1315 THE EFFECT OF Fe_2O_3 AND Al_2O_3 ON THE METABOLISM OF BENZO(A)PYRENE BY PULMONARY ALVEOLAR MACROPHAGE. J Cheu and D Warshawsky. Department of Environmental Health, University of Cincinnati, Cincinnati, OH.

The respiratory tract is a common route for entry of toxic materials from modern urban and working environments. Fe_2O_3 and Al_2O_3 particles and benzo(a)pyrene (BaP) are widely encountered in the occupational settings. The aim of this project is to study the role of particles on the modulation of metabolism of BaP. AM from male-Syrian Golden hamsters were incubated in a plate assay with BaP (5 μg) alone or BaP (5 μg)-coated respirable size Fe_2O_3 and Al_2O_3 from doses of 0.5 mg to 2.0 mg. After 24 hr the metabolic profiles indicate that the release of diol, phenol, quinone and total BaP metabolites was significantly greater with Fe_2O_3 compared to Al_2O_3 or BaP alone. The formation of 7,8-diol-BaP, the procarcinogen, was also consistent with the increase of Fe_2O_3 doses. Coadministration of 7,8-benzoflavone, an inhibitor of cytochrome P-450s, significantly reduced the BaP metabolism in BaP-coated Fe_2O_3 and Al_2O_3 treatments. These data suggest that particles enhance the metabolism of BaP in AM via the modulation of P-450 isozymes. Supported by NIOSH RO3-OH02972

1316 METABOLISM AND DNA BINDING OF BaP-COATED PARTICLES BY HAMSTER PULMONARY ALVEOLAR MACROPHAGE. D Warshawsky, R Reilman, T Collins, M Jaeger, J Cheu, M Radike, and G Talaska. Department of Environmental Health, University of Cincinnati, Cincinnati, OH.

Epidemiological and experimental studies indicate that particles and chemical carcinogens are related to the development of respiratory disease. The long term objective is to investigate the role that pulmonary alveolar macrophages (AM) play in the particulate-dependent response of the lung to benzo(a)pyrene (BaP) metabolism. The comparative metabolism and DNA binding of BaP-coated particles by AM using particles, ferric oxide and crystalline and amorphous silica, was undertaken to determine the differential metabolism of BaP. AM from male-Syrian Golden hamsters were incubated with BaP-coated respirable size particles at a dose of 3 μg of BaP and 50 μg particle. After 24 hours the metabolic products in the extractable fraction were greater for BaP-coated particles than BaP alone with the dihydrodiols of BaP being the major metabolites. Of the dihydrodiols present, the 7,8-dihydrodiol was significantly greater for the BaP-coated particles than BaP alone. This was associated with greater level of binding of the BaP-DNA adduct #2 relative to BaP-DNA adduct #1, the (+)antidiol epoxide of BaP using ^{32}P-postlabeling. The data indicate that these BaP-coated particles have a differential effect on the metabolism of BaP by the AM. Supported by OH02277

1317 STRUCTURE AND MODIFICATION OF MOUSE GLUTATHIONE S-TRANSFERASES. A E Mitchell[1] A D Jones[1] and D Morin[2]. [1]Facility for Advanced Instrumentation and [2]Veterinary Molecular Biosciences, University of California at Davis.
Sponsors: H.J. Segall and M. Miller

The glutathione S-transferases (GST, E.C. 2.5.1.18) are a multigene family of dimeric proteins which catalyze the nucleophilic attack of glutathione to a wide variety of electrophilic xenobiotic compounds. Recent studies indicate that covalent modifications to key metabolic enzymes, including GST, result in functional changes in enzyme activities *in vitro*. Characterization of the structures of GST isozymes as well as covalent modifications by reactive electrophiles has been investigated using electrospray ionization mass spectrometry.
Several isozymes of GST were purified from Swiss Webster CD-1 mouse livers using affinity chromatography. Molecular weights and purities of isozymes were determined by electrospray ionization mass spectrometry. These results were compared to molecular weights deduced from cDNA sequences to identify isozymes along with post translational modifications.
The reactivity of GST isozymes toward two model electrophiles, 1,4-naphthoquinone, an aromatic metabolite of naphthalene, and trans-4-hydroxy-2-nonenal (HNE) a byproduct of oxidative stress, is readily apparent from electrospray ionization mass spectra which will be presented.

1318 A NOVEL GLUTATHIONE S-TRANSFERASE ISOZYME CATALYZING CONJUGATION OF 4-HYDROXYNONENAL TO GLUTATHIONE IS DIFFERENTIALLY EXPRESSED IN HUMAN TISSUES. J T Piper, S S Singhal, S K Srivastava, S Awasthi, [1]P Zimniak, and Y C Awasthi. University of Texas Medical Branch, Galveston, TX, [1]University of Arkansas for Medical Sciences, Little Rock, AR.

