Appendix B

Guidelines for Public Health Responses to RMA Related Exposure and Observations of Health Concerns Among Communities and Visitors

Rocky Mountain Arsenal Medical Monitoring Program Recommendation
Guidelines for Public Health Responses to RMA Related Exposure and Observations of Health Concerns Among Communities and Visitors

I. Rationale: The Remediation Monitoring - Medical Referral & Biomonitoring Decision Tree establishes a process for determining the adequacy of exposure prevention during the Rocky Mountain Arsenal soil remediation and for determining when the RMA Medical Monitoring Program should consider implementing individual medical referral or other public health actions. The selection of the appropriate action will be based on a systematic evaluation of the available data. This guideline is designed to facilitate this selection process.

II. Incident Response:

A. Management of Site Emergencies

Immediate response to a site emergency (fire, explosion, significant release of COCs) will be guided by the (on-site and off-post emergency plan). In case of such an emergency, the RVO maintains primary responsibility for response, initiation of protective action and notification of the appropriate agencies. CDPHE, EPA, TCHD and the City and County of Denver are responsible for oversight of the RVO response and enforcement of applicable laws and regulations. It is expected that the RVO will ensure the availability of the appropriate technical support staff to assist in the response to site emergencies. That may include providing technical consultation, initiating environmental monitoring, analyzing data and supporting communication with the affected community, for example.

B. Management of Non-Emergency Risks

Response to non-emergency risks (i.e. long-term exceedance of fence line criteria, potential exposure to workers or volunteers or off-post population, physician network reports of suspected RMA related illness) is the responsibility of the RVO. Oversight and assurance that such situations are identified and the appropriate response is initiated is the responsibility of CDPHE, EPA, TCHD and the City and County of Denver. The limits of authority of those agencies to require RVO response or to initiate their own response will be determined on a case-by-case basis.

C. Physician Referral Panel
(As described in the guidance for the Medical Referral System)

D. Health Response Review Panel

The Health Response Review Panel (HRRP) is composed of representatives from all involved public health and environmental protection agencies (at this writing CDPHE, EPA, TCHD, and Denver). The Panel is chaired by a public health agency representative. Responsibility and authority for determining the appropriate public health response rests ultimately with the public health agencies, not the RVO.

E. Public Accountability

1. Citizen inquiries, complaints or medical concerns related to the Rocky Mountain Arsenal remediation can be communicated by contacting CDPHE, local physicians or clinics, the Rocky Mountain Poison Control Center, the Tri-County Health Department RMA hotline.

2. It is the responsibility of the agencies and the RVO to initiate and maintain effective communication with citizens, agencies and others, as necessary, during the evaluation and response to emergency and non-emergency risks. Communication should take place through a variety of methods such as public information meetings, information distributed to residents, telephone hotlines and print and broadcast media.

3. The Health Response Review Panel will periodically report and provide a public forum for the nature and status of their evaluation of the data, inquiries or complaints described above to any public groups which request the information such as the Restoration Advisory Board (RAB), the Site Specific Advisory Board (SSAB) and the RMA Medical Monitoring Citizen Advisory Board (CAB).

III. Initiating a Public Health Response:

A. Informational Sources

Response to a potential public health risk can be initiated as a result of:

1. The review of environmental monitoring or modeling data describing chemical concentrations measured or predicted at the fence-line, in the community and at RMA interior locations.

2. The review of medical data from surveillance (cancer, birth defects registries) or the medical referral system (symptoms or other health concerns among

communities members and RMA visitors).

3. Emergency conditions resulting in an unplanned release of COCs at a level that exceeds protective criteria or citizen inquiries or complaints.

4. Other data sources may be available and influential in evaluating citizen inquiries, complaints or medical concerns related to the Rocky Mountain Arsenal. For example, school attendance records may be useful for evaluating temporal and spatial patterns of illness among children in schools proximal to the RMA. Regional air pollution indices may contribute additional important non-RMA exposure information. Health agencies will be responsible for identifying and characterizing these data sources. Inquiries will also be made among local clinics to identify those interested in participating as sentinels for monitoring patterns in health complaints.

