Review of the Department of Labor's Site Exposure Matrix Database

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REVIEW OF THE DEPARTMENT OF LABOR'S SITE EXPOSURE MATRIX DATABASE

Committee on the Review of the Department of Labor's
Site Exposure Matrix (SEM) Database

Board on the Health of Select Populations

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Willing is not enough; we must do."
—Goethe

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Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Donna Cragle, Occupational Exposure and Worker Health Programs, Oak Ridge Associated Universities
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The

review of this report was overseen by **Frank E. Speizer,** Harvard Medical School, and **Mark R. Cullen,** Stanford University. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Preface

The Institute of Medicine (IOM) has a longstanding role in providing guidance to the federal government on improving and maintaining the health and well-being of people who have served the United States, both in the military and on the homefront. Service to our country includes those individuals who were instrumental in developing and manufacturing nuclear weapons before and during the Cold War. The Cold War has long since ended, but its effects remain. Workers who suffer from illnesses as a result of employment in the nuclear weapons industry are still seeking medical care and a means to pay for it.

In response to a request from the Department of Labor (DOL), this study is the product of a concentrated and careful endeavor by this committee to evaluate the scientific rigor of DOL's Site Exposure Matrix (SEM) database. SEM is used in support of the DOL claims process for former workers and contractors of the Department of Energy (DOE), as mandated in the Energy Employees Occupational Illness Compensation Program Act (EEOICPA). Though commenting on the claims process itself was beyond the scope of the committee's work, we believe that any effective compensation program should be based on sound scientific evidence. Therefore, we sought to provide guidance and a framework for DOL to create a better and more transparent system for identifying the most scientifically sound information to be included in SEM and thus improve the claims process. We are honored to have been of service to DOL and to the many men and women who worked at DOE facilities and their families and who helped maintain a secure nation.

The committee appreciates the presentations made by DOL staff (Karoline Anders and Rachel Leiton) and its contractors (Keith Stalnaker and Jay Brown) and by staff of the National Library of Medicine (Florence Chang, Lucie Chen,

and Pertti Hakkinen) in providing information for the study. In addition, the committee would like to thank the many claimants and worker advocates for the presentations and statements they submitted to the committee, particularly Terrie Barrie, Laurence Fuortes, and Deb Jerison.

Finally, I am deeply appreciative of the dedication of the committee members and the IOM staff who assisted them in producing this report. The committee trusts that it will assist not only DOL in its efforts to implement EEOICPA, but also will inform the broader research community.

Mark Utell, *Chair*
Committee on the Review of the Department of Labor's
Site Exposure Matrix (SEM) Database

Summary

Beginning with the development of the atomic bomb during World War II, the United States continued to build nuclear weapons throughout the Cold War. Thousands of people mined and milled uranium, conducted research on nuclear warfare, or worked in nuclear munitions factories around the country from the 1940s through the 1980s. Such work continues today, albeit to a smaller extent. The Department of Energy (DOE) is now responsible for overseeing those sites and facilities, many of which were, and continue to be, run by government contractors.

The materials used at those sites were varied and ranged from the benign to the toxic and highly radioactive. Workers at DOE facilities often did not know the identity of the materials with which they worked and often were unaware of health risks related to their use. In many instances, the work was considered top secret, and employees were cautioned not to reveal any work-related information to family or others. Workers could be exposed to both radioactive and nonradioactive toxic substances for weeks or even years. Consequently, some of the workers have developed health problems and continue to have concerns about potential health effects of their exposures to occupational hazards during their employment in the nuclear weapons industry.

In response to worker concerns, the U.S. Congress in 2000 authorized compensation for DOE workers in the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) (Public Law 106-398, Title XXXVI). Initially, former workers filed compensation claims with their state worker compensation offices, but in 2005 the compensation process was transferred to the Department of Labor (DOL) to expedite the claims process. To receive compensation, workers

must attest that they suffer from a disease that is linked to an exposure at one or more of the sites that are listed by DOL.

DOL uses a database, the Site Exposure Matrix (SEM), as a tool to assist with compensation determinations for DOE contractors who have illnesses related to their work for DOE. SEM was developed to organize, display, and communicate information on the toxic substances and possible health effects associated with them for each DOE site, buildings at the sites, and job processes conducted in those buildings. Originally developed for DOL claims examiners, the database is available to the public, and individuals can submit site-related and toxic substance–related information to it. However, the database has been criticized by claimants and their advocates, particularly regarding the accuracy of its substance–disease links. SEM has also been the subject of a study by the Government Accountability Office, which has evaluated its use in DOL's EEOICPA claims process.

COMMITTEE'S CHARGE AND APPROACH

In response to the concerns expressed by workers and their representatives, DOL asked the Institute of Medicine (IOM) to review the SEM database and its use of a particular database, Haz-Map, as the source of its toxic substance–occupational disease links. Accordingly, this IOM consensus report reflects careful consideration of its charge by the committee, and describes the strengths and shortcomings of both databases (see Box S-1 for the Statement of Task). To complete its task, IOM formed an ad hoc committee of experts in occupational medicine, toxicology, epidemiology, industrial hygiene, public health, and biostatistics to conduct an 18-month study to review the scientific rigor of the SEM database. The committee held two public meetings at which it heard from DOL Division of Energy Employee Occupational Illness Compensation (DEEOIC) representatives, the DOL contractor that developed the SEM database, the developer of the Haz-Map database, DOE worker advocacy groups, and several individual workers. The committee also submitted written questions to DOL to seek clarification of specific issues and received written responses from DEEOIC. The committee's report considers both the strengths and weaknesses of the SEM and the Haz-Map databases, recognizing that the latter was developed first and for a different purpose. The committee then discusses its findings and recommends improvements that could be made in both databases with a focus on enhancing the usability of SEM for both DOL claims examiners and for former DOE workers and their representatives.

BOX S-1
Statement of Task

The Institute of Medicine will convene a panel of experts to review the scientific rigor and organization of the Site Exposure Matrix (SEM) database. The committee's focus will be on the occupational disease links to chemical usage/exposure; the National Institutes of Health's (NIH's)/National Library of Medicine's (NLM's) review process with regard to Haz-Map, and the review process used by Haz-Map developer when including information in the Haz-Map database. Haz-Map is an occupational health database about the health effects of exposures to chemicals and biologicals at work; it links jobs and hazardous tasks with occupational diseases and their symptoms. The committee will identify strengths and weaknesses of the SEM and make recommendations for addressing any weakness. Additionally, the following questions, here described as tasks, will be addressed in the report issued by the committee.

Tasks:

1. What, if any, occupational diseases that might have affected the DOE contractor workforce are missing from SEM?
2. What, if any, links between occupational diseases and toxic substances present at the Department of Energy (DOE) sites are missing from SEM?
3. Is there additional literature (preferably human epidemiological in nature) that might be incorporated into SEM to strengthen or add to the existing links between toxic substances and occupational diseases? Are the existing links sufficiently robust?
4. What, if any, other occupational disease databases might be used to supplement the Haz-Map information in SEM?
5. How scientifically rigorous are the disease links contained in the SEM and Haz-Map?
6. What are the strengths and weaknesses of the NIH/NLM peer review process with regard to Haz-Map? How might this process be improved?
7. Can any known (epidemiologically significant) synergistic effects between chemicals/chemicals or chemicals/radiation be placed in SEM? If so, what are the sources of these links and are they occupational in nature?
8. What consistent process or approach could be used to consider a disease or cancer established when studies are inconclusive, inconsistent, or conflicted in some way?

HAZ-MAP

Overview

The Haz-Map database contains health effects information on approximately 7,000 hazardous agents (as of December 2012) found in the workplace. The database was "designed for health and safety professionals and for consumers seeking information about the adverse effects of workplace exposures to chemical and biological agents" (http://hazmap.nlm.nih.gov/about-us; accessed December 19, 2012). It was not designed for compensation purposes. The two major types of information in Haz-Map are lists of hazardous agents (also referred to as toxic substances); hazardous jobs, industries, processes, and job tasks (the industrial hygiene perspective); and lists of occupational diseases and symptoms and physical findings (signs) (the epidemiologic perspective). Information from numerous textbooks, journal articles, and electronic databases is cataloged and summarized to create the database and to establish causal links between hazardous agents and occupational diseases. Although Haz-Map was initially developed and maintained privately, since 2002 the National Library of Medicine (NLM) has published Haz-Map on its website (http://hazmap.nlm.nih.gov), where it is periodically updated for content with revisions provided by the Haz-Map developer.

The committee appreciates the enormous amount of work that has gone into the development and maintenance of Haz-Map to assist health providers in identifying and possibly preventing occupational diseases, but it identified several limitations of the database and focused on its use for SEM in the context of the EEOICPA compensation system. The limitations include the lack of transparency in data sources used for determining each toxic substance–occupational disease link and in the criteria for establishing the links, particularly in connection with noncancer end points; the lack of a clear weight-of-evidence approach; the lack of peer review; the overreliance on textbooks such that information may be neither comprehensive nor up to date; and lack of clarity on what toxic substances and fields have been updated by the Haz-Map developer.

Findings

The DEEOIC's interpretation of the statutorily imposed causative burden in the claims adjudication process is not part of the committee's charge. However, the committee felt that it was important to discuss how the substance–disease links in SEM, by relying on Haz-Map's criteria for establishing links, may affect the interpretation of causation.

The use of Haz-Map's disease links for EEOICP workers' compensation claims differs substantially from its original intent. The database uses strict criteria for identifying toxic substances that cause cancer; that is, they must be categorized as in Group 1 by the International Agency for Research on Cancer

(IARC). But it has ambiguous criteria for identifying toxic substances that cause diseases other than cancer. EEOICPA states that an illness or a disease may be compensable if "it is at least as likely as not that exposure to a toxic substance at a DOE facility was a significant factor in aggravating, contributing to, or causing the illness." However, the "Diseases" field of Haz-Map, which contains the toxic substance–occupational diseases links used in SEM, does not capture information on exposures that aggravate or contribute to disease; rather, it contains only links between exposure and disease that are designated as causative by its developer.

