CHAPTER 8

Arsine: Toxicity Data from Acute and Short-Term Inhalation Exposures

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INTRODUCTION

Arsine gas (AsH_3) is a potent toxic agent which has been known for centuries to produce fulminating hemolysis with subsequent renal failure following acute high dose exposure.[1] In recent years, arsine gas has been employed in the manufacture of silicon semiconductors[2] as a "dopant" and in the manufacture of III-V semiconductors such as gallium arsenide. Its use has generated concerns about the possible effects of prolonged low level exposures among workers exposed to this agent. The following report is intended as a brief overview of acute and prolonged exposure studies conducted on this agent at the National Institute of Environmental Health Sciences (NIEHS). More detailed publications on various aspects of this effort are currently in preparation and will be submitted to peer-reviewed journals.

MATERIALS AND METHODS

Male and female Fisher F344 rats and female B6C3F1 mice were exposed via inhalation to arsine gas at concentrations ranging from 10 ppb to 50 ppm 6 hours/day for 14 consecutive days, or 5 days/week for 4 or 13 weeks. Chamber concentrations were monitored by a gas chromatograph with a photoionization detector and maintained within 10 percent of nominal levels by a computerized control system. Animals were placed in metabolism cages for urine collections at weekly intervals for the 14-day and 4-week studies and once per month for the 13-week study. Mortality data body weights, packed cell volumes (hematocrits), measurements of red blood cell δ-aminolevulinic acid dehydratase (ALAD), and necropsy/histopathology findings were collected.

RESULTS

All treatment groups exposed to arsine at concentrations above 10 ppm showed 100 percent mortality within 4 days while those exposed to 5 ppm or less showed no mortality or overt signs of toxicity. Body weights showed no exposure-related differences except for male rats exposed to 5 ppm arsine for 4 weeks which manifested a significant decrease in body weight. The spleens of arsine-treated animals showed dose-related increases in weight while livers showed slight increases in weights as a result of arsine exposure. Histopathological examination of the spleens demonstrated sequestration of red blood cells in the red pulp, hemosiderin accumulation within the macrophages, and increased erythropoiesis. Blood samples taken at necropsy showed a slight dose-related decrease in the packed blood cell volume (hematocrit) and a marked dose-related increase in the activity of red blood cell ALAD. Differential analysis of the peripheral blood in rats and mice demonstrated immature red cells, reticulocytes, and the presence of Howell-Jolly bodies indicating the development of a regenerative anemia in animals exposed to arsine for prolonged time periods. Analysis of urine samples from animals placed overnight in metabolism cages showed greatly elevated concentrations of the 7- and 8-COOH uroporphyrins and a more modest increase in 4-COOH coproporphyrins at the 5 ppm arsine dose level (Figures 1 and 2). Female rats appeared to be slightly less sensitive than male rats to arsine during the 14-day studies, but the observed increase in the activity of red blood cell ALAD activity in females exposed to 5 ppm arsine for 4 weeks was much greater than that observed in males.

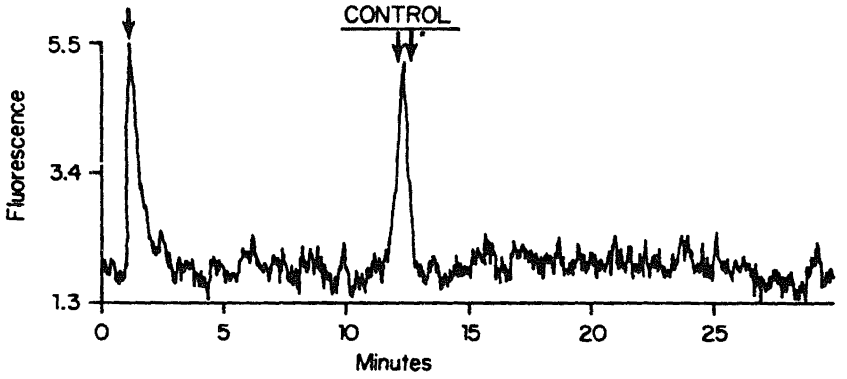

Figure 1. High performance liquid chromatogram of urinary porphyrins from a control rat showing the 8-COOH uroporphyrin (single arrow) and 4-COOH coproporphyrin (double arrow) peaks. Note relative fluorescence scale on ordinate.