B. Data Collection and Evaluation

1. Environmental monitoring data will be collected and analyzed under site-wide and site-specific air monitoring plans and the Interactive Comprehensive Air Pathway Analysis. Data collection, including initial background air concentrations, is the responsibility of the Remediation Venture Office (RVO). Data analysis will be the responsibility of both the RVO and the Colorado Department of Public Health and Environment (CDPHE). To facilitate data analysis by CDPHE, the RVO will transfer, in a timely manner, complete fence-line and close-in air monitoring and modeling data sets to CDPHE. As described in Attachment 1 of the Decision Tree, CDPHE and the RVO will engage in collaborative decision making, but CDPHE (and other public health agencies) has primary responsibility for determining the need for health related actions.

2. Collection of background air concentration data will include identifying specific COCs for which community background levels already exceed EPA criteria, describing the historical and predicted future concentrations for these COCs assuming there will be no contributions from the RMA, and comparing these levels with the concentrations predicted during RMA operations.

3. Health concern data will be collected through all Medical Monitoring Program individual and community contacts, but primarily through the Medical Referral, Birth Defect and Cancer Surveillance Systems. The Rocky Mountain Poison Control Center or members of the medical referral system will also be relied upon to communicate their observations of potential exposure that might suggest the need to evaluate a larger portion of the population.

4. CDPHE will maintain a centralized database for use in supporting decisions about implementing health studies. Data will be maintained in a manner that will support geographical information system analysis.

C. Agency and HRRP Responsibilities

1. The review of informational sources and the identification of potential public health risks is the responsibility of each agency represented on the Health Response Review Panel. This responsibility requires that each agency determine the health significance of observations and reports. Once any one on the agencies concludes that a potential public health risk is present, that agency may convene the Health Response Review Panel.

2. The HRRP has primary responsibility for the identification of need, determination of follow-up and oversight of all action necessary to protect health. Actions might include collection and analysis of additional data, determination of the appropriate response, implementation of the response and evaluation of the effectiveness of the action taken.

3. Participation on the Panel does not prevent any agency from responding to an incident on the basis of its own enabling authority. It is expected that the Panel will seek to collaborate and be responsive to the risks identified.

4. The Panel shall periodically review these Guidelines and make appropriate revisions. The Panel shall provide opportunities for input by agencies and the community.

IV. Guidelines for Determining the Need for and Selection of Public Health Actions:

A variety of public health actions may be considered. As described in the Decision Tree, actions may include modification of remedial action to control air emissions, medical referral, or a host of health-related studies. Determination of the appropriate response, based on environmental monitoring and modeling data and individual and community health information, will rely on the proven and standard concepts and methods of medicine, toxicology, risk assessment and epidemiology.

A. Evaluation of Chemical Exposure Data

A variety of factors determine when an exposure becomes medically significant. These factors are dose, as determined by air concentration, exposure frequency and duration and the chemical-specific toxicity. Fence-line chemical-specific air concentrations criteria take these factors into consideration so as to identify conservative

health-protective levels that are useful for primary prevention of exposure and control of remedial activities. Because of the conservatism built into these values, they are not appropriate triggers, in and of themselves, for pursuing public health actions. Rather, they are starting points for the evaluation of exposure significance.