SITE EXPOSURE MATRIX

Overview

SEM is a key resource for the EEOICPA Part E compensation program. It imports information from the Haz-Map "Diseases" field to provide toxic substance–occupational disease links for the SEM "Specific Health Effects" field. SEM was designed to function as a repository of information about toxic substances present at facilities covered under EEOICPA Part E that would "assist claimants and claims examiners by putting toxic substances present at DOE sites and scientifically established illness and disease links information in one convenient location." The claims examiner manual states that "the SEM is not used to establish or deny causation by itself, but is used as a tool to assist in the evaluation of causation in light of the evidence as a whole." DOL emphasizes that SEM is only one of the tools used by claims examiners to assist in determining eligibility for compensation under Part E.

As of December 2012, 13,697 toxic substances and 14 DOE facilities are listed in SEM. The database contains exposure information about a DOE facility, including uranium mining and milling sites and ore-buying stations, toxic substance information, and a record history. It should be emphasized that SEM is site-driven and that a user must first specify a DOE facility of interest to access information on toxic substances.

Findings

The committee noted several strengths of SEM, including its development with consultation from DOE experts and former workers and its attempt to be comprehensive in listing toxic substances found at DOE sites and their associated diseases. However, the committee also identified major weaknesses: difficulties in accessing information; lack of detailed exposure information; and poor handling of complex exposures, including exposures to mixtures, lack of clarity for why certain links are missing, incomplete or inconsistent exposure profiles for particular locations and jobs, disregard of epidemiologic studies of DOE workers, and the sole use of Haz-Map for toxic substance–occupational disease links.

The committee conducted an exercise to illustrate where toxic substance–disease links might be missing in SEM and to identify reasons for the omissions. Overall, the committee found that links may be missing in SEM for several reasons, including ambiguous criteria for establishing the links in Haz-Map (the source of the SEM links); lack of consistency between the Haz-Map "Diseases" field and the SEM "Specific Health Effects" field for some substances; an inability to deal with complex exposures, such as exposures to mixtures; and delays in updating links in Haz-Map and thus in SEM.

RECOMMENDATIONS

The committee found that focusing on information in only one SEM field, "Specific Health Effects," as imported from the Haz-Map "Diseases" field, without consideration of the EEOICPA claims process was difficult because its review lacked context. Furthermore, the "Specific Health Effects" field did not permit consideration of many aspects of occupational health, including level of exposure (concentration, frequency, and duration), strength of association, and exposure to more than one chemical at a time. Nevertheless, the committee came to three overarching recommendations for improving the toxic substance–disease links in SEM:

1. Add supplemental information sources to the health effects information imported from Haz-Map.
2. Improve the structure and function of SEM, including the addition of available exposure information.
3. Use an external advisory panel to review the health effects information in SEM.

Although those three recommendations focus on improving SEM, recommendations 1 and 3 and portions of recommendation 2 are also applicable to Haz-Map. The committee believes that establishing a formal oversight and review process for the Haz-Map database and using a weight-of-evidence approach are critical for both maintaining and expanding the Haz-Map database and for its use in SEM. Expansion of the information used in Haz-Map and inclusion of citations for all the information in each of its fields would greatly enhance its utility not only for SEM but also for other users. Peer review of the database would also increase public confidence in its accuracy and comprehensiveness and help ensure that it contains the most current information available, irrespective of its use for SEM.

Each of these recommendations is discussed in greater detail in the following sections.

RECOMMENDATION 1: Use supplemental information sources for the Site Exposure Matrix database.

The committee found that supplemental data sources, in addition to the occupational–disease links imported from Haz-Map, are necessary to provide a more comprehensive picture of the adverse effects that may be associated with exposure to the toxic substances found at DOE sites. The committee suggests that two types of information might be used to supplement the data field imported from Haz-Map: bibliographic information, such as that in TOXLINE, and evaluative information, such as that in the Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) database and the National Toxicology Program (NTP) substance–specific reports.

Use of bibliographic databases, such as TOXLINE and PubMed, would require the use of trained and knowledgeable staff to interpret the information from the documents cited in the databases and draw conclusions regarding links between toxic substances and possible occupational diseases. The committee suggests that those databases be searched periodically, but recognizes that incorporating information from them will be time-consuming and will require expert review.

Many toxic substances have already been evaluated by authoritative organizations, and the committee encourages use of the evaluations for SEM. The committee acknowledges that some sources of evaluative information are already used to make the toxic substance–disease links in Haz-Map, as listed in the Haz-Map reference list, but their use does not appear to be systematic or comprehensive, and in some cases, including NTP toxicology reports, they are not used at all. The advantage of including evaluative databases and documents is that they typically use a weight-of-evidence approach to draw conclusions about the strength of an association between exposure to a toxic substance and a disease. They also typically have a defined method, describe the evidence base of their conclusions, and, for the most part, are periodically updated with new evidence and documentation of whatever changes have been made in the conclusions. Among the databases and documents that evaluate health effects of individual toxic substances or groups of related chemicals are the EPA's IRIS database and background documents, the Agency for Toxic Substances and Disease Registry (ATSDR) toxicologic profiles, NTP toxicology studies, the background document for the preamble to the Occupational Safety and Health Administration's permissible exposure limits, IARC monographs, the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (Cal/EPA OEHHA) toxicity-criteria database and staff reports, documentation for the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (these are not publicly available but must be purchased), National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit documentation, and the NIOSH *Pocket Guide to Chemical Hazards*. For virtually all those information sources, conclusions on the toxicity of a substance

are drawn by a group of experts on the basis of established criteria and a weight-of-evidence approach.

RECOMMENDATION 2: Improve the structure and function of the Site Exposure Matrix database.

The committee has a number of specific suggestions for the SEM database that it believes will help users (both claims examiners and the public) to navigate the database and retrieve information more effectively. The committee has tried to be realistic about modifying the SEM and to limit the number of its suggested changes. However, it believes that such changes will greatly improve both the usability of the database for claims examiners and the public and the strength of associations between exposure to toxic substances and possible diseases.

First, the committee believes that the current links between toxic substances and occupational diseases must include appropriate bibliographic references in both SEM and Haz-Map. The committee spent considerable time in attempting to determine the evidence used to make the links in Haz-Map and thus in SEM and in many cases was unable to do so. The Haz-Map "Diseases" field does not reference the evidence base (or citations) used to determine a specific substance–disease link. Such information should be provided. If appropriate citations to the evidence were included in Haz-Map and in the SEM, the transparency of the database would be improved, and the strength of links could be assessed more easily.

Second, the committee recommends expanding SEM search capabilities. For example, better search capabilities would assist users in identifying toxic substances and subsequently the diseases associated with specific job descriptions (such as for a plumber) for more than one site. Currently, this must be done site by site.

Third, although the committee was asked to comment on the National Institutes of Health (NIH)–NLM review process for Haz-Map and on the Haz-Map developer's review process, the committee notes that several levels of review should be used for both Haz-Map and SEM. The peer review process is discussed in connection with Recommendation 3 below, but a quality-control review of both databases is critical for ensuring their accuracy. The committee suggests that DOL or its contractor conduct a quality control review of all records to ensure that the data abstracted from each information source are correctly cited, have no typographic errors, and are complete (that is, that no important information has been omitted).

RECOMMENDATION 3: Establish an expert advisory panel for the Site Exposure Matrix database.

To accomplish the two major recommendations given above, the committee recommends that DOL establish an expert advisory panel. This is not the first

time that such a panel has been suggested and there is a precedent for such a panel as required in Part B of EEOICPA. Furthermore, the proposed EEOICPA Amendment Act of 2011(H.R. 1030) would have required the President to establish an Advisory Board on Toxic Substances and Worker Health to review and approve the SEM database.

An expert advisory panel could perform several important functions with regard to the SEM. This IOM committee recommends that the expert advisory panel be broad based, external to DOL and its current SEM contractor, and include a variety of expertise such as epidemiology, occupational medicine, toxicology, and industrial hygiene. The committee also recommends that the advisory panel include representation of the claimants and their advocacy organizations.

The expert advisory panel would have several immediate tasks:

- Establish the criteria for the evidence base for causal links between exposure to a toxic substance and an occupational disease; criteria might be expanded to include a category of "evidence of no association" as is used by IOM and IARC.
- Determine the information sources that might be reviewed to identify information on possible links.
- Develop a worksheet or other documentation to capture the evidence taken from each information source, including Haz-Map.
- Oversee revisions of SEM to add appropriate fields for capturing supplemental information (such as, chemical interactions, route of exposure, and IARC 2A designations), supplemental information sources (such as NTP, ATSDR toxicological profiles, and IRIS), and update information (such as the date of the last revision of the record and the fields revised).

The expert advisory panel would also have several ongoing responsibilities in support of EEOICPA, Part E:

- Peer review of all new links in SEM that are based on both Haz-Map and the supplemental information described earlier. This might include determining whether the appropriate references are screened and the data are accurately cited.
- Assessment of occupational diseases that might result from complex exposures.
- Identification of potential new links and tracking them for possible future inclusion in SEM, including those suggested by external sources.
- As time permits, review of existing causal links in SEM that are based solely on Haz-Map.
- Periodic review of a sample of the toxic substance–disease links from both accepted and rejected claims to determine whether SEM links are actually assisting in the claims process and, if not, what improvements

could be made in the toxic substance–disease links or what other information might be added to the SEM that would help claimants and claims examiners, such as available monitoring information, disease terminology, or results of cohort studies of DOE workers.

The committee recognizes that peer review is not a simple task, but it is critical if the SEM is to provide both DOL claims examiners and claimants with comprehensive, accurate, and understandable information. The committee also acknowledges that several approaches may be used to institute a peer review process for SEM, all of which have advantages and disadvantages. These approaches might include having the expert advisory panel review contractor assessments of the evidence available on toxic substance, having the expert advisory panel review the available evidence on a substance that was gathered by a contractor, or having the available evidence assessed by an internal expert advisory panel and then having the assessments reviewed by external experts. A major feature of each option is that all information and actions are documented so that the evidence base used to make decisions about the links between toxic substances and occupational diseases is transparent.

In summary, the committee recognizes the pressing need for SEM and the urgency with which it was developed and understands its inherent dynamic nature and the need to be able to adapt to updated and new information. However, as the EEOICPA claims process has evolved and new claims have continued to be submitted to DOL, the need for peer review of SEM (as well as Haz-Map) has increased. The committee believes that implementation of the recommendations in this report will make it possible for the DOL claims process to be improved for both claims examiners and claimants.

