decreased XPC protein level and diminished assembly of the NER machinery.	
44.	Paiva L, Hernández A, Martínez V, Creus A, Quinteros D, Marcos R. Association between GSTO2 polymorphism and the urinary arsenic profile in copper industry workers. Environ Res. 2009 Dec 31. [Epub ahead of print] Two members of the recently identified Omega class glutathione S-transferase enzymes (GSTO1 and GSTO2) have been proposed to play a role in the response to arsenic exposure. Therefore, polymorphisms in these genes could be related with variations in the arsenic excretion profile and, consequently, with the individual response to chronic exposure. Exons and flanking regions of GSTO2 gene have been screened in two different ethnic groups (20 Europeans and 20 Chilean Indians), and the urinary arsenic patterns and the GSTO2 Asn142Asp polymorphism have been investigated in 207 copper mine workers occupationally exposed to arsenic. Three polymorphisms of GSTO2 already described were detected in Europeans and Chilean Indians, although with significant different allele frequencies. The genotyping for the Asn142Asp polymorphism revealed that almost no significant association exists between this change and the arsenic excretion profile. However, 142Asp change seems to be correlated with an increase in DMA excretion after age and total urinary arsenic adjustment (OR=3.61; P=0.05). Altogether, our findings indicate that ethnical differences should be taken into account for correlation studies between GST Omega polymorphisms and arsenic susceptibility, and that the 142Asp allozyme could modulate arsenic biotransformation and thereby arsenic toxicity. Copyright © 2009 Elsevier Inc. All rights reserved.	2009
45.	Suzuki S, Arnold LL, Pennington KL, Chen B, Le XC, Cohen SM. Effects of co-administration of dietary sodium arsenite and an epidermal growth factor receptor inhibitor on the rat bladder epithelium. Toxicol. Letters, 187: 124-129, 2009 Arsenite (As^{III}), an inorganic arsenical, is a known human carcinogen, inducing tumors of the skin, urinary bladder and lung. It is known to be metabolized to organic methylated arsenicals in vivo. As^{III} has been reported to have the ability to up-regulate the epidermal growth factor receptor (EGFR)-associated pathway in epithelial cells, including human urothelial cells in vitro. EGFR is a cell-surface receptor belonging to the ErbB family of receptor tyrosine kinases, and the EGFR-associated signaling pathway has been reported to play an important role in carcinogenesis and cancer progression, including in bladder cancer. In this study, we investigated the growth effects of As^{III} and an organic trivalent arsenical, dimethylarsinous acid (DMA^{III}), and the effects of co-exposure of gefitinib, an EGFR inhibitor, with As^{III} to a rat urothelial cell line (MYP3). We also investigated the effects of co-administration of dietary As^{III} and gefitinib *in vivo*. *In vitro*, concentrations of 1.0 μM As^{III} or 0.5 μM DMA^{III} induced cytotoxicity. However, lower concentrations of As^{III} treatment had a slight mitogenic growth effect whereas lower concentrations of DMA^{III} did not. Gefitinib blocked As^{III}-induced cell growth *in vitro*. *In vivo*, a high dose of gefitinib alone induced slight urothelial cytotoxicity, and did not reduce cytotoxicity and regenerative cell proliferation when co-administered with As^{III}. The majority of arsenic metabolites present in the urine of AsIII-treated rats were organic arsenicals, mainly dimethylarsinic acid (DMA^{V}). As^{III} was also present, and its concentration was higher than the concentration required to produce cytotoxicity *in vitro*. These data suggest that an EGFR inhibitor has the ability to block As^{III}-induced cell proliferation *in vitro* but not *in vivo* in a short-term study.	2009
46.	Suzuki S, Arnold LL, Pennington KL, Chen B, Le XC, Cohen SM. Effects of an epidermal growth factor receptor inhibitor on arsenic associated toxicity in the rat bladder epithelium. Toxicol Lett. 2009 Jun 1;187(2):124-9. Epub 2009 Mar 3. Arsenite (As(III)), an inorganic arsenical, is a known human carcinogen, inducing tumors of	2009

	the skin, urinary bladder and lung. It is known to be metabolized to organic methylated arsenicals in vivo. As(III) has been reported to have the ability to up-regulate the epidermal growth factor receptor (EGFR)-associated pathway in epithelial cells, including human urothelial cells in vitro. EGFR is a cell-surface receptor belonging to the ErbB family of receptor tyrosine kinases, and the EGFR-associated signaling pathway has been reported to play an important role in carcinogenesis and cancer progression, including in bladder cancer. In this study, we investigated the growth effects of As(III) and an organic trivalent arsenical, dimethylarsinous acid (DMA(III)), and the effects of co-exposure of gefitinib, an EGFR inhibitor, with As(III) to a rat urothelial cell line (MYP3). We also investigated the effects of co-administration of dietary As(III) and gefitinib in vivo. In vitro, concentrations of 1.0microM As(III) or 0.5microM DMA(III) induced cytotoxicity. However, lower concentrations of As(III) treatment had a slight mitogenic growth effect whereas lower concentrations of DMA(III) did not. Gefitinib blocked As(III)-induced cell growth in vitro. In vivo, a high dose of gefitinib alone induced slight urothelial cytotoxicity, and did not reduce cytotoxicity and regenerative cell proliferation when co-administered with As(III). The majority of arsenic metabolites present in the urine of As(III)-treated rats were organic arsenicals, mainly dimethylarsinic acid (DMA(V)). As(III) was also present, and its concentration was higher than the concentration required to produce cytotoxicity in vitro. These data suggest that an EGFR inhibitor has the ability to block As(III)-induced cell proliferation in vitro but not in vivo in a short-term study.	
47.	Suzuki, S., Arnold L.L., Pennington, K., Kakiuchi-Kiyota, S., and Cohen, S.M. Effects of co-administration of dietary sodium arsenite and a NADPH oxidase inhibitor on the rat bladder epithelium. Toxicology. 2009 Jun 30;261(1-2):41-6. Epub 2009 May 3. Arsenite (As(III)), an inorganic arsenical, is a known human carcinogen, inducing tumors of the skin, urinary bladder and lung. It is metabolized to organic methylated arsenicals. Oxidative stress has been suggested as a mechanism for arsenic-induced carcinogenesis. Reactive oxygen species (ROS) can be important factors for carcinogenesis and tumor progression. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is known to produce intracellular ROS, therefore, we investigated the ability of apocynin (acetovanillone), an NADPH oxidase inhibitor, to inhibit the cytotoxicity and regenerative cell proliferation of arsenic in vitro and in vivo. Apocynin had similar effects in reducing the cytotoxicity of As(III) and dimethylarsinous acid (DMA(III)) in rat urothelial cells in vitro. When tested at the same concentrations as apocynin, other antioxidants, such as l-ascorbate and N-acetylcysteine, did not inhibit As(III)-induced cytotoxicity but they were more effective at inhibiting DMA(III)-induced cytotoxicity compared with apocynin. In vivo, female rats were treated for 3 weeks with 100ppm As(III). Immunohistochemical staining for 8-hydroxy-2'-deoxyguanosine (8-OHdG) showed that apocynin reduced oxidative stress partially induced by As(III) treatment on rat urothelium, and significantly reduced the cytotoxicity of superficial cells detected by scanning electron microscopy (SEM). However, based on the incidence of simple hyperplasia and the bromodeoxyuridine (BrdU) labeling index, apocynin did not inhibit As(III)-induced urothelial cell proliferation. These data suggest that the NADPH oxidase inhibitor, apocynin, may have the ability to partially inhibit arsenic-induced oxidative stress and cytotoxicity of the rat bladder epithelium in vitro and in vivo. However, apocynin did not inhibit the regenerative cell proliferation induced by arsenite in a short-term study.	2009
48.	Taeger D, Johnen G, Wiethege T, Tapio S, Möhner M, Wesch H, Tannapfel A, Müller KM, Brüning T, Pesch B. Major histopathological patterns of lung cancer related to arsenic exposure in German uranium miners. Int Arch Occup Environ Health. 2009 Jul;82(7):867-75. Epub 2008 Nov 20. OBJECTIVE: The mechanisms of action of arsenic in the development of lung cancer are still	2009

	not yet elucidated. Considering the relationship between arsenic and squamous cell carcinomas of the skin, we hypothesized that arsenic exposure may be more closely associated with squamous cell carcinoma of the lung. METHODS: A comprehensive histopathological database and a detailed job-exposure matrix developed for former German uranium miners with exposure to arsenic, radon, and quartz were analyzed to quantitatively assess the effect of arsenic regarding cell type of lung cancer. The distributions of major lung cancer cell types in 1,786 German uranium miners were associated with levels of arsenic exposure under control for the other lung carcinogens. To evaluate the arsenic effects in association with a frequent occupational lung disease in miners stratification by silicosis was performed. RESULTS: There was an arsenic-related increase of the proportion of squamous cell carcinoma of the lung but restricted to miners without silicosis. The increase was found at all levels of co-exposure to radon and quartz dust. In miners with silicosis, the proportion of adenocarcinoma increased with rising arsenic exposure. Arsenic exposure was associated with non-small cell lung cancer. Silicosis turned out as major determinant of the cell type related with arsenic. CONCLUSION: These results indicate a cell type characteristic effect of arsenic in the development of lung cancer.	
49.	Wang C, Chen G, Jiang J, Qiu L, Hosoi K, Yao C. Aquaglyceroporins are involved in uptake of arsenite into murine gastrointestinal tissues. J Med Invest. 2009;56 Suppl:343-6. Aquaglyceroporins (AQGPs) are members of aquaporin (AQP) family and belong to a subgroup of this water channel family; they are transmembrane proteins that transport water as well as glycerol and other solutes of small molecules. Recent studies have also identified that AQGPs are important transporters of trivalent metalloid in some mammalian cells. However, the uptake routes of arsenite in mammals are still less defined. In this study, to understand the routes of arsenite intake in mammals, mice were treated with Hg(II), glycerol, and As(III) and uptake of As(III) into the gastrointestinal tissues was measured. The level of inorganic arsenic (iAs) in gastrointestinal tissues after As(III) stimulation was much higher than Hg(II) +As(III) or glycerol+As(III) group. RT-PCR results showed that AQGPs were extensively expressed in gastrointestinal tissues of mice. We also treated Caco-2 cells with Hg(II) and As(III); the level of iAs in a group treated with Hg(II)+As(III) decreased compared with As(III)-treated group. Our results suggested that AQGPs could be important transporters in arsenite uptake into gastrointestinal tissues of mice, but more data are need to prove if AQGPs is the only pathway involved in As transport in mammals or just one of them.	2009
50.	Wang YH, Yeh SD, Shen KH, Shen CH, Juang GD, Hsu LI, Chiou HY, Chen CJ. A significantly joint effect between arsenic and occupational exposures and risk genotypes/diplotypes of CYP2E1, GSTO1 and GSTO2 on risk of urothelial carcinoma. Toxicol Appl Pharmacol. 2009 Nov 15;241(1):111-8. Epub 2009 Aug 15. Cigarette smoking, arsenic and occupational exposures are well-known risk factors for the development of urothelial carcinoma (UC). Therefore, the aim of this study is to investigate whether the effect of cigarette smoking, alcohol consumption, arsenic and occupational exposures on risk of UC could be modified by genetic polymorphisms of cytochrome P450 2E1 and glutathione S-transferase omega. A hospital-based case-control study consisted of 520 histologically confirmed UC cases, and 520 age- and gender-matched cancer-free controls were carried out from September 1998 to December 2007. Genotyping of CYP2E1, GSTO1 and GSTO2 was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Subjects with both of cigarette smoking and alcohol consumption have a significantly increased UC risk (odds ratio [OR]=2.9; 95% confidence interval [CI]=1.9-4.4). Significantly increased UC risks of 1.5 and 1.9 were found for study subjects with high arsenic exposure and those who have been exposed to two or more occupational exposures, respectively. A significantly increased UC risk of 3.9 was observed in study	2009

	subjects with H2-H2 diplotype of GSTO1 and GSTO2. The significantly highest UC risk of 9.0 was found for those with all environmental risk factors of cigarette smoking, alcohol consumption, arsenic and occupational exposures and two or more risk genotypes/diplotypes of CYP2E1, GSTO1 and GSTO2. Our findings suggest that a significantly joint effect of cigarette smoking, alcohol consumption, arsenic and occupational exposures and risk genotypes/diplotypes of CYP2E1, GSTO1 and GSTO2 on risk of UC was found.	
51.	Yang L, Luo JM, Wen SP, Liu XJ, Du XY, Li Y. Effect of As2O3 on demethylation of SHP-1 gene in human lymphoma cell line T2. Chinese journal of cancer. 2009 Mar;28(3):209-13. BACKGROUND AND OBJECTIVE: Inducing gene demethylation may be a mechanism of arsenic trioxide (As2O3) in treating hematologic cancers. This study was to investigate the effect of As2O3 on demethylation of SH2-containing phosphatase-1 (SHP-1) in human lymphoma cell line T2 and on the proliferation of T2 cells. METHODS: T2 cells were treated with As2O3 and 5-aza-2'-deoxyoytidine (5-AC) alone or in combination. The methylation of SHP-1 in T2 cells was detected by methylation-specific polymerase chain reaction (MSP). The mRNA and protein expression of SHP-1 were determined by fluorescence quantitative-polymerase chain reaction (FQ-PCR) and Western blot. The expression of p-c-kit was detected by Western blot. Cell proliferation was detected by MTT assay. Cell apoptosis was detected by flow cytometry. RESULTS: As2O3 led to progressive demethylation and re-expression of SHP-1 in T2 cells, as well as down-regulation of phosphorylated c-kit. As2O3 inhibited the proliferation and promoted the apoptosis of T2 cells, and its effects were enhanced along with the increase of concentration and treatment time ($p<0.05$). The proliferation inhibition rates were significantly lower in As2O3 (2.5 micromol/L) group than in combination (2.5 micromol/L As2O3 plus 2 micromol/L 5-AC) group (9.8% vs. 11.0%on Day 1, 20.3% vs. 36.7% on Day 2, 47.5% vs. 61.0% on Day 3, $p<0.05$). The apoptosis rates were significantly higher in combination group than in As2O3 group (17.3% vs. 6.1% on Day 1, 37.9% vs. 26.5% on Day 2, 67.9% vs. 50.9% on Day 3, $p<0.05$). CONCLUSIONS: As2O3 could cause demethylation and re-expression of SHP-1 in T2 cells, and may inhibit proliferation and induce apoptosis of T2 cells via suppressing activation of c-kit receptor and its signal transduction.	2009
52.	Banerjee M, Sarma N, Biswas R, Roy J, Mukherjee A, Giri AK. DNA repair deficiency leads to susceptibility to develop arsenic-induced premalignant skin lesions. Int J Cancer. 2008 Jul 15;123(2):283-7. In West Bengal, India, although more than 6 million people are exposed to arsenic through drinking water, only 15-20% showed arsenic-induced skin lesions, including premalignant hyperkeratosis. This indicates toward some factors that confer susceptibility to arsenic-induced carcinogenicity. In this work, we wanted to explore whether differences in DNA repair capacity could impart arsenic-induced carcinogenicity, through Comet assay, chromosomal aberration (CA) assay and challenge assay. Sixty arsenic exposed (30 individuals with arsenic-induced premalignant hyperkeratosis and 30 without skin lesion, but drinking similar arsenic contaminated water) and 30 arsenic unexposed individuals were recruited as study participants. Alkaline comet assay, and challenge assay were carried out in whole blood and CA study in lymphocytes to find out the DNA damage and DNA repair capacity in both hyperkeratotic and without skin lesion individuals. DNA damage as well as CA were found to be significantly higher in the arsenic-exposed individuals compared to unexposed individuals ($p < 0.001$). Within the exposed group, there was no significant difference as far as the level of DNA damage is concerned ($p > 0.05$), but CA was significantly higher in exposed individuals with hyperkeratosis than exposed individuals without hyperkeratosis ($p < 0.01$). Challenge assay showed that upon induction of DNA damage, the repair capacity in the exposed individuals with premalignant hyperkeratosis is significantly less ($p < 0.001$) than that of individuals without skin lesion, although the basal level of DNA damage was similar in both. Thus, the	2008

	deficiency in DNA repair capacities in the hyperkeratotic individuals emerges as a prime contender for arsenic carcinogenicity. (c) 2008 Wiley-Liss, Inc.	
53.	De Chaudhuri S, Kundu M, Banerjee M, Das JK, Majumdar P, Basu S, Roychoudhury S, Singh KK, Giri AK. Arsenic-induced health effects and genetic damage in keratotic individuals: involvement of p53 arginine variant and chromosomal aberrations in arsenic susceptibility. Mutat Res. 2008 Jul-Aug;659(1-2):118-25. Epub 2007 Nov 26. In West Bengal, India, more than 6 million people are exposed to arsenic through drinking water. Chronic arsenic exposure results in several multisystemic non-cancerous as well as cancerous effects in humans. Among non-cancerous effects, arsenic-specific skin lesions, conjunctivitis, peripheral neuropathy and respiratory diseases are prominent. One of the major consequences of chronic arsenic exposure is keratosis, the precancerous state of skin cancer. The tumor suppressor protein p53 consists of a polymorphism proline72arginine reported to be associated with various types of cancers. Previously we have reported that the p53 codon 72 arginine (Arg) homozygous genotype is associated with the development of arsenic-induced keratosis. In the present study we have investigated the distribution of health effects and chromosomal aberrations (CAs) in the individuals with keratosis. We have compared individuals with keratosis with those without arsenic-induced skin lesions but drinking similar level of arsenic-contaminated water. Attempts have also been made to find out the association of the p53 risk genotype with health effects and chromosomal aberrations. This study comprises of 349 unrelated exposed individuals (162 individuals with keratosis and 187 individuals without arsenic-specific skin lesions) from highly arsenic-affected districts of West Bengal, India. The results showed that health effects (i.e. peripheral neuropathy, conjunctivitis and respiratory illness) and chromosomal aberrations were significantly higher in the keratotic group compared to individuals with no skin lesions. Moreover, individuals with the arginine homozygous genotype showed increased levels of chromosomal aberrations compared to individuals with other genotypes; however, we did not find any significant association of the risk genotype with health effects. This study suggests that individuals with keratosis are more susceptible to arsenic-induced health effects and genetic damage and that the arginine variant of p53 can further influence the repair capacity of arsenic-exposed individuals, leading to increased accumulation of chromosomal aberrations.	2008
54.	Eblin KE, Bredfeldt TG, Gandolfi AJ. Immortalized human urothelial cells as a model of arsenic-induced bladder cancer. Toxicology. 2008 Jun 27;248(2-3):67-76. Epub 2008 Mar 30. Arsenical-induced carcinogenesis in human bladder has been established through epidemiological evidence, and UROtsa cells, a normal, immortalized cell culture model of human urothelium, have proven to be a good model for the bladder epithelium. This cell line does not form tumors when injected into immuno-compromised mice nor does it have anchorage-independent growth. UROtsa can be easily manipulated for acute studies related to arsenical exposure. They have been shown to be sensitive to all arsenicals, in particular, the trivalent species, arsenite and monomethylarsonous acid. UROtsa cells have also opened the area of cellular signaling alterations following subcytotoxic exposure to arsenicals in both the acute and long-term time points. In addition, UROtsa cells were shown to be malignantly transformed following low-level exposure to both As(III) and MMA(III) providing additional models for studying arsenical-induced carcinogenesis of the bladder. These transformed cell lines allow researchers the ability to investigate the process of urothelial tumorigenesis at multiple time points of arsenical exposure. Overall, UROtsa cells are an effective model for cellular insult following arsenical exposure.	2008
55.	Ghosh P, Basu A, Singh KK, Giri AK. Evaluation of cell types for assessment of cytogenetic damage in arsenic exposed population. Mol Cancer. 2008 May 28;7:45.	2008

	BACKGROUND: Cytogenetic biomarkers are essential for assessing environmental exposure, and reflect adverse human health effects such as cellular damage. Arsenic is a potential clastogen and aneugen. In general, the majority of the studies on clastogenic effects of arsenic are based on frequency of micronuclei (MN) study in peripheral lymphocytes, urothelial and oral epithelial cells. To find out the most suitable cell type, here, we compared cytogenetic damage through MN assay in (a) various populations exposed to arsenic through drinking water retrieved from literature review, as also (b) arsenic-induced Bowen's patients from our own survey. RESULTS: For literature review, we have searched the Pubmed database for English language journal articles using the following keywords: "arsenic", "micronuclei", "drinking water", and "human" in various combinations. We have selected 13 studies consistent with our inclusion criteria that measured micronuclei in either one or more of the above-mentioned three cell types, in human samples. Compared to urothelial and buccal mucosa cells, the median effect sizes measured by the difference between people with exposed and unexposed, lymphocyte based MN counts were found to be stronger. This general pattern pooled from 10 studies was consistent with our own set of three earlier studies. MN counts were also found to be stronger for lymphocytes even in arsenic-induced Bowen's patients (cases) compared to control individuals having arsenic-induced non-cancerous skin lesions. CONCLUSION: Overall, it can be concluded that MN in lymphocytes may be superior to other epithelial cells for studying arsenic-induced cytogenetic damage.	
56.	Hsu LI, Chiu AW, Pu YS, Wang YH, Huan SK, Hsiao CH, Hsieh FI, Chen CJ. Comparative genomic hybridization study of arsenic-exposed and non-arsenic-exposed urinary transitional cell carcinoma. Toxicol Appl Pharmacol. 2008 Mar 1;227(2):229-38. Epub 2007 Nov 12. To compare the differences in DNA aberrations between arsenic-exposed and non-arsenic-exposed transitional cell carcinoma (TCC), we analyzed 19 arsenic-exposed and 29 non-arsenic-exposed urinary TCCs from Chi-Mei Hospital using comparative genomic hybridization. DNA aberrations were detected in 42 TCCs including 19 arsenic-exposed and 23 non-arsenic-exposed TCCs. Arsenic-exposed TCCs had more changes than unexposed TCCs (mean+/-SD, 6.6+/-2.9 vs. 2.9+/-2.2). Arsenic exposure was significantly associated with the number of DNA aberrations after adjustment for tumor stage, tumor grade and cigarette smoking in multiple regression analysis. The most frequent DNA gains, which were strikingly different between arsenic-exposed and non-arsenic-exposed TCCs, included those at 1p, 4p, 4q and 8q. A much higher frequency of DNA losses in arsenic-exposed TCCs compared with non-arsenic-exposed TCCs was observed in 10q, 11p and 17p. Chromosomal loss in 17p13 was associated not only with arsenic exposure, but also with tumor stage and grade. The p53 immunohistochemistry staining showed that chromosome 17p13 loss was associated with either p53 no expression (25%) or p53 overexpression (75%). The findings suggest that long-term arsenic exposure may increase the chromosome abnormality in TCC, and 17p loss plays an important role in arsenic-induced urinary carcinogenesis.	2008
57.	Jones FT. A broad view of arsenic. Poult Sci. 2007 Jan;86(1):2-14. Review. Erratum in: Poult Sci. 2008 Mar;87(3):602. In the mind of the general public, the words "arsenic" and "poison" have become almost synonymous. Yet, As is a natural metallic element found in low concentrations in virtually every part of the environment, including foods. Mining and smelting activities are closely associated with As, and the largest occurrence of As contamination in the United States is near the gold mines of northern Nevada. Inhabitants of Bangladesh and surrounding areas have been exposed to water that is naturally and heavily contaminated with As, causing what the World Health Organization has described as the worst mass poisoning in history. Although readily absorbed by humans, most inorganic As (>90%) is rapidly cleared from the blood with a half-life of 1 to 2 h, and 40 to 70% of the As intake is absorbed, metabolized, and excreted within	2008

	48 h. Arsenic does not appreciably bioaccumulate, nor does it biomagnify in the food chain. The United States has for some time purchased more As than any other country in the world, but As usage is waning, and further reductions appear likely. Arsenic is used in a wide variety of industrial applications, from computers to fireworks. All feed additives used in US poultry feeds must meet the strict requirements of the US Food and Drug Administration Center for Veterinary Medicine (Rockville, MD) before use. Although some public health investigators have identified poultry products as a potentially significant source of total As exposure for Americans, studies consistently demonstrate that <1% of samples tested are above the 0.5 ppm limit established by the US Food and Drug Administration Center for Veterinary Medicine. Although laboratory studies have demonstrated the possibility that As in poultry litter could pollute ground waters, million of tons of litter have been applied to the land, and no link has been established between litter application and As contamination of ground water. Yet, the fact that <2% of the United States population is involved in production agriculture and the overtones associated with the word "arsenic" could mean the matter becomes a perception issue.	
58.	Kim SC, Park SJ, Lee JR, Seo JC, Yang CH, Byun SH. Cytoprotective Activity of Glycyrrhizae radix Extract Against Arsenite-induced Cytotoxicity. Evid Based Complement Alternat Med. 2008 Jun;5(2):165-71. Licorice, Glycyrrhizae radix, is one of the herbal medicines in East Asia that has been commonly used for treating various diseases, including stomach disorders. This study investigated the effect of licorice on arsenite (As)-induced cytotoxicity in H4IIE cells, a rat hepatocyte-derived cell line. Cell viability was significantly diminished in As-treated H4IIE cells in a time and concentration-dependent manner. Furthermore, results from flow cytometric assay and DNA laddering in H4IIE cells showed that As treatment induced apoptotic cell death by activating caspase-3. Licorice (0.1 and 1.0 mg ml(-1)) treatment significantly inhibited cell death and the activity of caspase-3 in response to As exposure. These results demonstrate that licorice induced a cytoprotective effect against As-induced cell death by inhibition of caspase-3.	2008
59.	Lin MC, Liao CM. Assessing the risks on human health associated with inorganic arsenic intake from groundwater-cultured milkfish in southwestern Taiwan. Food Chem Toxicol. 2008 Feb;46(2):701-9. Epub 2007 Sep 26. The risk of consuming groundwater-cultured milkfish (Chanos chanos) was assessed. Samples of water and milkfish from groundwater-cultured ponds in southwestern Taiwan were analyzed. One third of the 12 sampled ponds had arsenic concentrations in the water higher than 50 microg/L, which is the maximum allowed concentration for arsenic in aquacultural water in Taiwan. Of the total amount of arsenic in water, the percentage of inorganic arsenic was 67.5+/-8.8%. The inorganic arsenic level in milkfish was 44.1+/-10.2%. The bioconcentration factors (BCFs) of milkfish for total arsenic and inorganic arsenic were 11.55+/-4.42 and 6.8+/-2.64, respectively. The target cancer risk (TR) for intake of the milkfish from those ponds was higher than the safe standard 1 x 10(-6), while in 8 of the ponds the TR values were higher than 1 x 10(-4). Among the 12 ponds, 7 of those had the target hazard quotient (THQ) for intake of the milkfish higher than the safe standard 1. The actual consumption (IRF) of milkfish from most of those ponds were higher than the calculated acceptable consumption (RBIRF), based on TR = 1 x 10(-6)-1 x 10(-4). Only three sampled ponds (Putai 2, Peimen 2 and Peimen 3) did not show differences between the IRF and the RBIRF. Based on the standard TR = 1 x 10(-6), both the risk-based concentration for inorganic arsenic in milkfish (RBC(f)) and the risk-based concentration for inorganic arsenic in pond water (RBC(w)) were lower than the levels of inorganic arsenic in reared milkfish (C(b)) and the concentration of inorganic arsenic in pond water (C(w)), respectively. When the calculation	2008

	was based on TR = 1 x 10(-4), only one sampled pond (Putai 3) had a RBC(f) value higher than C(b). The inhabitants might be exposed to arsenic pollution with carcinogenic and non-carcinogenic risks.	
60.	Mateuca RA, Roelants M, Iarmarcovai G, Aka PV, Godderis L, Tremp A, Bonassi S, Fenech M, Bergé-Lefranc JL, Kirsch-Volders M. hOGG1(326), XRCC1(399) and XRCC3(241) polymorphisms influence micronucleus frequencies in human lymphocytes in vivo. Mutagenesis. 2008 Jan;23(1):35-41. Epub 2007 Oct 29. A pooled analysis of five biomonitoring studies was performed to assess the influence of hOGG1(326), XRCC1(399) and XRCC3(241) gene polymorphisms on micronuclei (MN) frequency in human peripheral blood lymphocytes, as measured by the ex vivo/in vitro cytokinesis-block micronucleus (CBMN) assay. Each study addressed a type of occupational exposure potentially able to induce DNA strand breakage (styrene, ionising radiation, cobalt/hard metal, welding fumes and inorganic arsenite compounds), and therefore MN, as a result of base excision repair and double-strand break repair deficiencies. The effect of genotype, age, exposure to genotoxic agents and smoking habit on MN induction was determined using Poisson regression analysis in 171 occupationally exposed male workers and in 132 non-exposed male referents. The analysis of genotype-genotype, genotype-smoking and genotype-exposure interactions by linear combinations of parameters showed significantly higher MN frequencies in the following subsets: (i) occupationally exposed workers carrying either the Thr/Thr or the Thr/Met XRCC3(241) genotypes compared to their referent counterparts ($P < 0.001$) and (ii) carriers of the Met/Met XRCC3(241) genotype compared to Thr/Thr XRCC3(241) carriers, as far as they are non-exposed and bear the variant (Ser/Cys or Cys/Cys) hOGG1(326) genotype ($P < 0.01$). Significantly lower MN frequencies were observed in carriers of the variant hOGG1(326) genotype compared to Ser/Ser hOGG1(326) carriers in the subgroup of non-smokers with Thr/Thr XRCC3(241) genotype ($P < 0.01$). Stratified analysis by occupational exposure showed a significant MN increase with smoking in occupationally exposed carriers of the Arg/Gln XRCC1(399)genotype ($P < 0.001$). In contrast, a significant MN decrease with smoking was observed in referents carrying the Ser/Ser hOGG1(326) genotype ($P < 0.01$). These findings provide evidence that the combination of different DNA repair genes and their interaction with environmental genotoxic agents may modulate MN induction. Understanding the complexity of the relationships between exposure, DNA repair and MN frequencies require larger scale studies and complementary biomarkers.	2008
61.	Mink PJ, Alexander DD, Barraj LM, Kelsh MA, Tsuji JS. Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis. Regul Toxicol Pharmacol. 2008 Dec;52(3):299-310. Epub 2008 Aug 26. Although exposure to high levels of arsenic in drinking water is associated with excess cancer risk (e.g., skin, bladder, and lung), lower exposures (e.g., <100-200 microg/L) generally are not. Lack of significant associations at lower exposures may be attributed to methodologic issues (e.g., inadequate statistical power, exposure misclassification), or to differences in the dose-response relationship at high versus low exposures. The objectives of this review and meta-analysis were to evaluate associations, examine heterogeneity across studies, address study design and sample size issues, and improve the precision of estimates. Eight studies of bladder cancer and low-level arsenic exposure met our inclusion criteria. Meta-analyses of never smokers produced summary relative risk estimates (SRREs) below 1.0 (highest versus lowest exposure). The SRRE for never and ever smokers combined was elevated slightly, but not significantly (1.11; 95% CI: 0.95-1.30). The SRRE was somewhat elevated among ever smokers (1.24; 95% CI: 0.99-1.56), and statistical significance was observed in some subgroup analyses; however, heterogeneity across studies was commonly present. Although uncertainties	2008

	remain, low-level arsenic exposure alone did not appear to be a significant independent risk factor for bladder cancer. More studies with detailed smoking history will help resolve whether smoking is an effect modifier.	
62.	Mosaferi M, Yunesian M, Dastgiri S, Mesdaghinia A, Esmailnasab N. Prevalence of skin lesions and exposure to arsenic in drinking water in Iran. Sci Total Environ. 2008 Feb 1;390(1):69-76. Epub 2007 Nov 13. Prevalence of skin lesions was investigated among 752 participants in eight villages in Kurdistan province in Iran with emphasis on total lifetime intake of arsenic from drinking water (TLIA). The participants were selected from eight villages with different exposure levels using a cluster-sampling technique. TLIA was calculated for each individual taking into account the type of water supply and their mean annual arsenic concentration. The study showed that 49 persons (6.5%) were suffering from hyperkeratosis and 20 persons (2.7%) from hyperpigmentation. The correlation between hyperkeratosis and hyperpigmentation was significant (R=0.325, p<0.01). Using the logistic regression model it was found that the relationship between TLIA and hyperkeratosis (OR=1.14, 95% CI=1.039-1.249), and hyperpigmentation (OR=1.254, 95% CI=1.112-1.416) was also significant. In conclusion, TLIA can be applied as a reliable indicator for the assessment of exposure.	2008
63.	Mostafa MG, McDonald JC, Cherry NM. Lung cancer and exposure to arsenic in rural Bangladesh. Occup Environ Med. 2008 Nov;65(11):765-8. Epub 2008 Apr 16. BACKGROUND: Arsenic is a known carcinogen but the risk of lung cancer from the widespread contamination of drinking water in rural Bangladesh has not been estimated. OBJECTIVES: To determine whether estimated exposure of villagers in Bangladesh to arsenic in drinking water differed between those with lung cancer and those with non-malignant lesions. METHODS: Data were obtained from 7286 subjects who underwent lung biopsy in 2003-2006 at a diagnostic centre taking referrals from throughout Bangladesh. Analysis was limited to 5372 people living in villages for the last 10 years who reported using tube well water. Of these, 3223 with a primary lung tumour were enrolled as cases and 1588 with non-malignant lesions as referents in an unmatched analysis. Arsenic exposure was estimated by average concentrations for each of 64 districts. Logistic regression was used to test the effects of age, arsenic and smoking on risk and to investigate relationship to cell type. RESULTS: Male cases were older than referents and more likely to smoke, to smoke >20 units/day and to smoke bidi-small, hand-rolled cigarettes. Odds ratios for lung cancer increased steadily with mean arsenic concentration, but the confidence interval excluded 1.0 only at concentrations >100 mug/l (OR 1.45, 95% CI 1.16 to 1.80). This trend was seen only in smokers where the increased risk at >100 mug/l was 1.65 (95% CI 1.25 to 2.18). A similar trend was seen in women smokers. Squamous cell lung cancer was more frequent in smokers and, having adjusted for smoking, in districts with arsenic concentrations >100 mug/l. CONCLUSIONS: Among Bangladeshis who smoke, those whose drinking water is contaminated with arsenic at concentrations >100 mug/l are at increased risk of lung cancer. With high levels of exposure misclassification and short latency of exposure, the study cannot estimate or exclude the likely long term risk in non-smokers and at lower arsenic concentrations.	2008
64.	Nakamura K, Hisaeda Y, Pan L, Yamauchi H. Detoxification system for inorganic arsenic: transformation of As2O3 into TMAO by vitamin B12 derivatives and conversion of TMAO into arsenobetaine. Chem Commun (Camb). 2008 Nov 7;(41):5122-4. Epub 2008 Sep 25. A new two-step synthetic pathway developed for the transformation of arsenic trioxide [iAs(III); As(2)O(3)] into arsenobetaine (AB; Me(3)As(+)CH(2)CO(2)(-)) involves treatment of iAs(III) with native B(12) or biomimetic B(12) in the presence of glutathione (GSH) to give TMAO with a high selectivity and a high conversion rate; subsequent treatment of TMAO with	2008

	iodoacetic acid in the presence of GSH gives arsenobetaine.	
65.	Nascimento, M.G., Suzuki, S., Wei, M., Tiwari, A., Arnold, L.L., Lu, X., Le, S.C., Cohen, S.M. (2008) Cytotoxicity of combinations of arsenicals on rat urinary bladder urothelial cells *in vitro*. Toxicology. 2008 Jul 10;249(1):69-74. Epub 2008 Apr 22. Based on epidemiological data, chronic exposure to high levels of inorganic arsenic in the drinking water is carcinogenic to the urinary bladder of humans. The highly reactive trivalent organic arsenicals dimethylarsinous acid (DMA(III)) and monomethylarsonous acid (MMA(III)) are formed during the metabolism of inorganic arsenic in vivo in addition to the corresponding mono-, di- and trimethylated pentavalent arsenicals. The objective of this study was to determine if combining arsenicals was additive or synergistic toward inducing cytotoxicity in a rat urothelial cell line. The MYP3 cell line, an immortalized but not transformed rat urinary bladder epithelial cell line, was seeded into appropriate culture wells. Treatment with the arsenicals was begun 24 h after seeding and continued for 3 days. Combinations of arsenicals used were DMA(III) with arsenite, dimethylarsinic acid (DMA(V)) or trimethylarsine oxide (TMAO). Combinations of concentrations used were the LC50, one-quarter or one-half the LC50 of one arsenical with one-half or one-quarter the LC50 of the other arsenical. To determine if MYP3 cells metabolize arsenicals, cells were treated with arsenate, arsenite and MMA(V) as described above and the medium was analyzed by HPLC-ICPMS to determine species and quantity of arsenicals present. When cells were treated with one-quarter or one-half the LC50 concentration of both arsenicals, the cytotoxicity was approximately the same as when cells were treated with half the LC50 concentration or the LC50 concentration, respectively, of either arsenical. Treatment with one-quarter the LC50 concentration of one arsenical plus the LC50 concentration of a second arsenical had similar cytotoxicity as treatment with the LC50 concentration of either of the arsenicals. Quantitation and speciation of arsenicals in the cell culture medium showed that MYP3 cells have some reductase activity but the cells do not methylate arsenicals. The effect on the cytotoxicity of arsenicals in combination was additive rather than synergistic toward a rat urothelial cell line.	2008
66.	Park S, Bae J, Nam BH, Yoo KY. Aetiology of cancer in Asia. Asian Pac J Cancer Prev. 2008 Jul-Sep;9(3):371-80. Cancer has become the leading cause of death in many Asian countries. There is an increasing trend in breast, prostate and colon cancers, which are considered as typical of economically developed countries. Although breast and prostate cancer rates are still lower than in western countries, they are particularly rapidly increasing. In this paper, we review recently published literature to identify important etiologic factors affecting the cancer risk in Asian populations. Infectious agents such as Helicobacter pylori, hepatitis B and C viruses, and human papillomavirus were shown to be associated with elevated risks of stomach, liver and cervical cancer, respectively. Tobacco smoking was shown to be significantly associated with higher lung cancer risk and moderately increased all cancer risk. Excessive alcohol drinking appeared to increase the risk of colorectal cancer in Japanese and breast cancer in the Korean population. Betel nut chewing was associated with higher risk of oral and esophageal cancer. In terms of diet, various studies have demonstrated that high caloric and fat intake was associated with breast cancer risk, salted food intake with stomach cancer, aflatoxin B1 with liver cancer, and low fruits and vegetables intake with breast and lung cancer. Environmental exposure to indoor and outdoor air pollution, arsenic, radon, asbestos and second hand smoke was shown to increase the lung cancer risk. Reproductive factors such as late age at first childbirth, early menarche, late menopause, oral contraceptive intake, and short duration of lifetime lactation were shown to be associated with breast and/or colorectal cancer. Cancer has clearly become an emerging health threat in Asia and cancer control programs should be actively implemented and evaluated in this region. Various strategies for cancer control have been developed in some	2008

	Asian countries, including the set-up of national cancer registries, cancer screening programs, education programs for health behavior change, eradication of Helicobacter pylori and vaccination for hepatitis B and C viruses, and human papilloma virus high risk forms. However, more attention should also be paid to low- and medium-resource Asian countries where cancer incidence rates are high, but neither intensive research on cancer for planning effective cancer control programs, nor easy implementation of such programs are available, due to limited financial resources.	
67.	Sengupta SR, Das NK, Datta PK. Pathogenesis, clinical features and pathology of chronic arsenicosis. Indian J Dermatol Venereol Leprol. 2008 Nov-Dec;74(6):559-70. Arsenicosis is a multisystem disorder, with virtually no system spared from its vicious claw; though its predominant manifestations are linked to cutaneous involvement. Cutaneous effects take the form of pigmentary changes, hyperkeratosis, and skin cancers (Bowen's disease, squamous cell carcinoma, and basal cell epithelioma). Peripheral vascular disease (blackfoot disease), hypertension, ischemic heart disease, noncirrhotic portal hypertension, hepatomegaly, peripheral neuropathy, respiratory and renal involvement, bad obstetrical outcome, hematological disturbances, and diabetes mellitus are among the other clinical features linked to arsenic toxicity. The effects are mediated principally by the trivalent form of arsenic (arsenite), which by its ability to bind with sulfhydryl groups present in various essential compounds leads to inactivation and derangement of body function. Though the toxicities are mostly linked to the trivalent state, arsenic is consumed mainly in its pentavalent form (arsenate), and reduction of arsenate to arsenite is mediated through glutathione. Body attempts to detoxify the agent via repeated oxidative methylation and reduction reaction, leading to the generation of methylated metabolites, which are excreted in the urine. Understandably the detoxification/bio-inactivation process is not a complete defense against the vicious metalloid, and it can cause chromosomal aberration, impairment of DNA repair process, alteration in the activity of tumor suppressor gene, etc., leading to genotoxicity and carcinogenicity. Arsenic causes apoptosis via free radical generation, and the cutaneous toxicity is linked to its effect on various cytokines (e.g., IL-8, TGF-beta, TNF-alpha, GM-CSF), growth factors, and transcription factors. Increased expression of cytokeratins, keratin-16 (marker for hyperproliferation) and keratin-8 and -18 (marker for less differentiated epithelial cells), can be related to the histopathological findings of hyperkeratosis and dysplastic cells in the arsenicosis skin lesion.	2008
68.	Slotnick MJ, Meliker JR, Kannan S, Nriagu JO. Effects of nutritional measures on toenail arsenic concentration as a biomarker of arsenic exposure. Biomarkers. 2008 Aug;13(5):451-66. Correlations between drinking water and toenail arsenic concentrations have been demonstrated in previous studies, yet factors that may modify the exposure-biomarker association have not been adequately assessed. Using data from 500 controls enrolled in a bladder cancer study underway in Michigan, USA, the effects of demographic characteristics and nutritional measures on the biomarker response were evaluated. Drinking water and toenail samples were collected during a home visit and analyzed for arsenic and other elements. Participants reported dietary supplement intake habits and provided demographic data. Arsenic concentrations of drinking water and toenail samples were positively correlated. Of the nutritional measures evaluated, toenail iron concentration was a significant modifier of the exposure-biomarker association. No demographic characteristics or general measures of dietary intake affected the biomarker response. The results presented herein are critical for biomarker validation and prove promising for sound application of the arsenic toenail biomarker to future epidemiological investigations.	2008
69.	Suzuki, S., Arnold, L.L., Muirhead, D., Lu, X., Le, C.X, Bjork, J.A. , Wallace, K.B., Ohnishi, T., Kakiuchi-Kiyota,S., Pennington, K.L., and Cohen S.M. (2008) Inorganic arsenic	2008

	intramitochondrial granules in mouse urothelium. Toxicol Pathol. 2008;36(7):999-1005. Based on epidemiological data, chronic exposure to high levels of inorganic arsenic in the drinking water is carcinogenic to the urinary bladder of humans. Recently, models have been developed involving transplacental administration of inorganic arsenic and subsequent administration of another substance that produces a low incidence of urogenital neoplasms. Administration of arsenite or arsenate in the diet or drinking water to five-to eight-week-old mice or rats rapidly induces urothelial cytotoxicity and regenerative hyperplasia. In mice administered arsenite, we observed eosinophilic intracytoplasmic granules present in the urothelial cells. These granules were not present in urothelial cells of untreated mice or in treated or untreated rats. By transmission electron microscopy, the granules were located within the mitochondrial matrix, that is, mitochondrial inclusions. Arsenic, primarily as arsenite, was present in partially purified mitochondria containing these granules. Cells containing the granules were not usually associated with degenerative changes. Lack of these granules in rats suggests that they are not necessary for inorganic arsenic-induced urothelial cytotoxicity or hyperplasia. These granules have also been observed with exposures to other metals in other tissues and other species, suggesting that they represent a protective mechanism against metal-induced toxicity.	
70.	Suzuki, S., Arnold, L.L., Ohnishi, T., and Cohen, S.M. (2008) Effects of inorganic arsenic on the rat and mouse urinary bladder. Toxicol Sci. 2008 Dec;106(2):350-63. Epub 2008 Aug 26.. Inorganic arsenic (arsenate and arsenite) is a known human carcinogen, inducing tumors of the skin, urinary bladder, and lung. Understanding the mechanism of inorganic arsenic carcinogenesis has been hampered by a lack of animal models. To define the urothelial effects of inorganic arsenic, we administered arsenate and arsenite in the diet or drinking water to rats and mice in several short-term experiments (2-10 weeks). Treatment with arsenate or arsenite in the drinking water or diet induced cytotoxicity and necrosis of the urothelial superficial layer and hyperplasia in rats and mice. Arsenate-induced changes occurred later in mice compared with arsenite-induced changes, but not in the rat. Hyperplasia in rats was evident by light microscopy at an earlier time point (2 weeks) than previously observed after treatment with dimethylarsinic acid (DMA(V)). The bromodeoxyuridine labeling index was increased in treated rats. We were unable to determine the bromodeoxyuridine labeling index in mice. The effects of inorganic arsenicals on the bladder were greater when administered in the drinking water than in the diet in rats and mice, but so was the overall toxicity to the animal. The female rat appeared more sensitive to the effects of inorganic arsenic than the male rat, but effects were similar in female and male mice. The mode of action of inorganic arsenic in rats and mice appears to involve urothelial cytotoxicity, increased cell proliferation and ultimately tumors. Cytotoxicity is likely due to the generation of reactive trivalent arsenicals excreted in the urine.	2008
71.	Tan LB, Chen KT, Guo HR. Clinical and epidemiological features of patients with genitourinary tract tumour in a blackfoot disease endemic area of Taiwan. BJU Int. 2008 Jul;102(1):48-54. Epub 2008 Apr 25. OBJECTIVES: To evaluate the clinical and epidemiological characteristics of patients with genitourinary (GU) tract transitional cell carcinoma (TCC) in an endemic area of blackfoot disease (BFD), the arsenic-exposed group, to compare them with characteristics among other non-BFD endemic areas (unexposed group). PATIENTS AND METHODS: In all, 474 patients with pathologically diagnosed GU-TCC were enrolled in the study. All follow-up data were prospectively collected and entered into a database throughout the study period. Statistical analysis was used to determine the association between clinical variables and prognosis, and multivariate regression models were used to assess the association between arseniasis and mortality from GU-TCC. RESULTS: There were no significant differences between the groups	2008