1. Evaluation of Low-Dose Chronic Exposure

   a. Characterization of the public health significance of low-dose chronic exposure will rely primarily on measured and modeled atmospheric concentrations of chemicals. The following steps will guide this analysis:

      i. Evaluate the estimated magnitude of the potential exposure (concentration, frequency and duration)
      ii. Use time-weighted averaging of cumulative exposure to demonstrate the longer-term implications
      iii. Identify the toxicological implication of the exposure (dose-response relationship), including:
         - Toxicodynamics (e.g., persistence and distribution)
         - Health effects
      iv. Use the information generated in (iii) above to characterize the on-going or changing status of chronic exposure.

   b. Judging the seriousness of a chronic exposure will be guided by responses to the following step-wise questions:

      i. Does the hazard quotient, index or cancer risk exceed health-protective criteria ("1" or one in one million)?
      ii. To what degree does the hazard quotient, index or cancer risk exceed health-protective criteria?
      iii. What is the nature of the health effects associated with the excess hazard quotient, index, cancer risk or time-weighted average dose?

2. Evaluation of Acute Exposure

   a. Characterization of the public health significance of acute exposure will rely primarily on measured and modeled atmospheric concentrations of chemicals. The following steps will guide this analysis:

      i. Evaluate the estimated magnitude of the potential exposures

(concentration, frequency and duration)

ii. Identify the toxicological implication of the exposure (dose-response relationship), including:
- Toxicodynamics
- Health effects

b. Judging the seriousness of an acute exposure will be guided by responses to the following step-wise questions:

i. Does the hazard quotient/index exceed"1"?
ii. To what degree does the hazard quotient/index exceed "1"?
iii. What is the nature of the health effects associated with the excess hazard quotient, index or time-weighted average dose?

B. Evaluation of Health Concerns and Outcomes

1. Both medical and epidemiological tools and skills are required to evaluate the significance of individual and community health and its potential association with the RMA. Medical diagnosis by physicians will be used to determine the nature or identity of a disease or condition in an individual. Diagnostic tools will be important when attempting to identify the disease or condition contributing to a health complaint or symptoms. This identification will in turn help to determine etiology.

2. Epidemiology will also be used to evaluate disease etiology by investigating the distribution of disease in the community. Both medical and epidemiological investigations will rely on personal and community characteristics, such as occupation, habits and environmental circumstances to understand the factors which may contribute to health status.

3. Medical and epidemiological tools will be used to evaluate individual and community health concerns, as described in the Medical Referral System & Health Professional Education and Surveillance for Birth Defects and Cancer Surveillance recommendations. In brief, the steps are:

a. Individual case evaluation by the RMPDC
b. Case reporting to CDPHE - A standard reporting format and frequency will be established by RMPDC and CDPHE.
c. RMPDC and CDPHE have the responsibility to collaborate to identify individual suspect cases and multiple case patterns and trends through an analysis of:

i. Signs and symptoms and diagnostic test results
ii. Cumulative exposure and/or risk
iii. Frequency of reporting
iv. Temporal distribution
v. Spatial distribution
vi. Environmental and other relevant factors

RMPDC and CDPHE also have the responsibility for initiating more detailed case investigations if warranted by initial information.

C. Selection of Appropriate Public Health Actions

1. There are many approaches that might be considered when addressing health concerns or the needs of communities living near the RMA. As appropriate, these approaches might include different types of health studies or other public health activities.

2. The health action selection process will be designed so as to identify people at risk, evaluate relationships between exposures and adverse effects, recommend actions to reduce exposures, and mitigate adverse health outcomes.

3. The Decision Tree states that the types of programs and activities which should be considered include, but are not limited to, exposure investigations, health studies, surveillance, case-control studies and biomonitoring.

4. As discussed above, specific circumstances, including chemical(s) in question, exposure conditions, health effects, population at risk, and existing knowledge of the exposure and health outcome relationship, will influence the appropriate action.

5. If the selected public health action requires, a study control group will be selected at the time of study implementation. Controls will be selected to allow adjustment for important confounding variables such as age, gender, race, and socioeconomic status.

6. Attachment 1 to this guideline 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. The general principles of ATSDR=s guidance document are adopted here, as appropriate and necessary, for making similar decisions.

