F I N A L P E R F O R M A N C E R E P O R T

SUSCEPTIBILITY TO GENETIC DAMAGE FROM BUTADIENE

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SIGNIFICANT FINDINGS

The field portion of the study has been completed. Exposure to butadiene has been assessed with 8-hour time weighted average personal sampling as well as urine collection and metabolite determination. Significant data have been collected by questionnaire and blood has also been collected. Early analysis of the data reveals baseline cytogenetic changes in the exposed group to be unrelated to time-weighted average measurements of exposure. Urine was collected and there is no relationship between induced cytogenetic damage and urinary measures of exposure to butadiene. However, examination of high SCE frequency cells reveals that there is some relationship between length in the trade and high frequency SCE cells present in workers. Also, one individual who had previously been noted to have a very high hprt mutant fraction was also sensitive to diepoxybutane *in vitro*.

Thus, our work indicates that acute exposure to 1,3-butadiene was not associated with induction of chromosomal abnormalities. However, tenure in the trade was associated with production of high SCE frequency cells.

We have also determined that the homozygous gene deletion in glutathione-S-transferase (GST) class theta is responsible for heritable sensitivity to butadiene metabolites. This implies that GST theta detoxifies butadiene metabolites and individuals with this deletion may be susceptible to DNA damage from butadiene exposure.

Companion studies of molecular epidemiology are being carried out using these same techniques. These studies have shown that genetic damage, induced by exposure to radiation results in persistent genetic damage measured as sematic mutations. Further, we've noted that constitutional heterozygosity for the ataxia-telangiectasia gene results in heterogeneity in the clastogenic response to x-rays in lymphocytes from these individuals. In addition, molecular determination of the heterozygosity in glutathione transferase class μ does not modify venodilatory potency of nitroglycerin in human veins.

USEFULNESS OF FINDINGS

There remains considerable interest in the application of biomarkers of genetic susceptibility to cancer in studies of occupational exposure to carcinogens. Our work has broadened this discipline, specifically targeting worker exposure to butadiene. This model has been used by other researchers in studying butadiene in other countries as well as in the United States. NIOSH has funded a continuing competitive grant award to study the workplace that we have begun to study with our grant. Perhaps the most important finding and the most useful observation has been that butadiene is an apparent substrate for the polymorphic metabolic conjugation pathway, glutathione-S-transferase theta. This has significantly enhanced our understanding of the metabolism of this compound in humans and made research into the metabolism of butadiene in humans much simpler. We can now use simple polymerase chain reaction methods to obtain information on metabolic status. This makes the follow-up of workers in potential exposure situations much easier for future research.

RELATIONSHIP OF PUBLICATIONS TO THE PROJECT

1. Wiencke JK, Kelsey KT: Susceptibility to Induction of Chromosomal Damage by Metabolites of 1,3-Butadiene and Its Relationship to "Spontaneous" Sister Chromatid Exchange Frequencies in Human Lymphocytes, IARC Scientific Publications No. 127, (eds. M Sorsa, K Pelionen, H Vainio, K Hemminki), Lyon, International Agency for Research on Cancer, 1993.

Chromosomal sensitivity to diepoxybutane (deb) is described as bimodal. It also demonstrates that deb-sensitivity is associated with elevated baseline SCE. It implicates for the first time a heritable genetic polymorphism in the metabolism of butadiene.

2. Kelsey KT, Bechtold WE, Ward JB, Wiencke JK: Susceptibility to Genetic Damage from Occupational Exposure to Butadiene. Proceedings of the International Symposium on Health Hazards of Butadiene and Styrene, pp. 265-273, 1993.

This work reports on the major specific aims of the project. It reports on worker exposure to butadiene which was measured in collaboration with NIOSH and Texaco. It also reports the sister chromatid exchange frequencies in lymphocytes drawn from workers on-site. This addresses the major specific aims of the grant.

