

Manual for investigating suspected outbreaks of illnesses of possible chemical etiology

Guidance for investigation and control



World Health
Organization



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Foreword

Society depends on chemicals for a myriad of purposes, including food production, water sanitation, transport, heat and power generation and consumer products and pharmaceuticals. These requirements are met by a vast chemical industry that sources, synthesizes, stores, transports and uses chemicals in large amounts, before recycling and/or waste disposal. According to the European Chemical Industry Council (2), global chemical sales (excluding pharmaceuticals) in 2018 amounted to € 3.35 trillion, reflecting production of basic chemicals such as sodium hydroxide and chlorine and of agricultural fertilizers, speciality chemicals such as paints, dyes, herbicides, pesticides and insecticides, as well as petrochemicals.

The trend of overall growth in demand and production of chemicals is expected to continue. World chemical sales are predicted to reach € 6.6 trillion in 2030. Future industry growth is expected to be driven mainly by emerging markets, where the gains up to 2022 are likely to be 6–10% per year, whereas the gain will be 2–3% in higher-income economies. Brazil, China, India, the Russian Federation and South Africa together accounted for 44.1% of global chemical sales in 2017. In that year, nearly 75% of global chemical sales were made by those countries, the countries of the European Union and the USA together and the remaining 25% mainly by emerging countries in Asia, including the Middle East (2).

Production of chemicals undoubtedly contributes to job creation, economic prosperity and public health and well-being. Many high-production volume chemicals are, however, known to be toxic, and exposure during incidents, accidents and disposal may have both acute and chronic effects on health, the environment, livestock and wildlife. The harm may be individual or, in the case of a chemical incident, may affect a few people, communities or even large populations, and the consequent human and economic costs may be considerable. WHO (3) estimated that 2.7% of global mortality can be attributed to exposure to industrial and agricultural chemicals and to accidental poisonings; the figure rises to 13.4% when air pollution and naturally occurring chemicals are included.

In addition, chemicals may be deliberately released by disaffected individuals or terrorists and result in large-scale chemical incidents. The chemicals released may be toxic industrial chemicals and chemical warfare agents, such as organophosphate nerve agents and sulfur mustard.

The causes of many chemical incidents are obvious, such as an explosion, fire or leak resulting in the release of an airborne plume, tainting and polluting water or depositing particles on land. Some incidents can have international consequences, for example when a chemical release contaminates an environmental medium such as air or water and subsequently traverses national borders. Further information is available in a WHO publication on the public health management of chemical incidents (4). Occasionally, however, a chemical release may not be obvious and the possibility considered only when a number of cases present or are reported. Timely identification of the cause requires detection and verification of clusters and a subsequent outbreak investigation. The investigations may require a detailed study with epidemiological, environmental, clinical and toxicological approaches. As the number of candidate chemicals may be vast, including high production volume and toxic industrial chemicals, pesticides and obsolete substances such as persistent organic pollutants, it may be very difficult to link an exposure to the presenting signs and symptoms.

The potential impact of such exposures may be significant and may require reporting to WHO in accordance with the requirements of the International Health Regulations (2005) (5), which specify the obligations of Member States to identify, assess and subsequently report to WHO events that may be unusual, have serious public health consequences or potential for international spread and/or may result in restrictions on international travel or trade. WHO may in turn declare such events as constituting a public health emergency of international concern. To meet their obligations, Member States must establish and maintain structures and systems for disease surveillance and outbreak response for all hazards. The Regulations also require WHO to provide assistance on request to Member States in investigating and controlling such events. While the majority of such requests are likely to concern infectious disease outbreaks, some concern clusters or outbreaks in which the cause of disease is unknown or suspected to be chemical.

This manual describes methods for investigating clusters or outbreaks that may be of chemical origin and describes the importance of a structured, coordinated, collaborative multidisciplinary, multi-agency approach at local, regional, national and international levels.

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Glossary

Note that the definitions below apply only to the terms as used in this manual. They may have different meanings in other contexts.

Acute (effects)	Effects that occur rapidly after exposure and are of short duration
Accuracy	Difference between the measured concentration and the true value
Alerting	Warning of a problem, unusual data or potential health concern
Analytics	All processes in analysing collected specimens
Autonomy	Principle of respecting decisions made by others regarding their own lives
Beneficence	Bringing about good and taking steps to prevent harm
Biomarker	Xenobiotically induced, measurable alteration in cellular structure and function
Biomarker of effect	Any measurable biochemical or physiological alteration in an organism which, depending on its magnitude, may be recognized as an actual or potential public health impairment or disease
Biomarker of exposure	Indicator of changes or events in biological systems. Biomarker of exposure refer to cellular, biochemical, analytical, or molecular measures that are obtained from biological media such as tissues, cells, or fluids and are indicative of exposure to an agent (1)
Biomarker of susceptibility	Measurable indicator of an organism's susceptibility to a chemical after exposure
Biomonitoring	Measurement in biological media of an environmental chemical or a closely related metabolite
Case	A disease, health disorder or condition under investigation that is found in an individual, population or study group. A person with the disease, disorder or condition
Case definition	A set of diagnostic criteria for use during major incidents, outbreak investigations and surveillance that must be fulfilled. Cases must conceivably have been exposed to the chemical(s) in question, at a related time and place and have a clinical history that is consistent with the biologically plausible mechanism of action of a given chemical. Case definitions may be based on clinical, laboratory or epidemiological criteria.
Chain of custody	A written, agreed procedure for the collection, identification, transfer, receipt, analysis and subsequent storage or disposal of samples in a distinct chronological order
Chemical event	A manifestation of disease or an occurrence that creates a potential for disease after exposure to a chemical
Chemical incident	An incident in which two or more members of the public are exposed to or are threatened with exposure to a chemical
Chemical warfare agent	Any toxic chemical or its precursor that can cause death, injury, temporary incapacitation or sensory irritation through its chemical action
Chronic	An event or occurrence that persists over a long time
Clinical sign	Observation by a (trained) observer during clinical examination

Clinical symptom	Experience of the patient
Conceptual site model	A representation of the chemical, physical and biological processes whereby a contaminant can come into contact with a receptor
Crisis communication	Collection, collation, analysis and subsequent dissemination of information during a crisis
Decision instrument	An aspect of the International Health Regulations (2005) that provides the basis for informing WHO about an incident of event; the four criteria are probability, impact, spread, travel and trade.
Detection	Observation or identification of a set of circumstances leading to potential or actual adverse health effects
Deterministic	A model that excludes randomness and in which the same starting-point always produces the same output
Distributive justice	Socially just allocation of resources
Dose	Total amount of an agent administered to, taken up by, or absorbed by an organism, system or (sub) population (1)
Environmental monitoring	Assessment of environmental conditions for identifying trends and patterns and providing a basis for determining background levels of pollution
Environmental public health tracking	Collection, collation, analysis and dissemination of data on environmental hazards, exposure and health
Environmental sampling	Collection and subsequent analysis of samples, usually derived from air, water, food, a consumer product or soil
Epidemic intelligence	Detection, verification, analysis, assessment and investigation of signals that may represent a threat to the public
Exposure	Concentration or amount of a particular agent that reaches a target organism, system, or (sub) population in a specific frequency for a defined duration (1)
Exposure assessment	Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment (1)
External quality assessment	Assessment by an external body of how a laboratory's quality goals are met, including plans, policies and procedures
Geographical information system	Organized collection of computer hardware and software, geographical data and personnel for efficient capture, storage, updating, manipulating, analysing and displaying all forms of geographically referenced information. First and foremost, an information system with a geographical variable that allows users to process, visualize and analyse data or information spatially. Can be used in modelling trends in time and space. Scope extended by satellite imaging and remote sensing
Hazard	Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub)population is exposed to that agent (1)
High-production volume chemicals	Chemically and physically diverse group of chemicals, not necessarily toxic, that are imported or produced in large quantities
Internal quality control	Multistage process for ensuring day-to-day consistency among test results, typically involving frequent measurement of a known concentration of analyte

International Health Regulations (2005)	Legally binding agreement that provides a unique public health framework in the form of obligations and recommendations for States Parties to better prevent, prepare for and respond to public health emergencies of international concern, including chemical incidents and events
Latency	Time from exposure to occurrence of an observable health effect
Mass psychogenic illness	Rapid spread of medically unexplained signs and symptoms, which are interpreted by those affected as signs of serious physical illness
Mission plan	Aims, goals and objectives of a field investigation, with the resources necessary to ensure its success
Modelling	Application of mathematical models to interpret environmental data or assumptions that can subsequently be used for risk assessment and risk management
Non-maleficence	Doing no harm to others
Pathway	Physical route of a chemical through environmental media, from its release to the portal of entry into the human body; typically air, water, soil or food
Persistent organic pollutant	Organic chemical that is environmentally stable and which degrades slowly, resulting in persistence and potential bio-accumulation and bio-magnification, with potential adverse effects on human health
Plausibility	Feasibility that a given chemical can produce the reported or observed signs and symptoms according to current biology and toxicology
Post-analytics	Final phase of laboratory analysis of data and release and interpretation of accurate, precise, verifiable data in a timely manner
Pre-analytics	Procedures undertaken before the arrival of a sample at a laboratory, whereby representative samples are appropriately collected, labelled, stored and transported to ensure that results can be interpreted with confidence
Precision	Extent to which repeated measurements of a given value are in accordance; a measure of consistency
Preparedness	A state of readiness
Public health event of international concern	An extraordinary event that is determined to constitute a public health risk to States by international spread of disease and potentially to require a coordinated international response
Receptor	Recipient of pollution, whether an environmental sentinel or a human being
Reliability	Extent to which an analytical technique generates consistent data
Remediation	Making the environment safer and cleaner, as defined by national regulations, after contamination
Representative sample	A sample taken from a wider population that accurately represents it statistically
Residual risk	Risk remaining after risk mitigation
Risk	The probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent (<i>I</i>)
Risk acceptance	Acceptation of an identified risk without further action to reduce it

Risk assessment	<p>A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.</p> <p>The risk assessment process includes four steps: hazard identification, hazard characterization (related term: Dose–response assessment), exposure assessment, and risk characterization. It is the first component in a risk analysis (1)</p>
Risk communication	Interactive exchange of information about (health or environmental) risks among risk assessors, managers, news media, interested groups, and the general public (1)
Risk management	<p>Decision-making process involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard</p> <p>Risk management comprises three elements: risk evaluation; emission and exposure control; and risk monitoring (1)</p>
Risk prioritization	Prioritization of risk according to the likelihood of an event and its public health impact; semi-quantitative procedure
Sensitivity	Probability that a test will identify a case of disease in the population; thus, the probability of correct diagnosis of a case or the probability that a case will be identified by the test
Source	Location of origin of a given pollutant or contaminant
Specificity	Ability to distinguish a given analyte in an assay from other, often closely related chemicals
Spot map	Graphic illustration of the location of individuals, subpopulations or populations with a specific attribute or disease or toxidrome
Standard operating procedure	Standardized, step-by-step method for conducting an analytical test to ensure quality, consistency and uniformity
Stochastic	Modelling with a series of random variables, which can result in many outcomes
Surveillance	Systematic, continuous collection, collation and analysis of data for public health purposes and timely dissemination of public health information for assessment and response as necessary
Timeliness	Ability to generate data in a time appropriate to an investigation
Toxic industrial chemical	Chemicals with legitimate industrial usage that are also acutely and/or chronically toxic to human health; often synthesized, stored and transported in large quantities in the form of solid, liquid or gas. Include chemical (oncogenic, teratogenic, pulmonary or haematological hazards) and physical hazards (flammable, explosive or reactive) such as acids, pesticides and solvents
Toxicodynamics	Dynamic interaction between a xenobiotic and its biological target organ(s) and subsequent health effects
Toxicokinetics	Modelling and mathematical description of the absorption, distribution, metabolism and excretion of xenobiotics
Toxidrome	Collection of signs and symptoms characteristic of the toxicity of a given chemical agent or family of agents
Uptake	Process by which an agent crosses an absorption barrier (1)

Introduction

The first indication of a possible chemical-related incident or event may be the reporting or presentation of a number of cases, complaints or concerns at one location, which appear to be more numerous than the expected number for the place and/or time. This is often referred to as a “cluster”, defined as “an unusual aggregation, real or perceived, of health events that are grouped together in time and space and that is reported to a public health department” (6).

Further investigation may indeed confirm an increase in the observed number of cases of a disease over the number expected in a given place or a specific group of people over a particular period. This is referred to as a disease “outbreak”, which has been defined as

the occurrence of disease cases in excess of normal expectancy. The number of cases varies according to the disease-causing agent, and the size and type of previous and existing exposure to the agent (7).

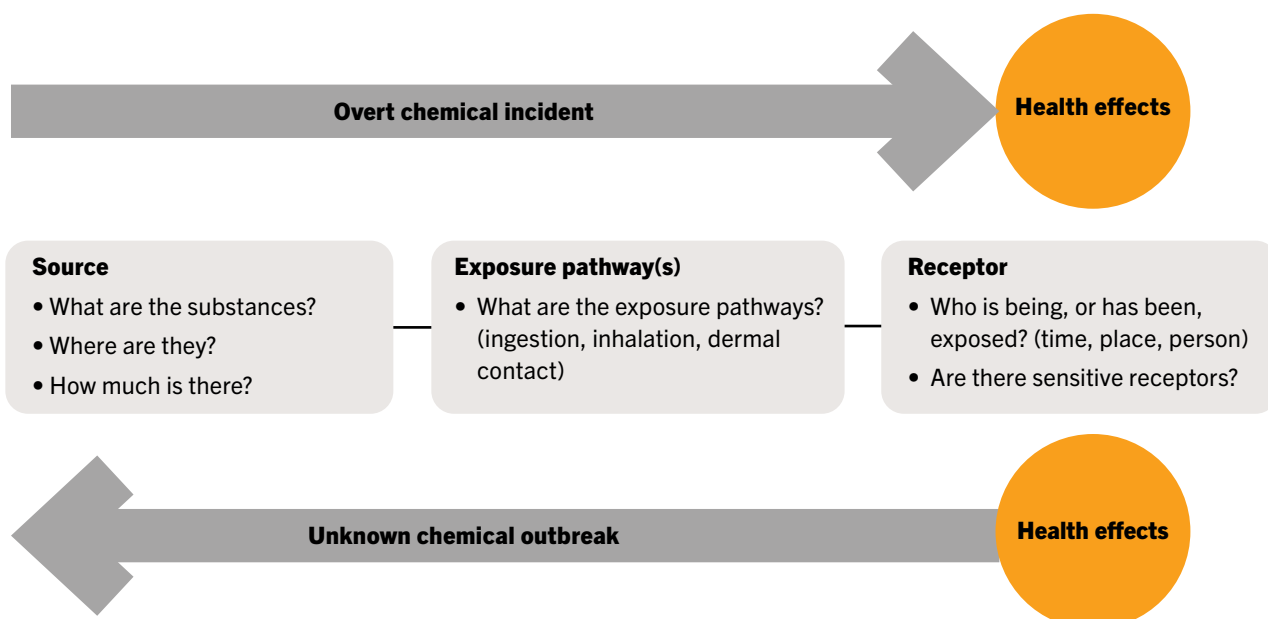
Even if a cluster is confirmed as being an outbreak and it is apparent that it is non-infectious, it may be difficult to establish the cause. Extensive investigation may be required to determine whether the outbreak is indeed due to exposure to an environmental hazard, such as a chemical substance, radiation, the physical environment or food or water contamination or adulteration. In some instances, a psychological etiology may be suspected or plausible, referred to as “mass psychogenic illness”.

Assessment and investigation of a cluster that may be caused by chemical exposure are similar

to those of infectious disease outbreaks, but with unique characteristics. The very large number of chemicals in international trade, potential chemical interactions, limited understanding of the toxicological consequences of some chemicals and the number of potential exposure pathways result in myriad potential scenarios, compounding the difficulty of establishing links between environmental contamination, exposure and subsequent health consequences. The investigation may involve instigation of a complex, integrated, coordinated process, including collection and assessment of epidemiological, environmental, clinical and toxicological data, review and assessment of the evidence and subsequent determination of whether a chemical exposure is possible and whether the signs and symptoms are consistent with such an exposure (plausibility). The assessment requires a multidisciplinary approach, involving environmental epidemiology, environmental science, environmental public health and clinical and laboratory medicine and toxicology, to provide the collective basis for risk assessment, risk management and communication.

In contrast to public health management of an overt chemical incident, which involves identification of the source, pathway and receptor, investigation of an outbreak due to a suspected but unknown chemical(s) proceeds in the opposite direction. It begins with a description of the reported health effects in receptors, elucidation of potential exposure pathways and identification of a possible chemical source(s) based on interpretation of clues and data (Fig. 1).

Fig. 1. Comparison of the investigation of overt and unknown chemical outbreaks



Purpose and scope of the manual

This manual provides a practical, pragmatic guide for public health and allied professionals for the investigation of clusters and outbreaks in which a noncommunicable cause (in particular a chemical substance) is considered a distinct possibility. It does not cover emergency response to chemical incidents, which is described comprehensively elsewhere.

The manual was prepared by a group of experts and specialists in investigating chemical-related outbreaks and builds on the experience of past emergency response operations, including WHO missions. The manual identifies the roles and responsibilities of organizations and individuals and covers management and organizational aspects for multidisciplinary investigation, communication and control.

The principal target audience is environmental public health practitioners, but environmental scientists, clinicians, toxicologists and epidemiologists (including environmental epidemiologists), as well as policy-makers, will also find this manual of interest.

Structure

The manual has two main sections: a practical guide to investigating clusters and outbreaks and principles and concepts of investigation.

Section 1 provides a pragmatic, practical approach to investigating clusters and for determining whether they constitute an outbreak of chemical etiology. It describes the five principal stages of such an investigation: (i) detection, alerting and reporting of cases and/or concerns; (ii) information gathering and evaluation to verify or refute an outbreak; (iii) preliminary investigation of the etiology to determine the likely cause and public health impact, before conducting (iv) a field investigation, comprising coordinated collection of epidemiological, clinical, toxicological and environmental data; culminating in (v) completion of the investigation and drawing the process to a close.

Key information is presented in text boxes, which highlight fundamental points. Case studies are provided to illustrate salient aspects of actual incidents and events.

Section 2 provides more detailed descriptions of the science required for the stages listed above, including planning and preparedness, environmental epidemiology, clinical and environmental science, toxicological investigation, field investigation and risk assessment, management and communication.

Terms of importance to investigations are highlighted in italics and defined in the glossary (above). Annexes provide examples of epidemiological, environmental, clinical and toxicological investigations.



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Section 1. A practical guide to investigating clusters and outbreaks

Prerequisites

Before conducting an investigation, consideration should be given to communication and ethical issues, which are central to each aspect of the investigation.

Communication is important at each stage of an investigation, to inform the community about how the investigation will be conducted and is proceeding and the findings and their interpretation. Communication does not consist merely of making information available to the public. It should be two-way, providing opportunities for both data dissemination and feedback. Traditional approaches have undervalued “active listening” and ignored human needs during investigation of a suspected outbreak (8).

Communication strategies should recognize that lay people may interpret facts about disease clusters and outbreaks differently from “experts” (9, 10). Worry and concern can lead to stress or anxiety, which may exacerbate existing conditions or increase reporting of symptoms, including those with no toxicological basis. Openness with the community can alleviate community and individual concerns and generate a positive working relationship (8, 11).

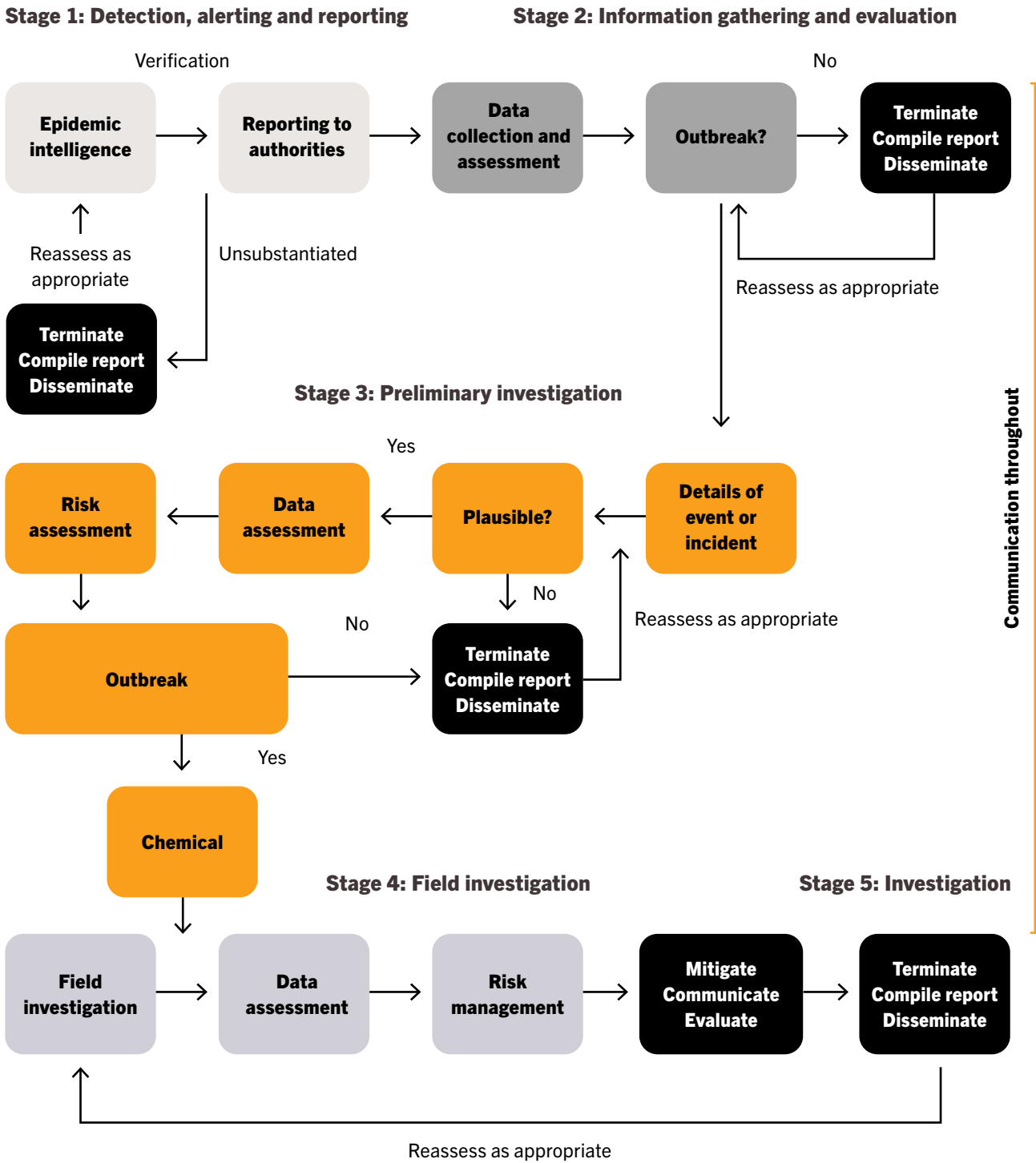
Although outbreak investigations are often conducted in the context of an emergency, they are also a form of research on humans, to which internationally established *ethical principles* apply (12). The principles include a

requirement that studies be conducted in such a way to respect human rights and to respect, protect and ensure equity in the study participants and the community. Studies must also be scientifically sound and yield information that is useful for the investigation.

An outbreak investigation has complexities that make it different from a conventional scientific study. The urgency of an outbreak often requires that decisions be taken quickly, in a context of scientific uncertainty, social and institutional disruption and an overall climate of fear and distrust. The countries most affected by an outbreak may have limited resources, underdeveloped legal and regulatory structures and health systems that lack the resilience to deal with crises. The outbreak itself may generate or exacerbate social crises that weaken already fragile health systems. In such contexts, all urgent needs cannot be satisfied simultaneously, so that decision-makers must weigh and prioritize potentially competing ethical values. Time pressure and resource constraints may force action without the thorough deliberation, inclusiveness and transparency demanded for robust, ethical decision-making (13). Addressing ethical issues in an outbreak investigation is discussed further in section 2.6.

Five stages collectively contribute to thorough investigation of a reported cluster and determination of whether an outbreak has occurred. These are (i) detection, alerting and reporting; (ii) information gathering and evaluation; (iii) preliminary investigation of etiology; (iv) field investigation and (v) completion of the investigation. Fig. 2 summarizes the key aspects of each stage.

Fig. 2. Key stages of an outbreak investigation



Stage 1: Detection, alerting and reporting

Objective: Rapidly detect clusters of cases possibly caused by chemical(s), and to notify public health authorities in a timely manner.

Key aspects of stage 1

Detection of a signal

Data analysis

Verification

Reporting

A cluster may be *detected* from data or from unverified information from single or several sources. *Alerting* may be by communications from members of the affected community or the media or reports from local health care professionals, hospitals, poisons centres, local or national public health teams, other government agencies, international and nongovernmental organizations or WHO staff in country or regional offices. Early alerts and

notifications tend to vary in detail and quality and must be screened, assessed and verified before a decision is taken about whether the reported cases constitute an outbreak and whether the source is chemical.

Rapid detection of a cluster usually requires a network of community, clinical, environmental and public health bodies and organizations that routinely gather, collate, assess, interpret and report on signals and events. This is the basis for *epidemic intelligence*, which comprises early detection, assessment and notification of clusters and suspected outbreaks (14, 15), which expedite the detection of potential health threats and allow timely implementation of appropriate public health responses. Many agencies, organizations and disciplines contribute to such intelligence, including local health care professionals, emergency departments, poisons centres, emergency services, local authorities, environmental, food and water agencies, nongovernmental organizations, the media and communities (15).

Table 1 lists examples of ways in which chemical events may present and the sector(s) likely to detect a cluster or suspected outbreak.

Table 1. Examples of chemical release scenarios and the contributions of various bodies to epidemic intelligence

Type of chemical incident or suspected event	Entities most likely to detect a signal
Release of a chemical from an installation or plant	Public health authorities informed by the operators of the site, emergency services, the media or the public
Fire or explosion during transport or storage	Public health authorities informed by the public, media and/or environmental health personnel or emergency services
Unpleasant smell or taste (e.g. in drinking-water), causing nuisance or symptoms	Community, with alerting of environmental health, utilities, public health professionals or poisons centre
Sudden occurrence of cases with similar signs and symptoms	Health care staff, poisons centre, the public or the media
Observation of environmental contamination or pollution at a particular location or over time	Environmental authorities, public health, the media or the public

Many countries have systems in place to detect cases of infectious disease, but fewer have systems for rapid detection of and response to events of possible chemical etiology. Epidemic intelligence systems to detect clusters and suspected outbreaks of all hazards protect public health; however, even when such systems exist, timely

detection and subsequent reporting of cases possibly related to exposure to chemicals is not necessarily straightforward and may be compromised (16):

- The reported or observed illness is too nonspecific and thus difficult to distinguish from other causes.

- Exposure to contaminated media may have gone unnoticed or occurred over a long time and a wide geographical area, and some exposed individuals may have moved away, making it difficult to link cases, identify a cluster and define an outbreak.
- The affected people may have been exposed simultaneously to two or more chemical agents, resulting in a mixed clinical picture.
- Health care and public health personnel may be unfamiliar with chemical-related illnesses, as they are less frequent than illnesses caused by infectious agents.

Once a cluster or suspected outbreak has been identified (signal), the data must be analysed and verified. If there is no tangible evidence of a cluster, and thus an outbreak, the investigation may be closed, on the understanding that further study may be required if relevant information comes to light. If the data received are consistent with a cluster, timely reporting to the relevant public health authority is essential (see case study 1). When at least two of the four criteria defined in the *decision instrument* of the International Health Regulations (2005) are fulfilled, the responsible authority should notify WHO and may also inform the appropriate regional public health agency and neighbouring countries, according to the national protocol.

Case study 1: Detection, reporting and alerting of unusual signs and symptoms

Date: September 2006

Location: Panama City, Panama

Background

Physicians in a hospital in Panama City detected a cluster of patients with unexplained acute renal failure, frequently accompanied by severe neurological dysfunction. Patients typically presented initially with gastrointestinal signs and symptoms such as nausea, vomiting, epigastric discomfort and diarrhoea, followed several days later by oliguria or anuria, anorexia and fatigue. Many patients also showed a spectrum of neurological effects, including cranial nerve palsy, acute flaccid paralysis and encephalopathy.

These cases were reported to the authorities; however, it remained unclear whether the cause was infectious or toxicological. Three leading hypotheses emerged. An infectious etiology was first suspected and then ruled out, as there had been no known person-to-person transmission and because bacterial cultures and viral tests for infectious causes of acute flaccid paralysis were negative. Subsequently, the anti-hypertensive angiotensin-converting enzyme inhibitor lisinopril was suspected, as many of the affected patients were prescribed this drug, the health authority having added it to its formulary as first-line treatment for hypertension some 2 months before presentation of the first cases. The final hypothesis was that the outbreak was due to contamination of a Panamanian-produced prescription liquid cough syrup that many of the patients were taking.

