Methods for Assessing and Reducing Injury from Chemical Accidents
Edited by Philippe Bourdeau and Gareth Green

8 *Biological Effects of Chemical Disasters: Human Victims*

C.R. Krishna Murti

ABSTRACT

A conceptual model is presented for a systems approach to the study of the biological effects of massive chemical exposures. The effects on the pulmonary system and on the skin are of immediate concern in accidents where toxic gases are released into ambient air of the neighbourhood. Effects on the cardiovascular system, haematopoiesis, liver and renal functions may follow depending on the nature of the accident and the chemicals released. Detoxification function will have to be assessed and manipulated for successful antidotal therapy. Mutagenic effects including cancer and behavioural disturbances have to be assessed by well-designed long-term studies on the entire community deploying epidemiological techniques.

8.1 INTRODUCTION

The decade 1974–84 witnessed an unusually large number of industrial accidents involving hazardous chemicals: the Flixborough explosion in 1974, the Beek disaster in the Netherlands consequent to the release of propylene, the Seveso disaster, the Mississagua explosion in Canada due to collision of train loads of chlorine and propane, the Houston incident involving the spill of anhydrous ammonia, the Somerville Massachusetts incident involving the spill of phosphorus trichloride and the worst in the history of chemical technology, the Bhopal disaster.

Admittedly, the scenario differed from accident to accident and the resulting tragic sequelae varied in magnitude and impact. In retrospect, however, one cannot fail to discern a uniform pattern in all the above accidents. According to WHO, a disaster represents a 'situation of unforeseen, serious and immediate threats to public health'. According again to the NATO Committee on the Challenges of Modern Society, a disaster is an act of nature or an act of man 'which is or threatens to be of sufficient severity and magnitude to warrant

emergency assistance'. All the accidents mentioned above fit very well into these definitions of a disaster.

If one were to consider ways of providing emergency assistance and help in minimizing injury, it becomes necessary first of all to make a clear distinction between natural calamities like earthquakes, floods, typhoons, etc., on the one hand, and the mostly man-made chemical disasters on the other. Past experience of natural calamities, gained globally, makes it possible to predict and be prepared to an extent for an emergency situation manifest as epidemics and the stress effects due to possible starvation and deprivation of shelter. Such stresses are superimposed on the community as a whole before it has even begun to absorb the shock caused by the irreparable loss of near and dear ones. In contrast, the sequelae of man-made chemical disasters are almost unpredictable. There is no warning signal and hence there is very little time to prepare the community to brave the calamitous onslaught of the disaster. Furthermore, there is no past experience for providing guidance. More often than not, the cause–effect relationship in a chemical disaster eludes immediate grasp and hence the process of coming to terms with the therapeutic management and rehabilitation of the victims can be painfully slow and the goals to be reached may not be clear.

It is against this backdrop of uncertainties that this chapter attempts to outline some of the problems related to the biological effects of massive chemical exposures. How best that information can be used to minimize injury in the aftermath of chemical disasters would depend largely on the preparedness of the community to face public health problems posed by chemical disasters.

8.2 TOWARDS A CONCEPTUAL FRAMEWORK FOR STUDYING CHEMICAL DISASTERS

Almost all the chemical disasters mentioned in the beginning of this chapter may conceptually be seen to be made up of three sequential steps:

The Event → Impact on Targets → Effects

Using this highly simplified linear model it is feasible to look at the three steps as distinct entities and then unravel their links by a systems approach (Krishna Murti, 1986). If one recognizes prevention and control of chemical pollution as the main objective of any worthwhile policy on chemical safety, the relevance of in-depth study of each one of the three steps becomes self-evident.

