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BHOPAL GAS TRAGEDY: REVIEW OF CLINICAL AND EXPERIMENTAL FINDINGS AFTER 25 YEARS

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Abstract
The Bhopal gas tragedy is undoubtedly one of the worst industrial disasters in the history of mankind resulting in mortality of 2500–6000 and debilitating over 200 000 people. Inhabitants in the township were exposed to different degrees and there are more than 500 000 registered victims that survived the tragedy. Clinical studies have shown chronic illnesses such as pulmonary fibrosis, bronchial asthma, chronic obstructive pulmonary disease (COPD), emphysema, recurrent chest infections, keratopathy and corneal opacities in exposed cohorts. Survivors continue to experience higher incidence of reported health problems including febrile illnesses, respiratory, neurologic, psychiatric and ophthalmic symptoms. *In-utero* exposure to methyl isocyanate in the first trimester of pregnancy caused a persistent immune system hyper-responsiveness, which was in an evident way genetically linked with the organic exposure. Recent experimental studies have provided mechanistic understanding of methyl isocyanate exposure at a molecular level. Immunotoxic implications, toxico-genomic effect, inflammatory response, elicitation of mitochondrial oxidative stress, chromosomal and microsatellite instability have been studied comprehensively in cultured mammalian cells. Besides providing a framework for understanding potential mechanisms of toxicity of a host of other exposures, these studies may also uncover unique abnormalities thereby stimulating efforts to design newer and effective diagnostic and therapeutic strategies. The authors recommend long-term monitoring of the affected area and use of appropriate methods of investigation that include well-designed cohort studies, case-control studies for rare condition, characterization of personal exposure and accident analysis to determine the possible elements of the gas cloud.

Key words:
Methyl isocyanate, Bhopal Gas Tragedy, Health effects, Industrial disasters

INTRODUCTION

The world's worst industrial disaster occurred in Bhopal on the night of December 2–3, 1984. An explosion at the Union Carbide India Limited (UCIL) pesticide plant resulted in the release of 30–40 tons of a toxic gas, methyl isocyanate (MIC) spreading over approximately 30 square miles, killing thousands of people and injuring hundreds of thousands [1]. A large number of the inhabitants in the township of Bhopal were exposed to different degrees, depending on their proximity to the plant and atmospheric factors; in fact there are more than 500 000 registered survivors of the tragedy.

The unprecedented mortality and morbidity due to the accident generated global scientific interest and a spectrum of multi-systemic studies were conducted on exposed individuals. Significant number of studies was conducted on varied aspects, but the published work has largely been restricted to histo-pathological findings, especially of lungs and small cross-sectional studies delineating symptomatology and clinical morbidity in the survivors. The Indian Council of Medical Research (ICMR) was one of the foremost organisations to initiate clinical research studies on the affected population. It has recently presented its first technical report of the research findings on the 'Health Effects of the Toxic Gas Leak from the Methyl Isocyanate Plant

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in Bhopal' gleaned out of the 24 research projects carried out between 1985 to 1994 [2]. As part of the ICMR investigations, epidemiological, clinical and toxicological studies were carried out on 80 000 persons at severely, moderately and mildly exposed areas and compared with controls from unexposed areas. According to the ICMR report, nearly three-fourth of the deaths occurred within the first 72 hours of the leak. Though the number of deaths declined rapidly, the extent of the impact on the survivors' health was compounded by the fact that nothing was known about the toxic effects of MIC, hence there was no clue about a possible antidote to minimise the impact. According to ICMR, a large fraction of the exposed population continues to be chronically ill with diseases of the respiratory, gastro-intestinal, reproductive, musculoskeletal, neurological and other systems [2]. It must be noted that scientific work has been published after this report that not only summarises the health effects of MIC but also highlights the limitations of the studies published. This and many other commentaries have strongly emphasised the need for continued vigilance for the long term ill effects of MIC [3–8].

