(100μg/kg). The animals were maintained for 90 days, thereafter. [^{3}H]hexamethonium iodide was used to monitor the changes in blood brain barrier (BBB) permeability in cortex, brainstem, midbrain and cerebellum. Brainstem exhibited a significant decrease (~58% of control) in uptake of [^{3}H]hexamethonium iodide at 1xLD_{50} dose. No significant changes were observed in BBB permeability in cortex, midbrain and cerebellum at any dose. Plasma butyrylcholinesterase (BChE) activity remained unchanged. Acetylcholinesterase (AChE) activity in the cortex remained inhibited (~29%) whereas, in the brainstem there was an increase(~20%) at 1xLD_{50} dose of sarin. m2-Selective muscarinic acetylcholine receptor(m2-mAChR) ligand binding was inhibited significantly at 1xLD_{50} in the cortex whereas, brainstem showed significantly increased (~45%) ligand binding at 1xLD50 dose. Nicotinic acetylcholine receptor (nAChR), on the other hand showed a biphasic response in ligand binding in the cortex with a decrease (~30%) at 0.01xLD_{50} but an increase (~40%) at 1xLD_{50}. Brainstem did not show any significant change in nAChR ligand binding. These results suggest that a single exposure of sarin could lead to changes that may play an important role in neuropathological abnormalities in the CNS. Supported, in part by the U.S. Army Medical Research and Materiel Command under contract #DAMD 17-98-C-8027. The views, opinion and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation

408 CHARACTERIZATION OF THE *IN VITRO* REACTIVITIES OF BUTADIENE MONOXIDE (BMO) AND DIEPOXYBUTANE (DEB) WITH HEMOGLOBIN IN MOUSE ERYTHROCYTES.

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1,3-Butadiene (BD) is carcinogenic to humans and rodents. Of particular interest is the greater sensitivity of mice to the carcinogenic effects of BD compared to rats. One possible explanation is that mice metabolize BD to DEB at higher rates, and that DEB is a more potent carcinogen than the primary metabolite of BD, BMO. Thus, there is great interest in developing exposure biomarkers to both BMO and DEB. The primary goal of the current studies is to compare the relative reactivities of BMO and DEB (both racemic) to hemoglobin (Hb) after *in vitro* exposure (50 μM - 50 mM) under physiological conditions using erythrocytes from B6C3F1 and C57Bl/6 mice. B6C3F1 mice, the primary strain used in toxicology studies of BD, is an F1 hybrid between C57Bl/6 and C3H, resulting in two different forms of α- and β-globin. Adduct formation was quantitated by ES/MS. The results from C57Bl/6 mouse erythrocytes show that BMO and DEB react with α-globin at the same rate, but that DEB reacts with β-globin faster than BMO. In addition, there is a marked difference in the globin-specific reactivities of BMO and DEB. In B6C3F1 mouse erythrocytes, BMO and DEB react similarly with the two α-globins, and BMO reacts equally with the two β-globins present. However, DEB shows a higher rate of reaction with the β-globin derived from the C57Bl/6 strain than the β-globin derived from C3H. Finally, the Hb adducts formed by BMO are stable and do not undergo further reaction. In contrast, DEB bound to Hb is able to undergo further reaction due to the presence of the second epoxide. Evidence for the formation of inter-globin crosslinks by DEB is provided by MALDI-TOF/MS. The results from these studies elucidate the variable reactivities of BMO and DEB towards Hb, both kinetically as well as globin specificity. The determination of Hb crosslinking by DEB could contribute to the development of a specific biomarker assay for DEB exposure. (Supported by NIH grant ES06841. T.S.M. was supported by NRSA Fellowship ES05835.)