V. Documenting the Selection of a Health Action: If appropriate indicators suggest the need

for a public health action, a document will be prepared describing the following:

A. Statement of Problem and Goal

1. Identify the technical basis (data and analysis) for a public health action.

2. Identify the target population.

3. Identify the needs of the target population and the goals of the action.

4. Describe how achieving the stated goal will address the needs of the target population and improve public health protection.

B. Selection of Most Appropriate Public Health Response

1. Identify the most appropriate public health action required. Health studies may be exploratory, detailed, or may combine a variety of public health elements.

2. Depending on the urgency and complexity of the need, actions may be phased. An initial phase may be responsive to the need for immediate action, such as a limited window of opportunity for data collection. A later phase might include a more detailed investigation.

3. Health study designs will be scientifically reviewed through the use of an appropriate peer review process. Studies will be designed to have adequate statistical power to assess the health risk of interest. Alternatively, if is appears that there will not be adequate statistical power for a particular study, the level of exposure or disease that could be ruled out by the study should be considered in determining whether to proceed with the study.

4. Funding for health studies shall be provided in accordance with the provisions of the Record of Decision.

C. Description of Methods

1. An appropriate method will be described and will constitute the public health action protocol and will address the issues covered the general outline presented in Appendix B of Attachment 1 to this recommendation.
2. The methods will follow standard practices, be scientifically and medically sound and defensible, and will minimize any action=s adverse impact to the community. The best available and most appropriate epidemiologic tools will

be used in the process (e.g. geographic information systems, meteorologic and dispersion modeling, production of isopleths, etc.).

3. Methods will be cleared through the CDPHE Institutional Review Board which evaluates protocols involving human subjects.

VI. Attachments: The attachments to this guideline provide materials which may be useful if public health actions are required.

Attachment 1: Guidance for ATSDR Health Studies - This document presents the process used by ATSDR in considering health studies for communities that might be exposed to hazardous substances.

Attachment 2: Baseline/Human Health Monitoring Subcommittee Criteria and Guideline for Laboratory Selection.

Attachment 3: Baseline/Human Health Monitoring Subcommittee Biomonitoring Goals - These goals define the purpose of biomonitoring. A statement describing each goals underlying expectation is included.

Attachment 4: Baseline/Human Health Monitoring Subcommittee: *Analysis of the Effectiveness of Biomonitoring Versus Air Monitoring for Evaluating Human Exposure to Environmental Contaminants*

Attachment 1
Guidance for ATSDR Health Studies

Science Corner

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

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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 studyATSDR, a contractor, an awardee of a cooperative agreement, or a granteethe 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

1. Neutra R, Goldman L, Smith D, Satin K, Deane M. Study endpoints, goals, and prioritization for a program in hazardous chemical epidemiology. Arch Environ Health 1988;43:94-9

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3. Schlesselman JJ. Case-control studies: design, conduct, analysis. New York: Oxford University Press, 1982.

4. Last JM, Wallace RB, editors. Public health and preventive medicine. 13th Ed. Norwalk (CT): Appleton & Lange, 1992.

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 evidence of human exposure or exposure at a sufficient level of concern.	1. 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.
		[*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.

For More Information Contact:

Division of Health Studies
Agency for Toxic Substances and Disease Registry
1600 Clifton Rd., NE
Atlanta, Georgia 30333
USA

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Link to ATSDR Science Corner

ATSDR Home Page

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Last Update - November 22, 1996

Attachment 2
Baseline/Human Health Monitoring Subcommittee
Criteria and Guideline for Laboratory Selection

