

Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research

The Chemical Manufacturers Association's Epidemiology Task Group

The Guidelines for Good Epidemiology Practices (GEPs) for Occupational and Environmental Epidemiologic Research address the conduct of studies generally undertaken to answer questions about human health in relationship to the work place or the environment. The GEPs propose minimum practices and procedures that should be considered to help ensure the quality and integrity of data used in epidemiologic research and to provide adequate documentation of the research methods. The GEPs address the process of conducting individual epidemiologic studies and do not prescribe specific research methods.

The Guidelines for Good Epidemiology Practices propose minimum practices and procedures in the following areas:

- I. Organization and Personnel
- II. Facilities, Resource Commitment, and Contractors
- III. Protocol
- IV. Review and Approval
- V. Study Conduct
- VI. Communication
- VII. Archiving
- VIII. Quality Assurance

During the development of the Guidelines for Good Epidemiology Practices, the following researchers were members of CMA's Epidemiology Task Group: William J. Bailey, MPH, Chevron Corporation; Claudia Berner, BS, Exxon Biomedical Sciences, Inc.; James J. Collins, PhD, Monsanto Company; Ralph E. Cook, MD, MPH, The Dow Chemical Company; Barbara J. Divine, PhD, Texaco Inc.; Harry Eichenbach, MS, Grace Specialty Chemicals Company; William E. Fayerweather, PhD, MPH, E. I. du Pont de Nemours and Co. Inc. (Chairman, Epidemiology Task Group); Lorraine Lucas, PhD, American Cyanamid Company; M. Gerald Ott, PhD, BASF Corporation; Gerhard K. Raabe, Dr PH, MS, Mobil Corporation; Robert Schnatter, PhD, Exxon Biomedical Sciences, Inc.; Sandra Selensky, PhD, Union Carbide Chemicals & Plastics Company Inc.; M. Jane Teta, Dr PH, Union Carbide Chemicals & Plastics Company Inc.; William Thor, MD, Exxon Biomedical Sciences, Inc.; Sandra L. Tivy, MS, Chemical Manufacturers Association.

Address correspondence to Dr. William E. Fayerweather, E. I. du Pont de Nemours and Co. N-11510-HE, 1007 Market Street, Wilmington, DE 19880.

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Although the Guidelines for Good Epidemiology Practices will not guarantee good epidemiology, they do provide a useful framework for ensuring that all research issues are adequately addressed. This framework is proposed as a first step in improving epidemiologic research practices through adherence to sound scientific research principles.

Appendices provide an overview of standard operating procedures, a glossary of terms used in the Guidelines, and suggested references on occupational epidemiology methods.

Epidemiologic studies provide unique, valuable information about the relationship between human health and exposure to substances in the environment and the workplace. While the contributions of toxicology and epidemiology are complementary, there is general agreement that reliable human evidence (epidemiologic studies) should take precedence over animal data (toxicological studies) in public policy and regulatory decision making. However, because of the nonexperimental nature of occupational and environmental epidemiologic studies, scientific controversy often surrounds the interpretation and significance of epidemiologic study results. In addition, controversy frequently concerns the quality of the data used, the appropriateness of the study design, and the process used to conduct the study. The nonexperimental nature of the epidemiologic studies cannot be changed, but the value of such research can be improved. The Guidelines for Good Epidemiology Practices address those issues—data quality, study design, and study conduct—that are under the control of the investigator.

Goals for the Guidelines for Good Epidemiology Practices

The Guidelines for Good Epidemiology Practices (GEPs) address the conduct of studies generally under-

taken to answer questions about human health in relationship to the workplace or the environment. The GEPs propose minimum practices and procedures that should be considered to help ensure the quality and integrity of data used in epidemiologic research and to provide adequate documentation of the research methods. The GEPs address the process of conducting individual epidemiologic studies and do not prescribe specific research methods.

Although Guidelines for Good Epidemiology Practices will not guarantee good epidemiology, they will provide a framework within which these issues might be addressed. The Guidelines have the following goals:

1. To provide a framework to assist researchers in adhering to good epidemiologic research principles.
2. To promote sound epidemiologic research by encouraging quality data collection and analysis.
3. To facilitate the continued development of improved epidemiologic research methodology.
4. To provide a framework for evaluating epidemiologic studies.
5. To improve the acceptance of studies that use sound scientific methods.
6. To improve the utility of epidemiologic studies in the formulation of public policy.
7. To improve public confidence in epidemiology as a scientific discipline.
8. To facilitate the conservation of technical resources by promoting careful study design and planning of study conduct.

