The Union Carbide Disaster in Bhopal: A Review of Health Effects

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ABSTRACT. The authors have reviewed studies of human health effects that resulted from exposure to methyl isocyanate gas that leaked from the Union Carbide plant in Bhopal, India, in 1984. The studies were conducted during both the early and late recovery periods. Major organs exposed were the eyes, respiratory tract, and skin. Although mortality was initially high, it declined over time, but remained elevated among the most severely exposed population. Studies conducted during the early recovery period focused primarily on ocular and respiratory systems. Major findings included acute irritant effects on the eyes and respiratory tract. In follow-up studies, investigators observed persistent irritant effects, including ocular lesions and respiratory impairment. Studies conducted during the late recovery period focused on various systemic health endpoints. Significant neurological, reproductive, neurobehavioral, and psychological effects were also observed. Early and late recovery period studies suffered from several clinical and epidemiological limitations, including study design, bias, and exposure classification. The authors herein recommend long-term monitoring of the affected community and use of appropriate methods of investigation that include well-designed cohort studies, case-control studies for rare conditions, characterization of personal exposure, and accident analysis to determine the possible components of the gas cloud.
<Key words: Bhopal, disaster, epidemiology, methyl isocyanate, Union Carbide>

THE WORLD'S WORST INDUSTRIAL DISASTER occurred in India on the night of December 2–3, 1984, at the Union Carbide plant in Bhopal (population: 900,000), the capital city of Madhya Pradesh—one of the largest states in India. Introduction of water into a methyl isocyanate (MIC [CH_3–N=C=O]) storage tank resulted in an uncontrollable reaction, with liberation of heat and MIC gas. Safety systems—such as a flare tower (for the burning of excess gas), a caustic soda scrubber (for neutralization), and a refrigeration unit—did not contain the reaction.[1] MIC is an intermediate product in the manufacture of carbaryl (Sevin®), a carbamate pesticide. As is shown in Table 1, a mixture of carbon monoxide (CO) and chlorine (Cl_2) forms phosgene ($COCl_2$). Phosgene is then combined with monomethylamine (CH_3NH_2) to form MIC.[2] Finally, MIC is mixed with naphthol to produce carbaryl.

Overview

MIC is a clear, colorless liquid with a pungent odor (boiling point = 39 °C, freezing point = –80 °C, specific gravity = 0.96, molecular weight = 57.1, vapor pressure = 348 mm Hg at 20 °C). MIC is moderately soluble in water, and hydrolyzes to form carbon dioxide and methylamine. When MIC is pyrolyzed between 427 °C and 548 °C, it decomposes to hydrogen cyanide and carbon dioxide.[3] MIC irritates the skin, eyes, and respiratory mucus membranes. It reacts with water to penetrate tissues, including skin[4]; interacts with protein; and

Table 1.—Manufacturing Process for Methyl Isocyanate

$CO + Cl_2 \rightarrow COCl_2$ (phosgene)
$COCl_2 + CH_3NH_2 \rightarrow CH_3NHCOCl + HCl$
$CH_3NHCOCl \rightarrow HCl + CH_3NCO$ (methyl isocyanate)

Source: Varadarajan S., et al.[2]

Table 2.—Lethal Dose (LD)/Lethal Concentration (LC) Values for Methyl Isocyanate, from Animal Studies

Route	Dose	Model	LD50/LC50
Oral	10% soln; single dose	Male rat	71 mg/kg
Inhalation	Vapors (4 hr)	Rat	1.25 mg/m^3
Skin	Undiluted	Rabbit	0.22 ml/kg

Source: Adapted from Gassert.[6]

has poor warning properties.[5] Lethal dose values for MIC are provided in Table 2.[6]

In this article, the authors have reviewed the health effects of exposure to MIC gas—on the basis of published human studies and on unpublished studies conducted by local physicians to highlight specific health problems and propose research. Some of the clinical and epidemiological issues being debated are also discussed. In addition, human and animal toxicology studies by Bucher and Mehta et al. are also discussed.[7,8]

Investigating agencies. The Bhopal Gas Disaster Research Centre, established in 1985 by the Indian Council for Medical Research (ICMR), classified the exposure of 80,021 persons as severe, moderate, or mild on the basis of mortality parameters.[9] An unexposed population of 15,931 in Bhopal served as controls. Each household was given a tracking number, and biennial symptom prevalence surveys were conducted. The ICMR also organized multiple clinical research studies on the affected population. Results from these studies have not been published to date. The Tata Institute of Social Sciences (TISS) in Bombay conducted a socioeconomic survey and registered the exposed households with a TISS number. It is unknown whether information from the survey was ever analyzed. The Industrial Toxicology Research Centre (ITRC), a branch of the Council for Scientific and Industrial Research, performed community and toxicological studies 3 mo following the accident. Various individual researchers conducted and published early clinical studies, which provided valuable information and insight into the health effects of the disaster.[10–17] Nine years following the accident, the International Medical Commission on Bhopal (IMCB) conducted the 1st long-term population study of symptom prevalence, lung function, and exposure estimation.

