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Bhopal Gas Disaster: Review on Health Effects of Methyl Isocyanate

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ABSTRACT

This study reviews health effects of gas exposures from published human studies and discusses some of the clinical and experimental issues being debated. Because of the relative paucity of information. Some of these studies have helped to highlight specific health problems from the disaster and initiate more organized research to address these problems.

Key words: Methyl isocyanate, morbidity, toxicity

INTRODUCTION

Reviewed the studies of human health effects that resulted from exposure to methyl isocyanate gas that leaked from the Union Carbide plant in Bhopal, India, in Dec. 1984. The studies were conducted during both the early and late recovery periods. 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 (Mishra *et al*., 2009).

The accident was apparently initiated by the introduction of water into the Methyl Iso Cyanate (MIC) storage tank resulting in an uncontrollable reaction with liberation of heat and escape of MIC in the form of a gas.

The multi-disciplinary study of histopathology and toxicology of Bhopal gas tragedy resolved several issues. First, the progression of severe pulmonary oedema to chronic fibrosis was confirmed experimentally, following a single exposure to MIC. Analysis of the residue in Tank 610 revealed over 21 chemicals. Apart from MIC and HCN, some of them were tracked down to the blood and viscera of dead and living exposees. The rationale of NaTS therapy was substantiated by elevated urinary NaSCN levels in Double Blind Clinical Trials as well as patients. Apart from cyanide, the 'cherry red' discolouration was also shown to result from binding of MIC to end-terminal valine residues of Hb, as shown by changes in 2-3DPG levels and blood gas profiles. The finding of Ncarbamoylation of several other end-terminal amino acids of tissue proteins confirmed the distribution of MIC within the body, although the underlying mechanism is not yet fully understood. Possibly, the much faster S-carbamoylated compounds of the blood like glutathione and other sulphydrylcontaining enzymes like rhodanese could be responsible for re-circulation of MIC and protracted cyanide toxicity. It is hoped that eventually the enigma of the Bio-chemical Lesion of MIC toxicity will be unraveled (Sriramachari, 2004).

The two ICMR projects on histopathology and toxicology have more than fulfilled the initial hopes and expectations. The sequence of pathological changes in the acute, sub-acute and chronic stages have been clearly delineated. Experimental studies with MIC and its aqueous derivatives have confirmed the pathogenesis and pulmonary changes after single exposure are comparable to human autopsy findings.

Toxicological properties of MIC: MIC is highly irritant to the skin, eyes and mucus membranes of the respiratory tract. This irritant property is based on its reactivity with water which enables it to penetrate tissues and interact with protein. Absorption through the skin is known to occur (Irving, 1979).

HEALTH EFFECTS

Mortality and morbidity: Of the more than 200,000 persons exposed to the gas, the initial death toll within a week following the accident was over 2500. In Nov. 1989, the Dept. of Relief and Rehabilitation, Govt of Madhya Pradesh the toll at 3598 and by 1994, the toll was estimated to be over 6000 (Governament of Madhya Pradesh, 1989).

Symptom prevalence surveys conducted by the ICMR indicate that morbidity was higher in the exposed areas (26%) as compared with the control area (18%).Respiratory, neurological, psychiatric and ophthalmic symptoms also showed a strong gradient by exposure category (Indian Council of Medical Research, 1985).

Clinical studies: 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 (Mishra *et al*., 2009).

Ophthalmic problems: The intensely irritating effect of MIC on the cornea resulted in severe ocular burning, watering, pain and photophobia (Anderson *et al*., 1988). Examination of the eye showed involvement of the corneal and conjunctival epithelium with redness of the eye, corneal ulceration and lid swelling (Andersson *et al*., 1984; Dwivedi *et al*., 1985).

Andersson *et al*. (1986) performed a follow-up study on the eyes of survivors 9 months after the accident and reported that no case of blindness could be found that could be attributed to gas exposure among the nearly 20,000 persons attending the Bhopal Eye Hospital. However, they did find persistent eye watering and other chronic irritant symptoms like burning, itching and redness. Raizada and Dwiwedi studied eye pathology 24 among 1140 exposed persons and found that the main chronic lesions were chronic conjunctivitis, deficiency of tear secretion and persistent corneal opacities (Andersson, 1989).

No information is given on the prevalence of these conditions in the control area. Though there is no evidence that severe damage to the eye's external and internal structures has occurred.

Respiratory and pulmonary problems: Acute symptoms of the respiratory tract were mainly due to the irritant action of MIC on tissues. Because MIC is moderately soluble in water, lesions were seen in both the upper and lower respiratory tract. Predominant symptoms were cough accompanied by frothy expectoration, a feeling of suffocation, chest pain and breathlessness (Mishra *et al*., 1988). Other symptoms included dryness and irritation of the throat and rhinorrhea.

Autopsies on 300 victims revealed severe necrotizing lesions in the lining of the upper respiratory tract as well as in the bronchioles, alveoli and lung capillaries. Enlarged and edematous lungs, consolidation, hemorrhage, bronchopneumonia and acute bronchiolitis were seen (Indian Council of Medical Research, 1985).