STATEMENT OF TASK QUESTIONS AND RESPONSES

In addition to offering recommendations to improve SEM, the committee provides here concise responses to the eight questions in its Statement of Task.

1. **What, if any, occupational diseases that might have affected the DOE contractor workforce are missing from SEM?**
   The committee examined the list of diseases in SEM and found that some diseases such as those of the cardiovascular system and ovarian cancer are not listed in it. Occupational diseases are listed in SEM only if they are associated with exposure to a toxic substance, so diseases associated with a particular job or worker population may not be included. Such organizations as IARC also look at associations between specific occupations (including painters and welders) and diseases in those workers without reference to exposure to specific toxic substances. DOL should consider those types of associations to identify other occu-

pational diseases that may affect the DOE contractor workforce. Furthermore, epidemiology studies conducted on DOE worker cohorts are not included in SEM. Given the opportunity to assess effects in the population of interest, results of those studies should be carefully considered by DOL and the recommended expert advisory panel.

2. **What, if any, links between occupational diseases and toxic substances present at DOE sites are missing from SEM?**
The committee notes that some links between toxic substances found at DOE sites and diseases associated with them are not in SEM, such as the link between asbestos and ovarian cancer. The committee notes, however, that given the lack of exposure information in SEM—including period of use and intensity and frequency of exposure—it is difficult to ascertain whether occupational exposures were acute or chronic and were sufficient to result in chronic occupational disease. The committee did not conduct a systematic review of all the substance–disease links in SEM, which includes more than 13,000 substances and more than 120 occupational diseases.

3. **Is there additional literature (preferably human epidemiological in nature) that might be incorporated into SEM to strengthen or add to the existing links between toxic substances and occupational diseases? Are the existing links sufficiently robust?**
Because SEM incorporates toxic substance–occupational disease links only from Haz-Map, any information missing from Haz-Map is necessarily missing from SEM. Because Haz-Map does not adequately reference the evidence used to establish each toxic substance–disease link (except for cancer), the committee was unable to determine what additional literature might make the Haz-Map links more robust. The committee strongly recommends that evidence used to establish the Haz-Map links be clearly referenced in the Haz-Map "Diseases" field. Furthermore, the committee has commented on the information sources used for Haz-Map (see Chapter 2) and on the use of additional epidemiologic information in SEM (see Chapter 3), particularly the use of DOE worker cohort studies. Better and more comprehensive use of the existing data sources, such as IARC and ATSDR, and new ones—such as Cal/EPA OEHHA background documents, NTP, and IRIS—would substantially improve the robustness of the links in both Haz-Map and SEM. The recommended expert advisory panel could provide advice on the best way to incorporate the epidemiologic studies conducted in DOE worker populations; the exposures of these workers are directly relevant to the claimant populations.

4. **What, if any, other occupational disease databases might be used to supplement the Haz-Map information in SEM?**
   Haz-Map is used for SEM because it provides causal toxic substance–occupational disease links in an easily captured field. Haz-Map is a unique database, and the committee was unable to identify any other databases that explicitly link occupational exposures to toxic substances to occupational diseases. However, the committee does not believe that lack of such databases means that other sources of information might not be used to supplement either Haz-Map or SEM. The committee emphasizes that databases alone, whether occupational or other, are not sufficient resources to supplement Haz-Map information in SEM, and it recommends that such documents as ATSDR toxicological profiles, NTP reports, and EPA background documents be reviewed by the proposed expert advisory panel. Many of those documents contain information on health effects seen in worker populations that have been exposed to the substances of interest. Another database that might be used is EPA's IRIS, which has clear documentation of the evidence on which EPA's conclusions are based.

5. **How scientifically rigorous are the disease links contained in SEM and Haz-Map?**
   The toxic substance–disease links in Haz-Map, and thus in the SEM, for cancer are scientifically rigorous inasmuch as they are based solely on IARC's determination that there is sufficient evidence that a given substance is carcinogenic in humans (Group 1). However, for noncancer health effects in Haz-Map and SEM, it is difficult to determine the evidence base for some of the links. Therefore, the committee is unable to state with certainty how rigorous the links are and finds that the rigor of links varies. In some cases disease links are based on one case report and in others on a substantial body of evidence. Furthermore, the links for mixtures are not robust.

6. **What are the strengths and weaknesses of the NIH/NLM peer review process with regard to Haz-Map? How might this process be improved?**
   There is no NIH or NLM peer review process for Haz-Map. The committee finds that that is a critical weakness for the database. NLM indicated that its staff copyedits the toxic substance profiles for Haz-Map and makes the links to other NLM databases, such as the Hazardous Substances Data Bank (HSDB), but NLM does not conduct any peer review of the substance–disease links determined by the Haz-Map developer. NLM also does not conduct peer review of any of the publications listed in PubMed; that is the responsibility of each journal. NLM does

not conduct peer reviews of any external publications, even manuscripts. It is merely a platform for Haz-Map, and has little involvement in content. NLM does facilitate the peer review process for the HSDB, a database cited in Haz-Map, using an external group of experts. There are several options for a peer review process for both Haz-Map and SEM.

7. **Can any known (epidemiologically significant) synergistic effects between chemicals/chemicals or chemicals/radiation be placed in SEM? If so, what are the sources of these links and are they occupational in nature?**
   Research on synergism underscores that this type of chemical–chemical interaction is a valid scientific phenomenon. Such interactions, some of which are occupational, could be flagged in SEM for evaluation case by case. ATSDR and EPA conduct health assessments of chemical interactions, and these could be included in SEM in a new field as supplemental information. The evidence base on chemical–radiation interactions is less robust, especially in humans. However, as more information becomes available, the proposed expert advisory panel could revisit this topic and determine whether such interactions should be flagged in SEM.

8. **What consistent process or approach could be used to consider a disease or cancer established when studies are inconclusive, inconsistent, or conflicted in some way?**
   As discussed above, the committee strongly recommends that an expert advisory panel be established to review the evidence on any potential toxic substance–disease link. Such a panel, using a weight-of-evidence approach, could determine how to assess inconclusive, inconsistent, or conflicted studies for purposes of evaluating whether there is a causal link. The panel may wish to develop its own criteria for weighing evidence or use criteria established by other authoritative organizations, such as IARC, NTP, and IOM.

1

Introduction

Atomic energy and nuclear weapons research and development in the United States began around 1939 and continued during World War II and throughout the Cold War. This effort was undertaken initially by the U.S. Corps of Engineers Manhattan Engineer District, more commonly referred to as the Manhattan Project. It was this effort that was ultimately responsible for the development of the atomic weapons used to help end World War II in 1945. After the war, the United States continued a massive effort to research, produce, and test nuclear weapons. The result was a large scale nuclear weapons industry. This effort encompassed a broad array of activities, including uranium mining, milling, and refining; nuclear reactor production and maintenance; chemical processing, and metal machining. Furthermore, maintenance facilities, laboratories, and testing sites were necessary to support this effort, often managed by contractors to the federal government (DOE, 1997).

At the peak of the Cold War, nearly 600,000 workers throughout the country were involved in the research and production of nuclear weapons (Silver, 2005). The workforce consisted of employees of the Department of Energy (DOE) or its predecessor agencies and various contractors who owned and operated mines and facilities or provided other goods and services in support of DOE's nuclear weapons programs. With the dissolution of the Soviet Union in 1991 and the end of the Cold War, U.S. production of nuclear weapons was significantly reduced. The United States began to turn its focus from production and maintenance to addressing many issues related to the storage and decommissioning of its nuclear arms inventory and associated material. DOE efforts shifted to the remediation of waste sites, and the storage and destruction of nuclear warheads. Today many facilities remain active in research, storage, and management of radioactive

materials, uranium production, and weapons assembly and disassembly (DOL, 2010a; GAO, 2010).

During the Cold War, research indicated that workers in the atomic weapons production process may have long-term health effects as a result of their employments. In the early years, some workers may not have been aware of potential health risks related to their jobs, nor did they necessarily know the identity of the materials with which they worked. Workers were often exposed to both radioactive and nonradioactive toxic substances.[1] In many instances, the work was considered top secret and workers were cautioned not to reveal any work-related information to family members or others. As these workers experienced adverse health effects, they began to express their concerns that many of their illnesses resulted from their exposures to occupational hazards during their work at DOE facilities (DOL, 2010a; GAO, 2010). In 2000, in response to growing health concerns among former DOE workers, Congress passed the Energy Employees Occupational Illness Compensation Program Act (Public Law 106-398, Title XXXVI), referred to as EEOICPA.

ENERGY EMPLOYEES OCCUPATIONAL ILLNESS COMPENSATION PROGRAM ACT

In 1996, following congressional directives, DOE established the Former Worker Medical Screening Program (FWP) to provide medical screening for and health monitoring of former DOE workers (FY 1993 Defense Authorization Act [Public Law 102-484]). The program was to assist workers with determining whether they had health issues related to their prior work with DOE. The program included both site- and population-specific medical screenings (DOE, 2012).

The FWP and former workers also garnered support for a federal compensation program to address the workers' growing treatment costs and disability resulting from their employment. The DOE assistant secretary for environment, safety and health, along with local leaders and often Congressional representatives, heard testimony from former workers or their survivors about their work and the illnesses that had subsequently befallen many of them or their coworkers. These workers, many of whom had previously been reluctant to share their experiences and illnesses with anyone, motivated Congress in 2000 to pass EEOICPA to provide compensation and medical coverage to former DOE employees, contractors, and subcontractors (Executive Order 13179—Providing Compensation to America's Nuclear Weapons Workers) (DOE, 2011). EEOICPA established two worker compensation programs: Part B and Part D. Part B compensates

[1]The committee uses the term *toxic substance* to refer to any hazardous agent, including chemicals and biologics, that has the potential to cause adverse health effects in an organism. In this report, the terms toxic substance and *hazardous agent* are used interchangeably, as are the terms *illness*, *disease*, and *health effects* as is done in the Haz-Map and SEM databases.

DOE workers who are suffering from adverse health effects as a result of their exposures to beryllium, ionizing radiation, and silica during the course of their nuclear weapons-related employment. Part D authorized DOE to enter into agreements with states to assist DOE contractor employees in filing state workers' compensation claims for various illnesses related to their work at DOE facilities.