Investigation and results

A case–control study was conducted to confirm the etiology and to identify the source of the outbreak. A questionnaire was designed to collect demographic and health information and to assess potential exposures. Blood and urine samples were analysed for various potentially nephrotoxic and neurotoxic substances, including metals, paraquat and organophosphate and carbamate pesticides. In addition, the investigators sent samples of lisinopril and cough linctus to the Centers for Disease Control and Prevention in Atlanta (GA), USA. The cough syrup samples were analysed by the laboratory of the US National Center for Environmental Health, which identified the presence of diethylene glycol, a colourless, odourless liquid and a human toxicant. It is commonly used in industry and can be found in commercial products such as resins, antifreeze, inks and glues. On the basis of the positive laboratory results, the clinical features and the documented toxicity profile of ethylene glycol, the cause of the cases was verified as being contaminated cough linctus.

Public health response

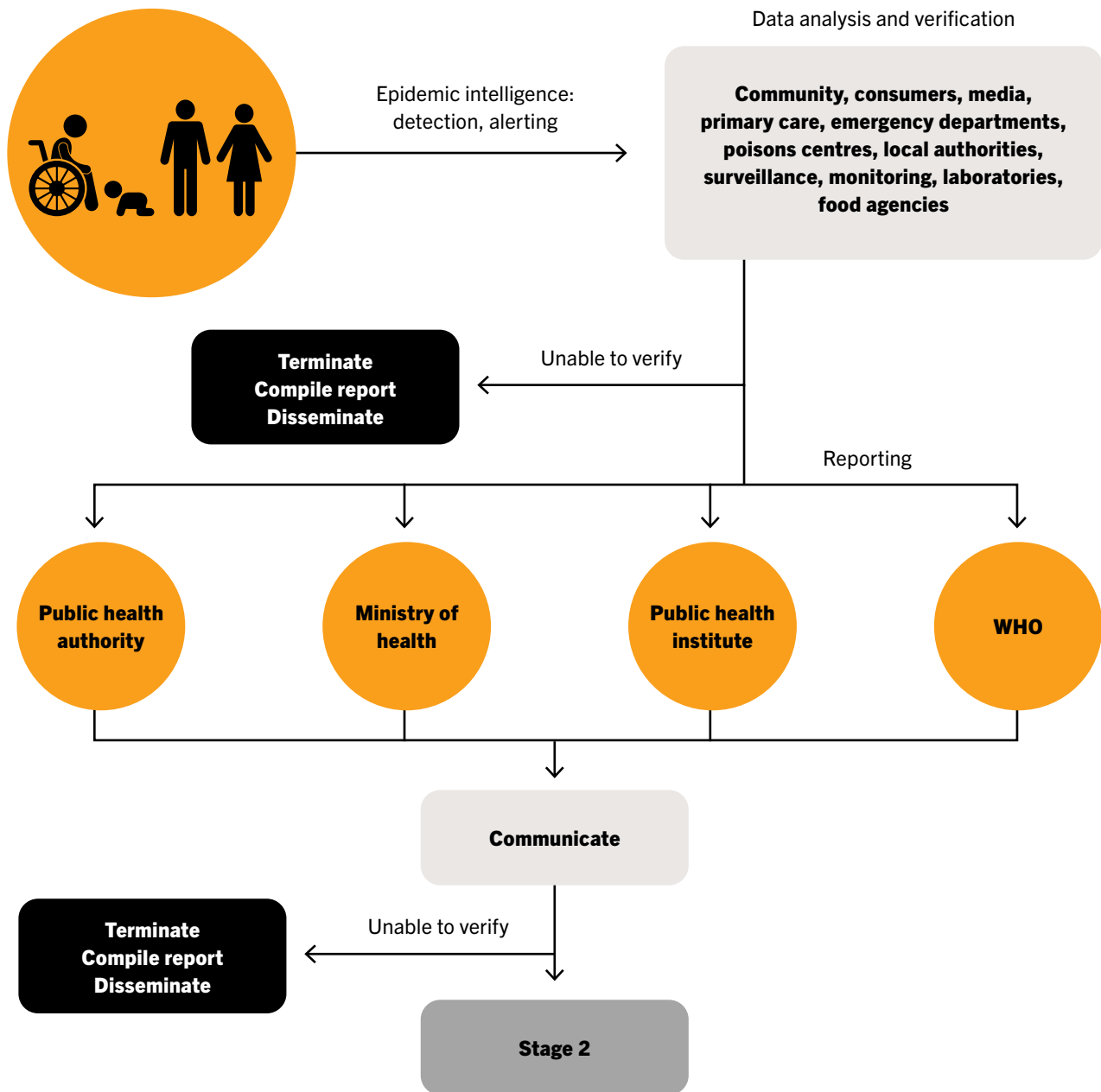
The presence of diethylene glycol was confirmed in a single lot of a product labelled as containing glycerine. The product had been imported to Panama from China via a European broker, and, somewhere along its journey, the label had been changed to misrepresent the contents. These findings led to the recall of over 60 000 medications presumed to be contaminated with diethylene glycol and to widespread screening for renal dysfunction in potentially exposed consumers. By April 2007, 119 cases had been confirmed, of whom 78 died, despite haemodialysis and supportive care (case fatality rate: 65.5%). Cardiac arrest, shock and cardiac arrhythmia were the most common causes listed for these deaths (17).

Key points

- A cluster may be detected after admission of a number of patients with unusual signs and symptoms.
- Timely alerting of and reporting to public health authorities allows epidemiological and toxicological investigation to confirm an outbreak and its etiology.
- International assistance may be required for the investigation.

Once the information is received, scrutinized and communicated, stage 1 is complete, and stage 2 can be started. Fig. 3 depicts the principal aspects of stage 1.

Fig. 3. Stage 1: Detection, alerting and reporting



Stage 2: Information gathering and evaluation

Objective: To review the evidence and verify or refute the presence of an outbreak

Key aspects of stage 2

Collection and collation of data

Review

Assessment

Verification of outbreak

After verification of reports, the next stage entails the collection, collation, review and assessment of all available information by the appropriate public health authority. The information may be obtained from both formal and informal sources and may include reports of illness in the community, patients presenting to primary care services or hospital outpatient and emergency departments and laboratory data, reports of chemical releases (suspected or actual) or episodes of environmental pollution. The data received must be

thoroughly reviewed to verify its accuracy and relevance to assessing the existence of an outbreak.

Any reported cases should be clearly and consistently documented, with construction of a clear *case definition* based on the presenting clinical features, the person (such as age, occupation, gender), time in relation to exposure, presentation of signs and symptoms and source or suspected source. This provides the basis for verification and effective subsequent investigation of an outbreak. Fig. 4 provides an overview of this stage.

Verifying that a reported cluster does indeed constitute an outbreak requires assessment of community, epidemiological, environmental, clinical and toxicological information regarding the current situation in the affected area or population. Consequently, it may require access to routine data from primary care centres, hospital departments and laboratories, as well as environmental agencies. Information from many different sources should be cross-referenced, corroborated and continually reviewed in order to determine its veracity and its value in guiding decisions on the next steps.

Such information will help in answering various questions for verifying an outbreak (Box 1).

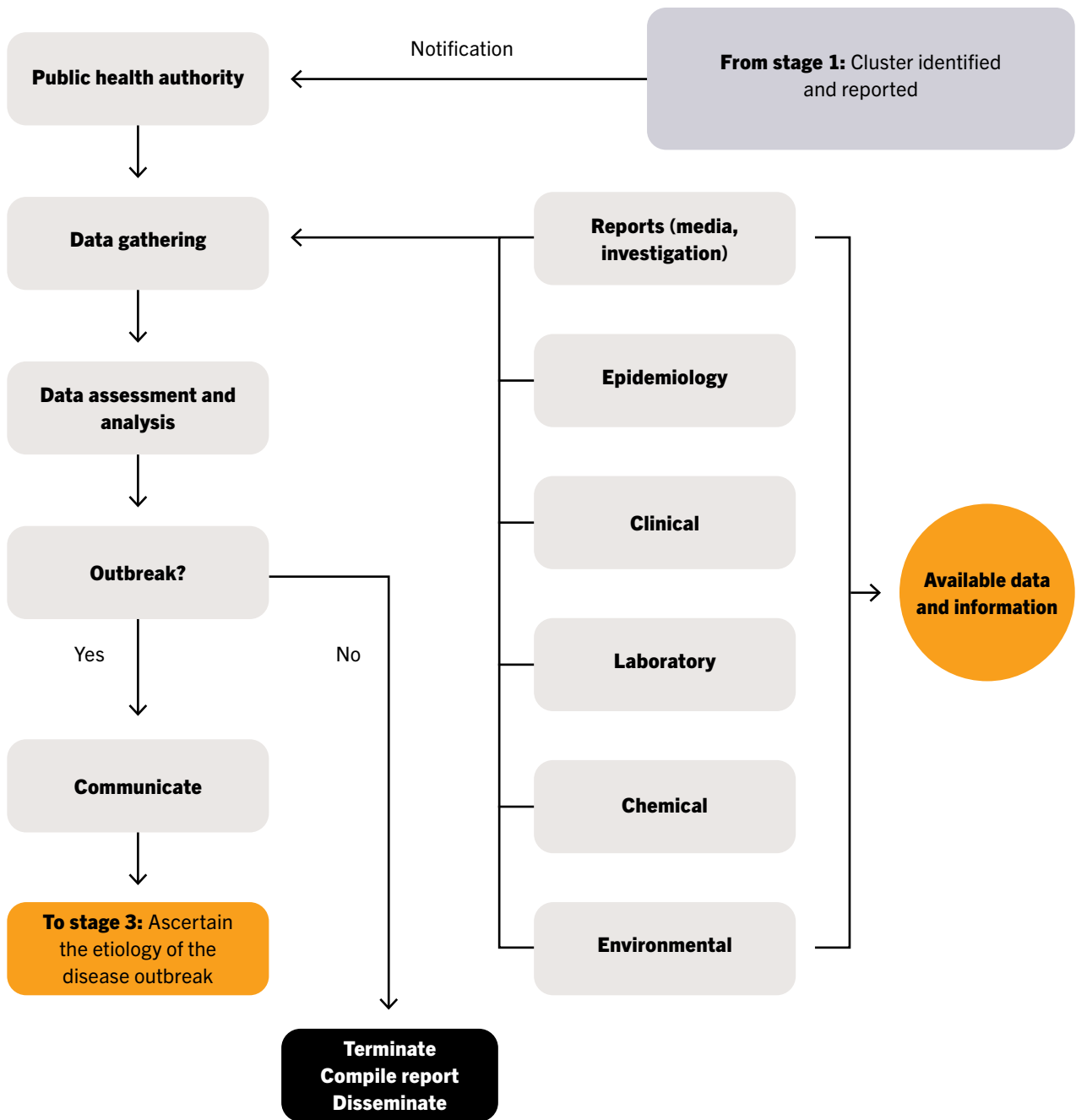
Box 1. Verify whether reported cases constitute an outbreak

- Has the reported cluster been corroborated by other sources?
- Are the reported cases linked in space and time?
- Do reported cases have the same clinical presentation, or can some be explained by another etiology?
- Is the baseline number of reported cases known?
- Has the number of cases increased above baseline?

The important information is whether the number of cases exceeds that expected in the population at that time by comparing observed with expected numbers (18, 19). In some outbreak situations, an increase in the number of cases may be apparent immediately, while in others it is less obvious, and the number of cases of illness in the potentially exposed population should be compared with a suitable reference population. Such analyses require good-quality data; methods for conducting them are described in standard texts of epidemiology.

If the initial assessment indicates the presence of an outbreak, it is appropriate to continue to stage 3. If, however, the assessment suggests that there is no outbreak, the reasons for deciding to stop the investigation should be documented and disseminated and the investigation concluded. The decision should be reviewed if new data come to light and that warrant further investigation.

Fig. 4. Stage 2: Information gathering and evaluation



Stage 3: Preliminary investigation of etiology

Objective: To ascertain the likely cause(s) of the outbreak in a preliminary assessment and exclude scenarios that are improbable or *implausible*.

The preliminary assessment should be systematic, iterative and integrated, with the aim of further understanding the nature of the outbreak and its cause(s) (20) (see Fig. 5).

Stage 3.1. Obtaining further information

Stage 3 starts with the collection of further information to determine the potential cause(s) of the outbreak. At this stage of the investigation, the available data may still be insufficient to determine the exact nature of the outbreak or its source, the contaminated environmental medium or media or the exposed community, obviating determination of the risk to public health. Further demographic, epidemiological, environmental and clinical

Key aspects of stage 3

- Early description of the nature and extent of the outbreak and identification of missing information and areas for further investigation
- Assessment of the public health impact of the outbreak according to the number of cases in the affected population and the profile and context of the illness
- Strengthening or refuting the case for a chemical cause on the basis of epidemiological, environmental, clinical and toxicological information
- Assessment of whether formal field investigations are required and their scope (stage 4)
- Identification of risk communication strategies and messages for the public, the media and others

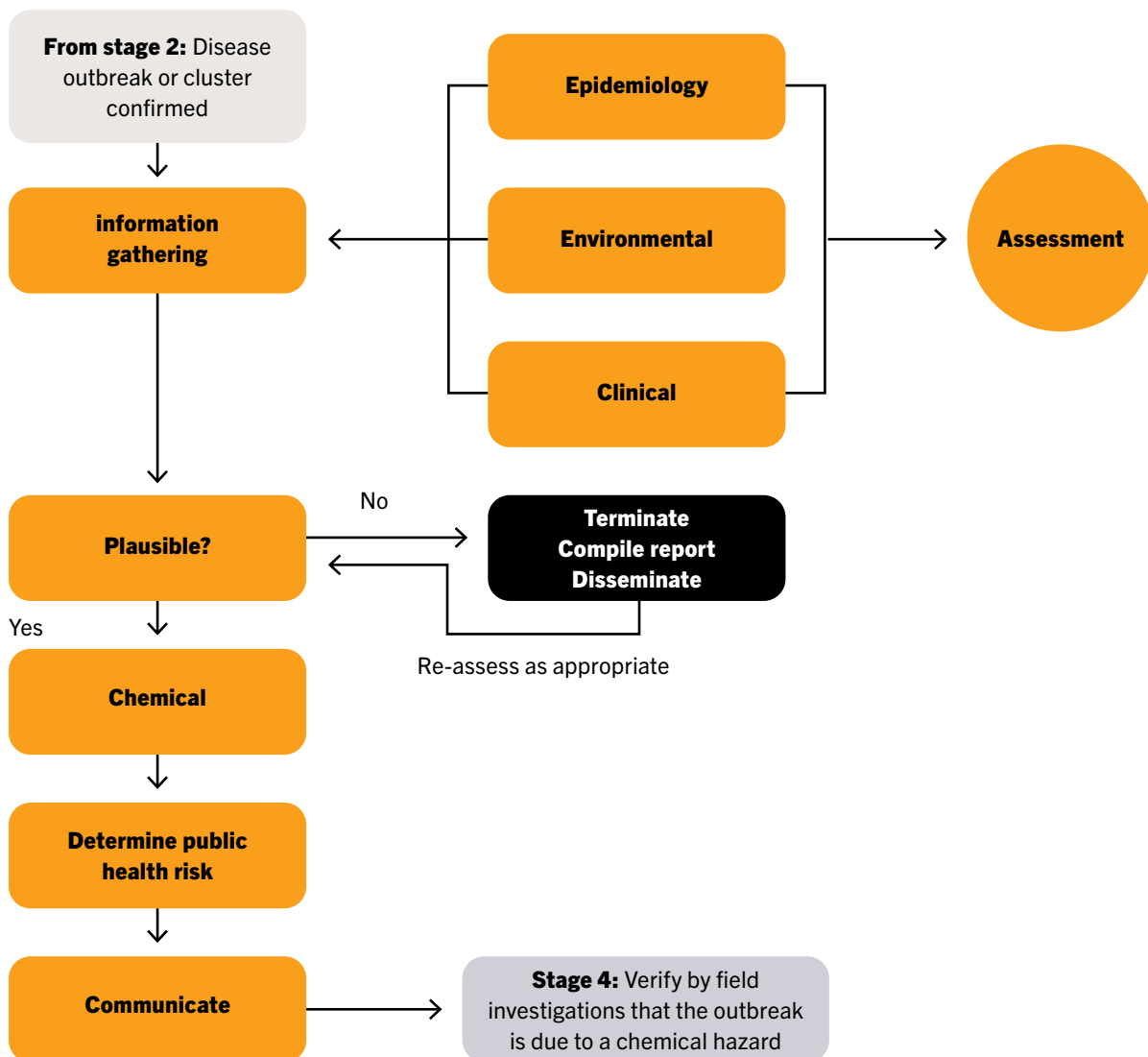
or toxicological information should therefore be sought from local sources. Information that might be required to determine the likely etiology is listed in Box 2. Annex 1 lists some questions that might be relevant during this stage of the investigation.

Box 2. Further information required to determine the potential etiology of an outbreak

- Demographic
 - Age, sex, ethnicity, location, occupation
- Clinical
 - Signs and symptoms and their evolution (may provide clinical clues, e.g. toxidromes)
 - Time course of illness (dates of onset and recovery)
 - Severity of illness (consultation for primary care, hospital admission, death)
 - Laboratory tests undertaken
- Epidemiological
 - Numbers of affected and unaffected people, characteristics of affected people (differences and similarities with the unaffected population)
 - Period (epidemic curve)
 - Geographical area affected
 - Specific epidemiological clues (e.g. family clusters, occupational clusters, consumption of a common food or drink)
- Environmental
 - Chemicals used near the outbreak location, presence of industrial sites and other industrial activities, waste or landfill sites, evidence of contamination of air, water, soil or food
- Previous outbreaks in the area
 - Findings of investigations, including details of biological and environmental sampling and its review
- Review of morbidity and mortality trends in various settings and populations (including animal populations)
- Review of anecdotal information on the likely cause of the outbreak and similar past events

Such information increases understanding of the possible cause(s) and can direct an assessment of plausibility and further investigation.

Fig. 5. Preliminary investigation of etiology (Stage 3)



Stage 3.2. Determining plausibility

The above information can be used to make an initial judgement of the plausibility of the reported outbreak and assess the strength of the evidence for an association between the reported health effects and potential exposure to one or more chemical hazards. The hypothesis that the outbreak is due to a chemical(s) is strengthened if the following criteria are fulfilled:

- Release of a chemical is feasible.
- Environmental contamination is possible.
- An environmental pathway for community exposure exists.
- The reported health effects are consistent with the toxicity of the suspected or possible chemical(s) cause.

- The postulated duration and magnitude of exposure could give rise to the observed effects.
- The possibility of an infectious cause has been excluded.

If these criteria are met, further epidemiological, environmental and clinical investigation is warranted to elucidate the nature of the chemical(s) responsible for the outbreak. If they are not, it is appropriate to conclude and terminate the investigation and proceed to stage 5.

Stage 3.3. Epidemiological Information

Epidemiological information may also suggest a chemical etiology. Epidemiological clues that can suggest a chemical-related outbreak are listed in Table 2.

Table 2. Epidemiological clues to the possibility of a chemical-related outbreak

Epidemiological clue	Interpretation
<p><i>Many people affected</i></p> <p>An unusual increase in the number of people with similar symptoms or toxidromes presenting during a short period (i.e. hours or days)</p>	<p>May suggest a single-source or continuing common-source exposure to a chemical agent.</p>
<p><i>Common demographic or other characteristics</i></p> <p>The affected people are from a similar age or occupational group, participated in a shared activity before the onset of illness, live in a common location or residence or used a common product (e.g. a medicine)</p>	<p>Clustering of affected people within defined occupational or social groups or geographical areas may indicate a shared, common, specific exposure.</p>
<p><i>No evidence of person-to-person transmission</i></p>	<p>An epidemiological pattern indicating person-to-person transmission is typical of an infectious disease outbreak. Lack of such evidence suggests a noncommunicable disease.</p>
<p><i>Geographical location</i></p> <p>Occurrence of illness or cases in a specified, defined location or outbreaks of similar illness in different geographical locations or an illness that is unusual for a given location (e.g. marine toxin poisoning in a non-coastal area)</p>	<p>Evidence of linkage in time and space may indicate exposure to release from a point source.</p> <p>Presentation of similar cases at different or unusual locations for the type of poisoning may suggest distribution of a contaminated product.</p>
<p><i>Mortality pattern – human</i></p> <p>Unexplained deaths, especially if rapid, among young and healthy members of the population</p>	<p>May be consistent with exposure to a toxic substance, with subsequent absorption and distribution to a target organ(s)</p>
<p><i>Mortality pattern – other organisms</i></p> <p>Unexplained and unusual pattern of deaths in plants, fish or animals (sentinel organisms)</p>	<p>Previously unknown contamination of the environment with subsequent ecological toxicity</p>
<p><i>Particular pattern in the onset and evolution of illness</i></p> <p>Rapid onset and evolution of illness</p> <p>Delayed onset of illness</p>	<p>Acute (minutes to hours) and sub-chronic (days to weeks) presentation of affected people with similar symptoms indicates a likely chemical etiology.</p> <p>A short latency between exposure and clinical presentation is characteristic of many chemicals.</p> <p>The onset of toxic effects may be delayed when toxicity is due to a metabolite.</p> <p>The latency between exposure and clinical effect may be long, e.g. carcinogens.</p> <p>Clinical effects may be apparent only after long exposure to low doses.</p>

Epidemiological clue	Interpretation
<p><i>Clinical course</i></p> <p>Unusual groupings of symptoms and signs</p> <p>Signs or symptoms match a recognized toxidrome</p> <p>Inconclusive or negative results in diagnostic tests for infection</p> <p>No response to usual therapy for infection</p>	<p>Presentation of cases with unusual signs and symptoms or recognized toxidromes and exclusion of infectious disease suggest an outbreak of noncommunicable etiology, possibly chemical.</p>
<p><i>Environmental features</i></p> <p>Altered taste or appearance of contaminated media (e.g. water or food)</p> <p>Unusual or distinctive odour or discoloration of contaminated media</p> <p>Community dumping of containers containing chemicals</p> <p>Reformulation of consumer products</p>	<p>May be consistent with contamination or adulteration of food and water, deliberate covert release of a chemical agent(s) or illicit dumping of toxic chemicals</p>

Adapted from references 16 and 21.

Each clue listed is not unique to a chemical outbreak, but, when taken together and in conjunction with other clinical, epidemiological and environmental information, they strongly suggest such an etiology.

Epidemiological investigation is discussed further in relation to conducting stage 4, and the fundamentals of the associated techniques are discussed in section 2.2.

Stage 3.4. Environmental information and data

At this stage, the source or sources of exposure, the environmental medium or media likely to be contaminated and the communities at risk should be identified. The information can be obtained during a site visit and/or discussion with local practitioners and residents. The scope of such visits may include inspections of homes, the workplaces of affected people, waste dumps, water sources, markets, industrial installations and warehouses. These activities should be done before deciding to conduct a field investigation and environmental monitoring or sampling to characterize the type and extent of exposure (see stage 4).

The basis of the approach is the identification and description of plausible relations among *source*, *pathway* and *receptor*, i.e. the source of exposure and the pathway(s) by which individuals and communities are exposed (for further details, see section 2.3).

The *source* is the origin of the pollutant or contaminant. It is the geographical location of the *hazard*, which may be unmodifiable and an inherent property of the chemical(s) of concern. For example, the suspected chemical(s) may be corrosive, irritant, sensitizing, acutely toxic, mutagenic, carcinogenic, toxic to a specific organ or teratogenic (22).

Environmental *pathways* are the means by which an individual or community comes into contact with the source, including air, water, dust, soil, consumer products and foods. Polluted or contaminated environmental pathways are sources of exposure of *receptors* (humans and plant or animal sentinel organisms) by various routes, including inhalation, ingestion and dermal contact (Table 3). A chemical etiology is feasible only if the source, pathway and receptor linkage is completed.

Table 3. Examples of sources of environmental contamination, pathways, exposure routes and likely human receptors

Source	Pathway (exposure route)	Receptors
Gaseous industrial emissions	Air (inhalation)	Populations downwind Susceptible individuals, including those with obstructive and restrictive airways disease
Dust from mining and grinding or particulate emissions from vehicles or industry	Air (inhalation) Deposition of dust on surfaces, clothes, food (ingestion, dermal exposure)	Workers, their families and downwind populations; commuters Susceptible individuals, including those with obstructive and restrictive airways disease
Industrial effluent	Air (inhalation of volatiles and soluble gases) Soil, water, food (ingestion; dermal contact, e.g. from bathing and washing)	Communities that receive a water supply from the polluted source; consumers of contaminated produce Susceptible individuals
Spills and leakages from containers	Water (ingestion) Soil (inhalation, ingestion and dermal contact with particles, contaminated crops and livestock) Air (inhalation of volatiles and gases)	Workers and populations living in the vicinity of the containers Communities that receive a water supply from the polluted source; consumers of contaminated produce Susceptible individuals
Deliberate or covert release of a noxious chemical(s)	Air (inhalation) Water (ingestion) Soil (inhalation, ingestion and dermal contact with particles, contaminated crops and livestock) Food (ingestion)	Communities downwind of an airborne release and people who consume contaminated water and food Susceptible individuals
Ingredients or contaminants in pharmaceuticals, food or consumer products	Food (ingestion) Water (ingestion, dermal contact) Medicines (ingestion, injection, dermal) Consumer products	People who take medicines and drugs and apply lotions and cosmetic products People who consume contaminated food Susceptible individuals

Understanding who was exposed is important in evaluating the likelihood of viable source–pathway–receptor linkages. This is usually done by collecting the environmental histories of those affected. One approach to collecting information on an environmental history is use of the mnemonic “CH²OPD²”, for Community, Home, Hobby, Occupation, Personal, Diet and Drugs (23).

Data from environmental *sampling and monitoring*, if available, may help to identify or confirm the presence of a chemical source, the media contaminated and the community or communities exposed. Such data might,

however, be limited, and it is prudent to consider how, when and where samples were collected in order to ensure that they are *representative* and have been analysed by a suitably *accredited* laboratory so that they can be interpreted with confidence. Environmental data should be used in conjunction with epidemiological data to determine the frequency, duration and magnitude of exposure and hence to make an *exposure assessment* (see section 2.3.5).

Case study 2 illustrates an outbreak in which history-taking and environmental sampling confirmed the source of chemical exposure.

Case study 2: Artisanal mining

Date: February 2010

Location: Zamfara, northern Nigeria

Background

Zamfara State is an agricultural region; however, after an increase in the price of gold, many villagers began mining and extracting gold. Subsequently, local public health officials reported a higher than expected number of illnesses and deaths among young children. Epidemiological investigation by representatives of Médecins Sans Frontières revealed nearly 300 cases in four villages, with an observed mortality rate among children < 5 years of age of 48% (24). Subsequent clinical investigation showed that cases presented with sudden onset of abdominal pain and/or vomiting and intractable seizures with or without fever, sometimes with rapid progression to death; affected individuals did not respond to conventional treatments for infectious disease. The possibility of lead poisoning was considered, as it was observed that many people were engaged in small-scale artisanal gold-mining and that the clinical presentation was consistent with exposure to lead.

Investigation

The Government launched an investigation and convened an international multidisciplinary, multi-organization team, including professionals from the Federal and State Ministries of Health, the Field Epidemiology and Laboratory Training Programme, the United States Centers for Disease Control and Prevention, WHO and Médecins Sans Frontières. The investigation included a cross-sectional survey of households, analysis of blood samples from children and analysis of water and soil samples, including the use of X-ray fluorescence for in-situ soil testing.

Findings

Gold ore in this area is contaminated with lead, and dry crushing of ore in flour mills produced large volumes of lead-rich dust, which caused significant environmental contamination and subsequent community exposure. Environmental sampling confirmed high levels of lead in soil and dust in villages and family compounds, as well as contamination of water sources. Testing of whole blood for lead indicated that, in some villages, 97% of children had levels > 45 µg/dL, requiring subsequent chelation therapy (25).

Intervention

Risk mitigation included remediation of some of the contaminated villages, raising public awareness of the toxicity of lead and encouraging safer mining and ore-processing practices (25). Hundreds of children were treated with several courses of chelation therapy (26). It was reported subsequently that childhood mortality fell to < 2% after the intervention, although Médecins Sans Frontières noted reports of a trend to increasing whole-blood lead since May 2011, suggesting continuing exposure (27).

Key points

- Significant increase in mortality rates unexplained by infectious diseases may suggest a chemical-related outbreak.
- Clinical examination and careful history-taking may suggest the cause.
- Environmental sampling and biological monitoring can confirm the chemical cause of an outbreak and its source.
- Risk mitigation strategies protect community health, including susceptible subpopulations.

