Personal Exposure and Long-Term Health Effects in Survivors of the Union Carbide Disaster at Bhopal

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Nine years after the Bhopal methyl isocyanate disaster, we examined the effects of exposures among a cross-section of current residents and a subset of those with persistent symptoms. We estimated individual exposures by developing exposure indices based on activity, exposure duration, and distance of residence from the plant. Most people left home after the gas leak by walking and running. About 60% used some form of protection (wet cloth on face, splashing water). Mean and median values of the exposure indices showed a declining trend with increasing distance from the plant. For those subjects reporting any versus no exposure, prevalence ratios were elevated for most respiratory and nonrespiratory symptoms. We examined exposure–response relationships using exposure indices to determine which were associated with health outcomes. The index total exposure weighted for distance was associated with most respiratory symptoms, one measure of pulmonary function in the cross-sectional sample [mid-expiratory flow ($FEF_{25–75}$, $p = 0.02$], and two measures of pulmonary function in the hospitalized subset [forced expiratory volume (FEV_1, $p = 0.02$; $FEF_{25–75}$, $p = 0.08$). Indices that correlated with FEV_1 and forced vital capacity in the hospitalized subset did not correlate with the cross-sectional sample, and most indices (except total exposure) that correlated with the hospitalized subset did not correlate with the cross-sectional sample. Incorporation of distance into every index increased the number of symptoms associated; an improvement was also noted in the strength of the association for respiratory symptoms, but not for pulmonary function. The sum of duration ($p = 0.02$) and total exposure ($p = 0.03$) indices independently demonstrated stronger associations with percent predicted $FEF_{25–75}$ than the distance variable ($p = 0.04$). The results show that total exposure weighted for distance has met the criteria for a successful index by being associated with most respiratory symptoms as well as $FEF_{25–75}$, features of obstructive airways disease. *Key words*: Bhopal, environmental disaster, lung disease, methyl isocyanate, pulmonary function, Union Carbide. *Environ Health Perspect* 110:487–500 (2002). [Online 2 April 2002]
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The methyl isocyanate (MIC) gas leak from the Union Carbide plant at Bhopal, India, in 1984 was the worst industrial disaster in history. The Department of Relief and Rehabilitation, Government of Madhya Pradesh, has stated that of the more than 200,000 persons exposed, more than 6,000 deaths have resulted, and about 50,000 persons are estimated to be suffering from long-term health effects (*1*).

Chronic inflammatory damage to the eyes and lungs appears to be the main cause of morbidity (*2*). Reproductive health problems in the form of increased spontaneous abortions and psychological problems have been reported (*3,4*). The presence of multisystem symptoms in survivors has raised questions about the nature of MIC toxicity (*5*). Animal studies using inhaled, radiolabeled MIC have shown that MIC is capable of crossing the lung membranes and being distributed to many organs of the body (*6*). Anderson et al. (*7*) studied rat muscle cells in culture and showed that MIC prevents muscle fiber formation and is toxic to fibroblasts and myoblasts. Studies on lung function show both obstructive and restrictive forms of impairment.

It has been estimated that about 27 tons of MIC escaped from the plant around midnight on 2–3 December 1984, in a period of 1–2 hr (*8*). Prevailing atmospheric conditions such as inversion and a low wind speed prevented dispersion of the gas (*8*). Eyewitnesses reported that a cloud of gas enveloped the area and moved slowly through the residential neighborhood.

Due to lack of planning, air monitoring for MIC was not possible, nor was it subsequently attempted. The Central Water and Air Pollution Control Board estimated MIC concentration to be about 27 ppm, a figure which is about 1,400 times that of the U.S. Occupational Safety and Health Administration workplace standard of 0.02 ppm over an 8-hr work day (*9,10*). This estimation was based on the quantity of chemical released, assuming equal concentration over the whole area of spread (40 km^2). Variability of concentration with distance is not accounted for.

Modeling of exposure concentrations downwind from the Union Carbide plant has been attempted by Singh and Ghosh (*11*). Using an analytic dispersion model, they simulated ground-level concentrations of MIC at various distances from the plant. These concentrations have correlated fairly well with mortality distribution, but they do not provide any estimates of individual human exposure. Limitations of the model arise from the fact that wind speeds used in the model were obtained from Bhopal airport (located 7 km due west of the plant beyond a hillock), rather than from the microenvironment in the areas of gas spread, and from an assumption of smooth terrain. The exposed area is surrounded both by smooth surfaces, such as lakes, and rolling terrain, as well as hillocks, which can cause swift changes in wind speed. The undulation in the topography as well as variation in wind speed may have resulted in a nonuniform distribution of the gas. The above assumptions of the model may result in errors in exposure concentrations. These concentrations have also not been verified, either by monitoring following a microscale recreation of the accident or tracer gas release. Due to the above limitations, it was decided not to use results from this model for epidemiologic purposes.

Factors that probably contributed to variability in human exposure on the night of the leak include the duration of an individual's

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exposure, activity during exposure, and the amount of protection their housing provided. Reconstruction of individual exposure based on these criteria has not been attempted. In the actual incident, activity during exposure to the gas was certainly a major dose-regulating factor. The acute irritant effects of MIC produced anxiety, disorientation, and panic, and, as a result, people ran out of their homes. Increased ventilatory rates from running may well have increased the dose of the chemical delivered to the respiratory system and other target organs.

The eye and respiratory tract were the main organs exposed to the gas. MIC was also probably dissolved in saliva and swallowed, resulting in exposure of the gastrointestinal tract. Skin exposure certainly took place but was clinically less significant than the respiratory tract.

Existing Health Studies

There is a paucity of morbidity and mortality data on the effects of MIC in the late recovery stage. Most followup studies that have been published on the victims relate to the first 6 months after the accident (i.e., the early recovery period).

Early cross-sectional studies done on the gas victims have used relatively crude methods of defining community exposure. Within a few days after the accident, Andersson et al. (*12*) carried out a survey of acute effects on eight exposed and two nonexposed household clusters in Bhopal. Exposure zones were marked out based on reports of human and animal deaths and on symptoms and perceptions of the presence of the gas. No information is available on how these reports were integrated to delineate the exposure zone. The ocular effects surveyed by Andersson et al. included photophobia, burning and watering sensations, red eyes, superficial interpalpebral erosion, Bitot spot, corneal opacity, pterygium discharge, and fundal changes. Other acute effects included nausea, vomiting, shortness of breath, chest pain, unconsciousness, dizziness, choking, twitching, headache, and convulsions. Though Andersson et al.'s results showed a marked difference in effects between exposed and nonexposed areas, a positive association with mortality alone was observed only for some effects (cough, diarrhea, fundal changes) but not others (shortness of breath, eyes burning).

Four months after the gas leak, the Medico Friend Circle carried out a cross-sectional study of a seriously affected slum near the Union Carbide plant using a less affected slum 10 km away as the control area (*13*). Symptoms, physical examination, and pulmonary function [forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC)] were the outcome parameters. Significant differences were found between the two areas in most symptoms and pulmonary function. Gupta et al. (*14*) analyzed acute symptoms according to distance from the factory (< 2, 2–4, > 4 km) and found an inverse relationship between the prevalence of acute symptoms and distance.

In 1985, the Bhopal Gas Disaster Research Centre, a field office established by the Indian Council for Medical Research (ICMR), had registered a cohort of 80,021 from the population around the plant and classified the subjects as severe, moderate, and mildly exposed based on mortality parameters (*15*). An unexposed population in Bhopal was used to select the control group of 15,931 individuals. The latter group was chosen on the basis of being similar in socioeconomic status, but no further specific demographic information is available to assess comparability of the two groups for symptom prevalence information. Each household registered was given a number (subsequently referred to as the ICMR number). The Tata Institute of Social Sciences (TISS), Bombay, also conducted a socioeconomic survey in 1985 on similar lines and registered the households with a TISS number. Although no information has ever been released from this survey, the TISS household numbers were available for use in this study.

The International Medical Commission on Bhopal

In 1993, the International Medical Commission on Bhopal (IMCB), comprising 15 professionals from 12 countries, was formed at the request of several gas victims' organizations. The purpose of the IMCB was to contribute to the relief of the victims of the accident and to suggest ways in which such catastrophic accidents could be prevented in the future or their effects mitigated (*16*). The commissioners divided their work into eight areas: epidemiology, clinical, family life, medical care, claims, drug therapies, accident analysis, and review of published literature. The epidemiology component of this effort represents the first long-term, population-based investigation into the disaster.

The data collection was done by the epidemiologic/clinical groups over 7 days in January 1994. To evaluate exposure response, the information was analyzed and presented in three phases. In the first phase, results from the symptom prevalence survey were assessed using distance as a surrogate for exposure. For this phase, Acquilla et al. (*17*) reported demographic information and respiratory, neurologic, and other systemic health effects attributable to gas exposure. In the second phase, respiratory morbidity, including symptoms and lung function measurement, were assessed according to distance. Results from the second phase were reported by Cullinan et al. (*18*), who showed an excess of respiratory symptoms and a reduction in mean lung function attributable to gas exposure.