Since that time, claimants and advocates have raised many concerns about the inconsistent administration and application of EEOICPA Part D by the individual states. In 2004, Congress directed the Government Accountability Office (GAO) to investigate these concerns. The GAO report found that the DOE got off to a slow start in processing Part D claims and faced a large backlog of more than 25,000 cases (GAO, 2004). It recommended a dramatic restructuring of the program, including transferring responsibility of the administration of the program to the Department of Labor (DOL). In response, on October 28, 2004, Congress passed an amendment to EEOICPA, which replaced Part D with a new program called Part E. All claims previously filed under the Part D program were transferred to the Division of Energy Employees Occupational Illness Compensation (DEEOIC), within the DOL Employment and Standards Administration's Office of Workers' Compensation Programs (OWCP). DEEOIC would now determine and administer the Part E compensation program. DOE transferred the backlog of Part D cases to DOL for consideration under EEOICPA Part E (Personal communication, Shelby Hallmark, DOL, May 21, 2008). The following section provides a brief overview of both Part B and Part E of EEOICPA.

Part B

Part B of EEOICPA provides compensation of up to $150,000 to DOE employees and eligible survivors, and $50,000 to uranium workers covered by the Radiation Exposure Compensation Act (RECA) (Table 1-1), as well as medical benefits for accepted conditions (Table 1-2). Part B covers three categories of employers: atomic weapons employers, defined as "an entity, other than the

TABLE 1-1 Employment Covered by EEOICPA Part B and Part E

Types of Covered Facilities	Part B	Part E
DOE facilities:		
DOE employees	Yes	No
DOE contractors and subcontractors	Yes	Yes
Atomic weapons employers	Yes	No
Beryllium vendors	Yes	No
RECA Section 5 facilities	Yes	Yes

SOURCE: Adapted from Anders, 2012.

TABLE 1-2 Illnesses Covered by the EEOICPA Part B and Part E

Part B	Part E
Radiogenic cancers	All of the covered illnesses in Part B
Chronic beryllium disease and chronic silicosis as defined in EEOICPA	
Beryllium sensitivity and RECA (Section 5) illnesses	+ Any illnesses resulting from exposure to toxic substances

SOURCE: Adapted from Anders, 2012.

United States, that processed or produced, for use by the United States, material that emitted radiation and was used in the production of an atomic weapon, excluding uranium mining and milling" (42 U.S.C. § 7384l); the DOE; and beryllium vendors, defined as processors or producers of beryllium. RECA, passed in 1990 and expanded in 2000, provides monetary compensation to individuals who contracted certain cancers or other specific diseases following exposure to radiation by way of habitation or work proximity to nuclear weapons testing sites and uranium nuclear weapons production sites (42 U.S.C. § 2210). Part B pertains to specific illnesses and medical conditions caused by exposure to radiation, beryllium, and silica. As of November 2012, $4.5 billion in total compensation has been paid to Part B claimants (DOL, 2012a).

The causation standard for Part B states that cancer, for example, is compensable if it is "at least as likely as not" to have been caused by exposure to ionizing radiation during the period of employment at the covered facility using the "upper 99 percent confidence interval of the probability of causation" (42 U.S.C. § 7384l; Anders, 2012). The "at least as likely as not" probability for cancer is determined by DOL from the dose reconstructions performed by the National Institute for Occupational Safety and Health (NIOSH). DOL has also established Special Exposure Cohort classes, whose members can be administratively approved and given a presumption of causation if they meet the employment requirements and have a diagnosis of any one of 22 specified cancers (Anders, 2012).

Part E

Part E of EEOICPA provides medical coverage and compensation of up to $250,000 for DOE contractors and subcontractors or their eligible survivors and workers also covered by RECA for illnesses resulting from exposure to toxic substances at DOE facilities. The amount of benefits paid up to the $250,000 maximum is based on the level of impairment or years of qualifying wage loss related to the covered illness. Part E covers all illnesses stipulated in Part B, but also includes any illness resulting from exposure to toxic substances present at DOE facilities. Part E defines a toxic substance as "any material that has the potential to

cause illness or death because of its radioactive, chemical, or biological nature." It is possible to receive compensation under both Part B and E of the program; however the maximum aggregated benefit is $400,000 plus medical benefits for accepted conditions. As of November 2012, $2.7 billion in total compensation had been paid to Part E claimants and total compensation and medical bills for both Part B and Part E claims exceeded $8.6 billion (DOL, 2012a).

For Part E, the causation standard is "it is at least as likely as not that exposure to a toxic substance at a Department of Energy facility was a significant factor in aggravating, contributing to, or causing the illness; and it is at least as likely as not that the exposure to such toxic substance was related to employment at a Department of Energy facility" (Public Law 108-375 § 3161). In its administration of Part E, DOL recognized that claims examiners needed a tool to provide information on covered sites and the toxic substances that may have been used at those sites. DOL created the Site Exposure Matrix (SEM) database to organize toxic substance information for all facilities covered by Part E and to give DOL claims examiners easy access to this information (DOL, 2010b). Claimants and their family members, as well as worker advocates, had little information about what toxic substances may have been present in DOE facilities in which they worked, although they bore the burden of proof in the claims process. In response to claimants concerns about the information in SEM, it was eventually made available to the public. In addition to SEM, claims examiners may also consult with a District Medical Consultant to assist in evaluating the medical evidence for a claimant's illness (DOL, 2012b).

SITE EXPOSURE MATRIX DATABASE

The SEM database was designed to function as a repository of information about toxic substances present at facilities covered by Part E to "assist claimants and claims examiners by putting toxic substances present at DOE sites and scientifically established illness and disease links information in one convenient location" (DOL, 2012c). According to the DOL claims examiner manual, SEM details possible toxic substances that may have been present at a DOE facility, and describes the relationship between a specific toxic substance and a covered illness (DOL, 2012b). The manual states that "the SEM is not used to establish or deny causation by itself, but is used as a tool to assist in the evaluation of causation in light of the evidence as a whole" (DOL, 2012b). DOL procedures and regulations indicate that SEM is only one of many tools, such as occupational history and medical records, used by claims examiners to evaluate the evidence as a whole to determine the existence of a causal link between employment at a DOE facility, exposure to a toxic substance, and a resultant illness arising from such exposure. As of October 2012, the database consists of information on more than 13,000 toxic substances that are or have been used at covered sites,

and health effect information, if available from the Haz-Map database, which is described briefly below and in detail elsewhere in this report.

SEM contains information in profiles for each DOE site. These contain information on the toxic substances that may have been present, organized by facility, area, building, process, labor category, and incidents. Information on toxic substances includes chemical identification, physical properties, and specific health effects, as well as references and a record history. The database may be queried and filtered based on these fields to help claims examiners and claimants determine potential exposures that may have caused a diagnosed disease in an exposed worker, based on the individual's work history. All links between a toxic substance and possible occupational disease are imported solely from the Haz-Map database that is published by the National Library of Medicine (NLM). This database lists more than 7,000 toxic substances and their potential health effects.

Although the DOE and DOL have made efforts to streamline and enhance the EEOICP claims process, including the development and use of the SEM, claimants continue to have concerns about the links between the toxic substances that are included in SEM and their illnesses. These concerns have prompted investigative reports in the popular press (particularly the *Rocky Mountain News* in Denver, Colorado), congressional inquiries, a GAO report, and several reports on the EEOICP claims process from the DOL Ombudsman's office. It is this series of reports and recommendations that prompted the DOL to look for an assessment of SEM.

COMMITTEE'S CHARGE

To address the scientific issues highlighted in the GAO report, as well as concerns from advocacy groups and claimants, the DOL DEEOIC approached the Institute of Medicine (IOM) in June 2010 to conduct a study of the scientific rigor of the causal relationships between exposure to toxic substances and occupational diseases cited in SEM. IOM was requested to "provide independent guidance on the scientific and technical information used to comprise SEM and to make recommendations on ways in which the SEM database can be improved."

To complete its task, the IOM formed an ad hoc committee of experts from a range of disciplines—including occupational medicine, toxicology, epidemiology, industrial hygiene, public health, and biostatistics—to conduct an 18-month study to review the scientific rigor of the SEM database. The committee was asked to address the issues and questions specified in Box 1-1.

COMMITTEE'S APPROACH

Over the course of the 18-month study, the committee held five meetings. Two of the meetings were open to the public and provided the committee the opportunity to hear from DOL, its contractors, and the public (see Appendix C).

BOX 1-1
Statement of Task

The Institute of Medicine will convene a panel of experts to review the scientific rigor and organization of the Site Exposure Matrix (SEM) database. The committee's focus will be on the occupational disease links to chemical usage/exposure; the National Institutes of Health's (NIH's)/National Library of Medicine's (NLM's) review process with regard to Haz-Map, and the review process used by Haz-Map developer when including information in the Haz-Map database. Haz-Map is an occupational health database about the health effects of exposures to chemicals and biologicals at work; it links jobs and hazardous tasks with occupational diseases and their symptoms. The committee will identify strengths and weaknesses of the SEM and make recommendations for addressing any weakness. Additionally, the following questions, here described as tasks, will be addressed in the report issued by the committee.

Tasks:

1. What, if any, occupational diseases that might have affected the DOE contractor workforce are missing from SEM?
2. What, if any, links between occupational diseases and toxic substances present at the Department of Energy (DOE) sites are missing from SEM?
3. Is there additional literature (preferably human epidemiological in nature) that might be incorporated into SEM to strengthen or add to the existing links between toxic substances and occupational diseases? Are the existing links sufficiently robust?
4. What, if any, other occupational disease databases might be used to supplement the Haz-Map information in SEM?
5. How scientifically rigorous are the disease links contained in the SEM and Haz-Map?
6. What are the strengths and weaknesses of the NIH/NLM peer review process with regard to Haz-Map? How might this process be improved?
7. Can any known (epidemiologically significant) synergistic effects between chemicals/chemicals or chemicals/radiation be placed in SEM? If so, what are the sources of these links and are they occupational in nature?
8. What consistent process or approach could be used to consider a disease or cancer established when studies are inconclusive, inconsistent, or conflicted in some way?

