Guidelines for Examining Unusual Patterns of Chronic Disease and Environmental Concerns

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Acronyms

ADH: Arkansas Department of Health
ATSDR: Agency for Toxic Substances and Disease Registry
CDC: Centers for Disease Control and Prevention
CD-CIT: Chronic Disease Cluster Investigation Team
EAP: Expert Advisory Panel
NCEH: National Center for Environmental Health
NPCR: National Program of Cancer Registries

Overview

The purpose of these guidelines is to ensure a standardized coordinated response from Arkansas Department of Health (ADH) employees or ADH representatives receiving calls from the public, health professionals, or others about potential clusters of chronic diseases (cancer, birth defects, or any unrecognized non-infectious syndromes or illnesses). The guidelines are also intended to be a reminder to ADH personnel about the importance of communicating and coordinating with appropriate entities, both within the central office and in the region where the potential cluster occurs.

This protocol only pertains to clusters of chronic diseases such as cancers, birth defects, or an unrecognized noninfectious syndrome or illness pertaining to environmental exposures. **It does not apply in emergency situations such as infectious disease outbreaks, bioterrorism events, or pertaining to environmental exposures**.

This document has been revised to align with the Centers for Disease Control and Prevention (CDC) National Center for Environmental Health (NCEH) and the Agency for Toxic Substances and Disease Registry (ATSDR)'s 2022 updated guidance "Guidelines for Examining Unusual Patterns of Cancer and Environmental Concerns."

This updated guidance was reviewed and approved by ADH Science Advisory Committee on April 8, 2025.

Chronic Disease Cluster Investigation Team (CD-CIT)

The Arkansas Department of Health (ADH) has formed a Chronic Disease Cluster Investigation Team (CD-CIT) to ensure a coordinated response for any suspected chronic disease clusters or concerns. The members include:

1. Deputy Chief Medical Officer or State Chronic Disease Director
2. Consultant Statistician/Epidemiologist
3. Epidemiology Branch Chief
4. Environmental Epidemiologist
5. Central Cancer Registry Director
6. Cancer Registry Surveillance Manager

Additionally, the following members of ADH may be involved in forming an Expert Advisory Panel (EAP) to resolve any issues as needed. The members of the EAP:

1. State Epidemiologist or Deputy State Epidemiologist
2. Director, Division of Health Advancement
3. Director, Division of Health Data & Analytics
4. Deputy Director for Public Health Programs
5. Chief Science Officer or Deputy Chief Science Officer
6. Director, Arkansas Department of Health
7. Secretary of Health, Arkansas Department of Health

Revised Definitions and Cluster Characteristics

Cancer is a broad term to encompass a disease with uncontrollable cell growth and division. However, each cancer type has its own characteristics, risk factors, causes, and treatments. As such, the revised 2022 CDC's ATSDR guideline defines a cancer cluster as:

*"A greater than expected number of the **same or etiologically related cancer** cases that occurs within a group of people in a geographic area over a defined period of time."*

Additional definitions are as follows:

- **A greater than expected number**: When the number of observed cases is greater than typically observed in a similar setting.
- **Of the same or etiologically related cancer cases**: Cases are of the same type, are within a family of tumors (e.g., Ewing's family of tumors), or have a known or suggested link to the same specific environmental or chemical exposures. It is possible to consider multiple cancer types when such a known exposure (e.g., radiation or a specific chemical) is linked to more than one cancer type or when more than one contaminant or exposure type has been identified.
- **Within a group of people**: The population in which the cancer cases are occurring is defined by its demographic factors (e.g., race, ethnicity, age, and sex).
- **In a geographic area**: The geographic area may be based upon pre-existing geopolitical boundaries (e.g., census tract, county, or ZIP code/ZIP code tabulation area). It may be defined according to the nature and extent of potential exposures that may cross multiple or partial boundaries. For example, air pollution from a hazardous waste incinerator which may cross multiple counties or census tracts. These geographic boundaries are used to determine the number of cancer cases as they relate to the total population in this predefined area. It is possible to create or obscure a cluster inadvertently by modifying the area of interest.
- **Over a period of time**: The time frame used to establish the beginning and end dates for analysis. The time period chosen for analysis will affect both the total cases observed and the calculation of the expected incidence of cancer in the population.

3-Phase Approach for Evaluating Suspected Unusual Patterns of Chronic Diseases

The following is an overview of the phases that are used in receiving, evaluating, and responding to reports of suspected unusual patterns of a chronic disease.

Phase 1:

- Suspected unusual pattern of chronic disease is reported to ADH. Report is routed to a CD-CIT member.
- CD-CIT member logs the information provided by the inquirer, evaluates legitimacy of concern, defines the study population, and refers to descriptive statistics.
- CD-CIT member decides whether to resolve the investigation and communicate the results to the caller, or if not resolved, to move to Phase 2.

Phase 2:

- CD-CIT member performs verification of diagnosis(es) reported by the inquirer.
- CD-CIT member conducts statistical analysis to calculate the standardized incidence ratio with 95% confidence intervals.
- CD-CIT reviews the literature on the risk factors and assesses possible associations between the risk factors and suspected excess.
- CD-CIT meets to evaluate the findings and decides whether to resolve the investigation and communicate the results to the caller, or if not resolved, to move to Phase 3.

Phase 3:

- EAP ascertains the plausibility of an association and feasibility to conduct epidemiologic study.
- If it is decided that it is **not feasible** to conduct a study, EAP decides whether to resolve the investigation and communicate the results to the caller.
- If it is decided that it **is feasible** to conduct an epidemiological study, the CD-CIT and EAP engages relevant stakeholders, external partners, and community members to conduct an epidemiological study.
- EAP participates in hypotheses generation, evaluation and potential study design.
- EAP and CD-CIT share the results of the investigation with relevant stakeholders, partners, and community members. Recommend interventions to address the issue as appropriate.

Phase 1. Initiating Lines of Communication

In this example, cancer has been utilized to illustrate the proceeding through the three-phase process. Since 1996, through funding from the National Program of Cancer Registries (NPCR) at the CDC, the Arkansas Central Cancer Registry (ACCR) has been collecting population-based cancer incidence data among all residents in Arkansas. The ACCR collects high-quality and complete data, and a flow chart of the data processes are available in **Appendix A: Arkansas Central Cancer Registry (ACCR) Data Flow Process**.

The purpose of Phase 1 is to collect and evaluate the information from the inquirer. The following outline lists action points to complete in Phase I:

A. Inquirer's Initial Contact to CD-CIT member(s):

ADH uses the CDC's standard **Cancer Inquiry Intake Form** to gather key information to log when a call or email is first received (**Appendix B: Cancer Inquiry Intake Form**). The intake form helps document if this is the first time the person is calling, if the geographic area or cancer(s) of concern has been mentioned previously, and if there are multiple people raising concerns about the same geographic area or cancer type(s). Upon reviewing the inquiry, the ADH ACCR will notify the ADH Environmental Epidemiology section when an environmental factor is reported in the inquiry.

A community member requesting/initiating a cancer inquiry can submit their communication via ADH.ACCR@Arkansas.Gov, or 501-661-2000.