Exposure conditions. Approximately 27 tons of MIC escaped from the 2 tanks in the plant within 1–2 hr.[1] Adverse atmospheric conditions (inversion and low wind speed) prevented dispersion of the gas.[18] Eyewitnesses reported that a cloud of gas enveloped the area and moved slowly. The MIC gas cloud may have included several toxic decomposition byproducts such as hydrogen cyanide, nitrogen oxides, and carbon monoxide. Contaminants such as phosgene and monomethylamine, which were used in the manufacture of MIC, might also have been present in the cloud. Air monitoring was not possible at the time of the incident, nor was it attempted subsequently. The estimated mean MIC concentration in the cloud was 27 ppm—1,400 times the U.S. Occupational Safety and Health Administration's (OSHA) workplace standard (Table 3). This calculation did not account for varying concentrations with distance from the source. Singh and Ghosh applied an analytic dispersion model and identified 27 sites with ground-level concentrations ranging from 0.12 ppm to 85.6 ppm (median = 1.8 ppm).[19]

Table 3.—Methyl Isocyanate Exposure Conditions

Exposure	Extent
Quantity released	27 tons
Area affected	40 km^2
Estimated mean concentration[18]	27 ppm
Estimated median concentration[19]	1.8 ppm
Range of concentration	0.12–85.6 ppm
OSHA standard	0.02 ppm

Note: OSHA = Occupational Safety and Health Administration.

The acute irritant effects of MIC created panic, anxiety, and disorientation, and it caused people to run out of their homes into the gas cloud, the result of which was an increased dose of the chemical. Variability in human exposure, therefore, was likely to have resulted from distance of the residence from the plant, duration of exposure, and activity during exposure.

A Medico Friend Circle study reported that, in a study sample of 158 persons, 124 ran out of their homes, and only 12 placed a wet towel or blanket over their face as a safety measure.[20] Data collected from a later IMCB study showed that more than 65% of subjects reported that they used some form of protection against the gas.[21] Use of a wet cloth to cover the face and splashing water on the face and body accounted for 80% of the preventive methods used. The major organs exposed to the gas were the eyes and respiratory tract. Skin exposure also occurred, and some MIC—most likely dissolved in saliva—was swallowed.

Characteristics of the exposed population. An ICMR survey conducted in 1985 in the exposed areas showed that approximately 53% of the population were Hindus, 45.6% were Muslims, and the remainder were Christians and Sikhs. In 1985, the monthly income of 80% of the population was below 6 U.S. dollars/mo, and only 1.25% earned *more* than 18 U.S. dollars/mo. By 1988, 65% of the population was earning less than 6 U.S. dollars/mo, thus indicating a slight improvement in economic level. However, these figures show that most exposed individuals were close to the government-defined poverty level of 12 U.S. dollars/mo. Of the aforementioned population, 9.9% were smokers, 1.4% were al-

coholics, and 5.5% chewed tobacco. Only 34% of the population lived in a "pacca" (i.e., permanent) house.[22]

As part of the IMCB study, Acquilla et al.[23] used "distance of residence from the plant" as a surrogate for exposure to conduct a symptom survey of the population 10 yr after the accident occurred. Investigators observed that migration was relatively low; 91% of the population remained in the same area subsequent to 1984. Socioeconomic data showed marked gender differences in literacy (education up to grade 5: male = 59%, female = 34%) and full-time employment (work > 20 days/mo: male = 33%, female = 5%).

Health Effects

Mortality. Of the more than 200,000 persons exposed to the gas, the death toll 1 wk following the accident exceeded 2,500.[1] In November 1989, the Department of Relief and Rehabilitation, Government of Madhya Pradesh, placed the death toll at 3,598, and by 1994 the toll was estimated at 6,000+.[24] Some uncertainty exists regarding the number of deaths because a portion of the population left the city after the accident and never returned. Independent agencies estimate that the number of disaster-related deaths is currently between 15,000 and 20,000.[25,26] A pulmonary physician[27] who studied many of the gas victims attributed "late" deaths to respiratory complications. During May 1989–March 1990, mortality rates declined, but rates remained elevated in the severely exposed area (8.75/1,000), compared with the control area (7.5/1,000).[28]

Overall morbidity. Symptom prevalence surveys conducted by the ICMR during November 1988–March 1990 indicate that morbidity was higher in the exposed areas (26%) than in the control area (18%).[22] Approximately 11% of people experienced 2 or more spells of illness in a 1-yr period. Respiratory, ocular, and gastrointestinal symptoms accounted for most of this morbidity. This trend appeared to persist in a survey conducted in the latter part of 1990.[28]

Results from the 1994 IMCB survey showed that many subjects reported general health problems (exposed = 94%, unexposed = 52%) and episodes of fever (exposed = 7.5/yr, unexposed = 2.5/yr). Respiratory, neurological, psychiatric, and ophthalmic symptoms also showed a strong gradient by exposure category.[23]

Ocular problems. Major findings from early ocular studies conducted 8–60 days after exposure to MIC revealed predominantly injuries resulting from the intensely irritating effect of MIC on the cornea. These included severe ocular burning, watering, pain, and photophobia.[29] Examination showed redness of the eye, lid swelling, and ulceration limited to the superficial layers of the cornea. Slit lamp examination showed discrete lesions in a band across the interpalpebral area, punctate keratopathy, conjunctival chemosis, and some pigmentary deposition on the cornea.[30] Relatively few cases of iritis were seen.[31] Treatment at the initial stage consisted of saline eyewashes, pupillary dilatation, and topical antibiotics.

Follow-up ocular studies, conducted 9 mo[32] to 2 yr[33,34] after exposure commenced, reported chronic irritant symptoms such as persistent eye watering, burning, itching, and redness. No cases of blindness could be attributed to gas exposure. The main chronic lesions were conjunctivitis, deficiency of tear secretion, and persistent corneal opacities. No information was given on the prevalence of these conditions in the control area.

