Effects of Exposure of Parents to Toxic Gases in Bhopal on the Offspring

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Background *Exposure to methyl isocyanate and other toxic gases in Bhopal, India, on December 3, 1984 resulted in thousands of acute deaths, pregnancy loss and long-term effects.*

Methods *From 1985 to 2007, we conducted successive surveys of vital status and health to determine whether the exposure of parents to toxic gases in the Bhopal incident affected the 5-year survival and anthropometric variables of their offspring.*

Results *Initial 5-year mortality of offspring of exposed parents was very high. Male but not female offspring who were exposed to gases in utero or who were born to exposed parents were stunted in growth until puberty, which was followed by a period of accelerated growth. Results also suggest a post-puberty effect on head circumference of females exposed to gases in utero.*

Conclusion *Exposure of pregnant women to toxic gases in Bhopal in 1984 resulted in high pregnancy loss, increased first 5-year mortality and delayed development of male progeny.*

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KEY WORDS: methyl isocyanate; infant mortality; catch-up growth; Union Carbide Pesticide Plant; Tanner score; pregnancy loss; peak expiratory flow rate; growth stunting

INTRODUCTION

Just past the midnight of December 2–3, 1984, approximately 40 metric tons of methyl isocyanate (MIC) and other toxic gases escaped from the Union Carbide Pesticide Plant in Bhopal, India, within a period of 45–60 min resulting in over 5,000 acute deaths and long-term effects in thousands of survivors [Varma, 1986; Bucher, 1987; Kamat et al., 1992; Vijayan and Sankaran, 1996; Dhara and Dhara, 2002; Varma and Mulay, 2006]. At the time of the Bhopal disaster, it was conjectured that the high chemical reactivity of MIC would result in its destruction upon contact with body surface and no systemic toxicity would follow [Varma, 1986]; this speculation and anecdotal reports of cyanide rather than MIC poisoning greatly influenced both clinical and experimental studies [Varma, 1986; Varma and Mulay, 2006].

We hypothesized that because lungs provide extensive surface area for absorption of gases, MIC is likely to enter the systemic circulation despite its high chemical reactivity and exert systemic effects including effects on pregnancy. To test our hypothesis, we conducted a survey of 3,270 households adjacent to the Pesticide Plant in September 1985 [Varma, 1987]. In these household, 865 women reported to have been pregnant at the time of the gas leak but only 486 of them gave birth to live babies, which amounted to 43.8% pregnancy loss [Varma, 1987]. Another study of 2,566 pregnant women from 18,978 households also found pregnancy loss in 23.6%

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women as compared with 5.6% in 1,218 control cohorts [Bhandari et al., 1990]. Exposure of expectant mothers to toxic gases also resulted in a decrease in placental and fetal weights [Kanhere et al., 1987]. These data were strongly suggestive of an effect of toxic gases on the mother and/or her fetus and have been confirmed in animal studies [Schwetz et al., 1987; Varma et al., 1987].

The present study concerns 5-year survival as well as pre- and post-puberty anthropometric data on boys and girls exposed to toxic gases in utero using unexposed cohorts as well as their older and younger siblings for comparison. An earlier study of a random sample of subjects [Ranjan et al., 2003] had found that boys, but not girls, exposed to gases in utero or born to gas-exposed parents were significantly shorter than their unexposed control cohorts. However, data by Ranjan et al. [2003] were collected in 2001 when the mean age of subjects was 17 years (range 14–19 years). Although the survey had 37 gas-exposed boys, 28 of the gas-exposed subjects were exposed as toddlers, six were conceived to exposed parents and only three were exposed in utero. Here, we report anthropometric data from a follow-up of the earlier study [Ranjan et al., 2003] as well as from additional in utero-exposed males and females and their siblings. The follow-up data were collected from mid-November 2006 to mid-January 2007 (termed 2007 here).