A CD-CIT member receives the inquiry, or report, of a suspected unusual pattern of cancer. The following information is requested from the inquirer:

- Inquirer information:
    - Name,
    - Residential address,
    - Email address,
    - Telephone number,
    - Length of residence at the current location, and
    - Organization affiliation (if any).

Note: If the inquirer requests anonymity, you should comply. However, explain that the inability to follow up with the caller might hinder further investigation. Keep in mind that the inquirer might not have information to differentiate between primary site and metastatic cancers and will most likely not be aware of all cases of cancer in the area or during the time frame of concern.

- Inquirer information about the suspected unusual pattern of cancer types:
    - Type(s) of cancer and number of cases of each type,
    - Age at diagnosis of people with cancer,
    - Geographic area of concern,
    - Time period over which cancers were diagnosed, and
    - How the inquirer learned about concerns of the cancer patterns.

Note: The inquirer may not know the true primary cancer diagnoses and will most likely not be aware of all cases of cancer in this area or during the period of concern.

- Other Information:
    - Any specific environmental concerns,
    - Other risk factors, such as, occupation, alcohol use, tobacco use, diet, infections, family history of disease, family history of cancer, and
    - Additional concerns in the affected area, such as the likely period of environmental contaminant exposures.

Note: If the individual is reporting an event that is **not a suspected cancer cluster**, but rather one involving a known or **possible environmental contamination**, the individual **should be referred to the ADH's Environmental Epidemiology Section.**

B. Initial Investigation by CD-CIT Member(s):

The CD-CIT appointed member will review cancer descriptive statistics in the appropriate context, and associated risk factors for the inquired cancer. Additionally, the CD-CIT member is to become familiar with the geographic profile within the area of concern in order to understand the health and environmental concerns of the community.

Use resources noted in **Data and Other Resources** (**Appendix C: Data and Other Related Resources**) to become familiar with the following:

Cancer Statistics: Review and compare incidence and mortality cancer statistics from the Central Cancer Registry for the inquired cancer. Consider comparing the distribution of diagnoses for the inquired cancer by characteristics such as age, sex, and histology (cell type) to national and state distributions.

Demographics: Review county-level geographic profile within the area of concern. This can include but not limited to geographic area, industrial and residential development.

C. Consult with the CD-CIT team:

Consult with the CD-CIT team to make an initial judgment about the advisability of the ADH pursuing an inquiry into the suspected unusual pattern of cancer:

- **Reach out to CD-CIT committee members to plan initial discussions about the cancer inquiry.** This may also include other health agencies.
- **Reach out to the state or other environmental regulatory agency if the inquiry is primarily regarding an environmental contaminant.** The ADH Environmental Epidemiology section will be make the determination if a state or other environmental agency involvement is needed, such as the Arkansas Department of Energy and Environment (ADEE), the United States Environmental Protection Agency (EPA).

D. Decisions at Phase 1

Based on the review of the cancer registry data, risk, and geographic profile, the suspected unusual pattern of cancer cases might be unrelated because the cancers are not likely to share a common, environmental etiology. However, the data gathered might suggest the need for further investigation, as determined by the CD-CIT. Follow the outline below to determine the next steps:

1. Decision to Close the Investigation at Phase 1

After reviewing the information collected and evaluated in Phase 1, if the CD-CIT team determines no further action, a CD-CIT member will notify the individual and explain the following:

- Nature of the inquired cancer (e.g., increase risk with age, other behavioral factors, etc.),
- The frequency and occurrence of the inquired cancer,
- How different types of cancers are related to different causes,
- Explain that rates of disease do increase and decrease in a population over time (random fluctuations), and
- Explain rates in the appropriate context, and provide easily accessible resources such as the CDC's cancer website (http://www.cdc.gov/cancer), etc.

If the individual is **satisfied with the decision** not to move forward, the inquiry will be closed.

If the individual is **not satisfied with the decision**, then the CD-CIT member should provide a written explanation and include resources related to the decision.

2. Decision to Continue the Investigation to Phase 2

CD-CIT member(s) will be appointed to perform the following action points:

- Notify the individual, provide initial investigative outcomes, and outline how the ADH will follow up.
- The CD-CIT member should ask if there are others in the community (e.g., other residents with this cancer type) who would like to have a report on the results of the next step.
- Additionally, the CD-CIT member will provide easily accessible resources such as the CDC's cancer website, (http://www.cdc.gov/cancer).

Regardless of the decision, all documentation should be included in a permanent log, including the CDC's **Cancer Inquiry Intake Form** information.

Phase 2. Examining the Criteria and Data

The primary purpose of Phase 2 is to build on the information gathered in Phase 1.

Phase 2 determines whether the inquired and verified cancer is in statistically significant excess requiring continued assessment. Due to the variety of issues involved in this phase, the entire CD-CIT may need to be involved.

A. Verifying Cancer Diagnosis

Verification is a multi-step process. The ACCR collects pathology reports in real-time from hospitals and private or commercial laboratories. This information, along with collected medical records from hospitals, oncology clinics, radiation treatment facilities, specialty clinics, and hospice and nursing facilities are used for verification purposes.

CD-CIT will consult with ACCR staff to confirm diagnoses of patients within the area of concern. Provisional cancer data years may be used if the latest year meets at least 90% completion threshold. This information is used to validate diagnoses among cases and may provide additional tumor characteristics (e.g., histology, behavior, grade). Personal health information about cases under investigation cannot be shared due to privacy concerns.

Note: Provisional cancer data may only be used for analysis and not for publication.

Obtain histological reevaluation, if needed. See **Appendix C: Data and Other Related Resources** for limitations about using and interpreting cancer registry data.

Note: The verification process of cancer diagnosis can only occur if the patient was a resident of Arkansas at the time of diagnosis, during the period between 1996 to present. If warranted by the CD-CIT, a data linkage between the cases of concern and the cancer registry or other vital records databases can be performed. Data items needed to match records include name, date of birth, SSN, sex, and race/ethnicity.

B. Examine the Data and Literature

The CD-CIT will evaluate the data in accordance with the criteria put forth by the CDC's **Decision Making Form** (**Appendix D: Decision Making Form for Examining Unusual Patterns of Cancer and Environmental Concerns**). These criteria promote further assessment of unusual patterns of cancer that may not always meet the formal definition of a cancer cluster but can be used as a decision-making guide for assessing the criteria. In general, this form is meant to assess the inquired cancer and/or related environmental risk factors. Resources and capacity may dictate the extent to which the criteria can be fully evaluated.

Section 1: Cancer and Related Risk Factors Data

In **Section 1**, there are six (6) criteria for evaluating the number of cases for the cancer(s) in question and its rate in the area of concern.

Criteria 1: Calculate a standardized incidence ratio (SIR) with 95% confidence intervals.

The SIR calculation provides an estimate of the likelihood that an excess of cases exists in the population of concern (study population) compared to the general or reference population (e.g., population of Arkansas residents). See **Appendix E: 'Statistical and Epidemiologic Approaches'** for more information on statistical and epidemiologic approaches.

