

THE NEUROTOXIC AND MUTAGENIC PROPERTIES OF CHLOROACETALDEHYDE (CAA) DEPEND UPON EFFICIENT DNA REPAIR

Glen E. Kisby¹, Hoja Lesselroth¹, Antoinette Olivas¹, Leona Samson², Mitchell Turker¹

¹Center for Research on Occupational and Environmental Toxicology (CROET), Oregon Health & Science University, Portland, OR, 97239 and ²Biological Engineering Div, Ctr Environmental Health Sciences, MIT, 77 Massachusetts Ave, Cambridge, MA 02139

Chloroacetaldehyde (CAA) is a chlorination by-product found in finished drinking water supplies and a toxic metabolite of a wide variety of industrial chemicals (e.g., vinyl chloride, TCE, PCE) and chemotherapeutic agents (e.g., ifosfamide). The cytotoxic and mutagenic properties of CAA are reportedly due to the formation of ethenobase DNA lesions, which are repaired by the base excision (BER) and nucleotide excision (NER) repair pathways. If CAA-induced DNA damage is a key event that triggers cell injury, then neuronal and non-neuronal cells that are defective in excision repair should be especially sensitive. Neuronal and non-neuronal cells (i.e., skin fibroblasts, kidney epithelial cells) from BER (i.e., *Aag*) and NER deficient (i.e., *Xpa*) mice were treated with CAA (0.1 μ M to 50 μ M) for up to 7 days and examined for viability, DNA damage, and oxidative stress (i.e., glutathione). *Aag*^{-/-} and *Xpa*^{-/-} neuronal and non-neuronal (fibroblasts, epithelial) cells were more sensitive to CAA than wild type cells suggesting that these repair pathways play an important role in protecting cells from the acute and delayed toxic effects of this metabolite. The inability of CAA to alter GSH levels in BER or NER deficient neurons and the ~1.5-8.0 higher in *Aag*^{-/-} neuronal cells (vs. wild type cells) treated with CAA suggests that CAA-induced toxicity occurs through a DNA damage mechanism. Moreover, studies in yeast cells demonstrate that CAA-induced ethenobase DNA lesions are associated with the altered expression of DNA damage-response genes (i.e., cell cycle, DNA replication, DNA repair). Parallel studies using DNA proficient and deficient kidney epithelial cell lines demonstrate that CAA is moderately mutagenic in wild type cells and more so in mismatch repair-deficient cells. These studies demonstrate that the neurotoxic and mutagenic mechanism of the organochlorine solvent metabolite CAA occurs (at least in part) through a DNA damage mechanism. These novel properties of CAA may be useful as potential biomarkers of solvent exposure. [Supported by NIH grant ES10338-02]