The Bhopal gas tragedy: Evidence for cyanide poisoning not convincing

Twenty years after the world's worst industrial disaster, the Union Carbide gassing tragedy in Bhopal, India, there has yet to be completed a comprehensive analysis and publication of medical information gathered by the Indian Council of Medical Research (ICMR).

S. Sriramachari[1] provides a welcome review of serious effects of methyl isocyanate (MIC) gas poisoning on organ systems of people who died. But he goes beyond MIC, to propose theories of acute hydrogen cyanide (HCN) poisoning among some of the deceased, and of ongoing cyanide poisoning among survivors. Sriramachari implies there is a medical basis for treatment of Bhopal gas victims with cyanide antidote, sodium thiosulfate (NaTS), but does not say so. It is our understanding that doctors who have treated Bhopal gas victims over the last 20 years have not been using NaTS.

Investigation of whether cyanide poisoning also occurred at Bhopal is important, but published studies individually and in aggregate do not support either an acute or ongoing chronic cyanide poisoning theory to a reasonable degree of scientific probability. That is, scientific studies have not yet provided a satisfactory therapeutic rationale for treating either Bhopal gas victims, or anyone else exposed in future to MIC, with NaTS.

Two overall concerns about Sriramachari's cyanide theories are: (a) lack of evidence of cyanide release, and (b) reliance in part upon unpublished and incomplete data. Specific concerns follow:

1. *Gas release:* Published scientific studies do not provide evidence that cyanide was released from Union Carbide MIC tank E-610 at Bhopal, or of cyanide presence in the tank residue. Cyanide toxicity and pathology in humans have been well known for at least a century[2,3]. Sriramachari alludes to a hypothetical HCN release at Bhopal citing two experimental animal studies in which small amounts were detected when pure MIC samples were heated to very high temperatures, 350°C in one study and between 427 and 548°C in another[4,5]. It has been estimated that the temperature during the MIC release from tank E-610 probably could not have exceeded 300°C. The Indian Government's Council of Scientific and Industrial Research (CSIR) demonstrated that cyanide of any type was not generated as a degradation product of pyrolysis, when samples of MIC from tank E-610 were heated for 30 min to 300°C, and found no cyanide when the five most prominent MIC degradation products were pyrolysed (CSIR, unpublished report). Because there was no fire or explosion at Bhopal, it is difficult to imagine that temperatures of 300°C or greater were reached, let alone sustained in tank E-610. From this, the correct scientific assumption is massive release of MIC, not cyanide. The correct medical assumption is massive MIC, not cyanide poisoning.

2. *Acute death autopsies:* Sriramachari bases his theory of acute cyanide poisoning upon observations of 'pinkish discolouration' of lung by another pathologist, the late Heeresh Chandra, in reference to 22 autopsies on the third day after the gassing. Sriramachari emphasizes 'cherry-red', suggesting it is characteristic of cyanide poisoning of lung tissue. In our review of published pathological findings of cyanide poisoning, 'cherry-red' is reported for skin, retinal veins, and airway and bronchial mucous membrane, but is not mentioned for interstitial lung. This may be semantic. We are not pathologists. But we believe exposure evidence strongly suggests that an observation of reddish discolouration of Bhopal acute gas victim lungs is due to acute MIC, not cyanide poisoning.

3. *Delayed death autopsies:* When referring to about 170 delayed death autopsies, Sriramachari does not provide demographic, gas exposure severity, or clinical medical data about these victims as temporary survivors, or how they were selected for autopsy among the many thousands who died. He does not report pink or cherry-red findings in lung tissue, or thyroid, pancreatic or neurologic sequelae characteristic of chronic low-level cyanide exposure. He does cite evidence of a powerful lung irritant: interstitial and fibrosing changes. Yet, cyanide is a mild airway/lung irritant. Without a comprehensive scientific publication of autopsies, we are left unconvinced about cyanide poisoning among the vast majority, if not all of those who died.

4. *Experimental animal studies:* Reference to experimental toxicology looking at lungs of 'over 240' MIC-exposed rats (how many total?) raises serious questions, because most of the study designs cited are not published. Published studies of animals exposed to MIC at both lethal and sublethal doses, provide strong evidence against cyanide poisoning[6,7].