Note: If an environmental concern is involved, the general or reference population should have a similar demographic area to the area of concern, but not similar in terms of environmental hazards/contamination.

Standardized Incidence Ratio (SIR)

$$\text{SIR} = \frac{\text{observed cases}}{\text{expected cases}}$$

Standard Error for SIR

$$\text{SE}_{\text{SIR}} = \frac{\sqrt{\text{observed}}}{\text{expected}}$$

95% Confidence Intervals for SIR

$$95\%\ \text{CI} = \frac{\left[\sqrt{\text{observed}} \pm (1.96 \times 0.5)\right]^2}{\text{expected}}$$

An SIR > 1.0 indicates the observed number of cases is greater than the number that would be expected for the population. The 95% CI is an indication of the statistical precision and significance of the SIR value. If the 95% CI includes 1.0, the SIR is not statistically significant.

An SIR >4 with CIs that do not overlap 1.0, and ≥10 cases that might be etiologically linked, should encourage advancing to Phase 3.

Criteria 2: Compare the cancer **incidence** rates and number of newly diagnosed cases for the inquired cancer(s) between the area of concern to a comparable population.

- In selecting a comparable population, areas should be similar demographically and not also similar in terms of environmental hazards and contamination.
- Technical assistance can be requested with ADH or from CDC/ATSDR if more guidance and expertise are needed.

Criteria 3: Evaluate the inquired and verified cancer geographically and temporally for the area of concern.

- Consider using mapping or geospatial method tools (see **Appendix E: Statistical and Epidemiologic Approaches > Considerations for Mapping Suspected Unusual Patterns of Cancer**).
- Consultation with other CD-CIT members may be required for the creation of maps and graphs.

Criteria 4: Compare the cancer **mortality** rates and number of cancer deaths for the inquired cancer(s) between the area of concern to a referent area (e.g., state, county).

- Consider examining other factors, such as access to care or recommended cancer screening rates, if available.

Criteria 5: Consult with other CD-CIT members to evaluate and interpret the inquired cancer(s) in relation to the geographic area of concern performed in **Criteria 3**.

Criteria 6: Map relevant risk factors to the inquired cancer(s). If there are multiple cancers in the inquiry, review the literature to see if there are similar risk factors or causes.

Section 2: Environmental Risk Factors Data

Section 2 presents four (4) criteria for considering environmental risk factors. If these criteria show an environmental factor of concern, the ADH ACCR will include and consult the ADH Environmental Epidemiology Section in the investigation for their evaluation of the environmental factor.

If the ADH Environmental Epidemiology Section recommends the involvement of state or other environmental agencies, their team will contact the necessary agencies on behalf of the CD-CIT members (e.g., such as Pediatric Environmental Health Specialty Units (PEHSU) and/or ATSDR Office of Community Health Hazard Assessment).

Criteria 7: Identify if an environmental concern was reported at the time of the inquirer's reporting in the **Cancer Inquiry Intake Form** (**Phase 1.A)**.

Criteria 8: If an environmental concern was mentioned (from **Criteria 7**), refer to peer-reviewed published scientific literature, such as PubMed or other sources, and toxicological profiles to determine if there is a plausible pathway of exposure (route by which a person or population can come into contact with a hazardous substance, or a stressor, from a source) between the suspected environmental concern and the inquired cancer's disease etiology.

Criteria 9: If an environmental concern was mentioned (based on **Criteria 8**), refer to peer-reviewed published scientific literature and toxicological profiles to determine if the literature suggests that the suspected environmental concern may play a role in developing the inquired cancer(s).

Criteria 10: If an environmental concern was mentioned, refer to peer-reviewed published scientific literature and toxicological profiles to determine the latency period between the exposure of the suspected environmental concern and the inquired cancer(s).

C. Consult with the CD-CIT team:

CD-CIT will review Section 1 and 2 and check the "no" and "yes" boxes on the **Decision Making Form**.

In addition to the data and literature examined in Phase 2B, the CD-CIT may consider examining trends of a cancer type that is unrelated to the cancer and/or other exposures of concern. If the inquired cancer(s) appears elevated or depressed in a similar time frame, other factors should be considered. These factors include the possibility that the community has an unusually high proportion of persons with high-risk health behaviors (e.g., smoking).

D. Decisions at Phase 2

1. Decision to close the investigation at Phase 2

If ALL answers to Sections 1 and 2 is "no": No further assessment needed at this time.

Next steps for the CD-CIT to conclude the investigation are as follows:

- Summarize collected information in a written report or letter.
- Provide summary to the inquirer/point of contact. The summary should include the following:
    - Background information on patterns of cancer observed (rates and geography),
    - An explanation of how the agency investigated the inquiry about unusual patterns of cancer,

    - A review of findings regarding the cancer(s) of concern,
    - A discussion of risk factors for the cancer(s) mentioned in the original inquiry,
    - Agency plans or next steps based on the findings, and
    - A note or reference about routine monitoring and follow-up.
- Continue routine monitoring as appropriate, and plan to include the cancer(s) and area of concern in routine evaluation of cancer data (to determine if the pattern changes).
- Conduct routine monitoring aimed at identifying unusual patterns of cancer using geospatial/statistical tools (and data that may be routinely available at geographic levels lower than the state as a whole).
- Maintain the feedback loop with the original inquirer and establish procedures for future updates (e.g., making more geographically granular data available on the health department website).

2. Decision to continue the investigation to Phase 3

If answer to Section 1, Criteria 1 is "yes" AND answer to any other criteria in Section 1 is "yes": Further assess the cancer(s) pattern.

This assessment may include consultation and/or referral to a cancer prevention and control program for consideration of intervention activities or additional information gathering such as a case series analysis, described more in Phase 3. Further assessment could also include defining the geographic area or time frame of concern using spatial and temporal methods.

If answer to any criteria in Section 2 is "yes": Consider information from Section 2 during the additional assessment and/or referral to, or collaboration with, another agency (e.g., the local water department, ADEE, ATSDR).

Conclusion

At the conclusion of Phase 2, whether the decision was made to close or continue the investigation, the CD-CIT should take the necessary actions for any decision made:

- Communicate with the inquirer about types of cancer and area of concern to help raise cancer awareness and provide a state/local health official the opportunity to explain how cancer rates are calculated.
- Summarize the information from the **Decision Making Form** (after completing Phase 2). This summary should describe the information evaluated and what type of follow-up steps might be taken. The summary can also include the next steps in terms of monitoring the pattern of the inquired cancer(s) in the area of concern to determine whether the pattern of cancer changes.
- Consider presenting the information in a community meeting or public availability session, prior to issuing any type of media release (if, for example, the inquiry was made on behalf of a neighborhood or organized group).

Phase 3. Consideration for Epidemiologic Studies

The primary purpose of Phase 3 is to determine the feasibility in conducting a study as a next step from Phase 2. All activities in this step should be carried out in collaboration with community, environmental, and other partners. This step involves a detailed epidemiologic study that tests a hypothesis of the association between the suspected exposure and specific cancer types, for which all the preceding effort has been preparatory. See **Appendix E: Statistical and Epidemiologic Approaches** for a guide to statistical and epidemiologic approaches for conducting investigations.