Andersson et al.[10] performed a follow-up of 93% of previously surveyed exposed and control Bhopal residents 3 yr after exposure. The ocular effects surveyed included photophobia, burning, watering sensation, red eye, superficial interpalpebral erosion, Bitot spots, corneal opacity, pterygium, discharge, and fundal changes. The investigators' findings indicated an increased risk of eye infections, hyperresponsive phenomena (watering, irritation, phlyctens), excess cataracts, and resolution of the corneal erosions in exposed persons. These phenomena have been characterized as the Bhopal Eye Syndrome. Andersson et al. stated, "In its response to MIC, the eye should be considered a 'sentinel organ' for more general phenomena in the body."

Although there is no evidence that severe damage to the eye's external and internal structures has occurred, the single acute exposure seems to have resulted in a chronic inflammatory process. The problems of persistent eye watering in some cases, and tear secretion deficiency in others, coupled with chronic conjunctivitis, indicate damage to the eye epithelium. It is conceivable that housing conditions in the Bhopal slum areas, including overcrowding, poor ventilation, and exposure to dust and smoke, could exacerbate the ocular effects, causing irritation and infections.

Respiratory toxicity. Acute symptoms of the respiratory tract occurred primarily from the irritant action of MIC on tissues. MIC is moderately soluble in water; therefore, 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.[35] Additional symptoms included dryness and irritation of the throat and rhinorrhea.

Autopsies of 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 also noted.[36] Follow-up studies were conducted 2.5–3 mo after the accident on a total of 1,279 exposed men, women, and children.[37] Of the 903 subjects who had radiological examination of their lungs, 164 had abnormal x-rays; 65 had radiological changes associated with gas exposure. Subjects with exposure-related changes were classified into groups. Group A (n = 48) contained subjects with changes such as haziness, hilar prominence, fine mottling, and reticulation, all of which were considered to result from gas exposure. Of these 48 subjects, 16 had respiratory symptoms (e.g., cough, chest pain/tightness, breathlessness); clinical

signs (adventitious sounds); and abnormal lung function. Twenty subjects had respiratory symptoms, but clinical examination was normal, as was lung function. Group B (n = 17) had abnormalities suggestive of preexisting disease (e.g., tuberculosis, chronic bronchitis, pneumonitis), which was aggravated by gas exposure. The investigators analyzed acute symptoms by distance of residence from the factory (i.e., < 2 km, 2–4 km, and > 4 km), and they found an inverse relationship between prevalence of acute symptoms and distance of residence from the factory.

Spirometry was performed on 783 subjects from the sample described earlier.[38] The results showed that 39% of the sample had some form of respiratory impairment. A combined pattern of impairment (i.e., obstructive and restrictive diseases) had the highest prevalence (22%) in the sample. Smoking had no effect on the prevalence of this impairment. Females suffered more mild and moderate impairment than did males, whereas severe impairment was distributed equally (2.4%) between the 2 sexes.

A survey of 164 Bhopal children who lived 0.5–2 km from the factory was conducted 105 days after the accident occurred.[39] Results from the survey were compared with a control group of children who lived 8–10 km from the factory. The investigators attributed the chronic health effects listed in Table 4 to MIC exposure. During examinations, investigators also noted that many of the exposed children were apprehensive, jittery, very verbal, or depressed.

Kamat et al. studied 113 exposed patients who were either Bhopal residents or visitors from Mumbai.[11,12,40] The exposed patients completed a symptom questionnaire and had a physical examination, chest radiography, and spirometry at 3 mo, 6 mo, and 2 yr after exposure. Symptoms included cough, sputum, chest pain, and dyspnea. Symptoms improved during the 1st year, but they intensified during the 2nd year. Dyspnea and cough with phlegm were more prevalent 2 yr postexposure than at 1 yr postexposure. Forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25–75\%}$ of FVC) declined progressively during the 2-yr period of observation, as did FVC.

Vijayan et al.[13] analyzed bronchoalveolar lavage fluid in 36 mildly, moderately, and severely exposed individuals, and in 12 unexposed persons, 1–2.5 yr following the accident. A significant increase in alveolar macrophages was found among severely exposed smokers and nonsmokers. The authors concluded that inflammatory alveolitis might have been present in severely exposed subjects and that long-term follow-up to determine impairment of lung function was, therefore, required. In a subsequent study, Vijayan et al. examined 60 MIC-exposed patients who presented with dyspnea and cough[14]—classified as mild, moderate, or severe exposure on the basis of respiratory and ophthalmic symptoms on the day of exposure, and deaths (if any) of family members. Pulmonary function abnormalities were most severe among individuals who had severe exposures, and abnormalities were attributed to accumulation of lung inflammatory cells.

One resident of the gas-exposed area continued to be exposed for a few days to trapped gases in victims.[62] This 60-yr-old nonsmoker had no respiratory symptoms, other than episodes of cough, until the beginning of 1989, at which time he complained of severe cough and breathlessness on exertion. Pulmonary function showed a mild obstructive ventilatory defect. A computerized tomography (CT) scan revealed subpleural thickening, punctate lesions, and bilateral septal scars of extensive pulmonary fibrosis, thus suggesting the toxic potential of MIC from secondary exposure.

Early cross-sectional studies of gas victims used relatively crude definitions of community exposure. Within a few days following the accident, Andersson et al.[29] conducted a survey of acute effects on 8 exposed and 2 nonexposed household clusters in Bhopal. Exposure zones were defined on the basis of reports of human and animal deaths, symptoms, and perceptions of the presence of the gas; however, no information was available on how these reports were integrated for the delineation of the exposure zones. Other acute effects included nausea, vomiting, shortness of breath, chest pain, unconsciousness, dizziness, choking, twitching, headache, and convulsions. Although their results showed a marked difference in effects between exposed and nonexposed areas, a positive association with mortality alone was observed for some effects (e.g., cough, diarrhea, fundal changes), but not for others (e.g., shortness of breath, burning eyes).