3. Wiencke JK, Kelsey KT: Inter-Individual Sensitivity and Cytogenic Response to Diepoxybutane. Proceedings of the International Conference on the Health Hazards of Butadiene and Styrene, 1993.

This outlines the phenotypic response of lymphocytes to butadiene metabolites. It is further research on the mechanism involved in metabolism of butadiene.

4. Bechtold WE, Kelsey KT, Ward JB: Measurement of 1,2-Dihydroxy-4-(N-Acetylcysteinyl-S)Butane in a Urine as a Biomarker of Exposure to 1,3-Butadiene. Proceedings of the International Conference on the Health Hazards of Butadiene and Styrene, 1993.

This work is an examination of use of urinary metabolite approach to the study of butadiene exposure. It further extends the technical approach to epidemiologic study of butadiene exposure in the same workers as were proposed to study in the grant.

5. Haefeli WE, Srivastava N, Kelsey KT, Wiencke JK, Hoffman BB, Blaschke TF: Glutathione-S-transferase μ Polymorphism does not Modify Venodilatory Potency of Nitroglycerin in Human Veins. Clinical Pharmacology and Therapeutics 53(4):463-468, 1993.

While not central to the original aims of the project, the techniques used to accomplish our grant contributed significantly to the technical developments allowing us to genotype these patients for the glutathione transferase class μ. Thus, the grant funding contributed to this in a technical sense.

6. Cullen MR, Solomon L, Pace PE, Buckley P, Duffy T, McPhedran P, Kelsey KT, Redlich CA: Morphologic Biochemical and Cytogenetic Studies of Bone Marrow and Circulating Blood Cells in Painters Exposed to Ethylene Glycol Ethers. Environ Res 59, 250-264, 1992.

This paper again studies the worker-solvent exposure using sister chromatid exchange as an outcome. Funds from the grant contributed in the development of the SCE assay and, thus, was an important part of this publication.

7. Smith CM, Kelsey KT, Christiani DC: Risk Assessment and Occupational Health: Overview and Recommendations. New Solutions, Winter:26-38, 1993.

This paper is a review and summary of the use of data such as that generated by this grant proposal in assessing risk. Thus, the grant contributed in the making of an overall approach to this problem.

8. Wiencke JK, Wara DW, Little JB, Kelsey KT: Heterogeneity in the Clastogenic Response to X-rays in Lymphocytes from Ataxia-Telangiectasia Heterozygotes and Controls. Cancer Causes and Control 3:237-245, 1992.

This paper is an additional look at variation in lymphocyte response to induced DNA damage. In its approach, it parallels the approach that we used in this grant on the project. Thus, the grant-funded project has contributed to this work through the design and use of techniques that were made possible by this funding.

9. Caggana M, Liber HL, Coleman MD, Mauch PM, Clark JR, Kelsey KT: A Prospective Study of *hprt* Mutant and Mutation Frequency in Treated Cancer Patients. Cancer Epidemiology, Biomarkers and Prevention 573-580, 1992.

Again, while not central to the specific aims of the project, the technique used in this project was developed in concert with the techniques mandated by the grant. The lymphocyte growth and testing proceeded in parallel with our work to develop the assays for studying the butadiene-exposed workers. Thus, the grant contributed to this publication as well.

10. Wiencke JK, Pemble S, Ketterer B, Kelsey KT. Gene Deletion of Glutathione-S-transferase theta: Correlation with Inducted Genetic Damage and Potential Role in Endogenous Mutagenesis. Cancer Epidemiology, Biomarkers and Prevention (in press) 1995.

This is the peer-reviewed report citing for the first time that butadiene metabolites are substrate for the polymorphic enzyme glutathione-S-transferase theta. This is an extension of the hypothesis of our work, and for the first time implicates polymorphic human metabolism as a source of variability for exposure and potential disease from butadiene exposure.

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FINAL INVENTION STATEMENT

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There are no inventions.

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