A. Feasibility Assessment

To determine if it is practical to perform an epidemiologic study with meaningful findings, there are a variety of factors to consider in designing and conducting the study. The feasibility assessment should address multiple issues, including, but not limited to:

- Data availability,
- Adequate sample size to detect meaningful differences or associations,
- Staff capacity,
- Funding availability and resources (at the federal, state, and/or local level), and
- Outreach.

B. Decisions

Conducting epidemiological investigations can take several years; the ADH will consider what should be done in the interim to help protect community health and keep members informed.

1. Decision to Close the Investigation at Phase 3

If the feasibility assessment suggests that little will be gained from proceeding further, the investigation should be closed and summarized in a report to the initial caller and other concerned parties.

2. Decision to Continue the Investigation through Phase 3

If the CD-CIT determines it **is feasible** to perform an epidemiologic study, the following steps should be followed:

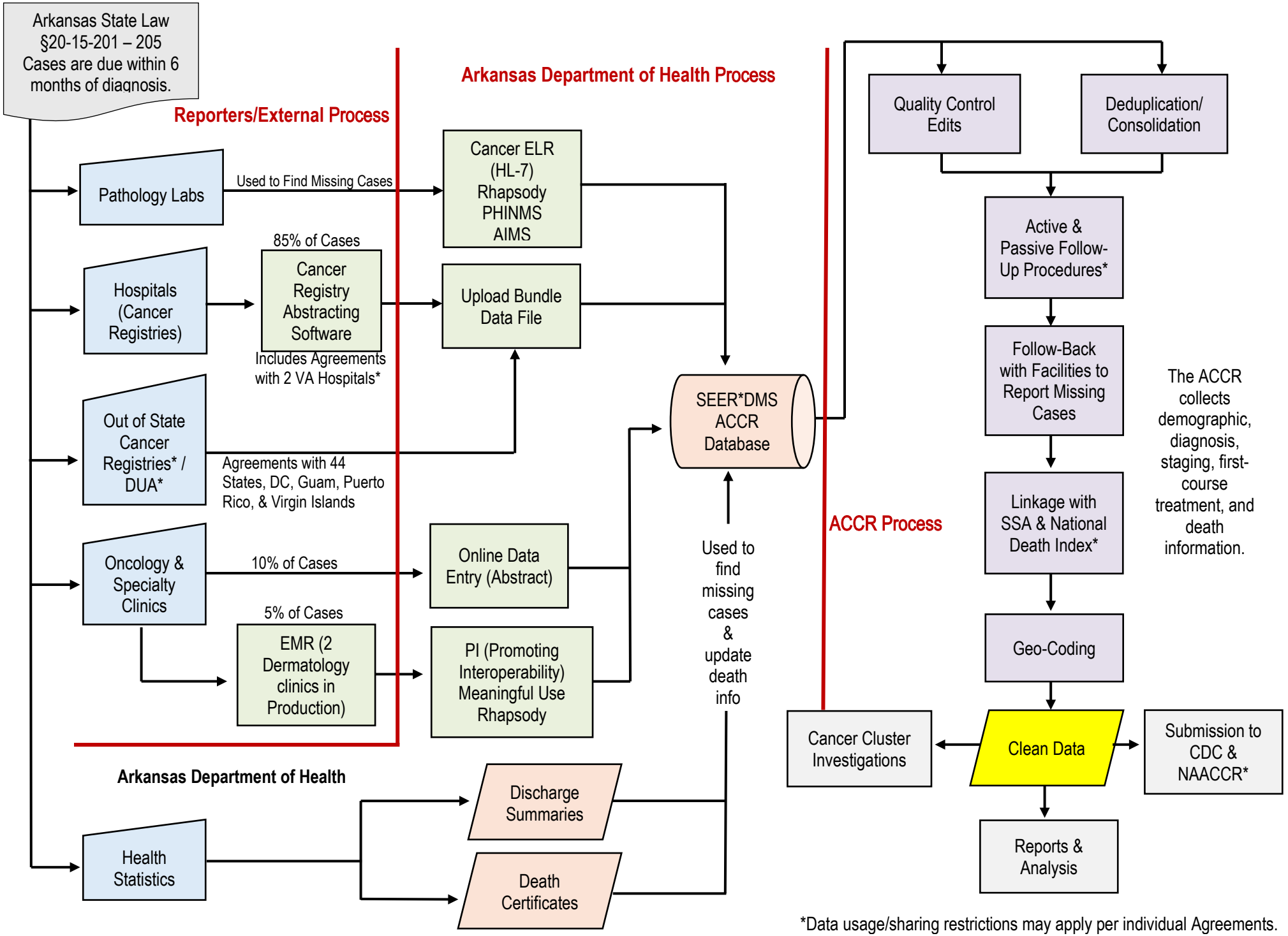
1. CD-CIT will engage the EAP to identify hypotheses and potential study design.
    a) Efforts will focus on known causes of the inquired cancer(s).
        i. CD-CIT will use past agency reports and logs to determine whether the same type of cancer(s) has led to other inquiries and investigations.
        ii. CD-CIT will conduct another literature search.
2. CD-CIT and EAP will identify study parameters and proceed with the investigation as follows:

a) Confirm the diagnosis.
b) Identify a comparison group that depending on the study design does not have the cancer(s) of concern (i.e., control group in a case-control study) or does not have the exposure of concern (i.e., unexposed group in a cohort study).
c) Explore feasibility of obtaining data on individuals in the comparison group and explore the willingness of persons to participate in interviews or studies for gathering data on health, possible exposures, the amount of time the affected persons lived in the area, and occupation.

3. CD-CIT and EAP will ascertain the plausibility that the cases and contaminants could potentially be associated, including:
    a) Verifying whether the environmental contaminants of concern are known carcinogens.
    b) Considering possible and plausible routes of exposure to affected persons.
    c) Asking whether persons with cancer actually were exposed to an environmental contaminant in sufficient doses for a sufficient time to make the association biologically plausible.
    d) Considering the possibility of historical records of chemical use or contamination at the particular location.
    e) Determining whether residential and occupational histories for affected persons are obtainable.
4. CD-CIT will assemble available information from standard sources on the environmental contaminant of concern.
    a) It is not recommended to engage in general, open-ended inquiry to identify potential contaminants in a community, in the absence of a suspected etiologic agent.
    b) Additional environmental testing should be carried out only when there is a clear scientific rationale, and;
        i. Because of the long latency of cancer, an historical exposure assessment might be more important than consideration of current exposures.
        ii. Investigators should determine whether they can characterize exposure to suspected environmental hazards accurately, at the individual level in a way that reflects the period of concern.
5. CD-CIT and EAP will determine study design, including:
    a) Geographic scope, study timeframe (allows for sufficient latency in cancers of concern), and demographics.
    b) Study design, sample size, and statistical tests necessary to study the association as well as the effect of a small sample size on statistical power.
    c) Resource implications and resource/funding requirements of the study.

The public or media may continue to request further investigation, regardless of cost or biological plausibility. Work with established community relationships, media contacts, and EAP, and ADH's Office of Health Communications to manage the response.

