

ly 13-fold higher than in unexposed cells. Epithelial cells that were made resistant to Cd by repeated culturing in Cd-containing medium also had γ -GCS-LS mRNA levels about 4-fold higher than cells that were not adapted to Cd. The studies presented support the conclusion that coordinate up-regulation in the gene expression of the regulatory and the catalytic subunits of γ -GCS occurs in the lungs of rats following inhalation of Cd aerosols and in AECs exposed to Cd *in vitro*. These responses may contribute to pulmonary Cd resistance.

1957 INHIBITION OF DNA-(CYTOSINE-5) METHYLTRANSFERASE ACTIVITY BY CARCINOGENIC METALS.

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Several different metal compounds have been identified as human carcinogens. The methylation of cytosine by the DNA-(cytosine-5) methyltransferase (DNA-MeTase) is the predominant post-replication base modification and defects resulting in hypo- or hyper-methylation of particular DNA sequences have also been shown to be either the cause or consequence of malignant transformation. Therefore, we have carried out a study on the effects of a series of metals (As^{3+} , As^{5+} , Cd^{2+} , Cr^{6+} , Ni^{2+} , Pb^{2+} , Zn^{2+}) on the DNA-MeTase activity. Both lysed rat liver epithelial cells (TRL 1215) or purified bacterial *M. SssI* were used as the source of DNA-MeTase. Regardless of source, the activity of DNA-MeTase was found to be strongly inhibited by a number of metal ions. Cd^{2+} ($IC_{50} = 25 \mu M$) was the most effective followed by Zn^{2+} , Pb^{2+} , and Ni^{2+} . Only in the case of mammalian cell lysis did As^{3+} inhibit the activity of DNA-MeTase. Kinetic analysis revealed Cd^{2+} to be a noncompetitive inhibitor with respect to DNA, and an uncompetitive inhibitor with respect to the methyl donating co-factor for DNA-MeTase, S-adenosylmethionine. These results indicate that Cd^{2+} interacts with DNA binding domain on DNA-MeTase. DNA-MeTase activity in intact TRL 1215 cells, when treated with $10 \mu M$ Cd for 24 hours, was depressed by up to 84%. During longer exposure experiments 0.5 - $2.5 \mu M$ Cd was used. After 1 week of Cd exposure, DNA-MeTase activity in cells was decreased in a concentration dependent fashion. Although Cd decreased DNA-MeTase activity, global DNA hypermethylation occurred after Cd exposure for 10 weeks. These results raise the possibility that one of the mechanisms of Cd^{2+} carcinogenicity could be an induction of abnormal DNA methylation. For other carcinogenic metals such as As^{3+} , Pb^{2+} or Ni^{2+} altering DNA methylation status may also contribute to their carcinogenic effects.

1958 ARSENIC-SELENIUM INTERACTIONS IN HUMAN AND RAT HEPATOCYTES.

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Arsenic (As) and selenium (Se) are metalloids that share chemical properties and metabolic fates. The metabolism of either metalloid involves glutathione (GSH)-dependent reduction and enzymatic methylation to mono-, di- and trimethylated metabolites. Each metalloid modifies the metabolism and toxicity of the other in laboratory animals. It has been suggested that Se might be used as an antidote to mollify the adverse effects associated with exposure to As in humans. The present work examines the effects of Se on the metabolism and toxicity of As in primary cultures of human and rat hepatocytes. The simultaneous addition of $2 \mu M$ sodium selenite (Se^{IV}) to cultures significantly increased cellular retention and inhibited methylation of $0.1 \mu M$ sodium arsenite (iAs^{III}) in both cell types. The ratio of the methylated metabolites, dimethylarsenic (DMAs): monomethylarsenic (MAs), decreased markedly in the presence of Se^{IV} , suggesting that synthesis of DMAs from MAs may be more susceptible to inhibition by Se^{IV} than is the production of MAs from iAs^{III} . The inhibitory effect of Se^{IV} was concentration-dependent and enhanced by concurrent addition of $2.5 mM$ GSH. The addition of $2 \mu M$ Se^{IV} into the culture 24 hours before addition of 0.1 or $1 \mu M$ iAs^{III} increased cellular retention of iAs^{III} but did not alter the rate and yield of the methylation reactions. 24-hour exposure to $2 \mu M$ Se^{IV} had no effect on the viability of cultured hepatocytes. Concurrent addition of $2 \mu M$ Se^{IV} increased the cytotoxicity of iAs^{III} and its trivalent metabolites, MAs^{III} and DMAs^{III}. GSH effectively protected cells against toxicity of arsenicals. However, the protective effect of GSH was significantly less in the presence of Se^{IV} . These data suggest that treatment with Se may in fact enhance the toxic effects of As, increasing its