The next component of data-gathering is clinical and toxicological information, including documentation of the clinical presentation and estimates of *dose* (uptake) are obtained, when possible.

Stage 3.5. Clinical and toxicological information

Clinical and toxicological information is obtained in three main ways, by taking a history, clinical examination and diagnostic tests.

History-taking

A diagnosis is generally established from a history. In some circumstances, however, the patient may present with reduced consciousness (e.g. coma) or reduced content of consciousness (e.g. delirium). A history should therefore be collected from as many sources as practically possible within the time and resource constraints of the situation. Potential sources of information include the patient, family members, rescuers, co-workers, community members, bystanders,

public health practitioners and other health care professionals.

The probability before testing that a suspected chemical is present affects the probability of a chemical-related diagnosis. Any background information about the likely presence or absence of chemicals in an area of interest is therefore valuable.

A full medical history should be taken for each affected person, if possible. Predisposing factors should be identified, such as respiratory illness. Open questions are preferable to elicit a detailed response. Consideration should be given to planning structured data collection to ensure standardization, especially if large numbers of casualties are anticipated or if the information is later required for forensic purposes. Pertinent questions are listed in Box 3.

Box 3. Taking a medical history: pertinent questions to facilitate diagnosis

- Who has been affected?
- What sources are suspected, e.g. workplace, consumer product, household chemicals, foods?
- Were any rescuers subsequently affected?
- Are there any visible sources of contamination?
- Were any animals also affected?
- What events occurred at the time of potential exposure?
- What symptoms were experienced, and when were they experienced and reported?
- What symptoms have persisted?
- What was the latency between possible exposure and the onset of symptoms?
- What was the location at the time of exposure?
- Was there any protective factor, e.g. shielding from buildings or personal protective equipment?
- When did the event(s) occur?
- Why did individuals attribute their symptoms to a possible exposure?
- How many other individuals are affected?
- Were casualties confined to a subpopulation, e.g. pre-school children?

Clinical examination

In the same way as for the history, a structured plan should be considered. If a patient presents moribund, the examination should be in accordance with international resuscitation practice and include a rapid primary examination to identify and correct airway compromise, ensure spontaneous breathing and

adequate circulation, manage disability and complete a detailed secondary survey.

Once the patient is stabilized or if stable and alert, he or she can be examined for *signs*. There are, however, few truly pathognomonic clinical signs in toxicology. Typical clinical features of exposure to environmental chemicals are listed in Table 4.

Table 4. Typical clinical features after exposure to environmental chemicals

Example	Clinical features
Contaminated food, drink or medicines	
Arsenic in drinking-water	Carcinomas, hyperkeratosis, hepatosplenomegaly, neuropathy
Bongkrekic acid in corn beer (<i>pombe</i>) (28)	Diarrhoea, vomiting, muscle pain, somnolence, hypotension, arrhythmia, hyperthermia, Cheyne-Stokes respirations, coma, death
Diethylene glycol in medicines (29)	Vomiting, abdominal pain, drowsiness, lethargy, coma, metabolic acidosis, oliguria, renal failure, cranial nerve palsy, encephalopathy
Ergot fungus on rye	Neuropsychiatric features, seizures, vasospasm, gangrene
Methylmercury in grain	Ataxia, deafness, dementia, dysarthria, hyperreflexia, paraesthesia
Pyrrrolizidine alkaloids (30)	Acute veno-occlusive disease, abdominal discomfort and distension, oliguria, pleural effusion, cirrhosis
Sodium nitrite mistaken for salt (31)	Dizziness, weakness, abdominal cramps, vomiting, diarrhoea, hypotension, cyanosis
Spanish toxic oil (Madrid, 1981) ^a (32)	Eosinophilia, pneumonitis, pulmonary hypertension, scleroderma
Noxious gases and toxic industrial chemicals	
Chlorine (Graniteville (SC), USA, 2005)	Acute respiratory distress syndrome, bronchospasm, cough, dyspnoea, eye irritation, retro-tracheal pain
Carbon monoxide	Coma, confusion, extrapyramidal features, neuropsychiatric features
Dioxins (Seveso, 1976)	Chronic lymphocytic leukaemia, lymphomas, sarcomas
Hydrogen sulfide (suicides, e.g. Japan, USA) (33)	Arrhythmia, bronchospasm, confusion, cough, diarrhoea, dyspnoea, eye irritation, neurological features
Methyl isocyanate (Bhopal, 1984)	Bronchospasm, bronchitis, extrinsic allergic alveolitis
Chemical warfare agents	
Cyanide	Arrhythmia, coma, fixed dilated pupils, headache, pulmonary oedema, respiratory failure, vomiting
Nerve agent (Tokyo, 1995)	Bradycardia, diaphoresis, dyspnoea, lachrymation, loss of sphincter control, miosis, muscle fasciculation, muscle paralysis, vomiting, wheeze
Vesicants	Conjunctivitis, blistering, dermatitis, erythema
Toxins	
Anthrax	Abdominal pain, chest pain, cough, diaphoresis, dysphonia, fever, fatigue
Botulinum	Autonomic anticholinergic features (dry mouth, postural hypotension, paralytic ileus), bulbar signs (dysphagia, dysarthria, dyspnoea), diplopia, mydriasis, ptosis, respiratory failure
Ricin or abrin	Abdominal pain, diarrhoea, hypovolaemia, multi-organ failure, necrotizing pneumonitis (inhaled), oedema

^a Possible aniline contamination

Exposure to some environmental chemicals (or classes of chemical) and poisons may result in a constellation of features, referred to as a *toxidrome*. Identification of a toxidrome requires integration of information from the history, clinical features found on examination and any available results of tests.

Clinical investigation

General clinical investigations may provide evidence of an effect of exposure to a given chemical(s) on a specific organ without identifying the cause of injury. Examples of such tests include liver function tests, renal profiles, full blood counts, measurement of electrolytes and electrocardiographic investigations. Poisoned patients may show abnormalities in these investigations, and the results should be interpreted by a suitably qualified clinician. Further information is provided in section 2.4.

In some cases, it may be appropriate to undertake *biomonitoring* to assess uptake of a chemical after environmental contamination and exposure by dermal contact, ingestion or inhalation. Biomonitoring involves detection of a suspected chemical, a metabolite of the chemical, a by-product of the chemical or a degradation product. A chemical may be identified quantitatively, semi-quantitatively or qualitatively. Whole blood, serum and urine samples should be obtained and a chain of custody documented if forensic analysis is required. Specific investigations may be used to rule out differential diagnoses such as an infectious etiology.

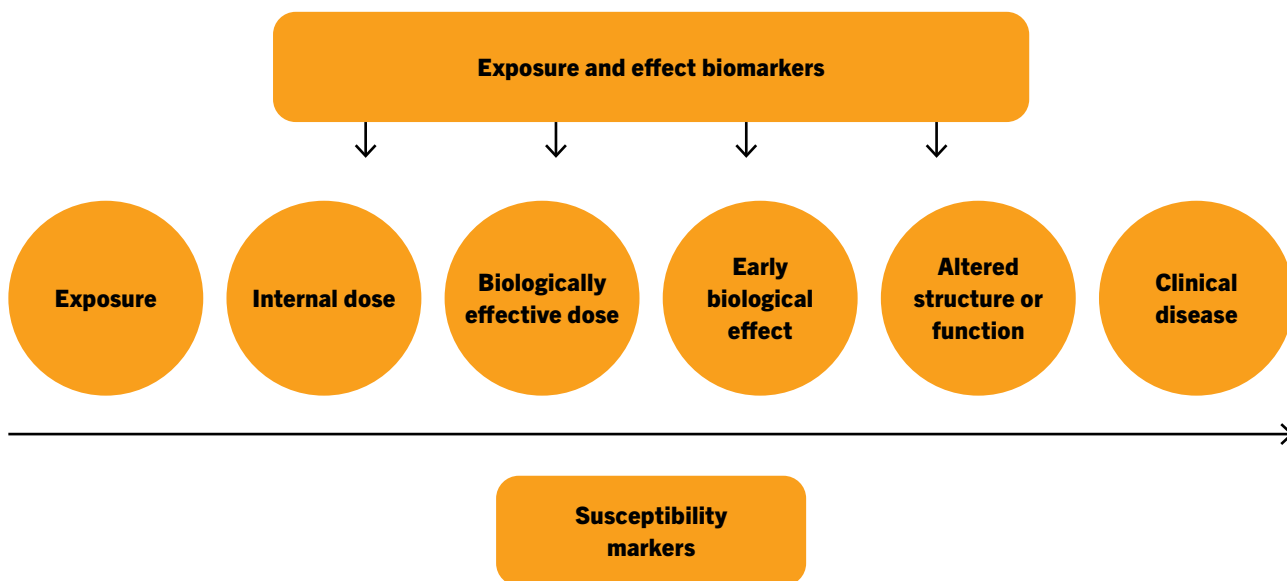
Biomarkers are biological characteristics that are measured objectively and evaluated as indicators of

normal biological or pathological processes. They may be used to determine whether the chemical exposure has caused cell, tissue or clinical injury (Fig. 6) (34). Such measurements support characterization of exposure pathways and health effects, thus contributing to identification of the source and control of the outbreak. Useful biomarkers to be considered in toxicological investigations are as follows.

- *Biomarkers of exposure*: Measurement of the contaminant itself, a metabolite or the product of interaction between a xenobiotic agent and some target molecule or cell. Examples include lead in whole blood, formate in serum after ingestion of methanol and *trans-trans*-muconic acid and S-phenylmercapturic acid in urine after exposure to benzene.
- *Biomarkers of effect*: A measurable biochemical, physiological, behavioural or other alteration that indicates an established or possible health impairment or disease, e.g. a physiological marker that indicates organ function, such as hepatic, renal, cardiac or neurological effects.
- *Biomarkers of susceptibility*: Indicators of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific xenobiotic substance. These are complex and difficult to interpret and are more suitable for long-term follow-up studies. Examples are the genetic polymorphism of metabolic enzymes, DNA repair genes or cytochrome P450 enzymes.

Use of biomonitoring for assessing exposure and effects is illustrated in Fig. 6.

Fig. 6. Human biomonitoring continuum for exposure and effect assessment



Source: reference 35

Biomarkers are also useful in cohort or case-controlled post-exposure studies. Early involvement of a public health practitioner in deciding on a post-exposure study design is recommended.

Assessment of risk to public health

The information gathered from the sources described above can be used to decide whether an outbreak is possibly of chemical origin and the potential impact on public health. Thus, a *risk assessment* should be conducted, which will guide discussion on managing and reducing the consequences on the affected population and preventing spread to other areas and populations (36). Further information is provided in section 2.1.

Outcome of the preliminary investigation

If the initial assessment does not support a chemical-related outbreak, a brief report should be written and shared with colleagues and key stakeholders and the investigation terminated (stage 5). It may be re-opened if further information comes to light.

If the assessment indicates that the data are consistent with an outbreak of chemical etiology and that there is a continuing risk to public health, the findings should be documented, and the investigation should proceed to a field investigation (stage 4).

Stage 4: Field investigation

Objective: To verify that an outbreak is due to exposure of a community to a chemical hazard and to determine the magnitude of the event.

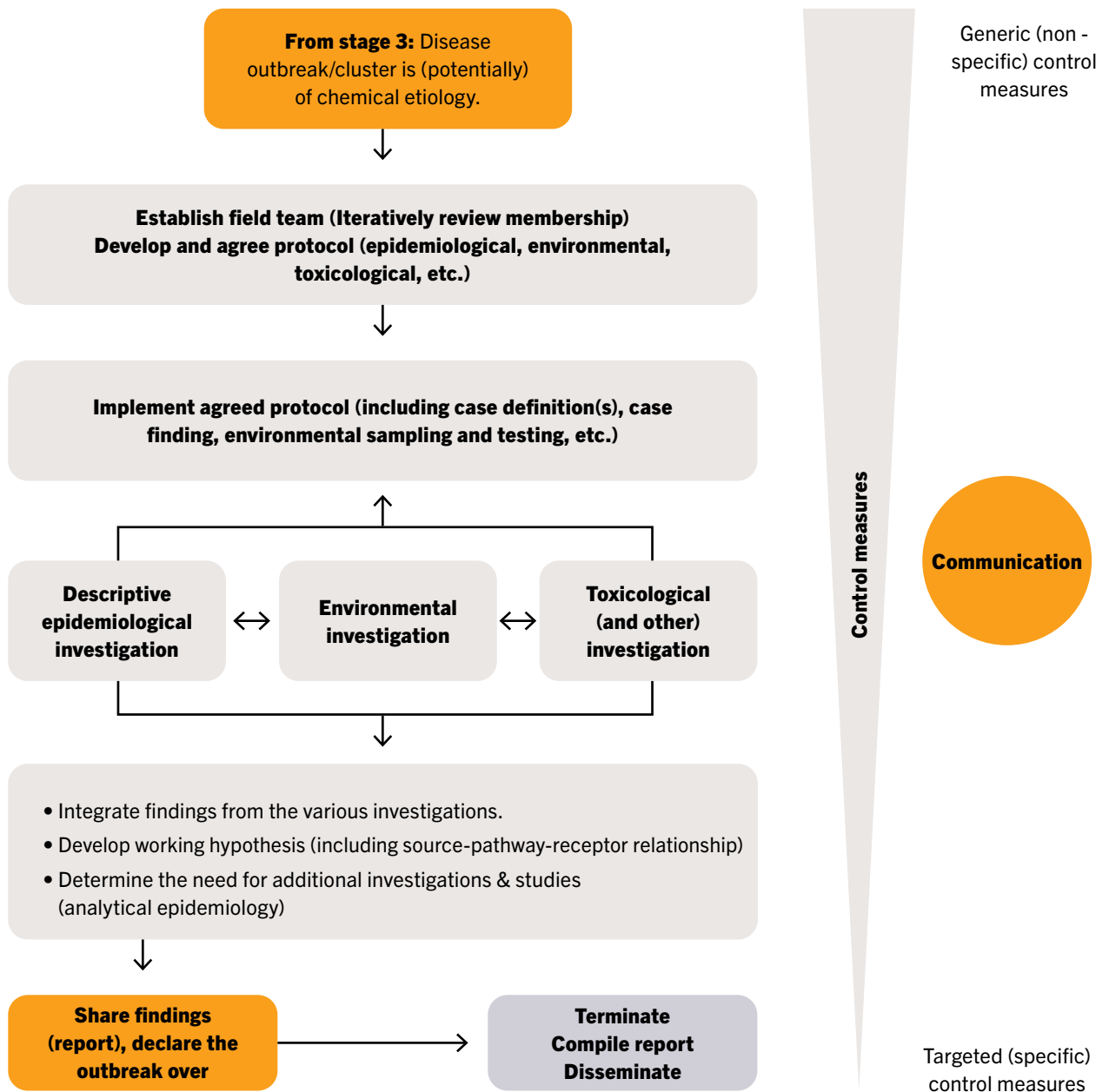
Field investigation is likely to be a major undertaking in terms of equipment, staff and resources, resulting in significant cost. It should therefore be done only after careful consideration of the objectives and with a clear *plan* and *preparation* to ensure optimal use of resources and to maximize the chances of operational success.

Key aspects of stage 4

- Determination of objectives
- Establishment of multidisciplinary team
- Preparation for field visit
- Ensuring safety and security
- Collection, collation and analysis of epidemiological, environmental and clinical data
- Communication
- Risk management
- Reporting

The elements of stage 4 are illustrated in Fig. 7.

Fig. 7. Stage 4: Key components of field investigation



Stage 4.1. Preparation

The function of the field study should be clearly specified in order to define the aims, objectives, the terms of reference of the investigation and, equally importantly, what will not be covered. The safety and security of the personnel must be assured, and the site investigation must be conducted in compliance with established health and safety protocols. All these considerations should be included in the framework of an ethical study. Annex 2 provides examples of forms and questionnaires and illustrations of basic epidemiological concepts that may be of value during this stage of the investigation.

Objectives

Although each field investigation will reflect the principal findings of stages 1–3, the likely objectives are:

- to identify any obvious sources of contamination at a site or location;
- to confirm the source(s) and environmental pathway(s) of receptor exposure;
- to establish a case definition and actively seek cases;
- to confirm a clinical diagnosis, with laboratory confirmation if appropriate;
- to identify and describe the population at risk and the likely causative agent by appropriate epidemiological and environmental investigations;
- to assess any continuing risk to public health of the chemical exposure;
- to identify what interventions are required immediately to protect public health along the source–pathway–receptor linkage;
- to coordinate with national and, if relevant, international agencies for outbreak investigation and response; and
- to communicate with professional groups or organizations, the media and the general public, as appropriate.

Meeting these objectives will require many disciplines, agencies and organizations, possibly international. Those likely to be required during this stage of the outbreak investigation are:

- behavioural science
- clinical toxicology
- engineering
- environmental chemistry
- environmental health

- environmental public health
- environmental sciences
- epidemiology
- food science
- geology
- health and safety
- hydrology
- laboratory medicine
- occupational medicine
- risk communication

The composition of the team will depend on the specific investigation and must be planned early. The composition should be flexible enough to accommodate any changes in the outbreak situation, especially in outbreaks of unknown illness, when uncertainty about the nature of the hazard, the extent and severity of exposure and the spectrum of health effects. It is important to include local investigators who speak the same language as the community and are familiar with local culture and customs (37).

Once the remit and disciplines have been decided, resource requirements should be determined, including arrangements for housing and transport of personnel to the field with the necessary equipment. The equipment may include material for sampling, sample storage and packaging for sample dispatch, local maps, cameras, telecommunication equipment, computers and GPS devices. These components form the basis of the *mission plan* (see Annex 3 for an example).

Depending on the resources available in the outbreak setting, much of the equipment might have brought into the country, particularly if there are specific requirements, such as special containers.

Safety and security

The safety and security of the investigation team and the affected and neighbouring populations must be assured. Security situations are not static, and safety and security should be reviewed regularly to determine whether additional resources and precautions are required. Basic considerations for the safety and security for the investigation team are:

- appropriate vaccination and prophylaxis;
- compliance with health and safety protocols;
- provision of tailored, contemporary training;
- provision of appropriate personal protective equipment;

- up-to-date information on local security issues and confirmation that all team members are aware of the necessary precautions;
- adequate telecommunication equipment suitable for the location; and
- awareness of local customs, habits and cultural norms.

Further considerations are listed in Annex 4.

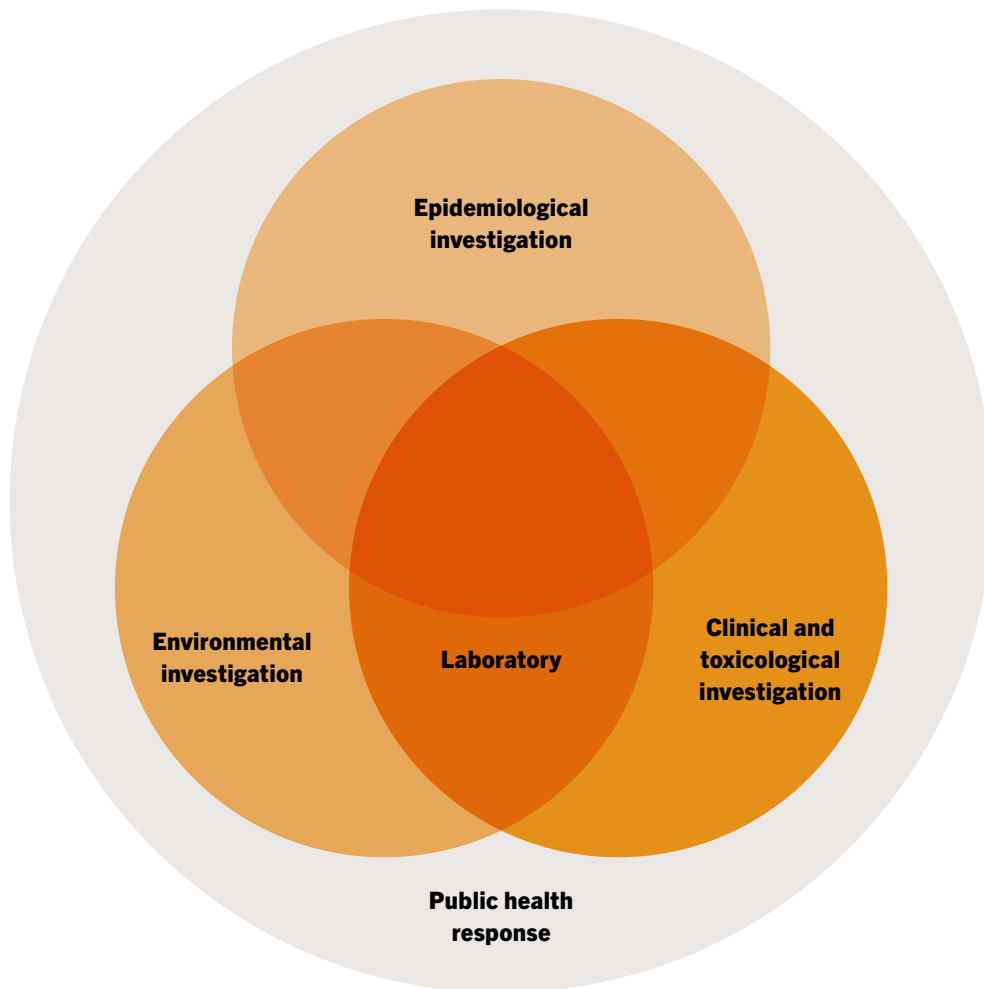
Stage 4.2. Conducting a field investigation

Field investigations of chemical-related disease outbreaks must take into account the complex interplay among *source*, *pathway* and *receptors*. More than one chemical hazard at the source might have to be considered, how their toxicological effects interact and the magnitude and duration of exposure. Susceptible populations must be identified, such as elderly, frail

or sick people and infants and any known genetic susceptibility, with the wider social determinants of health, such as culture, life-style and socioeconomic status (19). Exposure to the hazard(s) of concern might have occurred at some time in the past, even if the signs and symptoms are current, which will compound the difficulty of establishing the cause.

A field investigation might have to be conducted rapidly, as chemical-related outbreaks are often public health emergencies and associated with large numbers of casualties, severe illness or fatalities, particularly in susceptible subpopulations. The outbreak will have generated widespread political and media interest and public concern. A coordinated epidemiological, environmental and clinical–toxicological investigation is therefore essential as a basis for risk mitigation and communication (Fig. 8).

Fig. 8. Integrated approach for the investigation of disease outbreaks of suspected chemical etiology



Epidemiological, environmental and clinical–toxicological investigations are the basis of a field study, requiring integration and coordination to ensure a holistic approach and the best understanding of the causative role of a chemical hazard(s) in the outbreak. The order in which these investigations are conducted will depend on the nature of the event.

Stage 4.3. Descriptive epidemiological investigation

Epidemiological investigation provides the basis for all the other components of a field study for limiting further exposure and mitigating risks. Its aim is usually to provide an accurate description of the outbreak, identify and characterize the affected individuals and populations and identify possible causative agents and pathways of exposures. The main steps in an epidemiological investigation are:

- review of findings (clinical, toxicological and environmental) in stage 3 and verification of an outbreak;
- design of protocols for a step-wise, logical investigation;
- review and establishment of case definitions and case findings;
- a *descriptive* analysis of the data;
- identification and confirmation of the source and pathways of exposure; working hypothesis;
- decision on whether an *analytical* epidemiological investigation is required;
- recommendations for effective control measures and prevention of future outbreaks;
- liaison with other disciplines, agencies and organizations to ensure an integrated, coordinated, efficient investigation;
- preparation of a communication strategy; and
- dissemination of findings.

An epidemiological investigation thus allows establishment and verification of a case definition, exploration of temporal, geographical and demographic data (descriptive analysis), determination of the population at risk and hypothesis generation.

Case definition and verification

Establishment of a *case definition* is the first step in an epidemiological investigation. It provides the criteria for including only people who have the health effects under investigation and the basis for finding cases. Case definitions may comprise various combinations of

clinical, environmental, laboratory and epidemiological criteria:

- clinical presentation of agreed signs, symptoms and toxidromes;
- laboratory analyses (when available or appropriate) of biomarkers of exposure and of effect;
- chronology: the period during which identified cases can be considered part of the outbreak;
- geography: residence in a potentially exposed area; and
- demographics: inclusion of those most likely to be affected, e.g. by age group, occupation or gender

Their aim is correct identification of all outbreak-related cases (high *sensitivity*) and exclusion of unrelated cases (high *specificity*). A single, all-encompassing case definition might not be possible at the beginning of an investigation, as the source and the pathways of exposure may not be fully determined, and the case definition might have to be broad to ensure that all cases are captured. Presenting cases might have to be classified according to the strength of the evidence that they were exposed to the suspected chemical and have related clinical features. In an evolving outbreak, case definitions may be dynamic and be refined as new information becomes available. Cases may be classified as “suspected or possible”, “probable” or “confirmed” according to the certainty of the diagnosis:

- *Suspected case*: person presenting with clinical features consistent with the outbreak and considered for laboratory or other diagnostic investigation
- *Probable case*: person presenting with clinical features consistent with the outbreak and resident in the affected area during the defined period, or person presenting with the clinical features of concern and epidemiological links to an analytically confirmed case
- *Confirmed case*: person presenting with clinical features consistent with the outbreak, resident in the affected area during the defined period and with laboratory or diagnostic confirmation.

Additional information on case definitions is given in section 2.2.3.

Finding and interviewing cases

In order to determine the size of the outbreak and to characterize the population at risk, active case-seeking should be established by painstaking work, involving encouraging local hospitals, clinicians, poisons centres,

laboratories, workplaces and the community to notify cases that meet the definition to the team. Members of the field team might have to search admission records at local hospitals (in full compliance with local regulations for data governance) and also conduct occupational and household visits. They might also have to review surveillance and health care databases (see Annex 2 for suggested sources of data). Information could be sought from the public through the mass media, taking care to

minimize alarm and anxiety and prevent an overwhelming influx of people with unrelated illnesses or concern about (but no evidence of) exposure (38).

Once cases have been identified, individuals, family and other social contacts can be interviewed comprehensively and with a standardized approach to ensure collection of key information. Table 5 lists the areas to be covered in interviews with cases (and also with controls in a case–control study).

Table 5. Principal topics to be covered in a field investigation questionnaire

Data	Purpose
<i>Identifying data:</i> unique identification number, name, address, other relevant identifiers (N.B. This information must be protected to ensure privacy and confidentiality.)	For linkage with samples and to identify geographical clustering
<i>Demographic data:</i> e.g. age, sex, ethnic group, occupation	To characterize outbreak cases and define the population at risk of illness
<i>Clinical data:</i> date of onset of symptoms, duration of illness, severity of illness, hospitalization, treatment, clinical outcome, such as recovery or death	To describe the clinical course and outcomes and identify potential etiological factors
<i>Exposure and data on risk factors:</i> e.g. food and water exposure, occupational exposure, environmental risk factors, personal risk factors	To aid in identification of the source and exposure pathway of the outbreak and determine the cause
<i>Local understanding:</i> perceptions of what caused the illness and identification of cases	To assist in hypothesis generation

Suggestions for questionnaire design and a sample questionnaire are provided in Annex 2. The questionnaire should elicit the minimum data necessary to achieve the objectives of the descriptive epidemiological investigation. It should be in the local language and administered by trained interviewers fluent in that language.

All the data collected should be collated into a single database to generate a list of cases. Additional data from environmental, toxicological and laboratory investigations and other relevant sources may also be included. Annex 2 provides examples of case-based surveillance forms and weekly morbidity and mortality line list forms.

A thorough search for cases complemented by a comprehensive interview will minimize bias and ensure that the investigation is accurate and its findings are correct.

Descriptive analysis

Descriptive analysis comprises the collection of temporal, geographical and personal information.

Temporal distribution of cases

Recording the timing of cases provides valuable information on the evolution of the outbreak and insight into when and where exposure may have occurred. This information may be plotted graphically to produce an epidemic curve, the shape of which may indicate the type of exposure involved in the outbreak (see Annex 2 for further information).

If the physico-chemical and toxicological properties of the suspected chemical(s) and its source become apparent

during the investigation, the case definition might be refined to exclude cases that do not meet the temporal relation between exposure and health effects. For some chemicals, the *latency* between exposure and clinical presentation may be short, while for others the temporal association may not be obvious and may be unpredictable; an example is a chemical with delayed effects (37).

Geographical distribution of cases

The geographical distribution of the outbreak can provide clues to the source and the nature of exposure. Location data are best displayed and visualized as maps, such as *spot maps*, which illustrate the geographical distribution of a specific attribute such as the number of cases, and *choropleth maps*, which aggregate a variable such as population density, temperature, rainfall or number of cases. Additional layers of information can be added, such as the location of industrial sites and weather parameters. Maps can be created with commercial or freely available *geographical information systems (GIS)* software. If necessary, expert advice should be sought to identify a suitable GIS software package and to provide support in mapping.

