Agency for Toxic Substances and Disease Registry
Guidance for ATSDR Health Studies

The Board of Scientific Counselors of the Agency for Toxic Substances and Disease Registry has approved this document and was involved in its development. The Agency for Toxic Substances and Disease Registry uses this document as guidance for carrying out health studies.

Guidance for ATSDR Health Studies

Division of Health Studies
Agency for Toxic Substances and Disease Registry
U.S. Department of Health and Human Services
Public Health Service

April 1996

Note: While the original publication dates on some of ATSDR's documents may not appear to be current, the information int he documents is valid and may still provide relevant information.

Contents

Purpose

This guidance document presents the process used by the Agency for Toxic Substances and Disease Registry (ATSDR) in considering health studies for communities that might be exposed to hazardous substances. Health studies can be divided into two basic types: those that are primarily exploratory in their approach (Type-1 studies), and those that require rigorous scientific methods to evaluate specific exposure-outcome relationships (Type-2 studies). Specific guidance and criteria are provided for determining when to do a health study, determining what type of study to do, and ensuring that a study is of high quality.

This guidance document provides the following potential benefits:

- Clarification of important differences between the different types of health studies;
- Consideration of when and what types of health studies are appropriate;
- Identification of standard practices for ensuring high levels of study quality;
- Support for ATSDR's efforts to improve services to communities and enhance scientific knowledge; and
- Useful information for state and local health agencies and other researchers conducting similar health studies.

Background

At the November 1994 ATSDR Board of Scientific Counselors meeting, the quality and appropriateness of ATSDR health studies were reviewed. The Board recommended that ATSDR develop a guidance document with criteria for helping determine when health studies would be appropriate. In addition, the Board recognized that certain types of health studies require a higher level of scientific rigor to ensure validity and reasonable precision in making inferences about cause and effect relationships. Subsequently, a working group of Board members assisted ATSDR in preparing this guidance document. The document is written primarily for ATSDR use. However, it is hoped that this document could be of use to communities, public health agencies, and other researchers.

There are many approaches that might be considered when addressing health concerns or the needs of a community living near a hazardous waste site. As appropriate, these approaches might include different types of health studies or other public health activities. As the lead agency within the Public Health Service responsible for implementing the health-related provisions of Superfund (CERCLA), ATSDR has been charged with assessing the presence and nature of health hazards at specific Superfund sites, helping to prevent or reduce further exposures and the illnesses that might result, and expanding what is known about the health effects of exposure to hazardous substances. In addressing these mandates, ATSDR has developed programs and activities which identify people at health risk, evaluate relationships between exposures and adverse health effects, recommend actions to eliminate exposures, and mitigate adverse health outcomes. These programs and activities include, but are not limited to, public health assessments, health consultations, health advisories, health education activities, exposure investigations, health surveys, case-control and cohort studies, surveillance activities, and exposure registries. Site-specific circumstances (substance, exposure pathway, level of exposure, health outcomes, and population at risk) and existing knowledge of the exposure and health outcome relationship will influence the need for and type of health study that ATSDR might propose. In addition, whether there is adequate characterization of human exposure at a sufficient level to assess health effects should be determined before a health study is considered.

ATSDR is mandated to conduct public health assessments at every site on the National Priorities List and at other locations where petitions are used to request an assessment. The consideration of additional public health activities by ATSDR, in coordination with the community, can lead to health studies or other activities. For many sites, health studies might not be applicable.

There are major differences between the various types of health studies and the level of scientific rigor needed to ensure quality. The Type-1 studies can use a variety of investigational approaches to explore health concerns or potential exposures. The approaches might include descriptive studies, surveillance activities, exploratory data analyses, and exposure investigations. These studies are often conducted to determine if there is a need for a more definitive study. The Type-2 health studies require a higher level of scientific rigor in order to evaluate specific exposure-outcome relationships; these studies primarily use the case-control or cohort approach. Case-control studies determine differences in exposures and risk factors for two groups of study subjects--persons with a specific illness (cases) and those without the illness (controls). Cohort studies compare the differences in illness occurrence in exposed and unexposed (reference) populations followed over a specified period of time.