At its first meeting, the committee heard presentations on the SEM database from DEEOIC, the DOL SEM contractor, and the Haz-Map database developer (who receives money from DOL through its SEM contractor for research on toxic substances of interest to DOL) (Stalnaker, 2012). In addition, the committee heard from EEOICP claimants and their advocates regarding their concerns about SEM. The committee also submitted written questions to DOL about the content and functionality of SEM and Haz-Map and their role in the EEOICP compensation process. DOL and its contractors, including the Haz-Map developer, provided written responses to these questions. The committee also received written comments and materials from claimants and their advocates.[2] Committee members spent many hours searching the Haz-Map database (http://hazmap.nlm.nih.gov), the Haz-Map website (http://www.haz-map.com) that provides background information on the database, and the SEM database (http://www.sem.dol.gov).

Throughout the course of this study, the committee kept in mind that the benefits provided by EEOICPA have a real impact on current and former DOE workers, contractors, and their families. It recognizes that any improvements to the program, including SEM, are likely to have tangible effects on those beneficiaries. During its open sessions, the committee was informed about EEOICPA, its compensation structure, and the claims adjudication process to better understand SEM in context. However, the committee was not tasked with examining or evaluating the claims adjudication process nor was it asked to comment on other aspects of SEM including the site-specific information. Therefore, the committee did not address issues of compensation; the DEEOIC claims processes, or the training of DEEOIC staff. While these are important issues for developing and maintaining an efficient and fair compensation program, they were outside of the committee's scope. Furthermore, the committee did not evaluate either the administration of Part B or the technical or scientific merit of NIOSH's process for radiation dose reconstruction.

Most importantly, with more than 13,000 toxic substance profiles in SEM, the committee did not conduct an exhaustive or comprehensive evaluation of every toxic substance or potential health outcome that may be associated with exposures at an EEOICPA-covered facility. Rather, it sought to give advice on how to improve the substance–disease links contained in the SEM and to provide guidance for a better and more scientifically sound decision-making process using representative examples. The committee did not review the SEM database structure, as that was considered to be proprietary by DOL, but it did comment

[2]All information submitted to the committee, including responses to the committee's questions can be accessed online in the public access file for this report. For information on accessing the public access file, visit http://www8.nationalacademies.org/cp/projectview.aspx?key=49417. The written responses to the committee's questions from the Department of Labor and its contractors may also be found at http://www.iom.edu/Activities/PublicHealth/SEMDatabaseReview/2012-MAR-16.aspx.

on the functionality of SEM insofar as these factors were relevant to the committee's review of its content.

During the course of the study, the committee realized that information in both Haz-Map and SEM was periodically updated and, in the case of Haz-Map, reformatted. The committee emphasizes that it reviewed databases that were not static, but were continually evolving.

ORGANIZATION OF THE REPORT

The committee's examination of SEM and evaluation of its scientific rigor required considerations at the intersection of diverse fields, including environmental and occupational health, toxicology, epidemiology, and industrial hygiene. The committee's specific charge was to examine the scientific rigor and organization of the database and it was tasked with evaluating the completeness and validity of links between the toxic substances listed and their potential health effects.

The following chapters provide some brief, fundamental background on these topics as a basis for the committee's discussions and recommendations. Chapter 2 discusses Haz-Map, the source of occupational disease links in SEM and describes its content, processes, and approaches. The committee considers the strengths and weaknesses of Haz-Map as well as alternative approaches to the use and interpretation of health effects information. Chapter 3 discusses SEM in greater detail, including its function and content, the specific health effects recorded in it, how it is updated, and its strengths and weaknesses. The committee also describes its efforts to identify toxic substance–occupational disease links that are missing from the database and highlight some additional information sources that would strengthen the information it provides. Chapter 4 summarizes the committee's findings and provides recommendations to improve and supplement SEM. Overall, the committee focused on ways to enhance the process for linking exposures with disease outcomes in a credible and practical manner.

REFERENCES

Anders, K. 2012. *Energy Employees Occupational Illness Compensation Program Overview*. Presentation at First Committee Meeting, January 23, Washington, DC.

DOE (Department of Energy). 1997. *Linking Legacies: Connecting the Cold War Nuclear Weapons Production Processes to Their Environmental Consequences.* Washington, DC: DOE.

DOE. 2011. *Former Worker Medical Screening Program 2010 Annual Report.* Washington, DC: Office of Health, Safety and Security.

DOE. 2012. *Former Worker Medical Screening Program*. http://www.hss.energy.gov/HealthSafety/FWSP/FormerWorkerMed/ (accessed March 16, 2012).

DOL (Department of Labor). 2010a. *2010 Annual Report to Congress.* Office of the Ombudsman for the Energy Employees Occupational Illness Compensation Program. Washington, DC: DOL.

DOL. 2010b. *US Department of Labor Adds New Information to Site Exposure Matrices Website About Toxic Substances at Nuclear Weapons Facilities*. http://www.dol.gov/opa/media/press/OWCP/OWCP20101462.htm (accessed February 12, 2012).

DOL. 2012a. *EEOICP Program Statistics*. http://www.dol.gov/owcp/energy/regs/compliance/weeklystats.htm (accessed November 11, 2012).

DOL. 2012b. Establishing Toxic Substance Exposure. Chapter 2-0700 in *The Federal (EEOICPA) Procedural Manual*.

DOL. 2012c. *Site Exposure Matrix (SEM)*. www.sem.dol.gov/expanded (accessed February 12, 2012).

GAO (Government Accountability Office). 2004. *Energy Employees Compensation: Even with Needed Improvements in Case Processing, Program Structure May Result in Inconsistent Benefit Outcomes.* GAO-04-515. Washington, DC: GAO.

GAO. 2010. *Energy Employees Compensation: Additional Independent Oversight and Transparency Would Improve Program's Credibility.* GAO-10-302. Washington, DC: GAO.

Silver, K. 2005. The Energy Employees Occupational Illness Compensation Program Act: New legislation to compensate affected employees. *American Association of Occupational Health Nurses Journal* 53(6):267-279.

Stalnaker, K. 2012. *U.S. DOL Site Exposure Matrices, EEOICPA Part E*. Presentation at First Committee Meeting, January 23, Washington, DC.

2

Haz-Map Database

The Haz-Map database contains health effects information on hazardous agents found in the workplace. Haz-Map uses the term "hazardous agents" to refer to physical, chemical, and biologic substances that occur in the workplace. The original concept for Haz-Map asked the question: "Why can't we have a relational database of toxic chemicals and occupational diseases to store and query information similar to ones used by companies to manage data about employees, products, and customers?" (Brown, 2008b). The database was designed "for health and safety professionals and for consumers seeking information about the adverse effects of workplace exposures to chemical and biological agents" (http://hazmap.nlm.nih.gov/about-us; accessed December 19, 2012). It was not designed for compensation purposes. One field in Haz-Map, "Diseases," contains links between toxic substances and associated diseases, illnesses, or other adverse health outcomes. This field is incorporated into the Department of Labor's (DOL's) Site Exposure Matrix (SEM) database as a tool to assist Energy Employees Occupational Illness Compensation Program (EEOICP) Part E claims examiners in assessing whether occupational exposure to a toxic substance present at a Department of Energy (DOE) facility is associated with an occupational disease (see Chapter 3).

DEVELOPMENT OF HAZ-MAP

Haz-Map was developed in 1991 by Jay Brown, a physician board certified in occupational medicine who has substantial clinical primary care experience (Brown, 2008a). The initial development effort was to collect and distill information needed to recognize and prevent both acute and chronic occupational

diseases, thus only "the most useful information" was included (Brown, 2008b). It is a "decision-support relational database" designed to "map the knowledge domain of occupational exposures and diseases" for safety and health professionals (Brown, 2008b). In this respect, Haz-Map is a major endeavor. It provides an important information resource for health care professionals as well as for the public.

Although Haz-Map was initially developed and maintained privately, since 2002 the National Library of Medicine (NLM) has published Haz-Map on its website (http://hazmap.nlm.nih.gov). The database is updated quarterly for content based on changes made by the developer (Brown, 2008a). In addition to Haz-Map, NLM publishes other databases that contain information on toxicology, hazardous chemicals, environmental health, and toxic releases, such as TOXNET, MEDLINE, PubMed, and ClinicalTrials.gov.

NLM has a licensing agreement with the Haz-Map developer and NLM staff review the agent's identity and physical properties (the chemical profile) and make the links to other NLM sponsored databases, such as the Hazardous Substance Data Bank (HSDB) and PubMed (Hakinnen, 2012). However, NLM has indicated that other information in the database, such as exposure assessment information and the toxic agent–disease links, are not reviewed or verified by NLM staff, although NLM occasionally identifies opportunities to add new substances to the database, e.g., isocyanates, that are of interest to the scientific community (Hakkinen, 2012).

CONTENT OF HAZ-MAP

The two major types of information in Haz-Map are lists of toxic substances (the industrial hygiene perspective) and lists of occupational diseases (the epidemiological perspective). Information is contained in eight linked tables and numerous fields (see Figure 2-1). The database was not designed "to list every disease that could possibly be work related, but to focus on established occupational diseases and their causes" (Brown, 2008a). It should be noted that the database was developed to provide useful information to meet the needs of a wide range of health and safety professionals; therefore, the hazardous job tasks, industries, and occupations, and the industrial processes listed are broad and include many jobs and industries that may be unrelated to occupational activities that were performed at DOE sites (for example, bartender).