	in age, sex, tumour stage and grade. However, the exposed group had a significantly higher proportion of females. The overall 5-year survival rate of patients with upper urinary tract (UUT) TCC was 49%, and the two groups had similar 5-year survival rates. The overall 5-year survival rate of patients with urinary bladder (UB) TCC was 68.3%, and there was a statistically significant difference in survival between the groups, with a 5-year survival rate of 58.7% for the exposed and 72.4% for the unexposed group. For patients with early-stage (pTa and pT1) UB cancers, the death rate was five times higher in exposed patients with tumour progression and recurrence after transurethral resection of bladder tumour than in the unexposed group. CONCLUSIONS: There was a significantly higher mortality rate for UB-TCC among exposed patients in the area endemic for arseniasis than in those from other non-endemic areas. The arsenic content of artesian-well water might contribute to the increased ratio of female patients with GU-TCC and the unusually high incidence of UUT-TCC in the BFD endemic area in Taiwan.	
72.	Waalkes MP, Liu J, Germolec DR, Trempus CS, Cannon RE, Tokar EJ, Tennant RW, Ward JM, Diwan BA. Arsenic exposure in utero exacerbates skin cancer response in adulthood with contemporaneous distortion of tumor stem cell dynamics. Cancer Res. 2008 Oct 15;68(20):8278-85. Arsenic is a carcinogen with transplacental activity that can affect human skin stem cell population dynamics in vitro by blocking exit into differentiation pathways. Keratinocyte stem cells (KSC) are probably a key target in skin carcinogenesis. Thus, we tested the effects of fetal arsenic exposure in Tg.AC mice, a strain sensitive to skin carcinogenesis via activation of the v-Ha-ras transgene likely in KSCs. After fetal arsenic treatment, offspring received topical 12-O-tetradecanoyl phorbol-13-acetate (TPA) through adulthood. Arsenic alone had no effect, whereas TPA alone induced papillomas and squamous cell carcinomas (SCC). However, fetal arsenic treatment before TPA increased SCC multiplicity 3-fold more than TPA alone, and these SCCs were much more aggressive (invasive, etc.). Tumor v-Ha-ras levels were 3-fold higher with arsenic plus TPA than TPA alone, and v-Ha-ras was overexpressed early on in arsenic-treated fetal skin. CD34, considered a marker for both KSCs and skin cancer stem cells, and Rac1, a key gene stimulating KSC self-renewal, were greatly increased in tumors produced by arsenic plus TPA exposure versus TPA alone, and both were elevated in arsenic-treated fetal skin. Greatly increased numbers of CD34-positive probable cancer stem cells and marked overexpression of RAC1 protein occurred in tumors induced by arsenic plus TPA compared with TPA alone. Thus, fetal arsenic exposure, although by itself oncogenically inactive in skin, facilitated cancer response in association with distorted skin tumor stem cell signaling and population dynamics, implicating stem cells as a target of arsenic in the fetal basis of skin cancer in adulthood.	2008
73.	Applebaum KM, Karagas MR, Hunter DJ, Catalano PJ, Byler SH, Morris S, Nelson HH. Polymorphisms in nucleotide excision repair genes, arsenic exposure, and non-melanoma skin cancer in New Hampshire. Environ Health Perspect. 2007 Aug;115(8):1231-6. BACKGROUND: Arsenic exposure may alter the efficiency of DNA repair. UV damage is specifically repaired by nucleotide excision repair (NER), and common genetic variants in NER may increase risk for non-melanoma skin cancer (NMSC). OBJECTIVE: We tested whether polymorphisms in the NER genes XPA (A23G) and XPD (Asp312Asn and Lys751Gln) modify the association between arsenic and NMSC. METHODS: Incident cases of basal and squamous cell carcinoma (BCC and SCC, respectively) were identified through a network of dermatologists and pathology laboratories across New Hampshire. Population-based controls were frequency matched to cases on age and sex. Arsenic exposure was assessed in toenail clippings. The analysis included 880 cases of BCC, 666 cases of SCC, and 780 controls. RESULTS: There was an increased BCC risk associated with high arsenic	2007

	exposure among those homozygous variant for XPA [odds ratio (OR) = 1.8; 95% confidence interval (CI), 0.9-3.7]. For XPD, having variation at both loci (312Asn and 751Gln) occurred less frequently among BCC and SCC cases compared with controls (OR = 0.8; 95% CI, 0.6-1.0) for both case groups. In the stratum of subjects who have variant for both XPD polymorphisms, there was a 2-fold increased risk of SCC associated with elevated arsenic (OR = 2.2; 95% CI, 1.0-5.0). The test for interaction between XPD and arsenic in SCC was of borderline significance (p < 0.07, 3 degrees of freedom). CONCLUSIONS: Our findings indicate a reduced NMSC risk in relation to XPD Asp312Asn and Lys751Gln variants. Further, these data support the hypothesis that NER polymorphisms may modify the association between NMSC and arsenic.	
74.	Argos M, Parvez F, Chen Y, Hussain AZ, Momotaj H, Howe GR, Graziano JH, Ahsan H. Socioeconomic status and risk for arsenic-related skin lesions in Bangladesh. Am J Public Health. 2007 May;97(5):825-31. Epub 2007 Mar 29. OBJECTIVES: Arsenic contamination of groundwater is a severe public health crisis in Bangladesh, where the population is exposed to arsenic in drinking water through tube wells used for groundwater collection. In this study, we explored the association between socioeconomic status and arsenic toxicity. METHODS: We used baseline data from 11438 men and women who were recruited into the Health Effects of Arsenic Longitudinal Study (HEALS), a prospective cohort study on the health effects of arsenic exposure in Bangladesh. We conducted analyses with logistic regression and generalized estimating equations. RESULTS: We found a strong dose-response association with all measures of arsenic exposure and skin lesions. We also found that the effect of arsenic was modified by land ownership on a multiplicative scale, with an increased risk among non-land owners associated with well water arsenic (P=.04) and urinary total arsenic concentrations (P=.03). CONCLUSIONS: Our study provides insight into potentially modifiable host characteristics and identifies factors that may effectively target susceptible population subgroups for appropriate interventions.	2007
75.	Chen JG, Chen YG, Zhou YS, Lin GF, Li XJ, Jia CG, Guo WC, Du H, Lu HC, Meng H, Zhang XJ, Golka K, Shen JH. A follow-up study of mortality among the arseniasis patients exposed to indoor combustion of high arsenic coal in Southwest Guizhou Autonomous Prefecture, China. Int Arch Occup Environ Health. 2007 Oct;81(1):9-17. Epub 2007 Mar 27. OBJECTIVE: This study was directed to ascertain the mortality of a group of arseniasis patients in an endemic rural township in Southwest China, where the residents were exposed for decades to indoor combustion of high arsenic coal. METHODS: All the diagnosed arseniasis cases registered in 1991 were defined as the target population, which were assigned to three symptom subgroups by the severity of dermal lesions. The death cases were surveyed and checked. The follow-up period was 12.5 years. The standardized mortality ratio (SMR) of all death causes combined, all cancers combined, and the cancers at every site were analyzed. The age standardized mortality rates (ASMRs) were calculated in three subgroups using the procedure of standardization. RESULTS: One hundred and six death cases were recorded. Liver cirrhosis, non-melanotic skin cancer, lung and liver cancer were the four most prevalent death causes and referred to 70.8% (75/106) of the total death cases. The mortality of all death causes combined was not higher than that of the whole of China in 2001 (SMR = 0.76, 95% CI 0.63-0.93). The crude mortality rate of non-melanotic skin cancer in males reached up to 128.66/10(5). SMRs of lung cancer and larynx cancer in males (SMRs 2.84 and 27.27, 95% CIs 1.51-4.86 and 5.61-79.62, respectively) significantly exceeded the levels for all male Chinese. ASMRs of all death causes combined, all cancers combined and non-melanotic skin cancer in males of the severe dermal symptoms subgroup were significantly higher than those in medium and/or mild dermal symptom subgroups. CONCLUSIONS: A significantly increased mortality due to lung cancer and non-melanotic skin cancer was confirmed, alike the	2007

	situation in other arseniasis endemic areas in the world. No significant elevation of mortality due to liver cancer and bladder cancer was observed. Male arseniasis patients diagnosed with severe skin lesions face higher risks of malignancies and of non-melanotic skin cancer in particular in the following years.	
76.	Chu HA, Crawford-Brown D. Inorganic arsenic in drinking water and bladder cancer: a meta-analysis for dose-response assessment. Int J Environ Res Public Health. 2007 Dec;4(4):340-1. Most arsenic cancer risk assessments have been based solely on epidemiological studies to characterize the dose-response relationship for arsenic-associated cancer and to perform risk calculations. However, current epidemiological evidence is too inconsistent and fraught with uncertainty regarding arsenic exposure to provide reliable estimates. This makes it hard to draw a firm conclusion about the shape and slope of the dose-response relationship from individual studies. Meta-analysis is a statistical approach to combining results across studies and offers expanded opportunities for obtaining an improved dose-response relationship. In this study, a meta-analysis of arsenic studies was conducted by combining seven epidemiological studies from different regions to get an overall dose-response relationship between the amount of arsenic intake and the excess probability of bladder cancer. Both the fixed-effect and random-effect models were used to calculate the averaged coefficient of the linear-logistic regression model. A homogeneity test was also conducted. The final product of this research is an aggregated dose-response model in the range of empirical observation of arsenic. Considering the most recent arsenic MCL (maximum contaminant level, i.e. 10µg/L), the associated bladder cancer risk (lifetime excess probability) at this MCL is 2.29 10^{-5}. REVISED: http://www.mdpi.org/ijerph/papers/ijerph200704040010.pdf In our previous paper, "Inorganic Arsenic in Drinking Water and Bladder Cancer: A Meta-Analysis for Dose- Response Assessment", 2006, *3(4)*, 316-322, there were several errors in the table of data used in the analysis. In particular: 1. The paper of Bates et al. [1] incorrectly listed units of concentrations. They reported in units of milligrams rather than micrograms (see the last entries in Table 3 of their paper). 2. In the paper by Chiou et al. [2] we introduced an error ourselves. We listed the arsenic exposure level as ≤ 50; 50-70; 71+. These should be ≤ 50; 50-700; 710+. With these corrections, the pooled estimate of slopes from the seven studies using the fixed effects model becomes was 0.001 (95% CI: 0.001, 0.002), with the unit of lnRR per unit increase of exposure (exposure is in µg/L as in our original paper). The chi-square statistic was quite large (i.e. Q = 497.752 on 6 degrees of freedom, p= 0.00), which rejects the null hypothesis of homogeneity and means there was evidence of heterogeneity. Using the random-effect model, and including only the five studies identified in the original paper as most relevant (excluding Bates et al [1] and Kurttio et al [3]), the pooled estimate of the slopes from the five studies was found to be 0.002 (exposure also in units of per µg/L) (95% CI: -0.001, 0.006). The new result of the meta-analysis still supports the claim that there is a positive dose-response relationship between exposure to arsenic in drinking water and bladder cancer. Table 1 summarizes the revised results of the absolute risk (AR) calculation for bladder cancer associated with a variety of proposed MCLs (maximum contaminant levels) using different estimates from the meta-analysis: the best estimate, the upper-bound and lower-bound estimates of the slope factor. The best (revised) estimate of the slope factor from the metaanalysis is 1.64× 10-5 (with unit of probability per µg/kg/day), with the upper bound of 5.38× 10-5. These slope factors from the meta-analysis are lower than the ones from the EPA (1.5 × 10-3) and NRC (8.85× 10-4).	2007

77.	Ghosh P, Banerjee M, De Chaudhuri S, Das JK, Sarma N, Basu A, Giri AK. Increased chromosome aberration frequencies in the Bowen's patients compared to non-cancerous skin lesions individuals exposed to arsenic. Mutat Res. 2007 Aug 15;632(1-2):104-10. Epub 2007 May 18. Cytogenetic biomarkers are essential for assessing environmental exposure that can predict adverse human health effects such as cellular damage. Chromosomal aberrations are the most important cytogenetic end-points successfully used for the cancer risk assessment of populations occupationally or environmentally exposed to different toxic chemicals. Previous reports suggest that, increased frequency of chromosomal aberration (CA), in peripheral blood lymphocytes, is a predictor of cancer. Arsenic is a paradoxical human carcinogen, clastogen and aneugen. Despite of exposure at similar extent, only 15-20% of individuals show arsenic induced skin lesions including Bowen's disease (BD). Previously we have reported the significant increase in CA in the individuals with arsenic induced skin lesions when compared to individuals without any skin lesions, drinking arsenic contaminated water at similar extent. Presently, a matched case-control study was performed to examine whether biomarkers such as chromosomal aberrations can predict the development of arsenic induced Bowen's (in situ carcinoma) diseases. Chromosomal aberrations (both chromosome and chromatid types) and mitotic index were analyzed from the lymphocytes of 25 cases of Bowen's patient which was compared to matched control from the individuals with arsenic induced non-cancerous skin lesions such as raindrop pigmentation, keratosis of palm and sole, hypo and hyper pigmentation. Chromosomal aberrations/cell, chromosome type aberrations and total percentage of aberrant cells were significantly higher in cases compared to control ($p<0.01$). These results suggest that chromosomal aberrations can be used for cancer risk assessment of the population exposed to arsenic through drinking water.	2007
78.	Hore SK, Rahman M, Yunus M, Das CS, Yeasmin S, Ahmad SK, Sayed MH, Islam AM, Vahter M, Persson LA. Detecting arsenic-related skin lesions: experiences from a large community-based survey in Bangladesh. Int J Environ Health Res. 2007 Apr;17(2):141-9. A cross-sectional survey was conducted in Matlab, Bangladesh, to determine the prevalence of skin lesions (a three-step procedure) associated with arsenic exposure and discuss validity and feasibility in relation to recommended screening algorithms. Cases with skin lesions were identified by screening above 4 years of age (n = 166,934). Trained field teams conducted a careful house-to-house screening and identified 1682 individuals with skin lesions, who were referred to physicians for confirmation. Physicians diagnosed 579 cases as probable and documented all these with digital photographs. Two experts inspected all photographs for consensus agreement that was reached for 504 cases. Using the experts' opinions as reference, the positive predictive value of the physicians' diagnosis was 87% (male = 82% vs. female = 94%; $p < 0.01$). The physicians had difficulties in separating arsenic-induced keratosis from differential diagnoses, while probability for correct diagnosis was high for arsenic-related pigmentation changes. Including information on current arsenic concentration in drinking water (which was masked at time of skin examination) or urine in the diagnostic algorithm should have increased the number of false negative cases. In the present transition of drinking water sources these markers of current exposure levels provide no information on past exposure. A 2-3 step procedure with house-to-house screening and clinic-based confirmation of arsenic-induced skin lesions is a feasible approach. Information on arsenic concentration in current water sources or in urine should not have improved the precision in the diagnosis. These results may have policy implications for community screening of arsenic-related skin lesions in Bangladesh and elsewhere.	2007
79.	Hughes MF, Kenyon EM, Kitchin KT. Research approaches to address uncertainties in the risk assessment of arsenic in drinking water. Toxicol Appl Pharmacol. 2007 Aug 1;222(3):399-404.	2007

	Epub 2007 Feb 9. Inorganic arsenic (iAs), an environmental drinking water contaminant, is a human toxicant and carcinogen. The public health community has developed recommendations and regulations that limit human exposure to iAs in drinking water. Although there is a vast amount of information available to regulators on the exposure, disposition and the health-related effects of iAs, there is still critical information about the toxicology of this metalloid that is needed. This necessary information includes identification of the chemical species of arsenic that is (are) the active toxicant(s), the mode(s) of action for its various toxicities and information on potentially susceptible populations. Because of these unknown factors, the risk assessment of iAs still incorporates default assumptions, leading to uncertainties in the overall assessment. The characteristics of a scientifically defensible risk assessment for iAs are that it must: (1) quantitatively link exposure and target tissue dose of active metabolites to key events in the mode of action for major health effects and (2) identify sources of variation in susceptibility to arsenic-induced health effects and quantitatively evaluate their impact wherever possible. Integration of research to address these goals will better protect the health of iAs-exposed populations.	
80.	Jang CS, Liu CW, Lu KL, Lin CC. Delimitation of arsenic-contaminated groundwater using risk-based indicator approaches around blackfoot disease hyperendemic areas of southern Taiwan. Environ Monit Assess. 2007 Nov;134(1-3):293-304. Epub 2007 Apr 25. This work determined scopes of arsenic(As)-contaminated groundwater using risk-based indicator classification approaches in blackfoot disease hyperendemic areas of southern Taiwan. Indicator kriging was first used to establish a conditional cumulative distribution function at each cell. Three approaches--the p-quantile estimate, the E-type estimate and the minimization of the expected loss--were then adopted to delimit contaminated regions for a regulated standard of As concentrations in groundwater. According to a risk assessment model established in our previous research, the standard was set to 250 microg/l for aquacultural use, corresponding to the 77.1th percentile of observed concentrations. Misclassification risks and uncertainty were examined for the classification approaches. The analyzed results reveal that contaminated areas are the largest using the 0.771-quantile estimate, whereas they are the smallest using the minimization of the expected loss. Proportions of credible polluted areas with low risks to false positives maintain a constant, 12.9-13.2%, for the classification approaches. To reduce a great impact on human health, As-polluted groundwater should be strictly prohibited to cultivate fish in credible polluted zones and monitored persistently in polluted zones with high risks to false positives.	2007
81.	Jones SR, Atkin P, Holroyd C, Lutman E, Batlle JV, Wakeford R, Walker P. Lung cancer mortality at a UK tin smelter. Occup Med (Lond). 2007 Jun;57(4):238-45. Epub 2007 Apr 16. BACKGROUND: An earlier study of mortality among male former employees at a tin smelter in Humberside, UK, had identified excess mortality from lung cancer, which appeared to be associated with occupational exposure. AIMS: The aim of the present study was to investigate the relationship between lung cancer mortality and quantitative measures of exposure. METHODS: Using available records of occupational hygiene measurements, we established exposure matrices for arsenic, cadmium, lead, antimony and polonium-210 ((210)Po), covering the main process areas of the smelter. We established work histories from personnel record cards for the previously defined cohort of 1462 male employees. Three different methods of extrapolation were used to assess exposures prior to 1972, when no measurement results were available. Lung cancer mortality was examined in relation to cumulative inhalation exposure by Poisson regression analysis. RESULTS: No significant associations could be found between lung cancer mortality and simple cumulative exposure to any of the substances studied. When	2007

	cumulative exposures were weighted according to time since exposure and attained age, significant associations were found between lung cancer mortality and exposures to arsenic, lead and antimony. CONCLUSIONS: The excess of lung cancer mortality in the cohort can most plausibly be explained if arsenic is the principal occupational carcinogen (for which the excess relative risk diminishes with time since exposure and attained age) and if there is a contribution to excess mortality from an enhanced prevalence of smoking within the cohort. The implications of the dose-response for arsenic exposure for risk estimation merit further consideration.	
82.	Lu, M., Wang, H., Arnold, L.L., Cohen, S.M., Li, X-F., Lu, X., Cullen, W.R., and Le, X.C. (2007) Binding of dimethylarsinous acid to cys-13alpha of rat hemoglobin is responsible for the retention of arsenic in rat blood. Chem Res Toxicol. 2007 Jan;20(1):27-37. The metabolism, disposition, and carcinogenicity of arsenic differ dramatically between humans and rats. To understand the molecular basis of these differences, we have characterized arsenic species in rats that were treated with inorganic arsenate (iAsV), monomethylarsonic acid (MMAV), or dimethylarsinic acid (DMAV) for up to 15 weeks. Arsenic significantly accumulated in the red blood cells (RBCs) of rats in the form of hemoglobin (Hb) complexed with dimethylarsinous acid (DMAIII), regardless of whether the rats were treated with iAsV, MMAV, or DMAV, suggesting rapid methylation of arsenic species followed by strong binding of DMAIII to rat Hb. The binding site for DMAIII was identified to be cysteine 13 in the alpha-chain of rat Hb with a stoichiometry of 1:1. Over 99% of the total arsenic (maximum 2.5-3.5 mM) in rat RBCs was bound to Hb for all rats examined (n = 138). In contrast, only 40-49% of the total arsenic (maximum approximately 10 muM) in rat plasma was bound to proteins. The ratios of the total arsenic in RBCs to that in plasma ranged from 88-423 for rats that were fed iAsV, 100-680 for rats that were fed MMAV, and 185-1393 for rats that were fed DMAV, when samples were obtained over the 15-week exposure duration. Previous studies have shown an increase in urothelial hyperplasia in rats fed DMAV. This is the first article reporting that treatment with iAsV in the drinking water also produces urothelial hyperplasia and at an even earlier time point than dietary DMAV. Dietary MMAV produced only a slight urothelial response. A correlation between the Hb-DMAIII complex and urothelial lesion severity in rats was observed. The lack of cysteine 13alpha in human Hb may be responsible for the shorter retention of arsenic in human blood. These differences in the disposition of arsenicals may contribute to the observed differences between humans and rats in susceptibility to arsenic carcinogenicity.	2007
83.	McCarty KM, Smith TJ, Zhou W, Gonzalez E, Quamruzzaman Q, Rahman M, Mahiuddin G, Ryan L, Su L, Christiani DC. Polymorphisms in XPD (Asp312Asn and Lys751Gln) genes, sunburn and arsenic-related skin lesions. Carcinogenesis. 2007 Aug;28(8):1697-702. Epub 2007 Apr 29. BACKGROUND: Single-nucleotide polymorphisms in genes related to DNA repair capacity and ultraviolet exposure have not been well investigated in relation to skin lesions associated with arsenic exposure. This population based case-control study, of 600 cases and 600 controls, frequency matched on age and gender in Pabna, Bangladesh, in 2001-2002, investigated the association and potential effect modification between polymorphisms in Xeroderma Pigmentosum complementation group D (XPD) (Lys751Gln and Asp312Asn) genes, tendency to sunburn and arsenic-related skin lesions. METHODS: Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). RESULT: No significant association was observed between skin lesions and the XPD 312 Asp/Asn (adjusted OR = 0.87, 95% CI = 0.65-1.15) Asn/Asn (adjusted OR = 0.76, 95% CI = 0.50-1.15) (referent Asp/Asp); XPD 751 Lys/Gln (adjusted OR = 0.92, 95% CI = 0.69-1.23) Gln/Gln (adjusted OR = 0.98, 95% CI = 0.66-1.45) (referent Lys/Lys). While we did not observe any evidence of	2007

	effect modification of these polymorphisms on the association between well arsenic concentration and skin lesions, we did observe effect modification between these polymorphisms and sunburn tendency and arsenic-related skin lesions. Individuals with the heterozygote or homozygote variant forms (Asp/Asn or Asn/Asn) had half the risk of skin lesions (OR = 0.45, 95% CI = 0.29-0.68) compared with those with the wild-type XPDAsp312Asn genotype (Asp/Asp) and individuals with heterozygote or homozygote variant forms (Lys/Gln or Gln/Gln) had half the risk of skin lesions (OR = 0.47, 95% CI = 0.31-0.72) compared with those with the wild-type XPDLys751Gln genotype (Lys/Lys), within the least sensitive strata of sunburn severity. We observed effect modification on the multiplicative scale for XPD 751 and XPD 312. CONCLUSION: XPD polymorphisms modified the relationship between tendency to sunburn and skin lesions in an arsenic exposed population. Further study is necessary to explore the effect of XPD polymorphisms and sun exposure on risk of arsenic-related skin lesions.	
84.	McDonald C, Hoque R, Huda N, Cherry N. Risk of arsenic-related skin lesions in Bangladeshi villages at relatively low exposure: a report from Gonoshasthaya Kendra. Bull World Health Organ. 2007 Sep;85(9):668-73. OBJECTIVE: Arsenic concentrations in 25% of tube wells in Bangladesh exceed 50 microg/L, a level known to be hazardous. Levels in individual wells vary widely. We gathered data on arsenic exposure levels and skin lesion prevalence to address the lack of knowledge about risks where the average arsenic concentrations was lower. METHODS: The nongovernmental organization Gonoshasthaya Kendra did three related studies of keratotic skin lesions since 2004: (1) an ecological prevalence survey among 13 705 women aged > 18 in a random sample of 53 villages; (2) a case-control study of 176 cases and age- and village-matched referents; and (3) a prevalence survey of the entire population of 11,670 in two additional villages. We calculated prevalence as a function of average arsenic concentrations as reported in the National Hydrochemical Survey, and measured arsenic concentrations in wells used by subjects in the case-control study. FINDINGS: The prevalence of skin lesions was 0.37% in people exposed to arsenic concentrations below 5 microg/L, 0.63% at 6-50 microg/L, and 6.84% at 81 microg/L. In the case-control analysis, relative risk of skin lesions increased threefold at concentrations above 50 microg/L ($P < 0.05$). CONCLUSION: Little serious skin disease is likely to occur if the arsenic concentration in drinking water is kept below 50 microg/L, but ensuring this water quality will require systematic surveillance and reliable testing of all wells, which may be impractical. More research is needed on feasible prevention of toxic effects from arsenic exposure in Bangladesh.	2007
85.	Michaud DS, Kogevinas M, Cantor KP, Villanueva CM, Garcia-Closas M, Rothman N, Malats N, Real FX, Serra C, Garcia-Closas R, Tardon A, Carrato A, Dosemeci M, Silverman DT. Total fluid and water consumption and the joint effect of exposure to disinfection by-products on risk of bladder cancer. Environ Health Perspect. 2007 Nov;115(11):1569-72. BACKGROUND: Findings on water and total fluid intake and bladder cancer are inconsistent; this may, in part, be due to different levels of carcinogens in drinking water. High levels of arsenic and chlorinated by-products in drinking water have been associated with elevated bladder cancer risk in most studies. A pooled analysis based on six case-control studies observed a positive association between tap water and bladder cancer but none for nontap fluid intake, suggesting that contaminants in tap water may be responsible for the excess risk. OBJECTIVES: We examined the association between total fluid and water consumption and bladder cancer risk, as well as the interaction between water intake and trihalomethane (THM) exposure, in a large case-control study in Spain. METHODS: A total of 397 bladder cancer cases and 664 matched controls were available for this analysis. Odds ratios (OR) were estimated using unconditional logistic regression, controlling for potential confounders.	2007

	RESULTS: Total fluid intake was associated with a decrease in bladder cancer risk [OR = 0.62; 95% confidence interval (CI), 0.40-0.95 for highest vs. lowest quintile comparison]. A significant inverse association was observed for water intake (for > 1,399 vs. < 400 mL/day, OR = 0.47; 95% CI, 0.33-0.66; p for trend < 0.0001), but not for other individual beverages. The inverse association between water intake and bladder cancer persisted within each level of THM exposure; we found no statistical interaction (p for interaction = 0.13). CONCLUSION: Findings from this study suggest that water intake is inversely associated with bladder cancer risk, regardless of THM exposure level.	
86.	Mukherjee S, Roy M, Dey S, Bhattacharya RK. A Mechanistic Approach for Modulation of Arsenic Toxicity in Human Lymphocytes by Curcumin, an Active Constituent of Medicinal Herb Curcuma longa Linn. J Clin Biochem Nutr. 2007 Jul;41(1):32-42. Chronic exposure of humans to high concentrations of arsenic in drinking water is associated with skin lesions, peripheral vascular disease, hypertension, blackfoot disease and a high risk of cancer. Arsenic induces single strand breaks, DNA-protein crosslinks and apurinic sites in DNA, which are prerequisites for induction of cancer. Amelioration of such damages with natural compounds could be an effective strategy to combat arsenic toxicity. Curcumin is the active ingredient of turmeric, a common household spice, which is a rich source of polyphenols and this compound has been extensively studied as a chemopreventive agent against many types of cancer. The present study investigates whether curcumin could counteract the DNA damage caused by arsenic as assessed by single cell gel electrophoresis (SCGE) using peripheral blood lymphocytes, from healthy donors. It was observed that DNA damage induced by arsenic could be efficiently reduced by curcumin and the effect was more pronounced when lymphocytes were pre-incubated with curcumin prior to arsenic insult. Arsenic caused DNA damage by generation of reactive oxygen species (ROS) and enhancement of lipid peroxidation levels. Curcumin counteracted the damage by quenching ROS, decreasing the level of lipid peroxidation and increasing the level of phase II detoxification enzymes like catalase, superoxide dismutase and glutathione peroxidase. Curcumin also enhanced the DNA repair activity against arsenic induced damage. The expression of polymerase, a repair enzyme, was found to be highly elevated when arsenite induced damaged cells were allowed to repair in presence of curcumin. Results indicate that curcumin has significant role in confronting the deleterious effect caused by arsenic, which could be an economic mode of arsenic mitigation among rural population in West Bengal, India.	2007
87.	Pal A, Nayak B, Das B, Hossain MA, Ahamed S, Chakraborti D. Additional danger of arsenic exposure through inhalation from burning of cow dung cakes laced with arsenic as a fuel in arsenic affected villages in Ganga-Meghna-Brahmaputra plain. J Environ Monit. 2007 Oct;9(10):1067-70. Epub 2007 Sep 6. In arsenic contaminated areas of the Ganga-Meghna-Brahmaputra (GMB) plain (area 569,749 sq. km; population over 500 million) where traditionally cow dung cake is used as a fuel in unventilated ovens for cooking purposes, people are simply exposed to 1859.2 ng arsenic per day through direct inhalation, of which 464.8 ng could be absorbed in respiratory tract.	2007
88.	Ricci PF, MacDonald TR. Hormesis and precaution: the twain shall meet. Hum Exp Toxicol. 2007 Nov;26(11):877-89. Regulatory focus on quantifying risk of disease or death from exposure to hazardous substances via monotonic dose-response models has downplayed or even rejected potential benefits to human health from exposures to low (sub-threshold) doses, and thus represented by either U-shaped or J-shaped models. On the other hand, most environmental health policy hypothesizes, without firm evidence, that cancer risk is proportional to exposure at low doses	2007

	of current ambient exposures. An acceptable exposure is determined by either setting a somewhat arbitrary ;acceptable' level of risk, such as one in a million excess individual lifetime cancer risk or, in the case of several types of animal toxicological test results, applying multiplicative safety factors to a specific concentration, generally derived from a benchmark dose or NOAEL. This seemingly precautionary approach is questionable in light of much experimental evidence indicating protective effects of exposure at low doses - U-shaped or J-shaped models. We demonstrate that incorporating the possibility of hormesis into regulatory decision-making is precautionary, while use of default results in policy conflicts with precaution.	
89.	Slotnick MJ, Meliker JR, Nriagu JO. Intra-individual variability in toenail arsenic concentrations in a Michigan population, USA. J Expo Sci Environ Epidemiol. 2008 Mar;18(2):149-57. Epub 2007 Apr 11. Arsenic concentration in toenail clippings is used as a biomarker of exposure in epidemiological studies, often under the assumption that a single measurement represents long-term exposure. For this assumption to hold, the measured arsenic concentrations must be stable over time, yet temporal variability has not been adequately assessed. This study aims to evaluate temporal variability in multiple toenail samples collected from a population exposed to drinking water arsenic levels <100 microg/l. Our objectives are to investigate factors responsible for biomarker variability and to assess the suitability of single versus multiple measurements for determining exposure in epidemiological studies. Multiple toenail and drinking water samples were collected from 254 participants enrolled in a case-control study of arsenic exposure and bladder cancer in Michigan, USA; participants also answered questions on water consumption. Toenail samples collected an average of 14 months apart were positively correlated, although a substantial amount of variability was detected (r=0.43, P<0.0001, n=236). Arsenic concentration in drinking water was stable and small changes in drinking water arsenic concentration did not explain variability in toenail arsenic concentration. Change in drinking water consumption, however, was significant in predicting differences in toenail arsenic concentration. Stronger correlations between drinking water arsenic concentration and intake and toenail arsenic concentration were observed when two toenail samples were averaged, suggesting that multiple measurements may more accurately reflect exposure. When exposure was categorized into tertiles and other pre-determined categories, 25-40% of exposures were differentially classified. Only a small percentage (<4%), however, were classified as having low exposure using a single measurement and high exposure when an average of two measurements was used. These results suggest that the use of multiple measurements is unlikely to affect exposure classification of individuals into high- or low-exposure groups; however, collection of multiple samples may be advantageous for more refined exposure classification.	2007
90.	Tsuji JS, Yost LJ, Barraj LM, Scrafford CG, Mink PJ. Use of background inorganic arsenic exposures to provide perspective on risk assessment results. Regul Toxicol Pharmacol. 2007 Jun;48(1):59-68. Epub 2007 Jan 30 Background exposures provide perspective for interpreting calculated health risks associated with naturally occurring substances such as arsenic. Background inorganic arsenic intake from diet and water for children (ages 1-6 years) and all ages of the U.S. population was modeled stochastically using consumption data from USDA, published data on inorganic arsenic in foods, and EPA data on arsenic in drinking water. Mean and 90th percentile intakes for the U.S. population were 5.6 and 10.5 microg/day, assuming nationwide compliance with the 10 microg/L U.S. drinking water standard. Intakes for children were slightly lower (3.5 and 5.9 microg/day). Based on the current EPA cancer slope factor for arsenic, estimated lifetime risks associated with background diet and water at the mean and 90th percentile are 1 per 10,000 and	2007

	2 per 10,000, respectively. By comparison, reasonable maximum risks for arsenic in soil at 20 (higher typical background level) and 100mg/kg are 4 per 100,000 and 2 per 10,000, using EPA default exposure assumptions. EPA reasonable maximum estimates of arsenic exposure from residential use of treated wood are likewise within background intakes. These examples provide context on how predicted risks compare to typical exposures within the U.S. population, thereby providing perspective for risk communication and regulatory decision-making on arsenic in the environment and in consumer products.	
91.	van Vliet E, Eskes C, Stingele S, Gartlon J, Price A, Farina M, Ponti J, Hartung T, Sabbioni E, Coecke S. Development of a mechanistically-based genetically engineered PC12 cell system to detect p53-mediated cytotoxicity. Toxicol In Vitro. 2007 Jun;21(4):698-705. Epub 2006 Dec 20. The human wild type p53 gene, key for apoptosis, was introduced into the pheochromocytoma (PC12) cell line, to create a mechanistically-based in vitro test model for the detection of p53-mediated toxicity. Expression of the wt p53 gene was regulated by a system, which allowed or blocked expression p53 by absence or presence of tetracycline in the culture media. Western blot analyses confirmed an inducible and tetracycline-dependent expression of the wt p53 protein. Functionality of the p53 protein was verified by camptothecin treatment, known to induce p53-dependent apoptosis. Results showed that p53-expressing cells were significantly more sensitive to camptothecin induced cytotoxicity compared to non-expressing cells, and presented a significantly higher incidence of apoptosis. A screening study on 31 metal compounds, showed that the classified human carcinogens (NaAsO2, CdSO4 .8H2O, Na2CrO4 .4H2O, MnCl2, (NH4)2PtCl6) significantly increased cytotoxicity in p53-expressing cells compared to non-expressing cells, suggesting that their cytotoxicity was p53-mediated. Finally, acute and subchronic treatment with methyl mercury showed no significant differences in cytotoxicity and the percentage of apoptosis or necrosis between p53-expressing and non-expressing differentiated cells, suggesting that methyl mercury cytotoxicity was p53-independent.	2007
92.	Wang YH, Wu MM, Hong CT, Lien LM, Hsieh YC, Tseng HP, Chang SF, Su CL, Chiou HY, Chen CJ. Effects of arsenic exposure and genetic polymorphisms of p53, glutathione S-transferase M1, T1, and P1 on the risk of carotid atherosclerosis in Taiwan. Atherosclerosis. 2007 Jun;192(2):305-12. Epub 2006 Sep 14. To evaluate the joint effects between genetic polymorphisms of glutathione S-transferase M1, T1, P1, and p53, and arsenic exposure through drinking well water on the risk of carotid atherosclerosis, 605 residents including 289 men and 316 women were recruited from a northeastern area of Taiwan. Carotid atherosclerosis was diagnosed by either a carotid artery intima-media thickness (IMT) of >1.0 mm, a plaque score of > or =1, or stenosis of >50%. A significant age- and gender-adjusted odds ratio of 3.3 for the development of carotid atherosclerosis was observed among the high-arsenic exposure group who drank well water containing arsenic at levels >50 microg/L. The high-arsenic exposure group with GSTP1 variant genotypes of Ile/Val and Val/Val, and with the p53 variant genotypes of Arg/Pro and Pro/Pro had 6.0- and 3.1-fold higher risks of carotid atherosclerosis, respectively. In addition, the high-arsenic exposure group with one or two variant genotypes of GSTP1 and p53 had 2.8- and 6.1-fold higher risks of carotid atherosclerosis, respectively, and showed a dose-dependent relationship. A multivariate-adjusted odds ratio of 3.4 for the risk of carotid atherosclerosis among study subjects with the two variant genotypes of GSTP1 and p53 was also found. Our study showed the joint effects on the risk of carotid atherosclerosis between the genetic polymorphisms of GSTP1 and p53, and arsenic exposure.	2007
93.	Zhang JJ, Smith KR. Household air pollution from coal and biomass fuels in China: measurements, health impacts, and interventions. Environ Health Perspect. 2007	2007

	Jun;115(6):848-55. Epub 2007 Feb 27. OBJECTIVE: Nearly all China's rural residents and a shrinking fraction of urban residents use solid fuels (biomass and coal) for household cooking and/or heating. Consequently, global meta-analyses of epidemiologic studies indicate that indoor air pollution from solid fuel use in China is responsible for approximately 420,000 premature deaths annually, more than the approximately 300,000 attributed to urban outdoor air pollution in the country. Our objective in this review was to help elucidate the extent of this indoor air pollution health hazard. DATA SOURCES: We reviewed approximately 200 publications in both Chinese- and English-language journals that reported health effects, exposure characteristics, and fuel/stove intervention options. CONCLUSIONS: Observed health effects include respiratory illnesses, lung cancer, chronic obstructive pulmonary disease, weakening of the immune system, and reduction in lung function. Arsenic poisoning and fluorosis resulting from the use of "poisonous" coal have been observed in certain regions of China. Although attempts have been made in a few studies to identify specific coal smoke constituents responsible for specific adverse health effects, the majority of indoor air measurements include those of only particulate matter, carbon monoxide, sulfur dioxide, and/or nitrogen dioxide. These measurements indicate that pollution levels in households using solid fuel generally exceed China's indoor air quality standards. Intervention technologies ranging from simply adding a chimney to the more complex modernized bioenergy program are available, but they can be viable only with coordinated support from the government and the commercial sector.	
94.	Ahsan H, Chen Y, Parvez F, Argos M, Hussain AI, Momotaj H, Levy D, van Geen A, Howe G, Graziano J. Health Effects of Arsenic Longitudinal Study (HEALS): description of a multidisciplinary epidemiologic investigation. J Expo Sci Environ Epidemiol. 2006 Mar;16(2):191-205. Health Effects of Arsenic Longitudinal Study (HEALS), a multidisciplinary and large prospective cohort study in Araihazar, Bangladesh, was established to evaluate the effects of full-dose range arsenic (As) exposure on various health outcomes, including premalignant and malignant skin tumors, total mortality, pregnancy outcomes, and children's cognitive development. In this paper, we provide descriptions of the study methods including study design, study population, data collection, response rates, and exposure and outcome assessments. We also present characteristics of the study participants including the distribution of exposure and the prevalence of skin lesion at baseline recruitment. A total of 11,746 married men and women between 18 and 75 years of age participated in the study at baseline (a response rate of 98%) and completed a full questionnaire interview that included a food frequency questionnaire, with a response rate of 98%. Among the 98% of the participants who completed the clinical evaluation, over 90% provided blood samples and spot urine samples. Higher educational status, male gender, and presence of premalignant skin lesions were associated with an increased likelihood of providing blood and urine samples. Older participants were less likely to donate a blood sample. About one-third of the participants consumed water from a well with As concentration in each of three groups: >100 microg/l, 25-100 microg/l, and <25 microg/l. Average urinary As concentrations were 140 and 136 microg/l for males and females, respectively. HEALS has several unique features, including a prospective study design, comprehensive assessments of both past and future changes in As exposure at the individual level, a large repository of biological samples, and a full dose range of As exposures in the study population. HEALS is a valuable resource for examining novel research questions on the health effects of As exposure.	2006
95.	Arnold LL, Eldan M, Nyska A, van Gemert M, Cohen SM. Dimethylarsinic acid: Results of chronic toxicity/oncogenicity studies in F344 rats and in B6C3F1 mice. Toxicology 223 (2006) 82-100.	2006

	Dimethylarsinic acid (DMA(V), cacodylic acid), a foliar herbicide, was administered in the diet to B6C3F1 mice (at dose levels of 0, 8, 40, 200, and 500 ppm) and to F344 rats (at dose levels of 0, 2, 10, 40, and 100 ppm) for 2 years, according to US EPA guidelines. In mice, there were no treatment-related tumors observed at any site. Treatment-related progressive glomerulonephropathy and nephrocalcinosis were observed in the kidneys in both sexes. The incidence of vacuolation of the epithelium in the urinary bladder was increased in both sexes, but was not associated with cytotoxicity, necrosis or hyperplasia. Based on non-neoplastic lesions found in the urinary bladder, the NOEL for mice was assessed to be 40 ppm in males and 8 ppm in females. In rats, treatment-related mortality occurred early in the study in five males in the 100 ppm group and in one male in the 40 ppm group. Papillomas and carcinomas with degeneration of the urothelium, necrosis and urothelial cell hyperplasia, were found in the urinary bladders of both sexes. In male rats, one papilloma was found in each of the 10 and 40 ppm groups; one urothelial cell carcinoma was found in the 2 ppm group and two in the 100 ppm group. Four papillomas and six urothelial cell carcinomas were found in the female 100 ppm group. Non-neoplastic treatment-related kidney lesions were confined to the 40 and 100 ppm levels and included necrosis, pyelonephritis, medullary nephrocalcinosis and tubular cystic dilation, hyperplasia of the epithelial lining of the papilla, and pelvic urothelial cell hyperplasia. All of these kidney changes appear to be related to an increase in the aging nephropathy of the rat. Dose-related increases in the height of the thyroid follicular epithelium were also noted in males and females, however, such changes reflect an adaptive response of the thyroid to decreased levels of circulating thyroid hormone, rather than an adverse effect. Based on the kidney and bladder lesions, the NOEL for non-neoplastic and neoplastic lesions was considered to be 10 ppm in males and females. Based on these studies, DMA(V) is carcinogenic only in rats and only at relatively high doses, with the urinary bladder as the target organ. Female rats appear to be more sensitive to the effects of DMA(V) than male rats. DMA(V) is not carcinogenic in mice.	
96.	Ayotte JD, Baris D, Cantor KP, Colt J, Robinson GR Jr, Lubin JH, Karagas M, Hoover RN, Fraumeni JF Jr, Silverman DT. Bladder cancer mortality and private well use in New England: an ecological study. J Epidemiol Community Health. 2006 Feb;60(2):168-72. STUDY OBJECTIVE: To investigate the possible relation between bladder cancer mortality among white men and women and private water use in New England, USA, where rates have been persistently raised and use of private water supplies (wells) common. DESIGN: Ecological study relating age adjusted cancer mortality rates for white men and women during 1985-1999 and proportion of persons using private water supplies in 1970. After regressing mortality rates on population density, Pearson correlation coefficients were computed between residual rates and the proportion of the population using private water supplies, using the state economic area as the unit of calculation. Calculations were conducted within each of 10 US regions. SETTING: The 504 state economic areas of the contiguous United States. PARTICIPANTS: Mortality analysis of 11 cancer sites, with the focus on bladder cancer. MAIN RESULTS: After adjusting for the effect of population density, there was a statistically significant positive correlation between residual bladder cancer mortality rates and private water supply use among both men and women in New England (men, r = 0.42; women, r = 0.48) and New York/New Jersey (men, r = 0.49; women, r = 0.62). CONCLUSIONS: Use of well water from private sources, or a close correlate, may be an explanatory variable for the excess bladder cancer mortality in New England. Analytical studies are underway to clarify the relation between suspected water contaminants, particularly arsenic, and raised bladder cancer rates in northern New England.	2006
97.	Cha Y, Park DW, Lee CH, Baek SH, Kim SY, Kim JR, Kim JH. Arsenic Trioxide Induces Apoptosis in Human Colorectal Adenocarcinoma HT-29 Cells Through ROS. Cancer Res	2006

	Treat. 2006 Feb;38(1):54-60. Epub 2006 Feb 28. PURPOSE: Treatment with arsenic trioxide (As(2)O(3)) results in a wide range of cellular effects that includes induction of apoptosis, inhibition of cell growth, promotion or inhibition of cellular differentiation, and inhibition of angiogenesis through a variety of mechanisms. The mechanisms of As(2)O(3)-induced cell death have been mainly studied in hematological cancers, and those mechanisms in solid cancers have yet to be clearly defined. In this study, the mechanisms by which As(2)O(3) induces apoptosis in human colorectal adenocarcinoma HT-29 cells were investigated. MATERIALS AND METHODS: To examine the levels of apoptosis, HT-29 cells were treated with As(2)O(3) and then we measured the percentage of Annexin V binding cells, the amount of ROS production and the mitochondrial membrane potential. Western blot analysis was performed to identify the activated caspases after As(2)O(3) exposure, and we compared the possible target molecules of apoptosis. As(2)O(3) treatment induced the loss of the mitochondrial membrane potential and an increase of ROS, as well as activation of caspase-3, -7, -9 and -10. RESULTS: As(2)O(3) induced apoptosis via the production of reactive oxygen species and the loss of the mitochondrial membrane potential. As(2)O(3) induced the activation of caspase-3, -7, -9 and -10. Furthermore, As(2)O(3) treatment downregulates the Mcl-1 and Bcl-2 expressions, and the release of cytochrome c and an apoptosis-inducing factor (AIF). Pretreating the HT-29 cells with N-acetyl-L-cysteine, which is a thiol-containing antioxidant, inhibited the As(2)O(3)-induced apoptosis and caspase activation. CONCLUSION: Taken together, these results suggest that the generation of reactive oxygen species (ROS) by As(2)O(3) might play an important role in the regulation of As(2)O(3)-induced apoptosis. This cytotoxicity is mediated through a mitochondria-dependent apoptotic signal pathway in HT-29 cells.	
98.	Chang L, Liao W, Yu H, Cheng T, Lin P. Centrosome Abnormality And Cell Colony Formation (Cell Transformation) In Human Lung Cells Induced By Arsenic. Toxicol Sci 2006 Mar;90(1-S):90 Epidemiological studies indicated that residents, especially cigarette smokers, in arseniasis areas were significantly higher in lung cancer incidences than those living in the general population. Thus an interaction between arsenic and cigarette smoking in lung cancer development is suspected. p53 mutation in lung epithelial cells is generally accepted as a consequence in cigarette smoking. Our hypothesis was that p53 dysfunction (either via mutation or inhibition) would serve as a platform for arsenic to promote carcinogenesis in human lung epithelial cells. BEAS-2B human lung epithelial cells, with or without pifthrin (Pif, a known p53 inhibitor) treatment (30uM), and human lung adenocarcinoma cell line H1355 were used in our investigation. These cells were treated with different doses of arsenic (0, 1, 5, and 10 uM) for 48 hours. Based on our cell viability study, 5-10 uM was selected as our investigative dose for arsenic exposure. Our study demonstrated that arsenic induced apoptosis and G2/M cell cycle arrest in BEAS-2B cells but not in the H1355 (p53 mutated) or BEAS-2B+Pif (p53 inhibited) cells. Via gamma-tubulin immunostaining technique, we further demonstrated that there were an increased number of cells in the H1355 and BEAS-2B+Pif cell cultures showing centrosome abnormalities (existed in multiple numbers and located in atopic positions) with increasing dose of arsenic. Colony formation (an indication of cell transformation) was also observed in BEAS-2B+Pif cells cultures in soft-agar with arsenic treatment but not in BEAS-2B cells. Our present study demonstrated that p53- compromised (dysfunction) cells were more susceptible to arsenic's promotion on pre-carcinogenic changes (resistance to apoptosis, centrosome abnormality, and cell transformation). Our present findings also echoed and supported the epidemiological observations that arsenic exposure further increased lung cancer risk in cigarette smokers.	2006