Outlining the focus of postdisaster epidemiologic studies, Koplan et al. (*19*) stated that exposure needed to be accurately estimated and correlated with health effects to understand dose response and the interaction of other risk factors with exposure in producing health effects. Among other purposes, these data are needed to identify exposed and ill persons to provide long-term care and monitoring, to determine long-term effects, and to link exposure and effects for litigation and compensation.

In the first two phases of the IMCB study, a direct gradient in effects was seen, with morbidity decreasing with increasing distance of residence (at the time of the leak) from the plant. However, distance of residence was assigned ecologically without any consideration of individual differences in exposure.

The third phase, therefore, was devoted to the development of individual dose estimation using exposure time, activity, and location, as well as distance; these estimates were assessed with subjective symptom reporting as well as objective lung function measures. These estimates were then compared to the findings from the distance surrogate to determine whether their association is better than that of distance alone.

Study Purpose

The present study represents the third component of the IMCB epidemiologic/clinical investigation, which is an attempt to estimate individual exposure and explore associations between personal exposure and health effects. The study examines the role of various factors such as exposure duration, activity during exposure, and distance and type of residence in contributing to respiratory and systemic morbidity of the victims. The specific objectives were to *a*) estimate the prevalence of respiratory morbidity 9 years after the gas leak; *b*) develop individual exposure indices based on activity, exposure duration, type, and distance of residence from the plant at the time of the leak; and *c*) study exposure–response relationships using the individual exposure indices and outcomes of pulmonary function, respiratory symptoms, and a range of nonrespiratory symptoms.

Methods

Data Collection

Pilot testing of a standard questionnaire was conducted among 30 randomly selected

residents of both exposed and nonexposed areas of the city. These interviewees were not included in the larger study.

Population study. The victims groups informed the study team that the ICMR surveys indicated that the exposed population, for the most part, still resided in the homes they lived in at the time of exposure in December 1984. Therefore, we decided that sampling the current homes was likely to identify exposed persons correctly as related to their estimated exposures (distance from the gas leak). On the basis of this information, we used current residence in January 1994 as the basis for sampling households to participate in the survey. To verify that households selected were occupied by families who lived in the same homes in 1984, we verified each family's location in December 1984 by the presence of any one of four documents: ICMR number, TISS number, evidence documenting that the current resident had owned the plot in 1984, or a ration card documenting that the residence of the individual was the same as in 1984. A total of 1,618 residents were present in the sampled households (49% female, mean age 34.3 years).

As had been done previously, the population was stratified by distance of current residence from the Union Carbide plant. We selected four exposure zones, each 2 km in length, along the line of the gas dispersion from the plant. The direction of gas dispersion was determined from personal accounts of organizers from the victim groups. These persons provided information on the area of spread based on visual sighting of the gas cloud, mortality, and evidence of tree damage. This information coincided with the ICMR affected areas as well as the area delineated in the map developed for formulation of the gas dispersion model.

Households were sampled, by random number, in two wards lying on either side of the same line within each zone. (A ward is a geographic area in the city delineated for electoral purposes.) In each ward, the community consisted of several rows of contiguous, semipermanent or permanent houses. These rows had 10–12 houses per row and were not laid out in any particular geometric pattern. Upon arriving in a ward, the study team arbitrarily picked a nearby household in the first row for the first interview and then selected subsequent households in the row based on a list of previously generated random numbers (e.g., if the random number list was 2, 5, 8, 10, then the second, fifth, eighth, and tenth households were selected after the first household). On completion of the first row, the next row was then chosen for household selection. (Due to time and logistical constraints, the team was unable to obtain a complete list of households in each ward for purposes of randomization.) In the same way, households that were believed not to have been in the exposed areas, but with similar socioeconomic characteristics to the exposed areas, were selected, based on information from the victim group organizers. One of these areas was chosen so as to be well away from even low-level exposure. During interviews, it became apparent that at least part of the nonexposed area may in fact have been exposed (see below). It is unknown whether these areas were within the boundaries of the ICMR control area.

Verification of exposure of the household was done before the interview. The interviewer explained to the household members that the interviews were being conducted on behalf of the IMCB to determine the effects of gas exposure on the population and that the information gathered was unrelated in any way to compensation. If anyone in the household had been interviewed or examined by a medical team in the last 28 days, the interview was stopped (a rare occurrence). If the interviewers were asked why all family members were not being interviewed/tested, it was explained to them that only some of the interviewees would be selected for medical examination, and that the latter sample may comprise both sick and healthy persons. If necessary, the concept of sampling was explained to them as similar to the examination of a few rice grains to determine if the whole pot of rice had cooked. Neither the interviewers nor the participants were aware of the specific hypotheses of the study.

From each selected household, random numbers were used to identify an individual from the current resident adults between 18 and 60 years of age; these individuals were invited to undergo a face-to-face interview. The lower age limit of 18 was selected so that participants who were 9 years old at the time of the disaster would have a reasonable recall of events, as well as be able to participate in the clinical study. When the selected subject was not available for interview, another was chosen in the same way. No available randomly selected subject declined to be interviewed.

The modified, final version of the questionnaire was administered in Hindi by college students trained as interviewers. It enquired into the level of gas exposure, if any, in 1984, health status since the leak, and a variety of potentially confounding factors including socioeconomic variables such as literacy, income, and employment.

Literacy was defined as the completion of at least primary education up to class 5. Low income was defined as men with no paid work or a monthly wage of less than 500 rupees ($11). Most women did not do paid work.

Case-series group. In addition to the subjects selected for the population survey, there was interest in examining subjects who had been hospitalized for problems related to the gas leak. Case files of 100 victims who were admitted to the MIC Ward at the local hospital were made available to the investigators. These victims had been admitted in the months and years after the disaster on the basis of being severely affected by the exposure. A random sample of 22 subjects was selected from this group and were administered the questionnaire and pulmonary function testing. Mean age of this group (42 years) was slightly higher than that of the population sample. There were 15 males and 7 females, whose average distance of residence was 0.6 km from the Union Carbide plant. Only 3 subjects were current smokers. The population and case-series groups were compared to see if the types and relative distribution of symptoms were similar.

Clinical Investigations

Every fourth subject surveyed was invited to undergo a series of clinical investigations at the local clinic; transport to the clinic and refreshments (but no other incentives) were provided by the study team. The following tests were conducted by trained physicians who were not informed of the exposure status of the subjects.

Pulmonary function tests. Spirometry was carried out using a rolling-seal spirometer [Ohio 822; U.S. National Institute of Occupational Safety and Health (NIOSH), Morgantown, WV, USA]. After being instructed, the subjects carried out three or more forced expiratory maneuvers, at least two of which were reproducible according to the American Thoracic Society criteria (*20*). We measured of FEV_1, FVC, and mid-expiratory flow ($FEF_{25–75}$), corrected for body temperature and ambient pressure saturated with water. The spirometer was calibrated and leak checks were performed at the beginning and end of each clinical session.

Spirometry values were expressed as proportions of expected values, which were derived from regression equations provided by Udwadia et al. (*21*). The data for the expected values came from a study on 760 healthy, nonsmoking subjects (15–65 years old, 472 male, 288 female) from western India.

Exposure

Because ambient air concentrations were not available, we used distance of residence from the gas cloud source as a surrogate for exposure. Many subjects did leave their homes after the gas leak, and residence was only one of several microenvironments they experienced

during the exposure period. We believed, however, that construction of a composite distance of microenvironments for each individual would be very difficult, given the chaotic behavior of the fleeing population and the potential for inadequate recall of information on each microenvironment. To understand individual dose, therefore, we chose to attempt construction of a composite index based on distance of residence, activity, and duration of exposure.

Distance of residence was defined according to the electoral ward in which the subject had been living in 1984, as recorded during the interview. Using the distance of the approximate center of each ward from the Union Carbide plant, the electoral wards were categorized into four exposed and two comparison groups of decreasing exposure to the gas leak.

Exposure level. Exposure level was defined by electoral wards in 2-km distance increments (0–2, 2–4, 4–6, 6–8 km) along a southward gas dispersion line from the Union Carbide plant, using the center point of each electoral ward to determine the distance category. Electoral wards are approximately 0.25 × 0.5 km and lie on either side of the dispersion line.

Comparison groups. We used two control groups. One-half of control group C_1 resided 7.2 km west (range 6–8.3 km) and the other half 8.8 km southeast (range 7.2–10.4 km) of the factory. Control group C_2 resided 24 km south of the factory. Analysis of exposure assessments from questionnaire and its interpretation were done without knowledge of the health outcomes.

To assess the validity of this exposure stratification, responses to the question, Were you exposed to the gas on the night of the gas leak?, were examined according to exposure groups. All those in groups < 6 km, and none in the unexposed group C_2, reported gas exposure in 1984. Nineteen (52%) of those in group > 6–8 km and 59 (73%) in group C_1 reported that they had been exposed. These findings were unexpected and highlighted the variability and uncertainty of gas dispersion in areas that were in the periphery of the cloud. Using a gas dispersion model only to delineate boundaries of the gas cloud and determine exposure status may have shown that these areas were unexposed. One advantage of the direct interviews of individual subjects was that apparent exposures were identified among those who otherwise were considered unexposed. Because there were fewer exposed persons in the groups > 6–8 km and C_1 as compared to the other groups, exposure index data from these two groups were consolidated as group > 6–10 km for the purpose of analysis.