Site Assessments

When a site is being assessed by ATSDR, several follow-up health activities might be considered during the public health assessment or other site review processes. The evaluation of site information focuses on the public health hazard ranking of the site, community education needs, presence of hazardous substances, evidence of completed pathways of exposure, population demographics, and community health concerns. There are many situations in which health studies would not be appropriate or recommended for a specific site. In situations in which health studies are determined to be appropriate, further considerations for determining the type of study to be conducted and ensuring its quality are presented (see sections that follow).

There are other reasons for which sites can be considered for health studies. Health studies might be initiated prior to the completion of a public health assessment because of an urgent health threat or exposure situation, or both. The ATSDR research program on priority health conditions might identify specific health outcomes and contaminants or exposures that require additional health studies to assess the relationship between exposure and adverse health effects. Research needs might require multiple communities or regions of the United States to be included in studies of rare health outcomes. In addition, multisite studies might use the same study protocol to conduct studies at several sites that have similar contaminants and human exposure pathways.

Community Involvement

After conducting a public health assessment or health consultation, ATSDR determines whether a health study approach should be considered. When reviewing the options for health studies or other public health activities, ATSDR initiates a process of public involvement and coordination with the appropriate stakeholders, including community representatives, tribal representatives, local and state health agencies, and other state or federal agencies. The purposes of such involvement and coordination are to understand and respond to community needs and health concerns, discuss ATSDR activities and possible options, and promote coordination among the different government agencies. The goal is to have the community and local and state health agencies fully informed and involved early. It is very important to explain to the community the differences between the possible options for health studies or other public health activities. The community also needs explanations of what can be studied scientifically, the limitations of proposed activities, and any other decisions that are to be made. The scientific quality and design issues are ultimately the responsibility of the scientists conducting the studies and ATSDR, which provides oversight. An ongoing mechanism for communication and involvement should be established early by ATSDR. Though this document does not address all of ATSDR's community activities, educational efforts are needed to keep the community informed on exposures, health risks, and proposed activities.

A variety of community involvement activities might be considered, including public meetings or briefings, information dissemination, and media interaction. The type of community involvement activity will depend on the assessment of needs for each site. Most often the community wants its health concerns addressed and more information about the hazardous substances, possible exposures, and potential health outcomes. Before initiating an extensive health study, ATSDR might use a community assistance panel (CAP) approach. The CAP is composed of 12 to 15 members representing a broad range of community stakeholders. The purpose of the CAP is to ensure communication with communities and encourage involvement and understanding of ATSDR activities. It is critically important for the CAP to understand community needs and health concerns, the studies or evaluations being considered, the options and limitations for studies, and what ATSDR can do. The CAP provides an avenue for the community to be involved in each stage of a health study and to be kept informed on a regular basis.

There are other methods for community involvement and coordination with other governments and agencies. ATSDR works with Native American tribes using appropriate government-to-government relationships and supporting mechanisms to help ensure tribal involvement in health studies or other public health activities affecting their people or land. Under the Federal Advisory Committee Act, ATSDR and the Centers for Disease Control and Prevention have established a limited number of public advisory subcommittees that will address specific Department of Energy sites. In addition, ATSDR coordinates with local and state health agencies, and

other state or federal agencies involved with specific sites so that there are ongoing communications and involvement in planning and decision-making activities.

Considerations for Proceeding With a Health Study

Before a health study can be recommended for a particular site, several factors should be considered. The factors are used by ATSDR for setting priorities and are based on published qualitative criteria (1). Each factor should be considered in determining the relative importance and appropriateness of a health study. Each factor is important, but no order of priority has been assigned.

Public Health Significance

Public health significance is a key factor in considering the merits of a proposed health study. Issues for consideration include the hazard ranking of the site, toxicity of the hazardous substance, pathway of human exposure, severity and biological plausibility of the health outcome, need for new information (beyond what is already known or what has already been done), size and susceptibility of the population affected, ability to prevent or mitigate exposure or health outcomes, and relevance to other sites with similar contaminants and exposure pathways.