MATERIAL AND METHODS

Study Population and Survey Methods

This study was approved by the Ethics Committees of the Faculty of Medicine, McGill University, and Sambhavana Trust Clinic, Bhopal. Informed consent was obtained from all respondents on a form in *Hindi* script either in writing or by thumb impression. All subjects in this study except the control cohorts lived within 1 km northeast of the Union Carbide Pesticide plant at the time of the accident. This area was in the down wind direction of the escaping gases from the plant and recorded a death rate of more than 3% (150 times the normal rate) within a week of the accident [Varma, 1986; Kamat et al., 1992].

Identity of all subjects was verified on the basis of our records of the first survey conducted in 1985 [Varma, 1987] and the identification number allotted by the Indian Council of Medical Research. This report is based on five surveys as indicated in the flow-chart (Fig. 1). The first, second and the third surveys were performed 10, 21 and 56 months after the accident, which approximately corresponded to infants ages of 1 month, 2 years and 5 years. These three surveys were administered by high school graduates familiar with the area. It was in the immediate aftermath of the disaster and every precaution was taken to explain that the study was of no material benefit to the victims. The surveyors were from the area and cognizant of cultural sensitivity of the population.

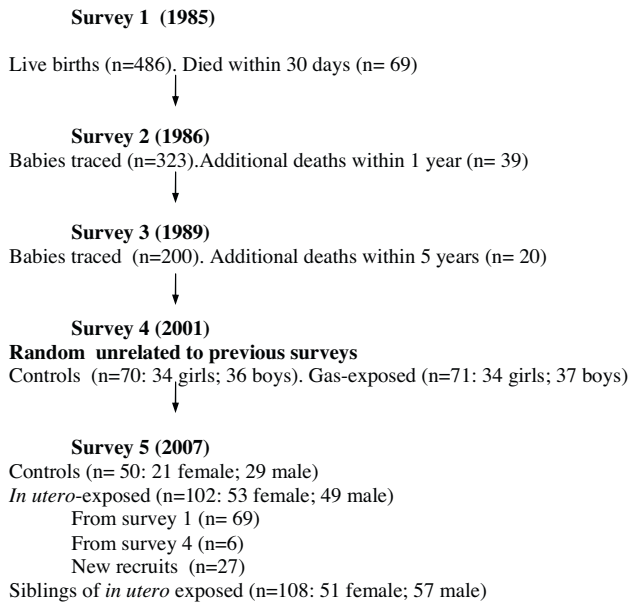

FIGURE 1. Flow-chart indicating details of survey dates and number of subjects.

Surveying students were instructed to record accurately responses without cross-examining the subjects.

The first survey included 3,270 households and was designed to record the outcome of pregnancy and infant mortality within 1 month of age. As mentioned above, these households were selected because they were located adjacent to the Union Carbide Pesticide Plant and in the down wind direction of the escaping gases and a convenient source of locating a large cohort of gas-exposed population. A detailed description of the survey method has been previously reported [Varma, 1987]. Briefly, all subjects were approached by the survey team in person at their homes. On the first encounter, surveyor obtained the consent and fixed an appointment for another meeting to complete the survey questionnaire and record anthropometric data. No household refused to volunteer the information sought although a few subjects did not agree to participate in the Tanner score study as indicated in Tables II and III. No one had moved away from their homes following the accident at the time of the first survey. Households which abandoned their original homes later on are indicated in Table I, columns 3 and 4. No physical examination or laboratory tests were performed to confirm the information on the status of pregnancy volunteered by the subjects.

The second and third surveys were performed 2 and 5 years after the accident to record survival of the children identified in the first survey as well as record the possible cause of death. In these and all other surveys, the follow-up was based on door-to-door visit. The fourth survey was carried out between May 10 and June 30, 2001. In this survey, anthropometric data were collected from adolescents

exposed to gases as infants or born to gas-exposed parents as well as age- and sex-matched unexposed controls [Ranjan et al. 2003]. The cohorts of this fourth survey were unrelated to the first three surveys. The last survey was performed between mid November 2006 and mid-January 2007 (termed 2007 here). This last survey was a follow-up of the subjects of the 2001 survey (fourth survey), but also included additional cohorts (Fig. 1). The respondents understood that the study was of no material benefit to them.