Appendix A: Arkansas Central Cancer Registry (ACCR) Data Flow Process

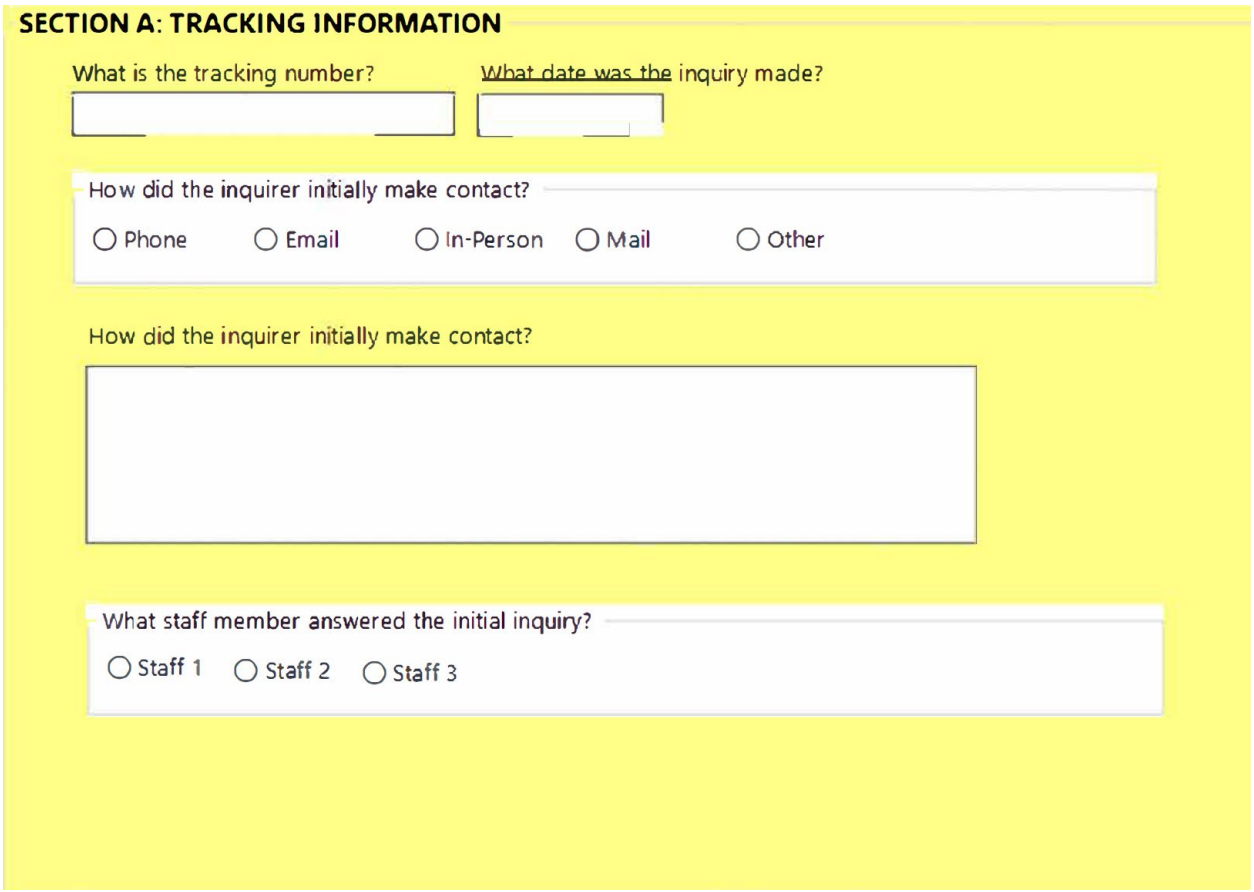


*Data usage/sharing restrictions may apply per individual Agreements.

Separates processes by group/organization responsibility

Appendix B: Cancer Inquiry Intake Form – Example Layout

This intake form is designed to assist State, Tribal, Local, or Territorial (STLT) health departments, including ADH, in collecting standardized information when receiving an inquiry about unusual patterns of cancer and environmental concerns. The layout below reflects the intake form as seen in the Research Electronic Data Capture (REDCap) software program. For further information, please reference CDC/ATSDR's "Guidelines for Examining Unusual Patterns of Cancer and Environmental Concerns."



Note: Example extracted from the CDC's Form Approved (OMB No. 0920-0879, Expiration Date: 01/31/2024). CDC estimates the average public reporting burden for this collection of information as 2 hours per response including the time for reviewing the instructions, searching existing data/information source, gathering and maintaining the data/information needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB Control Number. Send comments regarding this burden estimate or any other aspect of this collection of information including suggestions for reducing this burden to CDC/ATSDR Information Collection Review Office, 1600 Clifton Road NE, MS D-74, Atlanta, Georgia 30333; ATTN: PRA (0920-0879).

SECTION B: INQUIRER'S INFORMATION

Title:

First name:

Last name:

Mailing address:

City, town, village, or township:

Zipcode:

Phone number:

Email address:

Preferred method of communication:

○ Phone ○ Email ○ In-Person ○ Mail ○ Other

What is the inquirer's preferred method of other communication?

For future communication, what day and time works best for the inquirer?

SECTION C: AREA OF CONCERN

Define the geographic area of concern.

- ◯ City or Town or Village or Township
- ◯ County
- ◯ Neighborhood
- ◯ School
- ◯ Workplace
- ◯ Other

What is the the other geographic area of concern?

What is the county of the area of concern?

What is the ZIP code for the area of concern?

Please list additional notes about the area of concern. (If applicable, please include the name of the city/town/village, township, school, or neighborhood, etc.)

SECTION D: CANCER OF CONCERN

What type(s) of cancer are reported?

- ☐ Bladder
- ☐ Bone Tumor
- ☐ Brain and other Nervous System
- ☐ Breast
- ☐ Colorectal
- ☐ Esophagus
- ☐ Hodgkin Lymphoma
- ☐ Kidney and Renal Pelvis
- ☐ Laryngeal
- ☐ Leukemia
- ☐ Liver and Intrahepatic Bile Duct
- ☐ Lung and Bronchus
- ☐ Melanoma
- ☐ Mesothelioma
- ☐ Multiple Myeloma
- ☐ Non-Hodgkin Lymphoma
- ☐ Non-Melanoma Skin
- ☐ Oral and Pharyngeal
- ☐ Ovarian
- ☐ Pancreatic
- ☐ Retinoblastoma
- ☐ Soft Tissue Sarcoma
- ☐ Stomach
- ☐ Testicular
- ☐ Thyroid
- ☐ Uterine
- ☐ Unknown
- ☐ Other specify other cancer: _____

How many cases of cancer are being reported?
(Please indicate the number of cases for each cancer type reported.) _____

What year were the cancer cases diagnosed? _____

Is the given year of diagnosis an estimate or an exact year?

- ○ Estimate
- ○ Exact

Are the cancer cases adult, pediatric, or both?

- ○ Adult
- ○ Pediatric
- ○ Both

Please describe any other information mentioned regarding the cancer of concern.
(This includes, but is not limited to, who has the cancer of concern (i.e. self, neighbor, relative, co-worker, patient).