Clinical Studies

The acute toxicity of inhaled MIC or its reaction products was devastating; however, treatment was limited to symptom management, as it was still uncertain whether the effects observed were due to MIC, phosgene, HCN or other reaction products. Non-availability of any information about the toxicity of even the parent compound, MIC, had been a great impediment in therapeutic intervention and management of gas victims. Later, a careful re-examination revealed the presence of as many as 21 constituents, including 9–10 additional unidentified compounds [3]. The affected subjects are known to suffer from chronic illnesses such as pulmonary fibrosis, bronchial asthma, chronic obstructive pulmonary disease (COPD), emphysema, recurrent chest infections, keratopathy and corneal opacities [1,9–11]. Studies have shown that these survivors experience a higher incidence of reported health problems including febrile illnesses, respiratory, neurological, psychiatric and ophthalmic symptoms [12]. The ill effects of the exposure have also manifested as impaired immune competence of subjects [13]. Not surprisingly, an increase in spontaneous abortion rates was also reported in a large pregnancy outcome study involving the households in the severely affected areas around the UC plant [14]. Clinical symptoms observed during acute and sub acute phase (1–6 months) and chronic phase (6 months onwards) following methyl isocyanate exposure have been summarised in Table 1 and 2.

Respiratory health effects

The initial human autopsy studies, which revealed severe necrotising lesions in the lining of the upper respiratory tract as well as in the bronchioles, alveoli, and lung capillaries, suggested that the respiratory system was most severely affected. ICMR has concluded in its report that asphyxia arising from acute lung injury or acute respiratory distress syndrome (ARDS) could be central to most deaths following MIC exposure. Clinical status of the victims has been classified as acute, sub-acute and chronic based on the duration of appearance of these post-trauma symptoms. A significant number of subjects displayed abnormalities in lung function tests (LFTs). The studies by ICMR summarise that clinical symptoms did not recede completely. Furthermore, autopsies indicated generalised visceral congestion, cerebral edema, and anoxic brain damage [3]. Interestingly, forced expiratory flow between 25–75% of forced vital capacity ($FEF_{25-75\%}$ of FVC) declined progressively during the 2 years period of observation, as did FVC [15,16]. Bronchoalveolar lavage (BAL) analysis carried out 1–2.5 year after exposure to the 'toxic gas' at Bhopal by Vijayan et al. [17–18] indicate that there was an increase in cellularity in the lower respiratory tract (alveolitis) of the severely exposed patients (in both smokers and non-smokers). The increase in cellularity was due to abnormal accumulation of macrophages in severely exposed non-smokers while in severely exposed smokers, it was due to macrophages and neutrophils. In Bhopal victims, the vital capacity was low in the majority of subjects. Although the diffusion tests could be performed, the clinical, functional and radiological observations suggest that these subjects had a picture of acute extrinsic allergic bronchiolo-alveolitis due to exposure, which has gone into the chronic phase of the pathogenesis [19].

Table 1. Clinical symptoms observed during acute and sub acute phase (1–6 months) following methyl isocyanate exposure

Physiological systems affected	Clinical Symptoms	References
Ocular	Intense irritation, burning, photophobia, blurred vision, corneal ulcer, conjuctival and circumcorneal congestion	[2,22]
Respiratory	Breathlessness, chest pain, severe dry or wet cough, pulmonary edema, distress, pneumonitis	[2]
Psychological and neurological	Anxiety, neurotic depression, social adjustment problem, impaired auditory and visual memory, attention response speed and vigilance	[2,26]
Gastrointestinal	Persistent diarrhea, anorexia, abdominal pain	[2]
Immunological	Suppressed cell mediated immunity, reduced T cell count, downregulation of phagocytic activity of lymphocytes	[33]
Genetic	Increased chromosomal abnormalities	[36]
Reproductive	Spontaneous miscarriages, perinatal and neonatal mortalities, menstrual irregularities	[14]
General	Muscle weakness, sleepiness, loss of appetite, nausea, vomiting, fever	[2]

