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# Particulate chromate alters the localization of proteins that protect cells against chromosome instability

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## Abstract

Lung cancer remains a major concern for public health. Metals are potent human lung carcinogens; however, their carcinogenic mechanisms are uncertain and no unifying principle has been proposed. Chromosome instability (CIN) is a common feature of human lung cancer, but it is understudied for metal carcinogens. We studied particulate chromate (Cr(VI)) as a model metal lung carcinogen and considered its ability to disrupt the localization of key proteins to kinetochores as part of its carcinogenic mechanism. Shugoshin 1 (Sgo1) maintains and protects centromeric cohesion in G2 and continues to maintain proper sister-chromatid cohesion during mitosis. Disruption of Sgo1 localization can cause chromosome missegregation. We found chronic exposure to particulate Cr(VI) disrupts Sgo1 localization in G2 cells, but not mitotic cells. Specifically, there were no changes in Sgo1 localization after a 24 h exposure to lead chromate, but a 120 h exposure showed a concentration-dependent decrease in the percent of G2 cells with Sgo1 kinetochore localization; disrupting 90% of G2 cells at the highest dose. We also considered the effects on cell division cycle 20 (Cdc20) and Mad1. We found chronic particulate Cr(VI) exposure also caused a concentration-dependent decrease in Cdc20-kinetochore in prophase and pro-metaphase cells. Zinc chromate exposure did not appear to significantly alter Mad1 localization in mitotic cells; however, we did find that the percentage of mitotic cells with aberrant mitotic Mad1 localization increased after a 120 h exposure to zinc chromate. Altogether, the data indicate that particulate chromate exposure alters the localization of key kinetochore proteins, which may underlie particulate chromate-induced chromosome instability and may be involved in Cr(VI)-induced carcinogenicity. This work was supported by NIEHS grant ES016893 (J.P.W.), cooperative agreement #EP-08-01 through the Maine Space Grant Consortium (J.P.W.), EPA GRO Fellowship MA-91685401 (A.L.H.) and the Maine Center for Toxicology and Environmental Health.

## Biography

John Pierce Wise, Sr. is currently Professor of Toxicology and Molecular Epidemiology, the Director of the Maine Center for Toxicology and Health and the head of the Wise Laboratory of Environmental and Genetic Toxicology at the University of Southern Maine. He holds a Ph.D. in pharmacology focused on metal carcinogenesis from the George Washington University. He completed a postdoctoral fellowship in molecular epidemiology at the National Institutes of Health (NIH), which led to a faculty position as an Assistant Professor at Yale University. After several years at Yale, Wise joined The University of Southern Maine.