Exposure questions. We asked the following questions about exposure:

1. Were you exposed to the gas on the night of the gas leak? (Yes/No)

2. What type of house did you live in at the time of the gas leak? (Makeshift/Permanent)

3. Where were you? (Inside/Outside)

3a. If inside, were the windows open/closed/no windows?

The response to windows open/closed was used to assign a penetration factor for the period the person was at home (see below).

4. Actions following gas leak:

What did you do when you were first exposed to the gas? (open-ended):

First physical activity? How long?

Second physical activity? How long?

Third physical activity? How long?

The respondent was asked to list up to three physical activities during exposure to the gas (lying, sitting, walking, running) and recall the duration of each activity in minutes or hours. If the respondent recalled three activities and the duration, the interviewer asked for two more activities. No one was able to recall more than three activities. The description of the open-ended answers for physical activity were reviewed and then categorized and coded for analysis. We considered the following responses as physical activities: sleeping/lying down/unconscious, staying home/doing nothing, sitting, walking, and running. For these responses, the sum of the duration periods over all activities was used as the sum of duration index. A few responses were subject to varying interpretation; these were left home/went away, protected, and left home by transport. As an example, a subject reporting protection may actually have been fleeing the area. Because the physical activity of these responses during exposure was unknown, they were classified as "other," and their duration of exposure was not included in the sum of duration index.

5. Altogether, how long were you exposed to the gas? (open-ended)

The respondent was asked to give a single estimate of total time exposed to the gas. The response to this question was used as the time exposed overall index. This open-ended response is an approximate overall time and differs from the response to Question 4, which is a summation of time spent in different activities.

Although the questionnaire does not explicitly state that the activity and duration questions (Questions 4 and 5) are for the exposure period only, this was implicit in the interview because the set of questions for the exposure period begins with "What were you doing at the time of the gas leak?" and ends with "At what time did the gas clear?" We personally sat through a number of interviews and determined that the subjects understood that these questions were for the exposure period only.

6. After the gas leak, did you protect yourself? (Yes/No)

6a. If yes, how did you try to protect yourself? (Protected face with cloth/Fully covered with sheet or blanket/Closed window or ventilator/Splashed water on face or body/Other)

The descriptions of the "other" answers were reviewed and then categorized and coded for analysis. More than one answer was permitted for method of protection. Multiple methods in an individual were included in the total number of methods used.

Analytical Strategy

Data quality assurance/quality control. For epidemiology data, questionnaires were reviewed and checked for completeness and accuracy. All data from the questionnaire were computerized, and copies of the data file were given to each of the investigators. A random subset of the initial coding from India was checked and found to be inaccurate due to data transfer errors. Hard copies of all questionnaires were sent to England and the data were reentered. A random subset of the English data entry was also checked by comparison with the hard copy and found to be accurate. Consultations were held between the investigators to check for internal consistency and to resolve mismatch of data between the epidemiology and pulmonary function data sets. Differences were resolved by comparison of ID and names with age and sex.

For pulmonary function data, field reports were generated in Bhopal city using the predicted normal values for nonwhite races (–15%) from the NIOSH computer and given to gas victims. The data were taken back to the United States, and predicted normals were calculated using Indian reference values. Fresh reports generated using the Indian values were sent to Bhopal for distribution to the tested subjects. We attempted to inform every subject of the revised evaluation of the pulmonary function tests. The study coordinators were asked to explain to the subjects the reasons that the reports using Indian prediction values were a better estimate of the relevance of the findings to the individual's health. This was particularly important if a change in impairment was reported.

In both data sets, discrete variables were checked to determine whether the response for that variable was a valid response or within the appropriate range.

Imputation

Exposure data. We encountered two types of exposure data problems: missing data (a value of 999 was assigned in the field when the variable was missing); and erroneous data (values of ≥ 900 min). For these types of data problems, imputation was considered better than exclusion to minimize problems associated with power in the relatively small sample size of groups in our study. This was particularly true of the spirometry sample, in which seven subjects had missing data.

Among all subjects administered the questionnaire in all exposure groups, data were missing or erroneous for the variables time exposed overall and sum of duration. Differences in the proportion of persons with missing or erroneous data between the exposure groups did not appear to be related to distance of residence. Therefore, any underestimation of exposure due to missing data, if present, was likely to be randomly distributed across the groups. Both variables were missing in four subjects.

The variables time exposed overall (response to Question 5) and sum of duration (the sum of the estimates provided in the answer to Question 4) are different ways to measure the same time interval (the period of exposure to the gas cloud as estimated by the subject). When one of these was present in a subject, it appeared appropriate to use that value to estimate the other missing variable for that subject. In subjects who reported neither exposure time, only an affirmative response to Question 6 (Did you protect yourself?) was considered confirmation of exposure. To avoid a possible overestimation of exposure, these subjects were assigned the minimum ventilatory rate and exposure time in their respective groups. A subject with a negative or missing response to Question 6 was considered unexposed.

For time exposed overall, 12 subjects had missing data, and 2 were coded as 999. For these subjects, the value of sum of duration for that subject was assigned. As an example, in one subject who was interviewed from the 0–2 km group, the value of time exposed overall was reported as 999 min. The subject, however, did respond correctly to Question 4, which provided estimated values of duration of activity that were added to provide a total of 62 min for sum of duration. Therefore, 62 min was also assigned to time exposed overall for that subject.

For sum of duration, 38 subjects had missing data, and 10 subjects reported ≥ 900 min. As an example, for one subject who was interviewed from the 0–2 km group, the value of sum of duration was missing. The subject, however, did respond correctly to Question 1, which provided an estimated value of 300 min for time exposed overall. Therefore 300 min was also assigned to sum of duration for that subject. Similarly, in group C_1, a value of 2,350 min for sum of duration was considered erroneous and was therefore replaced by the time exposed overall value of 480 min. Among the subsample who underwent spirometry, the values of time exposed overall were assigned to sum of duration for seven subjects.

For all subjects in whom the sum of duration was missing or erroneous and assigned as described above, we conservatively used the minimum ventilatory rate (sleeping, lying down) in deriving the total exposure index. (Because of the variation in activity in each group, we were less confident that the median/mode rate was the best choice.) However, for five subjects in group > 6–8 km who underwent spirometry (two subjects who said they were exposed but gave no exposure time and three subjects with missing exposure information), no assignment of ventilatory rate was made because the response to Question 6 (Did you protect yourself?) was also missing.

For the four subjects with both variables missing, the sum of duration was assigned as the minimum time reported in that group because an affirmative response was given to Question 6.

Development of the Exposure Index

The exposure questions on activity and protection method permitted assignment of a ventilation rate for each subject and a penetration rate for each dwelling. The combination of these inputs with duration of exposure and distance of residence permitted development of six exposure indices.

The ventilation rate was estimated based on the physical activity of the individual during each activity. The rates were derived using estimates provided in the International Commission for Radiological Protection norms for reference man and reference woman (*22*). Similar values are found in the U.S. Environmental Protection Agency's Exposure Factors Handbook (*23*). For sedentary activities (sleeping, sitting, unconsciousness, staying home), the minute volumes used were 7.4 and 4.5 L/min for males and females, respectively. The values were 29 and 16 for walking, and 43 and 25 for running for males and females, respectively.

Penetration factors pertain to estimating the outdoor/indoor concentration ratio of the gas cloud. The vapor pressure of MIC is 348 mm Hg at 68°F, and its molecular weight is 57.1. MIC reacts with water, oxidizers, acids, alkalis, and some metals. Because of the exothermic reaction in the MIC tank at Union Carbide, the escaping aerosol mixture contained predominantly MIC and a number of other substances in liquid and particulate form. It is difficult to estimate the vapor pressure of such a cloud, but anecdotal reports confirm that it did penetrate homes. In certain instances, victims reported opening cupboards a day or two later and smelling a pungent odor, which made them nauseous and dizzy. A fine powder was also noted on windowsills and floors.

To estimate penetration factors to assign to the dwellings where the subjects resided at the time of the gas leak, we used information from a model that was developed to study ozone in ambient air (*24*). This model estimated the outdoor/indoor penetration coefficient of ozone based on air exchange rates as well as chemical decay. Using air monitoring to measure ozone concentrations under various conditions, the coefficients were estimated for homes with windows open and closed. The vapor pressure of ozone is > 760 mm Hg at 68°F, and its molecular weight is 48. Ozone is reactive with all oxidizable materials. Similarities between MIC and ozone are molecular weight and reactivity with various materials. Although we would prefer a model that uses a material with a lower vapor pressure, none was available. In the absence of an alternative model for outdoor/indoor concentration ratio, we assumed penetration factors of MIC similar to ozone. We surveyed makeshift homes in the exposed areas and found that their construction afforded less protection from penetration of outdoor ambient pollution than the permanent homes. In the absence of data for makeshift homes, an increase (somewhat arbitrary) was made in the penetration factors over that estimated for permanent homes.