Alternative Guidelines

A number of other organizations have also become interested in developing or applying guidelines to epidemiologic research.^{1,2} The Office of Management and Budget (OMB) published "Guidelines for Federal Statistical Activities" in which they defined "statistics" as the quantitative results of a survey or study collected for the purposes of reporting population characteristics.³ The Environmental Protection Agency (EPA) recently modified both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) good laboratory practice standards (GLPs) to specifically include epidemiology.^{4,5} In response to comments, EPA states that "all studies, including epidemiologic studies . . . [should] be performed under GLP standards. EPA recognizes that in such studies data used may not have been generated in conformance with . . . GLP standards. However, it is

EPA's position that the study itself can be conducted and submitted to EPA in accordance with the GLP standards."

The GLPs are directed primarily at experimental laboratory research, often involving the use of animals or cell culture systems. The GLPs address issues that confront researchers conducting experimental toxicological research. The Guidelines for Good Epidemiology Practices were developed in part to provide an alternative to the GLPs that would appropriately address the issues confronted by epidemiology researchers conducting nonexperimental studies.

Scope and Application

The Guidelines for Good Epidemiology Practices can be applied to all types of occupational and environmental epidemiologic research. Epidemiologic studies often evolve through a number of stages that might include proposals, feasibility studies, and measurement instrument validation studies that precede the development of a protocol. The GEPs should encompass all activities that begin with protocol development.

Clearly, large complex studies will benefit from the careful planning and thorough documentation implicit in these guidelines. Adherence to the spirit of the guidelines will be beneficial for those activities preceding protocol development as well as more informal investigations such as health hazard assessments/evaluation or small cluster investigations. Even in circumstances of immediate public health concern, the guidelines will provide a useful framework to ensure that all research issues are adequately addressed.

Further Development of the Guidelines for GEPs

The current document is a first step in developing a framework for improving epidemiologic research practices through adherence to sound scientific research principles. The guidelines emphasize data quality and integrity and adequate documentation of research methods. These guidelines should evolve based on the experiences gained through their application to studies.

A Special Note to Readers: As an aid to readers, a glossary of terms is provided in Appendix 2. These definitions reflect the use of the terms in this document. In an effort to be concise and clear, some sections of the guidelines for GEPs include examples and/or further explanation of the issue. Examples or elaborative text appear in *italics*.

Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research

I. Organization and Personnel

A. Organizational Structure

The organization or individual conducting the research shall be fully responsible for the operation and performance of the research. The organization shall be a legal entity with a governing body that sets policy and that is fully responsible for the administrative aspects of the organization and its related research activities.

The relationship, roles, and responsibilities of the organizations and/or individuals sponsoring or conducting the study should be carefully defined in writing.

For example, this should include delineating the roles and responsibilities to be assumed by the study sponsor and the contractor(s) in communicating various aspects of the study as well as data ownership, archiving, etc.

B. Personnel

Personnel engaged in epidemiologic research and related activities shall have the education, training, and/or experience necessary to competently perform the assigned functions. The organization shall maintain a current summary of training and experience of these personnel. A job description for each individual engaged in or supervising activities shall be maintained and updated periodically.

II. Facilities, Resource Commitment, and Contractors

A. Facilities

Adequate physical facilities shall be provided to all those engaged in epidemiologic research and related activities. Sufficient resources, eg, office space, relevant equipment, and office/professional supplies, shall be available to ensure timely completion of all studies. Suitable storage facilities shall be available to maintain research materials in a safe and secure environment.

B. Resource Commitment

Sufficient commitment shall be made at the beginning of each study to ensure its timely and proper completion (see section III(L): Protocol).

C. Contractors

For the purposes of ensuring and documenting the contractor's conformance with the Guidelines for Good Epidemiology Practices, it is recommended that the

study sponsor have the right during the course of the study, and for a reasonable period following completion of the study, to inspect the contractor's facilities, including equipment, technical records, and records relating to the work conducted under the sponsor's contract.

III. Protocol

Each study shall have a written protocol. This protocol must be approved before the study begins (see section IV: Review and Approval).

The protocol should include the following:

- A. A descriptive title.
- B. The names, titles, degrees, addresses, and affiliations of the study director, principal investigator, and all co-investigators.
- C. The name(s) and address(es) of the sponsor(s).
- D. An abstract of the protocol.
- E. The proposed study tasks and milestones, including study approval data (date protocol signed by all signatories), study start date (first date that the protocol is implemented), periodic progress review dates, and completion date.
- F. A statement of research objectives, specific aims, and rationale.