Personal characteristics

The personal characteristics of outbreak cases, such as age, sex, ethnic group and occupation, can help to define the population at risk and identify specific exposures. They can also indicate differences and similarities between cases and non-cases. Cases should also be described by their clinical characteristics such as symptomology, illness severity and outcomes.

Determining the population at risk

The population at risk is those people who do or may meet the case definition as determined by the findings of the descriptive analysis. Occasionally, additional information about affected people might be derived from special surveys (19).

The population at risk is not always homogeneous, particularly in outbreaks with a wide geographical distribution that affect several population groups. The investigating team should also be aware of the possibility of shifting patterns, such as spread to adjoining geographical areas or inclusion of new age groups, and should redefine the population at risk as required. A clear definition of the population at risk is necessary for accurate calculation of measures of disease occurrence, such as rates and ratios,

and some measures of association, such as rate ratio or relative risk. Information on rates and ratios commonly used in field epidemiology is given in Annex 2.

When the population at risk is unknown or poorly defined, it is difficult to estimate disease risk accurately. Description of the distribution of cases is nevertheless helpful in formulating a hypothesis.

Generating a hypothesis

This involves careful review of the findings of descriptive epidemiology and other information (19). A hypothesis is usually based on clinical data, the case definition, the likely source(s) of exposure and the hazard(s) and the environmental pathways likely to be involved. It is further based on the geographical or social setting of the outbreak and interviews with affected people (19, 39).

A hypothesis must be *plausible* according to epidemiological, clinical and environmental observations and data and be sufficiently robust to explain the clinical presentation of most or all cases. Repeated reappraisal of the information may be required, and the hypothesis should be compared with established facts. Once a working hypothesis has been constructed, it may form the basis for *analytical* investigation (see section 2.2.4).

If it is not possible to generate a plausible hypothesis, the possibility of a chemical etiology should not be discounted; rather, alternative sources and pathways should be considered until a suitable explanation is found or all reasonable possibilities have been exhausted. It is good practice to keep a record of the hypotheses made, with explanations of why any were rejected.

Analytical investigations

The findings from descriptive investigations may be sufficient to identify the cause of the outbreak and the pathway(s) of exposure and indicate targeted, effective control measures. If this is not the case, additional field investigations, including an analytical study, may be necessary. The circumstances under which an analytical epidemiological investigation might be required are (40):

- The source–pathway–receptor relation has not been fully elucidated.
- A number of hypotheses for the source and exposure pathway(s) were identified from descriptive epidemiology and should be tested formally.

- Further understanding of the nature of the outbreak is required (subject to resources and technical and operational constraints).
- Further, more valid data are likely to be obtained.
- The team agrees that an analytical epidemiological investigation is necessary as part of a strategic, coordinated investigation with environmental and laboratory studies.

Further information on epidemiological investigations, including analytical studies, is provided in section 2.2.

Stage 4.4. Environmental investigation

Principles

The purpose of the environmental component of a field investigation is to identify the source of the outbreak and to identify and characterize the hazard and its physico-chemical properties in order to elucidate the environmental medium or media likely to be contaminated. In this way, subsequent environmental monitoring and sampling can be directed to the medium or media of concern and provide a basis for determining the magnitude and duration of exposure.

The environmental investigation should begin with site visits, which may include inspection of the homes and workplaces of affected people, waste dumps, water sources, markets, industrial installations and warehouses. This will form the basis for deciding what environmental data are necessary and the subsequent step-wise approach.

The main objectives of an environmental investigation are:

- identification, evaluation and characterization of potential environmental hazards;
- development of a conceptual site model and description of plausible source–pathway–receptor relations;
- screening and prioritization of the identified risks and assessment of the likelihood of adverse health effects arising from exposure to the identified hazards; and
- identification of effective public health action to control the outbreak.

The steps in an environmental investigation are:

- establishment of a clear plan and the scope of the investigation and links with the epidemiological, clinical and toxicological investigations;
- a field visit to further develop the conceptual site model and confirm hypotheses about potential hazards;
- liaison with designated (accredited) laboratories to agree on sample collection and transport and interpretation of data;
- an assessment to determine where and how exposure is occurring, to estimate the environmental concentrations of suspected chemicals and to identify the populations who are potentially exposed;
- liaison with clinical colleagues to ensure coordination of biomonitoring in receptors;
- integration of findings with those from the other investigations to determine the cause of the outbreak; and
- preparation of a report of the findings, conclusions and recommendations, including whether further studies are required.

Environmental monitoring and sampling

The terms environmental “monitoring” and “sampling” are often used interchangeably, although there are subtle differences. *Sampling* usually comprises taking a discrete, often single sample of the environmental medium under investigation, whereas *monitoring* refers to regular or continuous collection of samples. For example, collection of a soil sample for laboratory analysis is considered to be environmental sampling, while routine sampling of air near a busy road is considered monitoring.

Box 4 lists a number of considerations to be made before environmental data collection and analysis.

Box 4. Factors to be considered before environmental sampling and monitoring

- Why are environmental monitoring and sampling necessary? Are there already data and information that could be used?
- What environmental media should be monitored (e.g. air, water, soil, food)?
- What hazard(s) should be measured?
- How should sampling be done?
- Where should samples be obtained?
- How many samples should be taken to ensure that sampling is representative?
- What equipment and methods are available, and do they require calibration and maintenance?
- How should samples be collected and transported?
- How should samples be collected, stored and transferred without compromising the chain of custody?
- Has an accredited laboratory been identified, and have arrangements been made to transport and store samples?
- Are protocols such as for quality assurance in place?
- Have the health and safety of the field investigation team been considered?

Environmental *monitoring* and *sampling* require different equipment and techniques, depending on the focus of the investigation. No one technique or instrument can be used to monitor all environmental media or all potential hazards. The nature of the *exposure* will determine whether air (indoor and outdoor), water (including drinking-water and recreational water), dust, soil and vegetation should be monitored or sampled. Various methods can be used for each environmental medium; for example, surface water can be monitored with handheld instruments, or single samples can be collected for laboratory analysis. Investigators may also use ecological indicators, such as fish or invertebrates, to assess environmental quality or may use remote sensing and satellite imagery (see section 2.3.4).

The analysis must be *representative* of the sampling site or medium and must be both *accurate* and *precise*. Samples to be analysed should be collected in suitable containers, appropriately labelled and identified, and stored and transported correctly (*pre-analytical* considerations), accompanied by appropriate paperwork. A correct procedure reduces the risk that samples were erroneously collected or accidentally or deliberately tampered with and ensures confidence in the results of analysis (*chain of custody*).

Specimens should be analysed by methods that ensure accurate, precise, specific identification of analytes and, ideally allow processing of many samples in a short time (*high throughput*). Moreover, the laboratory should participate in both *internal quality control* and *external quality assessment* and be suitably accredited to ensure

confidence in the results (*analytical considerations*). The data should be interpreted by a suitably qualified person with those conducting the investigation (*post-analytical considerations*). Further information on the role of laboratories in outbreak investigation is provided in section 2.5.

Existing data

Any existing data may be useful in determining background exposure and emission of pollutants. If the *hazard* was or is from a specific point source, such as an industrial facility, data or records of emissions may be available, which are useful in identifying an environmental hazard. Such data may be available if the industry is required to meet regulatory limits; furthermore, in many countries, environmental data are collected routinely for regulatory purposes by environment agencies and local authorities. Other sources of environmental data include those from continuous monitoring of ambient air in networks and around sources of pollution such as industries or main roads. Although such networks can provide data on background levels of pollution, they may not be located near the area or source under investigation or may not include the pollutants of concern.

When *exposure* occurred in the past, soil, sediments and vegetation may indicate previous exposure. Whereas pollutants in air and water tend to disperse and dilute quickly from the source of a release, soils and vegetation may trap pollutants and indicate past and even current exposure. For example, after the accidental release of a

large quantity of dioxin from a pesticide plant in Seveso, Italy, the extent and level of dioxin contamination in soil in the direction of the prevailing wind was used to identify the populations that were most exposed. Subsequent analysis of dioxin levels in the plasma of people from these affected areas showed that the body burden was closely correlated with the levels of environmental contamination (41).

Proxies of exposure

If monitoring or sampling is not possible, exposure can be estimated indirectly. A common approach is to use proximity to the suspected source as a proxy; however, this does not include the influence of meteorological conditions or the behaviour of the suspected pollutant in the environment, and exposure zones may be several kilometres beyond the point of release, resulting in considerable exposure misclassification and possible confounding exposures from other sources. Exposure will vary widely in these zones and may include people who were not exposed at all (42).

Another approach is use of computer models to predict exposure. Air dispersion models are a widely accepted method for regulating emissions to the atmosphere from major industries, and many commercial models are available to predict the worst-case ground-level concentration around industrial sources in the short and the long term. Similar models are available to predict the behaviour of chemicals in water and soil. The accuracy of any model, however, depends on the quality of the input data.

Investigators in the field may use a range of techniques, from proximity or industrial records to sampling and even use of computer models. Further information on the logistics of field visits, including inspection of sites and environmental sampling, is provided in section 2.3.

If the suspected contaminant is in a food, sampling and analysis may follow guidance provided by WHO (43).

Case study 3 gives an example of a field outbreak investigation with integrated clinical, epidemiological and environmental studies.

Case study 3: Mass bromide intoxication after food contamination (44)

Location: Luanda, Angola

Date: November 2007

Background

An outbreak of illness of unknown etiology affected over 450 people in Cacuaco municipality. The preliminary assessment suggested a chemical cause, which was subsequently confirmed in a full-scale field investigation.

Epidemiological investigation

Descriptive epidemiological analysis and a case–control study showed that the cases were mostly young children and women, often in the same household, although not all members were necessarily affected. The investigations (including the epidemic curve) suggested food-borne intoxication rather than an infectious cause.

Site visit

A site visit indicated the presence of a number of hazardous chemicals in the affected area, including petrochemical industry waste, expired pharmaceuticals and other industrial chemicals. At one waste site, a number of empty bags labelled sodium bromide were found. This suggested a plausible cause, which was consistent with the findings of the clinical investigation and the working hypothesis of the epidemiological investigation.

Environmental investigation

Community members in the affected area were interviewed to identify potential sources of exposure, and site visits were made to potentially contaminated sources (water collection and treatment points and hazardous waste sites). Environmental samples such as food items, water, soil, drugs and traditional medicines were collected, guided by the epidemiological findings.

Clinical and toxicological investigations

Clinical examination revealed severe central nervous system signs and symptoms, including ataxia, disorientation, memory loss and slurred speech. The clinical profile indicated that the outbreak was unlikely to be of infectious or psychological origin.

Toxicological investigation was guided by the clinical findings. Blood and urine samples were tested for known central nervous system depressants (e.g. long-acting benzodiazepines, organic solvents, γ -hydroxybutyrate), but the results were unremarkable. Subsequently, bromide levels in serum were found to be significantly elevated. The environmental samples were then tested, and some table salt samples were found to contain $\geq 80\%$ sodium bromide. In interviews with some cases, it was found that the table salt had been bought from an itinerant merchant.

Conclusions

The clinical features, documented evidence of adulteration of table salt and the presence of bromide in blood all suggested that the cases were due to sub-acute bromide toxicity.

Key points

- Epidemiological, environmental and clinical–toxicological investigations are complementary and are supported by laboratory analysis of biological and environmental samples.
- Site visits can provide further evidence of the etiology of an outbreak.
- Integration of different investigative streams can result in identification of the causative agent and the pathway of exposure.

Once the environmental data have been collected, collated and analysed and the potentially exposed population defined, individual exposure can be determined and potential cases examined to determine the dose received.

Stage 4.5. Clinical and toxicological investigations

The main components and functions of clinical–toxicological investigations are as follows.

- Contact poisons centres, hospital emergency departments, clinicians, primary care services, coroners and pathologists to obtain as full a picture of cases as possible.
- Review the available clinical information.
- Clinically examine a representative sample of affected individuals.
- Document signs and symptoms and determine whether they are consistent with a defined toxidrome.
- Define the appropriate clinical investigation, including biological specimens for biomonitoring.
- Interpret the clinical data, and formulate a working diagnosis.

- Facilitate clinical management, including monitoring, supportive symptomatic care, pharmacological intervention (including antidotes) and long-term follow-up.
- Liaise with other members of the field investigation team.
- Disseminate and communicate the findings.

The information derived provides insight into the etiology of the outbreak and may also inform epidemiological and environmental investigations, illustrating the importance of an integrated approach. Further information on the principles of clinical and toxicological investigations is provided in section 2.4.

Sometimes, however, there is no recognizable source or environmental pathway, or the clinical presentation is not consistent with known environmental hazards. Under such circumstances, it is appropriate to consider mass psychogenic illness.

Stage 4.6. Mass psychogenic illness

Perceived exposure to biological or chemical agents may result in episodes of medically unexplained illness,

variously known as *mass psychogenic illness*, mass sociogenic illness or mass hysteria. This consists of rapid spread of medically unexplained signs and symptoms in a group or setting, which is misinterpreted by the affected people as an indication of serious physical illness.

Episodes of mass psychogenic illness are surprisingly common. In a review of a random sample of apparent chemical incidents in England in which people reported symptoms, no chemical exposure could be identified in one in six episodes (45).

Mass psychogenic illness is a diagnosis of exclusion and should be considered only when all the appropriate investigations have been undertaken and have provided no objective evidence of a real outbreak. Rapid recognition of a mass psychogenic illness, however, provides an opportunity to intervene and reduce its spread. Common characteristics of mass psychogenic illness are as follows (46, 47).

- The symptoms have no evident organic basis.
- Most symptoms are transient and benign, such as headache, dizziness, weakness, fainting.
- There is rapid onset of and recovery from symptoms.
- The outbreak occurs in a defined or cohesive group.
- The affected group may already be under some form of psychological stress.
- The symptoms may be triggered by a real or perceived odour.
- The index case is a person of relatively higher status (e.g. an older student), and the symptoms spread to lower-status or younger people.
- The symptoms can spread from an affected person to others by sight.
- Females are more likely to be affected than males.
- The outbreak can be spread by rumour or media reporting.

Management of such episodes to the satisfaction of the affected population is difficult, and they are best managed in a coordinated public health response involving various stakeholders and experts (e.g. public health, environmental health and clinical specialists, behavioural scientists, psychologists and communications). The best approach has not been defined, but it is advisable to identify stress-related stimuli (e.g. incorrect media reporting or an odour in a building) and intervene to reduce their impact. It may be appropriate to close the site (e.g. school or workplace) at which the episode occurred until evidence indicates that there is no contamination. It may also be appropriate to conduct investigations, while managing expectations and ensuring that no inappropriate or uninterpretable testing is conducted.

Once clinical, toxicological and other clinical data become available, the information must be communicated carefully and empathetically. It is preferable to avoid suggesting that “there is nothing wrong” or that the episode is purely psychogenic or sociogenic, as this invalidates people’s experience and may incite them to prove that something is wrong by remaining ill. If the investigators are certain that the symptoms have no organic basis, they should emphasize the good news that there is no indication of toxic contamination, infection or physical disease, while stressing that medically unexplained symptoms are common throughout the world, the symptoms are non-fatal, and most people improve rapidly and continue to live satisfying, productive lives (46, 48). Case study 4 illustrates a case of mass psychogenic illness.

Case study 4: Mass psychogenic illness at a school

Location: Warren County (TN), USA

Date: November 1998

Background

A teacher at a high school noticed a “gasoline-like” smell and subsequently complained of a headache, nausea, shortness of breath and dizziness. Her pupils soon reported similar symptoms, and the classroom was evacuated. As more pupils began to report symptoms, the entire school was evacuated by activating the fire alarm. Large numbers of emergency personnel attended, and ambulances took the index case and several children to hospital. Of 100 additional people (students, staff and one family member) who made their own way to the emergency room, 38 were admitted for observation. After a 2-day closure, during which no exposure of concern was identified, the school was re-opened; however, 71 people reported additional symptoms, and the school was again evacuated, many attending emergency services.

Investigation

Blood and urine specimens were taken from affected people, and the environment was explored intensively, including aerial surveys to identify nearby sources of contamination, exploration of local caves, evaluation of the school’s plumbing and structural systems and analyses of air, water, waste and wipe samples, which were tested for a wide range of possible contaminants. Questionnaires were administered to the index teacher and her class and to pupils in other, randomly selected classes.

Indicators of mass psychogenic illness

Analysis of blood and urine samples proved unremarkable, and environmental testing failed to identify an obvious cause for the symptoms. While many symptoms were reported, they were almost all subjective. For example, while over 25% reported fever, only one was found to have an elevated temperature. The symptoms resolved quickly after removal from the school or administration of oxygen. No clear pattern of exposure was found, as students in buildings with different air supplies were affected. The questionnaires indicated that the risk factors for symptoms included being female, observing another ill person during the outbreak, knowing that a classmate was ill and detecting an unusual odour, which was described differently by different people.

Impact

The incident led to loss of an estimated 18 000 person-days and of 3000 person-hours of investigation, with the involvement of 12 government agencies, 8 laboratories and 7 consulting groups, at substantial financial cost to the health service. The psychological impact on the children and staff was not assessed but can be assumed also to have been substantial. Local media reports of potential exposures and rumours of incompetence and cover-up continued for 1 month after the incident.

Key points

- Mass psychogenic illness can become a major incident that is difficult to resolve.
- “Red flags” for mass psychogenic illness may sometimes be found at an early stage. These include an unusual distribution of cases, rapid resolution of symptoms and no readily apparent exposure.
- Dramatic interventions by emergency responders and intense environmental investigations may add to anxiety. When mass psychogenic illness is suspected, incidents should be de-escalated and reassurance given to the community.

Source: reference 49

Stage 4.7. Communication

Oral histories from community members help in fully understanding an outbreak, empower community members and demonstrate that the investigation team values their perspectives and experiences (8). Involvement of the community in designing the investigation will help to build trust in its conduct and outcomes (10); see section 2.1.3 for further details.

Once the information to be obtained has been agreed, there must be regular team meetings, updates through *situation reports* and regular communication with the public and the media. Annex 5 provides further information on communication and reporting in field investigations.

Stage 4.8. Control measures: risk management

Once comprehensive data have been obtained on the nature of the outbreak, its etiology and its public health impact, investigators should determine whether the risks associated with the exposure can be removed, reduced or accepted (*risk management*). The decision should be based on understanding of the nature of the source, the pathways contaminated and the receptors exposed and based on a pragmatic, practical, feasible approach. The interventions instigated may include a combination of regulatory, non-regulatory, political, economic, advisory and technological options. Examples of interventions at the source, exposure and receptor are given in Box 5.

Box 5. Risk management considerations

Source:

- Removal of the hazard by e.g. environmental remediation (case studies 2 and 3) or, in the case of a contaminated product, organizing product recall and replacement (e.g. case study 4)
- Stopping or preventing the cause of the risk, e.g. blocking a leak, closing an industrial process
- Informing people about dangerous activities or behaviour, e.g. to stop an activity that results in chemical release (e.g. case study 2) or to stop consuming food from contaminated land
- In an occupational setting, improving occupational hygiene
- Planning and implementing sustainable long-term measures to prevent reoccurrence, e.g. by:
 - policy, legislation, regulation and enforcement
 - chemical substitution, i.e. replacing a hazardous chemical with a safer one

Exposure:

- Greater site security to prevent access to hazardous chemicals in storage or at a factory
- Greater distance from point sources of pollution (e.g. case study 2: persuading people to move ore-grinding operations away from villages)
- Provision of clean, wholesome water; replacement of contaminated food
- Washing and peeling fruit and vegetables
- Use of personal protective equipment
- Public education (e.g. case study 2)

Receptors:

- Introducing systems to monitor the potential public health impact of chemical exposures
- Provision of safe, effective health care for the affected population
- Timely, open, transparent risk and crisis communication
- Altering the perception of risk through education and effective risk and crisis communication
- Timely, effective intervention

Successful risk management depends on the public's perception of risk and the effectiveness of risk communication. Different people perceive risks differently, depending on factors such as the probability of adverse effects, the people affected, how familiar, widespread and dreaded the effects are and whether individuals agree voluntarily to bear the risk. Although the public's opinion on acceptable risk is considered to be dynamic, it is usually in the direction of further risk reduction (50).

A decision may sometimes be made to accept the risk (*risk acceptance*), usually as a balance between the risks posed to the community and the sum of the social, political and economic advantages that individuals and communities accrue in return for tolerating the risk (34). For example, if a risk–benefit analysis indicates that there is little likelihood of harmful health effects and the economic and social costs of mitigation or elimination are high, communities may choose to accept the risk. There are diverse opinions on how risk–benefit analyses should be conducted and the weight to be assigned to conclusions about risk management. A detailed discussion of these issues is beyond the scope of this document, and further information should be sought from experts and textbooks.

Further information on risk analysis is provided in section 2.1.2.

Stage 5. Completion of the investigation

Objective: To bring the investigation to a conclusion and review the outbreak response

Investigations undertaken during stages 1–3 may suggest or demonstrate that the outbreak is unlikely to be of chemical etiology, and the investigation can be concluded. A report should be written, with a

critical analysis of the data, the conclusions drawn and recommendations, stating that a new investigation will be conducted if further evidence comes to light.

If a full field investigation is undertaken (stage 4), it will be concluded after satisfactory identification of the cause and source of the outbreak and implementation of control measures. The lead health agency, the outbreak control team, the ministry responsible for health and other stakeholders should formally decide when the outbreak is over and issue a public communication to that effect. A statement should also be issued that, although the event has been resolved, a *residual risk* may remain.

When completing an investigation, it is good practice to review the entire outbreak investigation and response with all stakeholders to identify lessons and steps to reduce the likelihood of reoccurrence. The main features of an incident review are:

- Assess the effectiveness of control measures (continuing surveillance).
- Arrange a comprehensive evaluation of the outbreak response (see Annex 5).
- Undertake a detailed debriefing to identify what went well and what went less well.
- Identify strategic medium- and long-term measures for prevention and control, and make clear recommendations to relevant agencies.
- Identify resources, technical support and training requirements (including guidelines) for resilience and to optimize future outbreak responses.
- Assess whether further research is required to address unresolved questions.

The team should prepare an interim mission report a few weeks after the end of the investigation, followed by a detailed final outbreak report. A suggested template for an outbreak investigation report is provided in Annex 5.

Fig. 9 illustrates the principal activities to be undertaken after an outbreak is declared to be over.

Fig. 9. Stage 5: Key components of incident completion

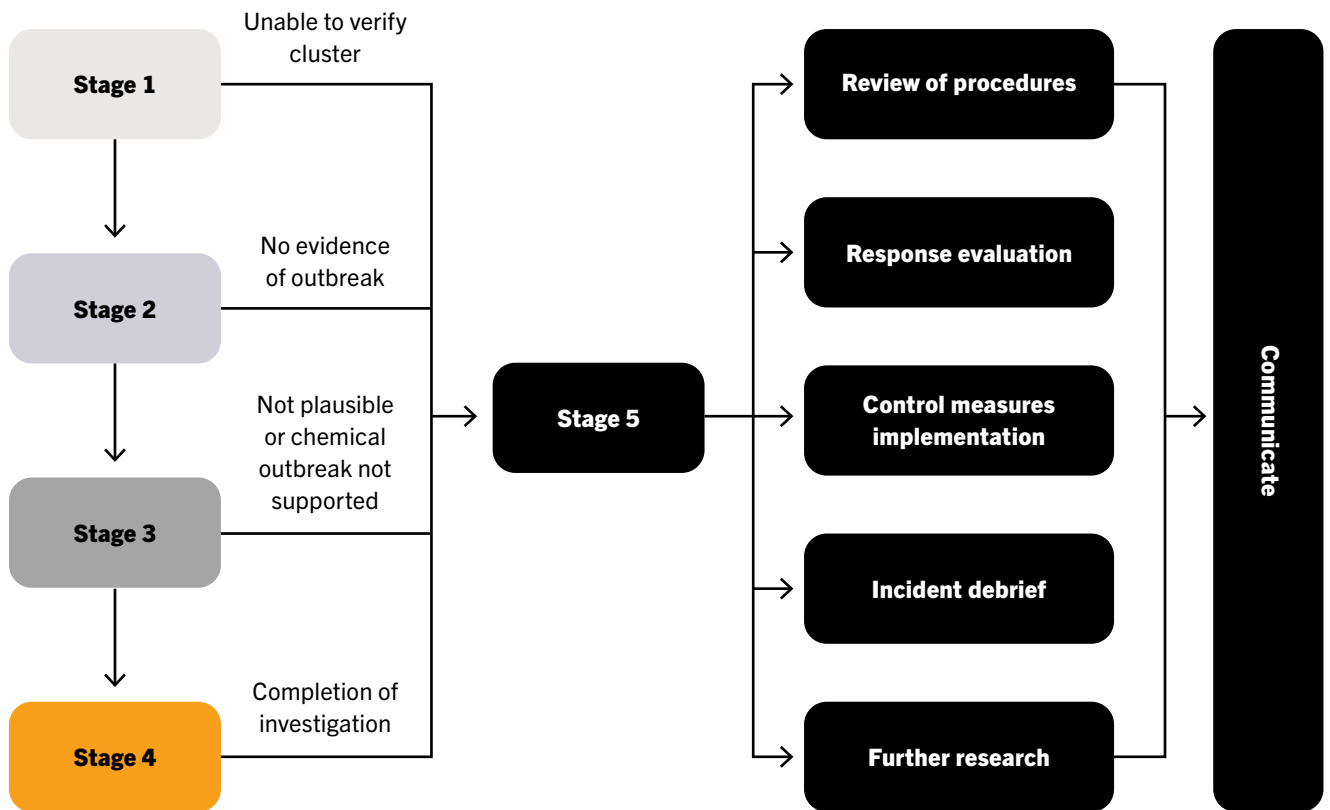




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2

Section 2. Principles and concepts of investigation

2.1. Risk: Assessment, prioritization, management and communication

2.1.1. Introduction

Risk assessment, risk prioritization and risk mitigation before an incident can inform *planning* and *preparedness* and provide information for subsequent cluster investigation. The activities include making inventories of the locations of hazardous chemicals and sites, transport routes and waste dumping facilities, mapping likely routes of exposure and identifying potentially vulnerable communities. Collection of such information beforehand will also facilitate the design of tailored and standardized data collection forms that can be adapted as necessary.

Furthermore, staff who are likely to investigate reported outbreaks must understand their roles and be suitably trained in environmental science, environmental public health, toxicology and epidemiology to determine the probable impact of exposure on public health. Understanding the concepts of *hazard* and *risk* is essential, with the ability to assess and publicly communicate risk in a clear, concise, honest, timely, transparent manner.

The resources, processes and procedures required may be considerable, and a multi-disciplinary, multi-agency approach should be used. Exercises could be conducted in implementing an incident management system (including use of an emergency operations centre when appropriate), using the results of reviews and monitoring and evaluation to improve coordination and response.

A risk and crisis communication strategy should be prepared according to the results of the risk assessment, and subsequent management should be adapted to the event.

2.1.2. Risk analysis

Risk analysis comprises assessment of the risks posed to a community and their management. It is a central component of the investigation of an outbreak of chemical etiology.

Risk assessment

Risk assessment involves determining the probable impact on community health of exposure to an environmental chemical. It has been defined as

the process intended to estimate the risk to a given target organism, system or (sub) population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the characteristics of the agent of concern as well as the characteristics of the specific target system (1).

It is an iterative process for evaluating the known or potential adverse health effects resulting from exposure to environmental chemicals. There are five main steps.

In *problem formulation*, the purpose of the risk assessment, the scope and depth of the analysis and the analytical approach and resources required are considered. The question and the desired outcome are defined.

In *hazard identification*, the adverse health effects associated with an environmental chemical are identified. When possible, this is based on studies in humans; when none are available, data from studies in experimental animals, in vitro testing and structure–activity relations should be used.

Hazard characterization consists of evaluating the qualitative and/or quantitative nature of the adverse effects associated with environmental chemicals to characterize the likely health consequences at different levels of exposure.

Risk characterization is usually a quantitative statement of the estimated exposure relative to the most appropriate health-based guideline. Estimated exposure is compared with the guideline value as a basis for estimating *risk*.

Further information on risk assessment in exposure to environmental chemicals is available elsewhere (37).

Risk management

In risk management, means to protect public health are evaluated. Examples of risk management include regulating the discharge of pollutants into a river, regulating emission of pollutants from an industrial stack, requiring chemical plants to be located at a minimum distance from communities and remediation of a contaminated site (51).

Risk management is complicated and depends on various considerations and factors in different disciplines and backgrounds.