Community Perspective and Involvement

Community involvement is critical to the success of any proposed health study. Based on an assessment of community needs and concerns, ATSDR will usually initiate a formal community involvement activity. As stated earlier, various community involvement methods can be used for health studies. Issues for consideration include an ability to involve key community stakeholders, an understanding of community health concerns, an understanding of the approach and limitations of proposed activities, and community support for the study being conducted.

Scientific Importance

Scientific importance is closely related to public health significance. Issues for consideration include the ability to provide new knowledge or information about an exposure-outcome relationship, address specific exposures or outcomes that have not been adequately studied, allow new laboratory tests or study methods to be used or evaluated, to generalize to other situations or populations, and provide confirmation or additional support to a preliminary hypothesis or theory.

Ability to Provide Definitive Results

Since health studies can end up with inconclusive findings, it is important to consider how definitive the study might be in providing scientifically useful results related to specific exposure-outcome relationships. Issues for consideration include the ability to obtain appropriate exposure measures, document health outcomes and exposure, use adequate control or comparison populations, obtain community support to improve the participation rate, state clearly the study objectives and specific hypothesis to be tested, have sufficient statistical power to detect predicted effects, obtain data on important potential confounders, and evaluate a dose-response relationship or gradients of exposure.

Resources

Resources are critical to the support, conduct, and completion of any proposed health study. Issues for consideration include the availability of qualified personnel and technical support, an ability to obtain necessary data and health information, an appropriate project time line and budget, proper administration and project management oversight, and availability of sufficient funds to meet the needs of the proposed health study.

Contribution to Program Goals

The contribution to program goals is also important, given the legislative mandates assigned ATSDR under Superfund. As stated earlier, ATSDR program goals include identifying people at health risk, evaluating relationships between exposures and adverse health effects, and intervening to eliminate exposures or mitigate adverse health outcomes. Issues for consideration include how the proposed health study addresses the program goals and complements other ATSDR program activities and priorities.

Authority and Support

It is critically important that local, state, and federal health agencies be involved early in discussions about potential health studies. Issues for consideration include the ability to support or provide technical assistance requested by the local or state health agency, the ability of local and state health agencies to address the community problem and health concerns, and the involvement of appropriate agencies with legislative and regulatory requirements.

When Not To Do Health Studies

Once the seven areas for consideration have been evaluated, the decision to proceed or not proceed with a health study can be made. Generally, Type-1 health studies would not be performed when there is insufficient information or other factors exist that severely limit ATSDR's ability to provide new and useful information on the health or exposure status of the community. Type-2 health studies would not be conducted when there is insufficient information or limited exposure documentation, or when other factors exist that severely affect ATSDR's ability to evaluate specific exposure-outcome relationships. The seven factors for consideration in the previous section cover a wide range of important issues that directly affect the feasibility and value of any health study being considered. These considerations for health studies have to be applied on a case-by-case basis, since information and circumstances differ by site. The next section provides additional guidance on when studies are appropriate and what study attributes are considered necessary. When the additional guidance or attributes are not met, health studies would not be recommended.

When To Do Health Studies

In the majority of situations, environmental contaminant and exposure information for populations living near hazardous waste sites is limited, and health outcome information is frequently incomplete or unknown. In other situations, there are sites with well-documented contaminants and identified potential exposure pathways, as well as sites with environmental data that do not support any human exposure pathways of concern. In Table 1, each of these three scenarios is briefly presented using a decision analysis approach with resultant actions or further considerations.

When the decision to conduct a health study is being considered, several criteria are used to determine the type of health study:

- Characterization of environmental contaminants by type, media, and concentration levels.
- Documented evidence of human exposure at a level of concern.
- Level of current knowledge about the relationship between exposure and specific adverse health outcomes.
- Documented excess of an adverse health outcome, when known.