99.	Chu HA, Crawford-Brown DJ. Inorganic arsenic in drinking water and bladder cancer: a meta-analysis for dose-response assessment. Int J Environ Res Public Health. 2006 Dec;3(4):316-22. Most arsenic cancer risk assessments have been based solely on epidemiological studies to characterize the dose-response relationship for arsenic-associated cancer and to perform risk calculations. However, current epidemiological evidence is too inconsistent and fraught with uncertainty regarding arsenic exposure to provide reliable estimates. This makes it hard to draw a firm conclusion about the shape and slope of the dose-response relationship from individual studies. Meta-analysis is a statistical approach to combining results across studies and offers expanded opportunities for obtaining an improved dose-response relationship. In this study, a meta-analysis of arsenic studies was conducted by combining seven epidemiological studies from different regions to get an overall dose-response relationship between the amount of arsenic intake and the excess probability of bladder cancer. Both the fixed-effect and random-effect models were used to calculate the averaged coefficient of the linear-logistic regression model. A homogeneity test was also conducted. The final product of this research is an aggregated dose-response model in the range of empirical observation of arsenic. Considering the most recent arsenic MCL (maximum contaminant level, i.e. 10microg/L), the associated bladder cancer risk (lifetime excess probability) at this MCL is 2.29 x 10-5.	2006
100.	Divine K, Bredow S, Cook DL, Walker DM, Walker VE, Nakamura J, Belinsky SA. Effects Of Chronic Low Level Arsenic Exposure On Immortalized Human Lung Bronchial Epithelial Cells. Toxicol Sci 2006 Mar;90(1-S):90 Inorganic Arsenic (As), is a known human carcinogen that poses a significant risk to human health. The primary route of exposure is via drinking As contaminated water. Epidemiological evidence links chronic As exposure to increased carcinogenic risk of the lung. However, the underlying molecular mechanisms of As induced lung cancer are not well understood. To investigate potential mechanisms of As induced lung cancer in humans we have continuously exposed immortalized human bronchial epithelial cells to environmentally relevant levels (250nM) of As(III) for 35 weeks. The cells were obtained from Dr. Jerry Shay at the University of Texas Southwestern Medical Center. They are diploid, non-tumorigenic, and were immortalized via viral infection to over express both hTERT and cdk4. Chronic exposure of the cells resulted in a 20% reduction in CpG methylation indicative of global hypomethylation, a significant reduction in Vascular Endothelial Growth Factor (VEGF) promoter activity (2.3 fold), and mitochondrial DNA mutations (in tRNA3). Alterations in global DNA methylation were determined using the Methyl Acceptor assay and VEGF-promoter activity was determined by transfecting the control and 250nM As(III) treated cells with a reporter plasmid containing the gene for firefly luciferase under the control of the wild type promoter for Vascular Endothelial Growth Factor (VEGF). Mitochondrial DNA mutations were detected using PCR based denaturing gradient gel electrophoresis (PCR-DGGE). We are currently conducting MSP analysis of the cells to determine if aberrant promoter methylation has occurred in the p16, DAPK, RassF1A and O6-MGMT genes. In addition we are also investigating As induced DNA damage. This study provides a human based model in which to investigate the molecular mechanisms underlying arsenic induced lung carcinogenesis.	2006
101.	Goytia Acevedo RC, Abril ER, Lantz R. Interaction Of Arsenic With Wnt/beta -Catenin Pathways In Human Colon Cancer Cells Lines.Toxicol Sci 2006 Mar;90(1-S):87 ABSTRACT: Arsenic, a known human carcinogen, affects the proliferation pathways of a variety of different cells. However, there is limited information about the association between arsenic exposure and gastrointestinal cancers. Mutations in APC, a negative regulator of beta-catenin, with subsequent aberrant regulation of the Wnt/beta-catenin signalling pathway, are	2006

	one of the major causes of colorectal cancer. The interactions and effects of arsenic on this pathway are unknown. We have examined this interaction using stably transfected colon cancer cell lines where APC expression is under experimental control. HT-29 cell variants were exposed to arsenic (as sodium arsenite) at 50 and 100 ppb for up to 7 days. The native cell line contains non-functional APC. Two transfected variant cell lines were examined: one contained a wild type APC under control of the metallothionein promoter; the second contained the same promoter but with no APC. Cell counts in non-APC expressing cells were 60% higher than those seen with APC, with arsenic exposure leading to increasing cell counts in a dose dependent manner. However, in cells expressing wild type APC, 100 ppb arsenite decreased the cell numbers. Degradation of beta-catenin, with inhibition of the Wnt signalling pathway, occurs through phosphorylation of beta-catenin. Functional APC is necessary to facilitate this degradation. We therefore also examined the levels of beta-catenin phosphorylation. In the presence of wild type APC, 100 ppb arsenic lead to a doubling of the levels of beta-catenin phosphorylation. No effect of arsenic on beta-catenin phosphorylation was seen in the absence of wild type APC. Taken together, these data suggest that the functional status of APC affects the interaction colon cancer cells with arsenic. Therefore, ingestion of arsenic may further exacerbate the effects of mutated APC in the development of colon cancer.	
102.	Gregus Z, Nemeti B, Csanaky I. Effect Of An Inactivator Of Glyceraldehyde- 3-Phosphate Dehydrogenase (GAPDH), A Fortuitous Arsenate Reductase, On Disposition Of Arsenate In Rats. Toxicol Sci 2006 Mar;90(1-S):90 The environmentally prevalent arsenate (AsV) is reduced in the body to the much more toxic arsenite (AsIII). Recently, we have demonstrated that the glycolytic enzyme GAPDH catalyzes the reduction of AsV in presence of glutathione, yet the role of GAPDH in AsV reduction in vivo is unknown. Therefore, we examined the effect of alpha-cholorhydrin (ACH), which forms a GAPDH-inhibitory metabolite, on the reduction of AsV in rats. These studies confirmed the in vitro role of GAPDH as an AsV reductase, inasmuch as 3 hrs after administration of ACH (100 or 200 mg/kg, ip) to rats both the cytosolic GAPDH activity and the AsV-reducing activity dramatically fell in the liver, moderately decreased in the kidneys and remained unchanged in the muscle. Moreover, the AsV reducing activity closely correlated with the GAPDH activity in the hepatic cytosols of control and ACH-treated rats. Some confounding effects of ACH prompted us to examine its influence on the disposition of injected AsV (50 umol/kg, iv) in rats with ligated bile duct as well as in rats with ligated bile duct and renal pedicles. These studies demonstrated that the hepatic retention of AsV significantly increased and the combined levels of AsV metabolites (i.e., AsIII plus methylated arsenicals) in the liver decreased in response to ACH; however, ACH failed to delay the disappearance of AsV from the blood of rats with blocked excretory routes. Thus, the GAPDH inactivator ACH inhibits AsV reduction by the liver, but not by the whole body, probably because the impaired hepatic reduction is compensated for by hepatic and extrahepatic AsV-reducing mechanisms spared by ACH. It is most likely that ACH inhibits hepatic AsV reduction predominantly by inactivating GAPDH in the liver, however, a slight ACH-induced glutathione depletion may also contribute. While this study seems to support the conclusion that GAPDH in the liver is involved in AsV reduction in rats, confirmation of the in vivo role of GAPDH as an AsV reductase is desirable.	2006
103.	Jiang G, States J. Arsenite Co-Exposure Disrupts P53-Mediated Responses To BPDE Induced Dna Damage In Human Lung Cells. Toxicol Sci 2006 Mar;90(1-S):107 Benzo[a]pyrene (BP) is a major carcinogen in cigarette smoke. The BP metabolite benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE) is the ultimate carcinogenic form of BP. BPDE induced mutagenesis is believed to play an important role in lung cancer. Arsenic is number 1 on the ATSDR list of hazardous chemicals and causes lung, skin and bladder cancer.	2006

	Epidemiological data suggest that lung cancer incidence in smokers may be exacerbated by consumption of arsenic contaminated water. In this study, we investigated how arsenic exposure affects p53 mediated responses to BPDE-induced DNA damage in human lung cells. Western blot analysis showed that induction of p53, p53S15P, p21CIP1/WAF1, cyclin D and CDC2Y15P by arsenite-BPDE co-exposure was both time- and dose-dependent. Arsenite-BPDE co-exposure increased expression of p53, p53S15P, p21CIP1/WAF1 and cyclin D in contrast to BPDE exposure alone in A549/LXSN cells (p53 expressing). In A549/E6 cells (p53 deficient), co-exposure increased expression of CDC2 and CDC2Y15P in contrast to BPDE exposure alone. In A549/LXSN cells, co-exposure decreased the expression level of CDC2 and phosphorylated pRB in contrast to BPDE exposure alone. Cellular sensitivity results showed distinguishable differences between A549/LXSN and A549/E6 cells after co-exposure. A549/LXSN cells with p53 expression are resistant to the exposure, whereas p53 deficient A549/E6 cells exhibit low survival. BPDE-DNA adduct removal is p53 dependent for efficient global genomic DNA repair. Immuno-slotblot assay of BPDE-DNA adducts indicated that arsenite-BPDE co-exposure decreases the BPDE-DNA adduct repair rate in p53 expressing cells but had no effect on BPDE-DNA adduct levels in p53 deficient cells. The results indicate that arsenite may exacerbate lung carcinogenesis by interfering with the p53 mediated responses to BPDE-induced DNA damage.	
104.	Lamm SH, Byrd DM, Penn C, Engel A, Chen R, Feinleib M. Epidemiological Data Suggest That Arsenic Has A Threshold For Human Cancers. Toxicol Sci 2006 Mar;90(1-S):177 Mortality from bladder cancer in the Blackfoot-disease endemic areas of SW Taiwan fits a linear non-threshold (LNT) model when the entire data set is used (Byrd et al., 1996). However, within the study, the bladder cancer risk has been shown to be quite variable by township (Chen et al., 1985). Three of six townships show in a new analysis evidence of a bladder cancer mortality risk that is independent of arsenic levels. Analysis of data from the three other townships shows a linear dose-response relationship between bladder cancer mortality and median village well water arsenic level with an apparent threshold or discontinuity at 84 ppb in drinking water for each sex. Removal of the influence of a confounder from the data analysis has revealed an underlying risk structure in the ecological study. This fit is consistent with a previous demonstration of the ecological data on skin cancer and arsenic levels showing a fit to a model with a threshold at 100 ppb (Byrd et al., 1996). Further, the epidemiological study on skin cancer and arsenic levels from Inner Mongolia, China, showed a threshold at 122 ppb (Tucker et al., 2001). The consistency of human data on arsenic exposure and specific cancers fitting a threshold model provides support for a variety of toxicological hypotheses about the mechanism of cancer induction by arsenic.	2006
105.	Lopez-Abente G, Aragones N, Ramis R, Hernandez-Barrera V, Perez-Gomez B, Escolar-Pujolar A, Pollan M. Municipal distribution of bladder cancer mortality in Spain: possible role of mining and industry. BMC Public Health. 2006 Jan 27;6:17. BACKGROUND: Spain shows the highest bladder cancer incidence rates in men among European countries. The most important risk factors are tobacco smoking and occupational exposure to a range of different chemical substances, such as aromatic amines. METHODS: This paper describes the municipal distribution of bladder cancer mortality and attempts to "adjust" this spatial pattern for the prevalence of smokers, using the autoregressive spatial model proposed by Besag, York and Mollie, with relative risk of lung cancer mortality as a surrogate. RESULTS: It has been possible to compile and ascertain the posterior distribution of relative risk for bladder cancer adjusted for lung cancer mortality, on the basis of a single Bayesian spatial model covering all of Spain's 8077 towns. Maps were plotted depicting smoothed relative risk (RR) estimates, and the distribution of the posterior probability of RR>1 by sex. Towns that registered the highest relative risks for both sexes were mostly located in	2006

	the Provinces of Cadiz, Seville, Huelva, Barcelona and Almer□a. The highest-risk area in Barcelona Province corresponded to very specific municipal areas in the Bages district, e.g., Sur□a, Sallent, Balsareny, Manresa and Cardona. CONCLUSION: Mining/industrial pollution and the risk entailed in certain occupational exposures could in part be dictating the pattern of municipal bladder cancer mortality in Spain. Population exposure to arsenic is a matter that calls for attention. It would be of great interest if the relationship between the chemical quality of drinking water and the frequency of bladder cancer could be studied.	
106.	McDonald C, Hoque R, Huda N, Cherry N. Prevalence of arsenic-related skin lesions in 53 widely-scattered villages of Bangladesh: an ecological survey. J Health Popul Nutr. 2006 Jun;24(2):228-35. A survey was carried out to provide a representative assessment of prevalence and risk of arsenic-related skin lesions in relation to geographical distribution of arsenic in wells of rural Bangladesh as a necessary background for research into effects in pregnancy and cancer risks. A systematic random sample of 53 villages in four divisions of Bangladesh served by Gonoshasthaya Kendra was selected, and all women aged 18 years or more (n=16,740) were listed. Trained paramedics recorded the presence of skin thickening and nodules on the palms and soles, together with information on tubewell use. The prevalence was related to the mean concentration of arsenic for the district as indicated by data from the British Geological Survey and to the date the first well in the village was installed. Overall, the observed prevalence was 176 cases (1.3%) in 13,705 women examined, varying from 0% in 26 villages to 23% in one; lesions were observed more frequently on hands than on feet. The estimate doubled with concentrations of arsenic from 11 to < or =50 microg/L and increased more than 20 times at >50 microg/L. In the absence of further information, priority for control measures should be directed at areas where the average concentrations of arsenic are above 50 microg/L, especially in villages where skin lesions have been identified.	2006
107.	McNally AJ, Barber DS. Identification Of An Alternatively Spliced Isoform Of The Human cyt19 Gene, An Sadenosyl- L-Methionine:Asmethyltransferase. Toxicol Sci 2006 Mar;90(1-S):91 Inorganic arsenic (iAs) exposure through potable water is a major problem in many parts of world. Chronic exposure to arsenic (As) is associated with tumors of the skin, liver, lung, urinary bladder, and prostate. Once in the body, iAs is methylated to methylarsonic acid (MMA) and dimethylarsinic acid (DMA). It has been shown that methylated arsenicals that contain trivalent arsenicals are more cytotoxic and genotoxic than either arsenate or arsenite. The role of methylated arsenic metabolites in toxicity remains unclear. We and others have previously demonstrated that the human cyt19 gene codes for a protein that catalyzed both arsenite and MMA methylation. Studies have shown differences in the amount of MMA and DMA excreted in the urine of exposed human populations which may be due to genetic polymorphisms of arsenic methyltransferase. However, only a single polymorphism has been identified in the coding region of cyt19 arsenic methyltransferase, which did not dramatically alter activity. In this study we identified an alternative splice variant of the human cyt19 (cyt19 delta E2), in which exon 2 is removed creating a premature stop codon. This variant was expressed in 7 out of 7 human liver samples and in HepG2 cells. Alternative splicing is frequently used to regulate human gene expression. Alternative splicing of cyt19 may represent a novel process for regulating arsenic methylation.	2006
108.	Meliker JR, Franzblau A, Slotnick MJ, Nriagu JO. Major contributors to inorganic arsenic intake in southeastern Michigan. Int J Hyg Environ Health. 2006 Sep;209(5):399-411. Epub 2006 May 30. Accurate estimates of inorganic arsenic intake are critical for evaluating potential health risks.	2006

	Intake estimates have not been critically examined in regions of the United States where people are at risk from arsenic concentrations in drinking water exceeding the maximum contaminant limit of 10 microg/l. In southeastern Michigan, approximately 8% of the population is exposed to arsenic in drinking water >10 microg/l. Four hundred and forty participants of a control group in this region, frequency matched to cases in a population-based bladder cancer case-control study, answered a questionnaire about water and food consumption and smoking history. Water samples were collected from participants' current residences and analyzed for arsenic. Water arsenic data were combined with questionnaire data and published data of inorganic arsenic concentrations in select foods and cigarettes to examine the influence of arsenic in water at home, at work, and at other places, as well as inorganic arsenic intake from food and cigarettes. Monte Carlo simulations and analyses of individual-level intake estimates were conducted to quantify the variability attributed to different parameters in this primarily elderly white male population of southeastern Michigan. The 95th percentile of total inorganic arsenic intake ranges from 11 to 24 microg/day, depending on the intake metric selected. Results indicate that arsenic in home drinking water is the largest source of inorganic arsenic, accounting for 55.1% of the variance in the intake estimates. Food intake explains 37.3% of the variance, with rice being the largest contributor. In the upper decile of intake, consumption of plain water and beverages made with water at home, and ingestion of arsenic in water at work, also contribute to intake estimates. Water used for cooking and arsenic from smoking, however, only minimally alter the intake estimates. This is due to a relatively small volume of water absorbed into cooked foods and low concentrations of arsenic in cigarettes. Results from this study will assist investigators in better characterizing exposure to inorganic arsenic.	
109.	Ng JC, Liu FF, Wang J, Maddelena R, Moore MR. Urinary Arsenic, Porphyrins And Malondialdehyde In A Population 16 Years After Arsenic Mitigation Program In Xinjiang, China. Toxicol Sci 2006 Mar;90(1-S):256 Arsenic contamination of groundwater (0.05 to 0.84 mg/L) in Kuitun, Xinjiang was first found in 1970's. Alternative clean surface water was introduced in 1985. We aimed to assess the exposure and heath outcome since the mitigation. In 2000, we collected a total of 360 urine samples from villagers from the endemic area and a nearby control area for arsenic (As), porphyrins and malondialdehyde (MDA) measurements. The averaged urinary As level of villagers from the endemic site (117±8.3 ug/g creatinine; 4.2 to 943.8 ug/g creat) was higher than that of the control site (73.6±3.2 ug/g creat). No significant differences were found in urinary porphyrins or MDA between the endemic and control sites. However, when the urinary arsenic was higher than 150 ug/g creat, these two biomarkers were higher in the exposed group than the control. Within the exposed group, villagers with arsenic- related skin symptoms had higher arsenic, uroporphyrin and MDA compared to those who had not shown symptoms. Sine the water mitigation, villagers whose urinary arsenic levels were < 90 ?g/g creat remained at 43% of the population compared to 40% prior to intervention. However, urinary arsenic > 270 ug/g creat dropped from 20% to 10% of the population. Population with arsenic-related skin symptoms remained unchanged at 31%. We noted that 7.8% of those who had skin lesions were born after the implementation of intervention and that some villagers still prefer to drink the groundwater. Further, in the dry season, lack of surface water and electrical power breakdowns are to blame for failure to ensure continuous supply of clean water. It is concluded that despite the prompt action and successful water mitigation program to curb arsenic poisonings, it is essential to continue to monitor the health outcome of this population.	2006
110.	Rahman M, Vahter M, Sohel N, Yunus M, Wahed MA, Streatfield PK, Ekström EC, Persson LA. Arsenic exposure and age and sex-specific risk for skin lesions: a population-based case-referent study in Bangladesh. Environ Health Perspect. 2006 Dec;114(12):1847-52. BACKGROUND: The objective of this population-based case-referent study in Matlab,	2006

	Bangladesh, was to assess the susceptibility to arsenic-induced skin lesions by age and sex, in a population drinking water from As-contaminated tube wells. METHODS: Identification of As-related skin lesions was carried out in three steps: a) screening of the entire population > 4 years of age (n = 166,934) by trained field teams; b) diagnosis of suspected As-related cases by physicians; and c) confirmation by experts based on physicians' records and photographs. A total of 504 cases with skin lesions were confirmed. We randomly selected 2,201 referents from the Matlab health and demographic surveillance system; 1,955 were eligible, and 1,830 (94%) were available for participation in the study. Individual history of As exposure was based on information obtained during interviews and included all drinking-water sources used since 1970 and concentrations of As (assessed by atomic absorption spectrophotometry) in all the tube wells used. RESULTS: Cases had been exposed to As more than referents (average exposure since 1970: male cases, 200 microg/L; female cases, 211 microg/L; male referents, 143 microg/L; female referents, 155 microg/L). We found a dose-response relationship for both sexes ($p < 0.001$) and increased risk with increasing socioeconomic status. Males had a higher risk of obtaining skin lesions than females (odds ratio 10.9 vs. 5.78) in the highest average exposure quintile ($p = 0.005$). Start of As exposure (cumulative exposure) before 1 year of age was not associated with higher risk of obtaining skin lesions compared to start of As exposure later in life. CONCLUSIONS: The results demonstrate that males are more susceptible than females to develop skin lesions when exposed to As in water from tube wells.	
111.	Reznikova TV, Rice RH. Divergent Effects Of Various Metals On Human Keratinocyte Homeostasis. Toxicol Sci 2006 Mar;90(1-S):89 Epidemiological studies have established arsenic as an environmental carcinogen, yet the mechanism behind arsenic induced cancer is not understood. It is known that arsenic and metal compounds of vanadate, cadmium, chromate and the metalloid antimony suppress expression of epidermal keratinocyte differentiation markers. In addition, arsenite treatment can preserve the germinative capacity or putative stem cell population of keratinocytes. More recently, we have discovered that antimony acts similarly to arsenite in preserving the germinative capacity of keratinocytes. To gain further insight into how these compounds act a third endpoint, cell size, was examined. The cell size of epidermal keratinocytes is proposed to be associated with their germinative state and differentiation status. Further, it has recently been established that c-myc plays a critical part in controlling epidermal cell size, since c-myc expression causes exit from the germinative pool. Whether the aforementioned compounds altered cell size and whether this correlates with c-myc expression was examined. Keratinocyte size was measured using a Coulter Counter. In untreated cultures, cell size increased as cells grew past confluence, whereas arsenite or antimony prevented this increase in cell size, paralleling previous results with preservation of the stem cell population. In contrast, vanadate treated cells were larger and cadmium and chromate had no effect on keratinocyte size. c-Myc mRNA, measured by real-time PCR, was also suppressed only by arsenite or antimony treatment. Thus, a decrease in cell size and myc expression correlates with higher germinative capacity rather than with suppression of differentiation and only arsenite and antimony alter all of these. These results demonstrate that arsenite and antimony have unique effects on cultured keratinocytes and may give insight into how arsenite disrupts normal keratinocyte function leading to skin cancer. In addition, these results identify antimony as possibly equivalent to arsenic in biologic effect, which merits further investigation.	2006
112.	Robinson JF, Yu X, Gribble EJ, Hong S, Kim E, Sidhu JS, Faustman EM. Examination Of Arsenic-Induced Alterations In Cell Cycle Progression And Global Gene Expression In P53 Transgenic Mouse Embryonic Fibroblasts. Toxicol Sci 2006 Mar;90(1-S):91-2 Arsenic is ubiquitous in the environment due to natural and anthropogenic sources. Several human health impacts have been associated with arsenic, including cardiovascular disease,	2006

	peripheral neuropathy, anemia, congenital malformations and cancer. The mechanism(s) underlying As3+-induced toxicity is poorly understood. Previous studies have shown that As3+ generates cytotoxicity, cellular stress and alterations in cell cycle progression. In response to toxicant-induced stress, the tumor suppressor gene p53 promotes activation of genes involved in cell cycle arrest and apoptosis and may act as an important mediator of arsenic-induced toxicity. To further explore the role of p53 in As3+-induced toxicity and related gene pathways, we utilized synchronized cultures of p53 transgenic mouse embryonic fibroblasts (MEFs) to examine dose and time dependent effects on cytotoxicity and cell cycle progression (BrdU/Hoechst). In addition, we assessed As3+-induced alterations in global gene expression using the CodeLink Mouse UniSet 10K platform (Amersham Biosciences) at 24h post-treatment (5לM). Furthermore, we conducted qRTPCR for six selected genes, Gst2a, Cdc25c, Ccnb1, Ube2c, SNCA, and Uchl1 to confirm our microarray results. We observed As3+-induced dose-dependent cytotoxicity at 24h and time-dependent (8, 24h) induction of genes involved in mediating As3+-induced stress in both p53+/+ and p53-/- MEFs. We also observed a significant reduction in cellular proliferation with As3+ irrespective of genotype. In contrast, at the transcriptional level we primarily only observed changes in genes controlling the cell cycle in p53+/+ MEFs. In summary, MEFs exhibited As3+-induced cytotoxicity, cytostasis, and p53 independent and dependent alterations in gene expression. This study provides insight into the underlying molecular mechanisms of As3+-induced toxicity.	
113.	Rossman TG. Genotoxic Profile Of AS, mRNAAnd DNA. Toxicol Sci 2006 Mar;90(1-S):154 The concept of genotoxicity is a fluid one. Originally, agents (or their metabolites) that reacted with DNA to cause genetic effects were considered genotoxic, and it was assumed that the carcinogenicity of those agents occurred by those genotoxic mechanisms. Later, the idea of "indirect genotoxicity" came into play, with similar assumptions about carcinogenic mechanisms. Arsenic compounds show genotoxicity in a number of assays, and also induce epigenetic and signaling changes. The specific genotoxic endpoints differ for different arsenic compounds, with arsenite (but not methylated compounds) showing weak mutagenic activity and trivalent methylated compounds (as well as arsenite) behaving as clastogens. No arsenic compound forms DNA adducts. Evidence suggests that both may be caused by reactive oxygen species. Arsenite causes delayed apoptosis. Because dead cells do not form tumors, in the absence of stringent toxicity criteria, no claims can be made as to the likelihood for any carcinogenic mechanism. The existence of new animal models for arsenic carcinogenesis (cocarcinogenesis for mouse skin cancer and transplacental carcinogenesis for some other organs) yields additional insight into carcinogenic mechanisms.	2006
114.	Shen DW, Liang XJ, Suzuki T, Gottesman MM. Identification by functional cloning from a retroviral cDNA library of cDNAs for ribosomal protein L36 and the 10-kDa heat shock protein that confer cisplatin resistance. Mol Pharmacol. 2006 Apr;69(4):1383-8. Epub 2006 Jan 4. Based on analyses of two-dimensional gel and cDNA microarrays, our laboratory and others have demonstrated that a number of genes show altered expression during the development of cisplatin resistance (CP-r) in human cancer cells, including genes associated with DNA damage repair, proto-oncogenes, apoptosis, stress-response, and transcription factors. To verify these results and find genes that are directly responsible for CP-r, as opposed to those reflecting a secondary response induced by cisplatin treatment or resulting from CP-r, we constructed a retroviral cDNA library in the vector pLNCX2 from KB-CP.5 (KCP.5), a cell line selected in one step after exposure to cisplatin at 0.5 microg/ml. Using a library of cDNAs (1.8 x 10(6) cDNA clones) and an intermittent cisplatin selection system to allow more effective functional cloning, 11 expressed cDNAs were identified in a primary pool of 93,000 transfected cell clones. Metallothionein 2A, a known CP-r gene, was among these 11 genes	2006

	found in the transfectants after CP selection. Several other genes, including those encoding ribosomal proteins (e.g., RPL36) and heat shock protein (e.g., HSP10), were also found among the cisplatin-selected clones. Transfection of either the RPL36 cDNA or HSP10 cDNA conferred on KB-3-1 cells 2.5- to 3-fold resistance to cisplatin by clonogenic assays. A subsequent transfection also identified RPL36 as a CP-r gene. The finding that a ribosomal protein gene, RPL36, contributes to CP-r should stimulate study of the role of ribosomal proteins in multifactorial mechanisms of cisplatin resistance.	
115.	Thirumaran RK, Bermejo JL, Rudnai P, Gurzau E, Koppova K, Goessler W, Vahter M, Leonardi GS, Clemens F, Fletcher T, Hemminki K, Kumar R. Single nucleotide polymorphisms in DNA repair genes and basal cell carcinoma of skin. Carcinogenesis. 2006 Aug;27(8):1676-81. Epub 2006 Feb 25. In addition to environmental exposures like UV radiation and, in some cases, arsenic contamination of drinking water, genetic factors may also influence the individual susceptibility to basal cell carcinoma of skin (BCC). In the present study, 529 cases diagnosed with BCC and 533 controls from Hungary, Romania and Slovakia were genotyped for one polymorphism in each of seven DNA repair genes. The variant allele for T241M (C>T) polymorphism in the XRCC3 gene was associated with a decreased cancer risk [odds ratio (OR), 0.73; 95% confidence interval (CI), 0.61-0.88; P = 0.0007, multiple testing corrected P = 0.004]. The risk of multiple BCC was significantly lower among variant allele carriers than in non-carriers (P = 0.04). Men homozygous for the C-allele for E185Q (G>C) polymorphism in the NBS1 gene showed an increased BCC risk (OR, 2.19; 95% CI, 1.23-3.91), but not women (OR, 0.84; 95% CI, 0.49-1.47). In men, the age and nationality adjusted OR for the genotype CC (XRCC3)/CC (NBS1) was 8.79 (95% CI, 2.10-36.8), compared with the genotype TT (XRCC3)/GG (NBS1). The data from this study show overall risk modulation of BCC by variant allele for T241M polymorphism in XRCC3 and gender-specific effect by E185Q polymorphism in NBS1.	2006
116.	Yih LH, Tseng YY, Wu YC, Lee TC. Induction of centrosome amplification during arsenite-induced mitotic arrest in CGL-2 cells. Cancer Res. 2006 Feb 15;66(4):2098-106. Arsenite-induced mitotic abnormalities result in mitotic death in several cancer cell lines. However, how arsenite induces these effects is not known. We have previously shown that arsenite induces mitotic arrest, mitotic abnormalities, and mitotic death in CGL-2 cells. To further delineate the mechanism of action of arsenite, we examined its effect on centrosome duplication and the possible link between centrosome dysregulation and arsenite-induced mitotic death. Immunofluorescence staining of gamma-tubulin revealed that centrosome amplification was induced in arsenite-arrested mitotic cells but not in nocodazole-arrested cells. When S phase-enriched cells were treated with arsenite, they progressed into and arrested at mitosis and then formed supernumerary centrosomes. A further increase in arsenite-induced centrosome amplification was seen during the prolonged mitotic arrest. The arsenite-induced supernumerary centrosomes might result from uneven fragmentation of centrosome, overexpression of pericentriolar materials, and inhibition of centrosomal coalescence during mitosis. Furthermore, termination of mitotic arrest by treatment of arsenite-arrested mitotic cells with cyclin-dependent kinase 1 inhibitors or by suppression of spindle checkpoint function by small interfering RNA-mediated silencing of BubR1 or Mad2 markedly reduced the induction of centrosome amplification and mitotic death in arsenite-treated cells. These results indicate that centrosome amplification is induced in arsenite-arrested mitotic CGL-2 cells in a spindle checkpoint-dependent manner and is involved in the induction of arsenite-induced mitotic death.	2006
117.	Yu HS, Liao WT, Chai CY. Arsenic carcinogenesis in the skin. J Biomed Sci. 2006 Sep;13(5):657-66. Epub 2006 Jun 29.	2006

	Chronic arsenic poisoning is a world public health issue. Long-term exposure to inorganic arsenic (As) from drinking water has been documented to induce cancers in lung, urinary bladder, kidney, liver and skin in a dose-response relationship. Oxidative stress, chromosomal abnormality and altered growth factors are possible modes of action in arsenic carcinogenesis. Arsenic tends to accumulate in the skin. Skin hyperpigmentation and hyperkeratosis have long been known to be the hallmark signs of chronic As exposure. There are significant associations between these dermatological lesions and risk of skin cancer. The most common arsenic-induced skin cancers are Bowen's disease (carcinoma in situ), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Arsenic-induced Bowen's disease (As-BD) is able to transform into invasive BCC and SCC. Individuals with As-BD are considered for more aggressive cancer screening in the lung and urinary bladder. As-BD provides an excellent model for studying the early stages of chemical carcinogenesis in human beings. Arsenic exposure is associated with G2/M cell cycle arrest and DNA aneuploidy in both cultured keratinocytes and As-BD lesions. These cellular abnormalities relate to the p53 dysfunction induced by arsenic. The characteristic clinical figures of arsenic-induced skin cancer are: (i) occurrence on sun-protected areas of the body; (ii) multiple and recrudescent lesions. Both As and UVB are able to induce skin cancer. Arsenic treatment enhances the cytotoxicity, mutagenicity and clastogenicity of UV in mammalian cells. Both As and UVB induce apoptosis in keratinocytes by caspase-9 and caspase-8 signaling, respectively. Combined UVB and As treatments resulted in the antiproliferative and proapoptotic effects by stimulating both caspase pathways in the keratinocytes. UVB irradiation inhibited mutant p53 and ki-67 expression, as well as increased in the number of apoptotic cells in As-BD lesions which resulted in an inhibitory effect on proliferation. As-UVB interaction provides a reasonable explanation for the rare occurrences of arsenical cancer in the sun-exposed skin. The multiple and recurrent skin lesions are associated with cellular immune dysfunction in chronic arsenism. A decrease in peripheral CD4+ cells was noticed in the inhabitants of arsenic exposure areas. There was a decrease in the number of Langerhans cells in As-BD lesion which results in an impaired immune function on the lesional sites. Since CD4+ cells are the target cell affected by As, the interaction between CD4+ cells and epidermal keratinocytes under As affection might be closely linked to the pathogenesis of multiple occurrence of arsenic-induced skin cancer. In this review, we provide and discuss the pathomechanisms of arsenic skin cancer and the relationship to its characteristic figures. Such information is critical for understanding the molecular mechanism for arsenic carcinogenesis in other internal organs.	
118.	Adonis M, Martínez V, Marín P, Berrios D, Gil L. Smoking habit and genetic factors associated with lung cancer in a population highly exposed to arsenic. Toxicol Lett. 2005 Oct 15;159(1):32-7. In order to find some relationship between genetic differences in metabolic activation and detoxification of environmental carcinogens and host susceptibility to chemically induced cancers, we have investigated the distribution of the GSTM1 null genotype and CYP450 *1A1 MspI polymorphism in lung cancer patients and healthy volunteers of the second region in the north of Chile highly exposed to arsenic. The main sources of environmental arsenic exposure in Chile are copper smelting and drinking water, specially in the second region, the most important copper mining region in the world that shows the highest lung cancer mortality rate in the country (35/100.00). The population of Antofagasta, the main city of the region was exposed between 1958 and 1970 to arsenic concentrations in drinking water of 860 microg/m3, presently declining to 40 microg/m3. For men the MspI CYP1A1 *2A genotype was associated with a highly significant estimated relative lung cancer risk (O.R. = 2.60), but not GSTM1 by itself. The relative lung cancer risk for the combined 2A/null GSTM1 genotypes was 2.51, which increased with the smoking habits (O.R. = 2.98). In the second region the cancer	2005

	mortality rate for As associated cancers, might be related at least part to differences in As biotransformation. In this work we demonstrate that genetic biomarkers such as CYP1A1 2A and GSTM1 polymorphisms in addition to DR70 as screening biomarkers might provide relevant information to identify individuals with higher risk for lung cancer, due to arsenic exposure.	
119.	Amundson SA, Do KT, Vinikoor L, Koch-Paiz CA, Bittner ML, Trent JM, Meltzer P, Fornace AJ Jr. Stress-specific signatures: expression profiling of p53 wild-type and -null human cells. Oncogene. 2005 Jun 30;24(28):4572-9. Gene expression responses of human cell lines exposed to a diverse set of stress agents were compared by cDNA microarray hybridization. The B-lymphoblastoid cell line TK6 (p53 wild-type) and its p53-null derivative, NH32, were treated in parallel to facilitate investigation of p53-dependent responses. RNA was extracted 4 h after the beginning of treatment when no notable decrease in cell viability was evident in the cultures. Gene expression signatures were defined that discriminated between four broad general mechanisms of stress agents: Non-DNA-damaging stresses (heat shock, osmotic shock, and 12-O-tetradecanoylphorbol 13-acetate), agents causing mainly oxidative stress (arsenite and hydrogen peroxide), ionizing radiations (neutron and gamma-ray exposures), and other DNA-damaging agents (ultraviolet radiation, methyl methanesulfonate, adriamycin, camptothecin, and cis-Platinum(II)diammine dichloride (cisplatin)). Within this data set, non-DNA-damaging stresses could be discriminated from all DNA-damaging stresses, and profiles for individual agents were also defined. While DNA-damaging stresses showed a strong p53-dependent element in their responses, no discernible p53-dependent responses were triggered by the non-DNA-damaging stresses. A set of 16 genes did exhibit a robust p53-dependent pattern of induction in response to all nine DNA-damaging agents, however.	2005
120.	Aposhian HV, Zakharyan RA, Chowdhury UK, Avram MD, Wollenberg ML, Hernandez A, Aposhian MM. Arsenic metabolism: Knockout mice and polymorphism studies. Toxicol Sci 2005;84(1-S):272. There are at present questions about how inorganic arsenic metabolism is regulated and why is there variability in the metabolic processing of inorganic arsenic in humans as judged by the concentration of arsenic species excreted in the urine. A critical enzyme in this process is MMA(V) reductase, which reduces arsenate, MMA(V), and DMA(V) to more toxic metabolites. The enzyme has an absolute requirement for GSH. The MMA(V) reductase protein is identical to the most recently discovered glutathione S-transferase omega. Our laboratory has given sodium arsenate to MMA(V) reductase knockout mice and to wild mice. Although exon 3 of the MMA(V) reductase gene has been removed, the livers of wild mice still have 20% of the MMA(V) reductase activity of the knockout mice indicating that another protein may have some supplemental MMA(V) reductase activity. No such studies are available for arsenic methyltransferases. The genetics of these mammalian enzymes is lacking. Polymorphism studies are becoming available to help to decipher and correlate changes in the genes responsible for arsenic metabolism and urinary arsenic species. These studies also will be reviewed.	2005
121.	Benbrahim-Tallaa L, Webber M, Waalkes M. The Role Of The RAS Signaling Pathway In Androgen-Independence Acquired During Arsenic-Induced Malignant Transformation Of Human Prostate Epithelial Cells. Toxicol Sci 2005 Mar;84(1-S):30. In humans progression of prostate cancer to androgen-independence (AI) signals a marked worsening of prognosis, and is linked to autocrine or paracrine growth. Evidence indicates that the androgen receptor (AR) and Ras can be involved in acquired AI in prostate cancer. Inorganic arsenic is a potential human prostate carcinogen but its role in prostate tumor	2005

	progression is undefined. Thus, we studied AI in CAsE-PE cells, a malignant transformant of the non-tumorigenic human prostate epithelial cell line RWPE-1 induced by chronic arsenic exposure. The transformant grew at a much faster rate in complete medium than control cells and also showed sustained growth in steroid-reduced medium. Although similar levels of AR occurred in control and CAsE-PE cells, androgens were less effective in stimulating cell proliferation and AR-related gene expression in CAsE-PE cells. For instance, dihydrotestosterone increased PSA transcript much more in control (4.5- fold) than CAsE-PE (1.5-fold) cells. CAsE-PE cells also showed relatively low levels of growth stimulation by non-androgen steroids, such as estradiol. These data indicate that arsenic did not induce AR over-expression or loss of AR ligand specificity, both of which can occur with acquired AI in prostate cancer. CAsE-PE cells did, however, display constitutively increased expression of unmutated K-Ras (13-fold). Ras is a common component of many signaling pathways activated in advanced prostate cancer. Indeed, events downstream of K-Ras, including A-Raf and B-Raf (both serine-threonine MAP kinases) showed increased constitutive expression in CAsE-PE cells (2.2-fold and 3.2-fold, respectively) compared to control. Thus, arsenic induced malignant transformation is associated with acquired AI in human prostate cells and Ras activation and up-regulation of down-stream pathways appear to correlate with this tumor progression.	
122.	Billings KE, Bredfeldt TG, Zheng XH, Kopplin MJ, Watts GS, Sens DA, Mash EA, Gandolfi AJ. Characterization of human bladder urothelial cells malignantly transformed by arsenite. Toxicol Sci 2005;84(1-S):31. Arsenic is implicated in development of human bladder cancer. Chronic arsenite [As(III)] exposure can cause the malignant transformation of human urothelial cells (UROtsa). Since monomethylarsonous acid [MMA(III)] is reported to be more toxic than As(III) in normal UROtsa cells, studies were undertaken to compare the toxicity of MMA(III) and As(III) between the UROtsa and As(III)-transformed UROtsa cells. MMA(III) and As(III) were equally cytotoxic to normal and transformed cell lines with MMA(III) being 12-fold more toxic. The ability of transformed cells to biotransform As (III) was determined. While the UROtsa cells were found to oxidize and methylate As(III) to As(V), MMA(III), and MMA(V), biotransformation of As(III) by the transformed cells was limited to redox cycling to As(V). Gene expression studies comparing transformed UROtsa to control UROtsa were conducted with a two-fold change/repetition (N=3) for significance($p > 0.05$). Increased expression was seen with genes associated with cell signaling (Ca++ binding protein A8), metabolism/biotransformation (GSH-S-transferase M3), and cell receptors (glypican 3 mRNA). Down regulation was seen in genes related to signal transduction (TTK protein kinase), cell cycle (cyclin A1 and D2), tumor suppressor genes (p53 activated fragment-1), structural and cellular matrix associated proteins (annexin A3 and actin protein 2/3 complex B1), and cell adhesion molecules (metalloproteinase 1 and 2 inhibitor). Studies are underway to transform UROtsa cells with MMA(III) to determine if similar effects will be seen. By characterizing the morphological and genetic differences between the normal and the transformed UROtsa, biomarkers of exposure or injury to the bladder may be identified that can be used in future epidemiological studies.	2005
123.	Bredfeldt TG, Billings KE, Zheng XH, Mash EA, Domann FE, Lau SS, Sens DA, Gandolfi AJ. Arsenite and monomethyl arsonous acid-induced toxicity in human urothelial cells. Toxicol Sci 2005;84(1-S):31. Arsenic is a known bladder carcinogen. However, the mechanism of arsenic-induced bladder injury or carcinogenesis is unknown. Studies investigating gene expression caused by arsenite [As(III)] and monomethylarsonous acid [MMA(III)] exposure in human urothelial (UROtsa) cells revealed the presence of both oxidative stress and protein damage. These results prompted	2005

	the study of reactive oxygen species generation in As(III) and MMA(III)-induced cytotoxicity in UROtsa cells. Reduction of intracellular glutathione levels via administration of buthionine S-Rsulfoximine (25 μM) increased cytotoxicity of MMA(III) and As(III) by 4 and 7 fold, respectively, indicating the critical role of cellular antioxidant status. However, concurrent treatment of UROtsa cells with radical scavengers [DPPD (10 μM and 100 μM) and DMSO (0.1% and 0.5%)] only ameliorated the cytotoxicity of higher concentrations of As(III) and MMA(III). Thus efforts to block the production of As(III) and MMA(III)-induced reactive oxygen species via adenoviral-mediated infection of both superoxide dismutase and catalase are underway. In addition, to demonstrate that As(III) and MMA(III) produce reactive oxygen species and induce oxidative DNA damage, the fluorescent probe CM-H2DCFDA is being used to detect oxyradical production using confocal microscopy and increases in 8-hydroxy- 2-deoxyguanosine (8-OHdG) are being detected via HPLC to illustrate oxidative DNA damage. These studies will improve the understanding of the role reactive oxygen species play in As(III) and MMA(III) toxicity in a target organ cell line.	
124.	Chowdhury UK, Zakharyan RA, Avram MD, Wollenberg M, Hernandez A, Kopplin M, Aposhian HV. Inorganic arsenic biotransformation and MMA(V) reductase/gsto1-1 knockout mice. Toxicol Sci 2005;84(1-S):32. The hypothesis that GSTO1-1 knockout mice biotransformed inorganic arsenic differently than wild mice was tested. In the biotransformation of inorganic arsenic, MMA(V) reductase catalyzes the reduction of arsenate, MMA(V), and DMA(V) to the more toxic arsenic species. MMA(V) reductase and human GST-Omega (hGSTO1-1) are identical proteins. Methods: Male knockout mice, in which Exon 3, of the gene for GSTO1-1 has been eliminated, were injected im with Na arsenate (4.16 mg As per Kg of body weight) and the arsenic species in tissues measured at 0.5, 1, 2, 4, 8, and 12 hours by HPLC-ICP-MS. The wild mice (W) used as controls were DBA/1LacJ. Results: The concentration of arsenate was greatest in the bladder and the kidneys and peaked in these tissues at 0.5 hour. The highest concentration of arsenite was in the kidneys and liver. MMA(V) concentrations were the lowest when compared with the other arsenic species. The highest concentration of MMA (III) was in the kidneys of both KO and W mice. DMA(V) accumulated more in the lungs and bladder, but the concentration of DMA(III) was highest in the bladder for both the KO and W mice. Conclusion: Our results suggest that there were only minor differences in the concentrations of arsenic metabolites in the tissues of KO and W mice. However, the MMA reductase/GSTO1-1 activity in the liver of KO mice was only 20% of that in wild mice. There appears to be another enzyme(s) able to reduce arsenic(V) species but to a small extent.	2005
125.	Davey JC, Ingram L, Batki C, Lariviere J, Hamilton JW. Arsenic Causes Dose-Dependent Enhancement And Suppression Of Retinoic Acid Receptor (RAR)-Mediated Gene Activation. Toxicol Sci 2005 Mar;84(1-S):28. Chronic exposure to arsenic is a significant human health threat and is associated with increased risks of various cancers, diabetes, heart disease, reproductive and developmental problems and other diseases. We previously demonstrated that arsenic acts as a potent endocrine disruptor at very low levels, altering steroid signaling at the level of receptor-mediated gene regulation for all five steroid receptors (i.e., ER, PR, GR, MR, AR). The goal of these studies was to investigate the effects of arsenic on other members of the nuclear receptor superfamily: in particular, the Retinoic Acid Receptor which is a type II receptor that is normally a heterodimer of the ligand- activated Retinoic Acid Receptor (RAR) and the common binding partner, Retinoic Acid X Receptor (RXR). Human NT2 cells were treated with 0.01 to 5 M sodium arsenite (As) for 24 hr, with or without the RAR ligand, all-trans retinoic acid (ATRA). Gene expression was measured in a transiently transfected RARE-luciferase construct or in the endogenous retinoid-inducible CYP26A1 gene. ATRA at 10 nM	2005