Using this approach, one can attempt to characterize the consequences of a chemical disaster somewhat as shown in Figure 8.1. It may be noted that the scheme or model suggested in Figure 8.1 can describe accidents at the site of manufacture, processing or formulation or accidents during storage or transport of hazardous chemicals. The scheme includes targets of the disaster both at the spot as well as outside the site of the accident in order to indicate the

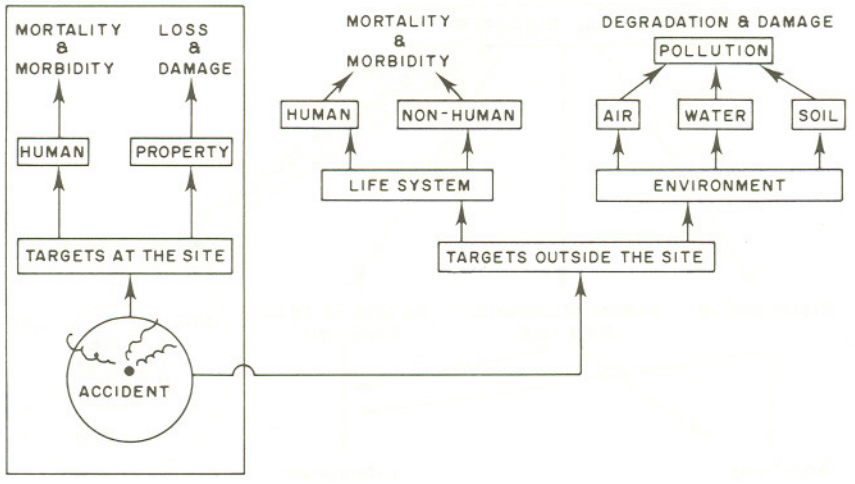

Figure 8.1 Elements of a major chemical accident

'trans-frontier' nature of chemical accidents as opposed to accidents due merely to mechanical failures within the site.

8.3 BIOLOGICAL EFFECTS OF MASSIVE CHEMICAL EXPOSURES

The effects produced by a chemical disaster will primarily depend upon the nature of the accident (leak, spill, 'run away' reactions including violent explosion and fire) and may vary from target to target. We can consider two examples: a disaster that is accompanied by manifestations such as explosion, fire or release of a highly corrosive chemical; and one that involves only the release of a toxic chemical. In either case, living systems in the vicinity of the accident become ready targets of attack and sustain serious injury. In contrast, the likelihood of non-living systems such as installations, building, etc., to become targets of attack is more in the first type of accident. Indeed, living systems are long-range targets for a chemical disaster which discharges a relatively stable toxic chemical into the environmental compartments. The effects can be immediate and deadly if the toxic gas pollutes the air of the neighbourhood at the site of the accident. If the toxic gas pollutes the source of drinking water, effects can still be serious though delayed and less dramatic. If the toxic gas pollutes land on which food crops are raised, long-term effects on the health of the community will have to be anticipated. The dimensions of the sequelae of chemical disasters are brought out in Figure 8.2.

Chemicals are known to evoke a wide spectrum of biological responses in man depending upon the extent of his exposure and their potential to interact