It is not customary in India for people to abandon their ancestral home. However, the Bhopal situation was greatly altered as a result of the disaster, government policy and compensation, and as a result many households moved out. We made the best efforts to trace as many households as we could. In many instances, one whole day was spent locating just one person and make an appointment for a second visit to elicit responses to a questionnaire and record anthropometric data.

In the last survey, all female subjects were interviewed and examined by female staff and male subjects by male or female staff. The subjects of this study included children exposed to gases in utero and controls and their younger and older siblings.

Data Collection

Anthropometric measurements were made as described before [Ranjan et al., 2003]. In addition, peak expiratory flow rate (PEFR) was measured using a mini-Wright peak flow meter (Alliance Tech Medical, Granbury, TX). Subjects were asked to exhale into the mouth piece as quickly and forcefully as they could. This was repeated thrice and the highest reading was used for the analysis. PEFR data were adjusted for age and height [Nunn and Gregg, 1989] and normalized against our controls.

In addition, a follow-up of all subjects of the 2001 survey [Ranjan et al., 2003] was carried out to verify the status of those found stunted in the previous survey. Of these subjects, three born before the disaster and five unexposed controls could not be traced. Of the 180 children who were alive and located 5 years after birth, only 69 could be located in the 2007 survey (Fig. 1). The remaining 33 in utero-exposed children included in this study had identical history and were identified for the first time. Younger and older siblings of the in utero-exposed group of children were used for comparison with in utero-exposed children to minimize effects of socio-economic and genetic factors. However, as the older siblings lived with their parents at the time of the disaster, they were also exposed to toxic gases as infants or toddlers and the younger siblings were born to gas-exposed parents. Therefore, completely unexposed controls were also included. These controls lived in areas farther away from the Union Carbide factory, opposite the wind direction at the time of the accident.

Statistical Analysis

Data were analyzed using SPSS version 15.0 (Chicago, IL). ANOVA was used to compare three or more groups, which were considered independent with respect to exposure. Experiment-wise level of significance was set at 5%. Test-wise type one error was adjusted according to Bonferroni's method.

RESULTS

First 5-Year Infant Mortality

Of the 486 live births, which constituted the follow-up studies, 128 died within the first 5 years (Table I). As all surviving children could not be traced in the succeeding surveys, the total death toll is likely to be higher than that being reported here. The response of the parents to our enquiry about the cause of deaths was not sufficiently specific. In most cases, parents attributed deaths to poor appetite, diarrhea and fever. Difficulty in breathing was not reported by parents as the cause of death in any instance. Female to male ratio of live children at birth was 1.07. However, female to male 5-year mortality was 1.8.

Stunting and Catch-up Growth

This part of the study was based on a very small number of in utero-exposed girls and boys. There was a significantly greater increase from 2001 to 2007 in body weight, height and arm circumference of boys exposed to gases than of controls so that the 2007 height of boys exposed in utero (161.1 ± 8.2, $n = 3$) or born to gas-exposed parents (161.2 ± 6.2, $n = 6$) was no more significantly lower than the

TABLE I. The First 5-Year Mortality in Children Born to Women Exposed During Pregnancy to Toxic Gases in Bhopal on December 3, 1984

Variables	One month after birth [Varma, 1987]	One year after birth	Five years after birth
Household surveyed (n)	3,270	2,622[a]	1,475[a]
Women pregnant during disaster (n)	865	638[a]	374[a]
Live babies born (n)	486	323[a]	200[a]
Infant deaths (n)	69	39	20
Cumulative infant mortality (n)[b]	69	108	128
Cumulative infant mortality (%)	14.2[c]	22.2	26.3
Female/male mortality ratio[d]			1.8

[a]Who could be traced.
[b]Any deaths in untraced subjects are not known.
[c]Infant mortality in the first 30 days after birth in the preceding 2 years in the same households was 3%.
[d]Female to male ratio at birth was 1.07.