- *Scientific*: Evidence such as for toxicological and exposure provides the basis for estimating the likely impact on public health.
- *Economic*: The benefit to public health of an intervention must be weighed against the financial cost.
- *Policy, legislation and regulation*: Risk mitigation measures are governed by a statutory framework.
- *Political*: the priorities for a government
- *Technological*: the feasibility of reducing the risk to public health on the basis of current knowledge
- *Social*: Susceptibility depends on many factors, including socioeconomic status, cultural and social behaviour, lifestyle and genetic predisposition (51).

2.1.3. Risk and crisis communication

Expertise in communications is an essential resource in any outbreak situation. If communication is efficient and effective, it increases community understanding and compliance with directives. This in turn promotes protective behaviour, thereby reducing the impact of the incident on health and reducing worry and disruption of society. Messages must be tailored to their intended audience and address local concerns, while a community's reaction to an identified risk depends on their perceptions of the risk and their confidence in the risk management process rather than on quantitative estimates of risk (34). Their perceptions and confidence are to a large extent generated and sustained through effective risk and crisis communication.

Risk communication is interactive exchange of information and opinion among individuals, groups and institutions about possible incident scenarios, protective actions and public involvement in the location and licensing of facilities where chemicals are produced, used or stored before an incident occurs.

Crisis communication refers to communication about actual risk and appropriate risk-reducing behaviour and measures during an incident (4). Well-developed plans to support risk communication open communication channels, build trust and thereby lay the foundations for effective crisis communication. Important features of effective risk and crisis communication are speed, openness, transparency, acceptance of uncertainty, discussion of data gaps and areas of disagreement among experts and continuity of communication (52).

Both phases of communication tend to be smoother and more effective when there is a communications plan, although risk and crisis communication without a plan may still be effective. Communication channels should be rapidly established and optimized within the outbreak control team and between the field team, stakeholders, the media and the public. Steps for avoiding communication problems, irrespective of the audience, setting or context, are listed in Table 6.

Table 6. Measures for successful risk communication

Communication issue	Mitigating measures
The message	<p>Avoid technical analyses and information, which are largely unintelligible to the public and can give the impression of hiding behind jargon.</p> <p>Ensure that messages are at appropriate literacy and numeracy levels to ensure that all members of the public understand them.</p> <p>Avoid disseminating conflicting risk estimates, and acknowledge uncertainty when appropriate.</p> <p>Remember that probabilities and numerical risk estimates are often poorly understood.</p> <p>When describing actions to be taken, explain why they are likely to protect health in order to increase their uptake (53).</p>
The source	<p>Disagreements among experts should not be allowed to negatively influence reception of the message by the public.</p> <p>Disclose any limitations in risk assessments, and acknowledge any uncertainty.</p> <p>Recognize the concerns, values, misperceptions and perspectives of the public, and take them into account when communicating.</p> <p>Prevent bureaucratic intrusion into formulation of honest, transparent messages.</p> <p>Demonstrate that responders, affected people and other stakeholders are working together to reduce the health risks, in order to improve trust (53).</p>
The media	<p>Manage and minimize selective, biased media reporting that is sensational or oversimplifies or distorts messages.</p>
The receiver	<p>Manage individual and public perceptions of risk if they are judged to be inaccurate.</p> <p>Address any community demand for scientific certainty.</p> <p>Educate and empower the public to take decisions that reduce their risk of exposure.</p>

Effective communication increases public resilience and encourages public participation in rapid containment of an outbreak, thus reducing avoidable morbidity and mortality. Important principles of communications with the public are outlined below (10).

- Decide that communication is part of the remit, and learn its basic principles.
- Tell all those who may have been affected what has happened as soon as possible, particularly those closest to the source of the outbreak or release.
- Make sure people understand what is being said and its implications.
- Involve representatives of the affected people in discussions on the design, implementation and interpretation of the investigation to ensure that their needs and concerns are taken into account and to facilitate communication.

- Acknowledge uncertainty promptly and thoroughly, and show respect for public concerns, even if they are not scientific.
- Ensure that communication is timely and reliable. Even if there is nothing new to say, it is important that people do not feel forgotten.
- Identify what the public want to know and what they need to know, and provide both.
- Expect that mistakes in communication will occur. Regularly seek feedback from representatives of the affected group to identify and correct any mistakes as quickly as possible.

Effective communication with the media is an important element of the investigation and management of an outbreak to establish public confidence in the ability of the investigation team and public health authorities and to provide a channel for communicating risk

management measures. Moreover, the media can provide additional information about the outbreak for the investigation team (50).

A detailed description of the principles and techniques of effective media communication is beyond the scope of this manual, and investigators should seek expert advice and consult international, national and local guidelines. Annex 6 provides some examples of worksheets, guidelines and checklists for perceiving and communicating risk and some examples of important stakeholders.

2.2. Epidemiological investigation

2.2.1. Introduction

The aim of epidemiological investigations is to characterize an *event*, define the population at risk, identify the cause, *source(s)* and *pathways of exposure*. The findings are used to identify and monitor appropriate, effective prevention and control measures. This section outlines epidemiological tools and methods that can be used in investigating outbreaks of illness with a suspected chemical cause. Although descriptive and analytical investigations are typically separate, in an integrated investigation framework they are undertaken with other activities.

2.2.2. Descriptive epidemiology

The aim of descriptive epidemiology is to clearly describe the cases linked to the outbreak according to time, place and personal characteristics. Differences in health outcomes in discrete exposure groups can be explored by analysing data on exposure and health effects. The findings may be sufficient to identify the cause of the outbreak within the limits of causal inference. When this is not the case, these studies will at least inform the planning and execution of analytical epidemiological studies.

The main steps in a descriptive epidemiological investigation are to:

- define the minimal information required for the investigation;
- develop and agree on a case definition, and refine it if necessary;
- agree on methods for finding cases;
- compile a line list to summarize initial case reports;

- conduct in-depth interviews with a standardized questionnaire with initial cases to identify any common risk factors;
- review the data collected, and describe the outbreak in time, person and place;
- identify and describe the population at risk; and
- make a preliminary hypothesis from the descriptive results and from comparison with established facts (e.g. investigate the plausibility of a suspected causative chemical agent).

The practical role of descriptive epidemiology in an investigation is described under stage 4.3.

2.2.3. Case definition

The importance of establishing a case definition and its role in furthering understanding of the etiology of an outbreak is described under stage 4.3. As described there, it might be appropriate to scale case definitions, classifying them as “suspected or possible”, “probable” or “confirmed” according to the degree of certainty of the diagnosis. In the early stages of an investigation, most cases may be classified as “suspected” or “probable”, and more cases may meet the criteria for a “confirmed” case as the investigation progresses. Important points to be considered in preparing a case definition are listed below (19).

- Case definitions should not include criteria related to an etiological hypothesis that might later be subject to epidemiological investigation, as it is then impossible to test the hypothesis. For example, in an investigation of an outbreak of a neurological illness with a suspicion that exposure to a particular product may be a risk factor, it would be counter-productive to restrict the case definition to people who used that product, as this would exclude genuine cases who had not used the product.
- Inclusion of any clinical or diagnostic criteria that might not be uniformly available under local conditions should be avoided, such as a case definition that requires findings from complex diagnostic procedures such as computed tomography.
- If possible, case definitions should not include clinical criteria based on subjective symptoms reported by cases and their families.
- Case definitions should not be used to guide clinical diagnosis and management of affected individuals, as they were developed for investigative and surveillance purposes and may not be sufficiently discriminatory to establish a medical diagnosis.

2.2.4. Analytical epidemiology

Analytical epidemiological investigations are undertaken to determine the nature and magnitude of any relation between putative *exposure(s)* and reported health effects in order to assess etiological hypotheses. The study designs commonly used are comparisons of the characteristics of unaffected or unexposed people (controls or non-cases) with those of affected or exposed cases (35). The choice of study design depends on factors such as the nature of the observed illness or disease, the frequency of the postulated risk factors in the population, available resources and time and the experience and preference of the investigators.

Case–control and cohort study designs are the most commonly used to investigate outbreaks with a suspected chemical cause. They differ in their approach to exploring the relation between putative exposure(s) and health effects, which are approached from opposite ends of the exposure–effect spectrum.

Case–control studies are used to compare the reported frequencies of exposure between cases of the health effects or disease and controls. This approach may be the best option during the early stages of an outbreak, particularly when there is no clear etiological hypothesis or several hypotheses have been proposed (19). In such studies, the frequency of exposure is compared in two broad groups defined according to their disease status (cases and controls) and typically expressed as an *odds ratio*, a measure of the strength of association between the illness of interest and the putative exposure. This study design is well suited to investigating dispersed, common source or community-wide outbreaks in which cases have been identified but not for the entire “at-risk population”.

Cohort studies are used to compare the frequency of disease in exposed and unexposed populations. The results are typically expressed as the association between a specific exposure and disease as a *relative risk* or rate ratio. The studies may be either retrospective or prospective, depending on the timing of data collection. This study design is well suited to investigations of outbreaks in which the entire at-risk population is easily defined and completely enumerated to allow calculation of actual population-based rates of illness or disease. Cohort studies can, however, be expensive and lengthy, particularly if the disease under investigation is rare. Cohort studies have been used in follow-up investigations of populations exposed to a known hazardous agent. An

example is studies of children living near Minamata Bay, Japan, who were exposed to methyl mercury (54).

Other study designs that can be used in analytical epidemiological investigations are:

- *ecological studies*, to examine hypothesized associations between exposure(s) and health effects at population level;
- *cross-sectional studies*, to examine associations at a single time or for a defined period;
- *time series studies*, which involve repeated observations of exposure and health outcomes over time in the same study population; and
- experimental studies, which have been used to investigate the effectiveness of prevention and control measures at population level.

Whatever the study design, the purpose of an epidemiological investigation is to determine whether an apparent association between a putative exposure(s) and an illness or disease is due to chance, bias and/or confounding, or whether it represents a true relation. The extent to which a relation can be judged as causal should be guided by considerations of temporality, strength of association, dose–response relations, plausibility and consistency. The most important benefit of demonstrating a true relation between exposure and health effects is, however, as a guide to control.

Investigators must not only decide on an appropriate study design but also resolve other issues, such as:

- the size of the study population (sample size);
- choice of control population(s);
- data management;
- statistical methods of analysis; and
- ethical considerations (see sections 1 and 2.6).

The practical role of analytical epidemiology in field investigations is described under stage 4.5.

2.2.5. Surveillance

Some form of *surveillance* of the health of the population should be established to assess the effectiveness of control measures and for medium- to long-term monitoring of the health of the affected population. Either a bespoke or an adapted system may be used. The choice and complexity of any surveillance system depend on the intended purpose, potential data sources and methods of collecting information

and available resources and time. Ideally, an active surveillance system should be used, particularly in the early phases of an outbreak investigation and when timely information is necessary to guide response

activities and public health control measures. Various types of surveillance systems with their purposes are summarized in Table 7.

Table 7. Surveillance systems

Type of surveillance	Description
Categorical	Defined programme conditions for an intervention programme, e.g. tuberculosis
Event	Scanning of several data sources, including the media and social media, e.g. Zika virus disease
Integrated	Combination of active and passive surveillance integrating information on several diseases and behaviour as a prelude to intervention
Laboratory	Measurement of biomarkers of exposure, e.g. whole blood lead, or biomarkers of effect, e.g. renal profile
Sentinel	Monitoring of the frequency of specific health events in a community or population to determine trends and patterns
Syndromic	Based on established case definitions

If the surveillance system is designed for the initial stages of the outbreak investigation but it is decided to extend it for long-term follow-up of exposed individuals, it must be modified for collection of more detailed information on cases (increased specificity). Detailed surveillance forms should be designed, and local public health staff should be implicated to a greater extent. Consideration should be given to including laboratory data in the surveillance database, if not already done.

The system may combine data from emergency services, public health, environmental and food agencies, hospitals, general practitioners and poisons centres to identify trends, patterns and emerging threats. The media or communities may also provide information.

Issues to be taken into account in establishing a new surveillance system or modifying an existing one for the purposes outlined above include (55):

A case-based surveillance system should:

- provide an *accurate assessment of trends* in the occurrence of the illness or disease under investigation in the affected area;
- inform *identification and implementation* of public health control measures;
- support *evaluation of the effectiveness* of the outbreak response, particularly control measures;
- provide *early warning of disease recurrence* and spread after the outbreak; and
- support *medium- to long-term follow-up* of the affected population and identification of future research.

- a clear understanding of the socioeconomic, political and health care infrastructure in the outbreak area;
- agreement on a clear statement of the problem, incorporating different perceptions to secure shared understanding;
- clear definition and focus on the purpose and objectives of the surveillance system;
- definition of the specific information required on cases, how quickly the information is required and the source(s) and method of data collection;
- the resources available for collecting information, including identification of personnel responsible for

overseeing the surveillance system in the field, and resolution of any funding issues;

- a simple, practical, explicit case definition with clinical and epidemiological criteria, which can be extended to include laboratory criteria as the information becomes available; should be similar to the case definition used in descriptive epidemiological investigations;
- a mechanism and instruments for collecting, processing, analysing and interpreting data and disseminating findings (see Annex 2 for examples of data collection forms); and
- pilot-testing of the system, although this is unlikely to be feasible in a rapidly evolving chemical outbreak if the system is implemented during the investigation.

Surveillance is one part of an *environmental public health tracking* programme. Routine collection, integration and analysis of health and environmental data have been established in some countries (56, 57).

Annex 7 provides examples of types of epidemiological investigation and the statistical significance of sample size.

2.3. Environmental investigation

2.3.1. Introduction

Environmental investigation is the “bridge” between epidemiological and toxicological investigations. Its purpose is to determine the source of a chemical that could plausibly be responsible for the observed cases and the environmental media through which exposure could conceivably occur to cause health effects. Its

role during a practical investigation is described in stages 3.4 and 4.4.

2.3.2. General principles

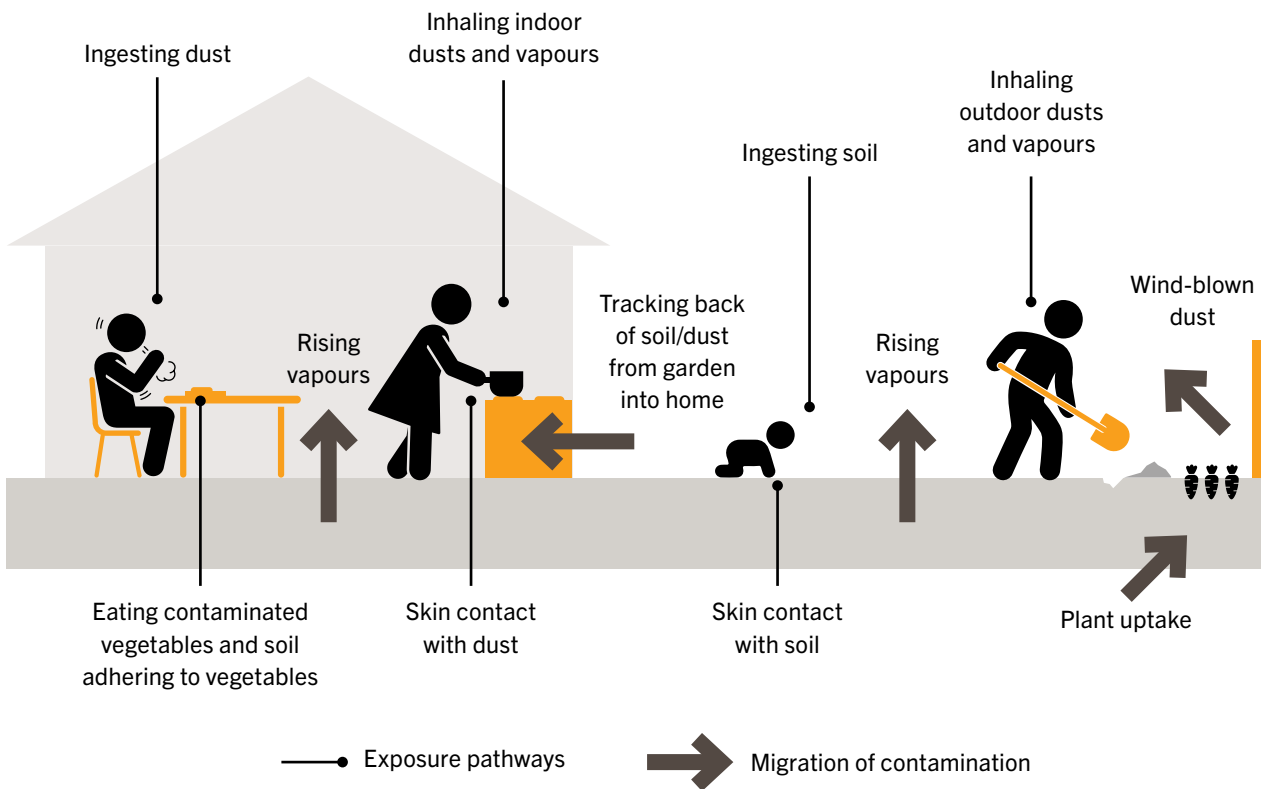
Environmental investigations may be simple (i.e. basic screening questionnaires with limited environmental sampling) or complex, involving extensive *sampling*, *GIS* and modelling techniques and field activities. In the early stages of a field investigation, it is best to adopt an incremental approach, from relatively simple but robust methods for identifying potential source–pathway–receptor links to more sophisticated analyses, as necessary. The investigation should be integrated into other field investigations to achieve the immediate public health goal of identifying and controlling the cause of the outbreak.

The environmental investigation should be dynamic and iterative, with the initial aim of identifying all potential environmental hazards and then prioritizing key hazards for detailed investigation and characterization. A *conceptual site model* is useful for guiding an environmental investigation.

2.3.3. The conceptual site model

The investigation should include identification and assessment of the main sources of hazards or pollutants and the pathways or media (e.g. air, water, soil, food, consumer products) through which the population (receptors) is likely to be exposed. These *source–pathway–receptor* links can be presented in a conceptual site model. The level of detail in such a model depends on the degree of complexity. An initial approach may simply be to detail the source–pathway–receptor links or a more schematic representation of the relations among the source of the hazard, environmental pathways and exposure routes (Fig. 10).

Fig. 10. Standard conceptual site model in a residential setting



Source: Reproduced with permission from reference 58

Conceptual site modelling is dynamic and iterative, with modification and updating as appropriate when more information becomes available (e.g. from field investigations). The first stage may be a “desk study” of readily available data or consultation with stakeholders.

Initial information gathering may include:

- the characteristics of the affected area (e.g. location; geological, hydrological and climatic conditions; physical hazards);
- demographic information, including size, characteristics, location and vulnerability of the affected population;
- the environmental history of the area, including potentially hazardous current and past activities (including industrial locations and waste dump sites), significant events in the area and in surrounding areas and documented climatic and geological changes;
- community health concerns and the environmental histories of potentially affected people, including health problems and diseases described by the affected community, potential environmental hazards, other sources of exposure, such as

the workplace, and other concerns voiced by the community, with remedial action by health authorities; and

- other information, such as the locations of public and private water supplies, uses of surface water, local drainage systems, agricultural activities and practices and flora and fauna affected.

Although many components may be available from written reports, a field investigation provides invaluable insight.

2.3.4. Environmental sampling

A good-quality environmental *monitoring* and *sampling* programme should be designed, although technical resources and capability may be lacking or it may be difficult to mobilize monitoring teams for timely sampling. No one instrument can measure the wide variety of chemical contaminants in environmental media during an incident, and different contaminants and environmental media require different monitoring and sampling techniques. The field team should decide on the appropriate methods and the *accredited* laboratories that will analyse the samples (see section 2.5 for further details).

Examples of sampling methods that can be used singly or in combination are listed below; the choice of method depends on the type and quality of data on exposure that is required (59).

- *Field screening techniques* involve use of chemical test kits, organic vapour analysers and other portable monitoring devices such as X-ray fluorescence. This approach may provide both qualitative and quantitative data; it does not necessarily provide rigorous measures of chemical-specific environmental contamination, and more complex sampling methods may be required.
- *Field laboratory techniques* are useful for a quick turnaround of sampling results, as in many acute outbreaks. They consist of a broad range of applications based mainly on collecting samples on site and analysing them in mobile laboratories.
- *Stationary laboratory techniques* are likely to be preferred, as they provide data of known high quality and do not require that the affected area have a well-developed laboratory infrastructure. Samples are collected and shipped to accredited laboratories identified by the lead agency.

Sampling locations may include households, communal water supplies and industrial and farming sites. Expert judgement should be used to decide on the most appropriate sampling locations and the numbers of samples. The frequency and timing of sampling and the numbers of samples collected each time should be balanced against laboratory capacity and resources. As a general rule, the more homogeneous the affected environmental media the fewer samples are required. If the media are heterogeneous, it is good practice to identify “hot spots” for sampling. Other considerations include temporal and meteorological factors, time, cost, the availability of expertise and equipment and the accessibility of the exposed area.

Sampling should be as *accurate* and *representative* as possible and practical, to ensure that the subsequent *exposure assessment* is realistic. Nevertheless, incidents may be highly complex, variable and fast-moving, and it may be difficult to obtain reliable data on the levels of contaminants in the environment. Capacity and capability to conduct environmental monitoring may be limited, especially if real-time monitoring during the incident is required. Examples of sampling methods, and the information likely to be obtained are listed in Table 8.

Table 8. Examples of environmental samples and sampling techniques for different media

Environmental medium	Analytes and methods	Information derived
Air, ambient and indoor	Air samples can be collected with passive or diffuse samplers, sampling bags, colour detector tubes, filter samplers, impingers, personal samplers and sorbent sampling tubes. The chemicals that can be analysed include metals, organic, inorganic and volatile organic compounds. The type of sampling depends on the chemical(s) investigated, and specialist advice should be sought.	Identification of the chemical hazard(s) and its concentration in air
Soil	Soil samples can be collected with hand augurs and spoons for surface and shallow sub-surfaces and push samplers such as core or split-spoon samplers, which can be manually or mechanically pushed or drilled into the ground to specific depths. The samples should be stored in appropriate containers for analysis for pollutants such heavy metals, volatile organic compounds and polychlorinated biphenyls. Information on distribution, persistence and fate may be obtained.	Identification of chemical hazard(s); concentration of the chemical and evidence of contamination Identification of “hot spots” of contamination Information for contamination mapping with geo-statistical or other methods
Surface water	Sampling techniques include grab, pole, depth and auto sampling.	Identification of a chemical hazard; current concentration of the chemical and evidence of contamination

Environmental medium	Analytes and methods	Information derived
Groundwater	Various compounds can be measured. Samples obtained by pump, grab, pole and auto-sampling	Identification of a chemical hazard; current concentration of the chemical and evidence of contamination
Food	Collect fresh domestic produce, household samples and samples of prepared food when indicated	Identification and quantification of the contaminant
Flora and fauna	Samples to be collected according to the prevailing patterns of use and exposure	Identification of chemical hazard(s); identification of possible pathways of exposure
Dust	Surface dust samples can be collected as either a bulk sample or a wipe sample for settled dust on floors, windowsills and similar surfaces. Disposable, moistened wipes or commercially available wipe sampling materials can be used.	Information on concentration of chemical in dust or surface loadings
Other, such as industrial emissions (e.g. emissions and effluents from stacks), traditional medicines and consumer products	Air samplers used to collect samples of stack emissions; individual samples taken of medicines and other substances	Identification of chemical hazard(s); identification of possible pathways of exposure

The investigation team must appreciate the capability and limitations of the sampling equipment and analytical techniques chosen, as misuse or use of inappropriate equipment may result in biased or non-representative samples. Consultation with the laboratory may circumvent such issues (see section 2.5 for further details).

All environmental sampling must be well documented and the results interpreted transparently according to relevant guidelines, with clear detail of any weaknesses of the data. Collection of representative samples is discussed in Annex 8.

2.3.5. Exposure assessment

Exposure assessment involves evaluating and describing the pathway and routes of exposure to determine possible settings, conditions and the extent of exposure to the *hazard*. This enables investigators to define points of *exposure*, estimate exposure parameters (i.e. environmental concentrations of implicated chemicals) and the population potentially exposed. The quality and rigour of exposure assessment is often a critical determinant of the validity of an investigation, as errors may introduce bias. Collection of data and information from the field investigation and environmental monitoring and sampling is therefore a critical part of the exposure assessment.

Environmental monitoring may be time-consuming, resource-intensive and costly. In an emergency, a more pragmatic approach may be necessary, based on indicative or semi-quantitative methods as opposed to more specific quantitative or continuous monitoring. The approaches to estimating exposure during an environmental incident, from the poorest to the best approximation of actual exposure, are (35):

- residence in a defined geographical area (e.g. county) of a site or event;
- residence in an exposed area;
- distance from or duration of residence in an exposed area;
- quantified, modelled estimate of exposure (e.g. air dispersion model, food uptake model);
- quantified environmental measurements in the exposed area or biota (e.g. air, food); and
- quantified personal measurement (e.g. biomonitoring).

Simply being exposed to a hazardous chemical does not necessarily lead to a harmful health effect. The magnitude, frequency, timing (for example, during pregnancy) and duration of exposure and the toxicity of the hazardous agent affect the nature and severity of the health effect. Demographic factors such as age,

health, occupational or other exposures and dietary patterns should also be considered in the exposure assessment. Susceptible populations include pregnant women, children and elderly, frail and sick people. Other subpopulations may have activities that increase their risk of exposure, such as consumption of contaminated fish.

Investigators should therefore consider a variety of information on exposure and health effects, which can be obtained from *primary* or *secondary data sources*. *Primary* data are collected specifically for investigation of the outbreak and include specific measurements of levels of contamination in defined media, continuous measurement of individual exposure with personal monitors and measurement of actual absorbed doses of chemical substances or their metabolic by-products and other relevant biomarkers from biological samples. They are also derived from interviews with questionnaires.

Secondary data are usually collected from databases routinely maintained for other purposes, such as registers of hazardous sites, diseases, hospital admissions and cancer cases, and from occupational health records and environmental monitoring and surveillance data. Usually, a combination of these data sources is used, the choice and balance depending

on availability, access, completeness, validity and representativeness.

A tiered approach is recommended to assess exposure, starting from relatively simple screening to a more comprehensive, integrative stage. The *screening* stage is based on use of readily available data to make conservative assumptions about exposure, assuming the worst- case scenario and thus involving uncertainty. The principle is to compare the concentrations of pollutants in contaminated media with guidelines and recommended thresholds (if any) and to judge whether the measured exposure levels could account for the health effects observed. The *integrative* stage consists of more refined, detailed assessments from site-specific data and complex models of the fate and behaviour of the chemical in the environment and its uptake and metabolic fate. Data on exposure are integrated with data derived from epidemiological and toxicological investigations to provide a quantitative assessment of the likelihood of occurrence of the observed health effects at the observed exposure levels. This stage is a more refined assessment and requires more specific environmental data and sophisticated models to predict exposure.

Table 9 provides examples of approaches to assessing exposure in different environmental media.

Table 9. Assessment of exposure after contamination of environmental media

Environmental medium	Source and pathway	Exposure assessment
Water	Contaminated water piped from municipal sources or obtained from wells, streams and springs for domestic, municipal, industrial, recreational and agricultural purposes. Uptake is primarily through ingestion but may occur from inhalation or skin absorption.	Estimate exposure parameters (e.g. quantity of water, frequency of use and concentration of pollutants) from samples collected at the source (e.g. water treatment plants, household pipes, storage containers).
Soil and dust	Direct contact during digging and excavating soil for domestic and commercial purposes; consumption of soil by children (i.e. pica) and adults; uptake of soil contaminants into food plants; contamination of water Direct contact and inhalation of airborne dust, ingestion of dust settled on crops	Establish an exposure gradient based on distance from source, and use a questionnaire to enquire about behavioural factors that affect intake and exposure. If feasible, combine individual measurements with these proxy exposure estimates.
Air	Outdoor pollution from traffic, industry, agricultural activities and natural sources (e.g. volcanic activity) Indoor sources including unvented combustion devices, building materials and solvents Indoor and outdoor exposure to airborne pollutants	Use fixed or mobile ambient air monitoring and personal monitoring devices to measure concentrations of the pollutant over time and space.

Environmental medium	Source and pathway	Exposure assessment
Sediment	Exposure to contaminants in water that sink and accumulate in sediments can occur by direct contact. Indirect exposure can occur by ingestion when contaminants in sediment are transferred and accumulate in the food chain. Contaminants may also be remobilized back into the water column or transported downstream.	Estimate the concentration of the chemical in sediment, and use physicochemical factors such as water solubility and partition coefficients to predict its availability for uptake into the food chain.
Food chain	Consumption of animals, plants and other food from contaminated domestic and commercial sources	Review dietary habits from questionnaires and food diaries. Combine the results with surrogate measurements in food samples and biomonitoring.
Others	Direct contact of workers and trespassers with contaminated materials at commercial or industrial sites (e.g. waste dumps, raw materials)	Use a combination of the above methods and model exposure with a deterministic or stochastic approach.