Table 2. Clinical symptoms observed during chronic phase (6 months onwards) following methyl isocyanate exposure

Physiological systems affected	Clinical Symptoms	References
Ocular	Damage to posterior ocular chamber, corneal opacity, conjunctivitis, chronic lesions, and deficiency of tear secretion	[2,22]
Respiratory	Cough (with or without expectoration), chest pain, dyspnea, wheezing, decreased lung functions, obstructive and restrictive airway diseases, acute extrinsic allergic bronchio-alveolitis	[11,15–16, 19–21]
Psychological and neurological	Defective standard progressive matrices, associated learning, motor speed precision test, muscle aches	[21,25,27]
Reproductive	Increased pregnancy loss, infant mortality, decreased placental/fetal weight	[2,14,29]
Immunological	Hyper-responsiveness of immune system in *in-utero* exposed individuals	[34,35]
Cancer	Marginal increase in oropharynx cancer	[38]
Adolescent growth pattern	Growth retardation in exposed adolescent males	[30]

The International Medical Commission on Bhopal (IMCB) conducted the first long-term population study for the estimation of individual exposure, occurrence of clinical symptoms and its correlation with lung functions. The observations showed that total exposure was clearly associated with most respiratory symptoms as well as $FEF_{25–75\%}$, features of airway obstruction [11]. In a similar study sponsored by IMCB, 454 adults were surveyed for respiratory symptoms and pulmonary function 10 years after the accident. In this study a consistent gradient was seen for all respiratory symptoms by residential distance from the plant [20]. A study carried out on two groups of pediatric population 105 days after the leakage showed that the predominant symptoms in Group I (n = 164), staying 0.5 to 2 km away from the Union Carbide Factory, were cough and breathlessness which persisted even 100 days later. On an average, 48.1% of children had abnormal respiratory findings in the form of rhonchus, rales and wheezing. In Group II (n = 47), staying 8–10 km away from the factory, there were no significant abnormal findings at the time of the study. The pulmonary function tests carried out in 33 of Group I children and 12 of Group II children showed that 28 Group I children were having obstructive disability as compared to 8 children in Group II [21].

Ocular health effects

During the first two months after the exposure, victims reported severe ocular burning, watering, pain and photophobia [22]. These findings are similar to the findings of ICMR clinical studies compiled in its recent report [2]. In most of the victims, acute phase ocular symptoms appeared to have healed up, except in few cases where the damage was to the posterior ocular chamber and required surgical replacement of corneal tissue. Comparison of frequency of ophthalmic symptoms in subjects staying at different distances from the factory showed that complaints were present in 80% of subjects residing 0,5 km away from the factory and in 40% of the people residing 8 km away from the factory. Finding of distant vision testing in both groups showed that those with vision between 6/12 and 6/60 were considered moderately affected while those with vision lower than 6/60 were considered more severely affected. No patient from either group complained of disturbance of colour vision. Ocular movements were normal in all the subjects [23].

Psychological and neurological health effects

The survivors of the Bhopal gas tragedy were reported with significant neurological, neurobehavioral and psychological effects. The ICMR report illustrated that the appearance of psychological implications in the exposed population led to anxiety and depression. In a randomised study of out patients at ten government run clinics 3 to 5 months after the disaster, 22.6% were found to be suffering from psychological disorders. A similar number suffered from neurotic depression, anxiety and social adjustment problems [2]. According to the ICMR, neuromuscular defects, such as tingling numbness, sensation of pins and needles in the extremities, and muscle aches, have continued among the victims after exposure [24]. Such effects of MIC exposure could be attributed to the prevention of formation of muscle fibres in the culture at low doses and causing death of fibroblasts and myoblasts at higher doses [22]. It was observed that out of 208 persons suffering from psychological problems, 45% suffered from neuroses, 35% from anxiety states and 9% from exacerbation of preexisting adjustment reactions [25].