In some clusters, apparently an inverse relationship was found between mortality and shortness of breath—a finding not easily explained by the "healthy-survivor" effect (inasmuch as cough was associated positively with mortality). The aforementioned finding suggested that the dose–response relationship was not necessarily log-linear, but that different pathological reactions might have occurred at different doses (a fact noted in some animal studies). The authors suggested that long-term follow-up might permit testing of the predictive value of the signs and symptoms associated geographically with high death rates.

Four months following the gas leak, the Medico Friend Circle conducted a cross-sectional study of a seriously affected slum area near the Union Carbide plant, with a less-affected slum 10 km away as the control area.[20] Acute symptoms, physical examination, and pulmonary function were the outcome parameters. Significant differences were found between the 2 areas with respect to ocular and respiratory symptoms and pulmonary function (i.e., forced expiratory volume in 1 sec [$FEV_{1.0}$] and FVC).

Although isocyanates are allergenic in the lung, the respiratory toxicity of MIC appears to be so as a result of its irritant nature.[57] Follow-up studies, which included lung biopsies performed 6 mo following exposure, revealed interstitial fibrosis and bronchiolitis obliterans. These findings were similar to findings of several animal studies, thus revealing the close association between animal data and clinical findings in Bhopal victims.[63,64]

On behalf of the IMCB, Cullinan et al.[48] surveyed 454 adults for respiratory symptoms and pulmonary function

Table 4.—Human Health Effects Studies on the Bhopal Methyl Isocyanate (MIC) Gas Leak: Early and Late Recovery Periods

Author	Design	No. of subjects	Time since gas leak	Major findings	Study limitations*
Ocular: Early					
Andersson et al.[30]	Case–series and survey	8,000	8 days	Chemosis, corneal ulcers, watering, photophobia, no blindness	
Andersson et al.[29]	Cross-sectional	379	2 wk	Photophobia, corneal erosions	Ecological exposure assignment
Dwiwedi et al.[31]	Case–series	232	Few weeks	Chemosis, redness, watering, corneal ulcers	
Andersson et al.[42]	Case–series	490	2 mo	Corneal ulcers, no blindness	
Maskati[43]	Cross-sectional	367	104 days	Conjunctivitis, corneal opacities	Ecological exposure assignment; no information on subject selection
Ocular: Late					
Andersson et al.[32]	Case–series	989	9–12 mo	Persistent watering	
Raizada and Dwiwedi[33]	Case–series	1,140	2 yr	Corneal opacities, chronic conjunctivitis	
Khurrum and Ahamad[34]	Cross-sectional	4,280	2 yr	Corneal opacities, chronic conjunctivitis, tear secretion deficiency	No information on subject selection, demographics, exposure, morbidity in controls

(Table continues)

Table 4.—Continued

Author	Design	No. of subjects	Time since gas leak	Major findings	Study limitations*	Author	Design	No. of subjects	Time since gas leak	Major findings	Study limitations*
		Respiratory: Early						*Respiratory: Late*			
Mishra et al.[44]	Case–series	978	2 days	Respiratory distress, pulmonary edema, pneumonitis		Kamat et al.[12]	Case–series	113	2 yr	Depression, muscle weakness, restrictive lung disease, decline in peak flow	
Sharma and Gaur[45]	Case–series	500 x-rays	> 72 hr	Pulmonary edema, emphysema, pneumothorax		Vijayan et al.[13,14]	Case–series	60	1–7 yr	Obstructive and restrictive airway disease, high bronchoalveolar lavage macrophage counts	
Misra and Nag[46]	Case–series	33	1 wk	Dyspnea, upper and lower respiratory irritation, lung edema, pneumonia		Acquilla et al.[23] (IMCB)	Cross-sectional	474	10 yr	Respiratory and neurological symptoms	Ecological exposure assignment
Bhargava et al.[47]	Case–series	224	1–4 mo	Obstructive and restrictive lung disease		Cullinan et al.[48] (IMCB)	Cross-sectional	74	10 yr	Obstructive airway disease	Small sample size, ecological exposure assignment
Kamat et al.[49]	Case–series	113	3 mo and 6 mo	Emphysema, pulmonary hypertension, pleural scars		Dhara[21] (IMCB)	Cross-sectional	312: symptoms 74: spirometry	10 yr	Individual exposure associated with symptoms, lung function	Recall bias; small sample size
Andersson et al.[29]	Cross-sectional	379	2 wk	Acute eye and respiratory symptoms	Ecological exposure assignment						
Medico Friend Circle[20]	Cross-sectional	273	4 mo	Obstructive and restrictive lung disease	Ecological exposure assignment						
Gupta et al.[37]	Cross-sectional	1,109	2.5 mo	65 subjects with +ve x-ray changes	Ecological exposure assignment						

(Table continues)