The database originally began with the 700 chemicals listed in the National Institute for Occupational Safety and Health (NIOSH) *Pocket Guide to Chemical Hazards* (available at http://www.cdc.gov/niosh/npg) and it has since been updated with additional chemical or biological agents associated with 235 occupational diseases, "using selected references from the scientific literature" (Brown, 2008b). As of December 2012, there were more than 7,000 hazardous agents listed. A description of the development of Haz-Map, the information

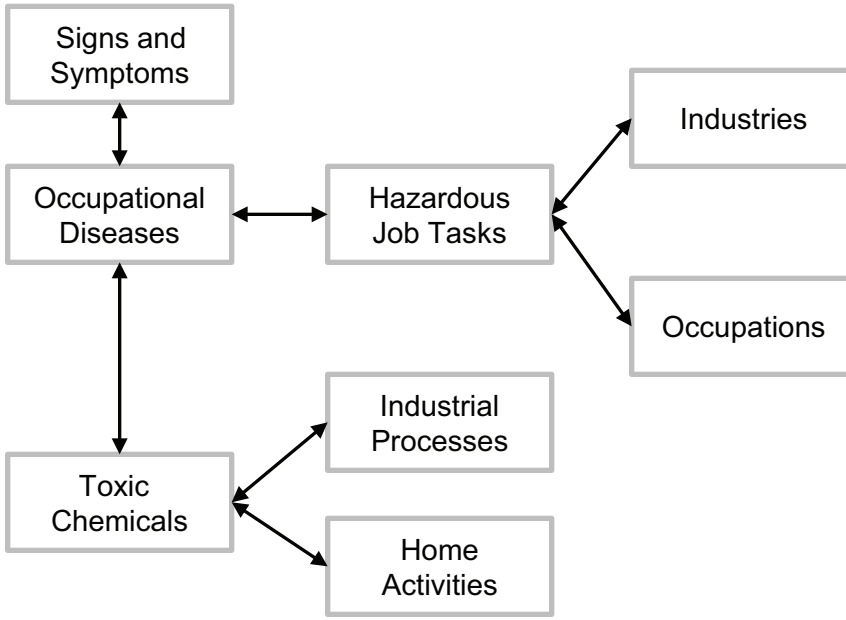


FIGURE 2-1 Links between fields in the Haz-Map database.
SOURCE: Brown, 2012c.

contained in many of its fields (see Table 2-1), and how and why that information was selected is given at www.haz-map.com.

Information is not always available for each field for every agent, particularly for the fields in the categories of Exposure Assessment and Adverse Effects. In part, this is because for many of the hazardous agents listed in Haz-Map, there is little or no industrial hygiene, toxicologic, or epidemiologic literature on the agent. The lack of information about a specific agent may be due to a number of factors, such as its low production, specialized use (that is, it is not commonly used in industrial processes), transient nature in the environment, that it is a by-product or occurs in a closed system, or has not been tested for toxicity. Blank fields are not included in the database; for example, there is no biological exposure index (BEI) for formaldehyde, so that particular field is not listed in the formaldehyde record (see Box 2-1). The category of Adverse Effects includes several fields for those health effects that have been associated with the hazardous agent based on the developer's review of selected references. See Box 2-1 for an example Haz-Map profile for kerosene.

TABLE 2-1 Categories and Fields for Each Hazardous Agent Record in Haz-Map[a]

Categories				
Agent Information	Exposure Assessment	Adverse Effects	Links to Other NLM Databases	Related Information in Haz-Map
Fields				
Agent Name	Skin Designation (ACGIH)	Skin Sensitizer	Health Studies	**Diseases (occupational diseases associated with exposure to this agent)[b]**
CAS Number	BEI	Asthma	Toxicity Information	
Formula	TIH	Toxic Pneumonitis	Chemical Information	
Major Category	TLV (ACGIH)	Dermatotoxin	Biomedical References	Symptoms/Findings (symptoms/findings associated with this disease)
Synonyms	Ceiling (ACGIH)	IARC Carcinogen		
Category	PEL (OSHA)	Lacrimator		Processes
Description	MAK	Hepatotoxin		Activities
Sources/Uses	IDLH and Excerpts from	Neurotoxin		
Comments	Documentation for IDHLs	Other Poison		
Restricted	Vapor Pressure	Methemoglobinemia		
Reference Link	Odor Threshold (low and high)	Anemia		
	RD50	Reproductive Toxin		
	Lethal Concentration	Nephrotoxin		
	WEEL	Hematotoxin		
	Explanatory Notes	and Other Endpoints		
	Half Life			
	Reference Link			
	Flammability (NFPA)			

NOTE: ACGIH = American Conference of Government Industrial Hygienists; BEI = biological exposure index; CAS = Chemical Abstracts Service; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health concentrations; MAK = Maximale Arbeitsplatzkonzentrationen (German occupational exposure limit); NFPA = National Fire Protection Association; NLM = National Library of Medicine; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RD50 = exposure concentration producing a 50% respiratory rate decrease; TIH = toxic inhalation hazard; TLV = threshold limit value; WEEL = workplace environmental exposure level.

[a]Categories and fields are based on those listed in agent profiles at http://hazmap.nlm.nih.gov.

[b]The "Diseases" field is the only one used by the SEM database.

SOURCE: http://hazmap.nlm.nih.gov (accessed November 1, 2012).

BOX 2-1
Haz-Map Profile for Kerosene

Agent Name	Kerosene
CAS Number	8008-20-6
Major Category	Solvents
Synonyms	Fuel Oil No. 1; Range oil; [NIOSH] Deodourized kerosene; Deobase; Deodorized kerosine; Ultrasene; [CHEMINFO] UN1223
Category	Petroleum, Refined
Description	Colorless to yellowish, oily liquid with a strong, characteristic odor; [NIOSH]
Sources/Uses	Used in jet, diesel, and tractor fuels; also used as a heating fuel and solvent; [Hawley]
Comments	TSCA Definition 2008: A mixture of crude oil distillates with carbon numbers of C9 to C16 and boiling points of 180 deg C to 300 deg C; [ChemIDplus] Petroleum distillates, e.g., VM & P naphtha and kerosene, can cause anesthesia, slowing of reflexes, and dermatitis. They may contain n-hexane with the potential to cause peripheral neuropathy. [LaDou, p. 500-1] Kerosene is a refined petroleum solvent (predominantly C9-C16), which typically is 25% normal paraffins, 11% branched paraffins, 30% monocycloparaffins, 12% dicycloparaffins, 1% tricycloparaffins, 16% mononuclear aromatics, and 5% dinuclear aromatics. [NIOSH] Gasoline (C8-C10) causes trivial liver injury in animal studies; No known injury in human cases; [Haddad, p. 226t] See "Distillates (petroleum), hydrotreated light," "Naphtha (petroleum), hydrotreated heavy," and "Solvent naphtha (petroleum), heavy aliphatic."
Reference Link	ATSDR - ToxFAQs - Fuel Oils / Kerosene

continued

BOX 2-1 Continued

Exposure Assessment

Skin Designation (ACGIH)	Yes
TLV (ACGIH)	200 mg/m3, total hydrocarbon vapor
Vapor Pressure	0.48 mm Hg
Odor Threshold Low	3 mg/m3
Lethal Concentration	LC50 > 5,000 mg/m3/4h
Explanatory Notes	Detection odor threshold from CHEMINFO;
Flammability (NFPA)	2: High ambient temperature required

Adverse Effects

Neurotoxin	CNS Solvent Syndrome
Hepatotoxin	Hepatotoxin, Secondary

Links to Other NLM Databases

Health Studies	Human Health Effects from Hazardous Substances Data Bank: • KEROSENE
Toxicity Information	Search TOXNET
Chemical Information	Search ChemIDplus
Biomedical References	Search PubMed

Related Information in HazMap

Diseases	Occupational diseases associated with exposure to this agent: • Encephalopathy, chronic solvent • Solvents, acute toxic effect
Processes	Industrial Processes with risk of exposure: • Metal Degreasing • Painting (Solvents) • Petroleum Production and Refining
Activities	Activities with risk of exposure: • Intalagio printing

NOTE: Only the "Diseases" field, in orange, is used in the Site Exposure Matrix database.
SOURCE: http://hazmap.nlm.nih.gov/category-details?id=172&table=copytblagents (accessed December 5, 2012).

HAZ-MAP INFORMATION SOURCES

Information from numerous textbooks, journal articles, and electronic databases is cataloged and summarized to populate the Haz-Map database and to identify causal links between hazardous agents and occupational diseases (Brown, 2008a). The list of references used for the database is available at http://hazmap.nlm.nih.gov/references. As of December 2012, there were 35 online books and databases; 60 books, compact discs, and journal articles; 15 references specific to ionizing radiation; and 12 other websites used as data sources.

Although some of the Haz-Map information sources, such as the HSDB, are available online to the general public, others, such as REPROTOX, are not. This makes it difficult to determine whether the most current information has been used for a database record, when a record was last updated, and what changes to the record were made. Furthermore, most of the cited textbooks are also not available online or in many libraries and reference collections, including DOL's and many university medical libraries.

With respect to journal articles, the Haz-Map developer informed the committee that

> periodically, all journal articles in selected journals are reviewed. The last reviews were done in 2008 and 2011. The selected journals are: *Am J Ind Med, Chest, Int Arch Occup Environ Health, J Occup Environ Hyg, J Occup Environ Med, Occup Environ Med,* and *Scand J Work Environ Health*. (Brown, 2012c,d)

There are no transparent selection criteria for the use of those particular journals or for the articles that are cited from them. The committee emphasizes that many other peer-reviewed journals (e.g., *Allergy*, *Annals of Occupational Hygiene*, *British Medical Journal*, *Environmental Health Perspectives*, *Journal of Allergy and Clinical Immunology*, *Thorax*) also publish studies on the health effects of occupational exposures to toxic substances. To be more comprehensive, these and other journals should also be reviewed for Haz-Map.

TOXIC SUBSTANCE–DISEASE LINKS

For EEOICPA Part E, the causation standard is "it is at least as likely as not that exposure to a toxic substance at a Department of Energy facility was a significant factor in aggravating, contributing to, or causing the illness; *and* it is at least as likely as not that the exposure to such toxic substance was related to employment at a Department of Energy facility" (Public Law 108-375 § 3161). The DOL claims examiners use the "Specific Health Effects" field in SEM, imported from the Haz-Map "Diseases" field, for an initial assessment of whether a claimant's occupational exposure to a toxic substance at a DOE site is causally associated with the claimant's diagnosed disease. Thus, SEM (and the links supplied by Haz-Map) has an impact on the claims examiner's preliminary decision

on whether a causal link between the claimant's potential exposure and disease meets the causation standard. To assess the adequacy of the evidence for causal links between toxic substances and diseases given in the Haz-Map "Diseases" field requires a more general discussion of how scientific data are used to assess association and causality.

The committee recognizes that concepts of association and causality for the assessment of the impact of agents on human health are complex. This section provides a brief primer on the concepts of strength of association and causality; more information on these topics may be found from a number of organizations, e.g., the Institute of Medicine (IOM), the U.S. Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP). How an organization addresses these concepts may depend on factors such as public perception, ethical approaches to the common good, or the purpose for which the information is to be used (e.g., regulatory, guidance). Regardless of the goal, determining a causal association must be based on a careful review of all the available evidence. For example, the EPA and the Occupational Safety and Health Administration (OSHA) might rely on the same animal and human toxicity data for a toxic substance, however, each agency might apply the information differently to determine an association or causation, or to conduct quantitative risk assessments.