Further clarification is provided in the following sections on the two different types of health studies (Type-1 and Type-2), and when each should be used. Descriptions of various study approaches by study type are presented in Appendix A. For additional information on scientific methodology and environmental epidemiology, the reader is referred to standard textbooks (2-4).

Clearly, there are important differences between Type-1 and Type-2 health studies in terms of the methods and procedures used to ensure quality. Type-1 health studies are primarily exploratory in that they provide additional information about human health effects or exposures. They are not designed to evaluate specific associations between adverse health outcomes and documented human exposures. However, they might suggest the possibility of an association and the need for an additional health study.

Type-1 Health Studies

Purpose

Type-1 health studies explore or generate hypotheses about exposure-outcome associations and address specific exposures, community health concerns, or specific information needs. Examples of Type-1 health studies follow.

Examples of Study Designs Used in Type-1 Health Studies

Cross-sectional study Survey of a sample of residents to obtain information about current and past health or environmental exposures, or both. These studies can include comparison populations with demographics similar to those of the exposed (target) population.

Other approaches There are other approaches, including pilot investigations, cluster investigations, comprehensive case reviews, surveillance activities, health statistics reviews, exposure registries, and exposure investigations. (See Appendix A for a more complete listing.)

Necessary Attributes

When a Type-1 health study is recommended and considered appropriate, there are several attributes that are considered necessary in order to improve the quality of the study effort:

- A reasonable ability to document and characterize exposure in the target area.
- An adequate study size for the type of study recommended.
- An ability to identify and locate subjects and records.
- Appropriate comparisons for rates of occurrence.
- An ability to control confounding factors and biases (when possible).

Type-2 Health Studies

Purpose

Type-2 health studies are specifically designed to test scientific hypotheses about the association between adverse health outcomes and exposure to hazardous substances in the environment. Examples of Type-2 health studies follow.

Examples of Study Designs Used in Type-2 Health Studies

Case-control study Assesses differences in exposures and risk factors among two study groups--people with a specific illness (cases) and people without the illness (controls). The cases and controls are identified first and then information is collected about past exposures and other risk factors.

Cohort study Assesses the occurrence of specific illnesses among two study groups--one with a defined or documented exposure and one without such an exposure. Both groups are identified and then followed over a specified period of time.

Necessary Attributes

There are several attributes of Type-2 health studies that are considered necessary in order to ensure valid scientific findings:

- An ability to reasonably estimate or document individual exposure.
- An ability to document or validate human health outcomes.
- An adequate study size and statistical power.
- An ability to identify and locate subjects and records.
- Availability of an appropriate control or comparison population.
- An ability to control confounding factors and minimize biases.
- An ability to determine influence of environmental, behavioral, or other factors.

How Is the Quality of a Health Study Ensured?

There are many aspects to ensuring the quality of a health study. Regardless of who conducts the health study ATSDR, a contractor, an awardee of a cooperative agreement, or a grantee the same standard practices are appropriate for both Type-1 and Type-2 health studies. A wide range of quality-related practices include standard ATSDR study procedures, contracts and grants management guidelines, Institutional Review Board procedures, Office of Management and Budget procedures, ATSDR scientific peer review procedures, and ATSDR review and clearance procedures. The reader might also be interested in previously published guidelines for good epidemiology practices (6).

Standard Practices

There are a number of standard practices that health studies must meet to ensure quality. With the few exceptions that are noted, the practices for Type-1 and Type-2 health studies are the same. No order of priority has been assigned.

- The organization conducting the health study must be capable and fully responsible for conducting the health study.
- Personnel conducting the health study must be identified and have appropriate training and experience.
- The facilities and resources must be appropriate for the successful completion of the health study.
- Contractors for the health study must follow written and approved work plans and their work must be carefully reviewed by the sponsoring organization.
- A detailed study protocol must be written following an ATSDR standard outline (see Appendix B), must undergo scientific peer review, and must be approved by ATSDR before any health study begins. By their own design, several Type-1 health study protocols might not need to be as detailed or require scientific peer review.
- As required by law, any health study involving human subjects must be submitted to and approved by an established Institutional Review Board; this review includes the protection of human subjects, consent, and data confidentiality procedures.
- When required, all questionnaires and data collection forms must be reviewed and approved by the Office of Management and Budget.