	(EC50) induced RARE-luc expression by 20-fold and CYP26A1 by 10-fold. Arsenic co-treatment increased ATRA induction of RAREluc by approximately 1.5-fold at the lowest As concentrations of 0.01 to 0.25 μM; whereas As above 1 μM caused a 40% decrease in ATRA-inducible expression. Similar results were seen with the CYP26A1 gene. Arsenic alone at 2 μM suppressed basal expression by approximately 50%. These results are essentially identical to those previously obtained for steroid receptor-mediated gene expression, indicating that arsenic has widespread effects on at least two classes of nuclear hormone receptors. These endocrine disrupting effects, particularly at the very low doses used, may by important for understanding the wide array of pathophysiological processes linked with chronic low level inorganic arsenic exposure. In addition, these results suggest there may be different patterns of biological responses at different exposure concentrations.	
126.	Dopp E, Hartmann LM, Florea AM, von Recklinghausen UV, Rauen U, Rettenmeier AW, Hirner AV. Uptake of inorganic and organic derivatives of arsenic and association with genotoxic effects in mammalian cells *in vitro*. Toxicol Sci 2005;84(1-S):371. The aim of our study was the elucidation of the uptake capabilities of different cell types in relation to the toxic effects of inorganic arsenic and its methylated metabolites. Chinese hamster ovary cells (CHO-9), human hepatoma cells (Hep G2) and primary rat hepatocytes (pRH) were exposed to arsenate [i-As(V)], arsenite [i- As(III)], monomethylarsonic acid [MMA(V)], monomethylarsonous acid [MMA(III)], dimethylarsinic acid [DMA(V)], dimethylarsinous acid [DMA(III)], trimethylarsen oxide [TMAO(V)] for 1 h.The chemicals were applied at different concentrations (0.1 microM to 10 mM) and cellular uptake was measured by ICPMS. Genotoxic effects were assessed in CHO-9 cells by micronucleus (MN) assay, chromosome aberrations (CA) and sister chromatid exchanges (SCE). Thiobarbituric acid-reactive substances (TBARS) were determined as indication for the formation of reactive oxygen species. Our results show that pRH are most active in cellular uptake of metal(loid)s followed by Hep G2 and CHO cells. Also, the highest generation of products of lipid peroxidation was found in pRH compared to Hep G2 and CHO-9. MMA(III) and DMA(III) induced genotoxic effects even more pronounced than i-As(V) or i-As(III). A significant increase in the number of MN, CA and SCE was found in CHO cells for DMA(III), MMA(III), i-As(III) and i-As(V). Altogether, we have shown that arsenic compounds in the trivalent oxidation state are better membrane permeable than the pentavalent species. The release of free radicals caused by organo-arsenicals might contribute to the damage of liver cells. This cell damage is dependent upon the uptake capabilities and the cellular extrusion mechanism.	2005
127.	Drobna Z, Waters SB, Devesa V, Harmon AW, Thomas DJ, Styblo M. Metabolism and toxicity of arsenic in human urinary bladder epithelial cells expressing rat arsenic (+3)-methyltransferase. Toxicol Sci 2005;84(1-S):31. The enzymatic methylation of inorganic arsenic (iAs) is catalyzed byarsenic (+3)-methyltransferase (AS3MT). AS3MT is expressed in rat liver and in human hepatocytes but not in a human urothelial cell line (UROtsa), which does not methylate iAs. Thus, UROtsa cells are an ideal null background in which the role of iAs methylation in the modulation of toxic and cancer promoting effects of this metalloid can be examined. A retroviral gene delivery system was used in this study to create a clonal UROtsa cell line (UROtsa/F35) that expresses rat AS3MT. The metabolism and cytotoxicity of arsenite (iAsIII) and methylated trivalent arsenicals were characterized in both UROtsa and UROtsa/F35 cells. In contrast to parental cells, UROtsa/F35 cells methylated iAsIII, yielding methylarsenic (MAs) and dimethylarsenic (DMAs) that contained either AsIII or AsV. When exposed to MAsIII UROtsa/F35 cells produced DMAsIII and DMAsV. MAsIII and DMAsIII were more cytotoxic than iAsIII in both URotsa and UROtsa/F35 cells. The greater cytotoxicities of MAsIII and DMAsIII as compared to iAsIII were associated with greater cellular retention of both	2005

	methylated trivalent arsenicals. Notably, UROtsa/F35 cells were more sensitive than UROtsa cells to the cytotoxic effects of iAsIII, but were more resistant to the cytotoxicity of MAsIII. Increased toxicity of iAsIII in UROtsa/F35 cells was associated with inhibition of DMAs production and intracellular accumulation of MAs at high exposure levels. The resistance of UROtsa/F35 cells to moderate concentrations of MAsIII was linked to a rapid conversion of MAsIII to DMAs and efflux of DMAs. However, concentrations of MAsIII that inhibited DMAs production by UROtsa/F35 cells were equally toxic for both cell lines. Thus, the extent of the production and accumulation of MAsIII is a key factor that determines the toxicity of iAs in methylating cells.	
128.	Fukushima S, Morimura K, Wanibuchi H, Kinoshita A, Salim EI. Current and emerging challenges in toxicopathology: carcinogenic threshold of phenobarbital and proof of arsenic carcinogenicity using rat medium-term bioassays for carcinogens. Toxicol Appl Pharmacol. 2005 Sep 1;207(2 Suppl):225-9. For the last 25 years, Prof. Nobuyuki Ito and his laboratory have focused on the development of liver medium-term bioassay system for detection of carcinogens in F344 rats utilizing glutathione S-transferase placental form (GST-P)-positive foci as an end point marker. In this presentation, the outline and samples of medium-term bioassay systems were described. Furthermore, our data demonstrated the presence of a threshold for the non-genotoxic carcinogen, phenobarbital (PB), and the lack of linearity in the low-dose area of the dose-response curve, providing evidence for hormesis. In addition, the establishment and applications of multiorgan carcinogenicity bioassay (DMBDD model), used for the examination of the carcinogenicity of genotoxic and non-genotoxic chemicals, are discussed. Dimethylarsinic acid, one of organic arsenics, was found to be carcinogenic in rat bladder using DMBDD model and carcinogenicity test.	2005
129.	Gregus Z, Nemeti B. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as an arsenate reductase in human red blood cells (HRBC) and rat liver cytosol (RLC). Toxicol Sci 2005;84(1-S):31-2. The mechanism for reduction of arsenate (AsV) to the more toxic arsenite (AsIII) is unknown. Purine nucleoside phosphorylase (PNP) works as an arsenate reductase (AsVR) in vitro, however, it appears irrelevant in vivo (Nemeti et al., Toxicol. Sciences. 74: 22, 2003). The accompanying poster (Nemeti and Gregus) demonstrated that hRBC lysate and rLC contain a PNP-independent AsVR activity that is supported by glutathione (GSH), NAD and glycolytic substrates, especially phosphoglyceric acids (PGA). Because NAD is substrate for GAPDH, whereas 3-PGA is substrate for phosphoglycerate kinase (PGK), the roles of these two functionally linked glycolytic enzymes in AsV reduction have been tested. AsIII formed in the assays from AsV was quantified by HPLC-hydride generation-atomic fluorescence spectrometry. A mix of purified GAPDH and PGK catalyzed GSH-dependent reduction of AsV, provided NAD was present and GAPDH was supplied with a glycolytic substrate, either with glyceraldehyde 3-phosphate (Ga3P) directly or indirectly by PGK (from 3-PGA and ATP). It was also shown that GAPDH (purifed from rabbit muscle or hRBC) alone exhibited AsVR activity that depended on the enzyme concentration, was enhanced in a concentration-dependent manner by its substrates (Ga3P, NAD) as well as GSH, and was strongly inhibited by NADH. Koningic acid, a selective GAPDH inhibitor, decresed both the classical enzymatic activity and the AsVR activity of rabbit muscle GAPDH in a concentration-dependent manner, abolishing both activities at 25 mM. Koningic acid also decreased both the GAPDH and the AsVR activities of intact hRBC, hRBC lysate and rLC, at high concentration abolishing AsIII formation in intact hRBC, almost completely inhibiting it in hRBC lysate and partially inhibiting it in rLC. Thus, GAPDH works as a GSH-dependent AsVR; it appears largely responsible for the PNP-independent AsVR activity in hRBC and partly responsible for such	2005

	activity in rLC. The in vivo relevance of GAPDH as an AsV reductase remains to be tested.	
130.	Han S, Vallyathan V. Comparison of metals in cytotoxicity, free radical generation, and heat shock protein expression in a human bronchial epithelial cell line, BEAS-2B. Toxicol Sci 2005;84(1-S):237. A number of toxic heavy metals such as arsenic (As), chromium (Cr), cadmium (Cd), mercury (Hg), nickel (Ni), vanadium (V), and manganese (Mn) are widely used in occupational settings, and exposure to these metals is associated with the development of pulmonary disease. Cytotoxicity,apoptosis, and reactive oxygen species (ROS) generation were tested to compare the biological reactivity of these heavy metals using a human bronchial epithelial cell line, BEAS-2B. Also, heat shock protein 70 (Hsp70) expression was observed as an early and sensitive biomarker of cellular stress. Exposure to metals (50 microM) for 24 hr caused significant cytotoxicity for all the metals tested. Among the metals tested, As (20%), Cr (10%), Cd (30%), and Mn (44%) showed less than 50% survival rate compared to control cells. Apoptosis was significantly increased in the cells exposed to 50 microM of As (2.2-fold), Cr (4.5-fold), and Cd (2.5-fold). Intracellular ROS generation has the capacity to induce DNA damage, alter signal transduction, and cause lipid peroxidation leading to either apoptosis or carcinogenesis. Electron spinresonance (ESR) was used to detect short-lived free radical intermediates generated in the reaction of metal with cells. Hydroxyl radical generation was greater in the presence of As, Cr, Cd, and Hg compared to the other metals. As, Cd, and Hg showed a high expression of Hsp70 protein in Western blotting and ELISA while Cr, Ni, V, and Mn did not show any significant increase of Hsp70 protein. These results suggest that both cytotoxicity and apoptosis were significant with all metals tested; however As, Cd, Cr, and Hg were relatively most toxic metals tested. Generation of ROS may be involved in metal induced lung cell damage. Metal-induced Hsp70 expression could be a sensitive indicator of lung cell injury by As, Cd, and Hg.	2005
131.	Hansen JM, Jones DP. Metal-induced oxidation of Thioredoxin-1 And Thioredoxin-2. Toxicol Sci 2005;84(1-S):237. Exposure to metals can elicit numerous deleterious effects leading to apoptosis, carcinogenesis and a variety of other diseases. Some metals have been described as being reactive and binding to free sulfhydryls en route to toxicity. While much data has been collected regarding the effects of metals on glutathione, the primary intracellular antioxidant, very little is known about the effects of metals on another important intracellular antioxidant system, the thioredoxin system. Here, we evaluate the effects of arsenic, cadmium, cesium, copper, iron, mercury, nickel and zinc on cytoplasmic/nuclear thioredoxin-1 (Trx1) and mitochondrial thioredoxin-2 (Trx2)redox states. HeLa cells were grown to 80% confluence and then treated with either 10 or 100 μM of each metal listed above for 4 h. Cells were collected and derivatized with iodoacetic acid for Trx1 and 4-acetamido-4'-maleimidylstilbene-2, 2'-disulfonic acid (AMS) for Trx2 and analyzed following separation of the reduced and oxidized forms via redox Western techniques. Trx1 was significantly oxidized up to +30 mV from control (-278 mV) with arsenic, cadmium and mercury. The other metals tested showed no Trx1 effects. Similarly, arsenic, cadmium and mercury significantly oxidized Trx2 (-352 mV in controls) but significant oxidation was also noted with cesium as well. Copper, iron, nickel and zinc showed no Trx2 effects. Mitochondria are believed to be protected by metallothionein during the toxic, oxidative effects of some metals, including cadmium and mercury. Our findings show that metal exposure can cause both cytoplasmic/nuclear and mitochondrial oxidation as principal effects of metal toxicity.	2005
132.	Hays A, Pandey R, Ahmed R, Andrew AS, Hamilton JW, Lantz C. Determination of Transcription factors important in arsenic-induced alterations in gene expression. Toxicol Sci 2005;84(1-S):32-3.	2005

	Chronic arsenic ingestion has been linked with an increased incidence of cardiovascular and vascular disease and cancer in multiple organs, including the lung. What remains unclear are the disease risks and biological effects associated with chronic ingestion of arsenic at lower levels commonly found in the water supplies of the United States. To investigate these effects, C57BL/6 mice ingested drinking water with or without 50 ppb arsenic for five or eight weeks. RNA from three control and three arsenic exposed animals was labeled and hybridized on six independent Affymetrix mouse 430(A) arrays, each containing over 14 k full length genes. Signals were normalized and statistical analysis for differential gene expression between the control and arsenic exposed groups was assessed. The genes with changing expression levels are involved in a variety of functional groups including: structural regulation, chaperones, receptors, signal transduction and immunological pathway members, cytokines, and enzymes. These data indicate that significant biological effects occur at drinking water arsenic concentrations routinely found throughout the US To investigate regulation of these genes we used TRANSFAC® analysis tool, which provides comprehensive information on gene regulation at the level of transcription, which is generally considered the most important step in controlling gene expression. We examined transcription factors that were exclusively associated with either arsenic-induced up regulated genes or with arsenic-induced down regulated genes. Of interest were the zinc fingers, MAP kinase, and stress-induced transcription factors that were associated with arsenic-induced down regulated genes. These included: KR, GATA-1, GBF, Ttk69K, CBF1, SRF, TGA1A, and v-Maf. These data indicate that arsenic may down regulate gene expression by affecting transcriptional activation.	
133.	Karagas MR, Park S, Nelson HH, Andrew AS, Mott L, Schned A, Kelsey KT. Methylenetetrahydrofolate reductase (MTHFR) variants and bladder cancer: a population-based case-control study. Int J Hyg Environ Health. 2005;208(5):321-7. Functional variants in the methylenetetrahydrofolate reductase (MTHFR) gene, including the 677C>T and 1298A>C polymorphisms, have been associated with a moderately reduced risk of several cancers, including colorectal cancers. While recent studies have investigated the role of these polymorphisms on bladder cancer susceptibility, results have been mixed. To clarify the role of MTHFR polymorphisms on bladder cancer risk, we genotyped MTHFR 677C > T and MTHFR 1298A > C in a population-based study of bladder cancer of 352 patients and 551 controls from New Hampshire, USA. The allelic frequency was 35.6% for MTHFR 677C>T and 40.4% for MTHFR 1298A > C among controls. We found no evidence of a main gene effect for either polymorphism (adjusted OR for MTHFR 677C>T variants versus the reference genotype = 1.1; 95% CI, 0.8-1.4 and adjusted OR for MTHFR 1298A>C variants versus the reference genotype = 1.0; 95% CI, 0.7-1.4). Odds ratios did not appear to differ by smoking status or gender. We observed differences in the risk estimates for the MTHFR polymorphisms by arsenic exposure, but they were not statistically significant (P = 0.67 for MTHFR 677C > T and P = 0.12 for MTHFR 1298A>C). Thus, our findings do not support the presence of a main gene effect. The possibility that MTHFR polymorphism affects susceptibility to environmental exposures warrants further consideration.	2005
134.	Kelsey KT, Hirao T, Hirao S, Devi-Ashok T, Nelson HH, Andrew A, Colt J, Baris D, Morris JS, Schned A, Karagas M. TP53 alterations and patterns of carcinogen exposure in a U.S. population-based study of bladder cancer. Int J Cancer. 2005 Nov 10;117(3):370-5. The molecular pathology of bladder cancer has been the subject of considerable interest, and current efforts are targeted toward elucidating the interrelationships between individual somatic gene loss and both etiologic and prognostic factors. Mutation of the TP53 gene has been associated with more invasive bladder cancer, and evidence suggests that TP53 mutation, independent of stage, may be predictive of outcome in this disease. However, there is no	2005

	consensus in the literature that bladder carcinogen exposure is associated with inactivation of the TP53 gene. Work to date has been primarily hospital based and, as such, subject to possible bias associated with selection of more advanced cases for study. We examined exposure relationships with both TP53 gene mutation and TP53 protein alterations in a population-based study of 330 bladder cancer cases in New Hampshire. Tobacco smoking was not associated with TP53 alterations. We found a higher prevalence of TP53 inactivation (i.e., mutation and nuclear accumulation) among hair dye users (odd ratio [OR] = 4.1; 95% confidence interval [CI] 1.2-14.7), and the majority of these mutations were transversions. Men who had "at risk" occupations were more likely to have mutated TP53 tumors (OR = 2.9; 95% CI 1.1-7.6). There also was a relative absence of TP53 mutation (OR = 0.4; 95% CI 0.0-2.9) and TP53 protein alterations (OR = 0.6; 95% CI 0.3-1.4) in bladder cancers from individuals with higher arsenic exposure. Our data suggest that there is exposure-specific heterogeneity in inactivation of the TP53 pathway in bladder cancers and that integration of the spectrum of pathway alterations in population-based approaches (capturing the full range of exposures to bladder carcinogens) may provide important insights into bladder tumorigenesis. (c) 2005 Wiley-Liss, Inc.	
135.	Khuda-Bukhsh AR, Pathak S, Guha B, Karmakar SR, Das JK, Banerjee P, Biswas SJ, Mukherjee P, Bhattacharjee N, Choudhury SC, Banerjee A, Bhadra S, Mallick P, Chakrabarti J, Mandal B. Can homeopathic arsenic remedy combat arsenic poisoning in humans exposed to groundwater arsenic contamination?: a preliminary report on first human trial. Evid Based Complement Alternat Med. 2005 Dec;2(4):537-48. Epub 2005 Oct 19. Groundwater arsenic (As) has affected millions of people globally distributed over 20 countries. In parts of West Bengal (India) and Bangladesh alone, over 100 million people are at risk, but supply of As-free water is grossly inadequate. Attempts to remove As by using orthodox medicines have mostly been unsuccessful. A potentized homeopathic remedy, Arsenicum Album-30, was administered to a group of As affected people and thereafter the As contents in their urine and blood were periodically determined. The activities of various toxicity marker enzymes and compounds in the blood, namely aspartate amino transferase, alanine amino transferase, acid phosphatase, alkaline phosphatase, lipid peroxidation and reduced glutathione, were also periodically monitored up to 3 months. The results are highly encouraging and suggest that the drug can alleviate As poisoning in humans.	2005
136.	Kitchin KT, Wallace KA. Arsenite Binding To Subsets Of The Human Estrogen Receptor-alpha. Toxicol Sci 2005 Mar;84(1-S):30. Enzyme inhibition by arsenicals has been described many times, but the underlying binding of trivalent arsenicals to peptides and proteins has received little attention. The purpose of this study was to determine Kd and Bmax values for arsenite binding to nine synthetic peptides (up to 25 amino acids long) which contained between 0 and 4 sulfhydryls. We selected the human estrogen receptor-á protein for study because arsenite is a potential nonsteroidal environmental estrogen and several interactions between arsenic exposure, estrogenicity and carcinogenicity are known. We utilized radioactive 73As labeled arsenite and vacuum filtration methodology to determine the binding affinity of arsenite to synthetic peptides based on a zinc finger region containing up to 4 free sulfhydryls and the estrogen binding region containing up to 3 free sulfhydryls. In our studies, amino acids other than cysteine (including methionine and histidine) did not bind arsenite. Peptides modeled on the estrogen receptor with two or more nearby free sulfhydryls (2 or 5 intervening amino acids) had Kd values in the 1-4 uMolar range. Peptides containing a single sulfhydryl or two sulfhydryls spaced 17 amino acids apart had higher Kd values in the 100-200 uMolar range, demonstrating lower affinity. With the exception of peptide 24 which had an unusually high Bmax value of 234 nmol/mg, the binding capacity of the studied peptides was proportional to the number of free cysteines. Based on our experimental Kd values and published literature values for tissue sulfhydryls, 99% or more of	2005

	arsenite in vivo should be bound to tissue sulfhydryls and not free. The binding of trivalent arsenicals to protein sulfhydryl groups and the ensuing enzyme inhibition and altered biological function can initiate at least five proposed modes of arsenic's carcinogenic action - induced chromosomal abnormalities, altered DNA repair, altered DNA methylation patterns, altered growth factors and enhanced cell proliferation.	
137.	Kligerman AD, Doerr CL, Tennant AH. The role of valence and methylation state on the activity of arsenic during mitosis. Toxicol Sci 2005;84(1-S):32. Trivalent methylated arsenicals are much more potent DNA damaging agents, clastogens, and large deletion mutagens than are their inorganic and pentavalent counterparts. Previously, we had noticed that many of the arsenicals induced "c-type" anaphases characteristic of spindle poisons. In the present study, we exposed human lymphoblasts for 6 h to six arsenicals: sodium arsenate (NaAs5), sodium arsenite (NaAs3), monomethylarsonic acid (MMA5), monomethylarsonous acid (MMA3), dimethylarsinic acid (DMA5), and dimethylarsinous acid (DMA3). Slides were then prepared, and the mitotic indices (MI) were calculated. NaAs5 caused a small but significant increase in MI. MMA5 also caused only a slight increase in MI that just reached statistical significance. In contrast, DMA5 caused a highly significant increase in MI producing ~75% the MI of demecolcine, the positive control. NaAs3 had no significant effect on MI and was quite toxic. MMA3 induced more than a twofold increase in MI compared to the control. DMA3 gave inconsistent results. We also exposed each arsenical directly to tubulin and spectrophotometrically measured the effect on polymerization. None of the pentavalent arsenicals had a substantial effect on polymerization of tubulin. In contrast, NaAs3 inhibited polymerization at 1 mM and above, and MMA3 and DMA3 at 10 µM and above. Taken together, these results give a complex picture of how arsenicals may affect cells. Some are cytotoxic, which may prevent the cells from cycling, thereby reducing the MI. Simultaneously, at lower concentrations, these same arsenicals may react with the spindle and cause an apparent increase in MI by arresting the cells at metaphase or anaphase. Thus, the metabolites of arsenic are active not only as chromosome breaking and DNA damaging agents but can also interfere with cell division. They can effect this through interaction with the spindle potentially leading to aneuploidy, a common driving force in genomic instability and ultimately in tumor formation.	2005
138.	Kobayashi Y, Hayakawa T, Hirano S. Arsenic methyltransferase Cyt19 expression and activity in rat tissues. Toxicol Sci 2005;84(1-S):32. Inorganic arsenicals such as arsenite (iAsIII) and arsenate (iAsV) are well-known worldwide environmental contaminants and human carcinogen. Arsenic is known to be metabolized by repetitive reduction and methylation, and excreted mainly in urine as methylated arsenicals such as monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV). Although it has been known that the arsenic methylation is catalyzed by arsenic methyltransferase, Cyt 19, very little is known about characteristics of the enzyme. In the present study we report gene expression and enzyme activity of Cyt19 in rat tissues. We investigated mRNA and protein levels of Cyt19 in rat tissues, such as heart, brain, spleen, lung, liver, skeletal muscle, kidney and testis, by Northern and Western analysis, respectively. The rat tissues cytosol was incubated at 37 °C for 3 h with 10 µM iAsIII, 5 mM GSH and 1 mM Sadenosyl- L-methionine in 75 mM phosphate buffer (pH 7.0). The reaction was stopped by boiling the reaction mixture for 5 min, and then treated with H2O2 to oxidize all arsenicals to pentavalency. The metabolites, MMAV and DMAV, were analyzed on a reversed phase column by high-performance liquid chromatographyinductively coupled argon plasma mass spectrometry (HPLC-ICP MS). Both mRNA and protein levels were highest in the liver. The intermediate expression of Cyt19 mRNA was observed in heart and testis. However, arsenic methylating activity was detected only in the liver cytosol using the current HPLC-ICP MS method.	2005

139.	Lantz C, Petrick JS, Hays AM. Altered protein expression following in utero exposure to arsenic. Toxicol Sci 2005;84(1-S):30. Inorganic arsenic is a known human carcinogen and common drinking water contaminant affecting millions of people worldwide. Though the effects of maternal arsenic exposure on the developing lung are unknown, this metalloid is known to cross the placenta. Using an in utero exposure model, we have previously identified genes that are altered by exposure to arsenic in the maternal drinking. A more complete understanding of the in utero effects of arsenic requires analysis of alterations in protein expression. We hypothesize that in utero exposure to inorganic arsenic through maternal drinking water causes altered protein expression in the developing lung, indicative of downstream molecular and functional changes. From conception to embryonic day eighteen, we exposed pregnant Sprague-Dawley rats to 500 parts per billion arsenic (as arsenite) via the drinking water. Protein was isolated from a single pup from 3 separate arsenic exposed liters. Protein was also isolated from three control pups (each pup from a different liter). Samples were pooled and arsenic-induced alterations in protein expression were determined using BD Power Blot analysis. This technique can analyze over 1000 separate proteins. Blots were run in triplicate and protein content was measured using densitometry. Each of the treated blots was compared against each of the control blots. Only those proteins in which expression was 1.25 up or down regulated by arsenic in each sample were considered as being altered. Thirty five proteins or posttranslationally modified proteins were identified as being altered (21 up- and 14 down-regulated). Analysis of potential protein function indicated that nucleus/nuclear transport proteins, cancer related proteins, tyrosine kinase substrates and cytoskeleton related proteins were altered by arsenic. The present study shows that arsenic induces alterations in protein levels in the developing lung. These data may be useful in the elucidation of molecular targets and biomarkers of inorganic arsenic exposure during lung development.	2005
140.	Liu CW, Huang FM, Hsueh YM. Revised cancer risk assessment of inorganic arsenic upon consumption of tilapia (Oreochomis mossambicus) from blackfoot disease hyperendemic areas. Bull Environ Contam Toxicol. 2005 Jun;74(6):1037-44. No abstract	2005
141.	Liu J, Benbrahim-Tallaa L, Xie Y, Qian X, Qu W, Otstot J, Waalkes M. Further Studies On Aberrant Gene Expression In Arsenic-Induced Malignant Transformation Of Liver Epithelial Cells. Toxicol Sci 2005 Mar;84(1-S):29. Inorganic arsenic induces liver tumors in humans and rodents. In prior research we found chronic exposure (> 18 wk) of rat liver epithelial TRL1215 cells to low level arsenite (500 nM) induces malignant transformation. Initial microarray studies revealed changes in gene expression in these chronic arsenic exposed (CAsE) cells that warrant further study. Real-time RT-PCR showed large increases in CAsE cell stress-response genes like glutathione S-transferase-pi (GST-pi, 3-fold), heme oxygenase- 1 (4-fold), superoxide dismutase-1 (5-fold) and metallothionein-1 (MT-1; 4- fold) compared to control. The positive cell-cycle regulatory genes cyclin D1 (10- fold) and PCNA (3-fold) were overexpressed in CAsE cells, while negative regulatory genes p21 (30% of control) and p16 (1%) were markedly depressed. In CAsE cells c-jun, c-met, c-myc,Wilms tumor protein-1 (WT-1) and alpha-fetoprotein (AFP) expression increased from 3 to 13-fold, while expression of insulin-like growth factor II (IGF-II) and fibroblast growth factor (FGF) were abolished. Western-blot analysis confirmed increases in GST-pi, WT-1, AFP and decreases in p16 and p21 protein. MT overexpression was not due to DNA methylation as bisulfite sequencing showed the MT-1 promoter region was slightly more methylated in CAsE cells than controls. Treatment of CAsE cells with the DNA demethylating agent 5-aza-deoxycytidine (Aza; 2.5 μM, 72 hrs) greatly increased MT-1	2005

	(19- fold) compared to control cells (5-fold), indicating CAsE cells are more sensitive to DNA demethylation stress. Conversely, Aza did not restore expression of p16, IGFII, or FGF to control levels in CAsE cells, indicating suppression was due to factors other than DNA methylation changes. Thus, an intricate variety of gene expression changes occur in arsenic-induced malignant transformation, including oncogene activation and increased and decreased expression of genes critical to growth regulation.	
142.	Lynch JP, Wise SS, Wise JP. Arsenic induces chromosomal and centromeric abnormalities, in human lung cells. Toxicol Sci 2005;84(1-S):31. Arsenic is a known human carcinogen, causing lung and bladder cancer. Studies have shown humans chronically exposed through drinking water, present increased micronuclei in oral mucosal cells, urothelial cells and lymphocytes. However, the genotoxicity of arsenic in human lung cells has not been investigated. Because lung is a major target for arsenic-induced carcinogenicity, we investigated its cytotoxicity, clastogenicity and centromeric effects in human lung fibroblasts. We found that arsenic is cytotoxic to human lung cells in a concentration-dependent manner, with 1, 5 and 10 uM inducing 65, 45 and 25% relative survival, respectively. Arsenic is also clastogenic to human lung cells in a concentration-dependent manner, with 1, 5 and 10 uM damaging 3, 7 and 15% of metaphases, respectively. Arsenic also caused concentration-dependent increases in centromere spreading, c-anaphase chromosomes and endoreduplication in human lung cells. Specifically evaluating cells treated with 5 uM arsenic, we found 16% of metaphases with at least one spread centromere or c-anaphase chromosome. When cells treated with 5 uM arsenic for 24 h were allowed to recover in arsenic free media, 20% fewer centromeric aberrations were noted and a 5% increase in endoreduplicated chromosomes when compared to those exposed to 5 uM arsenic for 24 h. These data suggest centromeric abnormalities and endoreduplication may be causative mechanisms in arsenic- induced lung cancer.	2005
143.	Maharjan M, Watanabe C, Ahmad SA, Ohtsuka R. Arsenic contamination in drinking water and skin manifestations in lowland Nepal: the first community-based survey. Am J Trop Med Hyg. 2005 Aug;73(2):477-9. A community-based, dose-response study on arsenic contamination was conducted in three communities in Terai in lowland Nepal. The arsenic concentration of all the tube wells in use (n = 146) and the prevalence of arsenic-induced skin manifestation among 1,343 (approximately 80% of the inhabitants) subjects indicated the existence of a highly contaminated area in Terai. It was found that overall prevalence of arsenicosis among the subjects > or = 15 years old was 6.9%, which was comparable to those found by the same examiner in arsenic-contaminated areas in Bangladesh, and that males had prevalence a twice as high as females, which could not be explained by the difference in the exposure level.	2005
144.	Martínez V, Creus A, Venegas W, Arroyo A, Beck JP, Gebel TW, Surrallés J, Marcos R. Micronuclei assessment in buccal cells of people environmentally exposed to arsenic in northern Chile. Toxicol Lett. 2005 Feb 15;155(2):319-27. To determine the genotoxic risk associated to environmental arsenic exposure, the frequency of micronuclei in buccal cells (BCMN) of people drinking arsenic-contaminated water has been evaluated. A group of 105 individuals from the Antofagasta region (north Chile), and 102 individuals from the area of Concepcion, used as reference group, were included in the study. Arsenic concentration in drinking water was high (0.75 mg/L) in the Antofagasta area, 75-fold the maximum recommended level by WHO (0.01 mg/L), while the values obtained in Concepcion were significantly lower (0.002 mg/L). Individual measures of arsenic exposure were also determined in fingernails, which clearly confirm the existence of chronic exposure in the sampled populations from the Antofagasta region (10.15 microg/g versus 3.57 microg/g).	2005

	The cytogenetic results indicate that, although the BCMN frequency is higher in exposed than in controls, this increase does not attain statistical significance. When the exposure biomarkers were related with the cytogenetic values, no correlations were observed between BCMN and arsenic content in water or in fingernails. In addition, the genotoxicity values do not seem to be related to the ethnic origin from people belonging to the exposed group. As a conclusion it appears that, in the studied population, the chronic ingestion of arsenic-contaminated water does not induce cytogenetic damage, measured as micronuclei, in the cells of the oral mucous in a significant extent.	
145.	Mitropoulos P, Norman R. Occupational nonsolar risk factors of squamous cell carcinoma of the skin: a population-based case-controlled study. Dermatol Online J. 2005 Aug 1;11(2):5. The purpose of this study was to investigate associations between occupation, nonsolar environmental exposures, and risk of squamous cell carcinoma (SCC) of the skin. Data from the Southeastern Arizona Health Study-2 were used. This was a population-based case-controlled study [n = 795) conducted during 1992-1996 in southeastern Arizona to primarily assess the risk of skin SCC in relation to sun exposure. Multivariate logistic regression was used to calculate odd ratios as the estimate of effect. High-risk occupations were identified through literature review. There was evidence of a slightly elevated risk of skin SCC for subjects reporting a history of construction work (OR = 1.38, 95 % CI = 0.61-3.14), and automobile and machine work (OR = 1.21, 95 % CI = 0.48-3.06) Furthermore, there were no statistically significant associations between risk of skin SCC and history of exposure to specific chemical and other nonsolar environmental agents. A slight indication of increased risk for skin SCC was noted for exposure to nonsolar light (OR = 1.33, 95 % CI = 0.92-2.26), construction/machinery materials (OR = 1.12, 95 % CI = 0.76-1.84), fluorescent light (OR = 1.56, 95 % CI = 0.92-2.61), gypsum (OR = 1.84, 95 % CI = 0.68-5.0), coal tar and dandruff shampoos (OR = 1.28, 95 % CI = 0.85-1.9), and cement dust (OR = 1.81, 95 % CI = 0.90-3.62). A large although statistically insignificant risk was seen for exposure to arsenic (OR = 4.21, 95 % CI = 0.40-43.9) and ethylene glycol (OR = 8.46, 95 % CI = 0.77-92.9). Several of the results of this analysis are consistent with literature and conclusions from previous epidemiological studies. However, lack of power and small sample size deem these results as inconclusive until more research and larger studies are conducted.	2005
146.	Patlolla AK, Tchounwou PB. Cytogenetic evaluation of arsenic trioxide toxicity in Sprague-Dawley rats. Mutat Res. 2005 Nov 10;587(1-2):126-33. Epub 2005 Oct 5. Acute exposure to arsenic trioxide has been reported to induce death and/or multiple organ damage with symptoms including nausea, vomiting, diarrhea, gastrointestinal hemorrhage, cerebral edema, tachycardia, dysrhythmias and hypovolemic shock. Its toxic effects are due to its ability to bind to sulfhydryl groups of proteins and to inhibit energy production. Although the chronic exposure to arsenic trioxide has been linked to various types of cancer, such as skin, liver, lung, bladder and kidney neoplasms, studies of its carcinogenic potential in animals have not been conclusive. In this study, we investigated the genotoxic potential of arsenic trioxide in bone-marrow cells obtained from Sprague-Dawley rats; using chromosomal aberrations (CA), mitotic index (MI) and micronuclei (MN) formation as the toxicological endpoints. Four groups of six male rats each, weighing approximately 60+/-2 g per rat, were injected intraperitoneally, once a day for 5 days with doses of 5, 10, 15 and 20 mg/kg body weight (BW) of arsenic trioxide dissolved in distilled water. A control group was also made of six animals injected with distilled water without chemical. All the animals were sacrificed at the end of the treatment period. Chromosome and micronuclei preparation was obtained from bone-marrow cells following standard protocols. Arsenic trioxide exposure significantly increased the number of structural chromosomal aberrations, the frequency of micronucleated cells and decreased the mitotic index in treated groups when compared with the control group.	2005

	Our results demonstrate that arsenic trioxide has a clastogenic/genotoxic potential as measured by the bone-marrow CA and MN tests in Sprague-Dawley rats.	
147.	Rahman MM, Sengupta MK, Ahamed S, Chowdhury UK, Hossain MA, Das B, Lodh D, Saha KC, Pati S, Kaies I, Barua AK, Chakraborti D. The magnitude of arsenic contamination in groundwater and its health effects to the inhabitants of the Jalangi--one of the 85 arsenic affected blocks in West Bengal, India. Sci Total Environ. 2005 Feb 15;338(3):189-200. To better understand the magnitude of arsenic contamination in groundwater and its effects on human beings, a detailed study was carried out in Jalangi, one of the 85 arsenic affected blocks in West Bengal, India. Jalangi block is approximately 122 km2 in size and has a population of 215538. Of the 1916 water samples analyzed (about 31% of the total hand tubewells) from the Jalangi block, 77.8% were found to have arsenic above 10 microg l(-1) [the World Health Organization (WHO)-recommended level of arsenic in drinking water], 51% had arsenic above 50 microg l(-1) (the Indian standard of permissible limit of arsenic in drinking water) and 17% had arsenic at above 300 microg l(-1) (the concentration predicting overt arsenical skin lesions). From our preliminary medical screening, 1488 of the 7221 people examined in the 44 villages of Jalangi block exhibit definite arsenical skin lesions. An estimation of probable population that may suffer from arsenical skin lesions and cancer in the Jalangi block has been evaluated comparing along with international data. A total of 1600 biologic samples including hair, nail and urine have been analyzed from the affected villages of Jalangi block and on an average 88% of the biologic samples contain arsenic above the normal level. Thus, a vast population of the block may have arsenic body burden. Cases of Bowen's disease and cancer have been identified among adults who also show arsenical skin lesions and children in this block are also seriously affected. Obstetric examinations were also carried out in this block.	2005
148.	Reichard JF, Puga A. Global Changes In Posttranslational Covalent Histone Modifications Mediated By Low-Dose Arsenic. Toxicol Sci 2005 Mar;84(1-S):28. In vitro, arsenic mediates induction of a large number of genes including the oxidative stress-response battery, a hallmark of arsenic exposure. In microarray experiments, arsenic also down-regulates at least as many genes as it induces, suggesting that arsenic triggers substantial alterations to chromatin structure through mechanisms that have yet to be elucidated. Gene promoter elements, when packaged as nucleosomes, exclude DNA-interacting proteins thereby preventing transcription, while active gene transcription necessitates relaxation of chromatin structure to permit protein access. Covalent modifications of promoter-region histones, spanning only a few nucleosomes, occur concomitantly with gene induction or repression. Here we investigate the global effects of low-dose arsenic treatment on covalent histone modifications. In general, acetylation relaxes histone structure permitting access of transcriptional proteins; onversely, deacetylation closes down chromatin structure, impairing transcription. Histones were isolated from human keratinocyte- derived HaCaT cells by acid extraction following exposure to 5 μM arsenic. Reverse-phase high-pressure liquid chromatography (HPLC) was used to separate raw histone extracts into each major histone constituent, namely histones H2A, H2B, H3 and H4. Covalent modifications on each core histone were analyzed by matrix-assisted laser-desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). In some instances, these modifications were confirmed using TAU-PAGE separation and immunoblot identification of specific modifications. The experiments presented here demonstrate that 1) at toxicologically relevant concentrations, arsenic modifies the pattern of covalent histone modification; 2) particular core histones are targets for arsenic-mediated covalent modification; 3) specific amino acid residues in each histone are targets for modification by arsenic.	2005
149.	Rossman TG, Uddin AN, Burns FJ. Prevention of arsenic co-carcinogenesis by selenium compounds. Toxicol Sci 2005;84(1-S):143-4.	2005

	Epidemiological studies show that inorganic arsenic (arsenite, arsenate) in drinking water increases skin, lung, bladder, and possibly other cancer risk in humans, but arsenite alone does not cause skin cancer in animals. Since arsenite is comutagenic and inhibits DNA repair, we hypothesized that arsenite is a cocarcinogen requiring a carcinogenic partner. This concept was tested in hairless mice. Mice given a suberythemic dose of solar UV (3 times a week) and 1.25-5 mg/l sodium arsenite in drinking water for 26 weeks had a dose-related increase in skin cancers compared with mice given solar UV alone. The maximum cocarcinogenic effect occurred at 5 mg/l arsenite. Tumors arising in mice given UV arsenite appeared earlier and were larger and more invasive than those in mice given UV alone. Thus, arsenite may be able to partner with UV or other genotoxic insults to increase various cancers in humans. Selenium deficiency maybe one such insult. It has been suggested that in some parts of the world with high arsenic in the drinking water, the low Se levels in soil may exacerbate the arsenic toxicity and carcinogenicity. In HOS cells, organoselenium compounds blocked both spontaneous and arsenite-induced delayed mutagenesis. In the hairless mouse, the synthetic selenium compound p-XSC prevented the arsenite enhancement of solar UV- induced skin cancer, but had a much smaller effect on UV-induced skin cancer. Selenium is reported to counteract some of the effects of arsenic in vivo and in vitro. We suggest that the antimutagenic effects of selenium may occur via the antioxidant action of selenoproteins. The anticarcinogenic effect may have additional mechanisms that are specific to arsenic-selenium interactions, such as stimulation by selenium of arsenic excretion or other affects on arsenic metabolism.	
150.	Sen B, Grindstaff R, Turpaz Y, Retief J, Wolf DC. Gene expression analysis to identify interspecies concordance of the mechanisms of arsenic-induced bladder cancer. Toxicol Sci 2005;84(1-S):371. Arsenic is a human carcinogen that induces urinary bladder cancer. Several mechanisms have been proposed for arsenic-induced cancer. Although inorganic arsenic (iAs) does not induce tumors in adult rodents, dimethylarsinic acid (DMA), a major metabolite of iAs, is a rat bladder carcinogen. DMA causes a dose-dependent increase in toxicity and induces modulation of genes that control apoptosis, cell proliferation, and the response to oxidative stress in transitional epithelium of the rat urinary bladder. For extrapolation of rat data to human, normal human transitional epithelial cells (Urotsa) were exposed to DMA at 2μM, 20μM, 200μM or 8000μM. Total RNA was isolated and microarray analysis was conducted using the Affymetrix Human U133 Plus 2.0 chips. One way ANOVA identified 1728 genes ($p < 0.05$) out of the 36, 967 known genes on the chip. Global expression changes were further characterized using Expression Analysis Systematic Explorer (EASE). In addition to confirming previously described processes, EASE identified additional pathways including phosphorylation, ion transport, protein synthesis and catabolism that were modulated after DMA exposure. Further analysis using Ingenuity Pathway Analysis suggest that altered ERK/MAPK signaling (ERK1/2, CMYC), apoptosis (CASP3, PARP), Wnt-beta signaling (WNT, AKT), cell cycle regulation (CYCLIN D, CDKN2A), and PI3K/AKT signaling (FRAP1, HSP90) all play a role in DMA induced cellular toxicity. These pathways are consistent with our previous in vivo studies. This study demonstrated that an in vitro human cell system predicted the same key pathways involved in DMA-induced toxicity as was identified after in vivo exposure in rats.	2005
151.	Shen J, Xie Y, Liu J, Diwan B, Waalkes M. Aberrant gene expression in the neonatal mouse lung following in utero exposure to inorganic arsenic. Toxicol Sci 2005;84(1-S):30. Inorganic arsenic is a lung carcinogen in humans. Our prior work showed in utero exposure to arsenic in mice can induce lung cancers in female offspring after they become adults. To define early molecular changes in the lung after in utero arsenic exposure, pregnant C3H mice were	2005

	given carcinogenic doses of arsenic in the drinking water (42.5 and 85 ppm arsenic as sodium arsenite) from day 8 to 18 of gestation and aberrant gene expression was examined in the lungs of female offspring as newborns. Real-time RT-PCR analysis was used to determine expression of thirty-six selected genes associated with carcinogenesis or arsenic exposure. After in utero arsenic exposure, estrogen receptor-alpha (ER-alpha) showed marked, dose-related increases in expression in newborn female lung. Compared to control, pulmonary ER-alpha increased over 9-fold after 42.5 ppm arsenic and over 14-fold after 85 ppm arsenic. Recent clinical evidence indicates ER-alpha overexpression is common in lung tumor specimens from women, and may contribute to gender linked difference in lung cancer risk. Another gene highly overexpressed in female lung after in utero arsenic exposure was alpha-fetoprotein (AFP) which showed a maximum increase in expression of over 11-fold compared to control. AFP is normally a fetal protein that is overexpressed in many tumors, including aggressive lung cancers. AFP is also considered a growth enhancing protein. Other gene expression changes in the lungs of arsenic-treated female newborn mice included increased expression of myc (2-fold), metallothionein-1 (3-fold), glutathione peroxidase (2-fold), betaine-homocysteine S-methyltransferase (10-fold), insulin-like growth factor-1 (IGF-1; 2-fold) and IGF-2 (2-fold). Overexpression of IGF-1 and IGF-2 is common in tumors. Thus, transplacental exposure to arsenic at doses that can be carcinogenic to the female lung produced rapid gene expression changes relevant to pulmonary carcinogenesis, such as increased AFP and ER-alpha.	
152.	Sikder MS, Maidul ZM, Ali M, Rahman MH. Socio-economic status of chronic arsenicosis patients in Bangladesh. Mymensingh Med J. 2005 Jan;14(1):50-3. The study showed that the maximum number of arsenicosis patients (71%) belonged to low income group and 29% belong to middle class income group but none was found in high income group and all these patients were from rural areas of the country. Majority of all these patients was related with the traditional occupation of the country like cultivation (53%) in addition to lower level of educational background (81.5%). Most of the patients of chronic arsenicosis were suffering from malnutrition (91%). The present study which reflects that the vast majority of patients of chronic arsenicosis in the country belonged to low income group, but also to low educational background and individuals, who had been suffering from malnutrition, needs a special consideration in the management of the problem. Emphasis has been given to have access to arsenic-free water and protein rich diet to people of arsenic affected areas.	2005
153.	Spallholz JE, Boylan LM, Palace V, Chen J, Smith L, Rahman MM, Robertson JD. Arsenic and selenium in human hair: a comparison of five countries with and without arsenicosis. Biol Trace Elem Res. 2005 Aug;106(2):133-44. The selenium (Se) content of the diet and/or selenium supplements might have an ameliorating effect on arsenic (As) toxicity as recently shown by Wang et al., Yang et al., and as reviewed by Spallholz et al.. The underlying principles of the ameliorating effect is the complexation of Se with As forming the seleno-bis (S-glutathionyl) arsinium ion excreted in bile and the complexation of Se with As in tissues forming nontoxic insoluble selenides. Additional protection afforded by Se supplementation from arsenicosis could be the elevation of glutathione peroxidase activity reducing the oxidative stress induced by As. The present study assessed the status of Se and As in hair by neutron activation analysis (NAA). Human hair samples were collected from the United States, Canada, The People's Republic of China (PRC), Bangladesh, and Nepal, the latter two countries now engaged in a struggle to find relief from human arsenicosis resulting from extensive domestic groundwater contamination by As. No statistically significant differences were observed in the samples between the Se and As content of hair from, Lubbock, Texas (USA) or Winnipeg, Canada. The concentration of As in	2005

	all hair samples analyzed correlated ($r = 0.960$, $p < 0.001$) with the amount of As in the drinking water. Selenium levels in hair were highest from Nepal. The results demonstrate the viability of hair as a noninvasive biomonitor in assessing aspects of dietary Se and environmental As exposure. The hair data confirmed the known low intake of Se in the Keshan disease area of the PRC, the very high accumulation in hair of As from subjects consuming contaminated groundwaters, and an adequate Se status in subjects from North America consuming municipal water of low As content. The high As content of hair from people in Bangladesh is the result of a high As consumption from contaminated water compounded by a less than desirable intake of Se. From Nepal, the As content of hair corresponded to the known low and high intake of As from contaminated groundwater. The very high Se content found in all hair samples from Nepal might be the result of the use of henna.	
154.	Tollestrup K, Frost FJ, Cristiani M, McMillan GP, Calderon RL, Padilla RS. Arsenic-induced skin conditions identified in southwest dermatology practices: an epidemiologic tool? Environ Geochem Health. 2005 Feb;27(1):47-53. Populations living in the Southwest United States are more likely to be exposed to elevated drinking water arsenic levels compared to other areas of the country. Skin changes, including hyperpigmentation and generalized hyperkeratosis, are the most common signs of chronic arsenic ingestion from drinking water. The purpose of this study was to determine the feasibility of using dermatology practices in New Mexico, Arizona, and western Texas as a surveillance system for arsenical skin disorders related to drinking water. Postcard questionnaires were mailed to practicing dermatologists. The number of cases of arsenical hyperpigmentation/keratoses seen by these dermatologists during the past 10 years and the past year were estimated. Of 240 dermatologists who were mailed questionnaires, 37 reported seeing 237 patients with arsenical hyperpigmentation/keratoses in the past 10 years and 35 patients in the past year. Since approximately one-eighth of dermatologists practicing in the Southwest saw at least one patient with arsenical hyperpigmentation/keratoses during one year, it appears feasible to complete a population-based study of these conditions.	2005
155.	Tseng CH. Blackfoot disease and arsenic: a never-ending story. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2005;23(1):55-74. Blackfoot disease (BFD) is an endemic peripheral vascular disease confined to the southwestern coast of Taiwan. This article reviews the epidemiology, clinical manifestations and diagnosis, pathology, etiology and pathogenesis of this disease. Sporadic cases of BFD occurred as early as in the early 20th century, and peak incidence was noted between 1956 and 1960, with prevalence rates ranging from 6.51 to 18.85 per 1,000 population in different villages. Typical clinical symptoms and signs of progressive arterial occlusion mainly found in the lower extremities, but in rare cases, the upper extremities might also be involved. Ulceration, gangrene and spontaneous or surgical amputation were typical fate. An extensive pathological study concluded that 30% of the BFD patients had histologic lesions compatible with thromboangiitis obliterans and 70% showed changes of arteriosclerosis obliterans. Epidemiologic studies carried out since mid-20th century revealed that BFD was associated with the consumption of inorganic arsenic from the artesian wells. Recent studies confirmed the existence of preclinical peripheral vascular disease, subclinical arterial insufficiency and defects in cutaneous microcirculation in the residents of the endemic villages. A more recent study suggested that the methylation capacity of arsenic can interact with arsenic exposure in the development of peripheral vascular disease among residents of BFD-endemic areas. The incidence of BFD decreased dramatically after the implementation of tap water in these villages over the past 2-3 decades. The atherogenicity of arsenic could be associated with its effects of hypercoagulability, endothelial injury, smooth muscle cell proliferation, somatic mutation, oxidative stress, and apoptosis. However, its interaction with some trace elements	2005

