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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | (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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>Millions of people worldwide are exposed to drinking water containing arsenic, and epidemiologic studies have identified associations between the ingestion of arsenic- | 2004 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>Chronic arsenic (As) poisoning has become a worldwide public health issue. Most human As | 2004 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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<br>Jan-Feb;21(1A):51-7.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>A number of chemical contaminants have been identified in drinking water. These contaminants reach drinking water supplies from various sources, including municipal and | 2000 |

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| | 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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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.<br><br>The effect on antioxidant defense system of liver and kidney of sub-acute i.p. exposure to | 2000 |

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| | 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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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 |

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| | Nov;20(11):2171-9.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |

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| | (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.<br><br>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.<br><br>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.<br><br>As part of a longitudinal investigation of environmental exposures to selected chemical | 1999 |

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| | 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.<br><br>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 ($\leq$ 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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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.<br><br>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 |

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| | 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.<br><br>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.<br><br>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 |