The statement should identify the immediate purpose of the investigation. For example, it might also indicate whether the study will be exploratory data analysis, hypothesis testing, or a combination of both as well as whether the proposed study will address previously unanswered questions, will attempt to corroborate or confirm previous findings, or will be routine epidemiologic surveillance.

- G. A critical review of the relevant literature to evaluate applicable findings.

For example, the literature review should encompass animal and human experiments, clinical studies, vital statistics, and previous epidemiologic studies. The literature review should be of sufficient depth to identify potential confounders and effect modifiers and to determine areas where new knowledge is needed.

- H. A description of the research methods, including:
 1. The overall research design and strategy and reasons for choosing the proposed study design.

For example, case-control, cohort, cross-sectional, nested case-control, or other hybrid designs.

2. The data sources for exposure, health status, and risk factors.

For example, questionnaires, biological measurements, exposure/work history record reviews, or exposure/disease registries.

3. Clear definitions of health outcomes, exposure, and other measured risk factors as well as selection criteria, as appropriate, for exposed and nonexposed persons, morbidity or mortality cases, and referent groups.
4. Projected study size and, if appropriate, statistical power.
5. The methods to be used in assembling the study data.

This should include a description of, or reference to, methods used to control, measure, or reduce various forms of error—eg, bias due to selection, misclassification, interviewer, or confounding—and its impact on the study. Pretesting procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders, or data entry personnel should be described or referenced.

6. Procedures for handling the data in the analysis.

This should include a description of procedures for defining or categorizing exposure and health outcome variables for purposes of analysis. It should also include provisions for assessing dose-response relationships and treatment of potentially confounding and effect modifying variables.

7. Methods for data analysis.

This should include procedures to control, if possible, sources of bias and their influence on results and a description of planned comparisons and methods for analyzing and presenting results.

8. Major limitations of the study design, data sources, and analytic methods.
9. Criteria for interpreting the results.

This should include a brief discussion of the characteristics of the proposed study design, including limitations, that will influence the discussion of the results. It also should state criteria for assessing biological plausibility, internal and external consistency of the findings, and causal inference. The statistical tests to be applied to the data and procedures for obtaining point estimates and confidence intervals of measures of occurrence or association should also be described.

- I. A description of plans for protecting human subjects.

This should include information about whether study subjects will be placed at risk as a result of the study, under what circumstances in-

formed consent will be required, and provisions for maintaining confidentiality of information on study subjects.

(See section IV: Review and Approval: section V: Study Conduct; section VI: Communication; and section VII: Archiving.)

- J. A description of, or reference to, quality assurance and quality control procedures for all phases of the study. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups (see section VIII: Quality Assurance).

- K. A description of plans for disseminating and communicating study results (see section VI: Communication).

- L. Resources required to conduct the study.

Describe, for example, time, personnel, and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.

- M. The bibliographic references.

- N. Addenda, as appropriate.

For example, correspondence, collaborative agreements, institutional approvals, and samples of the informed consent forms, questionnaires, and representative samples of other documents to be used in the study.

- O. A dated protocol review and approval sign-off sheet for the study director, principal investigator, co-investigators, and all reviewers (see section IV: Review and Approval).

- P. Dated amendments to the protocol.

IV. Review and Approval

Review of study protocols and final reports should encompass all aspects of a study outlined in the Guidelines for Good Epidemiology Practices (see section III: Protocol and section V(D): Study Conduct). All reviews should be conducted in a timely fashion. It may be appropriate to involve worker or community representatives in the planning and review of the protocol and study results.

A. Scientific Review

The study protocol shall receive appropriate scientific review by qualified person(s) who are not part of the investigative team to ensure that the study is designed to address the objectives of the research and that the protocol is written according to Guidelines for Good Epidemiology Practices. The nature and circumstances of this review shall be documented (see section III: Protocol).

The scientific aspects of the completed study shall receive appropriate technical review to ensure that the

abstract, summary, and conclusions are supported by the underlying data, methods, and analyses (see section V: Study Conduct).

B. Ethical Review

The ethical aspects of each study protocol shall be reviewed by an institutional review board or other comparable review procedure.

