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Inflammatory response to isocyanates and onset of genomic instability in cultured human lung fibroblasts

P.K. Mishra[1], A. Bhargava[1], G.V. Raghuram[1], S. Gupta[1], S. Tiwari[1], R. Upadhyaya[2], S.K. Jain[3] and K.K. Maudar[1]

[1]Department of Research, Bhopal Memorial Hospital & Research Centre, Bhopal, India
[2]Madhya Pradesh Biotechnology Council, Bhopal, India
[3]Department of Biotechnology, Dr. H.S. Gour University, Sagar, India

Corresponding author: P.K. Mishra
E-mail: pkm_8bh@yahoo.co.uk

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ABSTRACT. Lungs comprise the primary organ exposed to environmental toxic chemicals, resulting in diverse respiratory ailments and other disorders, including carcinogenesis. Carcinogenesis is a multi-stage phenomenon, which involves a series of genetic alterations that begin with genomic instability provoked by certain factors such as inflammation and DNA damage and end with the development of cancer. Isocyanates such as methyl isocyanate are the chief metabolic intermediates in many industrial settings with diverse applications; exposure to them can lead to severe hypersensitive, mutagenic and genotoxic alterations. We examined the molecular mechanisms underlying isocyanate-mediated inflammatory responses and their probable role in the onset of genomic instability in cultured IMR-90 human lung fibroblasts. The isocyanates induced inflammation, resulting in extensive DNA damage, evidenced by increases in ATM, ATR, γH2AX, and p53 expression levels. The apoptotic index also increased. Chromosomal anomalies in treated cells included over-expression of centrosome protein and variable amplification of inter-simple sequence repeats, further demonstrating isocyanate-induced genomic insta-

bility. This information could be useful in the design of new approaches for risk assessment of potential industrial disasters.

Key words: Inflammation; Genomic instability; DNA damage; Apoptosis; Isocyanates; Lung cancer