Exposure assessment shows how a chemical behaves in the environment. Its environmental fate indicates how the chemical behaves in air, soil, water and the food chain and therefore the likely exposure levels. An assessment requires information on the environmental conditions in the affected area, factors that may influence the persistence and movement of the chemical in the environment and possible transport methods. The physical and chemical properties of a chemical predict its behaviour. For example, vapour pressure is a measure of the tendency of a chemical to enter the gaseous or vapour state and thus contaminate air, while the octanol:water partition coefficient indicates a chemical's potential to bio-accumulate in the food chain.

When this information is unavailable or the fate and transport mechanism are difficult to determine, investigators should base their assessment on a worst-case scenario. Evaluations of fate and transport are not always necessary, particularly if the nature and extent of contamination of all relevant media have been adequately characterized.

2.3.6. Special techniques and methods: statistical modelling and geographical information systems

Statistical modelling of exposure indices and health outcomes is based on information obtained from epidemiological, clinical toxicological and environmental investigations. Models may be either *deterministic* or *stochastic*, depending on the purpose of the analysis and the availability of data, expertise and resources. Examples are regression, time–space and dispersion (plume) modelling.

A detailed description of GIS is beyond the scope of this manual, but these techniques have markedly improved assessment of the spatial extent of exposure. GIS techniques are computerized mapping systems for integrating data into a common spatial form and analysing them geographically to model e.g. local pollution patterns or define exposure surrogates by analysis of the proximity of contaminant sources (42). Data used in GIS models must, however, be geo-referenced, and they may be difficult to acquire in regions where no geo-referenced data are available.

2.4. Clinical and toxicological investigation

2.4.1. Introduction

Clinical and toxicological investigations consist of systematic generation of quantitative or semi-quantitative data for identifying the cause of an outbreak and improving the specificity of recommended public health control measures. The purpose and scope of such investigations and the resources required should be guided by the findings made in stage 3.5 and in the field investigation (stage 4.5) and early epidemiological and environmental investigations.

This section describes the technical basis of clinical and toxicological investigations, including general principles of toxicology and the roles of biological sampling, analysis

and laboratories. Interpretation of test results is not addressed in this manual, as it will be guided by the clinical toxicologist conducting the investigations.

2.4.2. General principles

“Sola dosis facit venenum” (The dose alone makes a thing a poison). Paracelsus, 1538

Toxicology is the study of poisons. The toxicity of a substance depends on its intrinsic physico-chemical properties and the dose, the product of concentration and time for which an individual is exposed. To be toxic, a substance must reach its site of action at a concentration sufficient to cause harm. In some cases, the site of action may be a specific molecular structure, such as the binding of morphine to the mu opioid receptors of the central nervous system. An environmental chemical may cause injury through a non-specific reaction with the cell membrane, as in the case of the corrosive effects of strong acids.

Toxicodynamics (“what the chemical does to the body”) describes the relation between the concentration of a substance at its site of action and the harm response. The magnitude of harm is usually proportional to the concentration at the site of action, the “augmented” or type A reaction. Susceptible individuals may, however, exhibit a “bizarre” or type B immunologically mediated reaction on exposure to a substance at a concentration that is not usually considered toxic. Examples of type B reactions include an anaphylactic reaction to penicillin or to a bee sting.

Toxicokinetics (“what the body does to the chemical”) describes the change in the concentration of the chemical in the body over time. It consists of four concurrent qualitative processes: absorption, distribution, metabolism and elimination. The concentration of a chemical is usually measured in whole blood, plasma, serum or urine, although it is the concentration of the chemical at its site of action rather than in the plasma that determines its toxicity.

Individuals vary widely in their susceptibility to poisoning by environmental chemicals and pollutants because of differences in toxicodynamics and toxicokinetics. Age, the presence of co-existing disease, genetic differences and wider sociological factors, including socioeconomic status, lifestyle, dietary factors and cultural habits, all contribute to susceptibility. The clinical features associated with common toxicants are illustrated in Annex 9.

2.4.3. Sampling for toxicological tests

When the exact nature of a chemical of concern is unknown, a broad range of chemicals that could conceivably be responsible for the outbreak could be tested. Such “blind” toxicological screening usually requires collection of blood and urine specimens, as specified in Table 10. Use of prepared sampling kits such as the specimen containers listed in Table 10 and the necessary packaging materials will ensure that the correct samples are taken, that they are not contaminated with chemicals migrating from containers and that the samples are correctly packaged and labelled (see Annex 10 for an example of a sample kit).

Table 10. Samples required for “blind” toxicological screening for an unknown toxicant (60)

In order of importance, the samples for blind toxicological screening should consist of:	
Adults	<ul style="list-style-type: none"> • 10 mL blood in plastic (polypropylene) lithium heparin tube • 5 mL blood in glass^a lithium heparin tube • 10 mL blood in plastic (polypropylene) EDTA-coated tube • 30 mL urine without preservative
Children	<ul style="list-style-type: none"> • 5 mL blood in glass^a lithium heparin tube • 5 mL blood in EDTA-coated tube • 30 mL urine without preservative

EDTA, ethylene diamine tetra-acetic acid

^a If glass tubes are unavailable, polypropylene tubes may be used.

Tubes for collecting blood or its components should have plastic or lined metal tops, as chemicals can leach from tubes with gel separators or containing mucous heparin solutions and contaminate the sample. If special containers are not available and no suitable alternatives can be found, investigators should use routine specimen containers. When they send them to a laboratory, however, they should also send empty specimen containers of the same type and from the same batch to be used as a control.

Other procedures should be established for avoiding sample contamination during collection, such as ensuring a clean location for collecting samples and adequate skin cleansing, handling, transport and storage. Health and safety should be assured during sample collection. All samples should be considered potentially hazardous and handled according to universal standard precautions (61, 62).

2.5. Laboratory investigation

2.5.1. Introduction

Laboratory investigation provides the basis for determining which environmental media are contaminated with the chemical(s) in question and sometimes also subsequent *uptake* and *dose*, which may be useful in clinical management. Some environmental and biological monitoring can be conducted in the field with hand-held and portable devices, such as X-ray fluorescence devices for measuring contaminants in soil. An investigation of a chemical-related outbreak is likely, however, to require access to laboratory services. This section briefly describes the ways in which laboratories support the response to outbreaks and issues of quality assurance and quality control.

2.5.2. Principles

The aim of laboratory analysis of clinical and environmental samples is to identify the presence and nature of toxic substances, metabolites or biomarkers relevant to investigation of the outbreak. Laboratory investigations should ideally be targeted and, when possible, guided by the findings of epidemiological and clinical investigations; non-specific or random testing of human and environmental samples should be avoided, as it is usually inefficient and resource-intensive.

If the affected country does not have adequate quality-assured laboratory capacity, suitable laboratories in other countries should be identified in advance and agreements made for use of their services under specific circumstances. The effectiveness of laboratory services in confirming the cause of illness or disease during an outbreak depends on:

- the adequacy of advance planning (including identification of designated laboratories);
- prompt collection of appropriate, adequate specimens;
- the adequacy of arrangements for storage, packaging and rapid transport to a designated laboratory;
- the technical capacity of the laboratory to conduct the appropriate tests;
- the adequacy of biosafety and decontamination procedures; and
- the adequacy of quality assurance and quality control measures.

Before conducting an investigation that will require laboratory analyses, detailed discussions should be held with the laboratory or laboratories regarding the analyses that can be provided in order to ensure that the correct samples are collected and that they are correctly handled and transported. The laboratory might be able to provide sampling kits.

2.5.3. Functions of laboratory services during an outbreak investigation

The function of laboratory services depends on the incident, but they generally consist of those to identify the causative agent, those to estimate the degree of exposure to the chemical(s) that affect health, those associated with medical treatment of patients and those to monitor the effectiveness of the response and recovery measures.

The clinical presentation of affected individuals and the results of epidemiological and/or environmental investigations provide clues to the likely cause of an outbreak. The clues may be confirmed with tests on clinical and environmental samples in accredited laboratories. Laboratories for food, water and environmental samples can confirm the presence of a suspected chemical in the media of interest (e.g. drinking-water, specific food items). When there are no clues about the causative agent but the investigation has indicated groups of chemicals that could cause the observed health effects, laboratories can conduct screening to identify the causative agent from a panel of tests.

Laboratory investigations can assess the exposure of populations, sub-populations or individuals by providing quantitative data on both exposure and uptake of chemicals of concern. Depending on the toxic substance concerned, ad-hoc or serial toxicological measurements can be made to support case management. For example, in some cases (e.g. chelation therapy for lead poisoning), the treatment regimen should be modified according to the internal dose. Monitoring of laboratory test results can also provide information about the effectiveness of treatment.

Monitoring and laboratory investigations should continue after the release has been controlled. Environmental and personal monitoring may be required to indicate the effectiveness of risk mitigation measures by determining the concentrations to which populations and individuals are actually exposed after implementation of these measures.

2.5.4. Laboratory services required for outbreak investigation

The types of laboratories that can support investigation of chemical-related disease outbreaks include diagnostic, clinical, toxicological, environmental, forensic, food safety and research laboratories.

Toxicology laboratories usually specialize in the analysis of biological samples such as blood, urine, hair, gastric contents and tissue samples. They may be part of a hospital laboratory service that also conducts routine biomedical analyses, be associated with a poisons centre, exist as a stand-alone service, usually on a commercial basis, or may be research laboratories. Most countries also have forensic laboratories for toxicological analyses in legal investigation of poisoning incidents.

Laboratories can provide qualitative and/or quantitative analyses of a wide range of substances, including illegal and therapeutic drugs, trace elements (e.g. lead, arsenic), pesticides and solvents. They may also be able to analyse biomarkers of effect, such as cholinesterase activity. They can usually run screening tests for groups of drugs and chemicals.

Environmental laboratories can analyse a wide range of chemicals (e.g. trace elements, pesticides, polychlorinated biphenyls and other persistent organic pollutants, petroleum products and volatile organic compounds) in environmental media such as water, soil, sediment and air. Such laboratories may be in the public sector, may operate

commercially or be managed by academic institutions, industry or agencies that address environmental, water quality, agricultural and occupational health issues. Agencies may have mobile units that can be deployed to the site of an incident for monitoring and analyses. They may also have access to networks of fixed monitoring stations for measuring compliance, e.g. for routine monitoring of the quality of surface water or ambient air. Some well-equipped environmental laboratories may have the capacity to identify unknown contaminants in environmental media with advanced analytical methods such as gas chromatography–mass spectrometry.

Food laboratories have the capacity to test for a wide range of organic and inorganic chemicals in food and beverages (43). Like environmental laboratories, they usually have procedures to test for specific chemicals in defined matrices or to screen for unknown chemicals.

The capacity of each laboratory is usually tailored to their mandate. For example, they may analyse only a given concentration range of specific chemicals in a specific matrix (e.g. biological samples, surface water). For an outbreak investigation, further analyses may be required, e.g. measurement of higher or lower concentrations than usual or analysis of a new substance. Whether and how quickly the laboratory can meet such requests will depend on the nature and volume of their routine work and the reagents, analytical standards, analytical equipment and trained staff available. The laboratory might have to recalibrate its analytical equipment or validate a new analytical method, which will usually take some time.

2.5.5. Laboratory quality assurance

Environmental samples collected for laboratory analysis should include a number of standards for demonstration of analytical quality. These include chemical assay standards to check the accuracy of the instrument, duplicate samples to measure the reproducibility of the analysis, laboratory and field blanks to check for cross-contamination of samples in the field and in the laboratory, and recovery standards to estimate recovery of the chemical under analysis. When possible, accredited laboratories should be used that conform to national and international performance standards.

Laboratory quality can be defined as the *accuracy*, *reliability* and *timeliness* of reported test results. Only if these conditions are met are data provided by a laboratory to clinicians and public health professionals of

value in determining exposure, assisting in diagnosis and guiding treatment. In order to provide a reliable, timely, accurate service to its users, a laboratory should have a quality management system that covers every aspect of laboratory practice, including pre-laboratory, laboratory and post-test processes.

Pre-analytical considerations serve to ensure that the collection, storage and transport of samples is adequate to maintain their integrity and that samples are accompanied by adequate documentation of patient identity or sample coordinates and relevant information, such as clinical and environmental data. The laboratory should follow *standard operating procedures* to ensure an appropriate, standardized approach.

Analytical considerations include motivated, competent staff, adequate premises and regularly maintained, appropriate diagnostic equipment with adequate supplies of good-quality reagents and consumables. Process control should cover all aspects of the laboratory's work to ensure the accuracy of results. This includes use of reference materials to calibrate analytical equipment and use of internal quality control samples. Staff should be supported by able management, and appropriate health and safety control should be assured.

Post-analytical considerations include ensuring that patient data and analytical results are appropriately logged, stored and reported to those responsible for investigating, assessing and managing the outbreak. An important component of a quality management system is a programme to ensure continual improvement in quality over time through a cyclical process of identifying sources of weakness or error, remedying them and checking the effectiveness of corrective measures. Participation in an external quality assessment scheme for specific analytes can contribute. WHO has published guidance on laboratory quality management systems (63) that can be applied in any clinical, public health or environmental laboratory.

Further information on protocols and guidelines for toxicological testing are provided in Annex 10.

2.6. Ethical issues

Ethical issues that may arise during investigation and management of disease outbreaks arise from the dual obligations of public health professionals and others to acquire and apply scientific knowledge in order to improve and protect public health while respecting and safeguarding individual autonomy (64, 65). After a chemical-related outbreak of disease has been identified, recommended (sometimes mandatory) public health measures such as movement restrictions, biological sampling and compulsory removal of products from sale can raise ethical issues, such as *beneficence, non-maleficence, autonomy and distributive justice*.

The response to a suspected chemical-related outbreak usually includes urgent determination of the nature and scale of the problem and rapid institution of effective control measures. Potentially coercive or restrictive public health measures and collection of data for public health surveillance and field (epidemiological) studies are usually not considered to be research activities, for pragmatic reasons, as this obviates a requirement for formal review and approval by a research ethics committee. It could, however, diminish individual autonomy in favour of the greater public health benefit of these actions. Investigators must be vigilant to the possibility that such a situation could arise and proactively deploy all the necessary measures to safeguard the ethical principles that guide use of public health measures and research involving human subjects. Before deployment to the field, the team should try to find solutions to potential ethical issues through critical review and consultation.

The ethics of outbreak investigation and management has been reviewed by several groups and organizations (12, 13), which have attempted to encapsulate the core values, virtues and ethical duties of epidemiologists by issuing public health ethics guidelines. All the guidelines stress the importance of minimizing risk and protecting the welfare of research participants and affected populations, optimizing benefits and protecting the confidentiality and privacy of individuals (Table 11).

Table 11. Ethical issues to be considered during an outbreak investigation

Ethical issue	Description and mitigation
Minimizing risk and protecting the welfare of the affected population and study participants	The activities of the field team should be monitored to ensure that they do little or no harm to the community or individuals. Intrusive or harmful activities should be avoided or at least kept to a minimum.
Providing benefits to the community	The team should maximize the potential benefits of public health interventions to the community.
Ensuring equitable distribution of risks and benefits	The team must avoid creating or widening any health or socioeconomic inequity and ensure that vulnerable, disempowered and at-risk communities have an equitable share of any benefits arising from the investigation and management of the outbreak.
Protecting confidentiality and privacy	Field investigators have a duty to ensure that a robust mechanism is in place to protect all data that are collected and that they are used only for the intended purpose(s). Individual privacy must be protected at all times, particularly in situations of potential stigmatization and persecution.
Obtaining informed consent	In the context of evolving and acute outbreaks, the requirement to obtain informed consent from potential participants may be waived if robust mechanisms have been introduced to protect the confidentiality and privacy of participants. In the absence of formal informed consent, investigators should still provide the community with information about the study, its anticipated benefits and risk and the right to withdraw from the study. This is especially important with respect to vulnerable groups such as displaced populations, children and prisoners.
Building and maintaining public trust	The team should adhere to the highest professional and ethical standards, follow local laws and regulations on the conduct of research and public health activities and, when appropriate, involve community representatives in planning and activities.
Fulfil obligations to the affected population	Field activities should be conducted in such a way as to respect the cultural norms of the affected community by involving the community as much as possible in planning and activities. All relevant information about risk and the findings of the investigation should be communicated rapidly to the community in the most appropriate media and format.
Avoiding conflicts of interest and partiality	The team should ensure that they remain objective and impartial in conducting the investigation and reporting the findings. All attempts should be made to ensure that the final report is free of distortions due to pre-conceptions or to organized pressure from groups with vested interests.
Communicating ethical requirements to colleagues, hosts and sponsors	All team members should sign declarations of interests before joining the field team. Any unacceptable conduct should be confronted.
Submitting proposed follow-up studies for ethical review	Long-term follow-up studies should undergo stringent ethical review, as such investigations are not urgent. Local, national and/or international ethics review committees should oversee long-term research projects initiated after an acute event to ensure that they conform to current ethical standards.

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Annex 1. Preliminary investigation

The list of questions below could be asked during the preliminary investigation (stage 3) of a suspected chemical-related event in order to characterize the outbreak and guide further investigation. It is not exhaustive but may serve as an *aide-mémoire*.

Characteristics of cases

What is the number of suspected cases?

How many deaths have there been; what is the mortality rate?

What are the age and sex characteristics of suspected cases?

How many suspected cases are there in the population?

What are the date and time of onset of cases?

What is the time course of the illness from onset to outcome (resolution or death)? In what order do clinical features appear?

What symptoms have been reported?

What signs have been observed?

Do cases require immediate medical treatment or hospitalization?

Do cases require decontamination?

What is the geographical distribution of suspected cases?

Is there any clustering of cases? Consider household, workplace, school, public place, water source, foods, consumer produce, ethnic and religious groups.

Where are cases being cared for (family, community, medical centre, other)?

Have others, such as first responders, medical staff or those caring for the suspected cases, developed symptoms?

Location

Is the area predominantly rural, urban or both?

Describe the land use or location in which cases originate (if known) e.g. camp for displaced people, residential, agricultural, commercial, industrial, educational, health care, open space, coastal area, recreational land, other

Are the dwellings temporary, permanent or other?

Are any nearby bodies of water used by those affected?

Possible sources of chemical exposure (food and water)

Did the cases eat a food in common (local, regional or imported)?

Has a particular traditional medicine or recreational substance been used by the majority of the cases?

Was a single brand of food or commodities (e.g. flour, sugar, salt, cooking oil), drink or medicine used by the majority of the cases or a range of products from a single distributor, manufacturer or market?

Is there a common source of drinking-water or recreational water?

Were any cases exposed to consumer products?

Agricultural and industrial activity

Have any unusual odours been noted in the locality?

Has there been a report of a recent chemical spill or release? What chemicals were involved? Where was the chemical released (e.g. air, water, land)? What quantity was released, approximately?

Is there visual evidence of mining in the area or any other activity that could contaminate the environment?

Is there visual evidence of current or past industrial or chemical manufacture, storage or disposal?

Are there any major industrial sites in the locality, and what do they produce?

Is there a significant trade or transport route in the vicinity?

Is chemical waste regularly imported to or exported from the area?

How and where are domestic wastes (solid and effluent) disposed or stored?

How and where is industrial or trade waste (solid and effluent) disposed or stored?

Are any unregulated domestic or industrial materials regularly recycled or sold?

Are there local cottage industries, and what are they?

Is it an agricultural area, and what are the main crops grown?

Has there been any recent pesticide application in the area? If so, which pesticide, how was it applied and for what purpose?

Are chemical fertilizers or other products applied to the land? Describe the frequency and when last used.

Military activity

Is there evidence of current or past military activity in the area?

Is the use of chemical agents known or suspected?

Other questions

What do local communities think is the cause of the illness?

Has a similar incident happened there or nearby in the past?

What are the print and broadcast media saying about the incident?

Are there any comments or speculation on social media?

Is there any reason to suspect mass psychogenic illness?

Environmental information (may not be readily available but should be collected with other data)

Have there been any unusual meteorological or extreme weather events recently (flooding, drought)?

Have there been any significant natural events that could trigger the release or mobility of a chemical?

What is the general direction of the prevailing wind?

What sources of water are used for drinking (aquifer, well, river)?

Where is drinking-water abstracted? Is it treated before use?

What water sources are used for bathing or recreational use?

Consider effluent discharges

What is the local geology (sand, clay, loam)?

Results of clinical and environmental testing

What medical investigations have been conducted? What are the results?

Have tests have been conducted on water (e.g. for heavy metals, organic solvents, pesticides)? What are the results?

Have tests have been carried out on food (e.g. for heavy metals, pesticides)? What are the results?

Have tests have been carried out on air? What are the results?

Have tests have been carried out on soil? What are the results?

Have any results been validated in quality-assured, accredited laboratories?

Annex 2. Conducting a field investigation

A2.1. Sources of surveillance data

Sources of mortality data

Health facilities

- Death records and other centralized vital registration database in hospitals and health facilities

Home visitors and community workers

- Grave-watchers trained to provide 24-h observation of designated burial sites and to report the number of burials (non-specific)
- Home visitors trained to use verbal autopsy method with standard forms
- Religious and community leaders
- Community workers trained to report deaths from a defined section of the population, e.g. a small hamlet

Other agencies

- Records of organizations responsible for burials

Sources of morbidity data

Health facilities

- Records (electronic and paper) from inpatient and outpatient registers and databases of hospital episodes, records from camp clinics, hospitals and local communities

Associated services

- Disease notifications and reporting of sentinel diseases
- Health workers and midwives in displaced populations
- Administrative or financial data from health care records (e.g. health insurance)
- Prescription records and databases
- Information from telephone health care systems, e.g. poisons centres

Other agencies

- Sickness absence records from workplaces and schools

Sources of demographic data

- Census data and other routine sources of vital statistics
- Registration records maintained by camp administrators, local governments, religious leaders, international organizations (United Nations agencies), etc.
- Cross-sectional (sample) surveys
- Interviews with community leaders
- Mapping
- Aerial photographs or global positioning systems

Surveillance data may also be received from event-based surveillance systems, including communities, the media, nongovernmental organizations, poisons centres, laboratories, hospital personnel and emergency services.

Reference

Connolly MA, editor. Communicable disease control in emergencies – a field manual. Geneva: World Health Organization; 2005:93 (<http://www.who.int/iris/handle/10665/96340>, accessed 8 January 2019).

A2.2. Field investigation questionnaire

A questionnaire is required for preliminary assessment of an outbreak and for descriptive and analytical epidemiological investigations. Questionnaires should be simple, accessible, relevant, complete and accurate. The level of detail will depend on the stage of the investigation and the nature of the outbreak. The content should be limited to the information required for the stated objectives of the investigation.

Questionnaires usually include both open- and close-ended questions. Open-ended questions are exploratory and are useful for identifying relevant topics and determining the full range of possible responses. The answers are, however, more time-consuming to collect and more difficult to categorize for subsequent analysis. Closed-ended questions require a limited number of responses (e.g. yes, no, don't know), are quicker to collect and easier to code and analyse but may miss relevant information.

In the field, questionnaires can be completed by respondents (self-administered), by a nominated person in the event of significant morbidity or mortality or by the interviewer. The first is preferable for a literate population, provided the questions are short and simple. The last is preferable if the questions are complex and require significant probing by a trained interviewer and for less literate populations. Details of questionnaire design and administration and interviewing techniques is beyond the scope of this manual, and investigators are advised to consult recommended textbooks and experts. A sample questionnaire that can be modified for each outbreak is provided in Annex A2.3.

Codes should be assigned to as many information items as possible, e.g. to locations and occupations, to facilitate data processing and analysis.

Before administering a questionnaire, its purpose should be explained to the respondents, and they should be assured of confidentiality, for which the necessary measures must be taken.

Factors to consider when drafting a questionnaire include the following.

- Ensure that every question is relevant to the purpose of the investigation.
- Keep the wording informal, conversational and simple.
- Avoid jargon and sophisticated language.
- Ensure that the questions are appropriate to the educational, social and cultural background of the respondents.
- Limit each question to a single subject.
- Avoid long questions (but vary their length).
- Avoid leading questions (“You surely agree with me, that ...”).
- Avoid negative questions.
- Avoid beginning questions with “Why”.
- Avoid hypothetical questions (“Imagine that ...”).
- Pay attention to sensitive issues.
- Ensure the adequacy of the list of responses to closed-end questions.
- Avoid a large proportion of responses in the “other (specify) ...” category.

References

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A2.3. Field investigation questionnaire that could be adapted to any outbreak of unknown etiology

This questionnaire should be completed by all individuals who meet the definition of an outbreak case or who form part of a definable group.

Interviewer's name and code:
 Date and time of interview: Date time
 Location of interview:
 Person interviewed: Suspected case
 Next of kin (specify relationship)
 Health care worker (specify)
 Interview ID number:

Section 1. Personal details

- (a) Family name:
- (b) Given name:
- (c) Sex:
- (d) Age:
- (e) Date of birth:
- (f) Home address (e.g. village, barrio or commune):
- (g) Telephone number (if applicable):
- (h) Height:
- (i) Weight:
- (j) Main occupation (own):
- (k) Main occupation (spouse or partner):
- (l) Main occupation (parents):
- (m) Workplace or educational institution contact (specify):
- (n) Other contact (specify):

Section 2. Clinical details (related to current disease outbreak):

- (a) Since (insert date from case definition), have you had an illness (insert illness description from case definition)
- (b) When did your symptoms start? Date time
- (c) How long did they last? Hours, days, months or years
- (d) Did you have any of the following symptoms?

Symptom	Yes	No	Don't know
List symptoms			
Other symptoms (please describe)			

- (e) Were you off work or school because of the illness?
- (f) Did you contact your doctor or hospital because of this illness?
 - a. When did you contact the doctor or hospital?
- (g) Were you admitted to hospital because of the illness?
 - a. When were you admitted?
 - b. What hospital were you admitted to?
 - c. How long were you in hospital for?

- (h) Have you experienced these symptoms before?
 - a. When?
 - b. For how long?
 - c. What did you do at that time?
- (i) Has any member of your family or any people you live with (household member) been ill with the same or similar symptoms since (*insert date from case definition*)?
 - a. Who are the affected members of your family?
 - b. What are the ages of the affected members of your family?
 - c. When did the symptoms start?
 - d. How long did the symptoms last?
- (j) Do the *affected* member(s) of your family consume the same food and drink?
- (k) Did the *affected* member(s) of your family consume food and drink at the same time as you did?
- (l) Do any of the *affected* member(s) of your family take the same medicines?
- (m) Have any members of your family or any people you live with *not been ill* with the same or similar symptoms since (*insert date from case definition*)?
 - a. Who are the *unaffected* members of your family?
 - b. What are the ages of the unaffected members of your family?
- (n) Do the *unaffected* member(s) of your family consume the same food and drink?
- (o) Did the *unaffected* member(s) of your family consume food and drink at the same time as you did?
- (p) Do any of the *unaffected* member(s) of your family take the same medicines?
- (q) In general:
 - a. Has a doctor or nurse ever told you that your child has any illness(es)?
 - b. Do you take any medication regularly (include local remedies)?
 - c. Please list all medication you take

Section 3. Risk factor history (dietary and environmental)

Food history

- (a) What do you usually eat for breakfast? (*please list*)
 - i. Where do you usually get the food from?
- (b) What do you usually eat for lunch?
 - i. Where do you usually get the food from?
- (c) What do you usually eat for dinner?
 - i. Where do you usually get the food from?
- (d) Do you eat food between meals?
 - i. Please list the food items eaten between meals.
 - ii. Where do you usually get the food from?

In relation to the current disease outbreak:

- (e) What meals did you eat in the period between (*insert relevant dates from case definitions*) (if different from your normal diet)?
- (f) When did you eat these meals?
- (g) Was there anything unusual about the taste, appearance or smell of the meal?
- (h) What was unusual?
 - How long after the meal did your symptoms start?
- (i) List all food items contained in the meal (e.g. meat, grains, fish)
- (j) List all ingredients of the meal (e.g. salt, pepper, spices)
- (k) Where (or from whom) were these food items and ingredients purchased?
- (l) When were these food items and ingredients purchased or received?
- (m) How were the food items and ingredients packaged?

- (n) How was the meal prepared before consumption (e.g. stove, oven)?
- (o) What type of fuel was used to heat the device used in preparing the meal (e.g. kerosene, wood, paper)?
- (p) Have you eaten any of the food items listed below since (*insert the date from the case definition*)?
- (q) Are there any food samples available for analysis?

Drink history

- (a) What kinds of drinks do you take regularly (e.g. tea, fruit juice, bottled or tinned soft drink, beer, spirits)?
- (b) What drinks did you take before the onset of symptoms?
- (c) Where did you obtain this/these drinks (e.g. bought from a shop, café, bar; taken at a social event)?

