

EPIDEMIOLOGICAL ASSESSMENT OF HEALTH EFFECTS FROM CHEMICAL INCIDENTS

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A chemical incident is the unexpected release of industrial material that is (potentially) hazardous either to humans, other animals or the environment. Common synonyms include the term “accident” but this presupposes an anticipated failure of control; “incidents” include also unanticipated disasters resulting from mechanical or organisational failures, and occasionally even sabotage.

The essence of a chemical incident is in its unexpectedness; the term is not used to describe predictable, continuing, and regulated releases of toxic substances from industrial sources. Neither does it generally include toxic releases contained entirely within an occupational setting where only employees are affected, although the principles of management are very similar. Such “industrial incidents” are usually managed by occupational health services. Major chemical incidents are those which pose a threat to a large number of people. This will depend on the size of the release, its area of distribution, and the magnitude of the population at risk.

FREQUENCY AND TYPE OF CHEMICAL INCIDENTS

The frequency of major chemical incidents is unmeasured although they are perhaps more frequent than many imagine; in the years 1975–77, for example, 30 were recorded.¹ In principle they are more likely to occur where there are situations combining both high hazard and high vulnerability. There is mounting concern, for example, that heavy industrialisation in some parts of the world is proceeding faster than appropriate regulatory and surveillance measures. At the same time, many of the most devastating chemical incidents have occurred in countries with a long industrial history. A list of some infamous incidents is provided in table 1.

Chemical incidents are most obviously “agent oriented”²—that is, they come to light following the unexpected release of a toxic agent. Infamous examples include those in Bhopal (India) (fig 1), Chernobyl (former USSR), and Meda (Seveso, Italy). “Effect oriented” incidents are manifest initially by an outbreak of disease, often detected by its unusual nature; outbreaks of acute asthma in Barcelona and “itai-itai” disease in Japan, for example, were eventually traced to (repeated) releases of soybean dust and cadmium respectively. The public health and epidemiological responses to agent and effect oriented incidents are somewhat different, if only in their timeframes. There is also some overlap between chemical incidents and both “natural” disasters, such as the Lake Nyos gas eruption in Cameroon in 1986³ which left 1700 people dead, and with incidents of widespread food contamination (table 1). The latter are often effect oriented without an obvious “point source”, and their investigation may take many years.

Most of what follows refers to agent oriented incidents where there has been an established toxic release into the community. Large scale chemical releases may be transmitted to human populations through air, soil, food or water. In some cases the effects may be immediate; in others there may also be long term adverse consequences. Where these are not specific, attribution of cause to the released agent(s) may be difficult and will rely almost entirely on epidemiological techniques. Toxicological information is obviously helpful where it is available; for most chemicals in wide industrial use, however, relevant information on human toxicity is simply unavailable.⁴

PRE-INCIDENT PREPARATION

The sorry experience of the immediate management of chemical incidents in the past has led to an increasing emphasis on preparedness.⁵ This is a continuous process that involves the establishment of inventories of local risk sources (chiefly industrial and transport), decisions about chains of command and networks of appropriate agencies, and the drafting of emergency procedures. An anticipatory system is really only feasible where there is a sophisticated integration between local public health, emergency, and regulatory services, but in principle it should permit the immediate introduction of appropriate and effective interventions. It is probable, also, that such prior consideration of potential chemical incidents will lead in itself to a reduction in risk through the identification and elimination of hazardous practices. Although there is, thus far, no clear evidence that

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Table 1 Selected, major chemical incidents

Place	Year (start)	Agent(s) (contaminants)
Airborne		
Meuse Valley, Belgium	1930	Sulphur dioxide, sulphuric acid, soot
Flixborough, UK	1974	Cyclohexane, related combustion products
Meda (Seveso), Italy	1976	2,3,7,8-tetrachlorodibenzodioxin
Bhopal, India	1984	Methylisocyanate, related combustion products
Schweizerhalle, Switzerland	1986	Agrochemicals, related combustion products
Chernobyl, USSR	1986	Radioactive isotopes
Foodborne		
Morocco	1959	Cooking oil (triarylphosphate)
Minamata, Japan	1965	Sea food (methyl mercury)
Yusho, Japan	1968	Rice oil (polychlorinated biphenyls)
Spain	1981	Rape seed oil (aniline?)
Skin contamination		
France	1972	Baby powder (hexachlorophene)
Ho-Chi-Minh, Vietnam	1981	Baby powder (warfarin)

preparation in this way significantly improves the outcome of a chemical incident, analogies with other public health emergencies suggest that it is a reasonable assumption.