Table 4.—Continued

Author	Design	No. of subjects	Time since gas leak	Major findings	Study limitations*	Author	Design	No. of subjects	Time since gas leak	Major findings	Study limitations*
		Pediatric: Early						*Pediatric: Late*			
Irani and Mahashur[39]	Cross-sectional	211	105 days	Respiratory, abdominal, and neurological symptoms; obstructive airway disease; conjunctivitis	No information on subject selection, ecological exposure assignment						
		Reproductive: Early						*Reproductive: Late*			
Daniel et al.[50]	Cross-sectional	28	6 mo	No effect on spermatogenic function	Small sample size, unclear exposure ascertainment	Varma[15]	Survey	865 pregnancies; 486 live births	9 mo	Increased pregnancy loss, increased infant mortality	Use of historic controls, recall bias
						Medico Friend Circle[51]	Survey	381	9 mo	Increased spontaneous abortion rate, alteration of menstrual cycle	Use of historic controls, recall bias
						Kanhere et al.[52]	Cross-sectional	158	9 mo	Decreased placental and fetal weight	No information on subject selection, ecological exposure assignment
						Bhandari et al.[53]	Cross-sectional	3,784	9 mo	Increased spontaneous abortion rate, perinatal and neonatal mortality	Ecological exposure assignment
		Genetic: Early						*Genetic: Late*			
Deo et al.[54]	Cross-sectional	35	11 days	Cell cycle delay	Unclear exposure ascertainment	Ghosh et al.[55]	Cross-sectional	129	3 yr	Increased chromosomal aberrations	Unclear exposure ascertainment
Saxena et al.[56]	Cross-sectional	62	2.5 mo	Increased chromosomal aberrations	Subject solicitation						

(Table continues)

Table 4.—Continued

Author	Design	No. of subjects	Time since gas leak	Major findings	Study limitations*	Author	Design	No. of subjects	Time since gas leak	Major findings	Study limitations*
		Immune: Early						*Immune: Late*			
Deo et al.[54]	Cross-sectional	85	4–8 wk	Decreased response to T- and B-cell mitogens	Unclear exposure ascertainment	Karol et al.[57]	Case–series	144	1–12 mo	Transient MIC antibodies in 12 subjects	
Saxena et al.[56]	Cross-sectional	71	2.5 mo	Decreased T-cell population and phagocytic activity	Subject solicitation						
		Psychological: Early						*Psychological: Late*			
Sethi et al.[41]	Case–series	208	2–6 mo	Neuroses, anxiety states, adjustment reactions							
		Neurobehavioral: Early						*Neurobehavioral: Late*			
Gupta et al.[37]	Cross-sectional	450	2.5 mo	Impaired auditory and visual memory, impaired vigilance and attention response speed	Subject solicitation	Misra and Kalita[58]	Case–series	83	1 yr	Impaired associate learning, motor speed, precision	
		Cancer: Early						*Cancer: Late*			
						Dikshit and Kanhere[59]	Surveillance and case–control	3+ million person-years 1,500	3–8 yr	Marginal increased risk of oropharyngeal cancer	Short latency and study period, ecological exposure assignment, socioeconomic differences
		Autopsy studies: Early						*Autopsy studies: Late*			
						Chandra et al.[60]	Case–series	34	7 yr	MIC trimer in blood	
						Chandra et al.[61]	Case–series	4	10 yr	MIC compound in blood similar to tank residue	

Note: IMCB = International Medical Commission on Bhopal.
*For epidemiological studies only.

10 yr after the accident. The authors used residential distance from the Union Carbide plant as a surrogate for exposure, and subjects were chosen randomly in the exposed and unexposed areas. Although symptoms of dyspnea and cough were more prevalent than phlegm and wheezing, a consistent gradient was seen for all respiratory symptoms by residential distance. The increased prevalence of symptoms among those who lived nearest to the plant could be explained, in part, by a lower socioeconomic status. However, this trend was the opposite of the higher symptom prevalence expected from the higher "ever-smoked" rate among those who lived farther from the plant. All lung-function measurements declined with proximity to the plant, but a statistically significant reduction was seen only for $FEF_{25–75\%}$ when distance was analyzed as a continuous variable. The authors concluded that the persistent small-airways obstruction seen might have been attributable to gas exposure. In addition, the findings of cough, dyspnea, and reduction in $FEF_{25–75\%}$ noted in the 2-yr follow-up study by Kamat et al. were persistent among the population 10 yr after the accident occurred.[12]

The occurrence of Reactive Airways Dysfunction Syndrome (RADS) as a consequence of MIC inhalation injury has not been addressed in the Bhopal investigations.[65] In view of the many subjects exposed to a wide range of concentrations, it appears that valuable information could be gleaned about the natural evolution of inhalation injury, the proportion of subjects with structural and functional lung damage, and relationships between exposure/initial injury and subsequent impairment.

Reproductive toxicity. Reports in early 1985 indicated that menstrual cycle disruption, leukorrhea, and dysmenorrhea had occurred in gas-exposed women.[66] In pregnant women, the fetus was at risk from exposure to the gas, as well as from factors such as stress, anoxia, and ingestion of various prescription drugs (e.g., antibiotics, bronchodilators, analgesics).

An epidemiological survey by Varma[15] showed that miscarriage and infant mortality were high in 865 gas-exposed women who lived 1 km from the plant at the time of the gas leak. Results indicated that 43% of the pregnancies did not result in a live birth. Of the 486 live births, 14% of those babies died during the 1st 30 days of life, compared with a death rate of 2.6–3% for deliveries during the 2 yr that preceded the accident in the same group of women.

The Medico Friend Circle conducted a pregnancy outcome survey 9 mo after the accident in 3 gas-exposed areas of Bhopal.[51] A total population of 8,165 in 1,632 households was surveyed by random sampling. Information on reproductive history and menstrual cycles was collected for the 1-yr time period that preceded the gas leak and served as the "historic control." A 4-fold increase in overall spontaneous abortion rate for the period after the gas leak was reported. Approximately 24% of women had altered menstrual cycle durations (i.e., 14% of the cycles decreased by ≥ 7 days, 6% were irregular, and 4% increased by ≤ 7 days). The authors concluded that these effects could be gas-related.