409 KINETICS OF AN INTRATRACHEALLY ADMINISTERED CHROMIUM CATALYST IN RATS.

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Chromium-based catalysts are used for the synthesis of polyethylene, but little is known about the hazard and biomonitoring possibilities of this type of chromium for workers who may be occupationally exposed to such compounds. In a preliminary study, the bioavailability and toxicokinetics of chromium were studied, in male Wistar rats, after a single intratracheal instillation (2 ml/kg body weight) of various doses (1, 5, 25 mg/kg body weight) of the catalyst (approximately 1% chromium bound to an amorphous silica matrix), either before [CAT-Cr(III)] or after [CAT-Cr(VI)] heat treatment. The results were compared with those of equivalent amounts of two chromium salts ($CrCl_3$ and $K_2Cr_2O_7$). Each dose group comprised three rats. The concentration of chromium was determined by atomic absorption spectrometry in urine (collected daily for 7 days) and in plasma, erythrocytes, lung and liver tissue obtained at autopsy 7 days after dosing. On the basis of body weights, lung weights and lung histology, there was no overt toxicity, except after the highest dose of CAT-Cr(VI). The elimination of all forms of chromium was rapid and apparently mono-exponential, with calculated half-life elimination times in urine of 4 - 8.5 h for Cr(III) [CAT-Cr(III) and $CrCl_3$] and 8.5 - 21 h for Cr(VI) [CAT-Cr(VI) and $K_2Cr_2O_7$]. In the erythrocytes, chromium concentrations (on day 7) were significantly increased above control values (3 μg/L) only in rats treated with the two highest doses of Cr(VI) compounds [12 and 64 μg/L for $K_2Cr_2O_7$, and 14 and 79 μg/L for CAT-Cr(VI)]. The present results suggest that the Cr(VI) catalyst has the same bioavailability and excretion kinetics as a water soluble Cr(VI) salt and that exposure could be monitored by measuring Cr concentrations in urine (shortly after exposure) and in erythrocytes (also at later times points after high exposition).

410 COMPARISON OF URINARY 8-HYDROXYDEOXYGUANOSINE, ISOPROSTANE AND TBARS FOR ASSESSING OXIDATIVE STRESS IN SMOKERS.

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Measurements of oxidative stress are used increasingly as biomarkers of biologically effective dose for assessing environmental and occupational exposures. Three frequently used indices of oxidative stress 8-hydroxydeoxy-guanosine (8-OHdG), thiobarbituric acid reactive substances (TBARS), and the isoprostane, 8-epi-prostaglandin F2alpha (8-epi-PGF) were measured in the urine (creatinine corrected) of 38 males employed in the construction industry. The objective was to determine the inter-relationship of these biomarkers and their utility in assessing the effect of smoking, a known inducer of oxidative stress. Urine samples were obtained at the start of a typical workweek, and again at the end of that workweek. Urinary 8-OHdG is considered an index of oxidative DNA damage repair. Mean 8-OHdG values at both the start and end of the week tended to be higher, but not significantly higher, in non-smokers than in smokers. TBARS and 8-epi-PGF were used to assess lipid peroxidation. TBARS and 8-epi-PGF were greater in smokers than in non-smokers, but the increase was significant only for the end-of-week 8-epi-PGF values. 8-epi-PGF and TBARS declined non-significantly during the workweek, whereas 8-OHdG increased, and the increase was significant within the smoking group. Although regression analysis did not reveal any significant correlations among the three biomarkers, TBARS paralleled 8-epi-PGF in terms of differences between smokers and nonsmokers and changes during the workweek. In contrast, intergroup differences and temporal changes in 8-OHdG were counter to TBARS and 8-epi-PGF. For the present population, urinary 8-epi-PGF was the most sensitive biomarker of oxidative stress associated with smoking.

411 ANALYSIS OF A NEW BIOMARKER FOR EXPOSURE OF HEMOGLOBIN TO DIEPOXYBUTANE (DEB).

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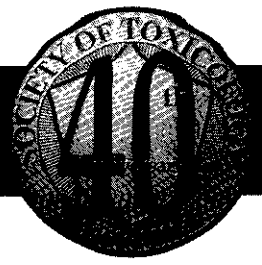
1,3-Butadiene is an important industrial and environmental chemical, shown to be a potent carcinogen in mice, a weak carcinogen in rats, and a probable human carcinogen. The 1,2,3-trihydroxybutylvaline (THBV) adduct, shown to be the main adduct of hemoglobin in rats, mice and humans, is primarily formed by the BD-metabolite epoxybutanediol (EBD). The cyclic adduct N,N-(2,3-dihydroxybuta-1,4-diyl)valine (NNDHBV) has been shown as a primary product formed in the reaction between valinamide (used as a model of N-terminal valine in hemoglobin) and diepoxybutane (DEB). The amount of NNDHBV in biological samples has not been measured due to lack of sensitive and specific analytical techniques. The objective of this research was to develop GC-ECNCI-MS and GC-MS/MS methods for quantitation of NNDHBV in biological samples exposed to DEB. Human RBC were exposed to DEB, the globin extracted and hydrolysed in 6N HCl. The released adduct was derivatized in two steps using pentafluorobenzyl bromide (PFBBr) for the carboxylic group, and N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) for trimethylsilylation of the two hydroxyl groups. A synthesized isotopically labeled internal standard NNDHB[$^{13}C_5$]V (IS), was used for quantitation. Selected ion monitoring (SIM) experiments using ions at m/z 346 and m/z 351



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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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