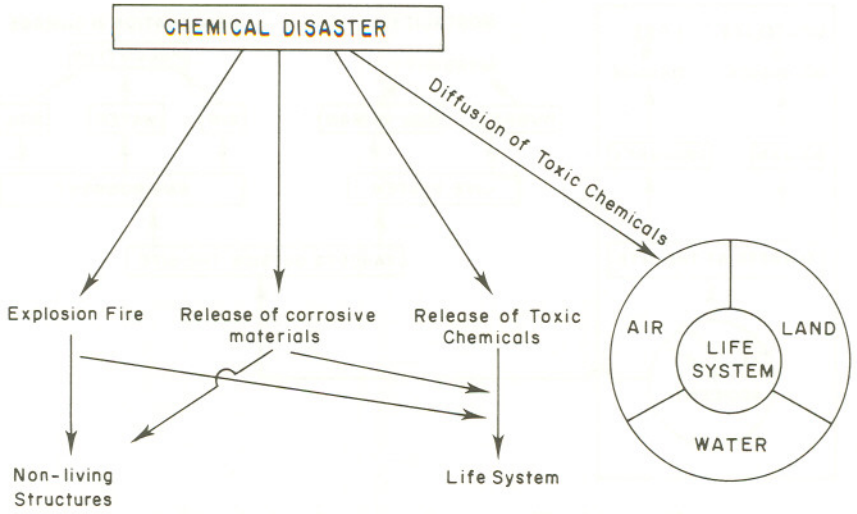

Figure 8.2 Dimensions of the sequelae of chemical disasters

with his anatomical structures and physiological functions. Adverse effects resulting from chemical disasters could be instantaneous death or disease clusters. Individual susceptibility, degree and duration of exposure and failure or success in countering the immediate effects of exposure could modify the effects significantly. Risk of cancer and mutagenic changes in the progeny are long-term effects. A recent Banbury Report deals with some aspects of risk quantitation of long-term effects of chemical exposures (Hoel *et al.*, 1985).

The possible biological effects likely to accrue from massive exposures to toxic chemicals as a result of accidents are summarized in Figure 8.3. Contamination of ambient air is presumably the most significant pathway by which the toxic chemical(s) reach the target. As far as the human victim is concerned, it follows, therefore, that intake by inhalation or absorption through skin would constitute the main ports of entry of the toxic chemical when the scenario presents release of toxic chemicals into the ambient air.

If exposure is through contaminated drinking water or food, the port of entry will be the mouth and therefore the target will be the functional systems associated with ingestion, assimilation and absorption of water and food.

8.4 PULMONARY UPTAKE OF TOXICANTS

Lungs are in intimate contact with both blood and the external environment and are extremely sensitive to many irritant chemicals which can selectively induce pulmonary damage (Witschi and Cote, 1977; Witschi and Nettesheim, 1982). It is also widely recognized now that the lungs not only take up, but