TABLE II. Anthropometric Data From 2007 Survey of Females Exposed In Utero to Toxic Gases in Bhopal and their Older and Younger Siblings

	Female	Female	Female	Female	Female
Variable	**Control (n = 21)**	**In utero-exposed (n = 53)**	**Older siblings (n = 31)**	**Younger siblings (n = 20)**	**Younger and older siblings combined (n = 51)**
BW (kg)	46.9 ± 7.2 (43.6–50.1)	41.0 ± 6.2* (39.3–42.17)	45.5 ± 8.8 (42.3–48.8)	48.6 ± 8.1 (44.8–52.4)	46.7 ± 8.6 (44.3–49.1)
Height (cm)	151.8 ± 6.5 (148.8–154.7)	150.6 ± 5.0 (149.2–151.9)	154.2 ± 6.6 (150.6–155.6)	152.0 ± 6.1 (151.1–157.3)	153.5 ± 6.6 (151.7–155.4)
Mid-arm cir. (cm)	23.6 ± 2.6 (22.4–24.8)	22.3 ± 2.1 (21.8–22.9)	23.0 ± 2.5 (22.1–23.9)	24.0 ± 2.6 (22.8–25.2)	23.4 ± 2.5 (22.7–24.1)
Head cir. (cm)	51.7 ± 4.2 (49.8–53.6)	51.1 ±3.8 (50.1–52.1)	52.8 ± 2.1 (52.0–53.5)	53.3 ± 1.2 (52.7–53.8)	53.0 ± 1.8 (52.5–53.5)
BMI (kg/m^2)	20.3 ± 2.7 (19.1–21.6)	18.0 ± 2.7 (17.2–18.7)	19.4 ± 3.5 (18.1–20.7)	20.5 ± 3.9 (18.7–22.4)	19.8 ± 3.7 (18.8–20.9)
Tanner < 5 (% of n)	26.3 (19) (6.5–46.1)	67.3 (52) (54.6–80.1)	21.4 (28) (6.2–36.6)	100 (18) (100–100)	52.2 (46) (37.7–66.6)
PEFR (L/min)	318 ± 32 (303.6–332.4)	259 ± 41 (247.9–270.1)	262 ± 54 (242.0–282.0)	265 ± 79 (228.5–301.5)	263.2 ± 64.9 (244.4–281.9)

Circ, circumference; BMI, body mass index; PEFR, peak expiratory flow rate.
All values are mean ± SD and 95% confidence interval shown in parentheses under the mean values. The numbers of subjects participating in Tanner score study are indicated in parentheses.
*$P < 0.05$, different from all other values in the same row.

height of control cohorts (165.1 ± 5.8, n = 26). However, data were still suggestive of incomplete catch-up of height but the very small sample size does not allow drawing unequivocal inference.

Anthropometric Data on Additional Cohorts

With the exception of body weight, there were no other significant differences in the in utero-exposed females compared with their siblings or unexposed controls (Table II). There was a small but significant ($P < 0.05$) difference in the height of in utero-exposed boys compared with younger siblings or younger plus older siblings combined (Table III). However, when in utero-exposed boys and girls were compared with older and younger siblings of the same sex rather than all the siblings as presented in Tables II and III, head circumference and BMI of in utero-exposed girls was less than that of both older and younger siblings (Table IV).

Tanner Score

Although a higher percentage of in utero-exposed males and females had Tanner scores less than 5, the difference was not significant (Tables II and III).

Pulmonary Function

PEFR values did not differ between in utero-exposed boys and girls and their respective siblings and unexposed controls (Tables II and III). We did not have sufficient resources to conduct other pulmonary function tests.

DISCUSSION

In the immediate aftermath of the Bhopal disaster of 1984, there were two major controversies of clinical significance. The high chemical reactivity of MIC is well known [Varma, 1986; Bucher, 1987]. Indeed MIC was used in Bhopal to make the pesticide carbaryl (Sevin^R) precisely

TABLE III. Anthropometric Data From 2007 Survey of Males Exposed In Utero to Toxic Gases in Bhopal and Their Older and Younger Siblings