- Reports of health study findings must undergo scientific peer review and ATSDR approval prior to any public release of information. Certain Type-1 health studies might not require peer review.

- Community involvement and knowledge of the health study are necessary; the involvement process will ensure that the community understands and supports the study focus, design, limitations, and expectations.

- Depending on the community involvement approach, public meetings might be held to present and discuss the study methods and findings. However, final study methods must be scientifically valid in order to proceed. As appropriate, all draft final reports must undergo open public comment periods and a summary of responses to the comments must be retained as a written document.

- All study reports and related documentation must be kept by ATSDR in the official record; copies of data files must also be retained as part of an archive.

- Any environmental sampling or biological testing must follow existing standards for collection, handling, chain of custody, storage, analysis, and reporting by an approved laboratory(ies); all standard quality control and quality assurance procedures must be followed and documented.

Review Process

For all health studies, a standard review and approval process is already well established and used by ATSDR. The five common steps or phases used in the ATSDR review process follow.

Preliminary Proposals

These proposals are initially developed so that the concepts, approaches, and considerations for proceeding can be fully discussed. These proposals are evaluated using the seven factors for consideration (see earlier section). Approval to proceed is obtained from the appropriate Division Director within ATSDR. Early community involvement and coordination with local and state health agencies begin during this phase.

Detailed Study Protocols

These documents are developed for formal scientific review and approval by ATSDR. All protocols are reviewed and approved within the appropriate division and then sent for scientific peer review (not required for some Type-1 health studies). The principal investigator responds in writing to the reviewer comments and makes appropriate changes to the protocol as necessary. Peer review of the protocol is considered final once the written response to peer reviewer comments is approved by the Associate Administrator for Science, ATSDR. Following peer review, additional community discussions are held on the proposed health study.

Ongoing Health Study Reviews

During the conduct of a health study, there are ongoing opportunities to review and oversee activities throughout the stages of the study. The principal investigator provides frequent updates and assessments of progress and any difficulties to management or the project officer (ATSDR technical staff that oversees grants or cooperative agreements). These reviews ensure that the study follows the protocol, appropriate changes are made, the project remains on a timetable, and enhancements to study quality are made when appropriate.

Draft Final Reports

The final health study reports undergo several reviews and revisions prior to being made public. The draft reports are reviewed for scientific content, completeness, and quality before leaving the appropriate division. The draft final reports are sent out for external scientific peer review. The investigator responds in writing to the peer reviewer comments and makes appropriate changes to the draft final report as necessary. The draft final report is considered final once the written response to peer reviewer comments is approved by the Associate Administrator for Science, ATSDR. Following peer review (when appropriate), the report is released for a 30-day public comment period. In addition, the affected community is informed and discussions are held on the

report findings. At the end of the public comment period, a summary of responses to the public comments will be prepared and retained as part of the written record.

Final Clearance

Agency clearance is required for all documents prepared or supported by ATSDR prior to their release to the public. There is a standard procedure for official approvals from the different review levels within ATSDR (usually the branch, division, and agency). The editorial aspects of the document are finalized before the document is submitted for printing. Investigators are encouraged to submit their findings for publication in peer-reviewed scientific journals.

There are few exceptions to this review process. Health studies that do not address a specific site or community area (for example, a case-control study using cases of a rare disease identified within a large region of the United States) do not require local community involvement or a public comment period.

References

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5. Agency for Toxic Substances and Disease Registry. National exposure registry policy and procedures manual (revised). Atlanta: US Department of Health and Human Services, Public Health Service, 1994.

6. Chemical Manufacturers Association's Epidemiology Task Group. Guidelines for good epidemiology practices for occupational and environmental epidemiologic research. Washington: Chemical Manufacturers Association, 1991.

Table 1. --Three scenarios for environmental contaminants and considerations for health studies or other activities.