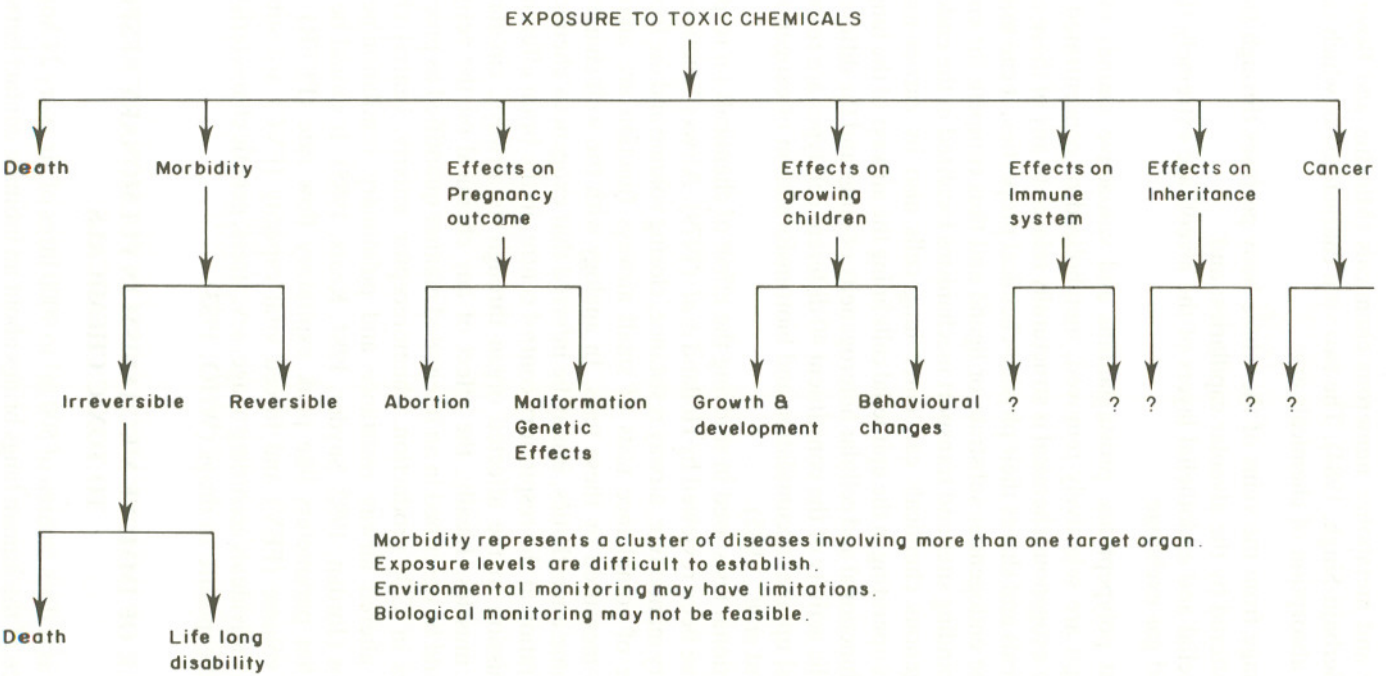

Figure 8.3 Profile of biological effects to be anticipated on exposure to toxic chemicals

accumulate and metabolize numerous chemicals (Minchin and Boyd, 1983; Bend and Serbajit-Singh, 1984). The two vital characteristics which facilitate pulmonary absorption of chemicals are:

- the drainage from the veins of the whole body perfuses through the large surface offered by the alveolar capillaries; and
- the epithelial and endothelial layers of the alveoli are extremely thin and help rapid gas exchange.

Important polypeptides, prostaglandins and vasoactive amines of endogenous origin are selectively removed, metabolized or concentrated by the lungs. If the exogenous chemical is structurally related to any of these endogenous chemicals and shares their physico-chemical properties, it can mimic the action of the endogenous substrate or ligand and thus compete for enzymes, receptors, binding sites and transport mechanisms localized in the endothelial cells. Exogenous chemicals can enter lung cells also by carrier-mediated mechanisms operating in the epithelial cells lining the airways of the lungs. The structural, functional and cellular heterogeneity of lungs and the differences in the metabolic activity of the constituent 40 different cell types are responsible for the rapid uptake, accumulation and biotransformation of exogenous chemicals (Bend *et al.*, 1985).

The functional tests used in studying the effect of chemicals on respiratory function have been reviewed by Holland *et al.* (1979). Airway function during an expiratory manoeuvre, airway resistance, closing volume and the frequency dependence of compliance tests of small airways function are among the parameters measured by these tests. In analogy with the well-characterized action of some anaesthetics, it may be inferred that exogenous chemicals can affect respiration at the respiratory control centre, in the brain efferent input and transmission to the affected organ through its airways, circulation or respiratory muscles. Ideally, the effect of any chemical on the respiratory system should be described in an integrated manner quantified as proportionate changes in CO_2 production, chemoreceptor activity, central chemical sensitivity, altered airway resistance and pulmonary ventilation/perfusion relationships (Jordan, 1982; Snyder, 1984; Keats, 1985). It should be noted, however, that parameters like peak expiratory flow rate (PEFR), forced expiratory volume (FEV) and forced vital capacity (FVC) are subject to variation in individuals according to age, sex, stress, genetic characteristics and background exposure to drugs (WHO, 1983).

8.5 ROLE OF IMMUNE MECHANISM IN PULMONARY RESPONSE TO TOXIC CHEMICALS

Presenting as it does an area of 500 m^2 to 9000 litres of air every 24 hours, the large surface of the human lungs brings about an intimate contact between air

and blood. At the same time the lungs possess a defence system to counter inhaled xenobiotics. The mucosal lined airways containing mucus-secreting cells are equipped with a special mechanism for antibody production. Depending upon whether the inhaled chemical reaches the alveoli after crossing the mucosal barrier, regional nodes process the same and stimulate specific antibody production by sensitized lymphocytes. These can be detected in bronchial washing or lavage. The lungs of some individuals are also hypersensitive to a number of small molecular weight substances such as platinum salts, aminoethanolamine and isocyanates. The evidence accumulating on the impairment of the normal pulmonary immune system in smokers is suggestive of a possible role of irritant chemicals in predisposing exposed individuals to different forms of lung fibrosis involving, presumably, the production of antinuclear antibodies (Liebow, 1975; Holtzman, 1982; Kay and Goetzl, 1985).

