for cholesterol biosynthesis. The active metabolite responsible for this inhibition is not known. To study the potential mechanisms of tellurium toxicity in humans, a truncated human squalene monooxygenase (HSM) was cloned, expressed and purified. We previously reported that tellurite inhibits HSM with an IC50 of 17 μM. Kinetic analysis of the tellurite inhibition shows slope-parabolic and intercept-parabolic inhibition with respect to squalene, implicating more than one binding site for tellurite. To date, a wide variety of related compounds have been tested as inhibitors: dimethyltellurium dichloride is the most potent compound tested, having an IC50 of 1.5 μM. Because tellurite has been shown to bind sulfhydryl groups we hypothesized that the compounds bind to cysteine residues in HSM. Preliminary support for this hypothesis is provided by the observation that the sulfhydryl reagents glutathione, dithiothreitol, and beta-mercaptoethanol are able to protect against as well as reverse the inhibition. The presence of seven cysteine residues in HSM is consistent with the kinetic evidence for multiple tellurite binding sites on HSM. (Supported by a grant from the Ohio Valley Affiliate of the American Heart Association, NIEHS Training Grant ES-07266, and the UK Medical Center Research Fund.)

170 METAL INTERACTION WITH PHYSICAL AND CHEMICAL AGENTS IN THE INDUCTION OF CYTOGENETIC EFFECTS IN HUMAN LYMPHOCYTES.

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Chromium and Nickel are widely spread environmental contaminants and known human carcinogens. Among the most frequently used cytogenetic endpoints to identify exposure to genotoxic agents are the induction of micronuclei (MN) and the induction of sister chromatid exchanges (SCE) in human lymphocytes.Treatment of human lymphocytes with NiSO4 (1-100 mM) or UV-light (200, 1000 ergs/mm2) induced micronuclei (MN) in a dose-dependent fashion. Statistical analysis of the interaction factor (IF), showed that combined treatments of Ni(II) (1-100 mM) with UV-light (200, or 1000 ergs/mm2) interacted antagonistically for the induction of MN. Furthermore Ni(II) [0.5-10 mM] with UV-light (200 or 1000ergs/mm2) or Cr(VI) interacted antagonistically for the induction of sister chromatid exchanges (SCE), in peripheral human lymphocytes. Based on the fact that Ni(II) alters DNA replication, we studied the toxicity of nickel in relation to the cell cycle of human lymphocytes. We also devised an index of cell cycle progression (ICCP) to quantitate the effect of Ni(II) treatments on the cell cycle. There was a delay of 2.1 h for the 5 and 10 mM Ni(II) treatments and a delay of 5.3 h for the 25 mM Ni(II) treatment. These observations has raised a concern that nickel present in complex mixtures may reduce the response, even in the presence of strong MN or SCE inducers, and may lead, therefore, to an underestimate of chemical exposure as assessed by these assays. Since metals affecting certain microsteps in the process of DNA replication or repair (eg. histones, polymerases, ligases) may have similar antagonistic effects, further studies, are recommended.

171 DIFFERENTIAL ABILITY OF TRANSITIONAL METALS TO INDUCE PULMONARY INFLAMMATION.

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Transition metals are components of airborne particles and have been implicated in adverse health effects. Relative toxicity and inflammatory potential of these metals are usually inferred from separate studies since little directly comparable data are available. The objective of this study was to compare the pulmonary effects of intratracheally-instilled, equimolar, soluble forms of six metal sulfates. Rats received either phosphate-buffered saline, 0.1 umol/kg, or 1.0 umol/kg of vanadium, nickel, iron (II), copper, manganese, or zinc. Bronchoalveolar lavage was performed at 0, 4, 16, or 48 hrs post-installation. At the 0.1 umol/kg dose, only Cu induced significant neutrophil influx at 16 and 48 hrs ($p<0.05$). For the 1.0 umol/kg dose at 4 hrs, Cu and Fe(II)-exposed animals had a significant increase in percent neutrophils compared to saline controls, and Cu had a significantly higher percentage than all other metals. After 16 hrs, each metal tested induced significant neutrophilia compared to controls, and Cu and Mn induced significantly higher neutrophilia than the other metals. At 48 hrs, neutrophilia was still increased in all metal exposures except Fe(II). Interestingly, Mn was the only metal to induce a significant increase in eosinophils (16 hr post-instillation, $p<0.05$). Additionally, Cu and Ni-exposed rats had significantly higher levels of lactate dehydrogenase in lavage supernatant compared to the other metals and controls. These results indicate that transition metals differ in their ability to induce pulmonary inflammation and toxicity. Cu appears to be the most pro-inflammatory metal, followed by Mn and Ni, while V, Fe(II), and Zn induced similar levels of neutrophila. We conclude that the extent and cellular nature of metal-induced pulmonary inflammation depends on the individual metal. (Supported by: ES00002, HL54958, HL07118, and HL05947.)