	and its association with hypertension and diabetes mellitus could also explain part of its higher risk of developing atherosclerosis. Although humic substances have also been suggested as a possible cause of BFD, epidemiologic studies are required to confirm its etiologic role.	
156.	Xie Y, Liu J, Benbrahim-Tallaa L, Diwan B, Waalkes M. Analysis Of Global And Gene Specific Dna Methylation In Livers Of Newborn Mice Transplacentally Exposed To A Carcinogenic Dose Of Arsenic. Toxicol Sci 2005 Mar;84(1-S):29. Arsenic is a human carcinogen that can target the liver. Our prior work has shown that exposure of pregnant mice to inorganic arsenic induces a high incidence of liver tumors in male offspring when they reach adulthood. Initial analysis of newborn mice exposed to a hepatocarcinogenic dose of arsenic in utero revealed remarkable gene expression changes. Some evidence indicates arsenic can alter gene expression by altering DNA methylation. Thus, this study examined early DNA methylation changes in arsenic-induced transplacental hepatocarcinogenesis. Pregnant mice received drinking water containing 85 ppm arsenic (as sodium arsenite) or unaltered water (control) from gestation day 8 to 18. Liver samples were taken from newborn males, and global genomic DNA methylation was determined by the methyl acceptance assay. Arsenic exposure in utero did not alter hepatic global DNA methylation in the newborn. Methylation in GC-rich regions was assessed using amplification of genomic DNA digested with methyl-sensitive restriction enzymes. Arsenic exposure resulted in 5 distinct regions of reduced methylation and 2 regions of increased methylation in GC-rich sites. PCR analysis of hepatic Ha-ras following methylation-sensitive enzyme digestion of DNA showed reduced methylation of a key CpG island after arsenic exposure. Although arsenic induced metallothionein-I (MT-I) overexpression, both methylation specific PCR and DNA sequencing following sodium bisulfite indicated the promoter region of MT-I gene was un-methylated in control and arsenic-treated mice, suggesting mechanisms other than methylation regulate arsenic-induced MT overexpression. Overall, hepatic global genomic DNA methylation status was not altered by arsenic, but GC rich methylation appeared reduced. Changes in gene specific methylation depended on the gene in question.	2005
157.	Zheng X, Bredfeldt TG, Watts GS, Gandolfi A. Toxicogenomical study on human bladder epithelium exposed to arsenic. Toxicol Sci 2005;84(1-S):238. In this study, human urothelium (UROtsa) cells were exposed to arsenite [As(III)- 30 μM], monomethylarsenous acid [MMA(III)1-5 μM], or buthionine sulfoximine [BSO-25 μM] followed by [As(III)-1μ M] for up to 18 hr and the changes in gene expression determined by using a human oligonucleotide chip (18, 861 genes). The hybridizations were performed at least three times using independent total RNA preparations to ensure reproducibility. Differentially expressed genes were identified based on 2-fold cut off and gene significantly different from the control cells (t-test analysis, $p < 0.05$). Only up-regulated genes have been assessed. Both As(III) and MMA(III) treatments produce an oxidative stress response. Interestingly, MMA(III) exposure for 6 hr did not induce any metallothionein genes but induced numerous unique genes [such as dual specificity phosphatase (DUSP1, DUSP2); CDC like kinase (CLK1); DNA damage inducible transcript (DD1T3)] and even caused greater increases in stress genes [e.g. heat shock protein (HSPA6, HSPA1A); DnaJ(HSP40)]. Reduction in cellular GSH content via BSO treatment followed by As(III) exposure for 6 hr exacerbrate the gene expressionmodifying effects of arsenite on UROtsa cells. The induction of heat shock protein (HSPA1A, HSPA6); metallothionein (MT1G); and solute carrier family (SLC30A) genes revealed synergistic effects of cytotoxicity for both AsIII and BSO. These results indicate that oxidative stress must be a common pathway in cellular response to exposure to different arsenicals. Furthermore, As(III) and MMA(III) induce genes involved in similar but different pathways. The absence of metallothionein gene induction by MMA (III) exposure may demonstrate different mechanism of recognition by the UROtsa cells or	2005

	mechanism of toxicity.	
158.	Andrew AS, Barchowsky A, Davey JC, Soucy NV, Mayka DD, Lantz CR, Hayes A, Hamilton JW. In Vivo Exposure To Drinking Water Arsenic Modifies Expression Of Genes In The Mouse Lung. Toxicologist 2004 Mar;78(1-S):145. Chronic ingestion of arsenic has been associated with increased incidence of vascular and cardiovascular disease, diabetes, hyperkeratosis, and cancer in multiple organs, including the lung. However, the disease risks and biological effects associated with arsenic ingestion at lower levels commonly found in the US remain unclear. To investigate these effects, C57BL/6 mice ingested drinking water with or without 50 ppb arsenic (the previous US maximum contaminant level) for five weeks. RNA from three control and three arsenic exposed animals was labeled and hybridized independently on six independent Affymetrix mouse 430(A) arrays, each containing over 14 k full length genes. Signals were normalized using Robust Multichip Analysis (RMA) and statistical analysis for differential gene expression between the control and arsenic exposed groups was assessed using a Bayesian approach. We ranked differentially expressed genes in ascending order by the p-values and our initial focus was placed on the 30 genes with p-values < 0.005. As we have observed previously, the levels of expression for the majority of the genes in the arsenic exposed group were decreased in comparison to controls. Genes involved in transcriptional regulation, DNA repair, and T-cell mediated immune response showed significant decreases in expression, while increases were observed in insulin regulating and xenobiotic metabolism genes. These data indicate that significant biological effects occur at drinking water arsenic concentrations routinely found throughout the US The specific pattern of gene changes that were observed will also guide further mechanistic studies of arsenic-induced disease.	2004
159.	Avruskin GA, Jacquez GM, Meliker JR, Slotnick MJ, Kaufmann AM, Nriagu JO. Visualization and exploratory analysis of epidemiologic data using a novel space time information system. Int J Health Geogr. 2004 Nov 8;3(1):26. BACKGROUND: Recent years have seen an expansion in the use of Geographic Information Systems (GIS) in environmental health research. In this field GIS can be used to detect disease clustering, to analyze access to hospital emergency care, to predict environmental outbreaks, and to estimate exposure to toxic compounds. Despite these advances the inability of GIS to properly handle temporal information is increasingly recognised as a significant constraint. The effective representation and visualization of both spatial and temporal dimensions therefore is expected to significantly enhance our ability to undertake environmental health research using time-referenced geospatial data. Especially for diseases with long latency periods (such as cancer) the ability to represent, quantify and model individual exposure through time is a critical component of risk estimation. In response to this need a STIS - a Space Time Information System has been developed to visualize and analyze objects simultaneously through space and time. RESULTS: In this paper we present a "first use" of a STIS in a case-control study of the relationship between arsenic exposure and bladder cancer in south eastern Michigan. Individual arsenic exposure is reconstructed by incorporating spatiotemporal data including residential mobility and drinking water habits. The unique contribution of the STIS is its ability to visualize and analyze residential histories over different temporal scales. Participant information is viewed and statistically analyzed using dynamic views in which values of an attribute change through time. These views include tables, graphs (such as histograms and scatterplots), and maps. In addition, these views can be linked and synchronized for complex data exploration using cartographic brushing, statistical brushing, and animation. CONCLUSION: The STIS provides new and powerful ways to visualize and analyze how individual exposure and associated environmental variables change through time. We expect to see innovative space-time methods being utilized in future environmental health	2004

	research now that the successful "first use" of a STIS in exposure reconstruction has been accomplished.	
160.	Basu A, Ghosh P, Das JK, Banerjee A, Ray K, Giri AK. Micronuclei as biomarkers of carcinogen exposure in populations exposed to arsenic through drinking water in West Bengal, India: a comparative study in three cell types. Cancer Epidemiol Biomarkers Prev. 2004 May;13(5):820-7. Contamination of groundwater by arsenic, a paradoxical human carcinogen, has become a cause of global public health concern. In West Bengal, India, the groundwater in 9 of 18 districts is heavily contaminated with arsenic. Various adverse health effects including cancer have been reported from these districts and are associated with prolonged arsenic exposure. A cross-sectional biomarker study was conducted to evaluate and compare the frequencies of micronuclei in peripheral blood lymphocytes, oral mucosa cells, and urothelial cells from the inhabitants of North 24 Parganas, one of the arsenic-affected districts. The three cell types were collected from 163 residents exposed to high levels of arsenic in drinking water (214.7213 +/- 9.0273 microg/l) and from 154 unexposed subjects residing in the unaffected East Midnapur district with very little or no exposure to arsenic through drinking water (9.2017 +/- 0.3157 microg/l). Our analysis revealed that micronuclei frequencies in the exposed group were significantly elevated to 5.33-fold over unexposed levels for lymphocytes, 4.63-fold for oral mucosa cells, and 4.71-fold for urothelial cells (increases in micronuclei frequencies significant at $P < 0.01$). The results indicate that chronic ingestion of arsenic in drinking water by the exposed subjects is linked to the enhanced incidence of micronuclei in all the three cell types, slightly higher level of micronuclei being observed in lymphocytes compared with oral mucosa and urothelial cells.	2004
161.	Beck BD, Schoen A. Arsenic Methylation: Considerations For Risk Assessment. Toxicologist 2004 Mar;78(1-S):129. Recent studies have demonstrated significant cytotoxicity and genotoxicity in vitro of the trivalent forms of methylated arsenic species (specifically monomethyarsonic acid or MMA and dimethylarsinic acid or DMA), often orders of magnitude more potent than the corresponding pentavalent forms. These studies have raised doubts about earlier understanding of methylation being a detoxification pathway. However, an analysis of both in vivo and in vitro studies indicates that generalizations about the toxicological significance of arsenic methylation are not appropriate for several reasons. First, a cell's capacity to methylate arsenic does not correlate with resulting toxicity or ability to undergo transformation. Moreover, distinctions must be made between MMA and DMA that are generated internally via methylation of inorganic arsenic versus MMA and DMA, which are directly administered. In the latter case, MMA and DMA are excreted rapidly from the body nearly unchanged and demonstrate relatively low toxicity. High doses of DMA cause bladder cancer in rats, possibly through oxidative damage from DMAIII formation and subsequent generation of trimethyl arsine oxide (TMAO); these metabolites are believed to cause urothelial cell necrosis followed by regenerative cell proliferation and tumorigenesis; however, this response appears to be unique to the rat, with hamsters, mice and humans forming much less (if any) TMAO than rats. It may also be necessary to make distinctions between acute and chronic exposure to arsenic. More research is required to clarify the toxicological significance of arsenic methylation. In particular, a better understanding of the amount and persistence of trivalent metabolites present in vivo at critical target sites would help clarify the role of such forms in injury and disease. Risk assessment considerations about arsenic methylation, the role of trivalent forms, and dose response implications must be made on a case-by case basis with emphasis on species-specific and dose and duration- specific responses.	2004

162.	Boffetta P. Epidemiology of environmental and occupational cancer. Oncogene. 2004 Aug 23;23(38):6392-403. Environmental carcinogens, in a strict sense, include outdoor and indoor air pollutants, as well as soil and drinking water contaminants. An increased risk of mesothelioma has consistently been detected among individuals experiencing residential exposure to asbestos, while results for lung cancer are less consistent. Several good-quality studies have investigated lung cancer risk from outdoor air pollution based on measurement of specific agents. Their results tend to show an increased risk in the categories at highest exposure, with relative risks in the range 1.5. A causal association has been established between exposure to environmental tobacco smoke and lung cancer, with a relative risk in the order of 1.2. Radon is another carcinogen present in indoor air, with a relative risk in the order of 1.06 for exposure at 100 Bq/m3. In several Asian populations, an increased risk of lung cancer results among women from indoor pollution from cooking and heating. There is strong evidence of an increased risk of bladder, skin and lung cancers following consumption of water with high arsenic contamination; results for other drinking water contaminants, including chlorination by-products, are inconclusive. A total of 29 occupational agents are established human carcinogens, and another 30 agents are suspected carcinogens. In addition, at least 12 exposure circumstances entail exposure to carcinogens. Exposure is still widespread for many important occupational carcinogens, such as asbestos, coal tar, arsenic and silica, in particular in developing countries. Although estimates of the global burden of occupational and environmental cancer result in figures in the order of 2% and less than 1%, respectively, these cancers concentrate in subgroups of the population; furthermore, exposure is involuntary and can, to a large extent, be avoided.	2004
163.	Burgess JL, Rowland H, Josyula A, Hysong TA, Sturup S. Reduction in total inorganic urinary arsenic and toenail arsenic with provision of bottled water. J Toxicol Clin Toxicol 2004;42(5):807. Background: Arsenic exposure is associated with increased cancer incidence. The purpose of this study was to measure the effectiveness of provision of bottled water in reducing inorganic urine and toenail arsenic concentrations in a population with elevated arsenic tap water levels. Methods: Urine, tap water, and toenail samples were collected from a random sample of nonsmoking adults (> =18) residing in Ajo and Tucson, Arizona. After the baseline sample, Ajo subjects were provided with bottled water and were asked to use it for cooking, drinking, and food preparation. Results: At baseline, 40 subjects in Ajo and 32 subjects in Tucson provided urine and toenails. Total inorganic urinary arsenic (ppb) was higher in Ajo (29.1±20.4) than Tucson (11.0±12.0) ($p < 0.001$). Creatinine-adjusted urinary total inorganic arsenic (ug/g) was also higher in Ajo (35.5±25.2) than Tucson (13.2±9.3) ($p < 0.001$). Toenail arsenic concentrations (ug/g) were 0.51±0.72 in Ajo and 0.17±0.21 in Tucson ($p < 0.001$). At follow up, 36 of the original 40 participants in Ajo again provided urine, water, and toenails. Mean urinary total inorganic arsenic dropped from 29.4±21.1 to 23.2±23.2 ($p=0.026$). Creatinine-adjusted urinary total inorganic arsenic was lower at follow-up (29.6±20.8) than baseline (34.8±27.4), although this change was not statistically significant ($p=0.776$). Toenail arsenic concentrations also decreased (0.49±0.68 vs. 0.26±0.19, $p=0.061$). Conclusion: Urinary and toenail arsenic were higher in Ajo, the town with higher tap water arsenic levels, than in Tucson. Provision of arsenic-free drinking water in Ajo reduced urinary total inorganic arsenic concentrations.	2004
164.	Chen Y, Ahsan H, Parvez F, Howe GR. Validity of a food-frequency questionnaire for a large prospective cohort study in Bangladesh. Br J Nutr. 2004 Nov;92(5):851-9. We have developed a thirty-nine-item semi-quantitative food-frequency questionnaire (FFQ) to assess the dietary consumption of 11,746 men and women in a prospective cohort study that	2004

	evaluates the health effects of As from drinking water in Bangladesh. In order to validate the FFQ, two 7 d food diaries (FD) were completed for 189 randomly selected cohort participants in two different seasons of the year. Nutrient values were converted based on both the United States Department of Agriculture's National Nutrient Database and a food composition table for the Indian subcontinent. Pearson product-moment and Spearman non-parametric rank correlation coefficients comparing food and nutrient consumptions estimated from FFQ and 7 d FD were calculated based on log-transformed consumption values with or without adjustment for total energy and correction for within-individual variation. Correlations of macronutrients and common micronutrients including total fat, monounsaturated fat, polyunsaturated fat, saturated fat, protein, carbohydrate, dietary fibre, Na, K, vitamin B6, vitamin B12, riboflavin, Mn, thiamin and Fe were moderately good, ranging from 0.30 to 0.76. However, correlations of other micronutrients were weak (<0.30). Large seasonal variations in intakes of retinol equivalents and vitamin C were observed. This analysis documents the degree of validity of the FFQ in measuring specific nutrient intakes in the study population. To our knowledge, the present study is the first to document the validity of a FFQ with the use of 7 d FD in a Bangladeshi population.	
165.	Chen Y, Ahsan H. Cancer burden from arsenic in drinking water in Bangladesh. Am J Public Health. 2004 May;94(5):741-4. We assessed the potential burden of internal cancers due to arsenic exposure in Bangladesh. We estimated excess lifetime risks of death from liver, bladder, and lung cancers using an exposure distribution, death probabilities, and cancer mortality rates from Bangladesh and dose-specific relative risk estimates from Taiwan. Results indicated at least a doubling of lifetime mortality risk from liver, bladder, and lung cancers (229.6 vs 103.5 per 100 000 population) in Bangladesh owing to arsenic in drinking water.	2004
166.	Chen YC, Xu L, Guo YL, Su HJ, Smith TJ, Ryan LM, Lee MS, Christiani DC. Polymorphisms in GSTT1 and p53 and urinary transitional cell carcinoma in south-western Taiwan: a preliminary study. Biomarkers. 2004 Jul-Oct;9(4-5):386-94. Little is known about the relevance of genetic polymorphisms to arsenic-related bladder cancer. A preliminary case-control study was conducted to explore the association between genetic polymorphisms of GSTT1, p53 codon 72 and bladder cancer in southern Taiwan, a former high arsenic exposure area. Fifty-nine urinary transitional cell carcinoma (TCC) patients from a referral centre in south-western Taiwan and 81 community controls matched on residence were recruited from 1996 to 1999. A questionnaire was administered to obtain arsenic exposure and general health information. Genotypes of p53 codon 72 and GSTT1 were analysed by polymerase chain reaction-restriction fragment length polymerase. The combined variant genotypes (heterozygous or homozygous variant) of p53 codon 72 and GSTT1 null were observed in 29% of cases and in 44% of controls, respectively. In this preliminary study, bladder cancer risk was slightly elevated for subjects carrying the variant genotype of p53 codon 72 or in subjects carrying the GSTT1 null genotype. Variants in p53 codon 72 increased the risk of bladder cancer among smokers. However, the results were not statistically significant and larger confirmatory studies are needed to clarify the role of candidate gene polymorphisms and bladder cancer risk in arsenic exposed populations.	2004
167.	Danaee H, Nelson HH, Liber H, Little JB, Kelsey KT. Low dose exposure to sodium arsenite synergistically interacts with UV radiation to induce mutations and alter DNA repair in human cells. Mutagenesis. 2004 Mar;19(2):143-8. Inorganic arsenic is a known human carcinogen, yet its mechanism of action remains poorly understood. Epidemiological data suggest that arsenic exposure interacts with UV radiation exposure to increase the risk of skin cancer. Studies have suggested that arsenic is able to	2004

	impair DNA repair enzymes and alter the repair of UV-induced DNA damage. Here we have tested the hypothesis that arsenite [As(III)] and UV interact synergistically to enhance mutagenesis. TK6 human lymphoblastoid cells that are functionally heterozygous at the thymidine kinase (TK) locus were pre-exposed to As(III) alone and in combination with UV. Our data suggest that As(III) is mutagenic only at high doses at the TK locus. As(III) enhanced UV mutagenesis in a more than additive fashion. To investigate the mechanism underlying this synergy we assessed the removal of UV-induced dimers in TK6 cells using the T4 endonuclease-incorporated Comet assay. Pre-treatment with As(III) specifically inhibited the repair of UV-induced pyrimidine dimer-related DNA damage. Taken together, these data suggest that pre-treatment of human cells with arsenic impairs the nucleotide excision repair pathway and leads to enhanced UV mutagenesis.	
168.	Del Razo LM, Valenzuela OL, Garcia-Vargas GG, Calderon-Aranda ES. Use Of Human Biomonitoring To Assess Arsenic Methylation. Toxicologist 2004 Mar;78(1-S):129. Metabolism of inorganic arsenic (Asi) in humans produces monomethylarsenic (MAsV), dimethylarsenic(DMAV), monomethylarsenic (MAsIII), and dimethylarsenic (DMAIII), which can be found in human urine. The concentration of arsenicals in urine is used as a biological indicator of Asi exposure, because excretion via kidney is the major route for elimination of most As species. Asi methylation is often evaluated by the relative distribution of urinary As species. Due to increased recognition of trivalent methylated and dimethylated arsenicals (MAsIII and DMAIII) as more cytotoxic and more genotoxic than Asi, we studied the relationship of trivalent methylated metabolites to skin signs of arsenicism in humans chronically exposed to Asi. A cross-sectional study was conducted in central Mexico (about 220 km NE of Mexico City). Seventy-six residents (ages 15-51) from an endemic As-area have been exposed to very high levels of Asi in drinking water (150 to 1, 350 ppb) for at least 10 years. The participants answered a questionnaire and were clinically examined. Fifty-five individuals presented skin signs of arsenicism, such as keratosis and hyper- or hypo-pigmentation. Participants provided drinking water and spot urine samples. Due to instability of methylated As species in urine, samples were immediately frozen in dry ice and trivalent As species were analyzed approximately 6 hrs after collection. Trivalent methylated arsenic species were present in almost all the urine samples (99 %), DMAIII being the major metabolite (51.2%), followed by DMAV (22.6%), MAsIII (7.2%), MAsV (2.7%) Asi III (8.8%) and Asi V (7.5%). Urinary MAsIII and DMAIII were directly correlated with Asi in water. Individuals with skin-lesions had higher concentration of MAsIII in urine than those without skin lesions. The main factor associated with arsenicism was cumulative Asi exposure. More studies are necessary to determine if the urinary excretion of MAsIII or DMAsIII provides a new biomarker of the effects of chronic exposure to Asi.	2004
169.	Gandolfi AJ, Kirkpatrick DS, Bredfeldt TG, Zheng XH. Effects Of In Vitro Exposure To Arsenic On The Ubiquitin Pathway In Human Renal And Bladder Cells. Toxicologist 2004 Mar;78(1-S):250. The ubiquitination of proteins within a cell plays a key role in maintaining the appropriate regulatory balance of processes such as cell cycle, apoptosis, and stress response. During cellular stress, such as following arsenic exposure, the ubiquitin pathway rapidly degrades damaged and misfolded proteins to maintain the fidelity of the cellular machinery. In studies performed in rabbit renal cortical slices, HEK293 cells, and UROtsa cells, low-level arsenic (0.5 uM - 10 uM) causes an accumulation of ubiquitin modified proteins within cells. Microarray analysis of arsenic exposed cells has shown a number of alterations in ubiquitin family genes that help to explain the changes seen. Studies from the rabbit slices and HEK293 cells show that 20S proteasome activity, but not ubiquitin-conjugating activity, was affected by arsenic. Depletion of glutathione with buthionine-L-sulfoximine during coexposure with As	2004

	(III) greatly increases the levels of ubiquitin-conjugated proteins compared to arsenic treatment alone. This suggests overlapping possibilities that glutathione is directly preventing arsenic mediated protein damage, or that oxidants are involved in the damage of proteins by arsenic. Understanding the effects of low-level arsenic on protein homeostasis will be instrumental to further characterization of the mechanisms behind arsenic carcinogenicity. Because the kidney and bladder are exposed to significant levels of arsenic during urine processing, and because exposed human populations are at increased risk of developing bladder cancer, these organ systems appear to be well suited for the study of the proteotoxic effects of arsenic.	
170.	Gawkrodger DJ. Occupational skin cancers. Occup Med (Lond). 2004 Oct;54(7):458-63. Skin cancer due to occupation is more common than is generally recognized, although it is difficult to obtain an accurate estimate of its prevalence. Over the past two centuries, occupational skin cancers have particularly been due to industrial exposure of men (it seems more so than women) to chemical carcinogens such as polycyclic hydrocarbons (e.g. from coal tar products) or to arsenic. Industrial processes have improved in most Western countries to limit this type of exposure, but those with outdoor occupations are still exposed to solar ultraviolet irradiation without this being widely recognized as an industrial hazard. Ionizing radiation such as X-rays can also cause skin cancer. Occupational skin cancers often resemble skin tumours found in non-occupational subjects, e.g. basal cell carcinoma, squamous cell carcinoma and malignant melanoma, but some pre-malignant lesions can be more specific and point to an occupational origin, e.g. tar keratoses or arsenical keratoses. An uncommon but well-recognized cause of occupational skin cancer is that which results from scar formation following an industrial burn. In the future it will be necessary to focus on preventative measures, e.g. for outdoor workers, the need to cover up in the sun and use sun protective creams and a campaign for earlier recognition of skin cancers, which are usually curable if treated in their early stages.	2004
171.	Guo HR, Wang NS, Hu H, Monson RR. Cell type specificity of lung cancer associated with arsenic ingestion. Cancer Epidemiol Biomarkers Prev. 2004 Apr;13(4):638-43. Arsenic is a well-documented human carcinogen. Previous studies on urinary bladder and skin cancers have shown that arsenic can cause specific cell types of malignancy. To evaluate whether this is also true for lung cancers, we conducted a study on 243 townships in Taiwan. We identified patients through the National Cancer Registry Program and compared the proportion of each major cell type between an endemic area of arsenic intoxication with exposures through drinking water, which includes 5 of the townships and the other 238 townships. To control for gender and age, we analyzed data on men and women separately and divided patients into four age groups. A total of 37,290 lung cancer patients, including 26,850 men and 10,440 women, was diagnosed between January 1, 1980 and December 31, 1999 in study townships. Patients from the endemic area had higher proportions of squamous cell and small cell carcinomas, but a lower proportion of adenocarcinomas. These findings were similar across all age groups in both genders, although the lack of data on smoking is a limitation of our study. The results suggested that the carcinogenicity of arsenic on lungs is also cell type-specific: squamous cell and small cell carcinomas appeared to be related to arsenic ingestion, but not adenocarcinoma. Whereas data in the literature are limited, the association between adenocarcinoma and arsenic exposures through inhalation appeared to be stronger than that of squamous cell carcinoma. Therefore, we speculate that arsenic may give rise to different mechanisms in the development of lung cancers through different exposure routes.	2004
172.	Hadi A, Parveen R. Arsenicosis in Bangladesh: prevalence and socio-economic correlates. Public Health. 2004 Dec;118(8):559-64.	2004

	The potential effects of arsenic-contaminated drinking water on health are of concern, but our understanding of the risk factors of arsenicosis remains limited. This study assessed the prevalence of and socio-economic differentials in arsenic-associated skin lesions in a rural community in Bangladesh. Data were collected from a village where the Bangladesh Rural Advancement Committee has operated a health surveillance system and a community-based arsenic mitigation project since 1999. In total, 1654 residents in the study village were examined in May 2000 for arsenic-associated lesions on their skin. Socio-economic information was extracted from the surveillance system database covering the village. Nearly 2.9% of the study population had clinical manifestations of arsenic poisoning. The prevalence of arsenicosis was associated with age, sex, education and the economic status of the household. Multivariate analysis identified age and economic status as significant predictors of arsenicosis controlling for education and gender. In conclusion, a clear understanding of the socio-economic distribution of arsenicosis in different demographic and socio-economic groups will be useful in identifying the high-risk groups from arsenic-affected communities. More studies are needed to design effective interventions to mitigate the effects of arsenic in Bangladesh.	
173.	Harrison RM, Smith DJ, Kibble AJ. What is responsible for the carcinogenicity of PM2.5? Occup Environ Med. 2004 Oct;61(10):799-805. AIMS: To test whether exposure to known chemical carcinogens in the atmosphere is capable of explaining the association between concentrations of PM2.5 and lung cancer mortality observed in the extended ACS Cohort Study. METHODS: Taking account of possible cancer latency periods, lung cancer rates due to exposure to As, Cr(VI), Ni, and polycyclic aromatic hydrocarbons (PAHs) were calculated based on a review of historic measurements from the United States and the use of unit risk factors. The predicted rates were compared with rates of cancer attributable to PM2.5 derived from data in the ACS study. RESULTS: Despite many uncertainties, the lung cancer rates predicted due to exposure to US urban concentrations of the carcinogenic substances arsenic, nickel, chromium, and PAHs measured in 1960 and earlier (and hence allowing for a latency period) were within the range predicted on the basis of the ACS Cohort Study due to exposure of PM2.5. There are, however, many caveats, most particularly that for the chemical carcinogens to be responsible for the effects attributed to PM2.5 by Pope and colleagues, the concentrations of chemical carcinogens at the time of relevant exposures would need to be correlated with the concentrations of PM2.5 in US urban areas measured between 1979 and 2000 and used in the ACS study. CONCLUSIONS: While many uncertainties remain, it appears plausible that known chemical carcinogens are responsible for the lung cancers attributed to PM2.5 exposure in the extended ACS Cohort Study. However, the possibility should not be ruled out that particulate matter is capable of causing lung cancer independent of the presence of known carcinogens.	2004
174.	Ihnat MA, Hess L, Curilla S, Clark C. Effect Of Low Dose As(III) In The Drinking Water Of Mice On Tumor Growth And Angiogenesis. Toxicologist 2004 Mar;78(1-S):236. Arsenite (As(III)), a major drinking water contaminant, is associated with many vascular abnormalities in contaminated populations. We have previously shown that As(III) at levels approaching the current US drinking water standard (10 PPB) stimulates angiogenesis and As(III) injected into tumor-bearing mice at levels below those used to treat cancer can actually stimulate tumor growth. We now show that B16-F10 melanoma tumor-bearing mice exposed to 10, 50, and 200 PPB As(III) in their drinking water for 10 weeks prior to tumor implantation show considerably higher tumor growth rates versus mice given nanopure water. Additionally, we show by immunohistochemistry that levels of HIF-1alpha and two of its regulated proteins, VEGF and PAI-1, are substantially increased in mice receiving 10 and 50 PPB As(III)), but not in mice receiving 200 PPB As (III). Interestingly, tumor blood vessel counts were substantially	2004

	higher in animals given all doses of As(III). In isolated B16 cells, a 4 hr exposure to high dose (75 and 750 PPB) As(III) stimulated HIF-1alpha protein levels by immunoblot analysis. In contrast, a 72 hr exposure to low dose (0.75 and 7.5 PPB) As(III) caused comparable HIF-1alpha protein induction. Using the CAM angiogenesis assay, the VEGFR kinase inhibitor SU5416 (10µM) and an inhibitor of HIF-1alpha, YC-1 (10µM), abrogated the angiogenic effects of As(III). Finally, the antioxidants tocopherol (100µM), NAC (1mM), DMSO (0.5 percent) and TEMPOL (1mM) all reduced As(III)-mediated vessel formation in the CAM assay. These results indicate that the angiogenic effects of low dose As(III) can enhance tumor growth and the angiogenic stimulation by low dose As(III) likely involves reactive oxygen species (ROS) and HIF signaling.	
175.	Jin Y, Sun G, Li X, Li G, Lu C, Qu L. Study on the toxic effects induced by different arsenicals in primary cultured rat astroglia. Toxicol Appl Pharmacol. 2004 May 1;196(3):396-403. Arsenic toxicity is a global health problem affecting millions of people. The objectives of this study were to determine if the toxic effects on primary cultured rat astroglia would be induced by different arsenicals. Based on alamarBlue assay and the single cell gel electrophoresis (SCGE, comet assay), the cell viability and DNA damage in the cells exposed to different arsenicals were evaluated. Treatment of astroglia with methylated arsenicals, that is, pentavalent monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV), resulted in no obvious changes in cell viability and DNA damage at micromolar concentrations. However, treatment of astroglia with inorganic arsenicals, that is, arsenite and arsenate, caused decreased cell viability and increased DNA damage at micromolar levels, and showing a dose-related decrease in mean alamarBlue reduced rate and a dose-related increase in mean comet length. Our study is therefore highly suggestive for a link between inorganic exposure and cellular toxicity or DNA damage. Based on the results of this study, the toxic effects induced by arsenite were stronger than those induced by arsenate.	2004
176.	Kadiiska MB, Nesnow S, Liu J, Waalkes M, Mason R. Arsenic Methylation And Oxidant Injury By ESR In Vivo And In Vitro. Toxicologist 2004 Mar;78(1-S):129. Arsenic is a serious environmental concern worldwide, because of the large number of known contaminated sites and millions of people at risk from drinking arseniccontaminated water. Inorganic arsenic undergoes metabolic conversion from pentavalent arsenate (AsV) to trivalent arsenite (AsIII) with subsequent methylation to generate organometallic forms of arsenic such as MMAV, MMAIII, DMAV, DMAIII and trimethylarsine oxide. Studies have shown that AsIII metabolites MMAIII and DMAIII are quite toxic and cause extensive damage to DNA. It has been postulated that the in vivo toxicity and carcinogenicity result from the catalysis of free radical generation. Using electron spin resonance (ESR) in conjunction with the spin traps phenyl-N-tert-butylnitrone (PBN), alpha (4-pyridyl 1-oxide)-N-tert-butylnitrone (POBN) and 5, 5-dimethyl-1-pyrroline-N-oxide (DMPO) we investigated free radical production by sodium arsenite (AsIII) and sodium arsenate (AsV) in a mouse model of acute poisoning. In addition, the role of free radicals in in vitro cytotoxicity of DMAIII using murine TRL 1215 liver cells was examined. And, in order to define the mode of action of DNA damage induced by DMAIII, this study investigated free radical generation by DMAIII in in vitro experiments with supercoiled phiX174 DNA. Simultaneous administration of PBN and AsIII to adult male 129/Sv mice resulted in the generation of free radical metabolites detected in the liver lipid extract by ESR. Free radical generation was subsequently observed in TRL 1215 liver cells subjected to an acute high dose of DMAIII exposure. Finally, ESR was used to identify the nature of the radical being trapped by DMPO in the DMAIII-DNA-damage studies. The complete system gave a characteristic spectrum of a DMPO-hydroxyl radical adduct. In conclusion, the present study provides the most direct ESR evidence for the generation of free	2004

	radicals by both inorganic and biomethylated forms of arsenic in vivo and in vitro. The relationship of these metabolites to effects of arsenic in humans will be discussed.	
177.	Liu Y, Li J, Gorospe M, Barnes J. Tumor Promoter Arsenite Stimulates Histone H3 Phosphoacetylation At C-fos And C-jun In Human Diploid Fibroblasts. Toxicologist 2004 Mar;78(1-S):237. Although epidemiological studies have clearly established that elevated arsenic levels in drinking water are associated with increased incidences of skin, lung, bladder, kidney, and liver cancers, the carcinogenic mechanism remains elusive. Recent studies have suggested that arsenic may act as a tumor promoter by perturbing key signaling pathways. We have shown that arsenite potently induces proliferation-associated genes, including c-jun and c-fos, through a pathway regulated by EGF receptor. Recent studies have demonstrated that chromatin remodeling mediated by histone H3 phosphoacetylation plays an important role in the induction of c-fos and c-jun. OBJECTIVE: To understand the molecular mechanisms underlying the tumor-promoting properties of arsenic and test the hypothesis that histone H3 phosphoacetylation are involved in the induction of c-fos and c-jun. DESIGN/METHODS: Early passage normal human lung fibroblast WI-38 cells were stimulated with arsenite. Expression of c-fos and c-jun was examined by Northern blot analyses. Histone H3 phosphorylation and acetylation at the global levels were assessed by immunofluorescence and Western blot analyses. Histone H3 phosphorylation and acetylation at the loci of c-fos and c-jun were measured by chromatin immunoprecipitation (ChIP) and real-time PCR assays. RESULTS: Both c-fos and c-jun by arsenite can be substantially inhibited by the MEK-selective inhibitor, but not by the p38 inhibitor. Arsenite dramatically induced the phosphorylation and acetylation of histone H3 preceding the mRNA induction of c-fos and c-jun. ChIP assays revealed that arsenite markedly induced histone H3 phosphorylation/ acetylation at the c-fos and c-jun loci through an ERK-dependent pathway. CONCLUSION: Our results suggest that arsenic-triggered alterations in chromatin structure perturb gene transcription and may contribute to the carcinogenic process.	2004
178.	Lu SN, Chow NH, Wu WC, Chang TT, Huang WS, Chen SC, Lin CH, Carr BI. Characteristics of hepatocellular carcinoma in a high arsenicism area in Taiwan: a case-control study. J Occup Environ Med. 2004 May;46(5):437-41 Arsenic contamination of drinking water is noticeably linked to the occurrence of skin, bladder, lung cancers, and hepatocellular carcinoma (HCC). Blackfoot disease (BFD) caused by arsenicosis is endemic in southwestern Taiwan, where artesian well water contains high concentrations of arsenic, and mortality from HCC shows a dose-response increase by concentration of arsenic in the well water. This case-control study was conducted to examine the clinical characteristics of HCC patients of BFD-endemic area. A total of 65 HCC cases (54 men and 11 women) were recruited from the BFD-endemic areas. The clinicopathological features were compared with 130 age- and sex-matched HCC control patients from non-BFD-endemic areas. Characteristics analyzed included hepatitis viral infection status, hepatitis activity, liver function, histological findings, computed tomography scan characteristics, and patient survival. No differences were observed between HCC patients or their tumors, from study and control areas.	2004
179.	Mahata J, Chaki M, Ghosh P, Das LK, Baidya K, Ray K, Natarajan AT, Giri AK. Chromosomal aberrations in arsenic-exposed human populations: a review with special reference to a comprehensive study in West Bengal, India. Cytogenet Genome Res. 2004;104(1-4):359-64. For centuries arsenic has played an important role in science, technology, and medicine. Arsenic for its environmental pervasiveness has gained unexpected entrance to the human body	2004

	through food, water and air, thereby posing a great threat to public health due to its toxic effect and carcinogenicity. Thus, in modern scenario arsenic is synonymous with "toxic" and is documented as a paradoxical human carcinogen, although its mechanism of induction of neoplasia remains elusive. To assess the risk from environmental and occupational exposure of arsenic, in vivo cytogenetic assays have been conducted in arseniasis-endemic areas of the world using chromosomal aberrations (CA) and sister chromatid exchanges (SCE) as biomarkers in peripheral blood lymphocytes. The primary aim of this report is to critically review and update the existing in vivo cytogenetic studies performed on arsenic-exposed populations around the world and compare the results on CA and SCE from our own study, conducted in arsenic-endemic villages of North 24 Parganas (district) of West Bengal, India from 1999 to 2003. Based on a structured questionnaire, 165 symptomatic (having arsenic induced skin lesions) subjects were selected as the exposed cases consuming water having a mean arsenic content of 214.96 microg/l. For comparison 155 age-sex matched control subjects from an unaffected district (Midnapur) of West Bengal were recruited. Similar to other arsenic exposed populations our population also showed a significant difference ($P < 0.01$) in the frequencies of CA and SCE between the cases and control group. Presence of substantial chromosome damage in lymphocytes in the exposed population predicts an increased future carcinogenic risk by this metalloid. Copyright 2003 S. Karger AG, Basel	
180.	Martínez V, Creus A, Venegas W, Arroyo A, Beck JP, Gebel TW, Surrallés J, Marcos R. Evaluation of micronucleus induction in a Chilean population environmentally exposed to arsenic. Mutat Res. 2004 Nov 14;564(1):65-74. In the present study we have evaluated whether or not environmental exposure to arsenic in ground drinking-water results in a significant increase in the frequency of micronuclei (MN) in peripheral blood lymphocytes. Thus, 106 individuals from the Antofagasta region (North Chile), together with 111 individuals from the area of Concepción, were used in this investigation. In the Antofagasta area, arsenic levels in drinking-water as high as 0.750 mg/L were measured. In Concepción, located about 2500 km towards the south and used as reference area, arsenic levels in tap water were as low as 0.002 mg/L. The total content of arsenic in fingernails was determined as a biomarker of individual exposure. The cytogenetic results obtained in this study indicate that in the exposed group the overall frequency of binucleated micronucleated cells (BNMN) is higher than in the reference group, the difference being statistically significant. In addition, no differences were found between the exposed and the reference groups, regarding the cytokinesis-block proliferation index (CBPI). No association was observed between BNMN and arsenic content in water or arsenic in fingernails. On the other hand, when the exposed group was divided according to their Atacameno or Caucasian ethnicity, no significant differences were observed between them. In addition, as usually found in other human biomonitoring studies, sex and age are factors that modulate the frequency of MN in both exposed and reference populations.	2004
181.	Molinelli AR, Nakamura J, Swenberg JA, Madden MC. Lack Of DNA Single Strand Breaks In A Lung Epithelial Cell Line After Exposure To Arsenic. Toxicologist 2004 Mar;78(1-S):390. Arsenic (As) is a carcinogen whose most important target organs include the skin and lungs. Exposure can occur via water ingestion, or inhalation, as As is a by-product of fossil fuel combustion and other industrial activities. The carcinogenic mechanism of action for As remains unclear. One hypothesis proposes As induces cancer by creating oxidative stress. In previous studies we found modest evidence of increased peroxidation after exposure of cells to inorganic As as arsenite (iAs). To study the possible mechanistic link between As exposure and lung carcinogenesis, we examined iAs induction of DNA single strand breaks (SSBs) using a human bronchial epithelial cell line (BEAS-2B). SSBs were assessed via the comet assay, and a novel colorimetric assay that indirectly measures SSBs repair. This assay is based on the	2004

	premise that DNA SSBs induce the activation of the repair enzyme poly(ADP-ribose)polymerase, which in turn depletes intracellular NAD+/NAD(P)H (Nucleic Acids Res. 31(17):e104, 2003). We did not find any statistically significant differences in DNA SSBs between the control and iAs (1nM-10µM) treated cells with the comet and NAD(P)H assays with up to 4h exposures at 37 degrees C. In addition, no increase in SSBs was observed when the cells were exposed at 4 degrees C, which inhibits DNA repair. In these studies, H2O2 and methyl methanesulfonate induced increased SSBs. These data suggest that iAs does not directly induce an increase in SSBs in this cell line, possibly because BEAS-2B cells may be more resistant to damage than other extrapulmonary cell types shown to have increased SSBs upon iAs exposure. Furthermore, iAs can be converted in vivo to methylated organic species that may be more potent inducers of oxidative stress and SSBs. Further analyses into the possible contributions of the aforementioned factors is underway.	
182.	Muscarella D. Interaction Of Arsenite With B-Cell Receptor- And CD40- Mediated Signaling And Effect On Apoptosis In B-Lymphoma Cells. Toxicologist 2004 Mar;78(1-S):333. Cell lines derived from human Burkitts lymphoma (BL) are an important in vitro model for receptor-mediated negative/positive selection of germinal center B-lymphocytes since they undergo apoptosis upon cross-linking of the surface IgM/B-cell receptor (sIgM) and are rescued from sIgM-induced apoptosis by ligation of CD40. These cell lines are also highly sensitive to the induction of apoptosis by many chemicals, including sodium arsenite, a significant environmental contaminant with immunotoxic activity. The purpose of this study was to identify the interactions of arsenite exposure with sIgM- and CD40- mediated signaling and subsequent effects on apoptosis induction. I found that cross-linking of sIgM initially provided protection against the early induction of apoptosis by arsenite. Specifically, sIgM-activation protected against arsenite-induced mitochondrial depolarization and the cleavage of caspase 9 and poly (ADP) ribose polymerase. The sIgM-mediated protection against apoptosis required the activation of two signaling pathways, the extracellular-signal regulated kinase (ERK) and the phosphoinositide- 3 kinase (PI3-K) pathways. Inhibition of either pathway partially blocked the ability of sIgM-activation to protect against apoptosis induction. However, sIgM-mediated protection was transient, and decayed over a period of several hours, consistent with a model in which initial engagement of sIgM induces an immediate and potent anti-apoptotic response, but in the absence of appropriate costimulation (i.e. by CD40 engagement) the protective signals decay and the cells undergo apoptosis. Importantly, I also found that arsenite blocked the ability of CD40 to rescue BL cells from sIgM-mediated apoptosis by interfering with an important pro-survival pathway activated by CD40 ligation, the nuclear factor kappa- B pathway. Moreover, I have identified several key regulatory points within this pathway that are differentially sensitive to higher (> = 200 uM) compared to lower (< = 20 uM) concentrations of arsenite.	2004
183.	Ngo MA, Patterson TJ, Rice RH. Arsenic Toxicity In Human Keratinocytes. Toxicologist 2004 Mar;78(1-S):155-6. Arsenic, a human carcinogen and drinking water contaminant, is encountered in the environment in the trivalent (AsIII) and pentavalent (AsV) oxidation states. AsV, the most prevalent form, usually appears much less toxic with its potency being enhanced by reduction to AsIII. To understand the importance of reduction in elucidating arsenic mechanisms we evaluated the responsiveness of human keratinocyte cultures to different oxidation states using Northern and quantitative PCR analysis of heme oxygenase-1 induction. We found AsV to be as efficacious as AsIII; however a longer time was required for AsV to reach maximal effect. These observations were correlated with ICP-MS measurements of cellular uptake and conversion rates. In parallel experiments, we found pentavalent antimony (SbV) to have limited biological activity, uptake, and conversion compared to the trivalent form (SbIII).	2004