Increased bronchial reactivity, hypertrophy of bronchial smooth muscle, inflammatory cell infiltrate, hypersecretion of mucus, narrowing of airways are characteristics seen in bronchial asthma patients who also exhibit hyper-reactivity of airways to irritant chemicals (Schleimer, 1985).

The nature of chemical mediators implicated in the constriction of airways following bronchial insult by chemicals has been under intensive investigation. Mast cell-derived factors such as histamine, leukotrienes, platelet activating factors all detected in serum have been suggested as possible mediators (Dahlen *et al.*, 1980; Martin *et al.*, 1980; Knauer *et al.*, 1981; Nagy et al., 1982).

8.6 BIOLOGICAL EFFECTS ON SKIN

Chemicals can induce direct local action on human skin or mediate systemic disorders. The following are some of the effects generally seen:

- Unwarranted pigmentation or loss of pigmentation; premature ageing with changes in subepithelial connective tissues; inflammation, necrosis and atrophy; eczematous dermatitis, photoactinic sensitization and skin cancer (basal cell carcinoma, epithelioma and malignant melanoma); precancerous conditions of mucosa and buccal cavity; acne; drying; maceration; hair loss or dystrophy of scalp hair; disorders of the nail.

Idiosyncracy, hyper-reactivity and hypersensitivity are host factors which can modulate these responses. Microbial infection of skin may complicate the picture. A predisposing condition that could render exposed persons hypersusceptible is atopic diathesis.

The tests used in the study of skin manifestations in victims of an accidental exposure to polybrominated biphenyls have been summarized by Selikoff and Anderson (1979).

Immune mechanisms have been suggested to operate in the induction of

atopic dermatitis by chemicals. Elevation of serum IgE levels, rise of FC receptor-positive lymphocytes and response to corticosteroids have been cited as evidence for the mediation of immune mechanism in skin disorders (Ogawa *et al.*, 1971; Spiegelberg *et al.*, 1979).

Techniques used for studying immune responses to chemicals in skin are:

1. Allergen challenge followed by tissue biopsy.
2. Denudement of a surface of skin, followed by challenge and then a coverslip later removed to classify the cells adhering to it.
3. Skin blister technique providing *in vivo* chamber for identifying mediators and cells.

The challenge reaction produces a cellular infiltrate with the following characteristics: polymorphonuclear leucocytes (PMN) infiltration (4–8 hours); followed by the influx of eosinophils and basophils; after 25 hours the filtrate is mostly mononuclear (lymphocytes, monocytes and macrophages); during the first 4 hours number of identifiable mast cells decreases suggesting mast-cell degranulation. (Please see review by Schleimer, 1985, for enumeration of tests.)

8.7 RESPONSES INDUCED BY TOXIC CHEMICALS ON REPRODUCTIVE SYSTEM

Methods for evaluating effects on reproductive organs, genetic and fetotoxic effects have been reviewed extensively in the relevant Environmental Health Criteria documents brought out by WHO (1983, 1984). The loss of conceptus and post-natal growth rate and malformation are useful criteria for assessment of the impact of massive chemical exposure on pregnant women and their progeny.

8.8 EFFECTS ON NERVOUS SYSTEM AND SENSE ORGANS

Alterations in structure or function of the various components of the central nervous system, the motor and sensory parts of the peripheral nervous system, functional and organic disorders of the autonomic nervous system are all known to be induced by neurotoxic chemicals. Electroencephalography, nerve conduction velocity measurements, slow nerve fibres, conduction velocity, electromyography and electroneuromyography are among the techniques which have been used in neurological examination of patients for evaluating the impact of chemical exposure (Friedlander and Hearne, 1980).

