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Future directions in butadiene risk assessment and the role of cross-species internal dosimetry

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Abstract

The 2005 International Symposium on the evaluation of butadiene and chloroprene health risks provided the opportunity to consider the past, present and future state of research issues for 1,3-butadiene. Considerable advancements have been made in our knowledge of exposure, metabolism, biomarkers of exposure and effect, and epidemiology. Despite this, uncertainties remain which will impact the human health risk assessment for current worker and environmental exposures. This paper reviews key aspects of recent studies and the role that biomarkers of internal dosimetry can play in addressing low to high exposure, gender, and cross-species differences in butadiene toxicity and metabolism. Considerable information is now available on the detection and quantification of protein adducts formed from the mono-, di- and dihydroxy-epoxide metabolites of butadiene. The diepoxide metabolite appears to play a key role in mutagenesis. Species differences in production of this critical metabolite are reflected by the diepoxybutane-specific hemoglobin adduct, *pry-Val*. To date, the *pry-Val* adduct has not been quantifiable in human blood samples from workers with cumulative occupational exposures up to 6.3 ppm-weeks; whereas, the *pry-Val* was quantifiable in the blood of mice and rats with similar cumulative exposures. Levels in mice were much higher than in rats. Further improvements in analytical sensitivity for the *pyr-Val* adduct are on the horizon. Epidemiology studies are also described and ongoing efforts promise to help bridge our understanding of past and future risks.

Keywords: Risk assessment; Butadiene; Mode of action; Biomarkers

1. Introduction

The 2005 International Symposium on the Evaluation of Butadiene and Chloroprene Health Risks provided a truly outstanding update on current knowledge related to exposure, metabolism, biomarkers of exposure and effect, and epidemiology of butadiene (BD). This international symposium was preceded by four previous meetings on butadiene health effects [1–4]. Future research directions proposed at the 2000 international meeting related to butadiene risk assessment are summarized in Table 1.

Abbreviations: BD, 1,3-butadiene; DEB, 1,2:3,4-diepoxybutane; DMDTC, dimethyldithiocarbamate; FISH, fluorescent *in situ* hybridization; Hb, hemoglobin; *Hprt*, hypoxanthine phosphoribosyltransferase gene; LOAEL, lowest observable adverse effect level; MF, mutation frequency; NOAEL, no observable adverse effect level; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure level; pyr-Val, *N,N*-(2,3-dihydroxy-1,4-butadiyl)-valine; SBR, styrene-butadiene rubber; TWA, time weighted average; UAB, University of Alabama; WHO, World Health Organization

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Table 1
Outstanding butadiene health effect research issues, 2000 International Symposium on Butadiene and Chloroprene Health Risks

- Resolve species differences in metabolism, including differences in origin of carbon dioxide
- Understand relative roles/binding properties of CYP 2E1 and epoxide hydrolase of different species
- Use sensitivity analysis to optimize predictive ability of toxicokinetic models
- Resolve discrepancy between human *Hprt* study findings
- Conduct additional study of altered metabolism of BD due to DMDTC exposure
- Quantify historical monomer exposure in the Divine and Hartman [19] butadiene monomer worker cohort using methods from SBR worker study
- Leukemia risk in other SBR & monomer worker cohorts (including women)
- Consider reproductive-related outcomes
- Analyze epidemiologic data using WHO lymphopoietic cancer classification

Many of the research questions in Table 1 have been addressed in studies conducted over the last 30 years, when potential adverse health effects of butadiene were first raised in the 1970s. Key studies conducted over this period are described in the time line provided in Fig. 1. These studies have been interdisciplinary in nature and included epidemiology, toxicology, and molecular biology. Despite extensive progress made and reported in this current symposium, several key aspects remain uncertain and require additional research. This paper reviews key aspects of recent studies and the role that biomarkers of internal dosimetry can play in addressing low to high exposure, gender and cross-species differences in butadiene toxicity and metabolism.

2. Applications of internal dosimetry

Detailed molecular studies of DNA and protein adducts suggest that these areas of research will continue to contribute to our knowledge of metabolic and stereochemical effects that drive biological events such as mutagenesis [5,6]. The session on Risk Assessment stressed that we clearly need *in vivo* data on metabolism and key events such as mutagenesis in animals and humans. Recent molecular epidemiologic studies by Albertini et al. [7,8] have collected excellent exposure data in the same individuals who were being evaluated for a variety of genotoxic endpoints, as well as biomarkers of exposure and metabolism. Thus, we are positioned to make major advances in our understanding of butadiene's mode of action in rodents and humans, as well as its application to more accurate risk assessment for current worker and environmental exposures.

In late 2004, the development of a new immunoaffinity LC-MS/MS assay for the *N*-terminal peptide adduct

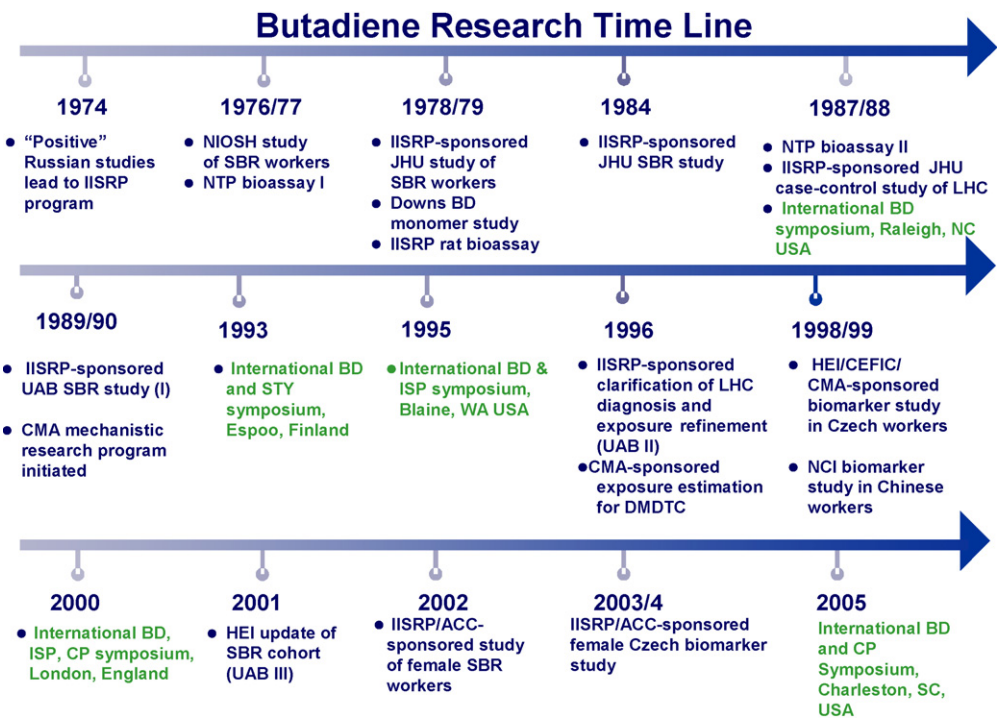

Fig. 1. Butadiene research time line.