I. Contaminants are sufficiently documented by type, media, and concentration. Potential human exposure pathways have been determined and an exposed at-risk population can be identified.	A. There <u>is</u> documented evidence of human exposure at a sufficient level of concern.	1. The association between exposure and health effects <u>is</u> already established.	Provide services that reduce or eliminate exposure, identify or prevent adverse health outcomes, and improve quality of life.
		2. The association between exposure and health effects <u>is not</u> already established.	Consider health studies that provide new knowledge about human health effects and exposures to specific hazardous substances. Studies help identify risk factors or recommend actions to prevent or mitigate adverse health outcomes.
	B. There <u>is no</u> documented	1. Consider community health	[*When appropriate*]

	evidence of human exposure or exposure at a sufficient level of concern.	concerns for important or biologically plausible health outcomes.	Provide support to the community that addresses its health concerns and site-specific issues.
			[*Else*] Site will remain under periodic review by ATSDR.
		[*When feasible*] 2. Conduct an exposure investigation to determine if human exposure has occurred at a sufficient level of concern.	If findings are positive and support human exposure....[go to I.A]
			If findings are negative or do not support human exposure....[go to I.B1]
		[*When feasible*] 3. Determine if site information can provide enough source, production, or release data to suggest current or past human exposure.	If there are sufficient data to support human exposure or reconstruct exposure or dose....[go to I.A]
			If the data are insufficient or do not further support exposure....[go to I.B1]

Table 1.--Continued.

II. Documentation of contaminants is incomplete, a complex mixture exists requiring some surrogate measure, or the potential exposure pathways are unknown.	[*When appropriate*] A. Review additional environmental sampling data when they become available or conduct additional focused sampling when indicated (could require EPA or state involvement).	If sampling data better define the contaminants and potential exposure pathway....[go to I]
		If sampling data provide little new information or do not change level of uncertainty....[go to II.B]
	B. Consider community health concerns for important or biologically plausible health outcomes.	[*When appropriate*] Provide support to the community that addresses its health concerns and site-specific issues.
		[*Else*] Site will remain under periodic review by ATSDR.

III. There is sufficient documentation with few contaminants identified and the environmental data do not support any exposure pathways of concern.	Consider community health concerns for important or biologically plausible health outcomes.	[*When appropriate*] Provide support or identify additional support from another agency that can address the needs or concerns of the community.
		[*Else*] Site will remain under periodic review by ATSDR.

APPENDIX A

Description of Specific Type-1 and Type-2 Health Studies

Type-1 Health Studies

Pilot investigations collect additional information to assess the feasibility and value of conducting a full-scale health study. The investigation might include assessments of data completeness and quality, the level of documentation of exposures or health outcomes, methods to identify and track individuals, study size and statistical power issues, and the adequacy of a control population or comparison.

Cluster investigations evaluate the reported occurrence of a specific disease or condition is above the expected number for a given geographic location and time period. These investigations can be conducted to confirm case reports, determine an unusual disease occurrence, and explore potential risk factors.

Comprehensive case reviews are medical or epidemiological evaluations of the medical status of one or more individuals through medical record reviews, interviews or biomedical testing to determine additional information about their health status or potential for exposure.

Site-specific surveillance is designed to assess the specific occurrence of one or more defined health conditions among a specific population potentially exposed to hazardous substances in the environment. Data collection might include using existing records of health events or records from specific health care providers.

State-based surveillance is similar to site-specific surveillance but incorporates multiple site locations or states. This evaluation approach will primarily use existing records to assess correlations between specific health events and proximity to sites, reporting of health events related to releases of hazardous substances, or other methods to collect and analyze health information.

Health statistics reviews use available health and demographic information to assess the occurrence of specific health effects in defined geographic areas and determine if the rates are elevated. Available information might include death certificates, birth certificates, census data, tumor or disease registries, surveillance data, or other computerized data files. A health statistics review can also be performed in response to a reported cluster of specific diseases or conditions.