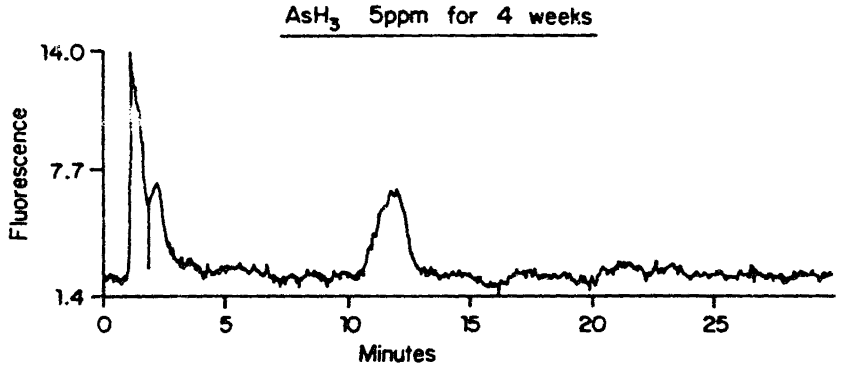

Figure 2. High performance liquid chromatogram of urinary porphyrins from a rat exposed to 5 ppm arsine for 4 weeks showing increased size of 8-COOH uroporphyrin peak, the presence of a 7-COOH uroporphyrin peak and an increase in the area of the 4-COOH coproporphyrin peak.

DISCUSSION

Results of the present studies indicate several major points with regard to the effects of prolonged exposure to arsine gas. The first is the apparently very sharp threshold between tolerated and lethal doses of this agent.

In these investigations, animals were able to tolerate arsine concentrations up to 5 ppm for 28 days but exposure to 10 ppm produced 100 percent mortality within 4 days. The mechanism(s) underlying this phenomenon are unknown and deserve further study.

A second major finding concerns development of a regenerative anemia in animals exposed to arsine for prolonged time periods. These data strongly suggest that differential analysis of peripheral blood from arsine exposed workers is necessary to determine whether a compensatory response to this agent is occurring. Simple measurement of packed cell volume (hematocrit) is clearly not sufficient for monitoring the effects from prolonged, low-dose arsine exposure.

Finally, results of these studies suggest that arsine-induced disturbances in the hematopoietic system produce marked, specific changes in the excretion of urinary proporphyrins, suggesting the possibility of utilizing urinary analysis of porphyrins as non-invasive "biological indicators" for detecting the effects of arsine or other agents present in semiconductor manufacturing processes.

In this regard, it is worth noting that the porphyrinuria pattern observed with arsine gas is somewhat distinct from that reported following prolonged oral exposure to arsenate[3–5] or acute intratracheal instillation of gallium arsenide,[6–8] suggesting different sites (e.g., blood vs. liver) and/or mechanisms of action for these various chemical forms of arsenic.

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Preface

Hazard Assessment and Control Technology in Semiconductor Manufacturing was a symposium co-sponsored by the Semiconductor Industry Association, the National Institute for Occupational Safety and Health, the Occupational Safety and Health Administration, and the American Conference of Governmental Industrial Hygienists. It was held in Cincinnati, Ohio, from October 20–22, 1987. The purpose of the meeting was to provide a forum through which information could be exchanged among researchers, health and safety personnel from industry, equipment and material suppliers, and representatives from governmental agencies. Stated objectives were to:

1. Transfer health and safety technology.
2. Share existing health and safety information.
3. Provide insight into future research needs.

Areas covered during the course of the symposium were 1) health studies, 2) hazard control technology of manufacturing processes, 3) catastrophic releases, and 4) emerging technologies.

The manufacture of semiconductor components is best characterized by the rapid utilization of state-of-the-art manufacturing technologies and by paying careful attention to details. This symposium was testimony to the fact that health and safety technology is also on the leading edge and goes hand-in-hand with the advances made in the industry.

For individuals who attended the symposium, this book will serve as a lasting record of the excellent papers presented. For those who were not able to attend and others wishing to gain insight into health and safety issues facing the semiconductor industry, this text will serve as an excellent reference.

Finally, the Program Steering Committee would like to thank its invited luncheon speakers, Philip Bierbaum of the National Institute for Occupational Safety and Health, David LeGrande of the Communications Workers of America, Dr. Pat Buffler of the University of Texas, and Dr. Larry Sumney of the Semiconductor Research Corporation, for their important