Laboratory Criteria

1. Test Capabilities
   - Can do the required testing?
   - Is certified by major accreditation organizations (CLIA & CAP)?
   - Quantitative or qualitative analyses or both?
2. Commitment & Quality
   - Wants to be involved & will devote required resources?
   - QA/QC programs?
     - participates in intra- and inter-laboratory verification programs (proficiency programs) if these exist for the analyte of interest? [Quebec Program for Heavy Metals]
     - Standards & Calibration Logs
     - Verification of reference intervals
3. Facilities & Resources
   - Has sufficient personnel, expertise & equipment? (Do they typically do this?)
   - Can provide sample collection resources?
     - Change of Command program? (Legal concern)
     - Inventory control of materials
   - How to transport the specimens, how long it takes to transport?
   - Can satisfy turn around time expectations?
4. Other concerns
   - Interference Info Collected? (Drugs and other factors that could interfere)
   - Appropriateness of Samples? (acute vs chronic exposure)

Sample Analysis Criteria

-Spot tests good for qualitative heavy metal analyses (**Pb,Hg,Cd**)
-Screening for organochloride pesticides can use spot testing of serum or whole blood.
Aldrin/Dieldrin = 4.5 ppb (mean); 1-25 ppb (normal range);
DDT = 12 ppb (mean); 2-100 (normal range).

Corroborating Clinical Outcomes to test for:

Albuminuria: many toxic substances
Aminoaciduria: Cadmium
Delta-aminolevulinic dehydratase activity (decreased): Lead
Hemolysis: Lead
Hypercalciuria: Cadmium
Liver damage: many toxic substances
Porphyinuria: Lead, Mercury, Chlorinated hydrocarbons (Chlordane)
Renal damage: many toxic substances
Uremia: Lead
Jaundice: Chlorinated hydrocarbons (Chlordane)

Specific Testing Information

LEAD DETERMINATION:

Methods:	Atomic Absorption Spectrophotometry (AAS) & Anodic Voltammetry (ASV)
Sample Collection:	Heparinized Whole blood in special lead-free evacuated tubes Urine: 24 hr specimen in lead-free container no preservative a minimum of 100 mL of entire specimen required
Normal Ranges:	<0.8 mg/L of urine 0.3 mg/L of blood (>45mcg/dL peds, medical attention, 10-24 mcg/dL in peds require medical monitoring and environ evaluation)

MERCURY DETERMINATION:

Methods:	Cold vapor AAS is the most widely used (CVAAS)
Sample Collection:	Blood: 1mL (for acute exps.); Urine: 1mL Screening Test: 24 hour urine is specimen of choice

CADMIUM DETERMINATION:

Methods:	AAS is the most widely used.
Sample Collection:	Blood reflects Cd body burden only several months after termination of chronic exposure. Urine: Better measurement of Cd levels; Urine methallothionein also good indicator of body burden

ALDRIN & DIELDRIN DETERMINATION: (Organophosphate Pesticide)

Methods: Gas chromatography (GC) coupled with electron capture detection (ECD)
(Since aldrin is converted so rapidly to dieldrin, exposure to aldrin or dieldrin is measured exclusively by determining levels of dieldrin in blood)

Sample Collection: serum or whole blood
(Blood chlorinated hydrocarbons are not clinically useful following acute exposures, they reflect cumulative exposure over a period of months or years)

CHLORDANE DETERMINATION: (Chlorinated Hydrocarbon)

Method: GC/ECD is the method of choice for quantification, because of its high sensitivity for chlordane compounds and its lack of sensitivity for the large excesses of lipids in the sample matrix.

Sample Collection: serum or whole blood
(Blood chlorinated hydrocarbons are not clinically useful following acute exposures, they reflect cumulative exposure over a period of months or years)

DDT DETERMINATION: (Organophosphate Pesticide)

Method: GC/ECD is the method of choice for quantification

Sample Collection: serum or whole blood
(Blood chlorinated hydrocarbons are not clinically useful following acute exposures, they reflect cumulative exposure over a period of months or years)

Attachment 3
Baseline/Human Health Monitoring Subcommittee
Biomonitoring Goals

Baseline/Human Health Monitoring Subcommittee Biomonitoring Goals
March 9, 1998

Baseline/Human Health Monitoring Subcommittee developed the following biomonitoring goals so as to identify the intent of community biomonitoring. Associated with each goal is a statement describing each goals underlying expectation.