Eye diseases caused by chemical exposure include irritation of the cornea and conjuctiva; corneal dystrophy; straining of cornea; lens changes; optic neuritis; visual cortical atrophy; derangement of accommodation; diplopia; visual field constriction, etc.

There has been considerable progress in the last few years in efforts to gain better understanding of the varied mechanisms behind the neurotoxic effects of chemicals (Spencer *et al.*, 1985). Degeneration of the distal axon fibres is recognized to be the most prominent response. The degeneration sets in concurrently in long-nerve-fibre tracts in both the central nervous system and the peripheral nervous system. The primary degeneration of axons is associated with secondary changes in the Schwann cells and oligodendrocytes manifest in myelin loss. The mechanisms of acrylamide axonopathy, recently reviewed by Miller and Spencer (1985), may be of interest to those concerned with acute and chronic toxic effects.

8.9 EFFECTS ON OTHER PHYSIOLOGICAL FUNCTIONS

The cardiovascular system, haematopoiesis, liver and renal functions are the other targets of attack by chemicals and appropriate tests will have to be applied for assessing the extent of injury, if any, and appropriate remedial measures instituted. Active functioning of the normal detoxification systems may be very critical in reversing the acute effects in the early phase of the episode. Antidotal therapy and management of the victims is facilitated by a knowledge of the biochemical mechanisms of the toxic chemical or chemicals to which exposure has taken place. In the absence of that knowledge, it will be prudent to adopt measures to stimulate the overall detoxifying function of the body. The redox system in cells mediating biotransformation reactions is regulated at the molecular level by ascorbic acid, glutathione and molecules which can function as scavengers of free radicals. As a specific substrate for glutathione peroxidase and glutathione-*S*-transferase, glutathione is involved in a number of detoxification reactions. The major part of the body's pool of glutathione is produced in liver which exports it to plasma and thus exercises inter-organ regulation (Kaplowitz *et al.*, 1985).

8.10 LONG-TERM EFFECTS OF MASSIVE CHEMICAL EXPOSURES

Mutagenic responses, occurrence of cancer and appearance of behavioural changes are among the most serious consequences of long-term effects to be anticipated even in the absence of precise information on exposure. The management of the related health problems, if and when they occur, is facilitated by instituting detailed epidemiological investigations immediately after the disaster. There may be an urgent need to establish new, or update existing, cancer and birth and death registries with an effective feedback from investigations and enquiries conducted on appropriately designed protocols. The progress in the development of reliable field techniques for revealing mutagenic changes is in a great flux although there seems to be no immediate substitute for conducting sister chromatid exchange rate and chromosomal

aberrations in lymphocyte cultures prepared from blood drawn from the exposed persons. Retrieval of conceptuses aborted immediately after the episode and subsequently for histopathological studies may need careful planning and creation of the requisite infrastructural facilities. Appropriate protocols should be designed for monitoring post-natal development of surviving deliveries. Parameters for development should include anatomical, functional and behavioural aspects. Two-dimensional electrophoresis of plasma proteins may be helpful in identifying the appearance of new marker products of translation of the genotoxic effect. Reference is made to the recent WHO publications on this subject (WHO, 1983, 1984, 1985).

8.11 CONCLUSION

Collation of information on biological effects evoked by chemical disasters is facilitated by a systems approach. The nature and type of the accident and the pathway of the hazardous chemicals released will largely determine the spectrum and intensity of the effects. More often than not it is not feasible to reconstruct exposure scenarios and hence it may be difficult to establish a direct dose–effect relationship. In accidents which involve release of toxic gases into the ambient air, inhalation and skin absorption will be the main ports of entry. Systemic effects can be anticipated if the accidental release of chemicals leads to contamination of drinking water or food. Knowledge of the biochemical mechanisms of toxicity of the implicated chemicals is essential for instituting antidotal therapy for reducing injury in the immediate wake of the accident. In the absence of such knowledge, methods must be available to stimulate the overall biotransforming ability of the body to flush out the toxic chemical and/or its degradation products from the body.

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