The finding of an increase in spontaneous abortion rates was confirmed by a larger study on pregnancy outcome conducted in 18,978 households in the severely affected areas around the Union Carbide plant.[53] All women who were pregnant (as determined by last menstrual period before November 18, 1984; n = 2,566) at the time of exposure were identified, and control subjects (n = 1,218) were recruited from 13,539 households in an unaffected area. Women who were up to week 20 of gestation on March 12, 1985, were considered at risk for miscarriage. Age-standardized miscarriage rates were significantly higher in the affected area (23.6%) than in the control area (5.6%). Although the stillbirth rates were similar in the affected and control areas (26 vs. 22.9, respectively, per 1,000 deliveries), the perinatal (69.5 vs. 50.5) and neonatal mortality rates (60.9 vs. 11.8) were significantly different. Congenital malformation rates were not significantly different between the 2 areas (i.e., 14.2 vs. 12.6, respectively).

Animal experiments conducted by Schwetz et al.,[67] who exposed pregnant mice to MIC via inhalation, showed that this exposure has, in fact, a fetotoxic effect. This finding was replicated by Varma et al.,[16] who observed a concentration-dependant increase in embryo loss, decrease in fetal and placental weights, and a 20% reduction in the length of the mandible and bones of the extremities.[14]

Varma et al.[17] studied the contribution of maternal hormonal changes and hypoxia from pulmonary damage to fetal toxicity of MIC in rats and mice, and they found that the fetal toxicity of MIC was partly independent of maternal pulmonary damage and that MIC could be directly fetotoxic. A review of animal studies, in conjunction with findings from human epidemiology, suggests that exposure to MIC is directly fetotoxic.

Genotoxicity and carcinogenicity. Investigators conducted chromosomal studies 2.5 mo after the gas leak occurred to evaluate genetic damage among a sample of 31 exposed adults and a similar number of matched controls.[56] The results show a significantly increased (p < .001) number of breaks and gaps in lymphocytes of the exposed subjects. Investigators did not perform follow-up studies to determine if this effect was persistent.

Cytogenetic studies were carried out 3 yr after exposure on a sample of 40 exposed males and 43 exposed females.[55] Statistically higher frequencies of chromosomal aberration were found in the exposed group than in 46 age- and sex-matched unexposed controls. The aberrations were in the form of breaks, gaps, dicentrics, rings, and tri- and quadri-radial configurations, and they were more pronounced in female subjects than in males. Sister chromatid exchanges were not significantly different. The authors concluded that, although the results might indicate a residual effect on T-cell precursors, additional studies are required to demonstrate an exposure–effect relationship. Although animal and in vitro studies demonstrate MIC's potential for genotoxicity—including induction of sister chromatid exchanges, chromosomal aberrations, negative Ames test, sex-linked recessive tests in *Drosophilia*, and delay of cell-cycle time—it is unclear if such toxicity has actually occurred in exposed humans.[55,68–72]

To assess carcinogenic potential, Bucher and Uraih[73] exposed rats and mice to MIC concentrations of 0, 1, 3, and 10 ppm for 2 hr via inhalation. Marginal increases in pheochromocytomas of the adrenal medulla were seen at 3 ppm and 10 ppm in the groups of male rats. Adenomas of the pancreas were also increased in male rats in the 10-ppm group, and the combined incidence of adenomas and hyperplasia showed increased proliferative lesions in the exposed groups. However, because authors of prior studies had not shown the adrenal medulla or pancreas to be target organs of inhaled MIC, these marginal increases were not considered relevant to the exposed Bhopal population.

Ennever and Rosenkranz[74] used the carcinogen-prediction and battery-selection method to predict the carcinogenicity of MIC. The authors integrated the results of several in vitro and in vivo short-term tests to calculate that MIC had a 76.6% probability of being a genotoxic carcinogen. The tests, however, were positive in assays that had a high sensitivity and a low specificity, but they were negative in assays with low sensitivity and high specificity—a pattern indicative of moderate to weak carcinogenicity. The authors concluded that if MIC was proven to be an animal carcinogen, its potency was likely to be relatively low.

A population-based cancer registry, categorized by exposure area, was established in Bhopal in 1986.[22] Dikshit[59] analyzed the incidence of cancer in males for the period between 1987 and 1992. Exposure status was based on residence in gas-affected vs. gas-unaffected areas of Bhopal. Assuming a 6-yr induction period for gas-related carcinogenesis, the authors considered the cases diagnosed from 1987 to 1990 to be the reference group. Relative risks (RRs) were 1.4, 1.3, and 0.7 (all nonsignificant) for lung, oropharynx, and oral cavity cancers, respectively, for 1992, compared with the years 1987–1990 and gas-unaffected regions combined. Using a case-control design, cancer cases from 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 for oropharyngeal cancer (RR = 1.5; 95% confidence interval [CI] = 1.1, 2.2), after adjustment was made for age and tobacco use. No dose–response relationships were evident in the geographic distribution of cases. The authors attributed nonconclusive findings to the brief study period, and they suggested that excess risk, if any, would be manifested only after 15–20 yr.

Immunotoxicity. Following the MIC gas leak in Bhopal, health authorities were concerned that the exposed population might experience increased rates of infections. Possible reasons for this increased susceptibility included depressed immune function from chemical effects, psychological and physical stress, disruption of normal life (particularly during the 2 mass migrations out of Bhopal), and pulmonary injury.

Immune function was studied in exposed subjects from the ITRC sample 2.5 mo after exposure.[56] Humoral and cellular immunity were assessed. No difference in mean immunoglobulin levels was found, compared with controls. The T-cell population (28%) was less than half that normally found in the population in India (65%). A significant depression of phagocytic activity of lymphocytes was found, compared with controls.