Goal I: Use biomonitoring techniques to assess the extent of intake to surrounding RMA communities from exposure to fence-line exceedances suggested by air monitoring data.

This goal will:

1. Assure that the air monitoring system is protecting human health (in the event of either a positive or negative exceedance).
2. Evaluate clinical significance.

Goal II: Use biomonitoring data to assist in clinical management of members of an exposed population by supplying health care providers with community exposure data and relevant clinical recommendations.

This goal will determine if the COCs correlate with symptoms exhibited in the community and show whether the amount of intake in the community was significant or not.

Goal III: Provide estimates of human intake for future epidemiological studies.

This goal will augment the atmospheric estimates which were used in air monitoring efforts and improve future air modeling efforts.

Goal IV: Use biomonitoring techniques to examine elevated disease rates, if indicated by preliminary investigations, in the community.

This goal will allow the evaluation of clinical significance in the case that biomonitoring is triggered by a scenario other than the air monitoring program.

Attachment 4

Baseline/Human Health Monitoring Subcommittee

Analysis of the Effectiveness of Biomonitoring Versus Air Monitoring for Evaluating Human Exposure to Environmental Contaminants

Baseline/Human Health Monitoring Subcommittee

Analysis of the Effectiveness of Biomonitoring Versus Air Monitoring for Evaluating Human Exposure to Environmental Contaminants

Originally reported to the RMA MMAG April 21, 1998

The Baseline/Human Health Monitoring Subcommittee has made significant progress on the topic of baseline health assessment. Much of the subcommittee=s discussions have focused on biomonitoring of chemicals in the human body. However, this perspective has significantly broadened and the subcommittee is now considering a greater variety of approaches to the human health evaluation. This status report supports this view and describes the subcommittees current direction.

- Biomonitoring for chemicals in human tissues is a tool with limited application. Only those chemicals with a prolonged residency in the body and for which effective measurement techniques exist, have potential as indicators of exposure.

- An analysis of the lower limits of detection and background concentrations for bioaccumulative chemicals of concern demonstrated that environmental monitoring is a more sensitive means of detecting potential exposure. Contaminant concentrations can be measured with lower limits of detection in air than in blood and that environmental concentrations (exposure concentrations) would need to be well above the respective detection limit in order for resulting blood levels to exceed the population background range. While small increases in the air/exposure concentration may be reflected in small increases in blood levels, this rise may not be discernable in the exposed population. We have also concluded that urine will be a less effective medium for monitoring than blood and that the general relationship for air/urine is the same as air/blood.

- A review of statistical considerations indicates that very large population sample sizes may be required to measure significant differences in contaminant concentrations in biological tissues of the magnitude likely to result from environmental exposures.

- Because (1) human body levels of chemicals may vary over time, (2) individuals within a population migrate, and (3) the characteristics of individuals which may influence the levels of these chemicals changes (occupation, age, diet, hobbies, etc), a baseline measurement is potentially unstable.

The above observations indicate that a one-time community-wide baseline biomonitoring effort, and one which will only address a limited number of chemicals, and one which may have only a short temporal application, is likely to be very restricted in its application. In lieu of baseline biomonitoring, the subcommittee is proceeding as follows:

- The subcommittee believes that the environmental monitoring plan must be adequate to ensure that the greater margin of protectiveness that environmental monitoring offers is used to our advantage.

- The subcommittee is preparing recommended guidelines which will facilitate selection of appropriate public health actions. These guidelines will be supportive of the *Remediation Monitoring - Medical Referral & Biomonitoring Decision Tree* which established a process for determining the adequacy of exposure prevention and for determining when the RMA Medical Monitoring Program should consider implementing public health actions. The selection of the appropriate action will be based on a systematic evaluation of the available data.