	These findings emphasize the importance of intracellular reduction of metalloids for biological activity.	
184.	Nishigori C, Hattori Y, Toyokuni S. Role of reactive oxygen species in skin carcinogenesis. Antioxid Redox Signal. 2004 Jun;6(3):561-70. Reactive oxygen species (ROS) are associated not only with initiation, but also with promotion and progression in the multistage carcinogenesis model. In the present review, we will focus on the involvement of ROS in skin carcinogenesis, especially that induced by ultraviolet (UV) radiation. UV-specific DNA damage has been well studied thus far. However, recent reports have revealed the previously unknown participation of oxidative stress in UV-induced skin carcinogenesis. Indeed, in addition to transition-type mutations at dipyrimidine sites, G:C to T:A transversions, which may be induced by the presence of 8-oxoguanine during DNA replication, are frequently observed in the ras oncogene and p53 tumor suppressor gene in human skin cancers of sun-exposed areas and in UV-induced mouse skin cancers. Recent studies have shown that not only UV-B, but also UV-A is involved in UV-induced carcinogenesis. A wide variety of biological phenomena other than direct influence by UV, such as inflammatory and immunological responses and oxidative modifications of DNA and proteins, appear to play roles in UV-induced skin carcinogenesis. Furthermore, it has become clear that genetic diseases such as xeroderma pigmentosum show deficient repair of oxidatively modified DNA lesions. The involvement of ROS in skin carcinogeneisis caused by arsenic and chemical carcinogens will also be discussed.	2004
185.	Paul PC, Chattopadhyay A, Manna AK, Dutta SK. Skin cancers in chronic arsenic toxicity--a study of predictive value of some proliferative markers. Indian J Pathol Microbiol. 2004 Apr;47(2):206-9. Prolonged exposure to arsenic contaminated water produces various clinical features, cutaneous features e.g. melanosis, keratosis and cancers being very common. Evaluation of such lesions by proliferative markers can provide useful information in regards to the biological behaviour of the lesions. Thus, cases with high proliferative status can be ominous sign for development of cancers. We studied skin biopsy of 42 cases. These were evaluated with AgNOR score and PCNA stain, in addition to H & E examination. Here, invasive cancer cases had mean AgNOR score of 3.56, those with severe dysplasia had 3.0, moderate and mild dysplasia scored 1.73, benign changes had mean score of 1.35 while normal control cases had 1.08. PCNA index in cancers was above 50, that of severe dysplasia 25-30, mild to moderate dysplasia 1.0-5.0, those with benign changes 0.5 -1.0 and normal control had LI of less than 0.5%. PCNA has the advantage of less chance of observer error over AgNOR stain.	2004
186.	Peplow D, Edmonds R. Health risks associated with contamination of groundwater by abandoned mines near Twisp in Okanogan County, Washington, USA. Environ Geochem Health. 2004 Mar;26(1):69-79. Abandoned mines are known to contaminate private drinking water wells with toxic metals and arsenic (As). Little attention is given, however, to sites in rural areas with low population densities where natural, geogenic sources of contaminants might also occur. This study measured arsenic and trace element exposure among residents consuming water from wells adjacent to abandoned mines near Twisp, in Okanogan County, Washington, USA, estimated the risk of adverse health effects, and considered the degree of uncertainty associated with the assessed risk. Water samples were collected between October 1999 and June 2001. Average As concentrations ranged from <1 to 298 microg L(-1), lead (Pb) ranged from 0 to 94 microg L(-1), cadmium (Cd) 0-5 microg L(-1), and selenium (Se) 0-390 microg L(-1). Concentrations varied seasonally with maximum concentrations occurring in conjunction with snow-melt. The calculated risk of mortality from cancer following exposure to As at average concentrations as	2004

	low as 8 microg L(-1) was greater than one in 10,000. Additional noncarcinogenic risks are associated with exposure to As, Cd, Pb and Se. A potentially affected population, estimated to be between 1000 and 1287 residents, live within a 6.5-km (4-mile) radius of the study site. This study emphasises the need to test drinking water wells in the vicinity of abandoned mines during times of maximum snow-melt to determine the extent of risk to human health. Residents drinking water from wells tested in this study who want to reduce the estimated carcinogenic risk and the noncarcinogenic hazard quotient should consider treating their water or find alternative sources.	
187.	Pi J, He Y, Bortner C, Huang J, Liu J, Qu W, Reece JM, Styblo M, Chignell CF, Waalkes MP. Arsenic-Induced Transformation Causes Generalized Resistance To Apoptosis In Cultured Human Keratinocytes. Toxicologist 2004 Mar;78(1-S):235. Inorganic arsenic (As) is a well-documented human carcinogen that targets the skin, although the underlying carcinogenic mechanism is not well understood. Tumorigenesis is a multistep process in which acquired apoptotic resistance is a common event. In this study, when HaCaT cells, an immortalized, non-tumorigenic human keratinocyte cell line, were transformed by continuous exposure to low level (100 nM) inorganic arsenite [As(III)] for 28 weeks, a generalized resistance to apoptosis was observed. This included resistance to apoptosis induced by ultraviolet A (UVA) radiation, a human skin carcinogen, or a high dose of As. Concurrent with this acquired resistance, the As-transformed cells exhibited morphological changes and increased secretion of matrix metalloproteinase 9, which plays a crucial role in tumor invasion and is often associated with malignant transformation. Since cellular apoptosis is dependent on the balance between proapoptotic and survival pathways, the roles of caspase and protein kinase B (PKB), a key antiapoptotic molecule, in As-induced apoptotic resistance were investigated. Western blot analysis indicated that the As-transformed cells exhibited much less caspase-3 and-7 activation than control cells after UVA or high dose As(III) exposure. In the control cells, UVA or high dose As(III) markedly decreased nuclear phosphorylated PKB (P-PKB) levels prior to the apoptosis, whereas the As-transformed cells exhibited an increased stability of nuclear P-PKB. Pretreatment of the As-transformed cells with LY294002 or wortmanin, which inhibit PKB phosphorylation, completely blocked the acquired apoptotic resistance. These data demonstrate that the acquired apoptotic resistance observed concurrently with As-induced cellular transformation is associated with increased stability of nuclear P-PKB. As induced acquired resistance to apoptosis may be an important event in skin cancer development by allowing damaged cells to escape normal cell population control.	2004
188.	Raisuddin S, Jha AN. Relative sensitivity of fish and mammalian cells to sodium arsenate and arsenite as determined by alkaline single-cell gel electrophoresis and cytokinesis-block micronucleus assay. Environ Mol Mutagen. 2004;44(1):83-9. To protect human and ecosystem health, it is necessary to develop sensitive assays and to identify responsive cells and species (and their life stages). In this study, the relative genotoxicity of two inorganic arsenicals: trivalent sodium arsenite (As(3+)) and pentavalent sodium arsenate (As(5+)), was evaluated in two cell lines of phylogenetically different origin, using alkaline single-cell gel electrophoresis (i.e., the Comet assay) and the cytokinesis-block micronucleus (MN) assay. The cell lines were the rainbow trout gonad-2 (RTG-2) and Chinese hamster ovary-K1 (CHO-K1) lines. Following optimization and validation of both assays using reference chemicals (i.e., 1-100 microM hydrogen peroxide for the Comet assay and 1-10 mM ethylmethane sulfonate for the MN assay), cells were exposed to 1-10 microM of both arsenicals to determine the relative extent of genetic damage. The unexposed controls showed similar (background) levels of damage in both cell lines and for both assays. Treatment with the arsenicals induced concentration-dependent increases in genetic damage in the two cell lines. Arsenite was more potent than arsenate in inducing DNA strand breaks in the Comet	2004

	assay; at the highest concentration (10 microM) arsenite produced similar levels of DNA damage in CHO-K1 and RTG-2 cells, while 10 microM arsenate was significantly more genotoxic in RTG-2 cells. MN induction was consistently higher in RTG-2 cells than in CHO-K1 cells, with 10 microM arsenite inducing an approximate 10-fold increase in both cell lines. MN induction also was positively correlated with DNA strand breaks for both arsenicals. Overall, the study demonstrated that the fish cells are more sensitive than the mammalian cells at environmentally realistic concentrations of both arsenicals, with arsenite being more toxic. Copyright 2004 Wiley-Liss, Inc.	
189.	Rossman TG, Komissarova EV, Uddin AN, Li P. Arsenite Depresses Poly(ADP-Ribosyl)Ation In Human Skin Keratinocytes And In Mouse Skin. Toxicologist 2004 Mar;78(1-S):390. Drinking arsenic-contaminated water is associated with neoplasias of the skin, lung, bladder, and possibly other sites. Previously, we demonstrated that arsenite in drinking water enhances solar ultraviolet irradiation-induced skin carcinoma in the mouse. We suggest that alterations in DNA repair and genomic stability play a role in arsenite carcinogenesis. Although DNA repair enzymes are not inhibited by arsenite, evidence suggests that poly(ADP-ribose) (PAR) synthesis is inhibited in arsenite treated cells. Poly(ADP-ribosyl)ation of proteins contributes to DNA repair and maintenance of genomic stability. Human skin keratinocytes (HaCaT) were exposed to 0.1µM sodium arsenite for different times, lysed, and levels of PAR and poly(ADP-ribose)polymerase (PARP-1) were analyzed by Western blotting. PARP- 1 protein levels increased up to 2.5 fold after 4 days exposure and remained high for at least 14 days. During this time, growth in arsenite caused decreases in total protein poly(ADP-ribosyl)ation, suggesting that arsenite inhibits PARP-1 enzyme activity. Because PARP-1 regulates its own transcription via PARP-1 auto-poly(ADPribosyl) ation, we suggest that the inhibition of PARP-1 activity by arsenite resulted in enhanced PARP-1 transcription. Arsenite's effects on protein poly(ADP-ribosyl) ation were also demonstrated in mice. Skh1 hairless mice were given 10 mg/l (non-toxic concentration) of sodium arsenite in drinking water for 29 weeks. Immunohistochemistry of normal skin obtained at the end of the experiment showed an increased epidermal thickness and decreased level of nuclear protein poly(ADP-ribosyl)ation, compared with control mice. Our results suggest that inhibition of poly(ADP-ribosyl)ation by arsenite may contribute to arsenite-associated carcinogenesis by its effects on DNA repair, DNA-damage-signaling, and transcription. We have constructed a vector for PARP-1 RNA interference to test the role of PARP-1 in arsenite-induced cell transformation.	2004
190.	Rossman TG, Uddin AN, Burns FJ. Evidence that arsenite acts as a cocarcinogen in skin cancer. Toxicol Appl Pharmacol. 2004 Aug 1;198(3):394-404. Inorganic arsenic (arsenite and arsenate) in drinking water has been associated with skin cancers in several countries such as Taiwan, Chile, Argentina, Bangladesh, and Mexico. This association has not been established in the United States. In addition, inorganic arsenic alone in drinking water does not cause skin cancers in animals. We recently showed that concentrations as low as 1.25 mg/l sodium arsenite were able to enhance the tumorigenicity of solar UV irradiation in mice. The tumors were almost all squamous cell carcinomas (SCCs). These data suggest that arsenic in drinking water may need a carcinogenic partner, such as sunlight, in the induction of skin cancers. Arsenite may enhance tumorigenicity via effects on DNA repair and DNA damage-induced cell cycle effects, leading to genomic instability. Others have found that dimethlyarsinic acid (DMA), a metabolite of arsenite, can induce bladder cancers at high concentrations in drinking water. In those experiments, skin cancers were not produced. Taken together, these data suggest that arsenite (or possibly an earlier metabolite), and not DMA, is responsible for the skin cancers, but a second genotoxic agent may be a requirement. The differences between the US and the other arsenic-exposed populations with regard to skin cancers might be explained by the lower levels of arsenic in the US, less sun exposure, better	2004

	nutrition, or perhaps genetic susceptibility differences.	
191.	Schoen A, Beck B, Sharma R, Dubé E. Arsenic toxicity at low doses: epidemiological and mode of action considerations. Toxicol Appl Pharmacol. 2004 Aug 1;198(3):253-67. Current approaches to risk assessment typically assume a linear dose-response for mutagenic compounds that directly interact with DNA or when the carcinogenic mechanism is unknown. Because the mode of action of arsenic-induced carcinogenesis is not well established, recent dose-response assessments for arsenic have assumed linearity at low doses despite evidence that arsenic is not a direct-acting mutagen. Several modes of action, including generation of oxidative stress, perturbation of DNA methylation patterns, inhibition of DNA repair, and modulation of signal transduction pathways, have been proposed to characterize arsenic's toxicity. It is probable that these mechanisms do not act in isolation, but overlap, and contribute to the complex nature of arsenic-induced carcinogenesis. All of the proposed mechanisms are likely to be nonlinear at low does. Furthermore, studies of populations outside the US exposed to arsenic in drinking water show increases in cancer only at relatively high concentrations, that is, concentrations in drinking water of several hundred micrograms per liter (microg/l). Studies in the US of populations exposed to average concentrations in drinking water up to about 190 microg/l do not provide evidence of increased cancer. Consideration of arsenic's plausible mechanisms and evidence from epidemiological studies support the use of nonlinear methods, either via biologically based modeling or use of a margin-of-exposure analysis, to characterize arsenic risks.	2004
192.	Schoen A, Beck B, Sharma R, Dube E. Evidence From Epidemiological And Mode Of Action Studies Support A Nonlinear Doseresponse Relationship For Arsenic-Induced Carcinogenesis. Toxicologist 2004 Mar;78(1-S):369. Recent risk assessments for arsenic conducted by both the USEPA (USEPA) and the National Research Council (NRC) have assumed a linear dose response for arsenic- induced carcinogenesis. In this presentation, we evaluate both epidemiological and mechanistic evidence and conclude that the dose-response for arsenic is likely to be nonlinear at low doses and unlikely to be of toxicological concern at levels commonly found in the US. While epidemiological studies of populations outside the US demonstrate that arsenic concentrations greater than several hundred mg/L are associated with cancer, studies in the US of populations exposed to elevated concentrations of arsenic in drinking water do not provide evidence of a doseresponse relationship between arsenic and increased cancer. We reviewed several proposed mechanisms of arsenic-induced carcinogenesis, including generation of oxidative stress, perturbation of DNA methylation patterns, inhibition of DNA repair, and modulation of signal transduction pathway. All of these mechanisms are consistent with a nonlinear (specifically sublinear) dose response relationship for arsenic. It is probable that these mechanisms do not act in isolation, but overlap, and contribute to the complex nature of arsenic-related cancers. Arsenic's toxicity can also be modulated by nutritional factors. Diets adequate in methyl donor groups (i.e., choline or methionine), selenium, and antioxidants (as is typical of the US diet) can mitigate arsenic's toxicity. Based on a consideration of arsenic's plausible mechanisms, modulation by nutritional factors, and of evidence from epidemiological studies, we recommend the use of non-linear methods, either via biologically based modeling or use of a margin-of-exposure analysis, to characterize arsenic cancer risks.	2004
193.	Sens DA, Park S, Gurel V, Sens MA, Garrett SH, Somji S. Inorganic cadmium- and arsenite-induced malignant transformation of human bladder urothelial cells. Toxicol Sci. 2004 May;79(1):56-63. Epub 2004 Feb 19. Arsenic and cadmium (Cd(+2)) are human carcinogens, and epidemiological studies have implicated both pollutants in the development of urinary bladder cancer. Despite this	2004

	epidemiological base, it is unknown if either Cd(+2) or arsenite (As(+3)) can directly cause the malignant transformation of human urothelial cells. The goal of this study was to determine if Cd(+2) and/or As(+3) are able to cause the malignant transformation of human urothelial cells. The strategy employed was to expose the nontumorigenic urothelial cell line UROtsa to long-term in vitro exposure to Cd(+2) and As(+3), with the endpoint being the ability of the cells to form colonies in soft agar and tumors when heterotransplanted into nude mice. It was demonstrated that a long-term exposure to either 1 M Cd(+2) or 1 M As(+3) resulted in the selection of cells that were able to form colonies in soft agar and tumors when heterotransplanted into nude mice. The histology of the tumor heterotransplants produced by UROtsa cells malignantly transformed by Cd(+2) had epithelial features consistent with those of a classic transitional-cell carcinoma of the bladder. The histology of the tumor heterotransplants produced by cells malignantly transformed by As(+3) was unique in that the cells displayed a prominent squamoid differentiation.	
194.	Sierra-Alvarez R, Cortinas I, Yenal U, Field JA. Methanogenic inhibition by arsenic compounds. Appl Environ Microbiol. 2004 Sep;70(9):5688-91. The acute acetoclastic methanogenic inhibition of several inorganic and organic arsenicals was assayed. Trivalent species, i.e., methylarsonous acid and arsenite, were highly inhibitory, with 50% inhibitory concentrations of 9.1 and 15.0 microM, respectively, whereas pentavalent species were generally nontoxic. The nitrophenylarsonate derivate, roxarsone, displayed moderate toxicity.	2004
195.	Somji S, Gurel V, Park S, Sens M, Garrett SH, Sens DA. Malignant Transformation Of Human Urothelial Cells By Arsenite And Cadmium. Toxicologist 2004 Mar;78(1-S):155. Cadmium and arsenite are human carcinogens and exposure to either of them has been associated with the development of bladder cancer. Neither cadmium or arsenite has been shown to elicit the malignant transformation of human urothelial cells under in vitro conditions, although such a model would be of value in elucidating the mechanism of carcinogenesis of both compounds. This laboratory has characterized an immortalized cell culture model of human urothelial cells (UROtsa) that does not form colonies in soft agar or produce tumor growth in nude mice. The goal of the present study was to determine if exposure of UROtsa cells to cadmium or arsenite would result in malignant transformation. UROtsa cells were grown on both serum-free and serum-containing growth medium to confluency and then exposed to cadmium and arsenite concentrations that produced greater than 90% cell death over a 30 to 60 day period. Surviving cells were allowed to grow back to confluency in the continued presence of cadmium or arsenite. At passage 4, 8, 12 and 16, the cultures were tested for their ability to form colonies in soft agar. At passage 4 and 8 no colonies were formed, at passage 12 a few colonies were formed, and at passage 16 a large number of colonies were formed in the soft agar assay. Cells at passage 16 from each treatment group were injected into nude mice and all 4 groups formed tumors. Control UROtsa cells of equal passage failed to form colonies in soft agar and did not form tumors in nude mice. Histological examination of the tumors demonstrated characteristics expected of transitional cell carcinoma of the bladder. Tumors produced from cells grown in serum tended to have features associated with high grade tumors while those from serum-free cells had features associated with low grade tumors. These studies show that both cadmium and arsenite can cause malignant transformation of human urothelial cells.	2004
196.	Steinmaus CM, Yuan Y, Smith AH. The temporal stability of arsenic concentrations in well water in western Nevada. Environ Res. 2005 Oct;99(2):164-8. Epub 2004 Dec 2. Millions of people worldwide are exposed to drinking water containing arsenic, and epidemiologic studies have identified associations between the ingestion of arsenic-	2004

	contaminated water and increased risks of cancer. In many of these studies, the assessment of arsenic exposure is based on a limited number of drinking water measurements, and the assessment of long-term or past exposure relies on the assumption that arsenic concentrations in sources of drinking water remain stable over time. In this investigation, the temporal stability of arsenic concentration was assessed in 759 wells in western Nevada state in the USA. Arsenic concentrations in these wells ranged from nondetectable to 6200 microg/L (median, 10 microg/L; standard deviation, 335 microg/L). Spearman correlation coefficients between arsenic concentrations measured in the same wells over a period of 1--5, 6--10, and 11--20 years apart were, respectively, 0.84 [95% confidence interval (CI), 0.81--0.86), 0.85 (95% CI, 0.81--0.88), and 0.94 (95% CI, 0.88--0.96). These findings suggest that, in this study area, arsenic concentrations in most wells remain stable over time and a limited number of measurements per well can be used to predict arsenic exposures over a period of many years.	
197.	Sun G. Arsenic contamination and arsenicosis in China. Toxicol Appl Pharmacol. 2004 Aug 1;198(3):268-71. Arsenicosis is a serious environmental chemical disease in China mainly caused by drinking water from pump wells contaminated by high levels of arsenic. Chronic exposure of humans to high concentrations of arsenic in drinking water is associated with skin lesions, peripheral vascular disease, hypertension, blackfoot disease, and high risk of cancers. Lead by the Ministry of Health of China, we carried out a research about arsenicosis in China recently. Areas contaminated with arsenic from drinking water are determined by 10% pump well water sample method while areas from burning coal are determined by existing data. Two epidemic areas of Shanxi Province and Inner Mongolia are investigated for the distribution of pump wells containing high arsenic. Well water in all the investigated villages of Shanxi Province showed polluted by high arsenic, and the average rate of unsafe pump well water is 52%. In Inner Mongolia, the high percentage of pump wells containing elevated arsenic is found only in a few villages. The average rate of unsafe pump well water is 11%. From our research, we find that new endemic areas are continuously emerging in China. Up to now, epidemic areas of arsenicosis mainly involve eight provinces and 37 counties in China. In the affected areas, the discovery of wells and coal with high levels of arsenic is continuing sporadically, and a similar scattered distribution pattern of patients is also being observed.	2004
198.	Thomas DJ. Enzymology Of Arsenic Methylation. Toxicologist 2004 Mar;78(1-S):128. A remarkable aspect of arsenic metabolism in many species is its conversion from inorganic species into methylated species. Thus, individuals ingesting inorganic arsenic excrete in urine inorganic and methylated arsenicals containing trivalent or pentavalent arsenic. Cyt19, an S-adenosyl-L-methionine-dependent-arsenic(III) methyltransferase purified from rat liver converts inorganic arsenic into methylated arsenicals. The protein is encoded by a cyt19 gene orthologous to mouse and human genes. Although exogenous reductants (dithiothreitol or tris (2-carboxylethyl) phosphine) support catalysis by recombinant rat cyt19 (rrcyt19), endogenous reductants that support its activity are unknown. Glutathione (GSH), the most abundant endogenous reductant, does not support catalysis by rrcyt19. However, the endogenous reductants, thioredoxin, glutaredoxin, and dihydrolipoic acid, coupled with thioredoxin reductase or glutathione reductase and NADPH, support its activity. Glutaredoxin and dihydrolipoic acid support its function in the presence of GSH. Aurothioglucose, an inhibitor of thioredoxin reductase, decreases arsenic methylation by rrcyt19 in thioredoxin-supported reactions. Endogenous reductants in guinea pig liver cytosol, a poor source of arsenic methyltransferase activity, support its catalytic activity. Dependence of enzyme activity on reductants is consistent with its function as an arsenate reductase. A CX7R motif in rrcyt19 resembles a CX5R motif of the P-loop structure in known arsenate reductases; like these proteins, cyt19 activity is stimulated by the presence of an oxyanion, phosphate. Endogenous	2004

	reductants may be required by rrcyt19 to catalyze the reduction of a methylarsonic (MAs(V)) intermediate to trivalency as a prerequisite for its conversion to a dimethylated product. Thus, cyt19 encodes a protein possessing both As(III) methyltransferase and arsenate reductase activities. Variation in cyt19 genotype may underlie phenotypic variation in the capacity to metabolize arsenic and interindividual differences in susceptibility to arsenic-induced diseases.	
199.	Tsuji JS, Benson R, Schoof RA, Hook GC. Health effect levels for risk assessment of childhood exposure to arsenic. Regul Toxicol Pharmacol. 2004 Apr;39(2):99-110. Health risks to children from chemicals in soil and consumer products have become a regulatory focus in the U.S. This study reviews short-term health effect levels for arsenic exposure in young children (i.e., 0-6 years old). Acute health effects are described mostly in adults in case reports of arsenic poisoning from water or food and in studies of medicinal arsenic treatment. Several epidemiological studies report health effects from subchronic arsenic exposure in children primarily from drinking water in developing countries. Acute health effects typically include gastrointestinal, neurological, and skin effects, and in a few cases facial edema and cardiac arrhythmia. Dermatoses are most consistently reported in both adults and children with subchronic exposure. With low exposure, the prevalence and severity of disease generally increases with age (i.e., length of exposure) and arsenic dose. The available data collectively indicate a lowest-observed-adverse-effect level around 0.05mg/kg-day for both acute and subchronic exposure. At low doses, children do not appear to be more sensitive than adults on a dose-per-body-weight basis, although data for acute exposures are limited and uncertainties exist for quantifying potential neurological or vascular effects at low-level subchronic exposures. Based on these data, possible reference levels for acute and subchronic exposure in young children are 0.015 and 0.005mg/kg-day, respectively.	2004
200.	Waalkes M, Beck BD, Thomas D, Kadiiska M, Del Razo M. The Role Of Methylation In Arsenic Toxicity & Risk: The Enigma Continues. Toxicologist 2004 Mar;78(1-S):128. Methylation of inorganic arsenic was originally considered to be solely a detoxification pathway. Recent studies have demonstrated that, in vitro, the trivalent monoand di-methylated species of inorganic arsenic are both highly cytotoxic and genotoxic. However, the relationship of these findings to in vivo responses and to risk assessment remains an area of on-going investigation and debate. This workshop will address toxicological differences among different states of arsenic as a function of methylation status and valence, and will consider how the role of methylation in toxicity may vary according to endpoint, tissue type, exposure duration, and animal species. Recent investigations into the enzymology of arsenic methylation including the role of co-factors will be described. The importance of reactive oxygen species in cytotoxicity and genotoxicity of inorganic versus methylated arsenic, both in vivo and in vitro, will be addressed. The use of human biomonitoring data, specifically arsenic species in urine, to elucidate the role of methylation in toxicity and to inform the role of methylation differences in susceptibility to arsenic will be discussed. Pharmacokinetic and toxicological differences between methylated species of arsenic as generated in the body via metabolism versus the same species when ingested will be discussed. Finally, the significance of these recent developments will be considered in the context of risk assessment for arsenic; the implications for the shape of dose-response curve as well as inter and intra-species variability will be discussed.	2004
201.	Waalkes MP, Liu J, Ward JM, Diwan BA. Mechanisms underlying arsenic carcinogenesis: hypersensitivity of mice exposed to inorganic arsenic during gestation. Toxicology. 2004 May 20;198(1-3):31-8. Inorganic arsenic is an important human carcinogen of unknown etiology. Defining carcinogenic mechanisms is critical to assessing the human health hazard of arsenic exposure	2004

	but requires appropriate model systems. It has proven difficult to induced tumors in animals with inorganic arsenic alone. Several groups have studied the carcinogenic potential of inorganic arsenic in rodents, finding it to act as co-promoter or co-carcinogen, but not as a complete carcinogen. As gestation is a time of high sensitivity to chemical carcinogenesis, we performed two in utero exposure studies with inorganic arsenic. In the first study, pregnant mice received drinking water containing sodium arsenite at 0 (control), 42.5 and 85 ppm arsenic from gestation day 8 to 18, and the offspring were observed for up to 90 weeks. As adults, male offspring developed hepatocellular carcinoma (HCC) and adrenal tumors after in utero arsenite exposure. Although liver tumors were not induced by arsenic in female offspring, they did develop lung carcinoma, ovarian tumors, and uterine and oviduct preneoplasia. In a second study, the same doses of arsenic were used and the skin tumor promoting phorbol ester, TPA, was applied to the skin after birth in an effort to promote skin tumors potentially initiated by arsenic in utero. TPA did not promote dermal tumors after in utero arsenite exposure. Otherwise, results from the second chronic study largely duplicated the first and, irrespective of additional TPA exposure, arsenic exposure in utero induced HCC and adrenal tumors in males and ovarian tumors in females. In addition, combined arsenic and TPA induced a significant increase in hepatocellular tumors in female offspring, although arsenic alone was not effective. Thus, in utero inorganic arsenic exposure can act as a complete carcinogen in mice, with brief exposures consistently inducing tumors at several sites. In addition, it appears gestational arsenic can act as a tumor initiator in the female mouse liver, inducing liver lesions that can be promoted by TPA.	
202.	Xia Y, Liu J. An overview on chronic arsenism via drinking water in PR China. Toxicology. 2004 May 20;198(1-3):25-9. Chronic endemic arsenism via drinking water was first found in Taiwan in 1968, and reported in Xinjiang Province in mainland China in the 1980s. Arsenism has become one of the most serious endemic diseases in China in the last two decades. Up to now, the disease has been found in Inner Mongolia, Shanxi, Ningxia, Jilin and Qinghai provinces. According to the Chinese maximum limit standard of arsenic (As) in drinking water, over 2 millions people have been exposed to high arsenic and about 10,000 persons were diagnosed as arsenism patients. There are different As concentrations in the water of different sites, even in the same area. Most of the As concentrations range from 0.05 to 2.0mg/l. The incidence of arsenism increases as As concentrations in drinking water and the drinking time increase. The age distribution of patients with arsenism ranged from 3 to 80 years old with peak prevalence in adults. A dose-effect relationship between the status of arsenism and arsenic level and drinking time has been shown. New high-arsenic areas in China have been discovered during recent investigations. In order to reduce the adverse health effects of arsenism, the central and local governments of China have provided significant funds to change water levels of As and at the same time take general measures to "reduce arsenic intake, remove arsenic from the body and treat the patients". After the implementation of these control measures in certain regions, the clinical symptoms and signs of 30% of the patients were improved. There was no change in 52% of patients and only 18% of patients got worse. It is suggested that future work in the research and control of arsenism in China should include: (1) identify all the high arsenic areas in China, (2) study the association of arsenism with fluorosis, (3) determine individual susceptibility, (4) select biomarkers for diagnosis in the early stage of a arsenism, and (5) investigate the molecular mechanisms of carcinogenesis.	2004
203.	Yoshida T, Yamauchi H, Fan Sun G. Chronic health effects in people exposed to arsenic via the drinking water: dose-response relationships in review. Toxicol Appl Pharmacol. 2004 Aug 1;198(3):243-52. Chronic arsenic (As) poisoning has become a worldwide public health issue. Most human As	2004

	exposure occurs from consumption of drinking water containing high amounts of inorganic As (iAs). In this paper, epidemiological studies conducted on the dose-response relationships between iAs exposure via the drinking water and related adverse health effects are reviewed. Before the review, the methods for evaluation of the individual As exposure are summarized and classified into two types, that is, the methods depending on As concentration of the drinking water and the methods depending on biological monitoring for As exposure; certain methods may be applied as optimum As exposure indexes to study dose-response relationship based on various As exposure situation. Chronic effects of iAs exposure via drinking water include skin lesions, neurological effects, hypertension, peripheral vascular disease, cardiovascular disease, respiratory disease, diabetes mellitus, and malignancies including skin cancer. The skin is quite sensitive to arsenic, and skin lesions are some of the most common and earliest nonmalignant effects related to chronic As exposure. The increase of prevalence in the skin lesions has been observed even at the exposure levels in the range of 0.005-0.01 mg/l As in drinking waters. Skin, lung, bladder, kidney, liver, and uterus are considered as sites As-induced malignancies, and the skin is though to be perhaps the most sensitive site. Prospective studies in large area of endemic As poisoning, like Bangladesh or China, where the rate of malignancies is expected to increase within the next several decades, will help to clarify the dose-response relationship between As exposure levels and adverse health effects with enhanced accuracy.	
204.	Andrew AS, Warren AJ, Barchowsky A, Temple KA, Klei L, Soucy NV, O'Hara KA, Hamilton JW. Genomic and proteomic profiling of responses to toxic metals in human lung cells. Environ Health Perspect. 2003 May;111(6):825-35. Examining global effects of toxic metals on gene expression can be useful for elucidating patterns of biological response, discovering underlying mechanisms of toxicity, and identifying candidate metal-specific genetic markers of exposure and response. Using a 1,200 gene nylon array, we examined changes in gene expression following low-dose, acute exposures of cadmium, chromium, arsenic, nickel, or mitomycin C (MMC) in BEAS-2B human bronchial epithelial cells. Total RNA was isolated from cells exposed to 3 M Cd(II) (as cadmium chloride), 10 M Cr(VI) (as sodium dichromate), 3 g/cm2 Ni(II) (as nickel subsulfide), 5 M or 50 M As(III) (as sodium arsenite), or 1 M MMC for 4 hr. Expression changes were verified at the protein level for several genes. Only a small subset of genes was differentially expressed in response to each agent: Cd, Cr, Ni, As (5 M), As (50 M), and MMC each differentially altered the expression of 25, 44, 31, 110, 65, and 16 individual genes, respectively. Few genes were commonly expressed among the various treatments. Only one gene was altered in response to all four metals (hsp90), and no gene overlapped among all five treatments. We also compared low-dose (5 M, noncytotoxic) and high-dose (50 M, cytotoxic) arsenic treatments, which surprisingly, affected expression of almost completely nonoverlapping subsets of genes, suggesting a threshold switch from a survival-based biological response at low doses to a death response at high doses.	2003
205.	Boffetta P, Nyberg F. Contribution of environmental factors to cancer risk. Br Med Bull. 2003;68:71-94. Environmental carcinogens, in a strict sense, include outdoor and indoor air pollutants, as well as soil and drinking water contaminants. An increased risk of mesothelioma has consistently been detected among individuals experiencing residential exposure to asbestos, whereas results for lung cancer are less consistent. At least 14 good-quality studies have investigated lung cancer risk from outdoor air pollution based on measurement of specific agents. Their results tend to show an increased risk in the categories at highest exposure, with relative risks in the range 1.5-2.0, which is not attributable to confounders. Results for other cancers are sparse. A causal association has been established between exposure to environmental tobacco smoke and	2003

	lung cancer, with a relative risk in the order of 1.2. Radon is another carcinogen present in indoor air which may be responsible for 1% of all lung cancers. In several Asian populations, an increased risk of lung cancer is present in women from indoor pollution from cooking and heating. There is strong evidence of an increased risk of bladder, skin and lung cancers following consumption of water with high arsenic contamination; results for other drinking water contaminants, including chlorination by-products, are inconclusive. A precise quantification of the burden of human cancer attributable to environmental exposure is problematic. However, despite the relatively small relative risks of cancer following exposure to environmental carcinogens, the number of cases that might be caused, assuming a causal relationship, is relatively large, as a result of the high prevalence of exposure.	
206.	Burnichon V, Jean S, Bellon L, Maraninchi M, Bideau C, Orsière T, Margotat A, Gérolami V, Botta A, Bergé-Lefranc JL. Patterns of gene expressions induced by arsenic trioxide in cultured human fibroblasts. Toxicol Lett. 2003 Jul 20;143(2):155-62. Arsenic exposure is associated with several human diseases and particularly, with neoplasia. Although the mechanism of arsenic toxicity is not fully understood, several recent works pointed out the involvement of oxidative stress in arsenic-induced DNA damage that, in living cells, correlates with changes in gene expressions. In cultured human fibroblasts exposed for 24 h to micromolar arsenic concentrations, we studied, using real-time RT-PCR, the expression profile of a limited number of genes: genes coding for a stress protein (HSP70), transcription factors (cJUN, cFOS, ETR103, ETR101 and TTP) and cell cycle or DNA repair proteins (P21, GADD153). We observed that the expression profile of genes followed individual different patterns that can be summed up in early-transient gene expression by contrast to delayed gene expression.	2003
207.	Cabrera HN, Gómez ML. Skin cancer induced by arsenic in the water. J Cutan Med Surg. 2003 Mar-Apr;7(2):106-11. Epub 2002 Nov 27. BACKGROUND: Arsenic (As) is a well-recognized poison. Exposure may be of an acute nature, leading to high concentrations and acute arsenic poisoning. Chronic exposure may lead to benign skin changes, skin cancer, and internal malignancy. OBJECTIVE: Our purpose was to study the nature, incidence, and sequelae of skin disorders in a group of Argentinean patients suffering from chronic arsenicism due to the intake of contaminated well water. METHODS: All patients who presented with chronic arsenicism at the Dermatology Department of Hospital Posadas (Buenos Aires, Argentina) during a 10-year period (1988-1998) were included in this study. The patient group compromised 9 women and 14 men, the age range was 37-72 years. Diagnosis was based on the clinical triad (keratoderma, leucoderma and epiteliomatosis). We performed clinical, laboratory, and histopathologic studies to confirm diagnosis. We screened for possible internal diseases. RESULTS: All patients included in this study had cutaneous lesions associated with long-term arsenic exposure. The mean age of the patients was 58.2 years. The estimated mean time of the beginning of the lesions was of 3.7 years. All patients were Argentinean from endemic areas of our country where the arsenic levels are higher than those accepted by the World Health Organization. CONCLUSION: This study allows us to conclude that the relationship between arsenic and cancer is frequent and it describes the principal characteristics of this entity in our group of patients.	2003
208.	Chen YC, Xu L, Guo YL, Su HJ, Hsueh YM, Smith TJ, Ryan LM, Lee MS, Chaor SC, Lee JY, Christiani DC. Genetic polymorphism in p53 codon 72 and skin cancer in southwestern Taiwan. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2003 Jan;38(1):201-11. The Pro/Pro polymorphism of p53 codon 72 has been reported to be related to bladder and lung cancer, but its relationship with skin cancer is unclear. We assessed the hypothesis that there is	2003

	a relationship between the p53 codon 72, Pro/Pro polymorphism, cumulative arsenic exposure, and the risk of skin cancer in a hospital-based case-control study in southwestern Taiwan. From 1996 to 1999, 93 newly-diagnosed skin cancer patients at the National Cheng-Kung University (NCKU) Hospital and 71 community controls matched on residence were recruited in southwestern Taiwan. The genotype of p53 codon 72 (Arg/Arg, Arg/Pro, or Pro/Pro) was determined for all subjects by polymerase chain reaction-restricted fragment length polymorphism (PCR-RFLP). A questionnaire was administered to each subject for collection of demographic information, personal habits, disease history, diet information, and other relevant questions. The Pro/Pro (homozygous) genotype was more frequent in skin cancer patients (cases, 20%; controls, 12%; P = 0.37). Subjects with the susceptible genotype Pro/Pro and heterozygous (intermediate) genotype Pro/Arg had 2.18 and 0.99 times risk of skin cancer than the wild type Arg/Arg (95% confidence interval, 0.74-4.38; 95% confidence interval, 0.44-2.21), respectively. Compared with subjects with 18.5 < BMI < 23, subjects with BMI > 18.5 had 5.78 times risk of skin cancer (95% confidence interval, 1.06 to 31.36) after adjusting for other risk factors. There was no interaction between BMI and genotype, but the sample size was small. The risk of skin cancer did not significantly vary by tumor cell-type. The risk of skin cancer is increased in individuals with the Pro/Pro genotype. Larger, confirmatory studies are needed to clarify the role of constitutional polymorphisms in p53 and skin cancer risk.	
209.	Frost FJ, Muller T, Petersen HV, Thomson B, Tollestrup K. Identifying US populations for the study of health effects related to drinking water arsenic. J Expo Anal Environ Epidemiol. 2003 May;13(3):231-9. The US Environmental Protection Agency recently set a new maximum contaminant level (MCL) for arsenic in drinking water of 10 micro g/l. In this paper, we review the completeness and accuracy of drinking water arsenic occurrence data in the United States and identify populations exposed to elevated arsenic concentrations that would be suitable for epidemiological studies of arsenic health effects. Using existing data from the Environmental Protection Agency Arsenic Occurrence and Exposure Database and additional data from state health and environment departments and water utilities, we identified 33 counties in 11 states with an estimated mean drinking water arsenic concentration of 10 micro g/l or greater. A total of 11 of these 'confirmed' counties had an estimated mean arsenic concentration of 20 micro g/l or more and two had an estimated mean arsenic concentration 50 micro g/l or more. Based on census data, between 1950 and 1999 there were approximately 51.1 million person-years of exposure to drinking water arsenic at levels of 10 micro g/l or more, 8.2 million at levels of 20 micro g/l or more arsenic and 0.9 million at levels of 50 micro g/l or more. Mortality and incidence of diseases known to be associated with arsenic exposure can and should be examined in these counties as part of a comprehensive assessment of arsenic health effects in US populations.	2003
210.	Haque R, Mazumder DN, Samanta S, Ghosh N, Kalman D, Smith MM, Mitra S, Santra A, Lahiri S, Das S, De BK, Smith AH. Arsenic in drinking water and skin lesions: dose-response data from West Bengal, India. Epidemiology. 2003 Mar;14(2):174-82. BACKGROUND: Over 6 million people live in areas of West Bengal, India, where groundwater sources are contaminated with naturally occurring arsenic. The key objective of this nested case-control study was to characterize the dose-response relation between low arsenic concentrations in drinking water and arsenic-induced skin keratoses and hyperpigmentation. METHODS: We selected cases (persons with arsenic-induced skin lesions) and age- and sex-matched controls from participants in a 1995-1996 cross-sectional survey in West Bengal. We used a detailed assessment of arsenic exposure that covered at least 20 years. Participants were reexamined between 1998 and 2000. Consensus agreement by four physicians reviewing the skin lesion photographs confirmed the diagnosis in 87% of cases	2003

	clinically diagnosed in the field. RESULTS: The average peak arsenic concentration in drinking water was 325 microg/liter for cases and 180 microg/liter for controls. The average latency for skin lesions was 23 years from first exposure. We found strong dose-response gradients with both peak and average arsenic water concentrations. CONCLUSIONS: The lowest peak arsenic ingested by a confirmed case was 115 microg/liter. Confirmation of case diagnosis and intensive longitudinal exposure assessment provide the basis for a detailed dose-response evaluation of arsenic-caused skin lesions.	
211.	He QY, Yip TT, Li M, Chiu JF. Proteomic analyses of arsenic-induced cell transformation with SELDI-TOF ProteinChip technology. J Cell Biochem. 2003 Jan 1;88(1):1-8. In this study, we demonstrated that low levels (1.5 microM) of arsenite induces B[a]P-treated lung cell transformation. We then used a proteomic approach to identify protein expression by ProteinChips, which could potentially be important for transformation induced by this toxic metal. Most of the protein peaks in cell extracts of all samples, including the control, B[a]P-treated, and B[a]P + As-treated cells are identical. However, surface-enhanced laser desorption/ionization time of flight (SELDI-TOF) analysis with Cu-ProteinChips and WCX-ProteinChips revealed several dramatically different protein peaks that appeared in lung cells after being transformed by a treatment of 1.5 microM arsenite for 12 weeks. SAX2 ProteinChip also identified a prominent protein peak that was preferentially expressed in control cells. Interestingly, by using a SAX2 chip, we were able to detect several protein peaks that increased their expression in lung epithelial cells (LEC) treated with only B[a]P. Identification and characterization of these proteins may reveal the molecular basis of As-induced cell transformation and provide insight into the mechanisms by which arsenic induces carcinogenesis. Copyright 2002 Wiley-Liss, Inc.	2003
212.	Khan MM, Sakauchi F, Sonoda T, Washio M, Mori M. Magnitude of arsenic toxicity in tube-well drinking water in Bangladesh and its adverse effects on human health including cancer: evidence from a review of the literature. Asian Pac J Cancer Prev. 2003 Jan-Mar;4(1):7-14. Only after a decade from 1993, arsenic contamination of groundwater in Bangladesh has been reported as the biggest arsenic catastrophe in the world. It is a burning public health issue in this country. More than 50 percent of the total population is estimated at risk of contamination. Already thousands of people have been affected by the disease arsenicosis. Many more may be on the way to manifest lesions in future. We conducted a review of previous studies and published articles including MEDLINE database on this issue. We found that 59 districts out of 64 have been already affected by arsenic in underground drinking water, where this particular source of drinking water is the main source for 97 percent of the rural people. The water is unfortunately now a great threat for the human being due to high level of arsenic. Continuous arsenic exposure can lead people to develop arsenicosis, which in turn elevates the risk of cancer. Skin lesions are the most common manifestations in arsenicosis patients. Relatively poor rural people and other socio-economically disadvantaged groups are more affected by this exposure. Until now cancer patients have been relatively limited in Bangladesh. One of the reasons may be that several years are needed to show cancer manifestations from the beginning of arsenic exposure. But it is suspected that after some years a large number of patients will appear with cancer in different sites for arsenic exposure in drinking water. Various studies have been conducted in arsenic affected countries - notably in Argentina, Chile, China, Japan, and Taiwan -to find the potential of arsenic exposure to cause development of cancer. Among the arsenic related cancers, liver, lung, skin, bladder and kidney cancers are reported to be prevalent in these countries. Unfortunately no scientific study has been yet conducted in Bangladesh to find the relationship between arsenic exposure and cancers in different sites of the body. So our aim is to conduct an ecological as well as a case-control study in the country in the future.	2003

213.	Lu, X., Arnold, L.L., Cohen, S.M., Cullen, W.R., and Le, C. (2003) Speciation of dimethylarsinous acid and trimethylarsine oxide in urine from rats fed with dimethylarsinic acid and dimercaptopropane sulfonate. Anal Chem. 2003 Dec 1;75(23):6463-8. Speciation of arsenic in urine from rats treated with dimethylarsinic acid (DMA(V)) alone or in combination with dimercaptopropane sulfonate (DMPS) were studied. Methods were developed for the determination of the methylarsenic metabolites, especially trace levels of dimethylarsinous acid (DMA(III)) and trimethylarsine oxide (TMAO), in the presence of a large excess of DMA(V). Success was achieved by using improved ion-exchange chromatographic separation combined with hydride generation atomic fluorescence detection. Micromolar concentrations of DMA(III) were detected in urine of rats fed with a diet supplemented with either 100 microg/g of DMA(V) or a mixture of 100 microg/g of DMA(V) and 5600 microg/g of DMPS. No significant difference in the DMA(III) concentration was observed between the two groups; however, there was a significant difference in TMAO concentrations. Urine from rats fed with the diet supplemented with DMA(V) alone contained 73 +/- 30 microM TMAO, whereas urine from rats fed with the diet supplemented with both DMA(V) and DMPS contained only 2.8 +/- 1.4 microM TMAO. Solutions containing mixtures of 100 microg/L DMA(V) or TMAO and 5600 microg/L DMPS did not show reduction of DMA(V) and TMAO. The significant decrease ($p < 0.001$) of the TMAO concentration in rats administered with both DMA(V) and DMPS suggests that DMPS inhibits the biomethylation of arsenic.	2003
214.	Perez DS, Armstrong-Lea L, Fox MH, Yang RS, Campain JA. Arsenic and benzo[a]pyrene differentially alter the capacity for differentiation and growth properties of primary human epidermal keratinocytes. Toxicol Sci. 2003 Dec;76(2):280-90. Epub 2003 Sep 11. Normal human epidermal keratinocytes (NHEK) have been chosen as an in vitro model to test the hypothesis that chemicals which alter or interfere in cellular differentiation will concomitantly induce growth perturbations and are, thus, potential carcinogens. In these studies, we have focused on two known skin carcinogens, arsenic and benzo(a)pyrene (BaP). Our results demonstrated that BaP inhibits terminal differentiation in NHEK, as measured by cross-linked envelope (CLE) formation, up to 5.8-fold in control and 1.7-fold in calcium (Ca2+)-treated cells. In comparison, arsenic decreased CLE formation 20-fold in control cells and 5.5-fold in Ca2+-treated NHEK. To characterize the effects of these agents on the growth rate and cell cycle distributions of NHEK, flow cytometric analysis was used. BaP at 2 microM increased proliferation rates by 29%. Altered cell-cycle distribution in BaP-treated cells indicated a more rapid progression through the cell cycle, possibly by a shortened G2 phase. In contrast, arsenic at 5 microM inhibited proliferation by 25%; growth arrest (9%) was also observed in NHEK treated with 2 mM Ca2+. Our findings suggest that, although both BaP and arsenic inhibit CLE production in NHEK, different mechanisms may be involved. Studies in progress will attempt to identify molecular markers involved in the observed chemical effects. These markers will facilitate a mechanistic understanding of how an altered balance between growth and differentiation may play a role in the transformation process in NHEK.	2003
215.	Rahman MM, Mandal BK, Chowdhury TR, Sengupta MK, Chowdhury UK, Lodh D, Chanda CR, Basu GK, Mukherjee SC, Saha KC, Chakraborti D. Arsenic groundwater contamination and sufferings of people in North 24-Parganas, one of the nine arsenic affected districts of West Bengal, India. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2003 Jan;38(1):25-59. To understand the magnitude of the arsenic calamity in West Bengal, a detailed study spanning 7 years was made in North 24-Parganas, one of the nine arsenic affected districts. Area and population of North 24-Parganas district are 4093.82 sq. km and 7.3 million, respectively.	2003

	Fourty eight thousand and thirty water samples were analyzed from hand tubewells of North 24-Parganas in use for drinking, cooking and 29.2% of the tubewells were found to have arsenic above 50 microg/L, the maximum permissible limit of World Health Organization (WHO) and 52.8% have arsenic above 10 microg/L, WHO recommended value of arsenic in drinking water. Out of the 22 blocks of North 24-Parganas, in 20 blocks arsenic has been found above the maximum permissible limit and so far in 16 blocks people have been identified as suffering from arsenical skin lesions. From the generated data, it is estimated that about 2.0 million and 1.0 million people are drinking arsenic contaminated water above 10 microg/L and 50 microg/L level, respectively in North 24-Parganas alone. So far, in our preliminary study 33,000 people have been examined at random from arsenic affected villages in North 24-Parganas and 2274 people have been registered with arsenical skin lesions. Extrapolation of the available data indicates about 0.1 million people may be suffering from arsenical skin lesions from North 24-Parganas alone. A sum of 21,000 hair, nail, and urine samples analyses from arsenic affected villages show 56%, 80%, and 87% people have arsenic in biological specimen more than normal/toxic (hair) level, respectively. Thus, many may be subclinically affected. Due to use of arsenic contaminated groundwater for agricultural irrigation, rice and vegetable are getting arsenic contaminated. Hence there is an additional arsenic burden from food chain. People from arsenic affected villages are also suffering from arsenical neuropathy. A followup study indicates that many of the victims suffering from severe arsenical skin lesions for several years are now suffering from cancer or have already died of cancer.	
216.	Roychowdhury T, Tokunaga H, Ando M. Survey of arsenic and other heavy metals in food composites and drinking water and estimation of dietary intake by the villagers from an arsenic-affected area of West Bengal, India. Sci Total Environ. 2003 Jun 1;308(1-3):15-35. An investigation of arsenic, copper, nickel, manganese, zinc and selenium concentration in foodstuffs and drinking water, collected from 34 families and estimation of the average daily dietary intake were carried out in the arsenic-affected areas of the Jalangi and Domkal blocks, Murshidabad district, West Bengal where arsenic-contaminated groundwater (mean: 0.11 mg/l, n=34) is the main source for drinking. The shallow large diameter tubewells, installed for agricultural irrigation contain an appreciable amount of arsenic (mean: 0.094 mg/l, n=10). So some arsenic can be expected in the food chain and food cultivated in this area. Most of the individual food composites contain a considerable amount of arsenic. The mean arsenic levels in food categories are vegetables (20.9 and 21.2 microg/kg), cereals and bakery goods (130 and 179 microg/kg) and spices (133 and 202 microg/kg) for the Jalangi and Domkal blocks, respectively. For all other heavy metals, the observed mean concentration values are mostly in good agreement with the reported values around the world (except higher zinc in cereals). The provisional tolerable daily intake value of inorganic arsenic microg/kg body wt./day) is: for adult males (11.8 and 9.4); adult females (13.9 and 11); and children (15.3 and 12) in the Jalangi and Domkal blocks, respectively (according to FAO/WHO report, the value is 2.1 microg/kg body wt./day). According to WHO, intake of 1.0 mg of inorganic arsenic per day may give rise to skin lesions within a few years. The average daily dietary intake of copper, nickel and manganese is high, whereas for zinc, the value is low (for adult males: 8.34 and 10.2 mg/day; adult females: 8.26 and 10.3 mg/day; and children: 4.59 and 5.66 mg/day) in the Jalangi and Domkal blocks, respectively, compared to the recommended dietary allowance of zinc for adult males, adult females and children (15, 12 and 10 mg/day, respectively). The average daily dietary intake of selenium microg/kg body wt./day) is on the lower side for the children (1.07 and 1.22), comparable for the adult males (0.81 and 0.95) and slightly on the higher side for the adult females (1.08 and 1.26), compared to the recommended value (1.7 and 0.9 microg/kg body wt./day for infants and adults, respectively).	2003
217.	Salim EI, Wanibuchi H, Morimura K, Wei M, Mitsuhashi M, Yoshida K, Endo G, Fukushima S. Carcinogenicity of dimethylarsinic acid in p53 heterozygous knockout and wild-type	2003