Concurrent with the human studies, immunotoxicological evaluation of rats exposed to MIC showed several positive results.[75] Delayed-type hypersensitivity and depressed alveolar and peritoneal macrophage function, with increased susceptibility to *Escherichia coli* endotoxin, led researchers to conclude that the gas had a suppressive effect on cell-mediated immunity. Karol et al.[57] found MIC-specific antibodies in guinea pigs injected with MIC, as well as in 12 of 144 human survivors. This result demonstrated that MIC was capable of eliciting an immunogenic response. The antibody titers in the human studies were low and transient, suggesting a weak response. Limitations of human studies included relatively small sample sizes, choice of control groups, and unclear exposure ascertainment. These limitations made it difficult for investigators to arrive at definitive conclusions regarding immunotoxicity from MIC exposure for the gas victims.

Psychological and neurobehavioral toxicity. Srinivasamurthy and Isaac[76] noted that the psychological problems of Bhopal survivors fell into 4 major categories: (1) *posttraumatic stress disorders*, which occurred as a result of the tremendous emotional stress of the disaster—symptoms were anxiety, emotional recall of the event, restlessness, sleep disturbances, generalized weakness, and fatigue; (2) *pathological grief reactions*, characterized by intense grief, depression, suicidal ideation, and feelings of guilt arising from a sense of failure to protect one's family; (3) *emotional reactions to physical problems*—victims with ocular, lung, and other problems developed feelings of depression, hostility, insecurity, and helplessness; and (4) *exacerbation of preexisting psychiatric problems*.

In a psychiatric outpatient service program established specifically for gas victims, Sethi et al.[41] detected 208 persons who suffered from mental problems. Of these individuals, 45% suffered from neuroses, 35% from anxiety states, and 9% from exacerbation of preexisting adjustment reactions.

Neurobehavioral tests were conducted on 350 exposed subjects, 2.5 mo after the accident occurred.[37] Auditory and visual memory, attention response speed, and vigilance were significantly impaired in this group, compared with controls. Manual dexterity did not appear affected.

Fifty-two MIC victims were subjected to detailed medical examination and clinical psychometric testing 1 yr after the accident occurred.[58] Mental status, cranial nerves, and motor and sensory systems were examined. Clinical psychometry included the Benton visual retention test, Wechsler memory scale, and standard progressive matrices (SPMs). Exposure level was based on the distance of residence (< 0.5 km) from the plant, history of fainting, respiratory signs, and hospitalization. The presence of 1, 2, or 3 of these factors indicated mild, moderate, or severe exposure, respectively. Normal values for psychometric parameters were obtained from 31 age- and education-matched healthy control

subjects who resided in a city located 500 km from Bhopal who had no known history of chemical exposure and were from similar ethnic backgrounds as the study subjects. Severely affected victims had significantly impaired SPM, associate learning, motor speed, and precision tests. In the moderately affected victims, associate learning, motor speed, and precision were significantly impaired. Some degree of a dose–response effect was noted in some tests, when compared with controls and within the exposed groups. The authors concluded that the persistence of cognitive impairment 1 yr after the accident suggested significant MIC neurotoxicity.

Neuromuscular toxicity. Neuromuscular symptoms in Bhopal survivors have persisted subsequent to the gas leak.[28] These symptoms consist mainly of tingling, numbness, a sensation of pins and needles in the extremities, and muscle aches. Anderson et al.[77] evaluated the effects of MIC on rat muscle cells in culture. 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.

Epidemiologic Considerations

During the early period following the Bhopal accident, clinical treatment of the injured took priority over the planning and conduct of epidemiological studies. This was particularly true given the limited health-care resources available for many of those affected and the general lack of experience in dealing with a disaster of this nature. The Bhopal Gas Disaster Research Centre, a branch of the ICMR, initiated approximately 10 different epidemiological studies to monitor long-term trends in morbidity and mortality. Results from these studies are currently being awaited. A few cross-sectional studies (Table 4) were conducted during the early (i.e., 60 mo) recovery period for various systemic health endpoints. These studies contain a number of defects in study design, resulting in bias (selection, recall, small sample size) and consequent difficulty in clearly establishing causal relationships. In 1 follow-up study performed 3 mo after the accident, exposed persons were contacted and were asked to voluntarily agree to examinations.[37] This method of subject selection might have introduced bias, depending on whether more severely affected persons did or did not present themselves for examination. Studies based on disease status, rather than on exposure, might also be biased toward the finding of greater pathology,[43] perhaps the result of preexisting disease or from the fact that they were examined as a series of cases.[34]

In a population-based study conducted through the cancer registry, Dikshit and Kanhere[59] found nonsignificant increases in the rates for lung and oropharyngeal cancer. These authors recognized that the study and latency period might have been too brief, inasmuch as only a few cancers could be studied. With exposure assignment based solely on location of residence, some degree of exposure misclassification was expected because it was not known whether the individual was actually exposed. Address and coding errors would have increased this type of misclassification. Socioeconomic differences between the exposed and unexposed areas might also have affected the incidence of cancer in the 2 groups.

Marked differences in respiratory, abdominal, neurological, and ophthalmic morbidity were found in a survey of exposed and unexposed children in Bhopal.[38] In that study, however, no information on population demographics, method of subject selection, or examination techniques was presented. The finding of almost no signs/symptoms among unexposed children leads one to consider that the investigators might not have been blinded to the exposure status, thus leading to differences in examination of the exposed and unexposed groups.

Mehta et al.[8] critically reviewed several studies on humans during the early recovery period and compared these findings with the results of animal toxicology studies. They stated that, in the human studies, "bias was pervasive and there was insufficient information to allow careful operational definition of crucial matters such as criteria for inclusion and exclusion of controls, and effects of independent and dependent variables on study outcome." Even though observational studies do not meet scientific criteria for causality, some of the studies' conclusions are supported by results from experimental studies.