We used the following penetration factors: outside home = 1; inside makeshift home, windows open = 0.8, windows closed = 0.5; and inside permanent home, windows open = 0.65, windows closed = 0.23.

Proposed exposure indices. Because ambient exposure monitoring was not performed, the only air concentration estimates available are those from the analytic dispersion model (*11*). Because the wind speeds and topography used in this model did not represent the area around the Union Carbide plant and because the results were not scientifically validated, we decided that these estimates were not sufficiently accurate to use in this study.

We used the exposure variables time and distance alone and in combination as predictor variables to construct three different pairs of exposure indices (Table 1). We used distance

as a linear measurement. The variables used are as follows:

1. Time exposed overall (minutes) was reported as a single estimate of total time exposed (in response to the question, Altogether, how long were you exposed to the gas?).
2. The sum of duration (minutes) is the sum of the reported exposure periods during all physical activities: Σ (duration$_1$+ duration$_2$ + duration$_3$).

Time exposed overall and sum of duration may differ because the response to the former was a single answer, whereas the response to the latter was a summation of duration of multiple and separate physical activities. The correlation between these two indices was moderate ($r = 0.43$, $p = 0.0001$). No participant reported more than three physical activities.

3. Time exposed overall weighted for distance (minutes per kilometer) = overall time exposed × (1/distance).

The distance variable was examined as a linear unit as well as with mathematical correction factors (square-root, square, cube, etc.). The linear unit was used in the formula because it showed the most biologically plausible associations in subsequent analyses.

4. Sum of duration weighted for distance (minutes per kilometer) = sum of duration × (1/distance).

The above variables were also used in the development of a third exposure index, which adjusted time estimates by different factors for penetration and for different ventilation rates resulting from physical activity to the pair of indices in variable 2.

5. Total exposure (liters) = (duration$_1$ × ventilation rate × penetration factor) + (duration$_2$ × ventilation rate × penetration factor) + (duration$_3$ × ventilation rate × penetration factor).

Adding distance to this index will produce:

6. Total exposure weighted for distance (liters per kilometer) = Total exposure × (1/distance).

These derived exposure indices incorporating ventilation rates were designed to be the closest approximation to target-organ dose given the current available data.

Statistical Analysis

We performed descriptive analysis to characterize the distribution of data in the exposed and unexposed groups. This included the distribution of questionnaire responses for exposure measures, activity patterns, protection methods, derived exposure indices, and pulmonary function data. Univariate statistics were generated for the exposure indices and pulmonary function data.

We performed bivariate analysis to examine the relationship between two dichotomous variables (e.g., symptom of cough > 3 months and exposure yes/no). The null hypothesis was that exposure is unrelated to the symptom of cough > 3 months. If the proportions of persons reporting cough were unequal in the two groups, the statistical question to be answered was whether the samples may have come from a population in which the null hypothesis is true. To estimate the magnitude of the association, the prevalence ratio was calculated using the data in the sample comparing those exposed at all to those reporting no exposure.

Exposure indices and pulmonary function data. All the exposure indices mentioned above are in the form of continuous variables. This permitted examination of the spread and distribution of each index.

We used the exposure indices in a variety of ways to assess exposure response: we calculated the geometric mean of each exposure index and used a *t*-test to compare differences in those with and without respiratory symptoms. This process was repeated with mean distance in those with and without respiratory symptoms. Each exposure index was divided by the median into low and high levels. Mean pulmonary function was calculated for each level and examined for difference with the *t*-test.

We tested the null hypothesis that there is no relationship between exposure index and pulmonary function by using a simple linear regression model in the form $y = a + b \times$ (exposure index), where y is a measure of pulmonary function, a is a constant, the exposure coefficient b is a measure of association, and exposure index is one of the six different indices constructed. This process was repeated with distance alone as the exposure variable. An association between exposure index and pulmonary function would mean that the null hypothesis is rejected [i.e., the slope of the linear regression model (coefficient b) is not equal to 0 at the $\alpha = 0.10$ level of significance]. We used pulmonary function in an unexposed Indian population as a predictor of normal. Because this study was designed to explore associations between exposure and response, tests of difference with $p \leq 0.10$ were considered significant.

Criteria for a successful index. An effective exposure index should demonstrate associations with both respiratory symptoms as well as objective measurements of pulmonary function. To evaluate the ability of the exposure index to predict adverse health outcomes, we established the following criteria: *a*) the symptoms would include at least one respiratory symptom previously known to be associated with MIC toxicity (*18*), and *b*) the index should be associated with at least one parameter of pulmonary function, as tested by spirometry.

We chose the respiratory system for exploring associations with the indices because multiple animal and human studies have shown MIC toxicity to the lung (*3–6*). Persistent respiratory symptoms include cough, phlegm, shortness of breath, and wheeze, all of which may be present in obstructive airways disease; shortness of breath is also a feature of restrictive airways disease. Pulmonary function testing has demonstrated both obstructive (i.e., decline in FEV_1, $FEF_{25–75}$) and restrictive types of disorders (i.e., decline in FVC) in the gas victims.

The validity of the index would be enhanced by its association with symptoms and signs that are clinically meaningful, as described above (e.g., wheeze/shortness of breath with FEV_1, or shortness of breath with FVC). Its robustness would be demonstrated by simultaneous significant associations with both respiratory and nonrespiratory health outcomes. If an index that takes account of important sources of variability in inhaled dose (activity patterns, time indoors versus outdoors, etc.) is as effective at predicting health outcomes as a simpler measure such as distance, the former would be preferred because of its greater biologic plausibility.

Results

The demographic and socioeconomic characteristics of the interviewed subjects in each exposure group are listed in Table 2.

Four hundred fifty-two persons were interviewed; there were more females in the interviewed groups (exposed 61%, unexposed 44%) than in the total number of residents of the sampled households (n = 1,618, 49% female, mean age 34.3 years) recorded in the

Table 1. Exposure indices and description of the index.

Index (units)	Description
Time exposed overall (min)	Single estimate of total time each victim was exposed
Sum of duration (min)	Sum of duration of physical activity periods during exposure
Time exposed overall weighted for distance (min/km)	Time exposed overall × (1/distance)
Sum of duration weighted for distance (min/km	)Sum of duration of physical activity × (1/distance)
Total exposure (L)	Sum of (duration × vent rate) for physical activity periods
Total exposure weighted for distance (L/km)	Total exposure × (1/distance)

survey. This was due to the fact that women were more likely to be at home than men in the exposed areas, especially among interviewees nearer the Union Carbide plant. The overall data, however, were reasonably close to that of the total population of the sampled households. The 0–2 km group also had a higher proportion of ever smokers as compared to the next two strata, and the > 6–8 km group had lower literacy and income. There were fewer women who were literate and employed full-time than men. With the exception of literacy in the > 2–4 km group, our sampling found that literacy and income were somewhat lower overall in the exposed population as compared to group C_2. Four hundred and thirty-one subjects (91%) had remained in the ward since 1984. Of the remainder, most had moved to adjacent wards. This low rate of migration indicated that the decision to sample current residence to find exposed subjects was a valid one.

Seventy-four subjects underwent clinical assessment; there were no important differences in their age, sex distribution, and literacy from those of the larger surveyed population. The prevalence of ever smokers among examined subjects was lower (16%) than in the whole interviewed group (32%). Sixty-two (84%) of those clinically assessed reported that they had been directly exposed to the gas leak. Among those who were invited but did not attend testing (n = 38) mean age and sex distribution (37 years, 39% male) were similar, but literacy was higher (58%) and fewer persons were of low income (16%). There was also a greater proportion of nonparticipants in group C_2 as compared to the exposed areas. Any differences in the proportion of persons sampled in the exposed and unexposed groups was either due to chance or due to the fact that they lived at a greater distance and family/work responsibilities hampered their participation even though we provided transportation.

The self-reported data on activity patterns confirmed the anecdotal reports that most people left home after encountering the gas cloud. Mean activity time of the exposed survivors is shown in Figure 1. Over all groups, subjects were mostly initially at home and then began walking. About 27% of all subjects reported running an average of 2.5 hr. Other significant activities included leaving home by transport and using protection against the gas. About one-half of the subjects in our sample either ran, walked, or left home by transport. Slightly less than one-fourth stayed home.

More than 65% of all subjects reported using some form of protection against the gas (Figure 2). Use of a wet cloth to cover the face and splashing water on the face and body accounted for 80% of the methods used (Figure 3).

Univariate statistics were generated for each exposure index (Table 3). These included the arithmetic and geometric mean, standard deviation, median, and range of the values. The distributions of all exposure indices were approximately log-normal, as expected. We performed log transformation of the indices and used these data for analysis. For almost all exposure indices, we noted a consistently declining trend in the mean and median with increasing distance from the factory. The only exception was for total exposure, where the decline was slightly less consistent. This declining trend was confirmed by the presence of an inverse correlation of all indices with distance. The pulmonary function data were found to be approximately normally distributed.