Glutathione S-transferases (GSTs), a complex group of enzymes which are involved in detoxification mechanisms have been classified into three major classes, α, π, and μ. We have previously characterized a mouse GST isozyme designated as mGSTA4-4, which is highly reactive towards 4-hydroxy-2-nonenal (4-HNE), a toxic endogenous product of lipid peroxidation. Using antibodies raised against the recombinant mGSTA4-4 expressed in E. Coli, we now demonstrate that an ortholog of this isozyme is selectively expressed in human tissues. The human isozyme designated as hGST 5.8 was immunologically distinct from the GSTs of the α, π, or μ class. hGST 5.8 was present in liver, pancreas, heart, brain, and bladder, and absent in lung, skeletal muscle, spleen, and colon. hGST 5.8 purified from human liver had a pI value of 5.8 and constituted approximately 1.7% of liver GST protein. Its subunit Mr was about 24.5 kDa and its N-terminus was blocked. The sequences of the CNBr peptide fragments of GST 5.8 showed more than 80% identity with the corresponding sequences of mGSTA4-4. hGST 5.8 showed about 17 fold higher activity towards 4-HNE as compared to 1-chloro-2,4-dinitrobenzene. In addition, it also expressed glutathione-peroxidase activity towards fatty acids as well as phospholipid hydroperoxides suggesting its role in the protection mechanisms against endogenous toxicants generated during lipid peroxidation. Supported in part by USPHS grant GM 32304.

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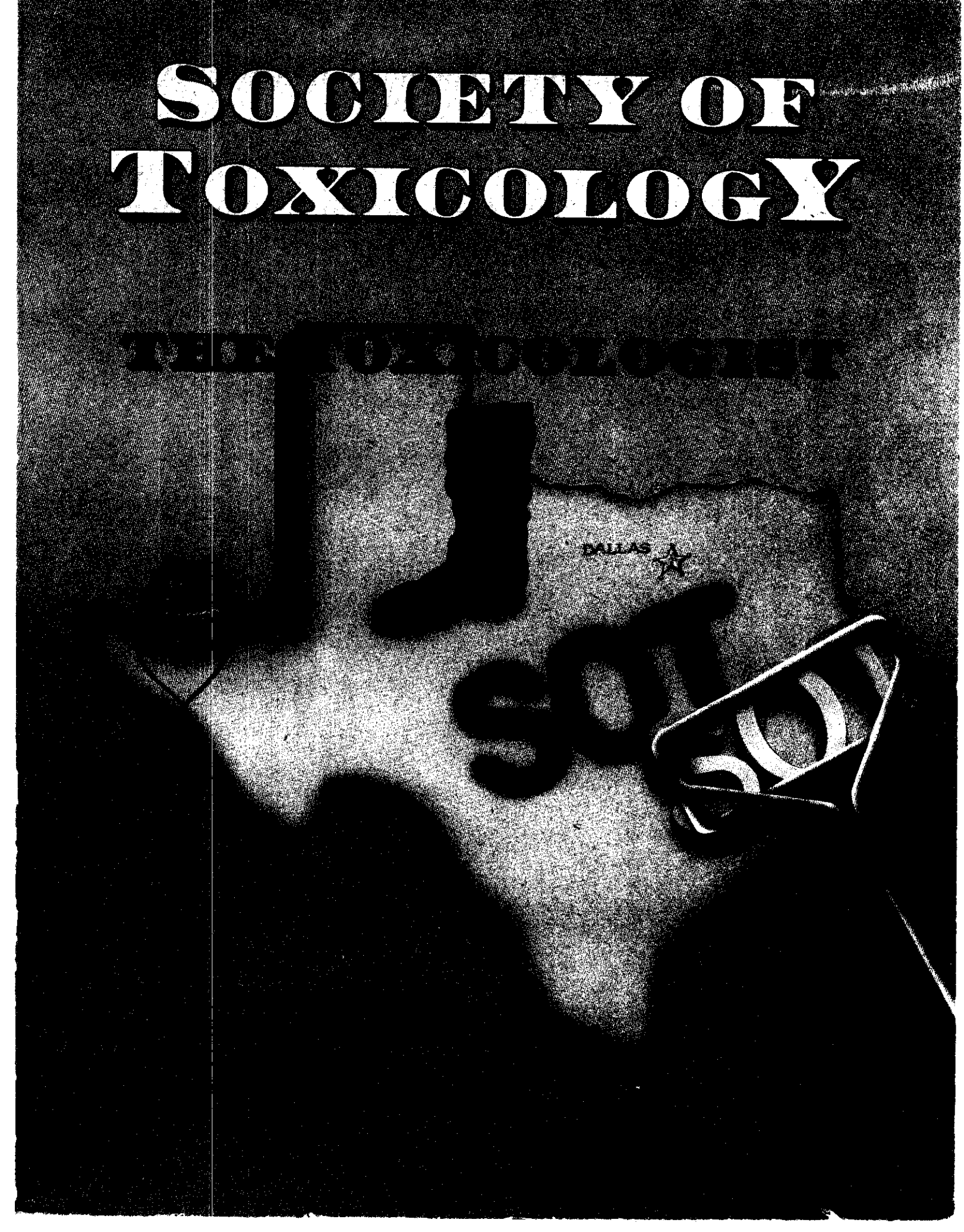

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster/discussion, and poster sessions of the 33rd Annual Meeting of the Society of Toxicology, held at the Loews Anatole Hotel, Dallas, Texas, March 13-17, 1994.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 439.

The issue also contains a Keyword Index (by subject or chemical) to the titles of all the presentations, beginning on page 467.

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