5. *Blood cyanide levels in survivors:* Findings in table 5 of Sriramachari's report regarding blood cyanide levels give no information about how the subjects and controls were selected, how much time had elapsed after gas exposure when blood analyses were done, and whether or not these victims were dead or alive when tested. The assumption is that these were autopsy studies.

6. *Ongoing chronic cyanide poisoning:* Sriramachari proposes that chronic cyanide poisoning occurred after a single acute exposure to MIC and HCN. He presents unreferenced, sketchy data regarding trial NaTS therapy, including actual names of victims (a breach of medical confidentiality). NaTS study methodologies, selection criteria, and MIC-exposure ranking criteria are not reported. The half-life for conversion of cyanide to thiocyanate from a nonlethal dose in humans[8] is between 20 and 60 min. He further postulates a deleterious shift in the oxygen-dissociation curve, which determines how the red blood cell normally sheds oxygen molecules at the cell level. He postulates that decrease of haemoglobin dissociation of oxygen is due to recurrent carbamoylation of haemoglobin in red blood cells. Carbamoylation has been demonstrated with MIC, but not with cyanide. It has been demonstrated that cyanide does not cause a haemoglobin oxygen saturation gap[9].

We are unconvinced that data Sriramachari presents provide a reasonable basis for treatment of MIC gas victims with NaTS, acutely or chronically. We summarized elsewhere medical and toxicological issues, and asked what we think are basic questions requiring answers[10,11].

As doctors who treat patients we look to the ICMR to provide, especially for victims of this tragedy and their doctors, timely, well-supported, scientific studies as long as the ICMR retains most of the data. We would accept and welcome a cyanide theory where its probability is demonstrated as a result of an evidence-based

scientific method. We believe doctors who wish to learn from Bhopal are waiting for ICMR doctors to report in peer-reviewed medical journals, all they have learned about MIC and the Bhopal gas tragedy.

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Response:

It must be clarified that the paper based on our scientific studies does not represent any ICMR report. Apart from salient points, details of each study were not included due to space constraints. Data in the *Current Science* paper were periodically reviewed by the PACs, under the aegis of BGDRC (ICMR), presented in several national/international conferences and also published[1,2].

This work under the exigencies of a disaster was aimed at time-bound solutions to pressing issues of clinical toxicology. Only experimental studies and DBCTs were according to planned protocols, details of which are available in published literature[3–5], as well as a thesis[2].

It is amusing that while criticizing us for relying on unpublished data, the critics themselves have used similar 'unpublished report(s) of CSIR' to contradict cyanogenesis.

MIC and cyanide toxicity

We have been advocating **dual toxicity** due to MIC and HCN and not cyanide alone. While a single exposure to HCN does not produce chronicity, one exposure to 'acrylonitrile', an organonitrile, required prolonged treatment with a NaTS[6]. Hence, far from 'weaving any imaginary theory of acute and ongoing cyanide toxicity', we were guided by scientific principles of clinico-pathological observation, toxicological evidence and conclusions aimed at prompt clinical relief. In retrospect, NaTS therapy appears to be the single major successful interventional agent in Bhopal compared with other modes such as Levimasol, steroids, bronchodilators[7], etc.

Acute deaths and autopsies

Late Heeresh Chandra, an eminent and seasoned forensic scientist, strongly believed that the very high mortality rate on the first day of the tragedy was unlikely to be solely due to MIC, which found support in UCC's reports on 85 non-fatal accidental exposures to MIC. History of convulsions and consistent autopsy findings of generalized pinkish hypostasis of the body and cherry red colouration of blood and viscera in victims, favoured cyanide toxicity in accordance with standard textbooks of forensic medicine[8–10] variations notwithstanding.

Delayed deaths and autopsies

The correspondents seem to be unaware of the Bhopal scenario. After majority of deaths in the first few days, there was a rapid decline in the mortality. Their statement '*How they were selected… amongst many thousands who died*' is puerile and they should realize that autopsies are not made to order, much less demographic exposure grading! All autopsies were done as when the cases turned up.

