LETTER to the EDITOR

Bhopal Methyl Isocyanate Affected Population and Cancer Susceptibility: Where Do We Stand Now?

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Dear Editor

Further to our recent publications on cancer morbidity of Methyl isocyanate (MIC) exposed long-term survivors and their offspring and carcinogenesis of MIC in this journal (Senthilkumar et al., 2011; 2012), my attention was drawn to express my views to Indian Council of Medical Research (ICMR) for the need to validate MIC in cancer etiology, in particular, to cancer risk prediction in the present and future generations of the affected population.

Since its occurrence, Bhopal MIC gas tragedy remains controversial and ambiguous. Uncontrolled release of MIC from the Union Carbide pesticide manufacturing plant in Bhopal, India on 3rd December, 1984 resulted in mortality of 3600 individuals and an estimated 2,00,000 was lethally exposed (Dhara and Kriebel, 1993). This infamous smog episode induced health effects in Bhopal population has received immediate attention of the medical community. In 1985 a governmental organization, ICMR launched a series of long-term medical studies focused on immune system functioning, ocular, respiratory, reproductive, psychological, neurobehavioral and genetic effects. ICMR followed-up MIC exposed population for 10 years till 1994. After completion of this first phase study ICMR finally declared that the effects of MIC are short-term and never persist in affected population (ICMR, 2004). However, ICMR findings were criticized by scientific experts due to self-selected sample, the lack of complete evidence regarding health effects of the exposure, and many other limitations also led to the controversy. Further to these findings, no biomonitoring strategies or follow-up protocols implemented by any scientific community to assess the long-term risk in MIC affected population. While there is an uncertainty and debate since 1994 regarding the long-term health effects in the MIC affected population. Increased cancer morbidity (Senthilkumar et al, 2011), genetic instability (Malla et al., 2011), pregnancy loss and delayed development in male progenies (Sarangi et al., 2010) were recently reported exposure-effects in the MIC affected population after 27 years.

In the wake of the controversies, ICMR is now re-searching for the neglected toxic evidence again after 17 years. ICMR launching a second phase study in MIC affected population of Bhopal. Being a researcher, I am striving to contribute to this issue for past six years investigating cancer epidemiology, immune status and cytogenetic effects in MIC affected population through biomonitoring, with the funding granted from Council of Scientific and Industrial Research (CSIR), India. Initiatively in 2009, I submitted a research proposal to ICMR describing a framework of biomonitoring to study the long-term effects in MIC affected population of Bhopal. Submission of this proposal laid foundation to the second phase study of ICMR (Times of India, 2012). After considering the proposal, ICMR invited a call for proposal to study the long-term effects from the clinical research community. In the context of long-term effects, genetic disorders, low birth weight, growth and developmental disorders, congenital malformation, biological markers of MIC exposure, mechanisms of toxicity in humans and risk management, and health effects of contamination drinking water with toxic material from Bhopal gas plant are the key concepts under consideration (ICMR, 2009). It is also worth noting that this time the ICMR addressing the long-term effects issue with well-defined biomonitoring design and strategies. At a recent meeting, overall 19 research proposals received from all over India and the experts presented their views. 10 of them are new and 9 ongoing projects were discussed by ICMR. Hopefully, soon there will be a call for action.

Although the second phase study seems to be more rigorous, intended and focusing on the long-term health effects, unfortunately the foremost considerable theme is missing. Cancer burden and susceptibility of MIC affected population is the primary theme needs more consideration and careful attention. Our recent epidemiological investigations in such population revealed increased cancer morbidity, especially a significant higher prevalence of breast and lung cancers (Senthilkumar et al., 2011).

Emerging evidence of MIC in cancer etiology is still confusing and controversial. Still, the underlying exposure – effect issue whether MIC is a carcinogen remains unclear and the pertinent literature concerning the same is also too limited. Our recent review expressed the plausible role of MIC in cancer causation, including gaps and needs (Senthilkumar et al., 2012). The bottleneck experienced by the scientific community in this regard is mainly due to the extrapolative analysis done in the animal studies till now. Hence, the present circumstance deserves full priority to validate the association of MIC in cancer risk. Moreover, there is a lack of association among the laboratory analysis *in vivo*, *in vitro* and human epidemiological research about the carcinogenic potential of MIC. *In vivo* studies observed pheochromocytoma of adrenal medulla and acinar cell tumors of pancreas in MIC exposed animals (Gassert et al.,

1986; Ennever and Rosenkranz, 1987; Bucher and Uraih, 1989), *in vitro* studies depicted tumorigenicity in ovary, liver and pulmonary arterial endothelial cells (Raghuram et al., 2010; Hariom and Mishra, 2011; Hariom et al., 2011) and human epidemiological data revealed lung and breast cancer among MIC affected population (Senthilkumar et al., 2011; 2012).

In addition, ICMR should also strengthen the cancer risk prediction by paying attention to laboratory analysis to identify the carcinogenic potential of MIC, if any. After comprehensive laboratory analysis, the consequential hypotheses need to link with human epidemiological data of the exposed population to elucidate the association of MIC exposure-induced cancers. Furthermore, such laboratory analysis would be helpful to better characterize the possible carcinogenic hazards posed by MIC and also raise risk awareness for cancer prevention and offer future insight to clinical settings in the risk management of MIC affected population.

To accomplish this mammoth task with reference to cancer risk in the affected population, there is an utmost need of clinical - experimental toxicologists and public health officials of non-governmental settings to unite with ICMR to contribute to resolve the issue of long-term effects, where the affected population could be benefited for cancer prevention. Surely we believe that second phase ICMR studies may definitely fill the gap and the significant output will end the controversy of long-term as well as carcinogenic effects of MIC.

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