This review should consider:

1. Obligations to research subjects.

For example, protecting the welfare of study subjects; the need for, and content of, communications and informed consent; protecting privacy; and maintaining confidentiality.

2. Obligations to society.

For example, avoiding conflicts of interest; avoiding partiality; disseminating the study's findings; data sharing; and pursuing responsibilities with due diligence.

3. Obligations to funders and employers.

For example, specifying obligations in contractual form of how research is to be conducted and how it may involve ethical, technical, administrative, or legal responsibilities; presenting methods and alternatives; and protecting privileged information.

4. Obligations to colleagues.

For example, promoting and preserving public confidence in epidemiologic research while not over- or underestimating the methods or results of epidemiologic inquiry; reporting methods and results; and disseminating the study's findings.

C. Administrative Review

The administrative aspects of the study protocol shall receive appropriate review and written approval by sponsors, contractors, and associated third parties to ensure that sufficient resources are available to complete the study in a timely and proper fashion.

Reports shall include a statement that the study was completed in accordance with the protocol, including any approved modifications to the protocol, and in accordance with the GEPs. Any deviations from the GEPs shall be explained and documented (see section VIII: Quality Assurance).

V. Study Conduct

While the study director shall be responsible for the overall research program, the principal investigator shall be responsible for the individual research project, including the day-to-day conduct of the study, interpretation of the study data, and preparation of a final report. These responsibilities extend to all aspects of

the study including periodic reporting of study progress as well as quality assurance. In some situations, the study director and the principal investigator may be the same person.

To ensure the proper conduct of the study, personnel shall adhere to sound research principles and practices established according to the protocol.

A protocol must be approved before the study begins. The study shall be conducted in accordance with the protocol; all deviations from the protocol shall be properly documented and authorized by the principal investigator.

If a decision is made not to complete a research project, the reasons for that decision shall be put in writing, dated, and signed by the responsible party, i.e. the individual who makes the decision to terminate the study.

A. Protection of Human Subjects

Procedures for protecting human subjects shall be followed (see section III(I): Protocol and section IV(B): Review and Approval). Confidential information about study subjects shall be protected using established procedures.

If stipulated by the study protocol and/or required by an institutional review board, each study subject shall be informed about the purpose of the study and any risks associated with participating in the study. Written consent, if required, shall be obtained from each study subject before he/she participates in the study.

Written consent shall include at a minimum:

1. Purpose of the research or study.
2. Name(s), address(es), and phone number(s) of personnel available to answer questions about the research and the rights of study subjects.
3. Expected duration of subject's participation.
4. Eligibility requirements for study participation.
5. Possible benefits to the study subject or others of study results.
6. Statement on the voluntary nature of participation in the study and the right of the study subject to discontinue participation at any time.
7. Statement of confidentiality of records identifying the study subject, including reasonable exceptions to absolute confidentiality, eg, sharing of information with the study subject's personal physician or as required by court order.
8. Description of any foreseeable risks or discomforts to the study subject.
9. Statement of availability of results.

B. Data Collection and Verification

All data collected for the study should be recorded directly, accurately, promptly, and legibly. The individual(s) responsible for the integrity of the data, computerized and hard copy, shall be identified.

All procedures used to verify and promote the quality and integrity of the data shall be outlined in writing (see section VIII: Quality Assurance). An historical file of these procedures shall be maintained, including all revisions and the dates of such revisions. Any changes in data entries shall be documented.

C. Analysis

All data management and statistical analysis programs and packages used in the analyses should be documented. All dated versions used in research shall be kept with accompanying documentation (see section VII: Archiving).

D. Study Report

Completed studies shall be summarized in a final report that accurately and completely presents the study objectives, methods, results, and the principal investigator's interpretation of the findings.

The final report shall include at a minimum:

1. A descriptive title.
2. An abstract.
3. Purpose (objectives) of the research as stated in the protocol.
4. The names, titles, degrees, addresses and affiliations of the study director, principal investigator, and all co-investigators.
5. Name(s) and address(es) of sponsor(s).
6. Dates on which the study was initiated and completed.
7. Introduction with background, purpose, and specific aims of the study.
8. A description of the research methods, including:
 - a. the selection of study subjects and controls,
 - b. the data collection methods used,
 - c. the transformations, calculations, or operations on the data, and
 - d. statistical methods used in data analyses.
9. A description of circumstances that may have affected the quality or integrity of the data (see section VIII: Quality Assurance).
10. A summary and analyses of the data.