172 CARCINOGENIC NICKEL INDUCES GENES INVOLVED WITH HYPOXIC STRESS.

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Carcinogenic nickel compounds altered the program of gene expression in normal cells and induced a pattern of gene expression similar to that found in nickel-induced cancers. Here we have demonstrated that exposure of mouse normal fibroblasts, or human A549 cells to 1 mM nickel induced hypoxic signaling pathways by inducing hypoxia-inducible transcription factor (HIF-1) which mediated the induction of genes required by cells to survive hypoxia. We also showed that a new gene Cap43 was dependent upon HIF-1 since only HIF-1 proficient mouse cells induced Cap43 gene expression when exposed to either hypoxia (1%O2) or 1 mM nickel. We also showed that GAPDH, a gene induced by hypoxia through HIF-1, was similar to Cap43 in that it required HIF-1 mouse proficient cells to be induced by either 1 mM nickel or hypoxia (1%O2). These data demonstrated that nickel exposure turned on signaling for a hypoxic cascade that may be important in its carcinogenesis.

173 INHIBITION OF HISTONE ACETYLATION BY NICKEL COMPOUNDS IN *S. CEREVISIAE* AND MAMMALIAN CELLS.

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Environmental factors influence carcinogenesis by interfering with a variety of cellular targets. Carcinogenic nickel compounds are inactive in most gene mutation assays, but they induce chromosomal damage in heterochromatic regions and cause gene silencing on reporter genes located near heterochromatin in both yeast and mammalian cells. Here we studied nickel effects on the acetylation in the N-terminal region of histone H4. We demonstrate that *in vivo* nickel compounds decrease histone H4 acetylation levels in both yeast and mammalian cells. The effects of nickel on the lysine residue targets in the N-terminal region of histone H4 are distinct. In both yeast and A549 cells, lysine 12 is the most sensitive residue. While in yeast the acetylation levels of lysine residues at sites 16, 8 and 5 are also affected by nickel, in A549 cells the effect is limited mostly to lysine 12. Unlike in yeast cells, where acetylation levels are reduced by soluble nickel, the acetylation in A549 cells is inhibited only by non-soluble nickel particles (nickel subsulfide). Comparison among the yeast cells treated with a variety of metals shows that CuSO4 causes similar effect on histone acetylation as nickel, while CdCl2 or CoCl2 only slightly inhibits acetylation. In vitro inhibition of H4 acetylation by nickel is also observed using a purified acetyltransferase (GCN5).

174 NICKEL COMPOUND-INDUCED TOXICITY AND MORPHOLOGICAL TRANSFORMATION IN 10T1/2 CELLS.

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Certain insoluble nickel compounds are carcinogenic. We wanted to determine whether short-term *in vitro* assays could predict relative carcinogenic potentials of nickel compounds. We therefore examined abilities of these compounds to be phagocytosed by and induce cytotoxicity, micronuclei, chromosomal aberrations, and morphological transformation in 10T1/2 mouse embryo fibroblasts. The overall ranking for genotoxicity showed that Ni subsulfide and Ni oxides were most genotoxic; elemental nickel particles of <1 μM reported size had intermediate genotoxicity; and elemental nickel particles of 3-7 μM reported size together with soluble nickel sulfate had the lowest overall genotoxicity. Phagocytosis of insoluble nickel compounds and cell transformation endpoints correlated best with existing animal and human carcinogenicity data. Ni subsulfide and green Ni oxide, but not soluble nickel sulfate, were carcinogenic when inhaled by rats. Interestingly, both elemental nickel particles ranked the lowest in cell transformation, together with soluble nickel sulfate. Overall results indicate these *in vitro* assays can be used to prioritize nickel compounds for carcinogenicity in animals. We next induced ten foci in 10T1/2 with black nickel oxide and ten with green nickel oxide, derived transformed cell lines from the foci, and characterized these trans-