_____

SECTION E: EXPOSURE OF CONCERN

Was an environmental concern mentioned?

What is the pollutant, contaminant, or environmental toxicant of concern?

- ☐ Perfluoroalkyl Substances
- ☐ Trichloroethylene
- ☐ Ethylene Oxide
- ☐ Radon
- ☐ Asbestos
- ☐ NDMA (N-nitrosodimethylamine)
- ☐ Benzene
- ☐ Arsenic
- ☐ Formaldehyde
- ☐ Vinyl Chloride
- ☐ Unknown
- ☐ Other — specify other pollutant, contaminant, or toxicant of concern

Describe the environmental concern:

Is the environmental concern related to any of the listed location types?

- ☐ Superfund site (State)
- ☐ National Priorities List (NPL) Superfund site
- ☐ Brownfield site
- ☐ Landfill
- ☐ Industry site
- ☐ Military base
- ☐ Other — specify other location type related to the environmental concern

SECTION F: STAFF ACTION AND FOLLOW-UP

What was the staff member's action and response?

What staff member responded to the inquiry?

○ Staff 1 ○ Staff 2 ○ Staff 3

What is the proposed staff response follow-up date?

Was the follow-up completed?

What date was the follow-up completed?

Appendix C: Data and Other Resources

SEER*Stat Software

The SEER*Stat statistical software provides a convenient, intuitive mechanism for the analysis of SEER and other cancer-related databases. It is a powerful PC tool to view individual cancer records and to produce statistics for studying the impact of cancer on a population. To use SEER*Stat with the SEER Research Data, you must have access to the data before using the software.

SEER*Stat provides access to various databases including:

- Surveillance, Epidemiology, and End Results (SEER) Program Research Databases
- U.S. Mortality Data obtained from the National Center for Health Statistics (NCHS)
- National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) Program Research Database
- National Childhood Cancer Registry (NCCR) Research Database

Central Cancer Registries

The Arkansas Central Cancer Registry (ACCR) receives reports of all new cancer cases from facilities that diagnose and/or treat cancer in the state, and will have numerator data (i.e., the number of new cancer cases) for calculating the SIR as well as data for the appropriate comparison measures for reference populations.

- ACCR: http://www.cancer-rates.info/ar/index.php
  - Phone: 501-661-2960
- State Cancer Profiles: http://statecancerprofiles.cancer.gov/
- Surveillance, Epidemiology, and End Results (SEER): http://seer.cancer.gov/faststats/index.php
- United States Cancer Statistics (USCS): https://wonder.cdc.gov/cancer.html
- USCS Data Visualization Tool: https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/

Limitations and cautions to the use and interpretation of data from cancer registries include the following:

- Registry information generally contains patient address at the date of diagnosis only.
- The ACCR collects information on possible risk factors (e.g., smoking history) and usual occupation, but the data are often incomplete.
- The types of cancer that are most likely to be underreported occur in persons with late-stage cancers that are treated with palliative care (e.g., persons who might not be hospitalized for surgery or treatment). Other likely underreported types include those who have been diagnosed in a physician's office without hospitalization (e.g., early-stage melanoma). Many hospitals routinely collect cancer data for their own purposes and for most hospitals reporting to central registries is routine. However, reporting from nonhospital facilities is less reliable. Consequently, data for cancer patients who are never hospitalized for diagnosis and treatment tend to be less complete and might be reported later than other cases.

- Codes and rules for counting cancer cases change over time. Occasionally, changes in diagnostic criteria might change how a cancer is diagnosed, possibly creating changes in the frequency in which the cancer is detected and reported. These types of changes are adopted at different rates by physicians and hence in reports to the registries.
- Data on race and ethnicity are captured in registry data; however, this data is collected inconsistently with some providers relying on a patient's self-report and others assessing race based on observation.
- Many registries are aware of "quirks" or "anomalies" in possible mismatching of numerator and denominator data of their regions as a result of rapidly growing or shrinking areas or large population centers that straddle county or other borders.

Data on Deaths

Data on deaths compiled by the Vital Records & Health Statistics Branch might be a useful supplement in identifying data on cancer cases. Death records are most useful for cancer with high mortality and a short survival period such as pancreatic, liver, lung, and some types of brain cancer. However, death records are not very useful for cancers with lower mortality, such as breast, thyroid, prostate, or colon cancers, from which patients are likely to survive.

CDC Wide-ranging Online Data for Epidemiologic Research (Wonder): https://wonder.cdc.gov/

Limitations and cautions in the use of death records in cancer cluster investigations include the following:

- Death records might be limited by the requirement that the residence of the deceased is recorded as the address at the time of death; this address might or might not be the place where the individual resided at the time of the cancer diagnosis.
- Death records are not necessarily completed by the physician who best knew the patient's medical history, meaning that the given cause(s) of death might not always be accurate.

U.S. Census Bureau

The U.S. Census Bureau can provide valuable data for use in determining the denominator for incidence calculation. State, county, census tract, and census block level data are available.

- U.S. Census Bureau: https://data.census.gov/cedsci/

Limitations and cautions about the use of census data include the following:

- Census numbers might be inaccurate for intercensal years when substantial population changes (rapid growth, shrinkage, or aging changes) occur.
- Census boundaries occasionally change, most often in rapidly growing areas that are often subdivided, making comparison between years or combining data from different years difficult.
- The census tract is defined by the U.S. Census Bureau, and it is a relatively homogeneous unit with respect to population characteristics. A census tract generally contains between 1,000 and 8,000 persons, with an optimum size of 4,000 persons. Cancer clusters of concern frequently are confined to areas smaller than a census tract. Because census tracts are subdivided into census blocks and block groups, blocks and block groups might be combined if a census tract does not give the needed geographic boundaries. The number of cases occurring within a block or a block group might be far too small to allow reporting of cancer cases without privacy concerns or

creating statistically unstable rates. Registries often will not release data at the block group level or even the census tract level because of privacy concerns.
- Census units might not be similar to contamination boundaries.

Zip codes can be and often are used as geographic areas for cluster investigations, especially if they are a better fit for communities at issue. There are two major limitations to using zip codes for cancer cluster investigations:

- Zip code boundaries might change more often than census boundaries, and
- Zip codes cross county and census boundaries. Moreover, a person might have a post office box or a rural route address that is in a different zip code than the actual residence.

National Environmental Public Health Tracking Network

CDC's National Environmental Public Health Tracking Network (Tracking Network) is a nationwide surveillance network that provides health, environmental hazard, and exposure data.

- Tracking Network: https://ephtracking.cdc.gov/DataExplorer/
- About the Tracking Network: http://www.cdc.gov/nceh/tracking/

Data from State and Territorial Environmental Agencies

State and local environmental protection agencies routinely collect environmental data. Because these data are collected in places and at times according to regulatory purposes, they might be useful in identifying environmental hazards in cancer cluster investigations, or they might only approximate the environmental conditions at the site of the potential cancer cluster.

