ARSENIC

Exposure Sources, Health Risks, and Mechanisms of Toxicity

Edited by J. CHRISTOPHER STATES

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J. CHRISTOPHER STATES

University of Louisville
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PREFACE

I became interested in arsenic toxicology in the late 1990s. I had engineered SV40-transformed human fibroblasts to express human cytochrome P450 IA1 for polycyclic aromatic hydrocarbon carcinogen activation studies. A biotechnology company was interested in licensing the cells but wanted me to test them with a variety of carcinogens to demonstrate specificity. Sodium arsenite was among the compounds. The SV40-transformed fibroblasts were sensitive to the arsenite but in a curious manner. The cells rounded up in what appeared to be mitotic arrest, and then the membranes "bubbled" like in apoptotic cells. At the time, the postulation of mitotic cells undergoing apoptosis was sheer heresy. Nonetheless, these odd observations set me off on a course investigating this enigmatic toxicant that never ceases to provide surprises and raise new questions.

Arsenic is the 20th most common element in the earth's crust, and its toxic potential has been known for millennia. Chronic exposure to arsenic, most commonly through natural contamination of drinking water, is a worldwide health problem. Arsenic has been number one on the ATSDR hazardous substances list for at least 15 years now. Over the past two decades, a vast amount of research has been performed on arsenic toxicity. Much of this research focused on carcinogenesis. However, more recently research has focused on the non-cancer disease endpoints of chronic arsenic exposure including cardiovascular disease (atherosclerosis and hypertension), and pulmonary, neurological, and ocular disease. Some epidemiological studies suggest a link with diabetes. How a single agent can cause such a wide variety of ailments has evaded a simple answer. A great variety of experimental systems, using wide-ranging exposures, have produced a mountain of published research. Despite all the published literature examining mode of action, there remains strong debate over how arsenic exerts its disease-causing effects, and no single unifying

theme has emerged that can explain the diversity of diseases caused by chronic arsenic exposure. In my view, this lack of a unifying mechanism is at the heart of the issue.

The complexity of arsenic chemistry and biochemistry confounds many efforts to understand the mechanism of toxicity. Recent appreciation of the toxicity of trivalent metabolic intermediates has added to the problems of understanding toxicity and of mitigating toxicity by reducing exposure. We have attempted to address the complexity of the arsenic problem in *Arsenic: Exposure Sources, Health Risks, and Mechanisms of Toxicity* by compiling into a single-volume discussions of the exposure sources, exposure mitigation, chemistry, metabolism, the various diseases induced by arsenic exposure, and the variety of experimental models used to investigate arsenic toxicity.

The book is divided into four sections: Fundamentals of Arsenic Exposure and Metabolism, Epidemiology and Disease Manifestations of Arsenic Exposure, Mechanisms of Toxicity, and Models for Arsenic Toxicology and Risk Assessment. The chapters discuss a variety of topics including history of arsenic, sources of exposure, chemical and biochemical properties, molecular mechanisms, role in various diseases, genetics of susceptibility, and human health risk assessment, and concludes with a chapter discussing translation of experimental findings to human studies.

This book is offered as a resource for toxicologists, epidemiologists, risk assessors, environmental chemists, medical scientists, and other practicing professionals and researchers in academia, government, and industry. The book aims to provide a better understanding of the potential health problems posed by arsenic exposure and discuss ways that toxicological sciences can contribute to a characterization of how arsenic causes those problems and associated risks.

I am deeply indebted to the friends and colleagues who have contributed to this volume.

J. CHRISTOPHER STATES

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PART I

FUNDAMENTALS OF ARSENIC EXPOSURE AND METABOLISM