Variables	**Control (n = 29)**	**In utero-exposed (n = 49)**	**Older siblings (n = 35)**	**Younger siblings (n = 22)**	**Siblings combined (n = 57)**
BW (kg)	51.5 ± 8.9 (48.1–54.8)	51.3 ± 6.1 (49.5, 53.1)	51.9 ± 7.5 (49.3, 54.4)	45.1 ±7.6 (41.7, 48.5)	49.3 ± 8.2 (47.1, 51.5)
Height (cm)	164.9 ± 6.6 (162.4–167.4)	167.0 ± 6.6* (165.1–168.9)	164.4 ± 7.0 (162.0–166.8)	160.4 ± 7.2 (157.2–163.6)	162.9 ± 7.3 (160.9–164.8)
Mid-arm cir. (cm)	24.1 ±2.8 (23.1–25.2)	24.4 ± 2.1 (23.8–25.0)	25.2 ± 2.1 (24.5–25.9)	22.9 ± 2.7 (21.7–24.1)	24.3 ± 2.2 (23.8–25.0)
Head cir. (cm)	55.0 ± 1.6 (54.4–55.6)	43.3 ± 1.9 (53.7–54.8)	54.4 ± 1.6 (53.8–54.9)	52.7 ± 2.4 (51.7–53.8)	53.7 ± 2.1 (53.2–54.3)
BMI (kg/m^2)	18.8 ± 2.3 (18.0–19.7)	18.4 ± 1.7 (16.5–23.8)	19.2 ± 2.1 (18.4–19.9)	17.5 ± 2.5 (16.4–18.6)	18.5 ± 2.4 (17.9–19.1)
Tanner<5 (% of n)	21.1 (19) (2.7–39.4)	39.6(48) (25.8–53.4)	42.9(35) (26.5–59.3)	47.6(21) (26.3–69.0)	44.6(56) (31.6–57.7)
PEFR (L/min)	456 ± 85 (417.8–494.2)	426 ± 86 (401.7–450.3)	427 ± 96 (395.2–458.8)	361 ±122 (308.8–413.2)	401.5 ± 111.6 (372.3–430.8)

Circ, circumference; BMI, body mass index; PEFR, peak expiratory flow rate.
All values are mean ± SD and 95% confidence interval shown in parentheses under the mean values. The numbers of subjects participating in Tanner score study are indicated in parentheses.
*$P < 0.05$ in utero exposed different from younger and combined siblings.

TABLE IV. Differences Between Anthropometric Data of In Utero-Exposed Group (IUEG) and Their Older Siblings (OS) and Younger Siblings (YS) of the Same Sex

Variables	Female OS − IUEG mean ± SD (n = 15)	Female YS − IUEG mean ± SD (n = 8)	Male OS −IUEG mean ± SD (n = 14)	Male YS − IUEG mean ± SD (n = 11)
Weight (Kg)	3.67 ± 6.3*	4.19 ± 5.1	2.05 ± 6.6	−3.5 ± 7.3
Height (cm)	1.5 ± 3.7	2.0 ± 7.2	−1.7 ± 7.1	−4.0 ± 9.6*
Arm Circ. (cm)	0.41 ±2.6	1.01 ±1.6	1.13 ± 2.8*	−0.92 ± 3.5
Head Circ. (cm)	1.52 ± 5.1*	3.56 ± 6.8*	0.56 ± 1.8	−1.42 ± 3.4
BMI (kg/m^2)	1.48 ± 2.7*	1.48 ± 1.9*	1.07 ± 2.0*	−0.49 ± 2.1

Circ. Circumference; BMI, body mass index.
Number of subjects is different from those in Table III because comparison of the in utero exposed group is made only between older and younger siblings of the same sex. Negative value means that the sibling value is less than that of IUE group.
*$P < 0.05$.

because of its high chemical reactivity [Varma, 1986; Varma and Mulay, 2006]. The controversies were the following: first, given the high chemical reactivity of MIC, can it produce systemic effect or will its effects be limited to exposed surface such as the eye [Andersson et al., 1984]? Second, was MIC or hydrogen cyanide (HCN) responsible for the deaths and long-term effects in Bhopal [Varma, 1986]?