	C57BL/6J mice. Carcinogenesis. 2003 Feb;24(2):335-42. There is abundant epidemiological evidence that arsenic is an environmental carcinogen related to human cancers of the skin, lung, liver and urinary bladder, in particular. Dimethylarsinic acid (DMA) has also been reported to act as a carcinogen/or a promoter in rat models. To elucidate molecular mechanisms, we conducted an 18 month carcinogenicity study of DMA in p53 heterozygous (+/-) knockout mice, which are susceptible to early spontaneous development of various types of tumors, and wild-type (+/+) C57BL/6J mice. Totals of 88-90 males, 7-8 weeks of age, were divided into three groups each administered 0, 50 or 200 p.p.m. DMA in their drinking water for 18 months. Mice that were found moribund or died before the end of the study were autopsied to evaluate the tumor induction levels, as well as those killed at the end. Both p53(+/-) knockout and wild-type mice demonstrated spontaneous tumor development, but lesions were more prevalent in the knockout case. Carcinogenic effect of DMA was evident by significant early induction of tumors in both treated p53(+/-) knockout and wild-type mice, significant increase of the tumor multiplicity in 200 p.p.m.-treated p53(+/-) knockout mice, and by significant increase in the incidence and multiplicity of tumors (malignant lymphomas) in the treated wild-type mice. By the end of 80 weeks, tumor induction, particularly malignant lymphomas and sarcomas, were similar in treated and control p53(+/-) knockout mice. No evidence for organ-tumor specificity of DMA was obtained. Molecular analysis using PCR-SSCP techniques revealed no p53 mutations in lymphomas from either p53(+/-) knockout or wild-type mice. In conclusion, DMA primarily exerted its carcinogenic effect on spontaneous development of tumors with both of the animal genotypes investigated here.	
218.	Tollestrup K, Frost FJ, Harter LC, McMillan GP. Mortality among children residing near the American Smelting and Refining Company (ASARCO) copper smelter in Ruston, Washington. Arch Environ Health. 2003 Nov;58(11):683-91. A retrospective cohort study was undertaken to determine whether childhood exposure to ambient arsenic was associated with increased mortality rates. Cohort members comprised children who had lived within 4.0 km (2.5 mi) of the American Smelting and Refining Company (ASARCO) copper smelter and arsenic refinery in Ruston, Washington, for at least 2 yr during the time period from 1907 to 1932. The cohort included 1,827 boys and 1,305 girls identified from school census records. Exposure intensity was computed as the total number of years a child had lived at a residence less than 1.6 km (1.0 mi) from the smelter stack during the study period. In only one exposure intensity group (i.e., residence > or = 10.0 yr less than 1.6 km [1.0 mi] from the smelter) for boys were Cox proportional hazards ratios significantly higher than 1.00: for all causes of death (1.52), ischemic heart disease (1.77), and external causes (1.93). For girls, hazard ratios were not elevated significantly for any cause of death in any exposure intensity group.	2003
219.	Yamaguchi F, Tsutsui T. Cell-transforming activity of fourteen chemical agents used in dental practice in Syrian hamster embryo cells. J Pharmacol Sci. 2003 Dec;93(4):497-500. Fourteen chemical agents used in dental practice were assessed for their cell-transforming activity using the Syrian hamster embryo (SHE) cell transformation assay system. The cell-transforming activity was quantitatively assessed by the frequency of morphological transformation (MT) in SHE cells induced by these agents. MT was induced by m-cresol, guaiacol, formaldehyde, sodium hypochlorite, hydrogen peroxide, sodium arsenite, acid fuchsin, and basic fuchsin, but not by p-chlorophenol, p-phenolsulfonic acid, glutaraldehyde, and erythrosine B. Iodine and chlorhexidine exhibited positive and pseudopositive responses, respectively. The chemical agents exhibiting a negative or pseudopositive response neither induced nor enhanced MT even in the presence of exogenous metabolic activation.	2003

220.	Yáñez L, García-Nieto E, Rojas E, Carrizales L, Mejía J, Calderón J, Razo I, Díaz-Barriga F. DNA damage in blood cells from children exposed to arsenic and lead in a mining area. Environ Res. 2003 Nov;93(3):231-40. In this work, we studied the frequency of DNA damage in children living in Villa de la Paz, Mexico, a mining site contaminated with arsenic and lead. DNA damage in blood cells was assessed using the Comet assay, and the results were compared to those found in children living in a less exposed town (Matehuala). In Villa de la Paz, high concentrations of arsenic and lead in surface soil and household dust were found. All of the soil samples had concentrations above 100 mg/kg of arsenic, and 58% of the samples were higher than 400 mg/kg of lead (these concentrations are used as intervention guidelines by the United States Environmental Protection Agency). In agreement with the environmental results, urinary arsenic in children living in Villa de la Paz (geometric mean 136 microg/g creatinine) was significantly higher than that found in children living in Matehuala (34 microg/g creatinine). Blood lead levels were also significantly higher in children from Villa de la Paz (11.6 microg/dL) than in children from Matehuala (8.3 microg/dL). The results of the Comet assay showed that the tail length and the tail moment in children living in Villa de la Paz were higher than those observed for children in Matehuala ($P<0.05$). Taking all the data into account, our study has shown increased DNA damage in children exposed to arsenic and lead in the mining site of Villa de la Paz.	2003
221.	Zhou X, Yoshida K, Kuroda K, Endo Y, Endo G. Effects of cysteine on the cytotoxicity of arsenic compounds. Arch Environ Contam Toxicol. 2003 Oct;45(3):324-30. Effects of cysteine on the cytotoxicity of arsenic compounds, such as arsenite, arsenate, methylarsonic acid (MMA), and dimethylarsinic acid (DMA), were investigated in cultured human HL-60 cells. Using adenosine triphosphate bioluminescence assay, the rank order of the mixtures of arsenicals with cysteine was: DMA > arsenite > arsenate > MMA. The IC50 of DMA with equimolar cysteine was approximately 7.7 microM, nearly two orders of magnitude lower than that of DMA alone. Apoptotic cells were examined by the TUNEL method, and cysteine was found to enhance the induction of apoptosis by arsenicals. Using LC-ICP-MS, trivalent arsenic was detected in the mixtures of arsenate, DMA, and MMA with cysteine. These results suggested that the trivalent arsenic in the mixtures of arsenicals with cysteine might account for the enhanced cytotoxicity as well as apoptosis, and that cysteine is involved in induction of the adverse effects of arsenicals in humans.	2003
222.	Baudouin C, Charveron M, Tarroux R, Gall Y. Environmental pollutants and skin cancer. Cell Biol Toxicol. 2002;18(5):341-8. We are increasingly exposed to environmental pollution. Pollutants can be inhaled, ingested or come into contact with the skin depending on the form in which they occur. On metabolization, activation, or accumulation, pollutants can become extremely toxic for the vital organs and this is often related to a strong genotoxic effect. Since the skin acts as a barrier between the organism and the environment, it is frequently directly exposed to pollution. It is very often degraded by polluting agents and acts as an inlet toward other tissues. Numerous studies in man recognize and demonstrate the carcinogenic power of certain pollutants in the digestive and respiratory tracts. The "pollutants" that react most specifically with the skin are: ultraviolet radiation, polycyclic aromatic hydrocarbons (e.g., benzo[a]pyrene), volatile organic compounds (e.g., benzene), heavy metals, and ozone. Ultraviolet radiation, a "physical" pollutant, has been described as being the factor responsible for most skin cancers in man. The genotoxicity of UV light is well documented (type of lesion or mutation, etc.) and its carcinogenic effect is clearly demonstrated in vivo in man. A few epidemiological studies describe the carcinogenicity of certain pollutants such as arsenic or lead on the skin. However,	2002

	most of the evidence for the role of pollutants in skin cancers comes from in vivo animal studies or from in vitro studies (e.g., PAHs). In this report, different studies are presented to illustrate the research strategies developed to investigate the mechanism of action of "chemical" pollutants and their potential role in human skin pathology. All the study models and the associated techniques of investigation are tools for a better understanding and thus more efficient prevention of the deleterious effects caused by the environment.	
223.	Beyersmann D. Effects of carcinogenic metals on gene expression. Toxicol Lett. 2002 Feb 28;127(1-3):63-8. Six metals and/or their compounds have been recognized as carcinogens: arsenic, beryllium, cadmium, chromium, cobalt and nickel. With the exception of arsenic, the main rote of exposure is inhalation and the main target organ is the lung. Arsenic is exceptional because it also produces tumors of skin and lung after oral uptake. With the exception of hexavalent chromium, carcinogenic metals are weak mutagens, if at all, and their mechanisms of carcinogenicity are still far from clear. A general feature of arsenic, cadmium, cobalt and nickel is their property to enhance the mutagenicity and carcinogenicity of directly acting genotoxic agents. These properties can be interpreted in terms of the ability of these metals to inhibit the repair of damaged DNA. However, because carcinogenic metals cause tumor development in experimental animals even under exclusion of further carcinogens, other mechanisms have to be envisaged, too. Evidence will be discussed that carcinogenic metal compounds alter patterns of gene expression leading to stimulated cell proliferation, either by activation of early genes (proto-oncogenes) or by interference with genes downregulating cell growth. Special reference will be devoted to the effects of cadmium and arsenic on gene expression, which have been studied extensively. Possible implications for occupational safety and health will be discussed.	2002
224.	Brown KG, Ross GL; American Council on Science and Health. Arsenic, drinking water, and health: a position paper of the American Council on Science and Health. Regul Toxicol Pharmacol. 2002 Oct;36(2):162-74. The purpose of this American Council on Science and Health report is to review issues and sources of uncertainty affecting assessment of potential health risks related to drinking water in the United States. Some background is included on how these issues arose, as is a review of the 1999 National Research Council report (with references to an updated version), to formulate a position based on the current science concerning how much of a risk of adverse health effects actually exists from arsenic in drinking water in the United States. ACSH concludes that there is clear evidence that chronic exposure to inorganic arsenic at concentrations of at least several hundred micrograms per liter may cause: (1) cancer of skin, bladder, lung (and possibly several other internal organs, including kidney, liver, and prostate), and (2) noncancer effects, including classic cutaneous manifestations that are distinctive and characteristic of chronic arsenic poisoning (diffuse or spotted hyperpigmentation and palmar-plantar hyperkeratoses). Noncancer effects may be multisystemic, with some evidence of peripheral vascular, cardiovascular, and cerebrovascular disease, diabetes, and adverse reproductive outcomes. Further study is needed to know if beneficial effects of arsenic in animal studies apply to humans. ACSH concludes that there is little, if any, evidence of a detrimental health effect in humans from inorganic arsenic in drinking water at the current maximum contaminant level (MCL) of 50 microg/L or below, either in the United States or elsewhere. As noted in the 1999 NRC report, "No human studies of sufficient statistical power or scope have examined whether consumption of arsenic in drinking water at the current MCL results in an increased incidence of cancer or noncancer effects" (NRC, 1999, p. 7). Based on our review, described in this article, ACSH finds that the limitations of the epidemiological data available and the state-of-the-science on the mode-of-action of arsenic toxicity, including can cer, are inadequate to	2002

	support the conclusion that there are adverse health effects in the United States from arsenic in drinking water at or below the limit of 50 microg/L. Copyright 2002 Elsevier Science (USA)	
225.	Chen F, Shi X. Intracellular signal transduction of cells in response to carcinogenic metals. Crit Rev Oncol Hematol. 2002 Apr;42(1):105-21. Epidemiological and animal studies suggest that several metals and metal-containing compounds are potent mutagens and carcinogens. These metals include chromium, arsenic, vanadium, nickel, and others. During the last two decades, chemical and cellular studies have contributed enormously to our understanding of the mechanisms of metal-induced pathophysiological processes. Although each of these metals is unique in its mechanism of action, some common signaling molecules, such as reactive oxygen species (ROS), may be shared by many of the carcinogenic metals. New techniques are now available to reveal the mechanisms of carcinogenesis in precise molecular terms. In this review, we focused our attentions on carcinogenic metal-induced signal transduction pathways leading to the activation of NF-kappaB, cell apoptosis and cell cycle progression, three crucial steps or events involved in the transformation and carcinogenesis. This review summarizes current knowledge and our recent studies concerning intracellular signal transduction pathways initiated by carcinogenic metals and the cross-talk that occurs among these pathways in cells in response to metals.	2002
226.	Frost F, Craun G, Brown KG. Detection of excess arsenic-related cancer risks. Environ Health Perspect. 2002 Jan;110(1):A12-3. No abstract	2002
227.	Hartwig A, Asmuss M, Ehleben I, Herzer U, Kostelac D, Pelzer A, Schwerdtle T, Bürkle A. Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. Environ Health Perspect. 2002 Oct;110 Suppl 5:797-9. Nickel, cadmium, cobalt, and arsenic compounds are well-known carcinogens to humans and experimental animals. Even though their DNA-damaging potentials are rather weak, they interfere with the nucleotide and base excision repair at low, noncytotoxic concentrations. For example, both water-soluble Ni(II) and particulate black NiO greatly reduced the repair of DNA adducts induced by benzo[a]pyrene, an important environmental pollutant. Furthermore, Ni(II), As(III), and Co(II) interfered with cell cycle progression and cell cycle control in response to ultraviolet C radiation. As potential molecular targets, interactions with so-called zinc finger proteins involved in DNA repair and/or DNA damage signaling were investigated. We observed an inactivation of the bacterial formamidopyrimidine-DNA glycosylase (Fpg), the mammalian xeroderma pigmentosum group A protein (XPA), and the poly(adenosine diphosphate-ribose)polymerase (PARP). Although all proteins were inhibited by Cd(II) and Cu(II), XPA and PARP but not Fpg were inhibited by Co(II) and Ni(II). As(III) deserves special attention, as it inactivated only PARP, but did so at very low concentrations starting from 10 nM. Because DNA is permanently damaged by endogenous and environmental factors, functioning processing of DNA lesions is an important prerequisite for maintaining genomic integrity; its inactivation by metal compounds may therefore constitute an important mechanism of metal-related carcinogenicity.	2002
228.	Hartwig A, Schwerdtle T. Interactions by carcinogenic metal compounds with DNA repair processes: toxicological implications. Toxicol Lett. 2002 Feb 28;127(1-3):47-54. Even though compounds of nickel, arsenic, cobalt and cadmium are carcinogenic, their mutagenic potentials are rather weak. In contrast, they exert pronounced comutagenic effects, which may be explained by disturbances of different DNA repair systems. Thus, cobalt, arsenic, nickel and cadmium interfere with base and nucleotide excision repair, even though	2002

	they affect different steps of the respective repair systems and act by different, not yet completely understood mechanisms. Potential target molecules for some metal ions are so-called zinc finger structures in DNA repair proteins, but each zinc finger protein exerts its own sensitivity towards toxic metal ions. Possible consequences of repair inhibitions are discussed in more detail for soluble and particulate nickel compounds, which have recently been shown to interfere with the repair of stable DNA adducts induced by benzo[a]pyrene (B[a]P). Since nickel compounds and polycyclic aromatic hydrocarbons such as B[a]P are frequently associated in the ambient air, in cigarette smoke and at many workplaces, an impaired removal of B[a]P-derived DNA adducts will lead to persistent DNA damage and thus increase the risk of mutations and tumor formation.	
229.	Liou SH, Chen YH, Loh CH, Yang T, Wu TN, Chen CJ, Hsieh LL. The association between frequencies of mitomycin C-induced sister chromatid exchange and cancer risk in arseniasis. Toxicol Lett. 2002 Mar 28;129(3):237-43. In order to examine whether biomarkers of cytogenetic damage and susceptibility, such as spontaneous and mitomycin C-induced sister chromatid exchange (SCE) can predict cancer development, a nested case-control study was performed in a blackfoot endemic area with known high cancer risk. A cohort of 686 residents was recruited from three villages in the arseniasis area. Personal characteristics were collected and venous blood was drawn for lymphocyte culture and stored in a refrigerator. The vital status and cancer development was followed using the National Death Registry, Cancer Registry, and Blackfoot Disease Registry. The follow up period was from August 1991 to July 1997. During this 6-year-period, 55 residents developed various types of cancer. Blood culture samples from 23 of these subjects were unsuitable for spontaneous SCE experiments and 45 of these subjects were unsuitable for mitomycin C-induced SCE experiments due to improper storage. Finally, a total of 32 cancer cases had cytogenetic samples that could be analyzed. About 32 control subjects were selected from those who did not develop cancer in the study period and these subjects were matched to cases by sex, age, smoking habits, and residential area. The results showed that there was no significant difference in the frequencies of spontaneous and mitomycin C-induced SCE between the case and control groups. There was also no significant difference in the net difference of spontaneous and mitomycin C-induced SCE between the case and control groups. These results suggest that SCEs, either spontaneous or mitomycin C-induced, might not be good markers to predict cancer risk.	2002
230.	Liu J, Zheng B, Aposhian HV, Zhou Y, Chen ML, Zhang A, Waalkes MP. Chronic arsenic poisoning from burning high-arsenic-containing coal in Guizhou, China. Environ Health Perspect. 2002 Feb;110(2):119-22. Arsenic is an environmental hazard and the reduction of drinking water arsenic levels is under consideration. People are exposed to arsenic not only through drinking water but also through arsenic-contaminated air and food. Here we report the health effects of arsenic exposure from burning high arsenic-containing coal in Guizhou, China. Coal in this region has undergone mineralization and thus produces high concentrations of arsenic. Coal is burned inside the home in open pits for daily cooking and crop drying, producing a high concentration of arsenic in indoor air. Arsenic in the air coats and permeates food being dried producing high concentrations in food; however, arsenic concentrations in the drinking water are in the normal range. The estimated sources of total arsenic exposure in this area are from arsenic-contaminated food (50-80%), air (10-20%), water (1-5%), and direct contact in coal-mining workers (1%). At least 3,000 patients with arsenic poisoning were found in the Southwest Prefecture of Guizhou, and approximately 200,000 people are at risk for such overexposures. Skin lesions are common, including keratosis of the hands and feet, pigmentation on the trunk, skin ulceration, and skin cancers. Toxicities to internal organs, including lung dysfunction,	2002

	neuropathy, and nephrotoxicity, are clinically evident. The prevalence of hepatomegaly was 20%, and cirrhosis, ascites, and liver cancer are the most serious outcomes of arsenic poisoning. The Chinese government and international organizations are attempting to improve the house conditions and the coal source, and thereby protect human health in this area.	
231.	McDorman EW, Collins BW, Allen JW. Dietary folate deficiency enhances induction of micronuclei by arsenic in mice. Environ Mol Mutagen. 2002;40(1):71-7. Folate deficiency increases background levels of DNA damage and can enhance the genotoxicity of chemical agents. Arsenic, a known human carcinogen present in drinking water supplies around the world, induces chromosomal and DNA damage. The effect of dietary folate deficiency on arsenic genotoxicity was evaluated using a mouse peripheral blood micronucleus (MN) assay. In duplicate experiments, male C57Bl/6J mice were fed folate-deficient or folate-sufficient diets for 7 weeks. During week 7, mice on each diet were given four consecutive daily doses of sodium arsenite (0, 2.5, 5, or 10 mg/kg) via oral gavage. Over the course of the study the folate-deficient diet produced an approximate 60% depletion of red blood cell folate. Folate deficiency by itself was associated with small but significant increases in MN in normochromatic erythrocytes (NCEs) and polychromatic erythrocytes (PCEs). Arsenic exposure was associated with significant increases in MN-PCEs in both folate-deficient and folate-sufficient mice. MN-PCE frequencies at the 10 mg/kg dose of arsenic were increased 4.5-fold over vehicle control in folate-deficient mice and 2.1-fold over control in folate-sufficient mice. At the 5 and 10 mg/kg doses of arsenic, MN-PCE levels were significantly higher (1.3-fold and 2.4-fold, respectively) in folate-deficient mice compared to folate-sufficient mice. Very few MN from either control or treated animals in either experiment exhibited kinetochore immunostaining, suggesting that the MN were derived from chromosome breakage rather than from whole chromosome loss. These results indicate that folate deficiency enhances arsenic-induced clastogenesis at doses of 5 mg/kg and higher.	2002
232.	Nakadaira H, Endoh K, Katagiri M, Yamamoto M. Elevated mortality from lung cancer associated with arsenic exposure for a limited duration. J Occup Environ Med. 2002 Mar;44(3):291-9. In 1959, arsenic poisoning was detected in the town of Nakajo in Japan. The cause was exposure to inorganic arsenic in well water during 1954 to 1959. To examine the long-term effects of limited-duration arsenic exposure, we conducted mortality and survival studies for patients with chronic arsenic exposure and for control subjects from 1959 to 1992. The ratio of observed deaths to expected deaths from lung cancer was significantly high (7:0.64) for male patients. The lung cancer mortality rate was elevated markedly in subgroups with higher clinical severities of symptoms. Small cell carcinoma was specific to the exposed patients. The cumulative change of survival declined significantly in the exposed patients compared with the controls. The decline disappeared when lung cancer deaths were treated as lost to follow-up. The results showed that a 5-year period of arsenic exposure was associated with risk of lung cancer.	2002
233.	Rossman TG, Uddin AN, Burns FJ, Bosland MC. Arsenite cocarcinogenesis: an animal model derived from genetic toxicology studies. Environ Health Perspect. 2002 Oct;110 Suppl 5:749-52. 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 (< or =5 microm) 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	2002

	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.	
234.	Schuliga M, Chouchane S, Snow ET. Upregulation of glutathione-related genes and enzyme activities in cultured human cells by sublethal concentrations of inorganic arsenic. Toxicol Sci. 2002 Dec;70(2):183-92. Inorganic arsenic (iAs), a known human carcinogen, acts as a tumor promoter in part by inducing a rapid burst of reactive oxygen species (ROS) in mammalian cells. This causes oxidative stress and a subsequent increase in the level of cellular glutathione (GSH). Glutathione, a ubiquitous reducing sulfhydryl tripeptide, is involved in ROS detoxification and its increase may be part of an adaptive response to the oxidative stress. Glutathione related enzymes including glutathione reductase (GR) and glutathioneS-transferase (GST) also play key roles in these processes. In this study the regulatory effects of inorganic arsenite (As(III)) on the activities of GSH-related enzymes were investigated in cultured human keratinocytes. Substantial increases in GR enzyme activity and mRNA levels were shown in keratinocytes and other human cell lines after exposure to low, subtoxic, micromolar concentrations of As(III) for 24 h. Upregulation of GSH synthesis paralleled the upregulation of GR as shown by increases in glutamate-cysteine lyase (GCL) enzyme activity and mRNA levels, cystine uptake, and intracellular GSH levels. Glutathione S-transferase activity was also shown to increase slightly in keratinocytes, but not in fibroblasts or breast tumor cells. Overall the results show that sublethal arsenic induces a multicomponent response in human keratinocytes that involves upregulation of parts, but not all of the GSH system and counteracts the acute toxic effects of iAs. The upregulation of GR has not previously been shown to be an integral part of this response, although GR is critical for maintaining levels of reduced GSH.	2002
235.	Tran HP, Prakash AS, Barnard R, Chiswell B, Ng JC. Arsenic inhibits the repair of DNA damage induced by benzo(a)pyrene. Toxicol Lett. 2002 Jul 7;133(1):59-67. In order to study the effect of arsenic on DNA damage, Sprague-Dawley rats were dosed with sodium arsenite (10 mg/kg) with or without 800 microg of benzo(a)pyrene (BP) by intramammilary injection. The animals were sacrificed on day 1, 3, 5, 10 and 27 and the mammary gland tissues were collected for DNA adduct measurement using a (32)P post-labeling assay. Animals dosed with arsenic alone did not show any DNA adducts. DNA adduct levels in rats dosed with BP alone reached a maximum level by day 5, reducing to 13% of this level by day 27. Adduct levels in rats dosed with arsenic and BP also reached a maximum by day 5 but only 80% of the level observed in the BP group. However, 84% of this amount still remained by day 27. The First Nucleotide Change (FNC) technique was used for the screening	2002

	of 115 samples of various tissues from mice that had been chronically exposed to sodium arsenate for over 2 years revealed that inorganic arsenic did not attack the two putative hotspots (codons 131 and 154) of the hOGG1 gene. These results support the hypothesis that arsenic exerts its biological activity through DNA repair inhibition.	
236.	Tsuji JS, Robinson S. Separating potential source exposure from background exposure in subsistence populations in developing countries. Toxicology. 2002 Dec 27;181-182:467-70. Risk assessment methods of developed countries have prescribed exposure assumptions for calculating health risks that are generally inappropriate for developing countries because of population, cultural, and social differences. For example, populations in developing countries are often subsistence users of natural resources with a more outdoor-oriented lifestyle. Assessments should thus measure specific dietary intake rates and contact rates with environmental media. Chemical analyses of food, environmental media, and any biomarkers of exposure should include a carefully matched reference population to distinguish between exposures due to naturally occurring metals in more mineralized areas and potential anthropogenic sources. Without a reference group, one might predict excess risk associated with the external source, even though exposure is due to background levels. For example, subsistence populations often have a simple diet with high ingestion rates of a few food types (e.g. 200 g/day wet weight of fish; 500 g/day of rice). These foods can be naturally elevated in arsenic (fish and rice) and mercury (fish). Conservative risk assessments that extrapolate toxicity from high to low doses can predict elevated risks for these naturally occurring elements (e.g. greater than 1 in 10,000 cancer risk for arsenic). Whether the calculated risks are actually indicative of harm to subsistence populations should be considered in light of the beneficial properties of the diet and the lack of alternative food choices.	2002
237.	Wang JP, Qi L, Moore MR, Ng JC. A review of animal models for the study of arsenic carcinogenesis. Toxicol Lett. 2002 Jul 7;133(1):17-31. As inorganic arsenic is a proven human carcinogen, significant effort has been made in recent decades in an attempt to understand arsenic carcinogenesis using animal models, including rodents (rats and mice) and larger mammals such as beagles and monkeys. Transgenic animals were also used to test the carcinogenic effect of arsenicals, but until recently all models had failed to mimic satisfactorily the actual mechanism of arsenic carcinogenicity. However, within the past decade successful animal models have been developed using the most common strains of mice or rats. Thus dimethylarsinic acid (DMA), an organic arsenic compound which is the major metabolite of inorganic arsenicals in mammals, has been proven to be tumorigenic in such animals. Reports of successful cancer induction in animals by inorganic arsenic (arsenite and arsenate) have been rare, and most carcinogenetic studies have used organic arsenicals such as DMA combined with other tumor initiators. Although such experiments used high concentrations of arsenicals for the promotion of tumors, animal models using doses of arsenicals species closed to the exposure level of humans in endemic areas are obviously the most significant. Almost all researchers have used drinking water or food as the pathway for the development of animal model test systems in order to mimic chronic arsenic poisoning in humans; such pathways seem more likely to achieve desirable results.	2002
238.	Wang X, Kong L, Zhao J, Yang P. Arsenic trioxide in the mechanism of drug resistance reversal in MCF-7/ADM cell line of human breast cancer. Zhonghua Zhong Liu Za Zhi. 2002 Jul;24(4):339-43. OBJECTIVE: To investigate the effect of drug resistance by arsenic trioxide (As(2)O(3)) and its possible mechanism in human breast cancer cell line MCF-7/ADM. METHODS: Cytotoxicity of As(2)O(3) and the sensibility to adriamycin (ADM) in MCF-7/ADM cell line, a ADM-resistance cell line of human breast cancer, were studied through MTT assay. The	2002

	concentration of intracellular ADM was detected by spectrofluorometry. With MCF-7/ADM cells treated with As(2)O(3) in combination with ADM, the glutathione-s-transferase (GST) activity was measured by biochemical method. The expression of GST-pi mRNA was assessed by RT-PCR. RESULTS: The non-cytotoxic dose of As(2)O(3) was 0.2 micro mol/L and the low cytotoxic dose was 0.8 micro mol/L to MCF-7/ADM cell line. 0.2 micro mol/L As(2)O(3) could significantly increase the intracellular accumulation of ADM in MCF-7/ADM cell line (P < 0.05). The medium inhibition concentration (IC(50)) was obviously reduced from 53.74 micro mol/L to 25.0 micro mol/L, with a reversal ratio of 2.1 as compared to its parental cell line. Before and after 0.2 micro mol/L, 0.8 micro mol/L As(2)O(3) were given, GST activities were decreased from 29.68 +/- 0.29 U/ml to 19.29 +/- 2.10 U/m l and 12.66 +/- 2.78 U/ml (P < 0.05). In addition, MCF-7/ADM cell line had overexpression of GST-pi mRNA. A significant down regulation of GST-pi mRNA was observed in MCF-7/ADM cells when As(2)O(3) and ADM (21.55 micro mol/L) were given for 24 hours. CONCLUSION: As(2)O(3) is able to enhance the cytotoxicity of ADM and partly reverse the ADM resistance of MCF-7/ADM cell line of human breast cancer, which may be related to the variation of GST-pi enzyme.	
239.	Bau DT, Gurr JR, Jan KY. Nitric oxide is involved in arsenite inhibition of pyrimidine dimer excision. Carcinogenesis. 2001 May;22(5):709-16. Arsenite is a human carcinogen reported to inhibit DNA repair. The binding of arsenite to functional thiol groups of DNA repair enzymes has in the past been suggested as a possible mechanism for the effect of arsenite on DNA repair. However, recent studies indicate that reactive oxygen species and nitric oxide are involved in arsenite toxicity. This research aims to elucidate the role of these possible mechanisms in the inhibition of UV-induced DNA repair by arsenite. As arsenite inhibits UV-DNA repair in Chinese hamster ovary cells, and this is a commonly used cell line for UV repair experiments, we used these cells to examine the effect of arsenite on the expression of UV-irradiated reporter genes. The T4 UV endonuclease V-incorporated comet assay was used to examine specifically the effect of arsenite on pyrimidine dimer excision. We showed that inhibition of UV-DNA repair by arsenite was suppressed by nitric oxide synthase inhibitors. Arsenite increased nitric oxide production and nitric oxide generators inhibited UV-DNA repair. The involvement of nitric oxide in the inhibition of pyrimidine dimer excision by arsenite was also confirmed in human fibroblasts. Investigation into the effect of oxidant modulators did not give a clear indication that reactive oxygen species are involved in arsenite inhibition of UV-DNA repair. Phenylarsine oxide, a strong thiol-reacting agent, did not inhibit pyrimidine dimer excision and also did not increase nitric oxide production. Our results show conclusively that nitric oxide is involved in the inhibition of pyrimidine dimer excision by arsenite. Reactive oxygen species and the binding of arsenite to functional thiol groups of DNA repair enzymes do not appear to be involved.	2001
240.	Cano M, Arnold LL, Cohen SM. Evaluation of diet and dimethylarsinic acid on the urothelium of syrian golden hamsters. Toxicol Pathol. 2001 Nov-Dec;29(6):600-6. Few studies have examined the carcinogenicity of chemicals toward the urinary bladder in hamsters, and the effect of diet on hamster urine and urothelium has not been reported. Our laboratory recently began investigating the effects of dimethylarsinic acid (DMA) on the hamster bladder, and we noticed subtle urothelial changes even in controls. The possible effect of various diets on hamster urothelium was evaluated by feeding different diets to 4-week-old Syrian Golden hamsters for 5 weeks. The diets examined were Tekland 8656, Purina 5002, Purina 5L79, and NIH-07. Light microscopic examination showed a slight increase in urothelial hyperplasia in hamsters fed Purina 5L79. An increase in the incidence of urinary bladder necrosis, exfoliation, and mild hyperplasia were noted by scanning electron microscopy (SEM) with all dietary preparations except NIH-07. The constituents in the diets producing the urothelial alterations are not known at present, but NIH-07 diet was chosen for	2001

	experiments to investigate the effects of DMA on the hamster bladder epithelium. Male and female 5-week-old Syrian Golden hamsters were fed 100 ppm DMA for 10 weeks. Examination of urinary parameters showed no treatment-related changes. Light microscopic examination and SEM revealed no changes of the urothelium of DMA-treated male or female hamsters.	
241.	Cantor KP. Invited commentary: arsenic and cancer of the urinary tract. Am J Epidemiol. 2001 Mar 1;153(5):422-3. Inorganic arsenic in drinking water is a recognized cause of cancers of the skin, lung, and bladder. In the absence of an animal model for studying arsenic carcinogenesis, epidemiologic studies provide the only quantitative data for guiding risk assessment at levels that commonly occur in drinking water. To date, most estimates of risk at low and moderate levels of exposure (<200 microg/liter) have been based on extrapolation from ecologic studies of populations exposed to much higher levels. Epidemiologic data from the prospective cohort study by Chiou et al. that appears in this issue of the JOURNAL: (Am J Epidemiol 2001;153:411-18) make an important contribution to improving the precision of the estimated risk of transitional cell carcinoma of the urinary tract associated with ingested arsenic from drinking water. The great strength of the study derives from having individually based measures of exposure and cancer diagnoses. Arsenic in water is a topic of great concern and controversy, and epidemiologic studies will continue to provide crucial information about the risks of cancer and other diseases associated with ingested arsenic.	2001
242.	Chattopadhyay S, Ghosh S, Debnath J, Ghosh D. Protection of sodium arsenite-induced ovarian toxicity by coadministration of L-ascorbate (vitamin C) in mature wistar strain rat. Arch Environ Contam Toxicol. 2001 Jul;41(1):83-9. Arsenic, a major water pollutant in India, produces toxic effects on female reproductive system in rodent models at the dose available in drinking water in arsenic-intoxicated zones. This study examines the coadministration of L-ascorbate (vitamin C) on ovarian steroidogenesis, plasma levels of gonadotrophins, brain monoamines, and ovarian as well as uterine peroxidase activities in sodium arsenite-treated rats. After sodium arsenite treatment, relative ovarian and uterine weights, ovarian Delta5-3beta-HSD and 17beta-HSD activities, plasma levels of gonadotrophins, norepinephrine levels in midbrain and diencephalon, and the activities of peroxidase in ovary and uterus were decreased significantly. On the other hand, serotonin levels in midbrain and diencephalon were increased significantly 28 days after sodium arsenite treatment at the dose of 0.4 ppm/100 g body weight/rat/day. All these parameters were protected significantly and in most cases were unchanged from control level when L-ascorbate at 25 mg/100 g body weight/rat/day was coadministered orally with sodium arsenite. This cotreatment of L-ascorbate with sodium arsenite also restored the estrous cycle in a regular manner. We concluded that L-ascorbate plays a pivotal role in maintaining normal ovarian activities and brain monoamines in arsenic-treated rats.	2001
243.	Cohen SM, Yamamoto S, Cano M, Arnold LL. Urothelial cytotoxicity and regeneration induced by dimethylarsinic acid in rats. Toxicol Sci. 2001 Jan;59(1):68-74. Inorganic arsenic is a known human carcinogen of the skin and respiratory tract. Epidemiologic evidence indicates that it is also carcinogenic to the urinary bladder and other internal organs. Lack of an animal model has limited progress on understanding the mechanism of arsenic carcinogenesis. It was recently reported that high doses of an organic arsenical, dimethylarsinic acid (DMA), increased urinary bladder tumors in rats when administered in the diet or in the drinking water for 2 years, with the female being more sensitive than the male. We previously showed that high doses of DMA (40 or 100 ppm of the diet) fed for 10 weeks increased urothelial cell proliferation in the rat. Treatment with DMA also increased renal	2001

	calcification and increased urinary calcium concentration. In 2 experiments, we examined the urothelial proliferative effects of treatment with 100 ppm DMA in the diet in female F344 rats for 2 and 10 weeks and for 6 and 24 h, and 3, 7, and 14 days. Cytotoxic changes in the urothelium were evident by SEM as early as 6 h after treatment was begun. Foci of cellular necrosis were detected after 3 days of treatment, followed by widespread necrosis of the urothelium after 7 days of treatment. The bromodeoxyuridine (BrdU) labeling index was not increased until after 7 days of treatment, suggesting that administration of DMA results in cytotoxicity with necrosis, followed by regenerative hyperplasia of the bladder epithelium. Although the rat provides an animal model to study the urothelial effects of DMA, the relevance of this finding to inorganic arsenic carcinogenesis in humans must be extrapolated cautiously, due to the high doses of DMA necessary to produce these changes in the rat and the differences in metabolism of arsenicals in rodents, especially rats, compared to humans.	
244.	Curnow A, Salter L, Morley N, Gould D. A preliminary investigation of the effects of arsenate on irradiation-induced DNA damage in cultured human lung fibroblasts. J Toxicol Environ Health A. 2001 Aug 24;63(8):605-16. Single-cell gel electrophoresis (the comet assay) was used to assess single-strand breaks (SSBs) produced in cultured lung human fibroblasts by xenon lamp irradiation alone, various concentrations of arsenate [As(V)], alone or various combinations of the two. It was found that significantly higher levels of SSBs were observed in the irradiated cells than the nonirradiated cells and that elevating levels of arsenate enhanced the level of damage detected in both irradiated and nonirradiated cells in a concentration-dependent manner; that is, incubating cells with arsenate alone produced marked DNA damage without an irradiation insult being necessary. The results of this study indicate that arsenate is acting as a cogenotoxin with irradiation in this cell line. This additive effect may also be cocarcinogenic, and as a result it is possible that less solar irradiation may be required to induce skin cancer in arsenic-exposed populations.	2001
245.	Feng Z, Xia Y, Tian D, Wu K, Schmitt M, Kwok RK, Mumford JL. DNA damage in buccal epithelial cells from individuals chronically exposed to arsenic via drinking water in Inner Mongolia, China. Anticancer Res. 2001 Jan-Feb;21(1A):51-7. The purpose of this pilot study was to assess DNA damage in buccal cells from individuals chronically exposed to arsenic via drinking water in Ba Men, Inner Mongolia. Buccal cells were collected from 19 Ba Men residents exposed to arsenic at 527.5 +/- 23.7 micrograms/L (mean +/- SEM) and 13 controls exposed to arsenic at 4.4 +/- 1.0 micrograms/L. DNA fragmentation by the DNA ladder and TUNEL assay were used to detect DNA damage in buccal cells. In the DNA ladder assay, 89% (17/19) of the arsenic-exposed group showed < 100 bp DNA fragments, in contrast to 15% (2/13) of the controls ($p < 0.0001$). For the TUNEL assay, the mean frequencies of positive cells were higher in the exposed group (15.1%) than in the controls (2.0%) ($p < 0.0001$). This study showed that high arsenic exposure via drinking water resulted in DNA damage and DNA fragmentation in buccal cells thus may be an appropriate biomarker for assessing chronic effects of arsenic in humans. A study investigating DNA fragmentation from the individuals with low levels of arsenic exposure in this population is in progress.	2001
246.	Gebel TW. Genotoxicity of arsenical compounds. Int J Hyg Environ Health. 2001 Mar;203(3):249-62. With respect to global human health hazard, arsenic (As) is one of the most important environmental single substance toxicants. Currently, millions of people all over the world are exposed to the ubiquitous element in exposure levels leading to long-term toxicity, in particular	2001

	cancer. Unfortunately, it has not been elucidated up to now how As mechanistically leads to the induction of neoplasia. Besides its tumorigenic potential, As has been shown to be genotoxic in a wide variety of different experimental set-ups and biological endpoints. In vitro, the element was shown to induce chromosomal mutagenicity like micronuclei, chromosome aberrations, and sister chromatid exchanges. It mainly acts clastogenic but also has an aneugenic potential. Instead, its potential to induce point mutations is very low in bacterial as well as in mammalian cell systems. However, in combined exposure with point mutagens in vitro, As was shown to enhance the frequency of chemical mutations in a synergistic manner. Additionally, As was shown to induce chromosome aberrations and micronuclei in vivo in experiments with mice. After long-term exposure to As-contaminated drinking water, the great majority of human biomonitoring studies found elevated frequencies of DNA lesions like micronuclei or chromosome aberrations. Respective occupational studies are few. Like it is the case for As carcinogenicity, it is not known through which mechanism the genotoxicity of As is mediated, although the data available indicate that As may act indirectly on DNA, i.e. via mechanisms like interference of regulation of DNA repair or integrity. Because of the indirect mode of action, it has been discussed as well that As's genotoxicity may underlie a sublinear dose-response relationship. However, various problems like non-standardized test systems and experimental variability make it impossible to prove such statement. Basically, to be able to improve risk assessment, it is of crucial importance to scientifically approach the mechanistic way of induction of As's genotoxicity and carcinogenicity.	
247.	Gradecka D, Palus J, Wasowicz W. Selected mechanisms of genotoxic effects of inorganic arsenic compounds. Int J Occup Med Environ Health. 2001;14(4):317-28. Chronic exposure to inorganic arsenic compounds is responsible for the prevalance of various tumors, as well as of other diseases. A major problem is the exposure to inorganic arsenic (i-As) in drinking water that affects millions of people, primarily in Asia and South America. In these regions, the concentration of arsenic in drinking water amounts to several thousand microg/l and considerably exceeds the standard of 50 microg/l, recommended by the US Environmental Protection Agency. It is interesting that not all populations are equally sensitive to i-As. Therefore, the existing standard should be verified and the environmentally safe i-As concentration should be established. Bearing this in mind, it would be helpful to know the mechanisms of toxicity of inorganic arsenic compounds. In vitro and in vivo studies and examination of people exposed to high concentrations of i-As in drinking water show its genotoxicity. Inorganic As increases the frequency of micronuclei, chromosome aberrations and sister chromatid exchanges both in humans and in animals, but it does not induce point mutations. If arsenic does not affect DNA directly, then what is the mechanism of its toxicity? The results of various studies suggest that it may intensify toxic effects of other physical and chemical agents, especially by DNA repair inhibition. Besides, it is believed that inorganic arsenic compounds may cause changes in the cell redox potential and alter DNA methylation and phosphorylation of cell-cycle control proteins. Some data also suggest that i-As increases celluar proliferation and apoptosis. The purpose of this work is to present some views on cytotoxic mechanisms of inorganic arsenic compounds.	2001
248.	Karagas MR, Le CX, Morris S, Blum J, Lu X, Spate V, Carey M, Stannard V, Klaue B, Tosteson TD. Markers of low level arsenic exposure for evaluating human cancer risks in a US population. Int J Occup Med Environ Health. 2001;14(2):171-5. Epidemiologic studies conducted in the US have not previously detected an association between regional drinking water arsenic concentrations and corresponding cancer occurrence or mortality rates. To improve our estimation of cancer risk and arsenic exposure in the USA, we have investigated the reliability of several exposure markers. In the current study, we specifically evaluated the long-term reproducibility of tap water and toenail concentrations of	2001

	arsenic, and the relation between water, toenail, and urinary measurement. Subjects included 99 controls in our case-control study on whom we requested a household tap water sample and toenail clipping three to five years apart. Additionally, participants were asked to provide a first morning void sample at the second interview. Tap water arsenic concentrations ranged from undetectable (<0.01 microg/L) to 66.6 microg/L. We found a significant correlation between both replicate water and toenail samples (intraclass correlation coefficient = 0.85, 95% confidence interval = 0.79-0.89 for water, and intraclass correlation coefficient = 0.60, 95% confidence interval = 0.48-0.70 for toenails). The inter-method correlations for water, urinary and toenail arsenic were all statistically significant (r = 0.35, p = 0.0024 for urine vs water; r = 0.33, p = 0.0016 for toenail vs water and r = 0.36, p = 0.0012 for urine vs toenails). Thus, we found both toenail and water measurements of arsenic reproducible over a three- to five-year period. Our data suggest that biologic markers may provide reliable estimates of internal dose of low level arsenic exposure that can be used to assess cancer risk.	
249.	Liao KH, Gustafson DL, Fox MH, Chubb LS, Reardon KF, Yang RS. A biologically based model of growth and senescence of Syrian hamster embryo (SHE) cells after exposure to arsenic. Environ Health Perspect. 2001 Dec;109(12):1207-13. We modified the two-stage Moolgavkar-Venzon-Knudson (MVK) model for use with Syrian hamster embryo (SHE) cell neoplastic progression. Five phenotypic stages are proposed in this model: Normal cells can either become senescent or mutate into immortal cells followed by anchorage-independent growth and tumorigenic stages. The growth of normal SHE cells was controlled by their division, death, and senescence rates, and all senescent cells were converted from normal cells. In this report, we tested the modeling of cell kinetics of the first two phenotypic stages against experimental data evaluating the effects of arsenic on SHE cells. We assessed cell division and death rates using flow cytometry and correlated cell division rates to the degree of confluence of cell cultures. The mean cell death rate was approximately equal to 1% of the average division rate. Arsenic did not induce immortalization or further mutations of SHE cells at concentrations of 2 microM and below, and chromium (3.6 microM) and lead (100 microM) had similar negative results. However, the growth of SHE cells was inhibited by 5.4 microM arsenic after a 2-day exposure, with cells becoming senescent after only 16 population doublings. In contrast, normal cells and cells exposed to lower arsenic concentrations grew normally for at least 30 population doublings. The biologically based model successfully predicted the growth of normal and arsenic-treated cells, as well as the senescence rates. Mechanisms responsible for inducing cellular senescence in SHE cells exposed to arsenic may help explain the apparent inability of arsenic to induce neoplasia in experimental animals.	2001
250.	Ryan PB, Scanlon KA, MacIntosh DL. Analysis of dietary intake of selected metals in the NHEXAS-Maryland investigation. Environ Health Perspect. 2001 Feb;109(2):121-8. As part of a large pilot investigation of multimedia exposure to several classes of environmental contaminants, the National Human Exposure Assessment Survey (NHEXAS)-Maryland study, we collected 388 semiquantitative food checklists and duplicate diet solid food samples, analyzed for arsenic, cadmium, chromium, and lead concentrations, from 80 individuals in Maryland in 1995-1996 in a repeated measures design. Here we explore several methods to infer foods most strongly associated with concentrations of these metals observed in the duplicate diet in our data set. We employed two techniques in which logarithmically transformed metal concentrations in the duplicate diet were regressed on individual food item consumption using algorithms designed to identify the foods most associated with the observed duplicate diet concentrations. We also employed an alternative strategy in which foods to be used as independent variables in regression were selected using data collected in national food consumption and residue surveys, with regression procedures proceeding with the selected	2001

	foods in a similar manner. The concordance of foods selected as major predictors among these three techniques is noteworthy and is discussed. Finally, the Dietary Exposure Potential Model (DEPM) was used with the Dietary Checklist data to predict duplicate diet concentrations within our sample. A comparison between the predicted values and those observed gave R(2) values of 0.180, 0.206, and 0.076 for As, Cd, and Pb, respectively ($p < 0.0001$ in all cases). We discuss the significance of these observations and the implications for dietary-exposure-based risk analysis and dietary intake epidemiology.	
251.	Saleha Banu B, Danadevi K, Jamil K, Ahuja YR, Visweswara Rao K, Ishaq M. In vivo genotoxic effect of arsenic trioxide in mice using comet assay. Toxicology. 2001 May 21;162(3):171-7. Although arsenic has been the subject of toxicological research, acute in vivo genotoxic studies using relevant animal models and uniform methodology are lacking. Hence, the present study aims to study DNA damage caused by arsenic trioxide in mice in in vivo using alkaline single cell gel electrophoresis (Comet) assay. Mice were administered orally 0,0.13,0.27,0.54,1.08,2.15,4.3 and 6.45 mg/kg body weight of arsenic trioxide dissolved in distilled water. The samples of whole blood were collected at 24,48,72 h, first and second week post-treatment and the assay was carried out to determine DNA damage as represented by comet tail-length. All the doses induced significant increase in comet tail-length at 24 h post-treatment ($P<0.05$) showing a clear dose dependent increase from 0.13 to 2.15 mg/kg b.wt. and a dose dependent decrease in higher doses (4.3-6.45 mg/kg b.wt). At 48 h post-treatment all the doses showed a significant increase ($P<0.05$) in comet tail-length when compared to 24 h post-treatment. A gradual decrease in the comet tail-length was observed for all the doses from 72 h post-treatment onwards indicating a gradual repair in DNA damage. This indicates a non-linear dose and time response between DNA damage and different doses of arsenic trioxide at different time-intervals. A significant increase in comet tail-length at all the doses clearly gives evidence that arsenic trioxide cause DNA damage effectively. The study indicates that the alkaline comet assay is a reliable and effective method to detect DNA damage caused by metals.	2001
252.	Scheers EM, Ekwall B, Dierickx PJ. In vitro long-term cytotoxicity testing of 27 MEIC chemicals on Hep G2 cells and comparison with acute human toxicity data. Toxicol In Vitro. 2001 Apr;15(2):153-61. Within the framework of the EDIT (Evaluation guided Development of In vitro Toxicity and toxicokinetic tests) programme, the long-term cytotoxicity of 27 chemicals was investigated on Hep G2 cells. The first step in the experiments was to determine the PI50(24h) of the chemicals. This is the concentration of compound needed to reduce the total protein content by 50% after 24 h of treatment. In the long-term experiments the chemicals were tested in six different concentrations, using the PI50(24h) as maximum concentration. The cells were treated twice a week with the same concentration of test compound and were trypsinised and counted once a week (dynamic culture). The number of cells was compared to the number of cells of the control. Three major long-term cytotoxicity patterns could be distinguished. After 6 weeks, the EC50(6w)s were determined. This is the concentration of compound needed to reduce the number of cells by 50% after 6 weeks of treatment. These values were compared with the PI50(24h). A good correlation was found for the 27 chemicals ($r(2)=0.860$). After 6 weeks, the concentration of test compound needed to reduce the total cell protein content by 50% after 24 h after 6 weeks of pretreatment of the cells with a particular concentration of test compound was measured: the PI50(24h-6w). For the majority of compounds there is no difference between the PI50(24h) and the PI50(24h-6w). For ethanol, arsenic (III) oxide, verapamil hydrochloride and orphenadrine, the PI50(24h-6w) increased in comparison to the PI50(24h). For some compounds a doseresponse was observed, indicating that the cells have	2001