Issues of chronic or delayed cyanide toxicity

Instead of primary release of HCN, we proposed the following alternate mechanisms for 'chronic cyanide toxicity':

- Protracted cyanogenesis due to inhaled organonitriles(s) from amongst the eleven unidentified compounds of the tank residue.
- Our initial observations on *N*-Carbamoylation of Hb led to worldwide speculations on *in vivo* cynogenesis[11–13]. Some reactions, however, may not extend beyond 120-day life span of erythrocytes and turnover of tissue proteins. The demonstration of *S*-Carbamoylation of glutathione[14], 30–40% reduction of GSH[15] observed in Bhopal victims and impaired detoxification of endogenous cyanide due to blocking of any of the three cysteinyl residues within the entrapment pocket of rhodanese[16], led us to propose a pivotal role of reversible *S*-Carbamoylation in the transport of MIC within the tissues.
- Possibly several other non-enzymatic and enzymatic mechanisms might have an *in vivo* role in neo-cyanogenesis via 'MIC-bound glutathione'.

Blood cyanide levels

The correspondents have wrongly assumed that all these were autopsy cases, although table 5 clearly indicates that as many as 15 and 34 subjects were live. The controls were drawn from unaffected areas of Bhopal, while subjects were from exposed areas. The samples collected in 1985–86 were cryo-preserved with added NaF and analysed subsequently.

Treatment with NaTS

As early as 8 December 1984, Daunderer reported 2-ppm cyanide levels in the blood of dead victims[17]. Ever since, prompt 'clinical and therapeutic response' to NaTS[18] was recognized. Elevated urinary thiocyanate in autopsy samples and in several series of clinically ill patients provided objective proof. The first DBCT conducted under the supervision of K. Ramachandran confirmed the hypotheses.

Immediately thereafter, Bang *et al.*[19] under the banner of **mfc** stated:

'In spite of clear evidence of cyanide poisoning from 3 December 1984, the administration of the known specific antidote sodium thiosulfate was banned . . . .'

Again in April 1985, mfc emphatically urged the need to administer NaTS in all symptomatic cases[20].

Up to early 1986 there was intermittent clinical recurrence, moderate SCN elevation and continued response to NaTS. Later, faced with 'declining trends', the majority of members of the Supreme Court Committee recommended cessation of NaTS therapy, when the need no longer existed. The statement '*at this point of time that doctors have not been using NaTS for last 20 years*', is fallacious.

Issue of gas release

The incontrovertible evidence of raised blood levels of cyanide and its detoxification product SCN in the urine of victims, constituted the central theme of the *Current Science* paper. Hence, details of our studies on the presence of HCN in the tank 610-E were not included in it.

In the CSIR report cited by the correspondents, studies were conducted on MIC samples from unaffected UCC tank-611, synthesized by a lab-X and a commercial source. The experiments carried out in Pyrex tubes under different conditions, in no way mimic the reactions that might have occurred in UCC steel tank 610-E.

Instead, our team has successfully demonstrated direct presence of HCN in the residue of tank 610-E, by five different methods, including pyridine–benzedine as well as para-phenylene diamine methods, and observed 500 ng% HCN after aqueous elution. Graded pyrolysis of composite tank residue even at 300–400°C yielded 0.03 to 0.91% HCN[2]. While the temperature attained in tank 610-E is a matter of conjecture, demonstration of HCN in tank residue at ambient temperature, even after a lapse of five years, is 'direct evidence of release of HCN' in Bhopal. Hence the correspondents' assumptions are untenable.

Experimental studies

The so-called serious questions should be set at rest by references 4, 5 hailed by reviewers as '*fundamental contributions to inhalation toxicology*'. The study designs are available in these papers. The references 6, 7 cited by the correspondents describe the results of experimental studies conducted with cold MIC, which is not as toxic as pyrolysed MIC. Hence the conclusion drawn from such studies may not help in understanding the events at Bhopal. In fact, Bucher[21] stated that:

'Before one can directly apply these results to exposed population in Bhopal, it should be kept in mind that while MIC was probably the primary chemical released during the accident, an as yet undetermined amount of reaction products was also released, perhaps including hydrogen cyanide'.

It can be concluded that the correspondents with pre-conceived notions, have tried to weave a criticism based on some unpublished and some irrelevant published reports to ridicule the cyanide hypothesis. On the contrary, our scientific findings of elevated blood cyanide and urinary SCN levels and response to NaTS therapy, up to 1986, as reported in *Current Science*, provide convincing evidence. No doubt, the underlying mechanisms discussed above may need reappraisal by the global scientific community.

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