There is evidence that despite the presence of dozens of residues in the Tank #610 from which MIC escaped [Varma, 1986], the main culprit for the short- and long-term effects was MIC and not HCN [Varma, 1989]. Cherry-red venous blood was more probably caused by hemoconcentration rather than as a result of MIC–hemoglobin interaction [Jeevaratnam and Vaidyanathan, 1992]. Furthermore, MIC can cause ocular, pulmonary and other effects notwithstanding its high chemical reactivity [Varma, 1986; Bucher, 1987; Kamat et al., 1992; Vijayan and Sankaran, 1996; Dhara and Dhara, 2002; Varma and Mulay, 2006]. As well, MIC can interact with proteins [Brown et al., 1987], act as a hapten [Karol et al., 1987] and rapidly cross the placenta [Ferguson et al., 1988].

An excessively high pregnancy loss as a consequence of exposure to toxic gases in Bhopal has been previously documented [Varma, 1987; Bhandari et al., 1990]. The 5-year mortality in India is 10.2% [Claeson et al. 2000]. We recorded a minimum of 26.3% 5-year mortality (Table I) in children exposed to toxic gases in utero, which would suggest that fetuses too were affected. It is very likely that some of the pregnancy losses were also caused by fetal developmental defects, which might have manifested as birth defects had they not died in utero. On the other hand, our data do not allow us to identify the cause of in utero deaths and high infant mortality. Parents were unable to attribute deaths to any specific ailment other than poor appetite, diarrhea and fever and did not report difficulty in breathing which could have been suggestive of childhood asthma-like ailment.

A significantly high infant mortality in the first 5 years further indicates that the health of the live-born children was seriously compromised. The female to male ratio at birth of 1.07 is normal and would suggest an absence of gender selectivity in intrauterine deaths; this also suggests that the population living in proximity of the Union Carbide plant did not resort to selective female feticide, quite common in India [Jha et al., 2006]. Whether a higher 5-year female to male mortality ratio of 1.8 was because of a greater neglect of the female child or more severe effect of intrauterine gas exposure on the female than on the male child cannot be answered on the basis of our data.

Our 2001 survey had revealed marked stunting in boys and but not in girls exposed to toxic gases in utero or born to gas-exposed parents [Ranjan et al., 2003]; neither in these cohorts nor in a larger population of in utero-exposed boys or girls we found a significant stunting during the 2007 survey. On the other hand, there was a significant increase in height in exposed males from 2001 to 2007 suggestive of catch-up growth. At the same time, this catch-up growth was more complete in subjects exposed as toddlers than in those exposed in utero or born to exposed parents.

The absence of a significant effect of gas exposure on the height of girls in the 2001 study [Ranjan et al., 2003] could be due to girls attaining their full height at a younger age, as suggested by an absence of correlation between height and age in girls and a significant correlation in boys. It is also possible that there was no significant stunting in girls at any stage of their life, which is suggested by experimental data showing a significantly low body weight of male but not of female mice pups up to 2 months of age when their mothers were treated with MIC metabolite trimethylamine from day 6 to day 15 of gestation [Guest and Varma, 1993]. At the same time, a significantly lower head circumference and body mass index of in utero-exposed girls relative to their older as well as younger sisters (Table IV) is suggestive of a post-puberty retardation in the development of females.

The mechanism underlying early stunting followed by a catch-up growth is unclear. This could have been caused by hormonal imbalance but these were not measured by us in Bhopal cohorts. Exposure to toxic gases in Bhopal in 1984 caused numerous short and long-term effects [Bucher, 1987; Dhara and Dhara, 2002; Varma and Mulay, 2006] including lasting pulmonary pathology [Kamat et al., 1992; Vijayan and Sankaran, 1996]. Childhood asthma can cause early stunting followed by catch-up growth [Russel, 1994; Doull, 2004]. However, our PEFR data (Tables II and III) are not suggestive of any significant compromise in pulmonary functions.

In conclusion, our data are suggestive of delayed growth of the male until puberty and some slowing of growth of the female after attaining puberty. We are following reproductive performance and gender-related variable of females who were exposed to the toxic gases in utero.

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