An observation conducted few months after the accident revealed impairment of auditory and visual memory, attention response speed, and vigilance [26]. In follow up investigations conducted after one year, associate learning and motor speed and precision were significantly impaired among affected victims [27]. Irani and Mahashur [21] noticed definite psychological problems such as apprehensiveness, jitteriness, depression and verbosity, in some children above 7 years of age, which were noteworthy.

Reproductive health effects

Twenty years after the gas disaster, menstrual abnormalities, vaginal discharge and premature menopause have emerged as common problems among Bhopal MIC exposed women and their female offspring/girl children. Besides affecting the reproductive health of the women, these conditions are also leading to social problems in conservative communities. Maternal-fetal, gynaecological effects have been illustrated through retrospective cohort studies. Clinicians at Bhopal have observed that now the girls who were exposed during their infancy and those in their mother's womb are experiencing 'menstrual chaos' [28]. During an early recovery phase, a comparative survey was undertaken to explicate the effect of exposure to the toxic gas in pregnant women both in exposed and unexposed area in Bhopal. A high incidence of spontaneous miscarriages (24.2%) in the pregnant women exposed to the toxic gas was observed as compared to those in the control (unexposed) area (5.6%). Other indices of adverse reproductive outcome, such as the rate of stillbirth and congenital malformations were not found to be different. The perinatal and neonatal mortalities were significantly higher in the affected area (6.9 and 6.1%, respectively), as compared to the control area (5.0 and 4.5%, respectively) [14]. The final technical report of ICMR [2] has also reported high miscarriage rates in the initial years after the disaster in addition to the increased menstrual irregularities and excessive bleeding among gas-exposed inhabitants. This pattern has been attributed to "post-disaster trauma". Unfortunately, it is reported that several of these women had episodes of miscarriages later on, and many could not conceive at all. Shilotri et al. [29],

observed a relatively higher incidence of abnormal uterine bleeding and abnormal pap smears amongst exposed women 15 weeks after the exposure. An anthropometric study on exposed adolescents, carried out almost sixteen years after the disaster, revealed that there was a selective retardation in boys, but not in girls, who had been exposed to MIC during their toddler age or those born to exposed parents [30].

Immunotoxic consequences

Several studies on Bhopal disaster survivors suggest long-term immunological effects, including the potential of MIC to produce hypersensitivity reactions; however, no significant hematological or biochemical abnormalities were noted in Bhopal disaster population, which was expected when the poison had gained entry into the blood stream [22]. The two clinical findings on the effect of MIC on immune function highlighted significant delay of the cell cycle and suggested a decreased response to mitogen activated stimulation of proliferative lymphocytes studied *in-vitro* [31].

In order to assess the production of anti-antibodies in the exposed subjects, sera from 99 subjects were studied along with sera from guinea pigs exposed to MIC. Although all the guinea pigs injected with reactive isocyanate produced specific antibodies in titres of 1:5120 to 1:10 240, only eleven human subjects produced specific antibodies belonging to IgG, IgM and IgE classes. Though titres were low and transient (declining after several months), these findings indicate that the single large exposure to MIC elicited a definite immunologic response. This was concomitant with chronic respiratory effects following MIC exposure [32].

Immune function was studied in exposed subjects at the Indian Toxicology Research Centre (ITRC) in sample 2.5 months after exposure. No difference in mean immunoglobulin levels were found when compared to controls. The T-cell population (28%) was less than half that normally found in the Indian population (65%). A significant decrease in the phagocytic activity of lymphocytes was found on comparision with controls, suggesting a potential suppression of cell-mediated immunity by MIC [33].

