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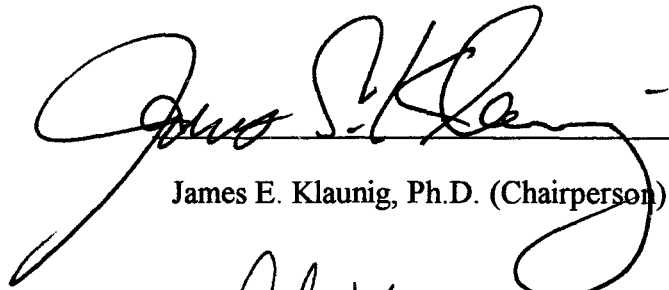
**MECHANISMS OF ACRYLONITRILE-INDUCED
MORPHOLOGICAL TRANSFORMATION IN SYRIAN
HAMSTER EMBRYO (SHE) CELLS**

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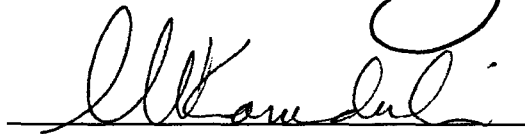
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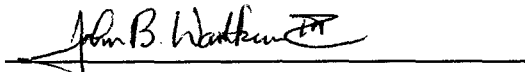


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ABSTRACT

Acrylonitrile (ACN) is an important industrial intermediate that is widely used in the synthesis of fiber, rubber, and resins for various applications. Chronic administration of ACN to rats resulted in an increased incidence of neoplasms of the brain (predominately astrocytomas). While the mechanisms for ACN-induced glial cell carcinogenicity have not been completely elucidated, investigations by our group and others have shown that ACN exposure is associated with an induction of oxidative stress selectively in rat brain. In order to further define the role of oxidative stress in ACN carcinogenesis, an *in vitro* carcinogenesis system, Syrian hamster embryo (SHE) cell transformation system, was used in the present study. ACN induced a dose-dependent increase in morphological transformation in SHE cells following a 7-day treatment. Oxidative stress (evidenced by formation of 8-hydroxy-2'-deoxyguanosine, OH8dG) was also produced by ACN treatment. Antioxidant supplements inhibited both induction of oxidative stress and morphological transformation induced by ACN. Additional studies showed that formation of OH8dG correlated with morphological transformation in SHE cells, providing direct evidence for a role of oxidative stress in morphological transformation by ACN. Further studies showed that ACN required P450 metabolism to cause oxidative stress and morphological transformation. The induction of oxidative stress by ACN appears to involve depletion of cellular antioxidants (GSH, catalase, superoxide dismutase) and DNA repair enzyme (MTH) at early time point followed by activation of oxidant enzyme (xanthine oxidase). Cyanide, one of the P450 oxidation metabolites of ACN, was also demonstrated to induce oxidative stress and morphological transformation and produce

effects on catalase and superoxide dismutase similar to ACN in SHE cells. All these data taken together suggest that induction of oxidative stress and resulting oxidative damage is involved in ACN-induced morphological transformation and carcinogenicity, and suggests a role for cyanide in the carcinogenicity process.

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