We examined the total exposure index both with and without the penetration coefficient. In all the analyses, a similar pattern of association with health outcomes was found with and without the coefficients, although there was some weakening of the association when the coefficient was used. The results presented in this study are those with the penetration coefficients incorporated.

We used a prevalence ratio to estimate the magnitude of the association between reporting various current symptoms and reporting exposure or no exposure to the gas leak 10 years previously. Results for respiratory and nonrespiratory symptoms are shown in Tables 4 and 5. Among all reported respiratory symptoms, asthma had the highest ratios, followed by phlegm and cough (Table 4). Among mucus membrane symptoms, eye redness had the highest ratios, followed by nose pain and eye pain.

Among systemic symptoms, taste problems had the highest prevalence ratios, followed by loss of appetite and chest pain (Table 5). Among musculoskeletal symptoms, bone pain and muscle pain had the highest ratios, followed by joint pain. Among psychological symptoms, nightmares and anxiety had elevated prevalence ratios. Symptoms of illness pertaining to urinary and skin systems, which were considered unrelated to gas exposure, were ascertained to evaluate response bias. The results showed that urinary and skin symptoms were only slightly more prevalent in the exposed groups as compared to the unexposed.

Mean exposure indices, as well as distance of residence, were calculated for subjects with and without respiratory symptoms (Table 6). In subjects reporting symptoms, almost all exposure indices were higher and mean distance was lower. Significant differences were observed in total exposure for shortness of breath (level ground and hill) and in time exposed overall for cough ≥ 3 months and asthma. For almost all indices, the significance of the difference in the index increased when distance was incorporated. Distance as an independent variable was significantly lower for all subjects reporting

Table 2. Demographics of study population by zone as of 1994.

Subjects	Exposure group 0–2 km	> 2–4 km	> 4–6 km	> 6–8 km	C_1	C_2	All
Interviewed							
No.							
Total	97	75	72	52	81	(75)[a]	452
Unexposed	—	—	—	(33)	(22)	(75)	(130)
Mean age (years)							
Exposed	38	39	36	38	37	—	38
Unexposed	—	—	—	35	36	38	37
Percent male							
Exposed	32	44	36	50	44	—	39
Unexposed	—	—	—	52	41	61	56
Percent literate	34	65	44	21	41	57	45
Percent low income[b]	55	48	35	64	37	33	43
Percent ever smoked[b]	39	15	15	40	31	48	32
Clinical							
No.	21	13	18	8 (7)	9	(5)	74 (12)
Mean age	36	36	39	33	39	30	36
Percent male	43	38	28	63	22	80	41
Percent literate	29	62	33	13	22	100	38
Percent low income[b]	67	40	60	80	100	25	60
Percent ever smoked[b]	56	100	60	60	50	50	63

[a]Numbers in parentheses indicate unexposed subjects. [b]Males only.

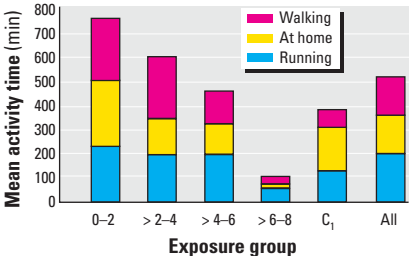

Figure 1. Mean activity time (min) by exposure group.

symptoms. No significant differences were found in any of the indices when stratified on smoking status. Logistic regression models of respiratory symptoms with exposure group, age, sex, and current smoking did not show any evidence of confounding (i.e., smoking did not contribute significantly to the variation in the log odds of having respiratory symptoms).

Mean exposure indices, as well as distance of residence, were also calculated for subjects with and without nonrespiratory symptoms (Table 7). The symptoms examined were fever in last 12 months, fatigue, chest pain, taste problems, and loss of appetite. In those subjects reporting symptoms, most mean indices were higher and mean distance was lower. Significant differences were seen in time exposed overall (with and without distance) for taste problems, and fever in last 12 months (with distance). Total exposure weighted for distance was significantly different only for chest pain at p = 0.06. When distance was examined independently, differences were found for fever in last 12 months, chest pain, and taste problems.

As a first step in studying exposure–pulmonary function relationships, we divided each exposure index by the median into low and high levels. We then calculated mean pulmonary function for each level. The null hypothesis that there is no relationship between exposure index and pulmonary function was evaluated with a test of the difference of mean pulmonary function between these two exposure groups (Table 8). For all indices, except time exposed overall, mean pulmonary function was higher in the lower level of the index, although these differences were not large and could have been due to chance. The largest difference in pulmonary function between low and high exposure groups was observed for the $FEF_{25–75}$. The nonsignificant differences in the mean percent predicted FEF_{25-75} between the higher and lower halves of the distributions of total exposure and total exposure weighted for distance were among the largest: a 17% difference (p-values ~ 0.14). No significant differences were found in mean pulmonary function between those subjects who lived < 4 km from the plant and those who lived > 4 km away. A similar finding was obtained for those who did and did not smoke, perhaps due to the small number of smokers (n = 12) in our sample.

Results of the regression of exposure indices against pulmonary function are shown in Tables 9, 10, and 11. In the model $y = a + b \times$ (exposure index), the coefficient b is the magnitude of the decrease in pulmonary function for one unit increase in the exposure index. As in the categorical analysis of Table 9, the exposure indices are most strongly associated with the pulmonary function parameter $FEF_{25–75}$. Other than the two indices based on reported time exposed, all other indices showed p-values for the slope that were ≤ 0.04. Coefficients for almost all pulmonary function measures were negative, indicating that pulmonary function decreased with increase in the exposure index. The data were adjusted for smoking by including current smoking in the regression model. The results showed that smoking did not have an

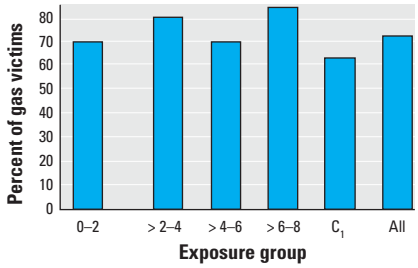

Figure 2. Percentage of gas victims using any protection by exposure group.

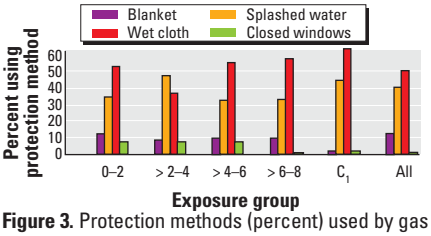

Figure 3. Protection methods (percent) used by gas victims.

Table 3. Descriptive statistics for exposure indices.

Exposure indices	0–2 km	2–4 km	4–6 km	6–10 km	All zones
Time exposed overall (min)					
Mean (GM)	257 (228)	212 (181)	229 (194)	168 (109)	219 (183)
Median	240	180	240	120	240
Range	30–720	60–480	20–720	15–600	15–720
No.	96	74	71	77	318
Time exposed overall weighted for distance (min/km)					
Mean (GM)	785 (622)	121 (103)	76 (64)	37 (24)	291 (112)
Median	660	103	80	27	100
Range	48–2,880	30–240	7–220	4–126	4–2,880
No.	96	74	71	77	318
Sum of duration (min)					
Mean (GM)	246 (182)	233 (166)	199 (145)	145 (95)	208 (144)
Median	240	240	180	120	180
Range	10–720	10–600	10–420	15–840	10–840
No.	96	73	67	77	313
Sum of duration weighted for distance (min/km)					
Mean (GM)	752 (507)	132 (95)	66 (48)	32 (21)	283 (95)
Median	600	134	60	27	100
Range	10–2,880	6–343	3–140	4–177	3–2,880
No.	96	73	67	77	313
Total exposure (L)					
Mean (GM)	2,193 (1,036)	1,504 (705)	2,114 (1,096)	1,393 (745)	1,838 (893)
Median	1,088	850	1,245	1,032	1,032
Range	12–14,909	23–5,271	24–7,740	36–6,192	12–14,909
No.	85	54	56	59	254
Total exposure weighted for distance (L/km)					
Mean (GM)	6,881 (2,975)	837 (402)	702 (361)	307 (163)	2,707 (623)
Median	3,523	486	415	229	663
Range	48–59,635	13–3,012	8–2,580	9–1,376	8–59,635
No.	85	54	56	59	254

GM, geometric mean.

Table 4. Prevalence ratio (PR) and 95% confidence interval (CI) for respiratory and mucous membrane symptoms in exposed versus unexposed subjects

Symptom	No. (exposed/not exposed)	PR	95% CI
Respiratory			
Shortness of breath (level ground)	359/88	1.7	1.5–1.9
Shortness of breath (hill)	384/63	1.5	1.4–1.7
Cough ≥ 3 months	226/115	1.8	1.4–2.3
Asthma	39/430	4.8	1.7–13.3
Wheeze	34/52	2.3	1.0–5.0
Phlegm	203/270	2.1	1.6–2.8
Mucous membrane			
Nose pain	52/423	2.6	1.3–5.3
Nose congestion	15/460	5.6	0.9–32.9
Eye redness	79/396	3.6	1.9–6.7
Eye pain	205/270	1.6	1.2–2.0

Because of missing data, the total numbers may not equal the total interviewed sample.

important effect on pulmonary function. Distance was also associated with $FEF_{25–75}$ but not with FEV_1 or FVC.