Determining a causal link is challenging and often requires decision making in the face of uncertainty. Relationships between exposure and health effects can be obtained from in vivo studies in humans or animals, or from ex vivo and in vitro studies in tissues or cells. To determine whether a hazardous agent is likely to be causally associated with a specific health effect, scientists evaluate the relationship between exposure to the substance and any subsequent biological responses. Observing a greater response (e.g., a greater number of individuals with a specific disease or increased severity of effect) at higher exposure levels provides evidence that a toxic substance may cause the observed response. Types of health effects observed following exposure to a toxic substance can be broadly categorized as acute effects (i.e., the effects occur within 24 hours following exposure) or chronic effects (i.e., long-term) and in terms of whether effects occur at the point of contact with the toxic substance (i.e., local effects) or elsewhere in the body, following absorption (i.e., systemic effects).

The result of many human epidemiologic studies is a measure of strength of the association between an exposure and a health outcome. Association is primarily a statistical concept referring to the quantification of the relationship (positive, negative, or none) between two variables (e.g., the exposure and the outcome). The observational nature of epidemiologic studies means that causality cannot generally be established directly using only one epidemiologic study because there may be other reasons for the positive association, including random error (chance), systematic error (bias), and reverse causality (where the outcome itself may have influenced the chance of exposure). Therefore, different approaches

have been developed for evaluating causality, all of which involve considering a body of evidence and confounding factors.

In the following sections, the committee comments briefly on the use of various types of evidence—epidemiologic studies, animal studies, and mechanistic studies—used in assessing associations between exposure and outcomes. It then presents an overview of various approaches used by several scientific organizations such as IARC and IOM for assessing causality and other levels of association. The committee concludes with a discussion of the Haz-Map approach to causal links and its implementation.

Types of Evidence

Many types of evidence can be considered when looking at the relationship between exposure to a toxic substance and health effects or disease. This evidence can include large, well-conducted clinical controlled trials such as those used for pharmaceutical agents; epidemiologic studies where groups of humans are evaluated to see if exposures have an impact on health; animal studies to determine the toxicity of an agent; and mechanistic studies, often conducted in vitro or at the subcellular level to determine the biological mechanisms by which an agent produces an outcome. Each of these studies is described briefly below to highlight the wealth of information that may be considered when evaluating the impact of an agent on the health of an organism. The committee notes that this section is not intended to be a comprehensive description of epidemiology, toxicology, or occupational medicine.

Epidemiological Studies

Most epidemiological studies are observational rather than experimental. Three study designs commonly used for epidemiologic research are cohort, case-control, and cross-sectional (IOM, 2010).

A cohort study follows a defined group over a period of time. Using data from a cohort study, investigators can test hypotheses about whether a specific exposure is related to the development of one or more health outcomes. A cohort study starts with people who are free of a disease (or other outcome) and classifies them according to whether they have been exposed to the agent of interest and, usually, the level of exposure. The rate of the occurrence of a health outcome in the group over a specific period of time is determined (incidence rate) (IOM, 2010).

Cohort studies can be prospective or retrospective. In a retrospective cohort study, investigators usually rely on records to determine past exposures for the cohort and another record system (e.g., medical records, death certificates, questionnaires) to ascertain the occurrence of disease. In a prospective cohort study, both the exposure and the disease assessment methods can be designed by the

investigator rather than relying on existing records. However, this study design will not be able to provide sufficient data on chronic disease risk factors until a number of years, if not decades, of follow-up time have accrued. This is because many exposure–disease associations have a long induction and latency period; that is, a protracted time interval between exposure to a toxic substance and the diagnosis of a resultant health outcome. For some exposure–disease associations, often involving chronic diseases that can occur at older ages (such as some cancers and cardiovascular disease), this induction and latency period can be 20 years or more. A hazard ratio or a rate ratio greater than 1.0 indicates that there is a potential association between exposure to the agent and the disease, and the further from 1.0, the stronger the association, whether the association is positive or negative. Statistical analysis methods allow the investigator to control for other factors that might influence the risk of the disease or the relationship between the exposure and the disease (e.g., age, sex, smoking status). Therefore, results are usually adjusted for these factors (IOM, 2010).

In a case-control study, subjects (cases) are selected on the basis of having a disease, and controls are selected on the basis of not having the disease. Information about cases and controls is collected from available records. Such potential factors as age, sex, and socioeconomic status that may affect results can be assessed in the epidemiologic analysis or by appropriately matching case and controls for those factors. An odds ratio is used in case-control studies to statistically describe the odds of having exposure among those with disease relative to the odds of having the exposure in the comparison group without disease. As with the epidemiologic parameters for a cohort study, an odds ratio of greater than 1.0 indicates that there is a positive association between exposure to an agent and the disease (IOM, 2010).

Case-control studies are especially useful and efficient for studying rare diseases and multiple exposures, and these have the advantages of ease, speed, and relatively low cost. However, they are vulnerable to several types of bias, such as recall (when reporting of an exposure is influenced by whether the participant has the outcome of interest), which can enhance (or dilute) apparent associations between disease and exposure. Other difficulties include the ability to identify representative groups of cases, choose suitable controls that represent the same population that gave rise to the cases, and collect comparable exposure information for both cases and controls (IOM, 2010).

In cross-sectional studies, exposure and disease information is collected at a point in time. The selection of people for the study—unlike selection for cohort and case-control studies—is independent of both the exposure to the agent under study and the disease characteristics. In such studies, disease or symptom prevalence (the proportion of people with the disease at a specific time) between groups with and without exposure to the specific agent is compared using a risk ratio or risk difference. For example, workers in one facility that used a chemical may be compared with workers at another facility that did not use the chemical.

The major difference between prevalence and incidence (as calculated in a cohort study), is that the latter is a measure of the new cases occurring over a given period of time (IOM, 2010), rather than a mere count of all cases in existence at a particular point in time.

Cross-sectional studies are easier and less expensive to perform than cohort studies and they can identify the prevalence of diseases and exposures in a defined population. They are not very useful for determining cause and effect relationships, because disease and exposure data are collected simultaneously (Monson, 1990). For this reason, it may be difficult to determine the temporal sequence of exposures and symptoms or disease (IOM, 2010).

Case reports of exposure to a chemical with resulting disease in one or more individuals, while not formally research studies, may provide additional support for causal links. Case reports by themselves rarely provide enough information to describe a causal association between exposure and disease that is free of bias and uncertainty (IOM, 2010).

Toxicological Studies

In animal toxicologic studies, it is possible to define and control exposures and factors such as diet and ancillary exposures that may influence response to a chemical much more precisely than in human studies. Thus, in animal studies it is much easier to identify substance-specific effects. Effects observed in animals, however, may differ both quantitatively and sometimes qualitatively from effects in humans. For example, rats are much more susceptible to the effects of perchlorate, which inhibits uptake of iodine by the thyroid, than are humans (Lewandowski et al., 2004). Conversely, rats and mice do not exhibit the same hemolytic toxicity to naphthalene seen in humans, and even the two species differ in their susceptibility to the chemical (Wakefield, 2007). Such toxicologic differences reflect species differences in how substances are distributed, modified, and eliminated once they enter the body. Because of these differences, results from animal studies alone are generally not sufficient to establish that exposure to a substance causes a specific health outcome in humans. Rather, animal studies can be used to support observations from human studies, to identify potential links between exposure and specific health outcomes in humans, or to provide hypotheses about what exposure and outcome relationships should be of concern. Furthermore, animal studies are often the best approach for understanding the mechanism of a toxic effect and for demonstrating interaction between substances (discussed in Chapter 3). The investigator must be aware that there may be substantial differences due to physiology and other factors inherent in any animal model. Animal studies are also useful when it is unethical or impractical to study potentially harmful exposures in humans.

Mechanistic Evidence

In vivo (within the body) studies in humans or animals, ex vivo (in tissues outside of the body) studies, and in vitro (in cells) studies can be used to evaluate mechanisms of toxicity. There are a variety of mechanisms by which toxic substances can elicit a biological response. Toxic substances that are highly reactive are more likely to cause local, acute effects, such as irritation. Most toxic substances that cause systemic effects must be absorbed into the body, typically through the skin, the respiratory tract, the gastrointestinal tract, or even through the eye. Following absorption, substances may be distributed throughout the body via the circulatory system. Many substances undergo metabolism, which typically facilitates elimination of the substance from the body, but can also generate reactive intermediates or metabolites, that can interact with cells or biological processes in the body to cause health effects. Mechanistic evidence can be used in conjunction with evidence from animal studies to evaluate whether effects observed in animals are likely to occur in humans. For example, IARC used mechanistic evidence to conclude that benzo[a]pyrene is carcinogenic to humans, despite the lack of epidemiologic data regarding this substance and cancer in humans (IARC, 2012).

The types of studies that may be conducted in human populations vary—cohort, cross-sectional, and case reports—and thus study results are not necessarily comparable. Because a causal association generally requires a strong evidence base, additional information from toxicological studies can be used to support or refute the available epidemiologic evidence. Thus, a weight-of-evidence approach that considers the strengths and weaknesses of all relevant studies, including toxicological and mechanistic studies, is most likely to provide a supportable conclusion about the link between a toxic substance and a disease.

Approaches for Establishing Causal Links

In 1965, following the U.S. surgeon general's report on the relationship between smoking and lung cancer, Sir Austin Bradford Hill, a British epidemiologist and statistician, described nine viewpoints (often referred to as criteria) that should be considered when trying to come to a decision about whether an observed association might be causal (Hill, 1965). While all viewpoints are relevant in making inference about causality there is only one of the nine viewpoints that is truly necessary—temporality—that is, the exposure must have occurred before the onset of the disease. The remaining eight viewpoints are neither necessary nor sufficient requirements for causation, but nonetheless provide a framework for consideration (see Box 2-2).

There are various approaches in addition to Hill's to evaluate causal associations between exposure to an agent and disease, most of which emphasize the need for a strong association and a defined biological mechanism based on a

BOX 2-2
Hill's Viewpoints

Strength: Causation is supported if the relative risk due to the exposure is very large.

Consistency: Causation is supported if the relationship is seen in different populations at different times and in different circumstances.