In a recent study conducted by our group [34,35] we compared the immune status of a group of 50 young individuals exposed to MIC gas while *in-utero* (first trimester) with that of two groups of 50 years age and gender-matched unexposed individuals. Our study showed, for the first time, that *in utero* MIC exposure during the Bhopal gas tragedy has caused a persistently hyper-responsive cellular and humoral immune state in affected individuals. This was suggested by increased cytokine secretions by stimulated lymphocytes *in vitro* and higher immunoglobulin levels in this cohort. The high prevalence of anti-nuclear antibodies in the *in-utero*-exposed group was also noteworthy. MIC exposure *in utero* in the first trimester of pregnancy has caused a persistently hyper-responsive state of the immune system [34,35].

Toxico-genomic effects

In an initial study by Goswami [36], it was observed that sister-chromatid exchanges (SCE) frequency in lymphocytes were found to be increased more than three times in MIC-exposed persons [36]. Chromosomal breaks were also observed in 10 out of 14 affected people (71.4%) studied, while only 6 out of 28 (21.4%) controls showed chromosomal breaks. Even chromatin bodies were observed in addition to the normal 46 chromosomes among some of the survivors. In another study, Goswami et al. [37], have formulated a chromosomal profile for 154 persons studied during 1986–1988. The exposed subjects developed at least two categories of chromosomal aberration, out of which Robertsonian translocation was repeatedly observed, mostly in acrocentric chromosomes 13 and 21 [37]. Such observations are suggestive of potential DNA damage by MIC. It is known that at least 50% of the subjects possessing such serious chromosomal abnormalities may have pathological implications such as tumors, recurrent miscarriage or transmission of defects to their offspring. A unique study conducted in 1990 clearly establishes genetic link of cancer patterns among gas victims of the tragedy with MIC exposure [38]. Such studies were not conducted during the late recovery phase that would have helped identify people with chromosomal aberrations and at high risk of developing cancer.

Experimental Findings

About two and half decades have elapsed since the incident and much remains to be done to evaluate the toxic effects of MIC using experimental modalities in a comprehensive manner. The global scientific community considers the exposure and toxicity assessment incomplete [39]. Similar thoughts have been voiced by international groups who have advocated investigations on the toxicogenomic effects of MIC using cutting edge technologies [3–4,7–8,11,40]. The importance of such experimental studies cannot be understated since any alterations at genomic and/or epigenetic level can have long term health consequences that may range from accelerated ageing, carcinogenesis, immuno-compromised states and, more importantly, vertical transmission of genetic aberrations.

Animal studies

Animal experiments have revealed the "special vulnerability" of alveolar membrane and tracheobronchial epithelial cell to MIC exposure. It is established that MIC is an extremely irritating chemical that causes bronchial lesions and, when given at a high enough dose, pulmonary edema may occur [1]. On the whole, mice surviving the acute exposure showed remarkable recovery, although residual lesions were evident in the airways, including possible obliterative bronchiolitis [41]. Jeevaratnam and Sriramachari [42] have studied the pathological effects of a single exposure of MIC and its aqueous derivatives, Methyl Amine and Di-Methyl Urea in rats. Edematous fluid was found filling up of the alveoli and eosinophilic necrosis of the bronchial epithelium at the end of 24 hours [42]. Bucher et al. [13] have tried to understand the pathology of acute inhalation in an animal model of MIC exposure. Early gross pathologic changes included a reddish white encrustation around the mouth and nose, a small thymus, and distension of the gastrointestinal tract with gas, consolidation and hemorrhage of the lungs (middle and median lobes) and failure to deflate, microscopic changes in the upper respiratory tract included marked erosion and separation of olfactory and respiratory epithelia from the basement membrane with accumulation of serofibrinous fluid. During the late phase, granulomatous inflammation and intraluminal fibrosis of the airways were observed. Lower airways become blocked by exfoliated cells, mucous plugs, and/or intraluminal fibrosis [13].