Results from the case-series group are shown in Table 12. The average distance of residence from the plant for this group was 0.6 km, although the mean exposure indices for the case-series group were slightly lower than those from subjects in the population survey who resided in the region closest to the plant (0–2 km). In this small sample, the three pulmonary function parameters behaved similarly. Only the exposure indices total exposure and total exposure weighted for distance were associated with the percentage of the predicted values of pulmonary function (p-values ≤ 0.08). The correlation of total exposure was better with FEV_1 and FVC than for $FEF_{25–75}$. Similarly, total exposure and distance was better correlated with FEV_1 than with $FEF_{25–75}$. The r^2 values for these models (0.20–0.29) were higher than those in the population sample. For those subjects with and without respiratory symptoms, mean total exposure weighted for distance (3,029 vs. 1,064, p = 0.02) was significantly different for cough ≥ 3 months and slightly weaker for time exposed overall and asthma (324 vs. 181, p = 0.07). Differences in correlation of the indices for pulmonary function between the population ($FEF_{25–75}$) and case-series (all three parameters) samples may perhaps be attributed, in part, to the greater exposure sustained by the latter sample. All exposure indices were similar to those in the population sample residing in > 0–4 km strata.

Table 5. Prevalence ratio (PR) and 95% confidence interval (CI) for nonrespiratory symptoms in exposed versus unexposed subjects.

Symptom	No. (exposed/not exposed)	PR	95% CI
Systemic			
Fever last 12 months	414/50	1.2	1.1–1.3
Fatigue	418/58	1.3	1.2–1.5
Chest pain	340/135	1.6	1.4–1.8
Problems in taste	171/305	3.4	2.4–4.9
Loss of appetite	138/338	1.8	1.3–2.6
Urinary			
Urine blood	12/464	4.4	0.6–27.9
Urine burn	134/318	1.3	1.2–1.5
Urinary frequency	54/422	1.0	0.6–1.8
Musculoskeletal			
Muscle pain	52/424	3.1	1.4–6.6
Joint pain	274/202	1.6	1.3–1.9
Bone pain	54/422	3.2	1.5–6.8
Limb pain	255/221	1.0	0.9–1.3
Skin			
Skin burn	22/453	1.8	0.6–5.1
Skin red spots	33/442	2.9	1.0–7.6
Brittle nails	40/436	2.3	1.0–5.1
Psychological			
Disaster memories	43/424	1.3	0.7–2.5
Anxiety	308/164	1.4	1.2–1.7
Poor concentration	185/283	1.2	0.9–1.6
Nightmare	162/306	1.7	1.2–2.3

Because of missing data, the total numbers may not equal the total interviewed sample.

Discussion

Findings from the early Bhopal studies conducted within a year of the accident confirm the general notion that morbidity decreases with increasing distance of residence from the plant. More accurate exposure–response relationships, however, cannot be modeled from the early studies. This was due to both the difficulty of performing epidemiologic studies during the acute phase as well as to inherent defects in study design. The early cross-sectional studies suffer from a number of defects in study design, resulting in bias

Table 6. Mean exposure index and mean distance in exposed subjects with and without respiratory symptoms.

	Time exposed overall (min)		Time exposed overall weighted for distance (min/km)		Sum of duration (min)		Sum of duration weighted for distance (min/km)		Total exposure (L)		Total exposure weighted for distance (L/km)		Distance (km)	
	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean
Cough ≥ 3 months														
Yes	183	191	183	167	183	153	181	124	162	992	161	880	161	1.8
No	135	153	135	87	134	134	70	66	57	788	57	399	57	2.8
Maybe	—	1.2	—	1.9	—	1.1	—	1.9	—	1.3	—	2.2	—	0.65
p-Value[a]	—	0.008	—	0.0004	—	0.23	—	0.0003	—	0.19	—	0.0005	—	0.0001
Asthma														
Yes	33	250	33	237	32	138	32	134	27	972	27	1,075	27	1.5
No	280	167	280	104	280	144	280	90	226	889	226	590	226	2.3
Ratio	—	1.5	—	2.3	—	0.9	—	1.5	—	1.1	—	1.8	—	0.63
p-Value	—	0.00	—	0.002	—	0.75	—	0.1	—	0.7	—	0.08	—	0.01
Phlegm														
Yes	163	181	163	134	161	147	161	110	128	916	128	735	128	1.9
No	153	166	153	93	151	138	150	79	125	888	124	544	124	2.5
Ratio	—	1.1	—	1.4	—	1.1	—	1.4	—	1.03	—	1.4	—	0.79
p-Value	—	0.29	—	0.002	—	0.55	—	0.05	—	0.93	—	0.25	—	0.01
Shortness of breath (level ground)														
Yes	272	171	272	118	270	145	270	102	218	1,480	217	672	217	2.1
No	29	179	29	73	28	121	28	49	22	897	22	230	22	2.9
Ratio	—	0.9	—	1.6	—	1.2	—	2.1	—	1.6	—	2.9	—	0.7
p-Value	—	0.74	—	0.04	—	0.39	—	0.01	—	0.05	—	0.005	—	0.002
Shortness of breath (hill)														
Yes	285	171	285	117	280	147	280	101	228	1,480	227	1,085	227	2.1
No	33	166	33	57	32	97	32	49	27	804	27	273	27	3.1
Ratio	—	1.03	—	2.0	—	1.5	—	2.0	—	1.8	—	3.9	—	0.67
p -Value	—	0.89	—	0.02	—	0.19	—	0.01	—	0.04	—	0.0009	—	0.002

Mean exposure index is geometric mean; mean distance is arithmetic mean. Because of missing data, the total numbers may not equal the total number reporting exposure time (n = 318).
[a]From t-test of difference in mean exposure index.

and consequent difficulty in clearly establishing causal relationships.

Dhara and Kriebel (*25*) outlined an epidemiologic method that would provide a valid estimate of respiratory impairment and exposure–response without including the total exposed population in Bhopal. Using this approach, the IMCB investigation attempted to address the above 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 accuracy of exposure estimation. In the first two papers published by the IMCB, distance of residence from the Union Carbide factory was shown to be significantly associated with respiratory and other symptoms as well as with pulmonary function measurements (*17,18*).

The study presented here had the objective of developing a more complete and biologically more relevant exposure index for examining the long-term effects of the MIC disaster. In this study exposure indices were developed by using details collected on self-reported exposure times and activity as measures of exposure and chronic symptoms and pulmonary function measurement as response variables. We chose health end points that were well documented in the published literature (*2,17,18*). For the respiratory system, symptom end points included shortness of breath, cough > 3 months, phlegm > 3 months, and wheeze. Obstructive airways disease as shown by spirometry was the predominant toxic effect on the lung. The IMCB respiratory study found a dose–response effect that was marked on $FEF_{25–75}$ and moderate with FEV_1 and FEV_1/FVC (*18*). Shortness of breath and wheeze in exposed subjects were also associated with reduction in the above measurements. Data from the current study showed elevated prevalence ratios for asthma, wheeze, phlegm, cough > 3 months, and shortness of breath. Among nonrespiratory symptoms, data from this study showed elevated prevalence ratios for taste problems, loss of appetite, chest pain, muscle/bone/joint pain, fever in last 12 months, and fatigue.

The evaluation of exposure response consisted of the development and testing of the exposure indices to determine which, if any, were associated with health outcomes. As previously stated, our criteria for a successful index were that it should be associated with at least one objective measurement of pulmonary function and one respiratory symptom. Several indices met these criteria (Table 13). Pulmonary symptoms were associated with all of the indices except sum of duration. Simple distance from the plant was also associated with all of the symptoms, as previously noted. The most sensitive pulmonary function measure, $FEF_{25–75}$, was not associated with the indices of time exposed overall or time weighted by distance. Neither were these two associated with changes in pulmonary function in the case-series sample. In fact, pulmonary function in the case series sample was most strongly associated with total exposure and total exposure weighted by distance. Because total exposure weighted by distance was consistently associated with most respiratory symptoms, as well as with pulmonary function changes in both the full and case-series samples, this appears to be the best exposure index. The index for total exposure not weighted for distance performs nearly as well, although only one symptom, shortness of breath, is associated with it. Total exposure and total exposure weighted for distance were associated with shortness of breath as well as with $FEF_{25–75}$, both of which are features of obstructive airway disease. Previous studies have shown an exposure–response relationship when distance alone is used as a surrogate for exposure, confirming that MIC concentration and toxicity decreased with distance. We believe that our results have shown that an exposure index that integrates duration, location, and physical activity is associated with health outcomes, independent of distance. This lends credibility to the hypothesis that these additional factors have also played a role in the severity of toxicity.

