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VARIABLE SUSCEPTIBILITY TO *IN UTERO* ARSENIC EXPOSURE IN FOLATE
TRANSPORT DEFECTIVE MICE

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Arsenic is a known teratogen in laboratory animals, and is suspected of being teratogenic in humans. It is well known that genetic differences in susceptibility modify individual risks to teratogens. In an effort to better understand the nature of these differing genetic susceptibilities, we have used both inbred and genetically manipulated (knockout) mouse models. Specifically, the models we are using include four knockout mice—the folate binding protein 1 (Folbp1), folate binding protein 2 (Folbp2), reduced folate carrier (RFC-1), and 5,10-methyltetrahydrofolate reductase (MTHFR) genes all having been inactivated, as well as two inbred strains, SWV/Fnn and LM/Bc/Fnn that have previously been shown to differ in their sensitivity to various teratogens. Previously, we have shown that Folbp2^{-/-} mice are more susceptible to arsenate-induced neural tube defects than are wild-type Folbp2^{+/+} mice, a phenomenon that was exacerbated in the presence of a diet-induced folate deficiency. In the current study, we tested the hypothesis that the enhanced susceptibility to arsenate is due to abnormal biomethylation in the mutant Folbp2 strain. Such differences in the methylation capacity of the mice created differences in exposure to teratogenic arsenical species. We tested this hypothesis by collecting urine over 24 hours following a single intraperitoneal injection of 1 mg/kg sodium arsenate. Preliminary results indicate that while no differences in urinary excretion of arsenicals were present; there may be other mechanisms involved. Ongoing studies are testing the influence of changing dietary folate intake on the excretion of arsenicals in Folbp1^{-/-}, Folbp2^{-/-} RFC^{+/-} mice. These studies hope to shed further light on the link between environmental teratogens and genetic susceptibilities in the exposed populations. These studies were supported in part by grants: ES04917, ES11775, ES09106