The research groups at Industrial Toxicology Research Centre (ITRC), India, have also contributed to the understanding of effects of MIC exposure on BALF constituents, reproductive health and germ cell mutagenicity using murine models. A marked increase in the total number of BALF cells was noticed following MIC exposure. The phagocytic ability of macrophages was decreased and cell free BALF showed increase in total protein, sialic acids and lactic acid content [43]. Ability of MIC to cause germ cell mutagenicity could not be established during these studies, owing to its poor biodistribution to the target sites [44]. Toxic effects of MIC exposure on respiratory system have also been established in the animal models. The autoradiographic analyses of guinea pig airway tissues have shown that following inhalation exposure to 14C-labeled MIC, the airway tissues have had the highest level of radioactivity. The persistence of airway radioactivity over the 48 h post-exposure period coincides with covalent modification of airway macromolecules. Further, the cellular localisation in the tracheabronchial region showed epithelial and subepithelial deposition in a dose-dependent manner with accumulation of the label at the sub-epithelial region [45]. Animal studies have also highlighted that fetotoxicity of MIC is concentration-dependent that also affects fetal and placental weights [46,47].

***In vitro* studies**

With regards to the genotoxic effects, there are only a few reports available based on conventional cytogenetic profiles of exposed individuals. While these reports document substantial linkage of MIC exposure to somatic mutagenesis, these handful of studies had several shortcomings in the methodological approach and therefore failed to impress the global scientific community. Despite these limitations, when the findings are combined with the data from animal studies, a strong case is made for in depth analysis and investigation into the persistent genetic effects of MIC. Therefore, it has been necessary to undertake the

same and examine molecular toxicological effects of MIC using whole genome scanning approaches. This has been achieved by amalgamating both conventional and modern technologies that capitalises on the power of cutting edge tools and techniques. The Research Department at BMHRC, Bhopal, India, has contributed to the understanding of effects of MIC exposure by investigating toxicogenomic potential of MIC. Immunotoxic implications, cytotoxic effect, inflammatory response, induction of mitochondrial oxidative stress, chromosomal and microsatellite instability have been studied in a comprehensive manner.

The genotoxic potential of MIC in cultured mammalian cells after *in vitro* exposure has been assessed. The studies were performed to investigate cellular DNA damage response through qualitative phosphorylation states of ATM, γH2AX proteins and quantitative state of p53 phosphorylation; DNA cell cycle analysis and measure of cellular apoptotic index. It has been demonstrated that methyl isocyanate, by negatively regulating the DNA damage response pathway, might promote cell cycle arrest, and apoptosis in cultured mammalian cells suggestive of causing genetic alterations [48]. Induction of genomic instability in cultured human colonocytes following exposure to methyl isocyanate was also investigated. Many treated cells were arrested at the G2/M phase of the cell cycle and had an increased apoptotic index and elevated inflammatory cytokine levels. Cytogenetic analyses revealed varied chromosomal anomalies, with abnormal expression of pericentrin protein. Analysis through ISSR PCR demonstrated increased microsatellite instability due to variable amplification of simple inter sequence repeats [49].

Investigation was carried out to study the role of isocyanate-mediated mitochondrial oxidative stress in eliciting chromosomal instability in cultured human kidney epithelial cells. Cells treated with 0.005 μM concentration of methyl isocyanate displayed morphological transformation and stress-induced senescence. Along the time course, an increase in DCF fluorescence indicative of oxidative stress, depletion of superoxide dismutase (SOD) and glutathione reductase (GR) and consistent accumulation of 8-oxo-dG were noticed. Thus, endogenous oxidative stress resulted in aberrant expression of p53, p21, cyclin E and CDK2 proteins, suggestive of deregulated cell cycle, chromosomal aberrations, centromeric amplification, aneuploidy and genomic instability [50].

The immunotoxic response of cultured human lymphocytes isolated from healthy human volunteers has been assessed and it has been demonstrated that MIC is capable of undergoing biotransformation reactions in human peripheral blood lymphocytes thereby causing DNA damage through phosphorylation of ATM and γH2AX indicative of DSBs at damaged sites. A dose and time dependent increased intracellular ROS generation through increased DCF fluorescence and accumulated 8-oxo-dG with simultaneous depletion in glutathione reductase, elevated pro-inflammatory cytokine response and finally leading to an inexorable cellular demise were observed upon exposure [51].