A comparison of the total exposure index with the independent variable distance revealed differences in their association with both subjective and objective outcomes. Although total exposure was associated strongly only with shortness of

Table 7. Mean exposure index and mean distance in exposed subjects with and without nonrespiratory symptoms.

	Time exposed overall (min)		Time exposed overall weighted for distance (min/km)		Sum of duration (min)		Sum of duration weighted for distance (min/km)		Total exposure (L)		Total exposure weighted for distance (L/km)		Distance (km)	
	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean
Fever in last 12 months														
Yes	290	181	290	118	286	148	286	102	231	895	231	665	231	2.1
No	19	153	19	62	18	144	18	60	15	992	15	412	15	3.0
Ratio	—	1.2	—	1.9	—	1.0	—	1.7	—	0.9	—	1.6	—	0.73
p-Value[a]	—	0.5	—	0.03	—	0.93	—	0.17	—	0.67	—	0.22	—	0.03
Fatigue														
Yes	301	174	301	96	295	145	295	96	239	919	239	919	239	2.2
No	17	169	17	79	17	150	17	79	14	889	14	713	14	2.9
Ratio	—	1.02	—	1.2	—	0.96	—	1.2	—	1.03	—	1.3	—	0.76
p-Value	—	0.9	—	0.6	—	0.87	—	0.5	—	0.88	—	0.46	—	0.11
Chest pain														
Yes	254	176	254	118	249	148	249	102	202	935	202	685	202	2.1
No	63	164	63	87	62	133	62	72	50	743	50	428	50	2.6
Ratio	—	1.1	—	1.4	—	1.1	—	1.4	—	1.3	—	1.6	—	0.81
p-Value	—	0.49	—	0.14	—	0.39	—	0.11	—	0.29	—	0.06	—	0.06
Taste problems														
Yes	147	198	147	147	144	155	144	117	119	919	119	773	119	1.9
No	171	154	171	88	168	138	168	79	134	889	134	523	134	2.5
Ratio	—	1.3	—	1.7	—	1.1	—	1.5	—	1.03	—	1.5	—	0.76
p-Value	—	0.003	—	0.002	—	0.33	—	0.03	—	0.87	—	0.09	—	0.002
Loss of appetite														
Yes	104	162	104	109	102	143	102	98	86	1,012	86	758	86	2.1
No	214	179	214	113	210	145	210	93	167	846	167	578	167	2.3
Ratio	—	0.9	—	0.96	—	0.99	—	1.05	—	1.2	—	1.3	—	0.91
p-Value	—	0.26	—	0.86	—	0.81	—	0.80	—	0.32	—	0.25	—	0.32

Mean exposure index is geometric mean; mean distance is arithmetic mean. Because of missing data, the total numbers may not equal the total number reporting exposure time ($n = 318$).
[a]From *t*-test of difference in mean exposure index.

breath, distance was associated with all respiratory symptoms and three systemic symptoms. Both total exposure as well as distance were associated with pulmonary function, but the strength of the association of $FEF_{25–75}$ with total exposure was greater. Thus, total exposure is considered to be a stronger risk factor for pulmonary function, although distance was a stronger risk factor for self-reported symptoms. Because subjective symptom reporting may be susceptible to reporting bias and is less reliable than a standardized measure of pulmonary function, we considered the overall performance of the total exposure index to be at least as good as that of distance. Finally, the integration of these two indices (i.e., total exposure weighted for distance) performed better than total exposure and has the benefit of incorporating a crude estimate of air concentration, because air concentration generally decreased with distance from the plant.

Because our subjects were questioned 9 years after the accident, recall bias is certainly a major potential cause of exposure misclassification. All exposure indices showed a decline in the mean and median values with increasing distance from the factory. This decline was slightly less consistent for total exposure, most likely due to the variability introduced by the incorporation of ventilatory rate and penetration coefficient, based on recall of activity and location. It may be argued that those living closer to the factory may have reported higher exposure times, as shown in Table 9 for the correlation of time exposed overall with distance ($r = –0.23$, $p = 0.0001$). However, distance was shown to have a substantially lower correlation with total exposure ($r = –0.12$, $p = 0.07$), in which the additional factors noted above were incorporated. Even though time is part of the total exposure variable, the variation in ventilation rates and penetration coefficients is large enough that the effect of reporting bias would likely have been reduced. This gradient in the indices strengthens the belief that recall of exposure time and activity may be reasonably accurate in most victims, perhaps due to the dramatic nature of the event. However, it is conceivable that a degree of overreporting may have occurred for certain activities (e.g., mean running time was 2.5 hr, which may have been overreported due to extraneous factors).

The unexpected finding of unexposed persons in the > 6–8 km group, all of whom were originally considered exposed, and exposed persons in group C_1, all of whom were thought initially to be unexposed, has potential for exposure misclassification. Because personal exposure estimates were used in the development of indices and correlated with health outcomes, we believe that the source of misclassification, if any, would more likely be from inadequate recall rather than true presence/absence of exposure.

We were aware of the possibility that some degree of disease misclassification may have occurred due to symptom overreporting. Even though our interviewers emphasized to the victims that there was no link between our questions and compensation, other factors such as lack of access to proper health care and monitoring, psychological strain, and disappointment with official policies may have led to an increase in felt or reported symptoms. Similar factors were hypothesized to be the cause of an increase in symptoms reported by parents of young children after the 1986 environmental accident at Schweizerhalle (*26*). After the 1983 Shetland oil spill, significantly more exposed individuals reported somatic and psychological symptoms than unexposed individuals (*26*). In the Bhopal gas victims, the observed decrease in symptoms with distance seen in the first IMCB study (*17*) leads us to believe

Table 8. Mean pulmonary function (among those indicating any exposure) in low/high exposure index, distance, and ever and current smokers.

Exposure indices	Percent predicted $FEF_{25–75}$	Percent predicted FEV_1	Percent predicted FVC
Time exposed overall (min)			
Low ($n = 29$)	89.6	102	100.2
High ($n = 31$)	87.4	103	100.2
p-Value[a]	0.83	0.93	0.99
Time exposed overall weighted for distance (min/km)			
Low ($n = 32$)	85.6	101.5	99.5
High ($n = 28$)	91.8	103.2	101
p-Value	0.55	0.8	0.8
Sum of duration (min)			
Low ($n = 29$)	98	107	102
High ($n = 32$)	82	99	99
p-Value	0.12	0.3	0.65
Sum of duration weighted for distance (min/km)			
Low ($n = 30$)	92	105.4	101.2
High ($n = 31$)	87	100.1	99.4
p-Value	0.6	0.44	0.74
Total exposure (L)			
Low ($n = 30$)	99	109	102
High ($n = 31$)	82	98	99
p-Value	0.14	0.16	0.65
Total exposure weighted for distance (L/km)			
Low ($n = 30$)	99	108	102.3
High ($n = 31$)	82	98.7	99
p-Value	0.13	0.23	0.65
Distance			
≥ 4 km ($n = 27$)	88.3	105	103.2
< 4 km ($n = 33$)	88.6	100.1	97.7
p-Value[a]	0.98	0.47	0.35
Ever smoked			
Yes ($n = 12$)	95	110	108
No ($n = 61$)	91	102	99
p-Value	0.8	0.5	0.2
Current smoker			
Yes ($n = 12$)	95	108	110
No ($n = 61$)	85	104	107
p-Value	0.6	0.7	0.9

[a]From *t*-test of difference in mean spirometry values.

Table 9. Regression of log exposure indices with percent predicted $FEF_{25–75}$ ($n = 74$).

Log exposure index	Intercept	Exposure coefficient	*p*-Value[a]	Smoking coefficient	*p*-Value[a]	r^{2b}
Time exposed overall	106.1	–3.2	0.16	0.1	0.99	0.03
Time exposed overall weighted for distance	104.2	–3.1	0.14	1.2	0.92	0.03
Sum of duration	113.4	–5.1	0.02	–0.9	0.94	0.07
Sum of duration weighted for distance	109.4	–4.5	0.03	0.9	0.94	0.07
Total exposure	112.2	–3.6	0.03	0.9	0.94	0.07
Total exposure weighted for distance	110.7	–3.6	0.02	1.9	0.87	0.07
Distance	83.3	2.7	0.04	0.22	0.99	0.05

[a]From test of difference between coefficient and null value. [b]For entire model.

that disease misclassification from overreporting, if any, was likely to be mostly nondifferential.

We considered the effect of important potential confounders such as smoking. Our analysis showed that smoking did not have an important effect on respiratory symptoms or function. Although most studies indicate that smoking affects the respiratory system, we believe the number of smokers in our study was too small to reveal smoking-related effects. Though other sources of ambient air pollution may have contributed to the health effects, we do not believe that these were significant enough to explain the differences in morbidity between the exposure groups. To our knowledge, no other major industries were present in the study areas.

The issue of socioeconomic status was addressed at the outset of our study, and a decision was made to stratify the population by multiple exposure levels, hopefully within similar socioeconomic classes. Although there were some socioeconomic differences between strata, we believe that the consistent decline in the exposure indices gives us confidence that at least a proportion of the observed associations were attributable to gas exposure. We remain aware, however, of the difficulty of completely controlling for confounding factors, particularly in populations of low socioeconomic status.