Although it is difficult for investigators to infer causal associations in the absence of exposure–response data, we believe that the early studies provide valuable descriptive information on the spectrum of acute effects experienced by the population. This information could have been used for the planning of medical treatment, for rehabilitation of the victims, and for providing some expectation of what chronic effects might occur. The early studies were also conducted in an atmosphere in which public and political pressure might have driven the need to perform epidemiological investigations, but at the same time might have imposed time and resource constraints that negatively affected the careful design and conduct of the studies.[78] Nevertheless, both early and long-term surveys on the disaster have shown the prevalence of all self-reported symptoms to be greater than expected—even for a highly exposed population. This over-reporting of symptoms might have resulted, in part, from the victims' psychological strain, fear, and distrust of authorities—a finding that has been noted in other environmental investigations.[79]

Relatively crude methods (based on mortality rates or distance of residence from the factory, for example) have been used to define community exposures. Koplan et al.[80] indicated that epidemiologic studies following disasters should accurately estimate exposure to enable correct dose–response relationship modeling. These data are useful for (a) identifying exposed and ill persons, (b) determining long-term effects, and (c) linking exposure and effects for use in litigation and to determine compensation. For epidemiological studies, Bertazzi[81] has recommended selection of a cohort—rather than use of a population registry—to avoid 2 major biases: (1) dilution of

exposure prevalence, and (2) selective migration of people from the disaster area. There is anecdotal evidence, however, that some of the exposed population that left Bhopal immediately after the accident might not have returned, thus resulting in some dilution of exposure prevalence in the selected cohort.

Dhara and Kriebel[82] outlined an epidemiological method that provides a valid estimate of respiratory impairment and exposure–response—without including the total exposed population in Bhopal. In the IMCB investigation this approach was used in an attempt to address the issues of study design and analysis by stratification of the study population, random selection of subjects, blinding of investigators to exposure status, and use of personal exposure measures to increase the accuracy of exposure estimation. In the 1st 2 papers[23,48] published by the IMCB, distance of residence from the Union Carbide factory was significantly, inversely associated with respiratory and other symptoms, as was pulmonary function. In the 3rd study, Dhara et al.[21] collected data on self-reported activity patterns of the survivors, and it was determined that most individuals left home after encountering the gas cloud. About half the subjects in the sample either ran, walked, or left home by transport, and slightly less than a 1/4 remained at home. The authors developed exposure indices, and they were able to use the self-reported data to reconstruct individual pulmonary dose. These indices incorporated surrogates of exposure—such as duration, activity, and distance of residence—either individually or in various combinations. Exposure–response relationships were examined, and it was determined whether these indices were useful in predicting health outcomes. The results showed that an index incorporating distance of residence, duration, and activity was associated with both respiratory and nonrespiratory symptoms, as well as with pulmonary function. The authors concluded that, despite the time elapsed since the accident and the potential for recall bias, it might be possible to estimate individual exposure in the survivors with some degree of accuracy, perhaps because of the dramatic nature of the incident.

For the Bhopal gas victims, further epidemiological studies are needed for the determination of morbidity prevalence in a population stratified by estimated pulmonary dose. Such an approach would allow scientifically valid and detailed studies of different health endpoints to be performed on relatively small sample sizes.[83] Exposure-based stratified random sampling would also reduce bias that results from self-selection and exposure misclassification, and it would enable dose–response and interaction relationships to be understood.

Fifteen years after the accident a survey was conducted to determine whether storage of hazardous waste in the plant site had affected the surrounding environment.[84] Results showed severe contamination in onsite soil with heavy metals such as mercury (20,000–6 million times higher than expected), chromium, copper, nickel, lead, as well as persistent organochlorine compounds. Drinking water samples from the local wells showed elevated concentrations of volatile organic compounds (chloroform, carbon tetrachloride), as well as chlorobenzenes.

Conclusions

Clinical and toxicological studies have shown that MIC is a potent toxin. Chronic inflammation of the eye and respiratory tract account for a major portion of the morbidity resulting from exposure. The potential definitely exists for these damaged organs to subsequently be more susceptible to other environmental insults, such as infections, irritants, and allergens. For example, a person with airway damage may be more prone to infections or may respond adversely to smoke and dust. Pulmonary function limitation may preclude survivors from working at jobs that require moderate or strenuous activity. Progressive pulmonary fibrosis and restrictive lung disease appear to be a major cause for concern among gas-exposed individuals. Given the completely unexpected and devastating nature of the disaster, and the resultant stress, we expect that a number of survivors will suffer from posttraumatic stress disorders for many years. Establishment of a specialized medical center that can address health problems resulting from the gas leak would permit coordination of both investigation and treatment for the injured.

Steps to eliminate ongoing exposure of surrounding communities to hazardous waste from the site should include containment and treatment of contaminated waste and soil, remediation of aquifers, and provision of clean drinking water.

For a disaster of this magnitude, there is a relative paucity of knowledge gleaned from epidemiological and clinical investigation. Some of the medical studies conducted on the survivors were deficient in design, and use of the resulting information with confidence is difficult. Long-term monitoring of the affected community must be conducted for at least the next several decades. Appropriate methods of investigation would include the selection of properly designed cohorts, use of case-control studies for rare conditions, characterization of personal exposure, and accident analysis for the determination of possible components of the gas cloud and the ambient air concentrations of MIC. Formal studies of ocular, respiratory, reproductive, immunological, genetic, and psychological health must be continued if we are to understand the extent and severity of long-term effects associated with this disaster.

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