Include sufficient tables, graphs, and illustrations to present the pertinent data and to reflect the analyses performed.
11. A statement of the conclusions drawn from the analyses of the data.
12. A discussion of the implication of study results.

Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research.
13. References.
14. A statement describing the location where all source data and the final report are stored. (see section VIII: Archiving).
15. A dated study report review sign-off sheet for the study director, principal investigator, co-investigators, and reviewers and/or auditors (see section IV: Review and Approval and section VIII: Quality Assurance).

VI. Communication

Each organization shall predetermine procedures under which communications of the intent, conduct, results, and interpretations of an epidemiologic study will occur, including what function individuals associated with the research must fulfill. These individuals should include the principal investigator, study director, and/or the sponsor. This procedure may be documented in the form of a company standard operating procedure, in the study protocol, or through contractual agreement.

Government agencies shall be informed of study results in a manner that complies with applicable regulatory requirements.

Scientific peers shall be informed of study results by publication in the scientific literature or presentations at scientific conferences, workshops, or symposia, to the extent possible.

All study subjects shall be informed of the study results and any interpretation of the study findings and conclusions, to the extent possible. Study subjects may be informed in person, through meetings, video tape, letters, newsletters, summary reports, or other appropriate communication. Information about study results shall be provided in language appropriate for the audience.

VII. Archiving

There shall be physically secure archives for the orderly storage and expedient retrieval of all study related material. An index shall be prepared to identify the archived contents, to identify their location, and to identify by name and location any materials that by their general nature are not retained in the study archive.

Access to the archives shall be controlled and limited to authorized personnel only. Special procedures may be necessary to ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected (see section III(I): Protocol).

At a minimum, the study archive should contain, or refer to, the following:

- A. Study protocol and copies of all approved modifications.
- B. A final report of the study.

- C. All source data and, where feasible, specimens. A printed sample of the master computer data file(s) with reference to the location of the machine readable master.

If the data include any employee medical records subject to the Access to Employee Medical Records Regulation (29 CFR 1910.90), the records shall be retained according to the provisions of this rule.

- D. Documentation adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate (see section V(C): Study Conduct).
- E. Copies of computer printouts, including relevant execution code, that form the basis of any tables, graphs, discussions, or interpretations in the final report. Any manually developed calculations shall be documented on a work sheet and similarly retained.
- F. Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits.

Include, for example, questionnaires, name, make and model numbers of relevant measurement instruments, calibration information and procedures.

- G. Original documents for the following research materials shall be included in the archives:

1. Laboratory/research notebooks.
2. Coder modification notebooks.
3. Signed and dated copies of the research protocol and final report.

VIII. Quality Assurance

Written procedures shall be established to ensure the quality of the data used in a study (see section III(J): Protocol and section V: Study Conduct). These procedures shall address data collection and completeness, coding and computer input, storage and retrieval, and data validation and analysis. Any deviations from the GEPs shall be explained and documented in the final report (see section IV(C): Review and Approval).

An individual who is not part of the investigative team should be assigned as a study quality assurance auditor. This individual shall, no less than annually, review study compliance with the written quality assurance procedures. The study quality assurance auditor shall prepare a written summary of the audit. The principal investigator should respond in writing to the audit report, including any remedial actions taken.

Quality assurance activities shall address the preceding sections of these guidelines as well as monitor conformance with established standard operating proce-

dures (SOPs) (see Appendix 1: Standard Operating Procedures).

APPENDICES

Appendix 1: Standard Operating Procedures

Appendix 2: Glossary of Terms Used in the Guidelines for Good Epidemiology Practices

Appendix 3: Suggested References on Occupational Epidemiology Methods

Appendix 1

Standard Operating Procedures

The Guidelines for Good Epidemiology Practices address the conduct of epidemiologic studies rather than the management of epidemiologic research programs. Many of the suggested guideline requirements can be fulfilled by reference to standard operating procedures for the research program.

Standard operating procedures (SOPs) are written, detailed descriptions of routine procedures involved in performing epidemiologic studies. Reproducibility, accuracy, and validity are ensured when SOPs are designed to clearly reflect each facility's research procedures. It should be the responsibility of a designated individual to develop and continuously review and update SOPs pertaining to his area of responsibility. Signatures of approval from the department's managing personnel or appropriate designees should be obtained for all new and updated versions. Significant changes in established SOPs should be maintained, including all revisions and the dates of such revisions. The manual of SOPs should be readily available to all research and administrative personnel.

