



STATEMENT

Synopsis of Research Report 116

HEALTH
EFFECTS
INSTITUTE

Biomarkers in Butadiene-Exposed Workers

BACKGROUND

Butadiene is a four-carbon gaseous chemical synthesized for the manufacture of resins, plastics, and synthetic rubber. It is also produced by combustion; butadiene is present in cigarette smoke and emissions from motor vehicles and some stationary sources. The highest exposures, those that occur in occupational settings, may present a health concern because butadiene is known to be carcinogenic in rats and mice and some epidemiologic studies have implicated it as a human carcinogen by inhalation. Those studies have indicated that workers exposed to butadiene in rubber-producing factories also have an increased incidence of two types of cancer: cancers of the lymphatic system and cancers of the organs and systems of the body that produce blood cells. More recent and comprehensive studies of the same workers have indicated an increased risk of leukemia (but not other types of cancers) in workers with a long duration of employment in the rubber industry. On the basis of these epidemiologic studies, various government and international agencies have conducted risk assessments of butadiene's carcinogenicity and designated it as "potentially carcinogenic to humans," "a probable human carcinogen," and a "known human carcinogen."

In 1994, HEI initiated a research program to address the health risks of exposure to a series of chemicals, including butadiene, designated as toxic air pollutants by the US Environmental Protection Agency. In 1995, HEI issued Request for Qualifications 95-3, "Transitional Epidemiology Studies for Benzene or 1,3-Butadiene Biomarkers," which sought researchers with access to human populations exposed to either benzene or butadiene. The goal of RFQ 95-3 was to fund research to determine whether human exposure could be quantified by measuring the levels of certain biomarkers. Biomarkers are chemical compounds or physical

characteristics that appear in bodily fluids or tissues after exposure to an exogenous agent. They can be specific indicators of exposure such as stable metabolites, metabolites bound to proteins or DNA, or genetic material that was altered because of the exposure.

Epidemiologic studies have encountered two primary difficulties in assessing exposure to carcinogenic agents. First, because the incidence of certain cancers is low, they have needed to study large populations to find an association between exposure and disease. Second, it is often difficult to accurately assess the level or time course of exposure to a possible cancer-causing agent in order to link past exposures to recent disease occurrences. In contrast with this, populations known to have been exposed to certain chemicals (such as groups of workers in a specific industry) show relatively high levels of biomarkers. Therefore, if biomarkers can accurately reflect the level or timing of exposure to a suspected carcinogen, they may be able to enhance exposure assessment in epidemiologic studies.

Dr Richard Albertini at the University of Vermont in Burlington organized groups of researchers from his own laboratory and laboratories in Galveston, Texas; Chapel Hill, North Carolina; Prague, Czech Republic; Amsterdam and Leiden, The Netherlands; and Sheffield, United Kingdom. Each group had expertise in identifying different biomarkers that appear after butadiene exposure. Dr Radim Šrám of the Laboratory of Genetic Ecotoxicology in Prague provided contact with butadiene-exposed workers in two production units of a factory near Prague.

APPROACH

The researchers proposed to determine whether biomarkers in the blood and urine of the exposed workers correlated with their personal exposure

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to butadiene. Šrám and coworkers in Prague collected blood and urine from male workers employed either in the butadiene monomer production plant or in the polymerization facility that used butadiene and styrene to produce rubber polymer. They also collected blood and urine from male administrative workers at the plant who had no direct occupational exposure to butadiene and served as control subjects. Each worker's personal exposure to butadiene in air was measured using a small air sampler attached to his clothes. Samplers were worn on several occasions over a 60-day period preceding and during the three days on which blood or urine samples were acquired. The air samplers were sent to a laboratory in Sheffield where butadiene levels were analyzed. For biomarker analyses, the Prague researchers sent portions of each blood and urine sample to the other research groups and kept a portion for their own use.

The study was conducted in a blinded fashion. Subject identities were known only to Albertini and the biostatistician for the study in Burlington, where codes were maintained, data were analyzed, and then matched to the three exposure groups.

The investigators focused their investigation on two types of biomarkers. The first type comprised *biomarkers of exposure* that were chosen specifically to indicate the level of butadiene in the body that resulted from an exposure. The researchers in Amsterdam and Chapel Hill determined the concentrations of two adducts that form when butadiene metabolites bind to hemoglobin in red blood cells. The Amsterdam researchers also measured levels of other exposure-related biomarkers, two metabolites that are excreted in urine when butadiene is detoxified in the body.

The second type of biomarker comprised *biomarkers of effect*, including gene mutations and structural

changes in chromosomes. The researchers in Leiden and Galveston analyzed mutations in the *HPRT* gene by different methods and the Prague researchers determined the types and degrees of chromosomal changes.

In addition, the Prague and Burlington groups looked at factors that may affect *susceptibility* to carcinogens, such as changes in the genes that code for enzymes that metabolize butadiene. Such differences can modify an enzyme's activity and may affect an individual's response to possible butadiene-induced effects.

RESULTS AND INTERPRETATIONS

All the biomarkers of exposure were correlated with the measurements of butadiene recorded by the air samplers. Although the correlation between hemoglobin adducts and exposure levels was strongest, urinary metabolites were also found to be very useful measures of butadiene exposure.

No statistically significant correlations were found between any of the biomarkers of effect and butadiene exposure. Although these biomarkers were investigated, they were evaluated against exposure, not against health outcomes. Thus, no conclusions about health outcomes can be drawn from these results.

This very important and valuable study established the linkage between exposure to butadiene, as measured by comprehensive conventional sampling techniques, and several biological markers of such exposures. The integration of a comprehensive exposure assessment with a series of logical biomarker analyses was an outstanding feature of this complex international study. Of the many biomarkers analyzed, the biomarkers of exposure (particularly hemoglobin adducts) may prove to be valuable in future epidemiologic studies of the health effects of butadiene exposure.