PRINCIPLES FOR EPIDEMIOLOGICAL ASSESSMENT

The period following a chemical incident can usefully be divided into immediate and subsequent phases. The priorities and tempos of these will be very different, but there are some principles that are common to both. Even in the maelstrom that tends to characterise the immediate response to an incident, it is valuable always to keep in mind the needs of any subsequent, longer term investigations.

Communication and coordination

In any coordinated response to an incident, the epidemiologist is likely to be only one of many involved professionals. Others will include members of the several emergency services, those responsible for the source of the toxic release, hospital and other clinical medical staff, toxicologists and environmental health experts, public health specialists, and often local community or government representatives. In most cases, leadership will be provided from within the public health service that also employs the epidemiologist(s). The coordination of activities by these groups, and of communication between them, is a highly skilled and sometimes thankless task. Other interested parties will include, importantly, political pressure groups, the media and legal experts. A strategy for the regular communication of accurate information across this spectrum, both in the short and longer terms, is vital. This is as true for smaller incidents as it is for large,⁶ and even where there remains considerable uncertainty over the impact of the incident. Regular evaluations of the strategy will allow it to be adjusted if it is proving unsuccessful.

Populations at risk

Persons who are at risk following a chemical incident comprise all those who suffered sufficient exposure to the released agent(s) to induce illness. In general they extend far beyond the population who seek local medical care following the incident, and their enumeration requires access to demographic data across the area of contamination. Identifying the complete at-risk population allows a valid estimate of the (potential) scale of the incident and of its expected effects, but is also essential for the design of subsequent epidemiological studies. Three factors should be considered before embarking on this difficult process; often only crude data are available in



Figure 1 The Union Carbide factory in Bhopal, source of the world's worst chemical incident.

the immediate aftermath of an incident, but these may be elaborated when time permits. First there is the nature of the chemical(s) involved, the mode of their distribution, and their likely impact on health. Some chemicals have particular effects on susceptible groups—such as pregnant women or growing children—and the definition of the populations at risk may need to be adjusted accordingly. Second is an estimate of the spatial distribution of contamination; and third is the availability of demographic data within this area of distribution. In some countries, including the UK, there are increasingly sophisticated tools for enumerating populations within defined geographical limits. These allow the combination of census data with the results of dispersion modelling using geographical information systems. If not included within the pre-incident planning phase, however, they may be too cumbersome for immediate use; in any case, they rarely accommodate non-residents, such as emergency service employees or commuters, who should also be considered for inclusion within the at-risk population. Less complex methods of “barefoot” or rapid appraisal can also prove very useful where there are resource constraints or where the requisite information is simply unavailable.⁷

Case definitions

Occasionally, at least in the immediate period following a chemical incident, case definitions may be straightforward. Many of the acute effects of the Union Carbide disaster in Bhopal, for example, were obviously attributable to the highly

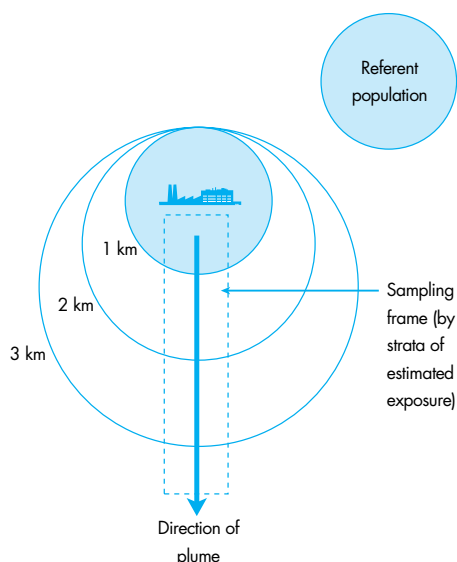


Figure 2 Sampling frame for assessment of health effects following major chemical incidents.