Reproductive toxicity: Concerns that the gas leak had effects on reproductive health were raised early in 1985 when reports indicated that menstrual cycle disruption, leucorrhea and dysmenorrheal had occurred in gas-exposed women (Bang and Sadgopal, 1990). Risk to the fetus was also considered not only because of exposure to the gas but other factors like stress, anoxia and ingestion of various prescribed drugs like antibiotics, bronchodilators, and analgesics. An epidemiological survey by Varma showed pregnancy loss and infant mortality to be high in gas-exposed women (Varma, 1987). In a sample of 865 women who lived within 1 km of the plant and who were pregnant at the time of the gas leak, 43% of the pregnancies did not result in a live birth. Of the 486 live births, 14% of babies died in the first 30 days as compared to a death rate of 2.6 to 3% for previous deliveries in the 2 years preceding the accident in the same group of women.

Animal experiments conducted by Schwetz exposing pregnant mice to MIC by inhalation showed that this exposure does indeed have a fetotoxic effect (Schwetz *et al*., 1987). This finding was replicated by Varma *et al*. (1987), who observed a concentration-dependant increase in embryo loss, decrease in fetal and placental weights and a 20% reduction in mandible length and bones of the extremities.

Genotoxicity and carcinogenicity: Methyle isocyanate (MIC) was assayed in a number of *in vitro* and *in vivo* genetic toxicity tests in mammalian cells to determine its ability to interact with DNA and to induce genetic damage. *In vitro* tests included the mammalian microsome test gene mutation. *In vitro* and *in vivo* tests provide convincing evidence that is capable of inducing chromosomal damage and that this genetic toxicity is not strongly expressed *in vivo*, perhaps because of the selective reactivity of MIC with proteins and up to now effects of MIC on bacterial DNA not documented and it's Possible that MIC may have caused mutations in bacteria, which may have led to their capacity to cause previously undocumented morbidities related to infection caused by these mutated bacteria.

Isocyanates are able to modulate biomolecules, resulting in a series of biotransformations (Shelby *et al*., 1987; Pearson *et al*., 1990; Slatter *et al*., 1991), which in turn may affect health adversely (Tamura *et al*., 1992), yet they have a wide array of industrial applications. MIC, a reactive byproduct, is a detrimental to numerous organ systems (Worthy, 1985; Gupta and Prabha, 1996). It forms DNA cross links/adducts by reacting with exocyclic amino group of dNTPs, in turn contributing to cytotoxicity (Yoon *et al*., 2001). MIC intermediates (N-methylcarbamate) are also toxic to cultured mammalian cells (Hagmar *et al*., 1993; Kuo *et al*., 2008).

Isocyanates, including MIC have wide industrial applications, although they are mutagenic, alter the genome (Mason *et al*., 1987; Anderson *et al*., 1988; Kar *et al*., 1989) and can produce varied chromosomal abnormalities in individuals exposed to them (Goswami *et al*., 1990; Ghosh *et al*., 1990). Details of the complex molecular mechanisms underlying genetic hazards of occupational or accidental exposures to these chemicals on bacteria are still unknown.

A single, 2 h exposure to concentration of 0, 3, 10 and 30 ppm MIC produced no evidence of chromosomal effects in the bone marrow, although significant cell cycle delay was observed. In four experiments involving exposure on 4 consecutive days to 0, 1, 3 or 6 ppm, delay in bone marrow cell cycle were again observed . Increases in SCE and chromosomal aberration were observed in bone marrow cell cycle were again observed (Shelby *et al*., 1987).

A population-based cancer registry has been established in Bhopal in 1986 to study possible carcinogenic effects of the gas leak. Relative risks of 1.4, 1.3 and 0.7 (all non-significant) were found for lung, oropharynx, and oral cavity cancers, respectively, for 1992 in comparison to the years 1987-90 and gas unaffected regions combined. Using a case-control design, cancer cases of

the above sites were selected from the registry and controls from a tobacco survey conducted in the Bhopal population. A marginally increased risk was found only for oro pharyngeal cancer (RR = 1.5, 95% CI = 1.1-2.2), after adjustment for age and tobacco use. No dose-response relationships were evident in the geographic distribution of cases.

Biochemical studies: Biochemical studies conducted by the ITRC, Lucknow , India, revealed that some multi-systemic complaints were persistent and occurred even in those patients who did not have significant respiratory damage (Gupta *et al*., 1988). In a sample from a gas exposed population studies 3 MO after the accident biochemical indicators of stress response were observed, blood ceruloplasmin levels were increased 200% over control values in more than 45% of those tested (Srivastava *et al*., 1988). In these studies, urinary creatinine was significantly higher than in controls. Blood glutathione was significantly depressed in approximately 40% of the population examined.