Water history

- (a) When did you last drink water before the onset of the symptoms?
- (b) Where was the water from (e.g. mains tap, bottled water, river, stream)?
- (c) When was the drinking-water collected or bought?
- (d) What quantity did you drink before the onset of symptoms (in litres)?
- (e) Do you store drinking-water?
 - i. How do you store drinking-water?
 - ii. How long was the drinking-water stored in the container?
- (f) How was the drinking-water treated?
- (g) Do you use the same water for cooking?
- (h) Has there been any change in the way you collect, treat or store drinking-water?
- (i) Have you noticed any unusual taste, appearance or smell of your drinking-water?

Residential (environmental) history

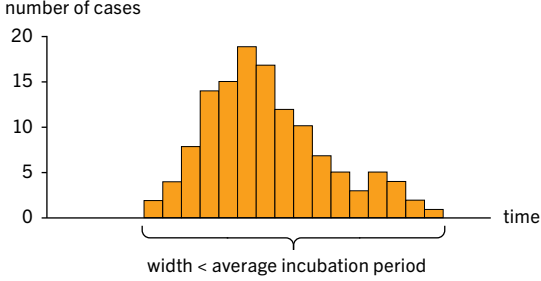
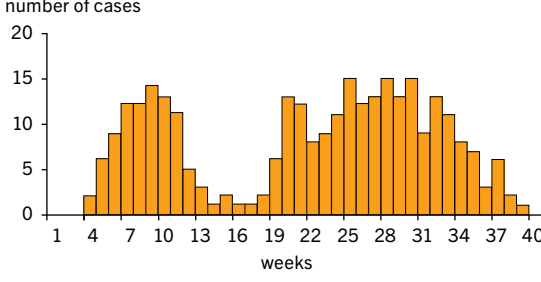
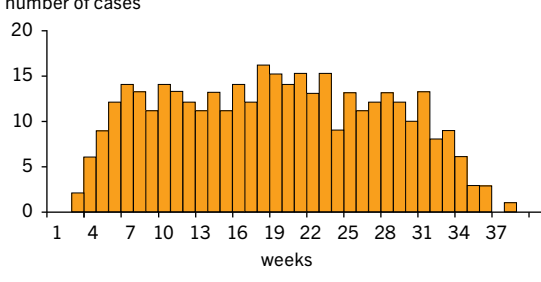
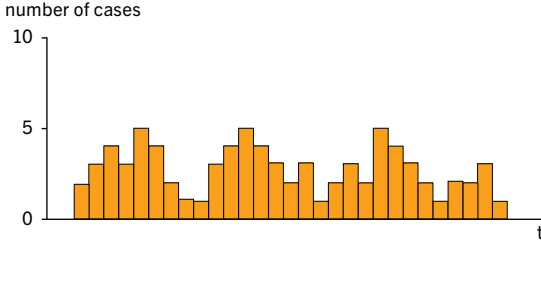
- (a) How long have you lived at your current address?
- (b) Where did you live before that and for how long?
- (c) What type of housing are you living in, and what material is it made of?
- (d) Did you use empty chemical containers or other non-traditional material to build the house?
- (e) Are there any chemical-related businesses nearby (e.g. industries, waste sites, tanneries)?
- (f) Do you have neighbours of the same age and sex who have *not* experienced the same or similar symptoms?

General comments:

A2.4. Case-based surveillance reporting form

Unique identification number		
Last name:	First name:	Initial(s):
Sex: Male Female (circle one)	Date of birth:	Ethnic group:
Occupation (please describe as appropriate):		
Address:		
Date of onset of clinical features:	Date of diagnosis:	Date of clinical specimen (if applicable):
Clinical symptoms: (Please list by affected organ or system)	Clinical signs: (Please list by affected organ or system)	
Working clinical diagnoses:		
Current clinical status: Dead Critical Stable Recovered (circle one)	Date of death (if applicable)	
Name of hospital (health facility):		
Name of responsible health professional:	Contact telephone:	
Laboratory results (if available):		
Other relevant information (e.g. affected family members, work colleagues)		
Reported by: Name: Address:	Date of report:	

A2.7. Epidemic curves

Epidemic curve	Description	Graphical example
Point-source outbreaks	Group of people exposed relatively briefly to a toxin from the same source. Affected individuals develop clinical disease in a short time.	<p>A. Point source</p> 
Intermittent and continuous common source	Group of people intermittently exposed to a toxin from the same source, such that cases of clinical disease occur intermittently.	<p>B. Intermittent common source</p> 
	Group of people exposed to a toxin from the same source for a long time, such that the date of onset of clinical disease is also spread out over a long time.	<p>C. Continuous common source</p> 
Propagated (person-to-person) outbreaks	This is an unlikely presentation in chemical incidents, unless the risk of secondary contamination is high.	<p>D. Propagated (person-to-person)</p> 

Reference

Foodborne disease outbreaks: guidelines for investigation and control. Geneva: World Health Organization; 2008 (http://www.who.int/foodsafety/publications/foodborne_disease/outbreak_guidelines.pdf, accessed 14 August 2018).

A2.8. Rates and ratios commonly used in field epidemiology

Rates are measures of the frequency of occurrence of disease(s) in an affected population. They are calculated from a defined numerator and denominator over a well-defined period. Crude rates are calculated for the total population in an area. Crude rates for different populations cannot easily be compared because of potential differences in the underlying demographic structure of the populations. Specific rates overcome this difficulty, as they are based on data for specific segments of the population (e.g. age- and sex-specific rates).

$$\text{Crude rate} = \frac{\text{Number of new cases of disease (or illness) in population at risk}}{\text{Number of people in the population at risk}}$$

$$\text{Specific (age, sex) rate} = \frac{\text{Number of new cases of disease (or illness) in males aged < 18 years}}{\text{Number of males aged < 18 years in the population at risk}}$$

Rates and ratios that may be calculated during an outbreak investigation include the following.

Attack rate: proportion of the population that becomes ill after exposure to the suspected environmental toxin during a defined period (e.g. week), usually expressed as a percentage. Specific attack rates allow investigators to identify people in the population who are at higher risk of being affected after exposure. Common specific attack rates are calculated by age group, sex, geographical location (residence) and occupation.

$$\text{Specific attack rate} = \frac{\text{Number of cases of disease (or illness) among people who ate food "X"}}{\text{Number of people who ate food "X"}}$$

Case fatality rate: proportion of people with the disease (or illness) who die as a result of the disease within a given period, usually expressed as a percentage. Important ratios include the *rate ratio* (risk ratio or relative risk) and the *odds ratio*, which are measures of the strength of the association between the exposure and the illness or disease. These ratios have no units. A test for statistical significance is used to determine the probability that a similar or larger ratio could have arisen by chance alone.

Reference

Last JM, Spasoff RA, Harris SS, Thuriaux MC, editors. A dictionary of epidemiology. 4th edition. New York City (NY): Oxford University Press; 2001.

Annex 3. Mission plan

Below is an example of a mission plan that could be used to prepare a clear plan for deploying a response team to an affected area. The mission plan should include a clear statement of the purpose and address operational and technical issues, such as team composition, programme of work, investigative methods, equipment, funding and timescales.

1. Introduction and background to the mission (summary of the current situation, including epidemiological, clinical and environmental information; any hypotheses; available resources and support; and current activities)
2. Risk analysis
3. Risk management
4. Aims and objectives of the mission
5. Investigation plan (summary of proposed epidemiological, environmental, toxicological and laboratory methods of investigation and a work programme)
6. Team composition and structure (source organization(s), terms of reference, team roles and responsibilities)
7. Activities, resources and timescales (may include information on planned and proposed meetings, types and frequency of communication, e.g. situation reports, and resources required)
8. Response and coordination framework (recommendations for the composition of an outbreak control committee to coordinate the inputs of various stakeholders)
9. Risk and crisis communication
10. Other issues

Annex 4. Considerations for the health and safety of the field team

A4.1. Checklist of security and safety issues before deployment

Item	Current situation	Comment or action
Preliminary risk assessment undertaken		
Field members briefed on the current risk assessment and a process for providing regular updates and situation reports finalized		
All field members have undertaken the necessary general and mandatory training and have clearance.		
Passports are current and visas obtained, with letters of authority.		
Immunization status of team members checked and compliant with recommendations for the area		
Prophylaxis and other protective measures that comply with recommendations for the area provided		
Field and personal first aid kits provided		
Relevant personal protective clothing and equipment secured		
Security clearance, accommodation and transport requirements of personnel secured		
Arrangements made for handling and transporting heavy equipment and other relevant kit		
Communications mechanism in place, particularly for emergencies		
Food and water safety assessed		

A4.2. Basic equipment for personal safety and investigation

The actual equipment required will depend on the setting, the circumstances and individual's role in the investigation; the list below is indicative only.

Personal items

- Identification card and copy of passport, visa and other important documents
- Contact lists
- Spare pair of glasses or contact lenses
- Personal first aid kit
- Personal medications
- Cash
- Field rations
- Water purification tablets or a portable water filter
- Portable flashlight
- Spare batteries
- Whistle
- Waterproof trousers and jacket
- Sun hat, sunglasses
- Insect repellent
- Insecticide-treated bed net

Personal protective equipment

- Hard hat
- Safety shoes or boots
- Gloves, preferably disposable nitrile
- Appropriate disposable particulate respirators (filtering face pieces)
- Eye protection
- Hearing protection
- High-visibility jacket
- Long-sleeved coveralls

Communications and information technology

- Mobile phone, with charger and adapter, and list of contact names and emergency numbers
- Satellite phone
- Two-way very-high-frequency portable radios
- Rugged laptop computer with charger and adapter, and spare battery pack
- Portable wifi hotspot
- GPS system

Investigation equipment

- Basic equipment for monitoring meteorological conditions, such as a portable anemometer
- Chemical quick reference cards and datasheets (laminated)
- Simple hazard and symptom database (e.g. wireless information system for emergency responders; WISER; <https://wiser.nlm.nih.gov/>)
- Appropriate air sampling equipment as required for each incident
- Binoculars
- Calculator
- Maps

Annex 5. Communication and reporting during a field investigation

A5.1. Example of an agenda for a meeting on outbreak control

Introduction:

- Membership
- Terms of reference
- Accountability

Minutes of last meeting (if applicable)

Update on outbreak:

- General situation
- Number and severity of cases
- Epidemiological report
- Clinical toxicology report
- Laboratory (toxicology) report
- Environmental report
- Other relevant report

Management of the outbreak:

- Control measures: patients, public health
- Care of patients, including antidotes: health care and community settings
- Laboratory (toxicological) aspects: sampling, specimen management and resource requirements

Communications:

- Agree on media arrangements, including nominated spokesperson and content of media releases
- Advice to public and professionals (e.g. fact sheets)
- Arrangements for responding to enquiries from the public

Administration and logistics:

- Contact details of all personnel
- Resources required

Agree on actions taken

Date and time of next meeting

Reference

Foodborne disease outbreaks: guidelines for investigation and control. Geneva: World Health Organization; 2008 (http://www.who.int/foodsafety/publications/foodborne_disease/outbreak_guidelines.pdf, accessed 8 January 2019).

A5.2. Example of a situation report

A situation report updates the status of an outbreak and provides information for the lead agency and partners to plan and modify their response strategy. The report provides current information about the emergency response, immediate and future activities, analysis of the impact of the emergency and identification of management issues. It may also be used for advocacy.

The information provided in the situation report must be factual, with little interpretation or conjecture. The information should cover the period between the last and the next report. Ideally, the first situation report should be sent to the lead agency and all stakeholders within 24 h of arrival in the field. The frequency of subsequent situation reports depends on the circumstances and available resources, but they should be issued at least twice a week. The report should be brief (e.g. 1–3 pages) and specific to the investigation. A suggested layout and content are outlined below.

Title: Outbreak situation report [event, country]

Situation report No:

Date of issue and period covered:

Location:

Prepared by:

Focal point and contact details:

1. Investigation team composition

- List members of the investigation team and their areas of expertise.
- State to whom the team reports and from whom they have support.

2. Summary of situation to date

Describe the type and extent of the outbreak:

- Identify the affected population.
- Provide details of e.g. surveillance, epidemiology, laboratory results.
- May include an epidemic curve, sites visited and maps.
- Should provide factual information about the outbreak situation.

3. Actions to date

- Brief report on completed activities, usually for the period covered by the situation report.
- It may include briefings, meetings, training, site visits, data analysis and information management.

4. Actions to be completed (planned activities)

- Brief report of scheduled and planned actions, usually for the period covered by the report
- May include reviews of procedures, training, site visits and briefings of relevant parties.
- Tables may be used to show repeated actions.
- Actions expected to be completed by the time of the next situation report

5. Identification of arising or anticipated issue(s)

- Briefly describe issue(s) that are known or reasonably expected to arise before the next report is issued, e.g. shortage of a given resource, difficulties in accessing sites of interest.
- Acknowledge significant achievements and describe failures.

Completed by (name and role):

Approved by (name and role):

Date:

Abbreviations and acronyms:

Reference

Protocol for the investigation of acute respiratory illness outbreaks of unknown etiology. Brazzaville: WHO Regional Office for Africa; 2016 (<http://apps.who.int/iris/bitstream/handle/10665/204592/9789290233008.pdf?sequence=1&isAllowed=y>, accessed 8 January 2019).

A5.3. Evaluation of an outbreak response

Questions that will assist evaluation of an outbreak response are listed below.

- When was the initial outbreak report received?
- How was the initial outbreak report received?
- How and when was it referred to the appropriate health agency or organization (including responsible personnel)? Was there any delay?
- Did the personnel designated to receive outbreak information conduct a thorough assessment and initiate a proper response?
- Was investigation of the outbreak initiated without delay?
- Did the responsible health agency(s) provide appropriate, adequate support to enable the health authorities in the affected area to mount an effective, timely response (i.e. technical assistance for investigation and control)?
- Was there smooth cooperation among local, regional, national and international agencies and stakeholders?
- Did local health authorities have sufficient expertise and capacity to deal with the outbreak?
- Were appropriate resource materials and personnel (experts) available?
- Are there appropriate standards and regulations to prevent similar outbreaks in the future?
- Are there appropriate guidance, protocols and plans to deal with similar outbreaks in the future?
- Was the communication strategy effective? Were communication channels with the media, the community and stakeholders appropriate and effective?
- Were the media properly engaged and used to disseminate information on the outbreak to the public?
- Was there a review or discussion of lessons learnt within 2 weeks of completion of the outbreak investigation?
- Will the outbreak investigation report be published? If not, why not?

A5.4. Suggested outline for an outbreak investigation report

Cover page

Title of report

Indicate whether it is a preliminary or a final report. Keep the title short and memorable, but include information on the type of problem investigated, the location and the date.

Date of report

Names and affiliations of the main authors and investigators

Abstract

The abstract should be written after the report has been completed. It should stand alone and contain the most relevant data and conclusions. All data cited in the abstract must also appear in the main section of the report. Sentences from the discussion section can be used verbatim in the abstract. No more than six priority recommendations should be included.

Introduction

- Statement of the problem and its public health importance
- Details and timing of initial information
- Reasons for investigating the event
- Type of investigations conducted and agencies involved

Background

- Provide generally available information to help the reader interpret epidemiological and other data presented in the report (e.g. population size, socioeconomic status of community, ethnicity).
- If the outbreak occurred in a defined area or institution, describe the area (e.g. size of school, industry or community, usual practices and operations).
- Describe the problem.
- List the sequence of events leading to the study or investigation.
- Briefly state the working hypothesis.

Objectives

- Specify the targets to be achieved by the investigations.
- Keep the objectives concise, and follow a logical, sequential pattern.
- The objectives may include any hypotheses to be tested.

Methods

Epidemiological investigation:

- description of study population
- type of study conducted
- case definition
- procedures for case ascertainment and selection of controls (if any)
- methods of data collection, including questionnaire design, administration and contents
- methods of data analysis.

Clinical and toxicological investigations

- examinations and investigations carried out
- hypotheses considered
- samples collected (type, number) and analyses done.

Laboratory investigation:

- methods of specimen collection and processing
- name of testing laboratory
- laboratory techniques used and methods of data analysis.

Environmental investigation:

- description of site visit
- methods of environmental sampling
- name of testing laboratory
- laboratory techniques used and methods of data analysis.

Results

Present all pertinent results from clinical, laboratory, epidemiological and environmental studies. Present results in same order as described in the methods section. Do not interpret or discuss the data in this section.

Epidemiology:

- number of cases, overall attack rate
- clinical details of illness (symptoms, duration, hospitalization, outcome, etc.)
- descriptive epidemiology by time (epidemic curve), place and person (age, sex, race, specific characteristics) expressed as rates
- exposure to risk factors
- further data analysis and data presentation depending on the studies undertaken
- (e.g. cohort or case–control study).

Clinical and toxicological

- number of cases examined
- findings of examinations and tests.

Laboratory (microbiology, chemical, toxicological):

- number of specimens collected
- findings by type of laboratory analysis.

Environmental investigation and testing:

- findings of inspection visits
- results of laboratory tests on environmental samples.

Discussion

The discussion is the most important part of the report. It should include:

- a summary of the major findings
- probable accuracy and limitations of the results
- conclusions, with justification, and rejection of alternative explanations
- relation of the results to those of other studies in the literature
- implications of the findings
- assessment of control measures
- future research required.

Recommendations

Initial recommendations and those for future prevention and control should be listed.

References

Select appropriate references, including reviews in major scientific journals. Follow a standard style of referencing (e.g. Vancouver style), numbering the references in the order in which they appear in the text.

Annexes

- Questionnaires and/or other survey forms
- Appropriate field reports
- Any other relevant documents, including press releases.

Reference

Foodborne disease outbreaks: guidelines for investigation and control. Geneva: World Health Organization; 2008 (http://www.who.int/foodsafety/publications/foodborne_disease/outbreak_guidelines.pdf, accessed 8 January 2019).

Annex 6. Risk perception and risk communication

A6.1. Risk perception

The factors that can influence people's perception of risk should be identified so that they can be addressed in communications.

Risk factor	Conditions that increase public concern and anxiety
Catastrophic potential	Many fatalities and injuries in time and space (i.e. over a short time)
Familiarity	Risk due to a new, unfamiliar, invisible or overlooked agent
Understanding	Poorly understood mechanism or process of risk, particularly when there is no consensus among experts
Controllability	Situation judged to be outside of personal control, particularly if it is judged to be controlled by people who are not trusted
Voluntary nature	Exposure is involuntary and perceived to be imposed externally
Population groups affected	Risk that specifically or predominantly affects children, the elderly and pregnant women
Manifestation of effects	Adverse effects with delayed onset and may occur years after exposure
Effects on future generations	Exposure that poses considerable, quantifiable risks to future generations
Victims	Threatens identifiable rather than anonymous or theoretical victims Poses a personal threat by singling out individuals
Dread	Adverse effects that threaten a form of death (or illness, injury) that is particularly dreaded
Institutional trust	Public distrust in responsible institutions and organizations, particularly those with regulatory oversight
Media	Extensive, unrelenting media coverage Multiple and contradictory risk assessment and risk communication messages
Equity	Evidence of inequitable distribution of health risk and benefit
Benefits	Offers little or no compensating benefit(s)
Reversibility	Irreversible risk
Origin	Adverse effects arising from human actions or errors rather than from natural sources

A6.2. Worksheet for identifying individuals and organizations to be contacted during an emergency

Group	Notifications (check those that apply)	Contact	Telephone, fax, e-mail day and night
Local government	Local health officer		
	Local health department public information officer		
	Local environmental health office		
	Local government officials		
	Local government public information officer		
	Local emergency response organizations (for example, fire, police, emergency management services and law enforcement)		
	Local public emergency response organization		
	Local hospitals		
	Other		
Regional (state) government	Regional health director		
	Regional health department public information officer		
	Regional government executive office		
	Other regional government officials		
	Other		
National government	National health director		
	Public information officer		
	National government executive office		
	Other national government officials		
	Other		
International organizations	WHO country office		
	WHO regional office		
	Other international organizations		
	Nongovernmental organizations		
	Other		
Other partner and stakeholder organizations (see Annex 3 for examples)			

Group	Notifications (check those that apply)	Contact	Telephone, fax, e-mail day and night
Local, regional (state), national and international media organizations			
Others			

A6.3. Examples of stakeholders in a major chemical-related outbreak

- Victims and their families
- Public at large and at risk
- Emergency response personnel
- Governmental and nongovernmental authorities
- The media
- Public health authorities and agencies (local, regional, provincial, national and international)
- Physicians, nurses, paramedics and other health care personnel
- Veterinarians
- Fire department personnel
- Police and other law enforcement personnel
- Hospital personnel
- Health agency employees
- Families of emergency responders, law enforcement personnel, hospital personnel and health agency employees
- Government agencies (regulatory and non-regulatory) at all levels
- Employees of other responding organizations
- Politicians, legislators, elected officials
- Union officials and labour advocates
- Legal professionals
- Contractors
- Consultants
- Suppliers and vendors
- Ethnic populations
- Minority populations
- Institutionalized populations
- Elderly populations
- Religious groups
- Special language groups
- Disabled populations
- Homeless people
- Home-bound populations
- Other vulnerable populations
- Illiterate populations
- Tourists or business travellers and their relatives
- Local residents who are out of town and their relatives
- Security personnel
- Service and maintenance personnel
- Advisory panels
- Nongovernmental and non-statutory organizations
- Educational leaders and community (all levels)
- Scientific leaders and community
- Business leaders and community
- Military leaders
- Professional societies.

A6.4. Guidelines for preparing clear, concise messages during public health emergencies

- Identify the most important topics for the target audience.
- Determine how to correct misperceptions or erroneous information.
- Prepare three key messages that communicate your core points.
- Prepare points for each key message.
- Develop supporting material for each message (for example, visuals, examples, quotes, personal stories, analogies, endorsements by credible third parties or directions for obtaining additional information).
- Keep messages simple and short.
- Write the recommended messages, and document supporting material.
- Practise delivery.

A6.5. Checklists for media communications

Content of a press release

Insert headline.

Insert the key messages to the public.

Insert 2–3 sentences describing the current situation.

Insert quote from the lead spokesperson or agency head demonstrating leadership and concern.

List actions currently being taken.

List actions that will be taken next.

List information on possible reactions of the public and on how the public can help.

List contact information, ways to get more information from the agency, links to other organizations and other resources.

Content of a media kit or pack

News releases

Fact sheets

Biographies of speakers, subject-matter experts and others as appropriate

Contact numbers

Copies of any reports or documents that would be useful to reporters covering the event

Visual material (such as maps, charts, timelines, diagrams, drawings and photographs)

Other material as appropriate

Sample press release template

[Organization's letterhead]

News release

FOR IMMEDIATE RELEASE

For more information, contact:

[DATE]

[Name of internal media representative/contact person]

[Name of organization]

[Telephone number]

[Fax number]

[Email address]

[After-hours telephone number]

[Web site for more information]

[Headline goes here, initial cap, bold]

[CITY, State] – [Date] – [Text goes here, double-spaced, indented paragraphs]

[First paragraph: short (less than 30–35 words); contains the most important information]

[Second paragraph: contains the who, what, why, where, when of the story. Try to include a quote from the lead spokesperson or agency leader within the first few paragraphs.]

If the news release is more than one page long, add:

– More –

Centre the word at the bottom of the page, and then continue onto the next page with a brief description of the headline, and page number as follows:

[Shortened headline] – Page 2

[The last paragraph should be an organization boilerplate, which is a brief description of the organization, and any information considered useful for people to know, such as type of organization, its location and web site address]

At the end of the release put:

End or ###

Centred at the bottom. This lets the reporter or reader know they have come to the end.

Time of enquiry: _____

Nature of enquiry: _____

Specific information requested: _____

Topic 1: _____

Topic 2: _____

Topic 3: _____

Topic 4: _____

Type of enquiry:

For information (if so, what): _____

For recommendation (if so, what): _____

For action (if so, what): _____

Other: _____

Outcome of call:

Able to respond to person: _____

Not able to respond to person: _____

Referred person to: _____

Other: _____

Further action needed:

None: _____

Provide further information: _____

Return call: _____

Urgency (*check one*):

_____ Critical (respond immediately)

_____ Urgent (respond within 24 h)

_____ Routine

Enquiry taken by: _____

Date: _____

This form should be adapted to local requirements.

Annex 7. Epidemiological data

A7.1. Features of study designs used in environmental epidemiology

Study design	Population	Exposure	Health outcome	Confounders	Disadvantages	Advantages
Descriptive	Several population groupings, including sub-groups	Records of past or current measurements	Morbidity and mortality statistics, case series, etc.	Difficult to measure and distinguish	Difficult to establish a real causal association between exposure(s) and outcome(s)	Inexpensive and quick; useful for formulating hypotheses
Cross-sectional	Community or special groups; exposed vs unexposed groups	Current	Current	Can be measured but not easily controlled	Difficult to establish a real causal association between exposure(s) and outcome(s)	Useful for estimating prevalence; rapid; can study large populations
Ecological	Population groupings	Measurements from records	Morbidity and mortality statistics	Difficult to measure and high risk of ecological bias	Findings not generalizable to individual level	Inexpensive; useful for studying rare diseases
Case-control	Small groups	Past exposure determined from records and interviews	Known and defined at the start of the study	Usually easy to measure and can be controlled for during design and analysis	Cannot study several health outcomes; findings may not be widely generalizable	Inexpensive, timely; useful for studying rare diseases
Prospective cohort	Community or special groups; exposed vs unexposed groups	Defined at outset of study (may change during the study)	Identified during study	Usually easy to measure and can be controlled for during design and analysis	Expensive; usually not timely; exposure status may change over time; problem of attrition	Can study several health outcomes linked to a single exposure; long-term follow-up

Study design	Population	Exposure	Health outcome	Confounders	Disadvantages	Advantages
Retrospective cohort	Community or special groups (occupational cohort); exposed vs unexposed groups	Occurred in the past; records of past measurements required	Records of past diagnoses required	Often difficult to measure because may not have been recorded	Reported temporal and dose–response changes in exposure–health effect may be incomplete or inaccurate	Less expensive and more rapid than prospective cohort studies; ideal when there are reliable records
Time series	Communities of several million people	Current (e.g. daily) changes in exposure	Current (e.g. daily) differences in mortality	Often difficult to distinguish	Several confounders may remain unmeasured and unadjusted for	Useful for studies on acute effects and for establishing trends
Experimental (interventional)	Community or special groups	Controlled and assigned at start of study	Measured during the study	Usually easy to measure and can be controlled for during design and analysis	Expensive; ethically, may be used only for assessing therapeutic and preventive interventions; issues of attrition	Provide the strongest evidence of causation
Monitoring and surveillance	Community or special groups	Current	Current	Difficult to distinguish	Difficult to prove causation	Cheap, especially when existing surveillance data are used

Reference

Investigating environmental disease outbreaks. A training manual (WHO/PEP/91.35). Geneva: World Health Organization; 1991 (http://apps.who.int/iris/bitstream/handle/10665/58374/WHO_PEP_91.35.pdf?sequence=1&isAllowed=y, accessed 8 January 2019).

A7.2. Sample size

The sample size for an epidemiological study is chosen as a balance between statistical precision and effective use of resources. Study sample size is determined by factors including the purpose of the study, the size of the population, the method of data analysis, the level of precision required, the level of confidence or risk and the variability of the attributes being measured.

The method most commonly used to determine sample size for hypotheses testing is power calculation. Various formulas for calculating sample sizes are described in statistical textbooks and used in computer software. These are beyond the scope of this document, and advice should be sought from a statistician. An alternative approach is to use of tables of samples sizes, in which an estimate of the required sample size is based on population size, confidence level, precision level and the variability of attributes being studied (Tables A7.1 and A7.2).

Table A7.1. Sample size for levels of precision of $\pm 3\%$, $\pm 5\%$, $\pm 7\%$ and $\pm 10\%$, with a confidence level of 95% and P (maximum variation in a population) = 0.5

Size of population	Sample size (n) for precision (e) of:			
	$\pm 3\%$	$\pm 5\%$	$\pm 7\%$	$\pm 10\%$
500	a	222	145	83
600	a	240	152	86
700	a	255	158	88
800	a	267	163	89
900	a	277	166	90
1 000	a	286	169	91
2 000	714	333	185	95
3 000	811	353	191	97
4 000	870	364	194	98
5 000	909	370	196	98
6 000	938	375	197	98
7 000	959	378	198	99
8 000	976	381	199	99
9 000	989	383	200	99
10 000	1000	385	200	99
15 000	1034	390	201	99
20 000	1053	392	204	100
25 000	1064	394	204	100
50 000	1087	397	204	100
100 000	1099	398	204	100
> 100 000	1111	400	204	100

^a Assumed that the normal population is poor and therefore the entire population should be sampled.