Exposure investigations use environmental or biological testing, or both, for the hazardous substance(s) of interest. The biological test might measure the level of the hazardous substance, a metabolite or another marker of exposure in human body fluids or tissues. The purpose of this investigation is to assess individual exposure levels to a specific substance associated with the site. The levels identified should be compared with that of some reference group or with a known standard reference level. Depending on the hazardous substance, the investigation can be used to explore for evidence of past or ongoing exposure.

Disease and symptom prevalence surveys are used to measure and compare the occurrence of self-reported diseases, in some instances using medical records or physical examinations to validate adverse health conditions. Addressing potential health concerns raised by the community, the survey compares an exposed population (target area) with an unexposed population (control area) with similar demographic characteristics. The purpose is to determine the need for further health studies in the target area, provided there are statistically significant excesses that are clinically important. Depending on the contaminants and circumstances, biological testing of exposure or effect, or both, might also be collected as part of the survey.

The **National Exposure Registry** (NER) program contains subregistries of persons exposed to specific hazardous substances who have been identified and are followed for the occurrence of a variety of health outcomes. In order to identify excess rates of illnesses, the NER compares its rate of reported illnesses to national norms; an example is the National Health Interview Survey, with population rates of self-reported specific illnesses or conditions. The purpose of the NER is to aid in assessing long-term health consequences to persons exposed to Superfund-related hazardous substances. The goals of the program include facilitating epidemiologic studies and health surveillance programs, and providing information that assesses the burden of the effects of an exposure or health outcome on a population. (*5*).

Type-2 Health Studies

Case-control studies are designed to collect information and compare differences in exposures and other risk factors in two groups of people: persons with specific illnesses or conditions (cases) and persons without the illnesses or conditions (controls). The controls are selected to represent the population from which the cases were identified. Usually the cases and controls are identified first, and then information is collected about past exposures and other risk factors.

Cohort studies are designed to collect information and compare differences in the occurrence of specific illnesses or conditions in two groups of people: persons with known or documented exposure to hazardous substances and persons not exposed but who have similar population characteristics. Groups of both exposed and nonexposed people are followed over a period of time, and information on the occurrence of specific illnesses or conditions is collected. Cohort studies can be prospective, meaning that individuals involved in the study are followed into the future, or cohorts can be retrospective, meaning that the cohort is reconstructed from historical records and then followed over a specified time period.

Nested case-control studies are another approach that uses both of the study designs previously mentioned. The nested case-control study uses cohort individuals who have developed a specific illness or condition (case) and persons sampled from the cohort who have not developed the illness or condition (control). The case-control method is then used to collect additional information and analyze the differences between these two groups.

APPENDIX B

Contents of a Health Study Protocol
(Based on existing ATSDR practices)

- Title and identification page
- Introduction and overview
- Background
    - Site description
    - Demographics
    - Site characterization
        - On site
        - Off site
    - Contaminants and pathways
    - Community health concerns
    - Literature review

- Purpose
- Study objectives
- Methods
    - Rationale for study design
    - Study description
    - Eligibility criteria
    - Selection of target area and population
    - Selection of comparison area and population
    - Sample size and statistical power estimates
    - Participant selection and definitions
    - Enrollment procedures
    - Location(s) of data and specimen collection
    - Informed consent procedure
    - Questionnaire procedures
    - Interviewer training and methods
    - Collection of biological specimens
    - Additional data collection or sources
    - Chain of custody and shipping
    - Laboratory methods and quality control
    - Privacy protection
    - Findings of immediate significance
    - Follow-up of abnormal lab results
    - Data analysis
        - Data entry, editing, and management
        - Data transformation
        - Data analysis plan and methods
- Study time line
    - Key activities or milestones (can use "study months" if no start date assigned)
- Community involvement and notification
- Interpretation of results
- Limitations of the study
- References
- Tables and figures
- Attachments
    - Data collection forms and questionnaire
    - Study letters of notifications and consent forms
    - Specimen collection and shipping protocol

NOTE: Protocols for health studies might not contain all of the items within this outline. The listing is more comprehensive in order to cover the wide variety of study approaches.

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Back to top of document

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