To elucidate the implications of isocyanates on the regulation of neutrophil function and its impact on immune system at molecular level, experiments were performed on cultured human neutrophils isolated from healthy human volunteers. It has been demonstrated that isocyanates induce neutrophil apoptosis via activation of mitochondrial mediated pathway as observed through increased annexin-V-FITC/PI and active caspase-3 staining along with characteristic apoptotic DNA ladder assay and enhanced mitochondrial depolarisation. The immunotoxic response of isocyanates in neutrophils was also revealed through reactive oxygen species production, depletion in antioxidant defence status and elevated pro-inflammatory cytokine response [52].

The molecular mechanisms underlying isocyanate-mediated inflammatory responses and their possible role in the onset of genomic instability in cultured IMR-90 human lung fibroblasts has been examined. Induced inflammation, resulting in extensive DNA damage, was evident in increased ATM, ATR, γH2AX and p53 expression levels and apoptotic index. Chromosomal anomalies in treated cells included overexpression of centrosomal proteins and variable amplification of simple inter sequence repeats, further demonstrates isocyanate-induced genomic instability [53].

FUTURE PERSPECTIVE

The Bhopal gas tragedy is undoubtedly one of the worst industrial disasters in the history of mankind. The incident triggered interest from industry, academia, and legislature, and is widely acknowledged as one of the defining events in the history of process safety. India has been experiencing rapid industrialisation with gross domestic product (GDP) per capita going up to US$ 2900 in 2004 and the economy continues to grow at over 7–8% every year. Rapid industrial growth has contributed immensely to the economic growth but there has been significant cost in the form of environmental degradation and increased public health risks. Increasing awareness of potential exposures to exogenous non-biological agents arising out of human activity will become an important issue for this century. These exposures and their consequences generate many questions like health safety, safety of progeny, issues on compensation and punishments and so on. Although accidents involving MIC or an accident of similar magnitude may or may not recur, but for a country like ours which is fraught with human, environmental and economical perils, dissecting out the long standing effects of the disaster will be of immense value and significance while encountering future chemical disasters.

Although there has been an international consensus on the fact that the nature, severity of damage and sufferings in the survivors of the accident are of superlative order, attempts at understanding the persistence of long standing effects are lagging from both academia and industry. The study of human aspect of the tragedy had perhaps lagged behind and there has been lack in strategic planning to institutionalise studies on the long-term health consequences of the tragedy. Investigations conducted so far have also raised a new question of for how long the gas victims would continue to suffer from multi system disorders and whether their forthcoming generations would also be affected by these abnormalities. In-depth molecular studies of ocular, respiratory, reproductive, immunological, genetic and psychological health must be continued if we wish to understand the extent and severity of long term effects associated with the disaster. To cover up the inadequacies in medical care, the authors strongly suggest the necessity for long-term monitoring of the affected community and use of appropriate methods of investigation that include well-designed cohort studies for such conditions, characterisation of personal exposure and accident analysis to determine the possible components of toxic cloud as the investigators have noted several clinical and epidemiological inadequacies, including poor study design, bias and inaccurate exposure classification. Studies aimed at understanding increasing morbidity of MIC exposure carried out on cultured cellular model systems will provide a framework of understanding the potential mechanism of toxicity of a host of other exposures and may also uncover unique abnormalities in the survivors thereby stimulating efforts to design newer and more effective diagnostic and therapeutic strategies for helping the survivors. While it is most unfortunate that the accident has occurred, this has opened up an immense opportunity to learn about adverse effects of MIC. In fact, the ramifications of such findings would aid in shaping strategies for preventive management of future industrial disasters and refining risks that mankind faces from chemicals and other environmental hazards.

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