Environmental agencies regularly collect data on water quality and air quality for compliance with air and water quality standards. These agencies also often permit and regulate industrial or other facilities that generate, transport, or store hazardous waste or other chemicals. The agencies will therefore have records of compliance and noncompliance that might indicate emissions into the environment. The state agencies are also involved, along with the Environmental Protection Agency (EPA), in monitoring pollution and in the oversight of the cleanup of contaminated sites. EPA collects environmental data for regulatory purposes, and the agency publishes the data on its website.

- EPA's list of State and Territorial Environmental Agencies: https://www.epa.gov/home/health-and-environmental-agencies-us-states-and-territories
- Arkansas Department of Environmental Quality (ADEQ) searchable databases: http://www.adeq.state.ar.us/compsvs/webmaster/databases.htm
- ATSDR: http://www.atsdr.cdc.gov/substances/index.asp
- ATSDR series of Toxicological Profiles: http://www.atsdr.cdc.gov/toxprofiles/index.asp

The staff located within state or local environmental protection departments can be a helpful resource for providing information about local environmental conditions that might lead to exposure to contamination. The staff's assistance should be engaged in evaluating available environmental data for relevance to a cancer cluster inquiry or investigation because the data collection areas are determined by regulatory requirements and might not provide information specific to a particular site of public health interest.

Sources of information on the association between specific environmental contaminants and cancer are available. Weight-of evidence-evaluations of carcinogens are published by the International Agency for Research on Cancer (IARC). To view IARC cancer classifications, please visit http://www.iarc.fr and the National Toxicology Program's (NTP) Report on Carcinogens is available at http://ntp.niehs.nih.gov/go/roc. These evaluations tend to focus on exposures that have been of concern for some time and therefore on which there are substantial data. Not all potential carcinogens have been evaluated by these organizations.

By using the community members' local knowledge about the hazards and risk factors in their community as well as data from environmental and other databases, the investigator can make more informed decisions during the investigation process. For example, information provided by the concerned community members and by available databases can be useful in defining the geographic area and time period for the population at risk, increasing the accuracy and precision of the population definition. Readily available information on environmental hazards in the area of interest can be reviewed to determine if any of the hazards have a space and/or time pattern that can be related to the suspected cancer cluster. A thorough evaluation of environmental hazards with input from the community is appropriate because it might suggest some relevant public health interventions that turn out to be valuable, independent of any suspected cancer cluster. For example, in a community concerned about contaminants in private well systems, proper maintenance of private well systems might be an appropriate public health education program, regardless of whether contaminants are found, particularly if residents' express confusion over how to maintain these wells.

Biomonitoring

Biomonitoring is the measurement, usually in blood or urine, of chemical compounds, elements, or their metabolites in the body. While biomonitoring indicates exposure to a substance, it does not identify the source, the duration of exposure, or the potential health effects that may result from it. Because of the long latency period associated with the development of cancer, the limitations of current environmental data also apply to using or collecting current biomonitoring data. The relevant exposure might have occurred years before and might not be detectable at the time that samples for biomonitoring are collected. Additionally, it is important to note that biomonitoring can be costly and may not be covered by health insurance.

Although a substance is detected in the body, it might not be a carcinogen, or it might not be at levels known to cause the disease. For the U.S., CDC's National Health and Nutrition Examination Survey (NHANES) provides reference data for over 200 chemicals in the blood and urine for a selection of the survey's participants. Biomonitoring is a relatively new field, and there is a need for more research to permit an understanding of which substances at what concentrations in the body contribute to cancer.

- NHANES Report on Human Exposure to Environmental Chemicals: https://www.cdc.gov/environmental-exposure-report/data-tables/index.html

Attachment D: Decision Making Form for Examining Unusual Patterns of Cancer and Environmental Concerns

Section 1: Considering the number of cancer cases and the rate of cancer in the area of concern

Criteria	Response	Notes
1. For the cancer(s) of concern, is the observed number of cases more than the expected number of cases?	No ☐ Yes ☐	
2. Is the difference (in cases or rates) between the area of interest and the comparison area statistically significant?	No ☐ Yes ☐	
3. Is there an individual year or group of years responsible for an elevated rate suggesting a temporal cluster and/or has the rate of that cancer increased over time?	No ☐ Yes ☐	
4. Are the number or pattern of cancer deaths (as shown in mortality/vital statistic data) elevated or unusual in the area of concern?	No ☐ Yes ☐	
5. Considering the geographic distribution of cancer cases, are cases concentrated in any area suggesting a spatial cluster?	No ☐ Yes ☐	
6. Do the cancers of concern share similar causes/risk factors and are they elevated in the area of concern or neighboring areas (regardless of geopolitical boundaries)?	No ☐ Yes ☐	

Section 2: Considering environmental risk factors

Criteria	Response	Notes
7. Has an environmental concern been raised as potentially being related to the pattern of cancer in the area of concern?	No ☐ Yes ☐	
8. Is there a plausible pathway of exposure between the suspected environmental contaminants and the cancer(s) of concern in terms of disease etiology?	No ☐ Yes ☐	
9. Does the scientific literature suggest that exposure to environmental contaminants may play a role in the development of the cancers of concern?	No ☐ Yes ☐	
10. What is the latency period for the cancer of concern and is it consistent with the contaminant exposure timeframe?	No ☐ Yes ☐	

If ALL answers to sections 1 and 2 above are "No"

1. **No further assessment needed** at this time.

2. **Summarize collected information** in a written report or letter; provide summary to the inquirer/community point of contact. The summary should include the following: ❒
    - Background information on patterns of cancer observed (rates and geography)
    - An explanation of how the agency investigated the inquiry about unusual patterns of cancer
    - A review of findings regarding the cancer(s) of concern
    - A discussion of risk factors for the cancer(s) mentioned in the original inquiry
    - Agency plans or next steps based on the findings
    - A note or reference about routine monitoring and follow up

3. **Continue routine monitoring as appropriate**, and plan to include this cancer and area of concern in routine evaluations of cancer data (to determine if the pattern changes): ❒
    - Conduct routine monitoring aimed at identifying unusual patterns of cancer using geospatial/statistical tools (and data that may be routinely available at geographic levels lower than the state as a whole).
    - Maintain the feedback loop with the original inquirer and establish procedures for future updates (e.g., making more geographically granular data available on the health department website).

If answer to question 1 is "Yes," AND answer to any other question in section 1 is "Yes"

Further assess the cancer pattern. This assessment may include consultation and/or referral to a cancer prevention and control program for consideration of intervention activities or additional information gathering such as a case series analysis, described more in Phase 3. Further assessment could also include defining the geographic area or time frame of concern using spatial and temporal methods. ❒

If answer to any question in section 2 is "Yes"

Consider information from section 2 (environmental data and environmental risk factors) during the additional assessment and/or referral to, or collaboration with, another agency ❒

Appendix E: Statistical and Epidemiologic Approaches

Standardized Incidence Ratio (SIR)

The measure typically used to assess whether there is an excess number of cancer cases is the SIR. The **SIR is a ratio of the number of observed cancer cases in the study population to the number expected** (what would be observed) if the study population experienced the same cancer rates as an underlying population (often called the "reference" population). The reference population could be the surrounding census tracts, other counties in the state, or the state as a whole (not including the community under study).

$$SIR = \frac{Observed\ Cases}{Expected\ Cases} \times 100$$

Confidence Interval

A confidence interval is calculated to determine the precision of the SIR estimate and the statistical significance.