	become more resistant or more sensitive. Linear regression analysis revealed a good correlation (r(2)=0.709) between the EC50(6w) and the human acute toxicity. All these data indicate that a good alternative test may be found for predicting the long-term human toxicity.	
253.	Tian D, Ma H, Feng Z, Xia Y, Le XC, Ni Z, Allen J, Collins B, Schreinemachers D, Mumford JL. Analyses of micronuclei in exfoliated epithelial cells from individuals chronically exposed to arsenic via drinking water in inner Mongolia, China. J Toxicol Environ Health A. 2001 Nov 23;64(6):473-84. The groundwater in Bayingnormen (Ba Men), located in Central West Inner Mongolia, China, is naturally contaminated with arsenic at concentrations ranging from 50 microg/L to 1.8 mg/L. Various adverse health effects in this region, including cancer, have been linked to arsenic exposure via drinking water. A pilot study was undertaken to evaluate frequencies of micronuclei (MN), as measures of chromosomal alterations, in multiple exfoliated epithelial cell types from residents of Ba Men chronically exposed to arsenic via drinking water. Buccal mucosal cells, airway epithelial cells in sputum, and bladder urothelial cells were collected from 19 residents exposed to high levels of arsenic in drinking water (527.5 +/- 24 microg/l), and from 13 control residents exposed to relatively low levels of arsenic in drinking water (4.4 +/- microg/L). Analytical results from these individuals revealed that MN frequencies in the high-exposure group were significantly elevated to 3.4-fold over control levels for buccal and sputum cells, and to 2.7-fold over control for bladder cells (increases in MN frequency significant at $p < .001$ for buccal cells; $p < .01$ for sputum cells; $p < .05$ for bladder cells). When smokers were excluded from high-exposure and control groups the effects of arsenic were observed to be greater, although only in buccal and sputum cells; approximately 6-fold increases in MN frequency occurred in these tissues. The results indicate that residents of Ba Men chronically exposed to high levels of arsenic in drinking water reveal evidence of genotoxicity in multiple epithelial cell types; higher levels of induced MN were observed in buccal and sputum cells than in bladder cells.	2001
254.	Yu HS, Lee CH, Jee SH, Ho CK, Guo YL. Environmental and occupational skin diseases in Taiwan. J Dermatol. 2001 Nov;28(11):628-31. This presentation focuses on the four most important skin diseases in Taiwan thought to be of environmental and/or occupational origin. The majority of work-related dermatoses are contact dermatitis patients. Among occupational contact dermatitis patients, 58.5% involved irritant and 41.5%, allergic dermatitis. Electronics, hairdressing, medical practice, and construction were the most important occupations causing contact dermatitis. An endemic occurrence of chronic arsenism causing hyperpigmentation, keratosis, and cancer has been reported in Taiwan. Arsenical skin cancers present as multiple lesions at different disease stages. The skin cancers are usually found in non-sun-exposed areas. UVB exerts an inhibitory effect on the proliferation of arsenical cancers; this may explain its non-sun-exposed nature. An outbreak of premalignant and malignant skin lesions was reported among paraquat manufacturers in 1985. The skin lesions were mainly distributed over the sun-exposed areas. Photodamage and photocarcinogenesis revealed a strong association with exposure to bipyridines among paraquat manufacturers. In 1979, a mass poisoning occurred in Taiwan from cooking oil contaminated by polychlorinated biphenyls (PCBs). Over 60% of patients were in grades O-II by the Japanese classification. The blood PCB levels of the Taiwanese patients were found to be higher than those of the Yusho subjects.	2001
255.	Calderon RL. The epidemiology of chemical contaminants of drinking water. Food Chem Toxicol. 2000;38(1 Suppl):S13-20. A number of chemical contaminants have been identified in drinking water. These contaminants reach drinking water supplies from various sources, including municipal and	2000

	industrial discharges, urban and rural run-off, natural geological formations, drinking water distribution materials and the drinking water treatment process. Chemical contaminants for which epidemiologic studies have reported associations include the following: aluminium, arsenic, disinfection by-products, fluoride, lead, pesticides and radon. Health effects reported have included various cancers, adverse reproductive outcomes, cardiovascular disease and neurological disease. In evaluating epidemiologic studies for risk assessment, considering whether the study design was qualitative (hypothesis generating) or quantitative (hypothesis testing) is important and whether sufficient epidemiologic data of a quantitative nature exists to determine the dose-response curve. Each of the chemical contaminants mentioned are summarized by study designs (qualitative and quantitative) and whether a dose-response curve based on epidemiologic data has been proposed. Environmental epidemiology studies are driven by environmental exposures of interest. For drinking water contaminants, the design of epidemiologic studies and their interpretation should consider the following exposure issues: the source of the contaminant; other sources of the contaminant; the route of exposure; the frequency, duration and magnitude of exposure; the ability to document an actual internal dose; and the ability to document the dose to the target organ. Health effects of concern have other risk factors that must be measured in the conduct of these studies. In evaluating epidemiologic studies, potential errors and biases that may occur must be considered given the very low magnitude of associations (less than 2.0 for either odds ratio or risk ratio). Given the issues, the next generation of drinking water epidemiologic studies should include a multidisciplinary team beyond traditional epidemiologists and statisticians. Study teams will require toxicologists, chemists, engineers and exposure assessors. Arsenic is briefly discussed as an example of the importance of susceptible populations. Disinfection by-products are discussed as an example of epidemiologic studies of mixtures.	
256.	Chongsuvivatwong V, Lim A, Dueravee M, Geater A, Ritsamitchai S, Oshikawa S. Follow up of water use in a tin mining area affected with arsenic poisoning. Southeast Asian J Trop Med Public Health. 2000 Dec;31(4):769-74. Ron Phibun district in southern Thailand has been known as an endemic area for arsenic contamination. The government has been trying to improve the situation by encouraging the use of rainwater and piped water. This study aimed to document the change of water use and to identify factors associated with safe water use in 1997 compared to that in 1994. Home visits and face-to-face questionnaire interviews were undertaken. Information on water use for drinking, cooking, washing food and washing utensils in 1994 and 1997 was obtained. Among 3,849 households from which data could be obtained (estimated 79% of total households), the percentages of using safe water (including water from bottled rain water, piped and artesian well water) for drinking and cooking rose from 72.5 and 57.9 in 1994 to 93.6 and 80.9 in 1997, respectively. The percentages for washing foods and for washing utensils rose from 28.6 and 20.5 to 59.1 and 53.8, respectively. In 1997, percentage of households using piped water for drinking and cooking was still low (3.6 and 12.3) compared to those using piped water for washing food and utensils (39.1 and 43.6). Multivariate analysis shows that independent factors of the household predicting safe water use are: high arsenic area, near main road and having piped water installed. The influence of these factors (as judged by the level of odds ratio) operates more or less equally on water use for all purposes, except that installation of piped water has more influence on washing water than drinking and cooking water. We conclude that safe water supply in the area is still inadequate. Even if piped water is installed, it is often not used for drinking and cooking. The reasons for not using piped water for drinking and cooking need to be identified.	2000
257.	Dougherty CP, Henricks Holtz S, Reinert JC, Panyacosit L, Axelrad DA, Woodruff TJ. Dietary exposures to food contaminants across the United States. Environ Res. 2000 Oct;84(2):170-85.	2000

	Food consumption is an important route of human exposure to pesticides and industrial pollutants. Average dietary exposures to 37 pollutants were calculated for the whole United States population and for children under age 12 years by combining contaminant data with food consumption data and summing across food types. Pollutant exposures were compared to benchmark concentrations, which are based on standard toxicological references, for cancer and noncancer health effects. Average food ingestion exposures for the whole population exceeded benchmark concentrations for arsenic, chlordane, DDT, dieldrin, dioxins, and polychlorinated biphenyls, when nondetects were assumed to be equal to zero. For each of these pollutants, exposure through fish consumption accounts for a large percentage of food exposures. Exposure data for childhood age groups indicated that benchmark concentrations for the six identified pollutants are exceeded by the time age 12 years is reached. The methods used in this analysis could underestimate risks from childhood exposure, as children have a longer time to develop tumors and they may be more susceptible to carcinogens; therefore, there may be several additional contaminants of concern. In addition, several additional pollutants exceeded benchmark levels when nondetects were assumed to be equal to one half the detection limit. Uncertainties in exposure levels may be large, primarily because of numerous samples with contaminant levels below detection limits.	
258.	Gu QL, Li NL, Zhu ZG, Yin HR, Lin YZ. A study on arsenic trioxide inducing in vitro apoptosis of gastric cancer cell lines. World J Gastroenterol. 2000 Jun;6(3):435-437. No abstract	2000
259.	Helleday T, Nilsson R, Jenssen D. Arsenic[III] and heavy metal ions induce intrachromosomal homologous recombination in the hprt gene of V79 Chinese hamster cells. Environ Mol Mutagen. 2000;35(2):114-22. In the present study the carcinogenic metal ions Cd[II], Co[II], Cr[VI], Ni[II], and Pb[II], as well as As[III], were examined for their ability to induce intrachromosomal homologous and nonhomologous recombination in the hprt gene of two V79 Chinese hamster cell lines, SPD8 and Sp5, respectively. With the exception of Pb[II], all of these ions enhanced homologous recombination, the order of potency being Cr>Cd>As>Co>Ni. In contrast, Cr[VI] was the only ion to enhance recombination of the nonhomologous type. In order to obtain additional information on the mechanism of recombination in the SPD8 cell line, individual clones exhibiting metal-induced recombination were isolated, and the sequence of their hprt gene determined. These findings confirmed that all recombinogenic events in this cell line were of the homologous type, involving predominantly a chromatid exchange mechanism. The mechanisms underlying the recombination induced by these ions are discussed in relationship to their genotoxicity, as well as to DNA repair and replication. Induced recombination may constitute a novel mechanism for induction of neoplastic disease. Copyright 2000 Wiley-Liss, Inc.	2000
260.	Kayajanian GM. Arsenic, dioxin, and the promotional step in cancer creation. Ecotoxicol Environ Saf. 2000 Mar;45(3):195-7. With an uncanny symmetry, both arsenic and dioxin act at the promotional step of cancer creation in a select but broad array of tissues: arsenic to promote initiated cancer cells and dioxin to promote blocking them. The symmetry is explored. Copyright 2000 Academic Press.	2000
261.	Maiti S, Chatterjee AK. Differential response of cellular antioxidant mechanism of liver and kidney to arsenic exposure and its relation to dietary protein deficiency. Environ Toxicol Pharmacol. 2000 Jun 1;8(4):227-235. The effect on antioxidant defense system of liver and kidney of sub-acute i.p. exposure to	2000

	sodium arsenite (3.33 mg/kg b.w. per day) for 14 days was studied in male Wistar rats fed on an adequate (18%) or a low (6%) protein diet. Following arsenic treatment, liver showed significantly enhanced concentration of glutathione and increased activities of glutathione reductase and glutathione-S-transferase on either of the dietary protein levels. Liver glutathione peroxidase and glucose-6-phosphate dehydrogenase activities increased significantly on an adequate protein diet while glutathione peroxidase activity decreased significantly on a low-protein diet. Lipid peroxidation and superoxide dismutase activity of liver remained unaltered on either of the dietary protein levels. On the other hand, kidney of arsenic-treated rats receiving either of the dietary protein levels showed significantly increased lipid peroxidation and decreased superoxide dismutase and catalase activities. Kidney glutathione content and glutathione reductase activity remained unaltered while glutathione peroxidase activity increased and glutathione-S-transferase activity decreased significantly on a low-protein diet following exposure to arsenic. On an adequate protein diet glucose-6-phosphate dehydrogenase activity in kidney, however, became significantly elevated following arsenic treatment. In Wistar rats, after 14 days of treatment with 3.33 mg As/kg b.w. i.p. the kidney seemed to be more sensitive to arsenic, and liver appears to be protected more by some of the antioxidant components, such as, glutathione, glutathione-S-transferase and glucose-6-phosphate dehydrogenase. It appears that low-protein diet influences the response of some of the cellular protective components against arsenic insult but does not lead to unique findings.	
262.	Ojajärvi IA, Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, Kauppinen TP, Kogevinas M, Porta M, Vainio HU, Weiderpass E, Wesseling CH. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med. 2000 May;57(5):316-24. OBJECTIVES: Consolidation of epidemiological data on pancreatic cancer and worksite exposures. METHODS: Publications during 1969-98 were surveyed. Studies without verified exposures were excluded. Meta-analyses were conducted on data from 92 studies covering 161 populations, with results for 23 agents or groups of agents. With a standard format, five epidemiologists extracted risk estimates and variables of the structure and quality of each study. The extracted data were centrally checked. Random meta-models were applied. RESULTS: Based on 20 populations, exposure to chlorinated hydrocarbon (CHC) solvents and related compounds was associated with a meta-risk ratio (MRR) of 1.4 (95% confidence interval (95% CI) 1.0 to 1.8). Nickel and nickel compounds were considered in four populations (1.9; 1.2 to 3.2). Excesses were found also for chromium and chromium compounds (1.4; 0.9 to 2.3), polycyclic aromatic hydrocarbons (PAHs) (1.5; 0.9 to 2.5), organochlorine insecticides (1.5; 0.6 to 3.7), silica dust (1.4; 0.9 to 2.0), and aliphatic and alicyclic hydrocarbon solvents (1.3; 0.8 to 2.8). Evidence on pancreatic carcinogenicity was weak or non-positive for the following agents: acrylonitrile (1.1; 0.0 to 6.2); arsenic (1.0; 0.6 to 1.5); asbestos (1.1; 0.9 to 1.5); diesel engine exhaust (1.0; 0.9 to 1.3); electromagnetic fields (1.1; 0.8 to 1.4); formaldehyde (0. 8; 0.5 to 1.0); flour dust (1.1; 0.3 to 3.2); cadmium and cadmium compounds (0.7; 0.4 to 1.4); gasoline (1.0; 0.8 to 1.2); herbicides (1.0; 0.8 to 1.3); iron and iron compounds (1.3; 0.7 to 2.5); lead and lead compounds (1.1; 0.8 to 1.5); man-made vitreous fibres (1.0; 0.6 to 1.6); oil mist (0.9; 0.8 to 1.0); and wood dust (1.1; 0.9 to 2.5). The occupational aetiological fraction of pancreatic cancer was estimated at 12%. In a subpopulation exposed to CHC solvents and related compounds, it was 29%; to chromium and chromium compounds, 23%; to nickel and nickel compounds, 47%; to insecticides, 33%; and to PAHs, 33%. CONCLUSION: Occupational exposures may increase risk of pancreatic cancer. High quality studies are called for on interactions between occupational, environmental, and lifestyle factors as well as interactions between genes and the environment.	2000
263.	Ryan PB, Huet N, MacIntosh DL. Longitudinal investigation of exposure to arsenic, cadmium, and lead in drinking water. Environ Health Perspect. 2000 Aug;108(8):731-5.	2000

	Arsenic, cadmium, and lead have been associated with various forms of cancer, nephrotoxicity, central nervous system effects, and cardiovascular disease in humans. Drinking water is a well-recognized pathway of exposure to these metals. To improve understanding of the temporal dimension of exposure to As, Cd, and Pb in drinking water, we obtained 381 samples of tap and/or tap/filtered water and self-reported rates of drinking water consumption from 73 members of a stratified random sample in Maryland. Data were collected at approximately 2-month intervals from September 1995 through September 1996. Concentrations of As (range < 0.2-13.8 microg/L) and Pb (< 0.1-13.4 microg/L) were within the ranges reported for the United States, as were the rates of drinking water consumption (median < 0.1-4.1 L/day). Cd was present at a detectable level in only 8.1% of the water samples. Mean log-transformed concentrations and exposures for As and Pb varied significantly among sampling cycles and among respondents, as did rates of drinking water consumption, according to a generalized linear model that accounted for potential correlation among repeated measures from the same respondent. We used the intraclass correlation coefficient of reliability to attribute the total variance observed for each exposure metric to between-person and within-person variability. Between-person variability was estimated to account for 67, 81, and 55% of the total variance in drinking water consumption, As exposure (micrograms per day), and Pb exposure (micrograms per day), respectively. We discuss these results with respect to their implications for future exposure assessment research, quantitative risk assessment, and environmental epidemiology.	
264.	Smith AH, Arroyo AP, Mazumder DN, Kosnett MJ, Hernandez AL, Beeris M, Smith MM, Moore LE. Arsenic-induced skin lesions among Atacameño people in Northern Chile despite good nutrition and centuries of exposure. Environ Health Perspect. 2000 Jul;108(7):617-20. It has been suggested that the indigenous Atacameño people in Northern Chile might be protected from the health effects of arsenic in drinking water because of many centuries of exposure. Here we report on the first intensive investigation of arsenic-induced skin lesions in this population. We selected 11 families (44 participants) from the village of Chiu Chiu, which is supplied with water containing between 750 and 800 microg/L inorganic arsenic. For comparison, 8 families (31 participants) were also selected from a village where the water contains approximately 10 microg/L inorganic arsenic. After being transported to the nearest city for blind assessment, participants were examined by four physicians with experience in studying arsenic-induced lesions. Four of the six men from the exposed village, who had been drinking the contaminated water for more than 20 years, were diagnosed with skin lesions due to arsenic, but none of the women had definite lesions. A 13-year-old girl had definite skin pigmentation changes due to arsenic, and a 19-year-old boy had both pigmentation changes and keratoses on the palms of his hands and the soles of his feet. Family interviews identified a wide range of fruits and vegetables consumed daily by the affected participants, as well as the weekly intake of red meat and chicken. However, the prevalence of skin lesions among men and children in the small population studied was similar to that reported with corresponding arsenic drinking water concentrations in both Taiwan and West Bengal, India--populations in which extensive malnutrition has been thought to increase susceptibility.	2000
265.	Waalkes MP, Keefer LK, Diwan BA. Induction of proliferative lesions of the uterus, testes, and liver in swiss mice given repeated injections of sodium arsenate: possible estrogenic mode of action. Toxicol Appl Pharmacol. 2000 Jul 1;166(1):24-35. Inorganic arsenic (As) is a human carcinogen but has not been unequivocally proven carcinogenic in rodents. For instance, one older study indicates that repeated iv injections of sodium arsenate might induce lymphomas in Swiss mice (58% incidence) (Osswald and Goerttler, Verh. Dtsch. Ges. Pathol. 55, 289-293, 1971), but it was considered inadequate for critical evaluation of carcinogenic potential largely because of issues in experimental design.	2000

	Therefore, we studied repeated iv sodium arsenate injection and neoplastic response in male and female Swiss mice. Groups (n = 25) of mice received sodium arsenate (0.5 mg/kg, iv) or saline (control) once/week for 20 weeks and were observed for a total of 96 weeks when the study ended. Differences in survival and body weights were unremarkable. In females, arsenate induced marked increases in the incidence and severity of cystic hyperplasia of the uterus compared against controls. Arsenate also was associated with a rare adenocarcinoma of the uterus. Hyperplastic uterine epithelium from arsenate-exposed animals showed strong positive immunostaining for the proliferating cell nuclear antigen (PCNA). There was also an upregulation of estrogen receptor (ER) immunoreactive protein in the early lesions of uterine luminal and glandular hyperplasia, although a progressive decrease in its expression was seen in the severe hyperplastic or neoplastic epithelium. In common with the preneoplastic and neoplastic gynecological lesions in humans, the levels of immunoreactive inducible nitric oxide synthase (iNOS) and 3-nitrotyrosine-containing proteins were greater in the uterine hyperplastic epidermis and their intensity was positively correlated with the severity of the lesions. Arsenate-induced uterine hyperplastic lesions also showed a strong upregulation of cyclin D1, an estrogen-associated gene product essential for progression through the G1 phase of the cell cycle. In other tissues, arsenate increased testicular interstitial cell hyperplasia incidence and severity over control but without affecting the incidence of tubular degeneration. Arsenate also induced increases in hepatic proliferative lesions (HPL; foci of alteration + neoplasia), but only in females. Significant skin changes (incidence of hyperkeratotic lesions) and renal lesions (severity of nephropathy) also occurred in arsenate-treated females. Thus, repeated arsenate exposure, though not outright tumorigenic in the present study, was associated with proliferative, preneoplastic lesions of the uterus, testes, and liver. Estrogen treatment has been associated with proliferative lesions and tumors of the uterus, female liver, and testes in other studies, supporting a hypothesis that arsenate might somehow act through an estrogenic mode of action.	
266.	Abernathy CO, Liu YP, Longfellow D, Aposhian HV, Beck B, Fowler B, Goyer R, Menzer R, Rossman T, Thompson C, Waalkes M. Arsenic: Health effects, mechanisms of actions, and research issues. Environ Health Perspect 1999;107(7):593-7. A meeting on the health effects of arsenic (As), its modes of action, and areas in need of future research was held in Hunt Valley, Maryland, on 22-24 September 1997. Exposure to As in drinking water has been associated with the development of skin and internal cancers and noncarcinogenic effects such as diabetes, peripheral neuropathy, and cardiovascular diseases. There is little data on specific mechanism(s) of action for As, but a great deal of information on possible modes of action. Although arsenite [As(III)] can inhibit more than 200 enzymes, events underlying the induction of the noncarcinogenic effects of As are not understood. With respect to carcinogenicity, As can affect DNA repair, methylation of DNA, and increase radical formation and activation of the protooncogene c-myc, but none of these potential pathways have widespread acceptance as the principal etiologic event. In addition, there are no accepted models for the study of As-induced carcinogenesis. At the final meeting session we considered research needs. Among the most important areas cited were a) As metabolism and its interaction with cellular constituents; b) possible bioaccumulation of As; c) interactions with other metals; d) effects of As on genetic material; e) development of animal models and cell systems to study effects of As; and f) a better characterization of human exposures as related to health risks. Some of the barriers to the advancement of As research included an apparent lack of interest in the United States on As research; lack of relevant animal models; difficulty with adoption of uniform methodologies; lack of accepted biomarkers; and the need for a central storage repository for stored specimens.	1999
267.	Arnold LL, Cano M, St John M, Eldan M, van Gemert M, Cohen SM. Effects of dietary dimethylarsinic acid on the urine and urothelium of rats. Carcinogenesis. 1999	1999

	Nov;20(11):2171-9. Dimethylarsinic acid (DMA), fed to rats for 2 years, produced bladder hyperplasia and tumors at doses of 40 and 100 p.p.m., more in females than males. No urothelial proliferation was seen in mice. Our objectives were to investigate the mode of action of bladder tumor formation, evaluate the dose-response and the role of diet and to determine if the urothelial effects were reversible. The study included groups of female F344 rats fed DMA in Purina 5002 diet at doses of 0, 2, 10, 40 or 100 p.p.m. for 10 weeks; two groups of females fed DMA (0 and 100 p.p.m.) in Altromin 1321 for 10 weeks; two groups of males fed DMA (0 and 100 p.p.m.) in Purina 5002 for 10 weeks; a female high-dose recovery group (100 p.p.m. in Purina 5002 diet for 10 weeks followed by control diet for 10 weeks); and two female groups (0 and 100 p.p.m.) in Purina diet for 20 weeks. Urothelial toxicity and hyperplasia were detected by light and scanning electron microscopy (SEM), and the bromodeoxyuridine labeling index was increased in the female 40 and 100 p.p.m. groups. The effects were less in males, but were similar in females fed DMA in Altromin 1321. SEM detected no abnormal urinary solids related to treatment in any group. Urinary calcium was increased in the females fed 40 and 100 p.p.m. in Purina diet, despite overall urinary dilution. Calcification was increased in kidneys of female rats fed Purina diet. The urothelial effects of DMA were reversible. The findings support a non-DNA reactive mechanism for DMA rat bladder carcinogenicity related to urothelial toxicity and regeneration. The toxicity is probably not due to urinary solids. The toxicity and regeneration are produced in a dose-responsive manner in female rats, are greater in female than in male rats, and are reversible.	
268.	Ayala-Fierro F, Barber DS, Rael LT, Carter DE. In vitro tissue specificity for arsine and arsenite toxicity in the rat. J Toxicol Sci 1999;52(1):122-9. The mechanism of arsine (AsH3) toxicity is not completely understood. In this investigation, we determined AsH3 and arsenite (AsIII) toxicity in Sprague Dawley rat blood, liver, and kidney. In all systems, there were dose- and time-dependent responses. Red blood cells were very susceptible to AsH3 toxicity. This was demonstrated by an immediate intracellular potassium loss and by hemolysis and lactate dehydrogenase (LDH) leakage that occurred by one h. AsIII concentrations up to 1 mM were not toxic to red blood cells using these indicators. Both AsH3 and AsIII produced toxicity in primary hepatocytes. Both produced significant LDH leakage and decreases in intracellular K+ by 5 h, but AsIII was more toxic than AsH3. At 24 h, both arsenic species showed similar toxicity. In renal cortical epithelial cells, AsH3 produced no effects on LDH and K+ over a 5-h period but produced significant LD H leakage by 24 h. In these cells, AsIII produced significant toxicity as early as in 3 h. These results showed that unchanged AsH3 produced toxicity in tissues, in addition to blood, and that toxicity of arsenicals is arsenic species- and tissue-dependent.	1999
269.	Biswas S, Talukder G, Sharma A. Prevention of cytotoxic effects of arsenic by short-term dietary supplementation with selenium in mice *in vivo*. Mutat Res 1999;441(1):155-60. Interaction between selenium and arsenic has been used to protect against the genotoxic effects of sodium arsenite through dietary intervention by an equivalent amount (1/10 LD50) of sodium selenite. The two salts were administered by gavaging to laboratory bred Swiss albino mice sequentially and in combination. Cytogenetic endpoints, including chromosomal aberrations (CA) and damaged cells (DC) were recorded 24 h after exposure from chromosome spreads in bone marrow cells. Administration of sodium selenite 1 h before sodium arsenite reduced the clastogenic effects of the latter significantly. The protection was less when the salts were given together and negative when arsenite was given before selenite. Histological changes were recorded. Such reduction of arsenic toxicity through dietary intervention by selenium is of significance in protecting against the widespread toxicity observed in human	1999

	populations exposed to arsenic through drinking water from contaminated deep tubewells in West Bengal and Bangladesh. Copyright 1999 Elsevier Science B.V.	
270.	Cöl M, Cöl C, Soran A, Sayli BS, Oztürk S. Arsenic-related Bowen's disease, palmar keratosis, and skin cancer. Environ Health Perspect. 1999 Aug;107(8):687-9. Chronic arsenical intoxication can still be found in environmental and industrial settings. Symptoms of chronic arsenic intoxication include general pigmentation or focal "raindrop" pigmentation of the skin and the appearance of hyperkeratosis of the palms of the hands and soles of the feet. In addition to arsenic-related skin diseases including keratosis, Bowen's disease, basal-cell-carcinoma, and squamous-cell carcinoma, there is also an increased risk of some internal malignancies. Arsenic-related diseases are common in areas of the world where the drinking water has a high arsenic content. In this paper, we describe a 35-year-old male patient who had arsenic-related keratosis, squamous-cell carcinoma in the palmar area of his left hand, and Bowen's disease on his left thigh. The patient worked in a borax mine for 15 years, so he was exposed to arsenic in drinking water, airborne arsenic in his workplace, and had direct contact. The patient was treated for 11 months for arsenic-related keratosis until an axillary lymph node metastasis occurred; the lesion was excised and diagnosed to be malignant. Bowen's disease was detected when the patient was being treated for cancer. No other malignancy was found. The patient is still receiving regular follow-up care.	1999
271.	Hsu C-H, Yang S-A, Wang J-Y, Yu H-S, Lin S-R. Mutational spectrum of p53 gene in arsenic-related skin cancers from the blackfoot disease endemic area of Taiwan. Br J Cancer 1999;80 (7):1080-6. To understand the role of p53 tumour suppressor gene in the carcinogenesis of arsenic-related skin cancers from the blackfoot disease endemic area of Taiwan, we collected tumour samples from 23 patients with Bowen's disease, seven patients with basal cell carcinomas (BCC) and nine patients with squamous cell carcinomas (SCC). The result showed that p53 gene mutations were found in 39% of cases with Bowen's disease (9/23), 28.6% of cases with BCC (2/7) and 55.6% of cases with SCC (5/9). Most of t und in four cases. These mutations were located at codons 174, 253, 289 and 298 respectively. In immunohistochemistry analysis, p53 overexpression was found in 43.5% (10/23) of cases with Bowen's disease, 14% (1/7) of cases with BCC and 44% (4/9) of cases with SSC. These findings showed that p53 gene mutation rate in arsenic-related skin cancers from the blackfoot disease endemic area of Taiwan is high and that the mutation types are different from those in UV-induced skin cancer.	1999
272.	Lien H-C, Tsai T-F, Lee Y, Hsiao C-H. Merkel cell carcinoma and chronic arsenicism. J Am Acad Dermatol 1999;41(4):641-3. Arsenic is a well-documented human carcinogen. Bowen's disease, squamous cell carcinoma, and basal cell carcinoma are the most common skin cancers found in patients exposed to arsenic over the long term. Merkel cell carcinoma has been documented in Taiwanese patients who resided in an endemic area of black foot disease, another condition found in patients with chronic arsenicism. We collected all cases of Merkel cell carcinoma diagnosed at two medical centers in Taiwan (N = 11) to find a possible association between chronic arsenicism and Merkel cell carcinoma. In our study 6 of the 11 patients were residents of the endemic areas for chronic arsenicism.	1999
273.	Matsui M, Nishigori C, Toyokuni S, Takada J, Akaboshi M, Ishikawa M, Imamura S, Miyachi Y. The role of oxidative DNA damage in human arsenic carcinogenesis: Detection of 8-hydroxy-2'-deoxyguanosine in arsenic-related Bowen's disease. J Invest Dermatol 1999;113(1):26-31.	1999

	Arsenic is widely distributed in nature in the form of either metalloids or chemical compounds, which cause a variety of pathologic conditions including cutaneous and visceral malignancies. Recently, reactive oxygen species have been hypothesized to be one of the causes of arsenic-induced carcinogenesis. 8-Hydroxy-2'-deoxyguanosine is one of the major reactive oxygen species-induced DNA base-modified products that is widely accepted as a sensitive marker of oxidative DNA damage. We studied the presence of 8-hydroxy-2'-deoxyguanosine by immunohistochemistry using N45.1 monoclonal antibody in 28 cases of arsenic-related skin neoplasms and arsenic keratosis as well as in 11 cases of arsenic-unrelated Bowen's diseases. The frequency of 8-hydroxy-2'-deoxyguanosine positive cases was significantly higher in arsenic-related skin neoplasms (22 of 28; 78%) than in arsenic-unrelated Bowen's disease (one of 11; 9%) ($p < 0.001$ by chi2 test). 8-Hydroxy-2'-deoxyguanosine was also detected in normal tissue adjacent to the arsenic-related Bowen's disease lesions. Furthermore, arsenic was detected by neutron activation analysis in the deparaffined skin tumor samples of arsenic-related disease (four of five; 80%), whereas arsenic was not detected in control samples. Our results strongly suggest the involvement of reactive oxygen species in arsenic-induced human skin cancer. Key word: neutron activation analysis.	
274.	O'Rourke MK, Rogan SP, Jin S, Robertson GL. Spatial distributions of arsenic exposure and mining communities from NHEXAS Arizona. National Human Exposure Assessment Survey. J Expo Anal Environ Epidemiol. 1999 Sep-Oct;9(5):446-55. Within the context of the National Human Exposure Assessment Survey (NHEXAS), metals were evaluated in the air, soil, dust, water, food, beverages, and urine of a single respondent. Potential doses were calculated for five metals including arsenic. In this paper, we seek to validate the potential dose calculations through spatial analysis of the data. Others report elevated arsenic concentrations in biological and environmental samples from residents of mining towns, particularly Ajo, Arizona. These reports led us to expect potential arsenic doses above the 90th percentile of the NHEXAS exposure distribution to be from residents of mining communities. Arsenic dose was calculated using media concentrations, time activity patterns, and published exposure factors. Of the 179 homes evaluated, 54 were in mining communities; 11 of these were considered separately for reasons of population bias. Of the 17 homes with the greatest potential arsenic doses, almost half (47%) were in mining communities. We evaluated the potential doses by media from nonmining and mining areas using the nonparametric Mann-Whitney U test. Statistically significant ($p = 0.05$) differences were found between mining ($n = 43$) and nonmining sites ($n = 122$) for total exposure and for each of the following media: house dust, yard soil, outdoor air, beverage consumed, and water consumed. No differences were found in either food or indoor air of mining and nonmining areas. We eliminated outliers and repeated the test for all media; significance increased. Dietary, organic arsenic from fish consumption contributed to elevated arsenic exposure among people from nonmining communities and acted as an initial confounder. When controlling for fish consumption, we were able to validate our potential dose model using arsenic, particularly in Ajo. Further, we identified three mining communities lacking elevated arsenic exposure. Additional work is needed speciating the arsenic and evaluating health risks. The utilization of Geographic Information System facilitated spatial this project and paves the way for more sophisticated future spatial analyses.	1999
275.	Parrish AR, Zheng XH, Turney KD, Younis HS, Gandolfi AJ. Enhanced transcription factor DNA binding and gene expression induced byarsenite or arsenate in renal slices. J Toxicol Sci 1999;50(1):98-105. Although the kidney represents a target for the accumulation and toxicity of arsenic, little is known about the molecular targets of arsenic in this organ. Therefore, these studies were designed to examine the molecular impact of arsenite (As(III)) and arsenate (As(V)) at low	1999

	(nanomolar) concentrations. Precision-cut rabbit renal cortical slices were challenged with As(III) or As(V) for up to 8 h. Neither form of the metal induced overt cytotoxicity as assessed by intracellular K+ levels over th NA binding activity of ATF-2 was induced by As(III) or As(V), both forms enhanced the DNA binding activity of Elk-1. Enhanced DNA binding activity of AP-1 and Elk-1 correlated with increased gene expression of c-fos, but not c-jun, at 2 h. c-myc gene expression was also induced by As(III) and As(V), albeit at a later time point (6 h). These results suggest that acute arsenic challenge, by either As(III) or As(V), is associated with discrete alterations in the activity of signaling pathways and gene expression in renal tissue.	
276.	Rojas E, Herrera LA, Poirier LA, Ostrosky-Wegman P. Are metals dietary carcinogens? Mutat Res. 1999 Jul 15;443(1-2):157-81. Humans have been in contact with metals almost since the beginning of our existence. In fact, one cannot even think on human evolution without considering the great role played by metals in mankind's development. Metals are common moieties of molecules involved in a wide variety of biological processes, and hence are found in virtually all living organisms. Some metals are essential for human nutrition; others are found as contaminants in foodstuffs. One feature of the normal human diet which is frequently found is the simultaneous presence of both essential and toxic metals. Other factors important in the risk-evaluation analysis of metals are their pharmacokinetics, interactions among them and with other major components of the diet, and, especially, the great differences in the dietary habits of different populations and in the regional distribution of metals. In attempting to understand the role which dietary metals could play in human carcinogenesis, we found that the many factors involved and the lack of specific information made it difficult to reach firm conclusions on the hazards of dietary metals. We hope that this paper will raise the interest of genetic toxicologists in the subject and will consequently facilitate a risk analysis of the carcinogenic potential of dietary metals. Copyright 1999 Elsevier Science B.V	1999
277.	Rossman TG, Wang Z. Expression cloning for arsenite-resistance resulted in isolation of tumor-suppressor fau cDNA: possible involvement of the ubiquitin system in arsenic carcinogenesis. Carcinogenesis. 1999 Feb;20(2):311-6. Arsenic is a human carcinogen whose mechanism of action is unknown. Previously, this laboratory demonstrated that arsenite acts as a comutagen by interfering with DNA repair, although a specific DNA repair enzyme sensitive to arsenite has not been identified. A number of stable arsenite-sensitive and arsenite-resistant sublines of Chinese hamster V79 cells have now been isolated. In order to gain understanding of possible targets for arsenite's action, one arsenite-resistant subline, As/R28A, was chosen as a donor for a cDNA expression library. The library from arsenite-induced As/R28A cells was transfected into arsenite-sensitive As/S5 cells, and transfectants were selected for arsenite-resistance. Two cDNAs, asr1 and asr2, which confer arsenite resistance to arsenite-hypersensitive As/S5 cells as well as to wild-type cells, were isolated. asr1 shows almost complete homology with the rat fau gene, a tumor suppressor gene which contains a ubiquitin-like region fused to S30 ribosomal protein. Arsenite was previously shown to inhibit ubiquitin-dependent proteolysis. These results suggest that the tumor suppressor fau gene product or some other aspect of the ubiquitin system may be a target for arsenic toxicity and that disruption of the ubiquitin system may contribute to the genotoxicity and carcinogenicity of arsenite.	1999
278.	Scanlon KA, MacIntosh DL, Hammerstrom KA, Ryan PB. A longitudinal investigation of solid-food based dietary exposure to selected elements. J Expo Anal Environ Epidemiol. 1999 Sep-Oct;9(5):485-93. As part of a longitudinal investigation of environmental exposures to selected chemical	1999

	contaminants, the National Human Exposure Assessment Survey (NHEXAS), food consumption and duplicate diet samples were obtained in each of six sampling cycles from up to 80 individuals in Maryland during 1995-1996. Duplicate diet samples were weighed and analyzed for arsenic, cadmium, chromium and lead and were used to derive average daily intakes of each element. Mean log-transformed concentrations of arsenic and cadmium in duplicate diet samples and derived intakes of chromium were found to vary significantly among sampling cycles. Repeated observations of dietary exposure metrics from the same individual over time were highly variable. The results suggest that distributions of dietary exposure to arsenic and cadmium do vary for a population within a 1-year period, while those for chromium and lead do not. This may result in single measurements of exposure being sufficient to characterize population variability for these latter two elements. However, even for those elements not displaying statistically significant temporal variability for the population, a single dietary exposure measurement may still not be sufficient to characterize accurately chronic dietary exposure levels for individuals.	
279.	Snow ET, Hu Y, Chouchane S, Yan CC. Changes in the DNA repair and redox capacity of human keratinocytes exposed to very low doses of arsenic. Environ Mol Mutagen 1999;33(Suppl. 33):59. Inorganic arsenic (iAs) is a human carcinogen that does not interact directly with DNA, but inhibits DNA repair and is a comutagen. Our results suggest that a major effect of low dose iAs is to modulate DNA repair and redox levels through transcriptional control of specific genes. iAs is very toxic; 24 hour exposure to 5 µm kills 50% of cultured human keratinocytes. Keratinocytes treated with µm iAs for 24 hours also show a dose-dependent loss of ligase function. However, purified human DNA ligases and other repair enzymes are not inhibited by less than mM iAs, either *in vitro* or in extracts from untreated cells. GSH metabolizing enzymes, *e.g.*, GST-pi, GSH peroxidase, and GSSG reductase, are similarly insensitive to iAs. However, pyruvate dehydrogenase is 50%inhibited by 6 µm As(III) and may be a critical target for cytotoxicity. At the same time, nontoxic doses of iAs (≤ 1 µm) induce a 2- to 3-fold increase in human AP endonuclease (HAP1/Ref-1) expression and a significant increase in the expression of ligase I and III in treated keratinocytes. Subtoxic concentrations of iAs also produce a dose- and time-dependent increase in GSH, due in part to increased cystine uptake and γ-GCS activity. At higher, more toxic, doses GSH levels off and induction of repair proteins drops. Pretreatment with iAs, then MNNG produces a synergistic increase in viability (dye uptake) at low doses and synergistic toxicity and higher doses. Micromolar iAs also alters the DNA binding activity of AP-1, CREB, and other transcription factors and induces a variety of cellular stress response genes. These low dose effects are likely critical for As-induced carcinogenesis and the mechanism of iAs-dependent regulation of these genes is now under investigation.	1999
280.	Thomas KW, Pellizzari ED, Berry MR. Population-based dietary intakes and tap water concentrations for selected elements in the EPA region V National Human Exposure Assessment Survey (NHEXAS). J Expo Anal Environ Epidemiol. 1999 Sep-Oct;9(5):402-13. A National Human Exposure Assessment Survey (NHEXAS) field study was performed in U.S. Environmental Protection Agency (EPA) Region V, providing population-based exposure distribution data for selected elements in several personal, environmental, and biological media. Population distributions are reported for the 11 elements that were measured in water and dietary samples. Dietary intakes and home tap water concentrations of lead, arsenic, and cadmium were further examined for intermedia associations, for differences between dietary exposure for adults and children, and to estimate the proportion of the population above health-based reference values (dietary) or regulatory action levels or maximum contaminant levels (water). Water lead and arsenic concentrations were significantly associated with dietary	1999

	intake. Intake of all elements was higher from solid foods than from liquid foods (including drinking water). Dietary intakes of Pb, As, and Cd were greater than those calculated for intake from home tap water or inhalation on a microg/day basis. Median dietary intakes for the Region V population for Pb, As, and Cd were 0.10, 0.13, and 0.19 microg/kg bw/day, respectively. While Pb, As, and Cd concentrations in the foods consumed by 0 to 6-year-old children were similar to or lower than those for adults, dietary intakes calculated on a body weight basis were 1.5 to 2.5 times higher for young children. Intrapersonal intake differences accounted for most of the variance in short-term (daily) dietary intakes for Pb and As, while interpersonal differences accounted for more of the intake variance for Cd. Only small percentages of the population exceeded health-based intake reference values or concentrations equal to regulatory levels in water for Pb, As, and Cd.	
281.	Trouba KJ, Glanzer JG, Vorce RL. Wild-type and ras-transformed fibroblasts display differential mitogenic responses to transient sodium arsenite exposure. J Toxicol Sci 1999;50(1):72-81. Arsenic is a human carcinogen whose mechanism of action remains undefined. Based on the hypothesis that arsenic sensitizes cells to mitogenic stimulation by affecting the receptor tyrosine kinase (RTK) signal transduction pathway, these studies first examined the response of fibroblasts to specific mitogens using a defined media system. In both rodent and human fibroblasts, DNA synthesis was found to be stimulated in cells exposed to a transient, sub-lethal concentration of sodium arsenite follo se of the cell cycle; conversely, the percentage of ras-transformed cells in S-phase is decreasedby arsenic. No evidence of arsenic-induced cytotoxicity was detected using the neutral red assay, ensuring that decreased DNA synthesis in ras-transformed cells is not due to cell death. Taken together, the results of experiments presented herein indicate that arsenic produces sustained alterations in the growth characteristics of rodent and human fibroblasts. It is postulated that the proliferation-enhancing effect of arsenic on wild-type cells contributes to its ability to cause cancer.	1999
282.	Villanueva C, Kogevinas M. Comments on "Drinking water arsenic in Utah: a cohort mortality study". Environ Health Perspect. 1999 Nov;107(11):A544; author reply A544-6. No abstract	1999
283.	Viren J, Silvers A. Nonlinearity in the lung cancer dose-response for airborne arsenic: apparent confounding by year of hire in evaluating lung cancer risks from arsenic exposure in Tacoma smelter workers. Regul Toxicol Pharmacol. 1999 Oct;30(2 Pt 1):117-29. Most analytic studies of human epidemiologic data have affirmed the linear association between excess lung cancer risk and airborne arsenic exposure. Recent Canadian analyses, however, based on the mortality follow-up of Tacoma smelter workers from 1940-1976, provided strong evidence of a nonlinear dose-response when lung cancer risk was expressed in terms of the standardized mortality ratio. Using recently updated data covering ten additional years of mortality experience among Tacoma workers (1940-1986), new analyses were undertaken to further explore nonlinearity in the lung cancer dose-response in this worker cohort. Lung cancer risk was expressed in terms of both the standardized mortality ratio (SMR) and the excess mortality rate (EMR). As in Canadian analyses, nonlinearity was assessed through a three parameter model containing both linear and negative exponential terms for dose. Dropping the negative-exponential dose-term lead to the standard suite of linear dose-response models, with and without intercept, used for comparative purposes. Analyses were undertaken by subcohort as there was strong evidence of confounding by year of initial hire, which largely explained the nonlinearity in the dose-response observed in Canadian analyses. Subcohort analyses based on initial employment, prior to 1940 or thereafter, showed that the nonlinearity in the dose-response was strongly influenced by date of initial hire. whether the	1999

	cohort risk was measured by either the SMR or EMR, a nonlinear dose-response was evident only among workers hired prior to 1940. This, however, was strongly related to the artifactually low lung cancer mortality seen among workers hired between 1930 and 1939. Among workers hired after 1940, analyses showed that a linear dose-response provided a clearly superior fit. While analyses showed comparable goodness of fit when models were fitted to the SMR and EMR. Only those based on the EMR provided strong evidence of a dose-response. Overall, nonlinearity as observed in Canadian analyses was likely the result of several sources of bias not taken into account by Canadian investigators. Copyright 1999 Academic Press.	
284.	Waxman S, Jing Yk, Chen Z, Chen GQ. RESPONSE: re: apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide at clinically achievable concentrations. J Natl Cancer Inst. 1999 Oct 6;91(19):1691. No abstract	1999
285.	Yager JW, Kirchner SC, Kavanaugh TJ, Faustman EM. Analysis of gene expression in uroepithelial cells from workers exposed to arsenic. Environ Mol Mutagen 1999;33(Suppl. 33):69. Chronic exposure to high concentrations of arsenic is associated primarily with skin, lung, and bladder cancer in humans. The purpose of this study was to examine the feasibility of using gene expression analyses as a biomarker of exposure to arsenic by examining this endpoint in uroepithelial (UE) cells. Boiler cleaning operations in Slovakian power plants can lead to relatively high airborne levels of arsenic due to the high concentration of arsenic in the local coal. UE cells were isolated from a small number of workers before they began the cleaning process and again after several days of exposure using a protocol developed for field laboratory conditions. The cells were carried through RNA amplification and hybridized to reverse northern blots. Genes included for analysis were those involved in stress responses (HSPs 25, 60, 70 and metallothionein I and II); cell cycling (Cyc A, Cyc B, p21, p53) and DNA damage (Gadd 45 and 153). Control genes included were actin, puc 18 and G3PDH. Approximately 80% of the samples successfully amplified and hybridized with fold amplification ranging from 1.4 to 71. Expression levels for each gene have been determined. Analysis is being carried out to assess the magnitude of the association(s) between specific gene expression changes and exposure as estimated both by the concentration of arsenic metabolites in urine and by individual occupational breathing zone arsenic concentrations.	1999