irritant effects of the gases released on the eyes and respiratory tract. Where the effects are less specific, or unknown, it may be more difficult to establish an appropriate definition of a case. Nonetheless, the process is essential for considering the impact of the incident and for subsequent epidemiological investigation. In the early phase, it is often useful to cast the net wide—but not overly so—whereas in later phases, where specific hypotheses are to be tested, tighter case definitions are desirable. Among other potential outcomes, the effects of stress—both in those with demonstrable other health effects and in those exposed but otherwise unaffected—should be considered. Anxiety may be manifest as an array of minor symptoms, but may also have more important long term effects.⁵ It may also be very difficult to distinguish from directly toxic disease.

Two particular principles of case definition are worth considering. First, and essentially, the definition should not include criteria of exposure or other facets of any aetiological mechanism; otherwise, later epidemiological studies are rendered uselessly circular. Second, where possible, it is valuable to include criteria that have some degree of “objectivity” such as the results of laboratory, radiological or other clinical investigations.

Exposure assessment

Estimating exposure among cases, members of the at-risk population or referent subjects (fig 2) is helpful in assessing the impact of a chemical incident and in the analysis and interpretation of epidemiological studies. Indeed, the establishment of an exposure–response relation may be crucial in attributing probable cause where the outcomes are not specific. Examples of the usefulness of this approach include studies which examined the incidence of cancer after Seveso⁸ or the prevalence of chronic airflow obstruction 10 years after Bhopal.⁹

“Exposure” is not “dose”. The latter is often impossible to estimate with any certainty, being dependent on a large number of environmental and host factors that are difficult to measure. These include:

- ▶ the pattern and mode of distribution of the initial toxic release and any chemical transformations it may undergo

- ▶ the extent of any secondary route of exposure, such as ground water contaminated by chemical run-off following a gas explosion
- ▶ the mode(s) of personal exposure: inhalation, mucous membrane or skin contact, ingestion etc
- ▶ any modifying influences such as hyperventilation through exercise, the use of protective equipment or simply whether exposure took place outdoors or in
- ▶ the internal dose
- ▶ the speed and efficacy of individual metabolism and excretion
- ▶ the biologically effective dose.

The last of these—the biologically effective dose—is probably most closely determinant of any health effects; unfortunately it is universally unobtainable. In using any of the alternative surrogates in the spectrum above, alone or in combination, the potential gains in specificity derived from incorporating extra detail may be offset by an increase in misclassification. Thus, complex but poorly measured exposure estimates may be less useful than crude, “broadly correct” ones. Exposure (or outcome) misclassification that is essentially random will tend to reduce subsequent risk estimates towards the null (1.00); those that are systematic, however, may introduce bias, often in the direction of suggesting an exposure–response effect when there is none.¹⁰ Individual measures of exposure are to be preferred, but often it is feasible only to apply estimates across subpopulations in an “ecological” manner.

There is increasing interest in biological markers of exposure (“biomarkers”) which aim to estimate internal dose through biochemical or occasionally molecular assays of serum, urine, hair or other biosamples. The assays may be of the index compound(s) or of metabolites. At present, few chemicals can be validly and specifically measured in this way (see below) but the approach is promising. Non-technical factors which should be considered if it is to be used are the timing of sample collection, the availability of, and acceptability to, target populations, and the facilities for appropriate storage which may need to be over a long period.

Other samples may also prove very helpful in assigning exposure estimates to the population at risk. Thus air, water or soil samples frequently provide valuable supportive information and have the advantage that they may be collected relatively easily and over extended periods following an incident. Chemical assessments in animals or plants within the exposure zone (“bioindicators”) may also be useful. In a crude way, bioindicators were useful following both the Seveso and Bhopal incidents.

These principles are intended to be equally applicable to both the immediate and subsequent responses to a chemical incident. Issues that are more particular to either phase are described below.