retention in tissues and reducing its methylation which may be pathway for the detoxification of As. (This abstract does not necessarily reflect EPA policy.)

1959 DMPS MODULATION OF ARSENIC SPECIES, INCLUDING MONOMETHYLARSONOUS ACID (MMAIII), IN HUMAN URINE.

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The administration of sodium 2,3-dimercapto-1-propane sulfonate (DMPS) to humans chronically exposed to inorganic arsenic in their drinking water resulted in the increased urinary excretion of arsenic, the appearance and identification of monomethylarsonous acid (MMAIII) in their urine and a large decrease in the urinary excretion of dimethylarsinic acid (DMA). Experiments were designed to understand the appearance of MMAIII and decrease of DMA in the urine. DMPS, *in vitro*, inhibited rabbit liver MMAIII methyltransferase. This and other evidence supports the hypothesis that DMPS competes with endogenous ligands for MMAIII, forming a complex that is readily excreted in the urine and points out the need for studying the toxicology of MMAIII. The results of these studies raise many questions about the potential central role of MMAIII in the toxicity of inorganic arsenic and to the potential involvement of MMAIII in the little understood etiology of hyperkeratosis, hyperpigmentation and cancer that can result from chronic inorganic arsenic exposure. (Supported in part by Superfund Basic Research Program NIEHS Grant ES-04940 and Southwest Environmental Health Sciences Center Grant P30-ES-06694.)

1960 MEDICAL MONITORING SURVEY RESULTS AND BERYLLIUM EXPOSURE AT A BERYLLIUM MINE AND EXTRACTION FACILITY.

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A survey to evaluate employees for beryllium sensitization and chronic beryllium disease (CBD) was conducted at the Brush Wellman Inc. mine and beryllium extraction mill in Delta, Utah, using a medical history and the beryllium blood lymphocyte proliferation test (BLPT). Historical industrial hygiene data, including general area, breathing zone, and limited personal lapel measurements were used to assess the levels of ambient beryllium exposures at this worksite. Beryllium exposures at this facility occur as a result of the presence of dust from bertranite (hydrated beryllium silicate) and beryl (beryllium aluminum silicate) ores, mists containing soluble beryllium salts (beryllium sulfate, beryllium ammonium carbonate and beryllium carbonate), and the precipitation and packaging of the plant's end product, hydrated beryllium hydroxide. 76 of 85 current employees agreed to participate. The rates of beryllium sensitization (4%) and CBD (1.4%) at Delta were intermediate compared to rates expected in the general population (1% and 0% respectively) and those found in other company beryllium surveillance programs (6% and 4% respectively), but were not significantly different from either reference point (P values > 5%). Furthermore, the one case of CBD detected was in the only individual who had spent significant time working elsewhere with beryllium (10 years) where clinical and subclinical CBE is more prevalent. Excluding this individual, the plant has never detected a case of CBD in current or former workers, which yields a rate of CBD significantly lower than that observed in persons ever employed at either the Elmore and Tucson facilities. Former and current levels of occupational exposure to airborne beryllium at the three plants are comparable. We hypothesize that differences in rates of sensitization and CBD result from the a) low bioavailability of beryllium in ore dusts, b) low potency of soluble beryllium salts, and c) localized presence of beryllium hydroxide and/or d) differences in work practices and personal protection controls.