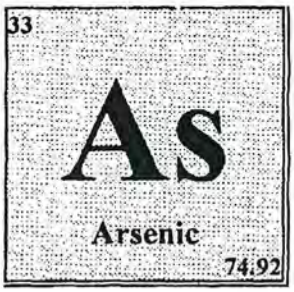
ARSENIC ENHANCEMENT OF SKIN NEOPLASIA BY CHRONIC STIMULATION OF GROWTH-PROMOTING CYTOKINES

Dori R. Germolec, Ph.D., Judson Spalding, Ph.D., Alessandra Bruccoleri, Ph.D., National Institute of Environmental Health Sciences; Petia P. Simeonova, Ph.D., Michael I. Luster, Ph.D., National Institute for Occupational Safety and Health; Hsin-Su Yu, M.D., G.S. Chen, M.D., Kao-Hsiung Medical College

While numerous epidemiological studies have shown that inorganic arsenicals cause skin cancers and hyperkeratoses in humans, there are currently no established mechanisms for their action or animal models. Previous studies in our laboratory using primary human keratinocyte cultures demonstrated that inorganic arsenite increased cell proliferation via the production of keratinocyte-derived growth factors. As recent reports suggest that overexpression of keratinocyte-derived growth factors may promote the formation of skin tumors, we hypothesized that similar events may be responsible for those associated with arsenic skin diseases. Thus, the influence of arsenic in humans with arsenic skin disease and on mouse skin tumor development in transgenic TG.AC mice which carry the v-Ha-*ras* oncogene was studied. Following low-dose application of TPA, a marked increase in the number of skin papillomas occurred in transgenic mice receiving arsenic in the drinking water as compared to control drinking water, while no papillomas developed in arsenic/TPA-treated wild-type FVB/N mice. Consistent with earlier *in vitro* findings, increases in GM-CSF and TGFα mRNA transcripts were found in the epidermis of these mice at sites that appeared clinically normal within 10 weeks following arsenic treatment. Immunohistochemical staining localized GM-CSF and TGFα overexpression to the hair follicles. Injection of neutralizing antibodies to GM-CSF following TPA application reduced the number of papillomas in TG.AC mice. Analysis of gene expression in samples of lesioned skin obtained from humans chronically exposed to arsenic via their drinking water also showed similar alterations in growth factor expression. These results suggest that arsenic enhances development of skin neoplasias via the chronic stimulation of keratinocyte-derived growth factors and may be a unique example of a chemical carcinogen which acts as a co-promoter.

Corresponding author: Dori R. Germolec, Ph.D., Environmental Immunology Laboratory, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709, USA.



THIRD INTERNATIONAL CONFERENCE ON ARSENIC EXPOSURE AND HEALTH EFFECTS

BOOK OF ABSTRACTS

SAN DIEGO, CA

JULY 12-15, 1998