The following are points to keep in consideration when using confidence intervals with SIR:

- 95% confidence intervals are commonly used and serves as a balance between being confident in the result while still maintaining a reasonable level of precision.
- If the confidence interval includes 1.0, the SIR is not statistically significant.
- The narrower the confidence interval, the more confidence one has in the precision of the SIR estimate.

One difficulty in unusual patterns of cancer-specific investigations is that the population under study is generally a community or part of a community. This typically results in a small denominator, and such small denominators frequently yield wide confidence intervals, meaning that the SIR is therefore not as precise as desired.

Considering Alpha and Beta Level Values

The **alpha** (α) is the probability of rejecting the null hypothesis when the null hypothesis is true (no difference in cancer rates between the study population and reference population). Although there are no absolute cut-points, responders often use an alpha value of 0.05 (or equivalently a 95% confidence interval).

Beta (β) **and power** are related to each other. Both are related to the sample size of the study. The larger the sample size, the larger the power. Power, or 1- β, is the probability of rejecting the null hypothesis when the null hypothesis is actually false. Like alpha, the beta has no absolute cut-points; however, responders often use a beta value of 0.20 or less (or equivalently a power of 0.8 or more).

Power Analysis

Power analysis is useful in determining the minimum number of people (sample size) needed in a study in order to test the hypothesis and detect a possible association. In most suspected unusual patterns of cancer-specific investigations, the cases and study population are defined prior to the analysis. Therefore, a power analysis can be used to determine if the number of cases in the investigation is sufficient, usually a power of 0.8 or greater.

Descriptive and Spatial Statistical and Epidemiologic Methods

Frequencies, rates, and descriptive statistics are useful first steps in evaluating the suspected unusual patterns of cancer during investigations. **Confidence intervals** can also be calculated for rates. Other statistical approaches include **Poisson regression**. Often, the number of cases is limited, therefore limiting the type of analysis. If an investigation progresses to a case-control study, the odds ratio can be calculated.

- **Confidence intervals for rates:** Similar to SIR confidence intervals, the narrower the confidence interval for rates, the more confidence one has in the precision of the rate estimate.
- **Poisson regression:** This is a type of regression analysis for count and rate data. Often, the number of cases is limited, therefore limiting this type of analysis. If an investigation progresses to a case-control study, the odds ratio can be calculated. Other points to consider are related to the exposure or outcome analysis using aggregate data and not data collected on an individual level. Responders must use caution when interpreting this type of analysis because the association with a particular environmental contaminant might not be true for individual cases, especially if there is heterogeneous distribution of the exposure over the geographic area. The related bias is known as ecological inference fallacy.

As with any other epidemiologic analysis, there might be methodological issues with the use of cluster analysis tools. Many of these concerns include limitations associated with small populations, environmental data quality, disease latency periods, and population migration.

Cluster Analysis

Many methods have been developed to facilitate what is termed "space/time cluster analysis." These methods assess whether cases are closer to one another than would be observed if the cases had been distributed at random. The concept of "close" might mean closer geographically, or in time or both geographically and in time.

The numeric value of "close" is determined by the responder. For a responder to make a determination of clustering, the space-time distances have to be summarized and then evaluated with any of a variety of statistical techniques. This task can be performed by summarizing where and when each case occurred, typically using the individuals' residence and the reported date of incidence. Some of the simplest methods merely compare the average distances between nearby cases to the average distances between cases and nearby non-cases (or controls). If, on average, the cases are sufficiently closer to other cases (in space, time, or both space and time) than they are to non-cases, the situation may be described as a cluster.

Clusters can be detected by using spatial autocorrelation techniques:

- Global clustering statistics, such as Geary's C, detect spatial clustering that occurs anywhere in a study area. They do not identify where the cluster(s) occur, nor do they identify differences in spatial patterns within the area.
- Local clustering statistics, such as Local Indicators of Spatial Autocorrelation (LISA), identify potential clustering within smaller areas inside a study area. Often, global techniques are used first to identify potential clustering; then, local methods are used to pinpoint the clusters in the sample area.
- Many global statistics have local counterparts. For example, global Moran's I is the summation of local Moran's I statistics.

Clusters reported to health agencies most often are local. It is beyond the scope of this report to describe more than a few of the most commonly used methods, and even then, these methods are described only briefly.

A popular technique for detecting clusters is called the spatial scan statistic:

- One of the most commonly used implementations is the SaTScan software (available at https://www.satscan.org/), a free software that analyzes spatial, temporal and space-time data using the spatial, temporal, or space-time scan statistics.
- Another implementation includes the nearest neighbor test and the Small Area Health Statistical Unit (SAHSU)'s "Rapid Inquiry Facility" (RIF) in a choice of a statistical cluster method. This tool is also freely available from the RIF GitHub repository.
- Other implementations include GeoDa and R packages that are publicly available, and several global statistics are available within other proprietary software packages, such as ClusterSeer. **However, these types of software packages are either freely available or for purchase and do not represent an endorsement of any specific product by the Arkansas Department of Health, Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.**

When considering which technique to use, it might be useful to consider several criteria, such as ease of use and availability, cost, the clarity and transparency of the method, its statistical power to detect the cluster of interest, and the method's ability to produce the desired output.

Considerations for Mapping Suspected Unusual Patterns of Cancer

When considering the geographic distribution of cases, responders have various methods they can use. For example, they might develop a visual representation showing the location of each case superimposed on the underlying population density to get an approximation of the distribution of the relative rates of cancer.

Plotting can also be useful in determining the location of suspected environmental risk factors on the map for the purpose of making a crude assessment of their proximity to the cases. However, responders must be careful in avoiding the “clustering illusion.”

- **What is clustering illusion?** A situation in which cases are noticed first and then the "affected" area is selected around them, making there appear to be a geographical relationship.
- This is similar to an instance in which a sharpshooter shoots the side of the barn first and then draws the bull's-eye around the bullet holes.

To avoid clustering illusion, responders must first outline their definitions, assumptions, and methods. Often, a few different spatial (e.g., spatial: census block, census tract, zip code, municipality, or county) or temporal scales (e.g., week, month, year, or several years) can be mapped to look for possible patterns related to specific space and/or time units that merit more careful investigation. This process is systematic. The patterns in such maps often differ dramatically, and they might suggest specific exposures that warrant further consideration. This practice is more useful when longer periods of time are under study, as well as larger numbers of cases (e.g., >10 cases).

Cancer registries and state health agencies typically have criteria related to release of data for small geographic areas. The ACCR does not release information on <10 cases at the state or county-level. Limited numbers can lead to a lack of statistical power and therefore to an instability of rates. For example, a pin-point map of a small geographic area that identifies the residence of a cancer patient should not be made public. Similarly, many health agencies are prohibited from publicly releasing a table for a small geographic area with a small population, for each table cell might have only a few cases.