Buchner (Tice *et al*., 1987), in this review of the health effects research done on MIC, states that if MIC is shown to bind to normal hemoglobin (Carbamoylation), this would provide evidence that the chemical crosses the alveolar barrier and would, therefore, support MIC's potential for systemic exposure.

While N-carbamoylation cannot be undone, it would appear that sulphydryl radicals contained in Acetyl Choline Esterase (ACE), aldolase and especially rhodanese are periodically reactivated and 'chronic cyanide metabolism' corrected. Normalcy is attained only when the MIC stored in the body is fully depleted. But, in the exigencies of an alarming human disaster, it has not been possible to try other potent sulphane donors described by Cohen and Oppenheimer16. It seems that the Biochemical Lesion of Bhopal disaster may lie between the interplay of N- and S-carbamoylation (Sriramachari, 2004).

Immunotoxicity: Following exposure to the gas in Bhopal, there was concern amongst the health authorities that the population might experience an increased rate of infections. Immune function was studied in exposed subjects from the ITRC sample two and a half months after exposure to ascertain whether any change had occurred in the immune status (Saxena *et al*., 1988). Humoral immunity was assessed by quantitation of immunoglobulins (IgG, IgM, IgA) in over 300 exposed and 10 non-exposed persons. Cell-Mediated Immunity (CMI) was assessed by phagocytic activity of lymphocytes and quantitation of T-cell rosettes in 19 exposed and 8 non-exposed persons. Results from this study showed that no difference in mean immunoglobulin levels was found when compared to controls. The T-cell population (28%) was found to be less than half that found normally in the Indian population (65%). Significant depression of phagocytic activity of lymphocytes was found as compared to controls.

Limitations of the human studies include the relatively small sample sizes, choice of control groups and unclear exposure ascertainment. The above limitations make it difficult to arrive at definitive conclusions regarding immunotoxicity from MIC exposure for the gas victims.

Psychological and neuro-behavioral toxicity: Srinivasamurthy and Isaac noted that psychological problems of Bhopal survivors fell into four major categories (Murthy and Isaac, 1987). These observations were based on visits by the authors to medical clinics as well as the homes of affected victims.

Fifty-two MIC victims were subjected to detailed medical examination and clinical psychometry one year after the accident (Misra and Kalita, 1997). The neurological included examination of

mental status, cranial nerves, motor and sensory systems. Clinical psychometry included the Benton Visual Retention Test (BVRT), Wechsler memory scale, and Standard Progressive Matrices (SPM). Severely affected victims had significant impairment on SPM, associate learning, motor speed, and precision test. In the moderately affected victims, associate learning, motor speed, and precision was significantly impaired. Some degree of dose-response was noted in some tests when compared with controls and within the exposed groups. The authors concluded that the persistence of cognitive impairment one year after the accident suggested significant MIC neurotoxicity.

Neuromuscular toxicity: Neuromuscular symptoms in Bhopal survivors have persisted since the gas leak. These symptoms are mainly tingling, numbness, a sensation of pins and needles in the extremities and muscle aches.

To assess whether MIC was toxic to muscle, Anderson et al evaluated the effects of MIC on rat muscle cells in culture (Anderson *et al*., 1988). At lower doses, the formation of muscle fibers was prevented. At higher doses, death of fibroblasts and myoblasts was seen. The findings suggested either an effect on muscle differentiation or selective toxicity to myoblasts.

There has been no evidence to support the second hypothesis that MIC is converted to a form of cyanide in the body. Animals exposed to MIC by inhalation have not shown any evidence of cyanide in the blood (Bucher *et al*., 1987).

Ferguson and Alarie have demonstrated that there may be a physiopathological basis for the persistence of multi-systemic symptoms in Bhopal survivors (Ferguson *et al*., 1988). Their studies on experimental animals have shown that radio-labeled MIC is capable of being absorbed and distributed throughout the body. These findings have been confirmed by Bhattacharya et al who have shown that MIC binds covalently to tissue proteins in its active form and not as its breakdown product, methylamine (Bhattacharya *et al*., 1988). There is no known antidote for MIC toxicity.

EXPERIMENTAL STUDIES

Recent experimental studies have provided mechanistic understanding of methyl isocyanate exposure at a molecular level. Immuno toxic 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 (Mishra *et al*., 2009).

CONCLUSIONS

In-depth molecular studies of ocular, respiratory, reproductive, immunological, genetic and psychological health carried out so far have helped to understand the extent and severity of long term effects associated with the disaster.

Long-term monitoring of the affected community and use of appropriate methods of investigation that include well-designed cohort studies for such conditions, characterization of personal exposure and accident analysis have helped to determine several clinical and epidemiological inadequacies, including poor study design, bias and inaccurate exposure classification of studies conducted previously on victims of the tragedy.

Studies aimed at understanding increasing morbidity of MIC exposure carried out on human cultured cellular model systems have provided a framework of understanding the potential mechanism of toxicity of a host of other exposures and that might uncover unique abnormalities

in the survivors thereby stimulating efforts to design newer and more effective diagnostic and therapeutic strategies for helping the survivors.

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