IMMEDIATE PHASE

Much of the essential activity within the immediate phase is of an emergency, clinical nature and will be carried out by the relevant emergency medical services. Nonetheless, careful attention to epidemiological principles at this stage will prove invaluable in understanding the immediate and subsequent impacts of a chemical incident. Information (particularly concerning exposure) not collected soon after the incident may be irretrievable later. Thus epidemiologic activities in this phase, while being concerned with immediate events, should have one eye for the longer term.

Table 2 Specimen collection for biomarkers following a chemical incident

Specimen	Preservative	Volume*	Agents
Blood	Lithium heparin	10 ml	Unknown, pesticides, herbicides
Blood	EDTA	5 ml	Unknown, solvents, metals, trace elements
Blood	None (for separation and retention of both serum and clotted blood)	10 ml	Unknown, rodenticides
Urine	None	50 ml	Unknown, metals, trace elements, pesticides, herbicides
Hair	None		Unknown, trace elements

* Halve for children.

A rapid—and necessarily crude—health risk assessment should be carried out. In the first place this will require the following:

- ▶ Identification of the released chemical(s)—and their source—and an appraisal of any chemical changes that may have occurred after release. In the case of fires, where complex combustion processes will have taken place, precise identification may be impossible.
- ▶ An understanding of the probable health effects of the identified compounds, including issues concerning high risk individuals. These should form the basis for early case definition(s).
- ▶ An analysis of the spatial and temporal distributions of the released chemical(s). Meteorological data will be useful when considering compounds released into the atmosphere. Mapping, even if crude, of the geographical dispersion is very useful at this stage.
- ▶ A description of the population immediately at risk: to include at least its approximate geography and size.

Case finding in the immediate phase tends to be reactive. The following sources should be considered in the light of the health risk assessment:

- ▶ attendances at hospital emergency services; admissions to hospital
- ▶ attendances at local family practice services
- ▶ activity in other medical or paramedical facilities such as off peak family practice services, pharmacies, etc
- ▶ mortality—all cause and cause specific—figures, collected locally in the immediate aftermath and, with the necessary lag, from routine sources; postmortem information may be available.

Depending on the specificity of the adverse health effects, the numbers of cases involved, and the tempo of the incident it may be difficult to distinguish cases arising from an incident from those which occur normally. Comparisons with “non-incident” periods may be required, as may more sophisticated methods of assessing temporal and/or spatial clustering. In the repeated Barcelona soybean releases, which caused repeated epidemics of a severe and acute, but otherwise unremarkable, asthma, the identification of an epidemic pattern took several years.¹¹ Classification matrices for disaster related outcomes exist¹² and may be adaptable to a particular chemical incident.

Exposure assessment

As above, the opportunity to gather exposure information within the immediate period should not be missed. Ideally a standardised method for recording time and location of exposure for all cases in the immediate period should be used; this may be easier for those attending hospitals than for those consulting family doctors, etc. It may also be helpful to record types and level of activity during and immediately after the incident. Pre-incident protocols are obviously helpful.

Equally helpful is a predetermined protocol for the collection, from all potential cases, of clinical specimens that may be used later as biomarkers of exposure. It is better to collect too many specimens, and to collect them “too early”, than to miss what may later turn out to be an irretrievably lost opportunity. Table 2 displays a list of specimens and appropriate preservatives for situations where known chemicals are involved, and also for those where the (precise) nature of the toxic exposure is unknown.

Blood specimens should be collected without using alcohol impregnated swabs and, preferably, stored in plastic capped (rather than rubber stoppered) tubes. Most specimens can be stored (at 4°C) for later assay; important exceptions include mercury which tends to leach rapidly into any storage tube.

A number of substances that may be released in chemical incidents do not, currently, have an appropriate assay. These include acetic and other acids, ammonia, asbestos, chlorine, diesel fume, formaldehyde, methane, natural gas, phosphoric acid, and sodium hydroxide. Nonetheless, it is still preferable to collect specimens (as “unknown” in table 2) in the immediate phase; assays may become available and it may subsequently come to light that other, testable, chemicals were also involved.

While biomarker specimens are being collected, the opportunity to collect samples for routine haematology and biochemistry testing should be taken. These will serve either as early indicators of toxic damage—and perhaps be helpful in case definitions and ascertainment—or as baseline measures if long term health effects are anticipated (or discovered). In both instances, serial measurements may become helpful. Measurements of lung function and chest radiology may be similarly valuable.