Standard operating procedures should include:

1. A statement of the purpose of the standard operating procedure.
2. A detailed description of the procedure.
3. The person responsible or the training level required to perform the procedure.
4. The date of issue (effective date).
5. The issue number/revision number.
6. Signature of preparer.
7. Authorizing/reviewing signature of management.

Examples of research program activities for which SOPs could be established include:

1. Procedures for collecting raw data.
2. Procedures for validating the completeness of the study population.
3. Procedures for coding death certificates.
4. Procedures for assessing error rates in data abstraction and coding.

5. Security procedures for ensuring the integrity of the raw data and computer records.
6. Procedures for archive management.
7. Procedures for standard industrial hygiene sampling and analytic methods.
8. Procedures for scientific review.
9. Required composition of scientific review boards.
10. Procedures for data analysis.
11. Procedures for communications.

Appendix 2

Glossary of Terms Used in the Guidelines for Good Epidemiology Practices

The definitions below reflect the use of these terms in the Guidelines for Good Epidemiology Practices. These terms may have additional or different meanings in another context.

Descriptive Studies—a description of the population under study and the occurrence of disease or disease-related phenomena in populations. The latter may be presented as incidence or prevalence rates according to basic group characteristics such as age, sex, race, and/or geographic area.⁶

Epidemiologic Surveillance—periodic scrutiny of a defined population using epidemiologic techniques to detect changes and trends in the distribution of morbidity, mortality, or disease risk factors within that population.

Exploratory Data Analysis—analysis of a data set without a predetermined hypothesis, sometimes referred to as a descriptive study. This can be done with or without tests for statistical significance. Exploratory data analysis can be used to generate hypotheses, to suggest the most appropriate analytical techniques, to set priorities for future research, and to help focus subsequent analyses. A study may be a hybrid design and combine both exploratory data analysis and tests of the null hypothesis.

Hypothesis Testing Study—an analytic study that, through the use of tests of statistical significance, seeks to refute specific predetermined null hypotheses; the process of answering a specific *a priori* question or group of questions. A study may be a hybrid design and combine both exploratory data analysis and tests of the null hypothesis.

Legal Entity—legal existence. An entity, other than a natural person, who has sufficient existence in legal contemplation that it can function legally, be sued or sue, and make decisions through agents as in the law of corporations.

Null Hypothesis—the study question stated in a null fashion so that it can be tested for statistical significance, eg, tested to determine whether the results might occur by chance alone.⁷

Principal Investigator—the research investigator who has direct responsibility for the initiation, conduct, analysis, and interpretation of a specific study or investigation.

Quality Assurance—the overall program that ensures conformance to established performance standards. The quality assurance process encompasses all aspects of the research operation from the protocol to the final report.

Scientific Review—critical evaluation of a scientific study or investigation at any stage of development by peers of the principal investigator.

Standard Operating Procedure (SOP)—any standard method or process for conducting or accomplishing a routine research procedure not unique to a specific study.

Study—epidemiologic research relating to the distribution and determinants of health-related outcomes in specified populations and the application of this research to control of health problems.

Study Director—the research director, manager, or administrator who is responsible for managing the research program and who provides oversight of studies or investigations conducted within the research program.

Appendix 3

Suggested Bibliography on Occupational Epidemiology Methods

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Manuscript Reviewers

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Thomas J. Albin, MA, MS
Thomas J. Armstrong, PhD
Mahmoud A. Ayoub, PhD
Charles E. Becker, MD
Aaron Blair, PhD
Steven N. Blair, PhD
Margit Bleecker, MD, PhD
Gregory G. Bond, PhD, MPH
Pearlie Boyd
Irvin Broder, MD
Stuart M. Brooks, MD
C. Ralph Buncher, ScD
Joseph M. Cannella, MD
Ralph R. Cook, MD
Robert Crapo, MD
Roy L. DeHart, MD
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Thomas Golaszewski, EdD
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W. K. C. Morgan, MD
Lisa Morrow, PhD
Royce Moser, Jr., MD

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Kyle Stenland, PhD
Nancy Sunsham, PhD
Barbara C. Tilley, PhD
Sally W. Vernon, PhD
Donald M. Vickery, MD
Julian A. Waller, PhD
W. Dixie Ward, PhD
Kenneth E. Warner, PhD
Donald E. Wasserman, MSEE, MBA
Roberta F. White, PhD
Myron L. Wolbarsht, PhD
C. Craig Wright, MD