Table A7.2. Sample size for levels of precision of $\pm 5\%$, $\pm 7\%$ and $\pm 10\%$, with a confidence level of 95% and P (maximum variation in a population) = 0.5

Size of population	Sample size (n) for precision (e) of:		
	$\pm 5\%$	$\pm 7\%$	$\pm 10\%$
100	81	67	51
125	96	78	56
150	110	86	61
175	122	94	64
200	134	101	67
225	144	107	70
250	154	112	72
275	163	117	74
300	172	121	76
325	180	125	77
350	187	129	78
375	194	132	80
400	201	135	81
425	207	138	82
450	212	140	82

These sample sizes reflect the number of responses obtained and not necessarily the number of questionnaires completed or interviews planned. These numbers are often increased to compensate for non-response and other sources of attrition. The sample sizes are based on the assumption that the attributes being measured are distributed normally or nearly so. If this assumption cannot be met, the entire population might have to be surveyed.

Reference

Israel GD. Determining sample size (PEOD-6). Gainesville (FL): Institute of Food and Agricultural Sciences, University of Florida; 2013:1–5.

Annex 8. Environmental sampling

A8.1. Standard operating procedures for collecting environmental samples

Air sampling

Procedures for collecting ambient air samples. Athens (GA): Science and Ecosystem Support Division, Environmental Protection Agency; 2016 (<https://www.epa.gov/quality/procedures-collecting-ambient-air-samples>).

Surface water sampling

National field manual for the collection of water-quality data (NFM). Reston (VA): United States Geological Survey; 2018 (https://www.usgs.gov/mission-areas/water-resources/science/national-field-manual-collection-water-quality-data-nfm?qt-science_center_objects=0#qt-science_center_objects).

Groundwater sampling

ISO 5667-11:2009. Water quality – Sampling – Part 11: Guidance on sampling of groundwaters. Geneva: International Standards Organization; 2009 (<https://www.iso.org/standard/42990.html>).

Groundwater well sampling. Standard operating procedure 2007. Washington DC: Scientific Engineering, Response Analytical Services; 2017 (<https://clu-in.org/download/ert/2007-R00.pdf>).

Soil

ISO 18400-104:2018. Soil quality – Sampling – Part 104: Strategies. Geneva: International Standards Organization; 2018 (<https://www.iso.org/standard/65223.html>).

Soil gas sampling. Standard operating procedure 2042. Washington DC: Scientific Engineering, Response Analytical Services; 2001 (<https://response.epa.gov/sites/2107/files/2042-R00.pdf>).

A8.2. Environmental sampling checklist

1. Objectives of sampling are clearly specified.
2. Area to be sampled is identified.
3. Locations to be sampled are identified.
4. All media to be sampled are agreed.
5. Sampling methods are decided.
6. Number of samples to be taken (including duplicates) is specified.
7. Parameters to be analysed are specified.
8. Accredited laboratories are identified.
9. Advice is obtained from relevant laboratories.
10. Minimum sizes of samples specified.
11. Expected time frame for results is agreed.
12. Appropriate containers are available.
13. Required preservatives are available.
14. People to take samples are identified.
15. Necessary personal protection equipment is available.

A8.3. Sample documentation

Each environmental sample must be adequately documented. The minimum information that should be recorded for each sample is:

- Unique sample number
- Date and time of sample collection
- Name of the person who took the sample
- Location from which the sample was obtained
- Source of material
- Sampling techniques used
- Suspected hazards in sample
- Results of any field tests
- Name and address of the destination laboratory
- Date and time dispatched
- Other details

A8.4. Assessing the representativeness of environmental samples

Some questions that should be addressed to determine the representativeness of environmental samples are listed below. The list is not exhaustive and may not be applicable in every outbreak.

1. Were enough samples taken to determine the spatial extent of potential exposure?
Example: In outbreaks in which groundwater contamination is suspected, the number and placement of monitoring wells must be sufficient and an adequate number of residential and municipal water supply wells tested.
2. How are contaminants distributed? Are there “hot spots”?
Example: When surface water (e.g. a river) is contaminated, hydrophobic contaminants tend to accumulate in deposits, often resulting in hot spots. Were sampling locations specifically selected to identify areas of high contamination?
3. Were samples taken in the areas most likely to be affected by contamination? If a specific source is suspected, sampling should be conducted at locations close to the source.
4. Were samples collected over time to determine the temporal extent of contamination?
Example: Data from past monitoring of a particular contaminant may make it possible to establish background concentrations of the chemical and assess whether the concentrations have changed recently in a manner that may be related to observed health effects.
5. Are the data based on grab samples or long-term sampling?
Example: In the acute phase of an outbreak, grab samples are likely to be taken (unless past data are available). Grab samples provide only a snapshot of overall trends in environmental contamination.
6. Is the frequency of sampling adequate to characterize the threat to public health?
Example: If an outbreak of illness occurs in a community living close to a landfill site, the frequency of on-site gas monitoring wells should be sufficient to characterize hazardous acute exposures.
7. What is the measured concentration at the point of contact?
Example: After contamination of any medium, measurement of the environmental concentration alone might not be an appropriate proxy for the exposure dose and the internal dose, which should also be measured, if possible.
8. In what forms were contaminants sampled and analysed?
9. On the basis of current knowledge of the affected area, is the pattern of contamination plausible?

Reference

Public health assessment guidance manual. Atlanta (GA): Agency for Toxic Substances and Disease Registry; 2005 (<https://www.atsdr.cdc.gov/hac/phamanual/toc.html>, accessed 27 January 2019).

A8.5. Examples of items in an environmental investigation kit bag

Kit bags for field investigators contain equipment, templates and other tools that are essential or desirable for environmental investigation of outbreaks. The list below is not exhaustive and is likely to be suitable mainly for environmental grab sampling. The requirements depend on the outbreak scenario.

- Tape measure
- Camera, preferably a digital camera
- Air-tight, pre-labelled amber glass and polyethylene or polypropylene plastic bottles of appropriate size
- Pre-labelled zip-lock plastic bags
- Logbook
- Chain of custody records and custody seals
- Field data sheets
- Marker pens (permanent)
- Spatula
- Scoop
- Plastic or stainless-steel spoons
- Trowel(s)
- Hexane-washed stainless-steel shears
- Ladle
- Stainless-steel bucket
- Rope and stout string
- Pipettes (disposable plastic)
- Cool box with ice packs
- pH indicator paper
- Air detector tubes, such as Draeger tubes

A8.6. Surface wipe sampling

A standard method for collecting wipe samples of particulates, metals and low-volatility liquid contaminants is outlined below. It is not suitable for polychlorinated biphenyls. The method is intended only as a guide, and advice should be sought from the analytical laboratory to ensure that the sampling tool and collection procedures are compatible with the laboratory's procedures. The typical equipment required is listed first.

Equipment type	Details
Sample container	Sealable plastic bag (zip-type seal preferred)
	Glass or plastic vial (glass necessary for samples of organic solvents)
Sample media (any of these)	Cotton gauze: 5 x 5 or 10 x 10 cm
	Ashless quantitative filter paper (typical diameter, 4–10 cm)
	Pre-moistened wipes: manufacturer foil-wrapped, solvent-soaked disposable cloths
Personal protective equipment: gloves	Appropriate for contaminant, solvent and suspected site hazard
Solvent (wetting agent)	Distilled water, isopropanol, ethanol, methanol, <i>n</i> -hexane, or pre-moistened, depending on the analyte. Check with the laboratory.
Template	Plastic or cardboard frame 10 x 10 cm or other standard size.

Samples from non-porous surfaces are collected by wiping or swabbing a moistened, absorptive medium across a pre-determined area. The absorptive medium, wetting agent and containers used to transport samples should be selected according to advice from the designated laboratory.

The method below is a standard operating procedure used by the US Environmental Protection Agency.

1. Choose the appropriate sampling points, measure off the designated area, and record the surface area to be wiped, or use a 10 x 10 cm paper or plastic template.
2. Put on a new pair of disposable, contaminant-free gloves.
3. Open the sampling medium (e.g. a sterile gauze pad), and record the lot number.
4. Moisten the sample medium (gauze pad) with 1–2 mL of an appropriate solvent, such as distilled water, or use pre-moistened wipes. Apply no more solvent than necessary to moisten about 80% of the area of the gauze pad. Try to avoid excess solvent on the pad, as sample may be lost in drips from the pad.
5. Wipe the marked surface area with about 10 firm strokes, vertically and horizontally, until the surface has been completely covered. After the first 10 strokes, fold the exposed surface of the sampling medium inwards, and continue wiping. After 10 more strokes, fold the exposed surface inwards again, if possible.
6. Place the sampling medium in a 40-mL amber vial or an appropriately prepared sample container with a Teflon-lined cap.
7. Cap the sample container, attach the label, and place in a plastic bag.
8. Record the sample identification, surface area sampled and description of the sample and surface on an appropriate form.
9. Include one blank pad or appropriate sample medium (moistened and placed in bags or vials) with each set of samples, with one blank per six samples.
10. As appropriate, store samples in a cool box out of direct sunlight.
11. Clean reusable templates, or discard paper templates, in preparation for the next wipe sample.
12. Discard the gloves appropriately before handling the next sampling medium (i.e. pad).

Reference

Chip, wipe, and sweep sampling. Standard operating procedure 2011, rev 1.1. Washington DC: Scientific Engineering, Response Analytical Services; 2017 (<https://response.epa.gov/sites/2107/files/2011-r11.pdf>, accessed 27 January 2019).

Annex 9. Clinical features

A9.1. Examples of clinical presentations associated with poisons and environmental chemicals (toxidromes)

Toxidrome	Mechanism of action	Syndrome ^a	Poisons and environmental chemicals
Anticholinergic	Muscarinic receptor antagonism	Agitation, confusion, dry mouth, dry skin, hyperthermia, mydriasis, paralytic ileus, tachycardia and urinary retention	Antihistamines, antimuscarinics, antipsychotics, atropine, <i>Inocybe</i> mushrooms, Jimson weed (<i>Datura stramonium</i>), tricyclic antidepressants
Antimitotic	Cytotoxic to dividing cells	Alopecia, bone marrow suppression, diarrhoea, mucositis, vomiting	Arsenic, colchicine, chemotherapy agents, immunosuppressants, ionizing radiation, podophylline, thallium
Cardiac glycosides	Inhibition of Na ⁺ /K ⁺ -ATPase pump Increased vagal tone	Arrhythmia, confusion, hypotension, nausea, vomiting, xanthopsia	Digoxin, foxglove (<i>Digitalis</i> spp), lily of the valley (<i>Convallaria majalis</i>), oleander, ouabain, red squill
Cholinergic	Muscarinic and/or nicotinic receptor agonist Acetylcholinesterase inhibition	Bradycardia, diaphoresis, dyspnoea, lachrymation, loss of sphincter control, miosis, muscle fasciculation, muscle paralysis, vomiting and wheeze	Carbamates, chemical warfare nerve agents (sarin, soman, taban, VX, fourth-generation novichoks), hemlock, <i>Inocybe</i> mushrooms, laburnum, nicotine, organophosphates
Corrosives	Direct chemical irritation or reaction with tissues	Drooling, dysphagia, dyspnoea, haematemesis, melaena, localized pain, vomiting, blisters, skin burns	Acids, alkalis, copper sulfate, hydrofluoric acid, iron salts, paraquat
Hydrocarbons	Central nervous toxicity (volatile hydrocarbons) or aspiration pneumonitis	Arrhythmia, coma, confusion, cough, dyspnoea, gastrointestinal upset	Benzene, diesel, gasoline, kerosene, toluene
Toxic metals and metalloids	Oxidation–reduction reactions	Arrhythmia, confusion, hypotension, gastrointestinal disturbance, metal fume fever, peripheral neuropathy	Arsenic, chromium, iron, cobalt, lead, thallium
Ion-channel blockers	Inhibition of fast voltage-dependent Na ⁺ channels	Arrhythmia, confusion, hypotension, gastrointestinal disturbance, perioral paraesthesia, seizures	Aconite, anti-arrhythmics, local anaesthetics, tetrodotoxin
Methaemoglobin formers	Oxidation of haemoglobin	Cyanosis, headache, weakness, dizziness, anxiety, confusion, dyspnoea, coma, seizures	Sodium nitrite, sodium or potassium nitrate, chlorates, aniline, nitrobenzene, dapsone, propanil

Toxidrome	Mechanism of action	Syndrome ^a	Poisons and environmental chemicals
Mitochondrial toxicity	Impairment of oxidative metabolism	Nausea, vomiting, headache, altered mental status, dyspnoea, hypotension, seizures, metabolic acidosis	Bongkrecic acid (fermented foods), carbon monoxide, cyanide, hydrogen sulfide, phosphine, sodium azide, sodium monofluoroacetate
Opioid	mu-receptor agonists	Coma, hypotension, hypoventilation, miosis, non-cardiogenic pulmonary oedema	Opioids, γ -hydroxybutyrate (GHB), olanzapine
Pulmonary irritants	Direct chemical irritation or reaction with tissues	Bronchospasm, cough, dyspnoea, pulmonary oedema, retrosternal chest pain	Chlorine, nitrogen oxides, sulfur oxides, dioxins, industrial chemicals, smoke inhalation
Salicylates	Weak acids, uncoupling of mitochondrial respiration	Coma, deafness, diaphoresis, hyperventilation	
Sedatives	GABA-receptor agonists	Ataxia, dysarthria, incoordination, nystagmus, reduced level of conscious	Alcohols, barbiturates, benzodiazepines, GHB, γ -butyrolactone (GBL), bromides
Serotonin syndrome	5-HT receptor agonists 5-HT reuptake transporter inhibitors	Autonomic instability: haemodynamic instability, hyperpyrexia, sphincter disturbance Neurological: clonus, hyperreflexia, tremor, seizures Neuropsychiatric: agitation, confusion, fluctuating level of consciousness	Amphetamine, cocaine, methylenedioxy-methamphetamine (MDMA), methylene blue, monoamine oxidase inhibitors, selective serotonin re-uptake inhibitors, St John's wort, tricyclic antidepressants, tramadol, triptans, venlafaxine
Sympathomimetics	Adrenergic agonists Catecholamine metabolism or reuptake inhibition	Agitation, diaphoresis, excitation, haemodynamic instability, hyperpyrexia, hyperreflexia, mydriasis, seizures, tremor	Amphetamine, cocaine, MDMA
Withdrawal	Change in receptor density or ligand sensitivity of relevant receptor Excessive sympathetic nervous system discharge	Agitation, diaphoresis, excitation, haemodynamic instability, hyperpyrexia, hyperreflexia, mydriasis, seizures, tremor	Antidepressants, antipsychotics, clonidine, cocaine, ethanol, GHB, GBL, opioids

^a Features often depend on dose

References

1. Bateman N, Jefferson R, Thomas S, Thompson J, Vale A, editors. Oxford desk reference: toxicology. Oxford: Oxford University Press; 2014.
2. Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, editors. Goldfrank's toxicologic emergencies. New York City (NY): McGraw-Hill; 2007.

A9.2. Clinical features associated with exposure to chemicals and apparent in a secondary survey

Clinical feature	Agents (examples)
Acne	Anabolic steroids, dioxins
Acute respiratory distress syndrome	Chlorine gas, phosgene, metal fumes, nickel carbonyl, opioids
Agitation	Anticholinergics, benzodiazepines (paroxysmal), caffeine, ergot derivatives, serotonin syndrome, sympathomimetics, tramadol, withdrawal reactions
Alopecia	Alkylating agents, ionizing radiation, thallium
Arrhythmias	Aconite, antiarrhythmics, anticonvulsants, antidepressants, antipsychotics, cardiac glycosides, lithium, methadone, phenytoin, sympathomimetics, tetrodotoxin, theophylline, volatile solvents
Ataxia	Alcohols, benzodiazepines, carbamazepine, carbon monoxide, lithium, mercury, phenytoin, sodium bromide
Bleeding (prolonged clotting time)	Anticoagulants (rodenticides e.g. brodifacoum and bromadiolone, pharmaceutical e.g. warfarin), snake venom
Blindness	Mercury, methanol, nicotine, quinine, thallium
Blisters	Corrosive chemicals, mustard gas, plants e.g. <i>Toxicodendron spp</i> , rue (<i>Ruta graveolens</i>), secondary effect of coma e.g. from carbon monoxide, barbiturates, opioids, phenytoin
Bradycardia	Cholinergics, beta-blockers, calcium channel blockers, digoxin
Bronchospasm	Chlorine, beta-blockers, histamine, hypersensitivity reactions, pulmonary irritants
Coma	Alcohols, anticholinergics, antihistamines, barbiturates, benzodiazepines, cyanide, carbon monoxide, essential oils, total petroleum hydrocarbons, GHB, GBL, hypoglycaemic agents, insulin, opioids, sodium bromide
Confusion	Alcohols, benzodiazepines, carbon monoxide, digoxin, hemlock, mercury, phenytoin, sodium bromide
Constipation	Anticholinergics, botulism, calcium channel blockers, opioids
Diarrhoea	Cholinergics, colchicine, histamine, ionizing radiation, metals (arsenic, iron, lithium)
Diaphoresis	Anthrax toxin, cholinergics, hypoglycaemic agents, insulin, salicylates, sympathomimetics, withdrawal reactions
Extrapyramidal features	Antipsychotics, carbon monoxide (chronic), copper, dopamine antagonists, heroin contaminated with MPTP, manganese, mercury, oral contraceptives
“Flu-like” illness	Carbon monoxide, metal fume exposure, noxious gas exposure
Hepatic encephalopathy	Carbon tetrachloride, paracetamol, fungi e.g. <i>Amanita phalloides</i> , plants e.g. <i>Xanthium strumarium</i> , <i>Cassia occidentalis</i>
Hepatic veno-occlusive disease	Pyrrrolizidine alkaloids e.g. <i>Heliotropium</i> and <i>Senecio</i> spp.
Hyperpyrexia	2,4-Dinitrophenol, pentachlorophenol, anticholinergics, metal fume fever, sympathomimetics
Hypertension	Lead, liquorice, scorpion venom, serotonin syndrome, sympathomimetics, withdrawal reactions

Clinical feature	Agents (examples)
Hypotension	Anticholinergics, beta-blockers, calcium channel blockers, volatile general anaesthetics
Inner ear (deafness, tinnitus)	Aminoglycosides, loop diuretics, metals, salicylates
Miosis	Cholinergics, chemical warfare nerve agents, GHB, GBL, olanzapine, organophosphates, opioids
Mydriasis	Anticholinergics, botulism, sympathomimetics
Neuropathy	Alcohols, arsenic, botulism, colchicine, dapsone, gold, lead, mercury, nitrous oxide, organophosphates, thallium, methyl bromide, bitter cassava (konzo)
Nystagmus	Alcohol, anticonvulsants, barbiturates, lithium, quinine
Paraesthesia	Marine toxins e.g. brevetoxin, saxitoxin, ciguatoxin, hexane
Pulmonary fibrosis	Amiodarone, bleomycin, cyclophosphamide, paraquat, diacetyl
Seizures	Anticholinergics, camphor, carbon monoxide, lithium, metals, organophosphates, organochlorines, phenytoin, quinine, salicylates, serotonin syndrome, tetramine (<i>Du-shu-qi</i> ang), theophylline, tramadol, volatile hydrocarbons, withdrawal reactions

References

1. Bateman N, Jefferson R, Thomas S, Thompson J, Vale A, editors. Oxford desk reference: toxicology. Oxford: Oxford University Press; 2014.
2. Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, editors. Goldfrank's toxicologic emergencies. New York City (NY): McGraw-Hill; 2007.

Annex 10. Toxicological investigation

A10.1. Biomonitoring matrices for use in population-based studies

Sample	Sampling	Exposure timeframe	Biomarker category	Example
Blood	Invasive	Medium to long term	Exposure and effect	Heavy metals/metalloids, organic compounds, drugs, pesticides
Blood fat	Invasive	Long term: months to years	Exposure uptake	Dioxins, polychlorinated biphenyls
Urine	Non-invasive	24–48 h	Exposure and effect	Heavy metals/metalloids, phthalates, organic solvent metabolites
Milk	Non-invasive	Reflects longer term	Exposure	Dioxins, polychlorinated biphenyls, mercury
Exhaled air	Non-invasive	Short term: hours	Exposure	Organic solvents
Hair	Non-invasive	Short to medium term	Exposure	Heavy metals, metalloids (arsenic, mercury), organic compounds
Nails	Non-invasive	Short to medium term	Exposure	Heavy metals/metalloids (arsenic)
Saliva	Non-invasive	Short to medium term	Exposure and effect	Mercury Atrazine
Post-partum umbilical (cord) blood	Non-invasive	Medium to long term	Exposure and effect	Heavy metals, organic compounds

Reference

Baker DP, Hogan K, Keshishian C, Murray V, Parkinson N, editors. Essentials of toxicology for health protection: a handbook for field professionals. London: Health Protection Agency; 2009.

A10.2. Toxicology testing kits

In preparing for an investigation, it is important to ensure that the correct sampling and packaging equipment is available. Pre-packed sampling kits may be used, with containers, needles and syringes that are guaranteed free of contaminants. Such a kit may contain:

- 1 x 10-mL polypropylene lithium heparin tube
- 1 x 5 mL glass (or polypropylene if glass not available) lithium heparin tube
- 1 x 10-mL EDTA-coated tube
- 1 pair of medium nitrile gloves
- 1 sterile water-based swab
- 1 x 50-mL screw-top universal container for urine (the top being wide enough for both males and females to urinate into directly, thereby minimizing risk of cross-contamination)
- 1 x 30-mL syringe, 1 x 5-mL syringe, 1 x 21-g 1.5" needle
- All packaging labelled as complying with UN3373 regulations and a request form filled in for each patient
- An instructions leaflet

The blood tubes in the kit should have plastic or lined metal tops, as chemicals can leach from tubes with gel separators and those containing mucous heparin solutions.

The International Air Transport Association has published Packing instructions 650, which gives the requirements for packaging liquids and solids that classified as UN 3373, Biological substance, category B, in the Dangerous Goods Regulations.

References

1. Initial Investigation and management of outbreaks and incidents of unusual illness, version 5.0. London: Public Health England; 2010 (http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1201265888951, accessed 8 January 2019).
2. Packing instructions 650. Geneva: International Air Transport Association; 2017 (<https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx>, accessed 22 January 2019).

A10.3. Guidance on the collection and handling of biological samples for toxicological analysis

Before collecting samples

1. Consult the laboratory that will be carrying out the analyses to determine which samples should be collected, the minimum sample size and any special requirements for sample collection, handling and transport, e.g. whether and which anticoagulant to use, whether samples should be spun down before dispatch and whether samples can be frozen.
2. Agree with the laboratory on the number of samples that will be sent, the turnaround time, the requirements for reporting results and the name of a contact person for any queries.
3. Ensure that all of the equipment and materials necessary for sampling are available at the site of the outbreak (see below), with any special instructions.
4. Decide who will collect the samples, e.g. a member of the investigation team, local health personnel, and ensure that they have the necessary training.
5. Prepare a sampling protocol, and ensure that the personnel responsible for sample collection and dispatch are familiar with it.
6. Ensure the necessary logistical arrangements for sample collection, storage and transport.

Sample collection

The following materials and equipment will be required:

- Disposable nitrile gloves
 - Tourniquet
 - Sterile water-based cleaning swabs
 - Sample collection tubes as specified by the laboratory, e.g. 10-mL polypropylene lithium heparin tube, 5-mL glass lithium heparin tube, 10-mL EDTA-coated tube, 50-mL screw-top universal container for urine
 - Syringes and needles
 - Sharps box
 - Labels and indelible marker pen
 - Laboratory request form
 - Cool box for storing samples
 - Packaging materials for samples
1. As far as possible, ensure that patients have been decontaminated externally before collecting biological specimens, to avoid contaminating the sample during collection.
 2. Make every effort to avoid external contamination of sample containers during collection.
 3. Avoid the use of proprietary wipes or swabs to pre-clean venepuncture site, as they contain solvents and trace elements that could interfere with assays. Sterile water (or dry cotton wool if the skin is reasonably clean) should be used instead.
 4. Try to use blood specimen bottles with plastic or lined metal tops, as chemicals can leach from blood tubes with gel separators or those containing mucous heparin solutions. Vacutainers, soft plastic bottles, reusable containers and rubber bungs can contaminate specimens. If the use of vacutainers cannot be avoided, a blank control should be sent with the specimens.
 5. Specimen tubes such as the 5-mL glass heparinized blood tube, should be filled so that there is minimal air space in the tube. All tubes should be screwed tight. Do not centrifuge unless instructed by the laboratory.
 6. Sample containers and request forms should be clearly labelled and identified as high risk (if appropriate) according to local or international protocols. The label should show the unique identification number, patient name, specimen type, date and place of collection and name or initial of person who collected the specimen. If plastic specimen bags are available, place the specimen in the sealable section of the bag.
 7. Complete a laboratory request form (Annex 8D) for each patient and place with the specimen, e.g. in the other section of a plastic specimen bag. When a large number of patients are tested, it may be more practical to submit the requests to the laboratory as a line list (see Annex 8E for an example of a line-list form)

8. Wrap the plastic bag tightly in corrugated cardboard or any other suitable cardboard material to avoid damage in transit, and place in a cardboard container. Tape the cardboard container shut.
9. The address labels on packages should have display the name of the sender and the laboratory, with complete addresses and telephone numbers for both the sender and receiver. Documents should also include specimen details, appropriate hazmat or biohazard labels and storage temperature requirements.
10. Specimens should be safely transported in a timely manner to the designated laboratories according to best practice protocols for high-risk specimens. When possible, the receiving laboratory should be contacted by telephone or electronically about the samples. Investigators should refer to the most recent regulations and guidelines from the International Air Transport Association (IATA) for detailed packaging, documentation and handling requirements.
11. To maintain the recommended temperature (4–8 °C) during transportation, the transport package should have a minimum of four ice packs, or more if room is available, around the secondary container. This will maintain refrigeration for 2–3 days. If available, a cold chain monitor should be inserted in the package.
12. When transport is delayed, samples should be temporarily stored (without opening or centrifuging them) at 4 °C, unless otherwise instructed by the laboratory. Attempts should be made to transfer the samples (at least within 24 h) to the designated medical toxicology laboratory to avoid degradation of the toxins or adsorption onto sample tubes, which occurs on prolonged storage.
13. When possible, it is good practice to store all remaining samples collected from possible and probable cases for as long as practicable for further testing if necessary. All collected samples may not require toxicological testing once the clinical and epidemiological picture of the outbreak is clear, but it may not be possible to identify an agent retrospectively without adequate specimens collected at the appropriate time.
14. In the event of suspected deliberate release or other forensic considerations, documentation of the chain of evidence (custody) (Annex 8F) should accompany specimens, as the findings of the investigation may lead to civil and/or criminal prosecution.

References

1. Packing instructions 650. Geneva: International Air Transport Association; 2017 (<https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx>, accessed 22 January 2019).
2. Initial Investigation and management of outbreaks and incidents of unusual illness, version 5.0. London: Public Health England; 2010 (http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1201265888951, accessed 8 January 2019).
3. Guidelines for the collection of clinical specimens during field investigation of outbreaks. Geneva: World Health Organization; 2000 (WHO/CDS/CSR/EDC/2000.4) (http://apps.who.int/iris/bitstream/handle/10665/66348/WHO_CDS_CSR_EDC_2000.4.pdf;sequence=1, accessed 22 January 2019).

A10.4. Example of a laboratory analysis request form

Requesting laboratory or organization (Req lab/Req org):

Analytical toxicological laboratory (ATL):

Patient details

Surname:	First name:	Sex:
Unique identification number:	Date of birth:	Age:
Hospital:	Ward:	
Analysis requested by:	Investigator or consultant:	

Sample details

Sample date	Sampling time	Sample type	Req Lab/Req Org number	ATL number
		Heparinized blood (10 mL)		
		EDTA blood (10 mL)		
		EDTA blood		
		Heparinized blood (5 mL) glass		
		Urine (30 mL)		

Exposure details

Place and nature of exposure:

Date (dd/mm/yyyy) of exposure:

Time of exposure (24-h clock):

Probable agent(s) to which exposed (give CAS number(s) if known):

Length of exposure (estimate in minutes):

Clinical features (please describe as fully as possible):

Brief description of incident (incident reference number if available):

Name and address for report:

Telephone number:

A10.5. Example of a chain of custody form

Submitting agency:		Telephone:		
		Fax:		
Person initiating chain of custody:				
Outbreak number (if applicable):				
Sample details:				
Collection location:				
Sample number	Sample type and description of sample (container, collection method, condition, volume)			
Comments				
Transfer of sample:				
Date	Item number(s)	Sample released by	Sample received by	Reason for transfer
		Signature	Signature	
		Name	Name	
		Signature	Signature	
		Name	Name	
		Signature	Signature	



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