SUBSEQUENT PHASES

It is, perhaps, in the later stages following a chemical incident that epidemiological expertise is most clearly required. Again, and in the light of immediate events, a health risk assessment is desirable. This should take into account the possibility of persistent contamination/exposure (including that from secondary sources), the likelihood of persistent health effects or those with a long latency, and the estimated size of impact of the initial incident. Special attention should be paid to potentially vulnerable subgroups of the exposed population, such as women who were pregnant at the time of the incident or to growing children.

Epidemiologic assessment in these phases tends to be conducted at a more leisurely pace, and is analytic rather than descriptive. Appropriate and specific aetiological hypotheses may be carefully constructed and tested using one or more study designs. The design(s) should be selected according to the issues in question, with due reference to available resources. The following are the most widely adopted.



Figure 3 Conducting a cross sectional survey following the Union Carbide gas leak in Bhopal.

Cross sectional survey

This design, a popular choice for its rapidity and low cost, measures the prevalence of disease within a population and at the same time estimates individual exposures and any other factors which may modify the relationship between exposure and outcome. Comparisons of prevalences across different strata of exposure may then be made and, if necessary, tested for statistical significance. The choice of study population is, as always, important but the survey should be conducted on every member regardless of whether they were exposed or not (fig 3). Often, a comparison population which is unexposed but otherwise similar, is also surveyed; an alternative approach is to examine the effects of different degrees of exposure within an entirely exposed population. An important drawback of a cross sectional approach is that of "survival" whereby those who have suffered unusually severe effects of exposure may be selected out of the study population—perhaps through a high mortality but also through migration out of the area of study. Such selection is likely to result in an underestimate of the health effects of an incident; the opposite may be true if survival (usually migration) is systematically related to low exposures. A particular example of a cross sectional survey is restricted to a "panel" of exposed persons. This is often restricted to a group with severe health "effects"; although it is frequently unavailable, individual information from before the incident may allow each subject in the panel to act as their own control.¹³ Without some kind of comparator information, however, panel studies are often inconclusive.

Case referent study

Cases within the study population are identified by their disease status. The exposure histories are then compared with those of referent (or "control") subjects who are disease-free and selected from the same population. This is a powerful and efficient approach for rare diseases (such as many cancers or birth defects) or where collecting exposure information is either expensive or difficult. Frequently, cases and referents are identified within the setting of a cross sectional survey. Case referent analyses, rarely helpful unless they are used to test a particular exposure hypothesis, are often valuable following chemical incidents but require both careful case definition and referent selection.

Cohort study

Cohort studies are generally used for the long term follow up of exposed populations; it is not necessary to use the entire population, and a representative sample in whom good exposure data exist may be a more efficient approach. Sophisticated healthcare

systems that allow the flagging of registered individuals will assist with extended follow up periods. Using a cohort approach, the incidence rate(s) of a variety of outcomes may be estimated and, given good exposure data at an individual level, compared across a spectrum of exposures. An entirely unexposed population may also be included for comparison, but careful measurement of potential confounding factors may be required. Where they are available the use of routinely collected (national or regional) health statistics for comparison also requires consideration of confounding exposures. Cohort studies may need to be continued for many years in which instances the follow up of mobile populations may be difficult. Such studies are, without exception, expensive.

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QUESTIONS (SEE ANSWERS ON P 516)

Which of the following statements are true and which are false?

- (1) Worldwide, there are approximately 10 major chemical incidents per year
- (2) The human toxicology for most chemicals in common industrial use is adequately understood
- (3) Exposure estimation in the immediate phase after a chemical incident is of low importance and can appropriately be ignored until formal epidemiological studies are undertaken later
- (4) Biomarkers are available for most industrial chemical exposures
- (5) Case definitions in the immediate phase following a chemical incident should be broad and should not include reference to estimated exposure
- (6) Misattribution of exposure across a population inevitably leads to an overestimate of an exposure–response relation
- (7) Cross sectional surveys following a chemical incident are a relatively rapid and low cost method of assessing the health effects of a major chemical incident
- (8) Cohort studies should include the entire exposed population