Information from the prior Bhopal studies indicates that MIC toxicity appears to be persistent, with episodes of exacerbation (*27*). Our choice of a cross-sectional design had the disadvantage that the sampling of prevalent cases of MIC toxicity whose respiratory symptoms and bronchial hyperreactivity have temporarily improved may have resulted in an underestimation of morbidity. Victims who had died could not be included in the study. These and other factors such as a relatively small sample size and inadequate recall due to length of time since the episode may have resulted in a weaker exposure–response relationship. In spite of these potential limitations, we believe that the strength of this study was its ability to demonstrate an association between some of the exposure indices, particularly total exposure, and subjective and objective measures of health.

Other studies. In a community-based exposure and response study, Andersson et al. (*12*) reported duration of exposure for 379 subjects. About 57% were exposed for 1–3 hr, and 29% reported staying in the exposed area throughout the estimated exposure period of 4 hr. Our data (n = 318, time exposed overall) had slightly higher exposure times, with 10% exposed for up to 1 hr, 40% for 1–4 hr, and the rest for > 4 hr. Mean exposure time was about 3 hr in all zones, with a range of 15 min to 12 hr. Only two persons reported exposure for 12 hr.

Kamat et al. (*27*) reported that a followup cohort of MIC-exposed patients in Bhopal experienced more dyspnea and cough than phlegm, as well as a decline in $FEF_{25–75}$. A similar finding was observed in the IMCB population study (*18*). Vijayan and Sankaran (*28*) studied 60 MIC-exposed patients presenting with dyspnea and cough. They were classified as mild, moderate, and severe exposure based on respiratory and ophthalmic symptoms on the day of exposure as well as on the death of a family member. Their results showed that pulmonary function abnormalities may be due to accumulation of lung inflammatory cells and were most severe in those with higher exposures. A cross-sectional study of pulp mill workers compared the pulmonary function of those who reported having been exposed to an accidental chlorine leak with those reporting no exposure (*29*). Among 82 nonsmoking workers, a small, significant decrement in $FEF_{25–75}$ was detected among the 50% who reported such an exposure at least once in their careers. Various cross-sectional studies of occupational and community cohorts have reported associations between respiratory symptoms and spirometry (*30–32*). There is some evidence that breathlessness and wheezing may better reflect persistent changes in pulmonary function than cough and phlegm (*33*).

One possible consequence of these kinds of exposures is the development of reactive airways dysfunction syndrome (RADS) in a proportion of exposed individuals. This condition was identified in 1985 by Brooks et al. (*34*) from a retrospective analysis of 10 previously healthy subjects who had developed persistent airway hyperreactivity after a single, high-level exposure to a chemical irritant. Clinically, the syndrome is characterized by a 20% drop in FEV_1 after provocation with methacholine or histamine. RADS has been described in industry, agriculture, the health sector, and communities with exposures ranging from single agents such as chlorine and ammonia to complex mixtures of fire smoke, paints, pesticide degradation products, and swine confinement gases (*35,36*).

The above studies show that a single, acute exposure can produce chronic effects in the lung. Although our study did not address the issue of RADS, our results were consistent with findings from these studies in that respiratory symptoms such as shortness of breath, asthma, and cough were more prevalent in those who reported any versus no MIC exposure. Also, the total exposure index we tested was associated with specific health outcomes known to result from MIC toxicity: shortness of breath and obstructive airways disease (*18,27*). This observation was supported by a similar association in the case-series sample.

Conclusions

The exposure indices studied here are a first attempt toward the important goal of estimating individual exposure based on

Table 10. Regression of log exposure indices with percent predicted FEV_1 (n = 74).

Log exposure index	Intercept	Exposure coefficient	p-Value[a]	Smoking coefficient	p-Value[a]	r^{2b}
Time exposed overall	106.8	–0.9	0.52	6.0	0.47	0.02
Time exposed overall weighted for distance	107.9	–1.3	0.33	6.0	0.47	0.02
Sum of duration	109.5	–1.6	0.27	5.6	0.50	0.03
Sum of duration weighted for distance	109.7	–1.8	0.17	5.9	0.47	0.04
Total exposure	110.9	–1.5	0.16	5.9	0.47	0.04
Total exposure weighted for distance	111.5	–1.7	0.10	6.3	0.44	0.05
Distance	100.5	0.9	0.29	6.3	0.45	0.02

[a]From test of difference between coefficient and null value. [b]For entire model.

Table 11. Regression of log exposure indices with percent predicted FVC (n = 74).

Log exposure index	Intercept	Exposure coefficient	p-Value[a]	Smoking coefficient	p-Value[a]	r^{2b}
Time exposed overall	98.7	0.05	0.97	9.2	0.19	0.03
Time exposed overall weighted for distance	100.5	–0.4	0.74	8.8	0.20	0.03
Sum of duration	99.4	–0.1	0.93	9.1	0.20	0.03
Sum of duration weighted for distance	100.8	–0.5	0.65	8.9	0.20	0.03
Total exposure	109.6	–1.6	0.32	9.1	0.19	0.03
Total exposure weighted for distance	101	–0.4	0.66	8.9	0.19	0.03
Distance	98.9	0.39	0.59	9.1	0.19	0.03

[a]From test of difference between coefficient and null value. [b]For entire model.

activity, duration, and microenvironment. Improvement of the predictive ability of individual exposure estimates will require study of the exposure–response relationships in larger data sets with both respiratory and nonrespiratory outcomes. There is, of course, a need for multiple formal studies of ocular, respiratory, reproductive, immunological, endocrine, genetic, skin, neurologic, and psychological health. A combination of panel, cohort and case–control designs may be used to provide a more detailed description of the range of health effects experienced by the population. Information generated from these studies may then be used to determine if the exposure–response relationships we have observed are applicable to a broader spectrum of illness. Such an undertaking may have the goal of developing an exposure estimate that may be used in the legal context for the purposes of attribution and compensation.

Even after 17 years, the process of providing compensation has not been completed for the gas victims. It is estimated that about one-half of all claims have been processed to date. The judicial process is currently reputed to be subject to delays and uncertainties due to various political and social conflicts (*16*).

Ascertaining exposure is important for the purposes of identification of exposed and ill persons to provide long-term care and monitoring. In the clinical setting, a physician may enquire about a patient's exposure time and activity to find links with severity of illness or form hypotheses about illnesses not previously known to be associated with MIC toxicity. A health care planner may use aggregate exposure index information to identify the most severely exposed populations for the provision of health-care services. We recommend that the total exposure weighted for distance index, or components of it, be seriously considered when estimating the exposure of gas victims. For example, the sum of duration weighted for distance component may be adequate for victims who remained at home with little or no activity; however, for individuals who left home and spent considerable time in the gas cloud, the total exposure weighted for distance index is a better tool for exposure assessment. It is hoped that a validated method of exposure ascertainment will greatly help public health planning in monitoring, care, and therapy of the gas victims and provide a model for initiating such studies at the outset of environmental problems.

Table 12. Mean index value and regression of log exposure indices and pulmonary function in case-series sample ($n = 22$).

Log exposure index	Arithmetic mean	Percent predicted FEV_1		Percent predicted FVC		Percent predicted $FEF_{25–75}$	
		p-Value[a]	r^2	p-Value[a]	r^2	p-Value[a]	r^2
Time exposed overall	236	0.5	0.07	0.5	0.03	0.7	0.12
Time exposed overall weighted for distance	610	0.5	0.06	0.7	0.01	0.5	0.13
Sum of duration	213	0.8	0.05	0.7	0.01	0.7	0.12
Sum of duration weighted for distance	518	0.9	0.04	0.7	0.01	0.9	0.12
Total exposure	1,650	0.02	0.29	0.04	0.2	0.09	0.24
Total exposure weighted for distance	3,444	0.05	0.21	0.2	0.07	0.08	0.25
Distance	0.6	0.86	0.002	0.85	0.002	0.65	0.01

All regression coefficients are negative except for the sum of duration and distance.
[a]From test of difference between coefficient and null value.

Table 13. Summary of associations between health outcomes and exposure indices.

Exposure index	Respiratory symptoms				Pulmonary function			
	Cough > 3 months	Asthma	Phlegm	Shortness of breath	Full sample $FEF_{25–75}$	Case-series $FEF_{25–75}$	Case-series FVC	Case-series FEV_1
Time exposed overall	X	X	—	—	—	—	—	—
Time exposed overall weighted for distance	X	X	X	X	—	—	—	—
Sum of duration	—	—	—	—	X	—	—	—
Sum of duration weighted for distance	X	—	X	X	X	—	—	—
Total exposure	—	—	—	X	X	X	X	X
Total exposure weighted for distance	X	X	—	X	X	X	—	X
Distance	X	X	X	X	X	—	—	—

An X indicates that the exposure index and health outcome were associated in these data, based on the ratio of mean exposures in those with and without symptoms or the slope of regression line for pulmonary function parameter, as well as on p-value from test that the mean difference or slope was zero.

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