Specificity: Causation is supported if an exposure appears to cause only the specific effect.

Temporality: Causation is supported if the exposure precedes the effect.

Biological Gradient: Causation is supported if the magnitude of the exposure is associated with an increase in the magnitude of the effect.

Plausibility: Causation is supported if data elucidating the biological pathways leading from the exposure to effect are useful.

Coherence: Causation is supported if "the cause and effect interpretation of data should not seriously conflict with the generally known facts of the natural history and biology of the disease."

Experiment: Causation is supported in some circumstances, evidence that removing the exposure lessens or removes the effect can be used to draw conclusions about causality.

Analogy: Causation is supported in some circumstances, comparison between weaker evidence of causation between an exposure and its effect and strong evidence of causality between another exposure and its similar effect is appropriate.

SOURCE: Hill, 1965.

combination of human, animal, and mechanistic data (EPA, 2012). Organizations such as the NTP, the EPA, and IARC periodically conduct evaluations of agents that are suspected causes of disease. Such evaluations are typically peer-reviewed by a panel of experts who have been selected after consideration of scientific background and potential conflicts of interest, and for federal groups such as advisory committees, of bias. The resulting evaluations consider the available

evidence derived from human and animal experiments, epidemiological research, and basic mechanistic studies.

The approaches used by the aforementioned organizations to evaluate causality by a group of experts all use a weight-of-evidence approach to characterize the degree of uncertainty in the evidence base. This uncertainty is frequently expressed by categories describing the strength of the evidence base irrespective of the strength of the association between exposure and health effect. Given the variable quantity and quality of evidence for many toxic substances, it is helpful to have a panel of experts review the evidence and come to a consensus on the conclusion. The breadth and depth of knowledge gained from using a number of experts gives additional support to conclusions and can help minimize bias and error. The committee discusses the approaches used by IARC, NTP, and the IOM as representative of organizations that have earned respect for high-quality reviews of scientific evidence regarding potential causal associations between substances and health effects.

International Agency for Research on Cancer

The approach used by IARC to evaluate whether an agent is a carcinogen includes consideration of human, animal, and mechanistic evidence (see Figure 2-2). The methods and criteria IARC uses to evaluate the various kinds of evidence are clearly described (IARC, 2006). In evaluating human evidence, for example, after the quality of individual epidemiologic studies of cancer has been summarized and assessed, a judgment is made concerning the strength of evidence that the agent in question is carcinogenic in humans. In making its judgment, each IARC working group considers several criteria for causality (e.g., the Hill viewpoints) (Hill, 1965). A strong association—for example, a large relative risk, with a confidence interval that does not include 1.0, representing a greater probability of the disease in the exposed group versus that in a nonexposed group—is more likely to indicate causality than a weak association, although it is recognized that estimates of a small effect do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that are observed using different epidemiologic approaches or under different exposure scenarios are more likely to represent a causal relationship than are isolated observations from single studies. If there are inconsistent results among investigations, possible explanations are considered (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound (IARC, 2006).

In evaluations of carcinogens published in the IARC monograph series, the evidence of cancer in humans and in experimental animals has four descriptors—"sufficient evidence," "limited evidence," "inadequate evidence," or "evidence suggesting lack of carcinogenicity" (for definitions of these terms, see IARC,

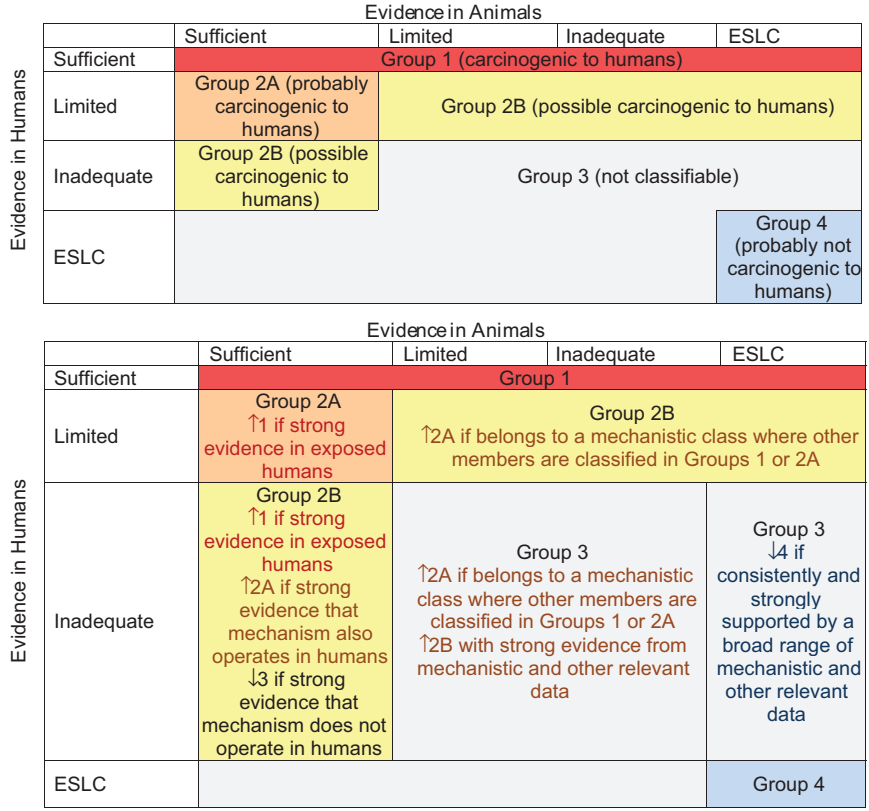


FIGURE 2-2 IARC approach to evaluating the evidence to determine the carcinogenicity of hazardous agents.
NOTE: ESLC = evidence suggests lack of carcinogenicity. Arrows indicate a potential change in a substance's carcinogenicity group based on the strength of evidence and availability of mechanistic evidence.
SOURCE: Cogliano, 2006, with permission.

2006). These evaluations regarding human and animal evidence are combined into an evaluation that the agent is

- carcinogenic to humans (Group 1),
- probably carcinogenic to humans (Group 2A),
- possibly carcinogenic to humans (Group 2B),
- not classifiable as to its carcinogenicity to humans (Group 3), or
- probably not carcinogenic to humans (Group 4) (see Figure 2-2).

When a judgment has been reached that there is sufficient evidence that an agent causes disease, it means that a working group of subject matter experts has evaluated and judged the body of evidence and concluded that a relationship has been observed between the exposure and cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence (IARC, 2006).

National Toxicology Program

The NTP Office of Health Assessment and Translation (OHAT) of the National Institute of Environmental Health Sciences also reviews data to describe the health effects caused by exposure to a toxic substance. As with many other government agencies, the process used by OHAT to develop its monographs on substances includes a "methods" section that explicitly indicates how the literature search was conducted, how studies were selected and reviewed, how the evidence was evaluated and weighed to come to the conclusions in the reports, and the peer review process (including the names of peer reviewers) used for each report. The NTP evaluates toxic substances using categories of association similar to those of IARC, IOM, and other organizations—sufficient evidence of association, limited evidence of association, inadequate evidence of an association, and evidence of no association. These categories of evidence and association are described in the methods section of each NTP report, for example, *Health Effects of Low-level Lead Evaluation* (HHS, 2012).

Institute of Medicine

Many IOM committees use a formal system similar to those of IARC and NTP to assess the weight-of-evidence and determine the strength of association between exposure to a hazardous agent and a health outcome (IOM, 2010). As with other approaches to assessing cause and effect, the IOM uses committees of experts who first evaluate the available evidence (typically from peer-reviewed studies). All committee members then reach a consensus on the conclusion and assign a category of association for each health outcome based on the number and quality of studies and expert judgment (see Box 2-3). The committees do not use a formulaic approach to assign a specific category of association; rather they have found that each health outcome requires a more considered and nuanced approach (IOM, 2010). EPA has used the IOM approach for its integrated scientific assessments for criteria air pollutants since 2008.

Establishing Hazardous Agent–Occupational Disease Links in Haz-Map

The committee's understanding of the Haz-Map database approach to linking hazardous agents and occupational diseases is based on information provided by its developer and found at www.haz-map.com. The committee notes that this

BOX 2-3
Categories of Associations Used by Several IOM Committees

- *Sufficient Evidence of a Causal Relationship:* Evidence is sufficient to conclude that a causal relationship exists between an exposure and a health outcome. The evidence fulfills the criteria for sufficient evidence of a causal association in which chance, bias, and confounding can be ruled out with reasonable confidence. The association is supported by several of the other considerations used to assess causality: strength of association, dose-response relationship, consistency of association, temporal relationship, specificity of association, and biologic plausibility.
- *Sufficient Evidence of an Association:* Evidence suggests an association, in that a positive association has been observed between an exposure and a health outcome in humans; however, there is some doubt as to the influence of chance, bias, and confounding.
- *Limited/Suggestive Evidence of an Association:* Some evidence of an association between an exposure and a health outcome in humans exists, but this is limited by the presence of substantial doubt regarding chance, bias, and confounding.
- *Inadequate/Insufficient Evidence to Determine Whether an Association Exists:* The available studies are of insufficient quality, validity, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between an exposure and a health outcome in humans.
- *Limited/Suggestive Evidence of No Association:* There are several adequate studies, covering the full range of levels of exposure that humans are known to encounter, that are consistent in not showing an association between an exposure and a health outcome. A conclusion of no association is inevitably limited to the conditions, levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small increase in risk at the levels of exposure studied can never be excluded.

SOURCE: IOM, 2010.

information is not provided on the NLM Haz-Map website—located at http://hazmap.nlm.nih.gov—although there is a link for direct users to more information at www.haz-map.com. The developer told the committee that he tries to answer the following questions when determining whether exposure to a hazardous agent may cause an occupational disease: "Is there consensus in occupational medicine textbooks that this occupational disease is caused by these hazardous

agents? Can the disease be prevented by good occupational hygiene practices?" (Brown, 2012d).

The Haz-Map developer has determined that

> linkage between a chemical or biological agent and a disease indicates that sufficient exposure to the agent is associated with increased risk of developing the disease. For chronic diseases, links between an agent and a disease means that a causal relationship has been determined based on human case reports or epidemiological studies. (Brown, 2012b)

He further states that

> In Haz-Map, there is a distinction between adverse effects (includes animal toxicology and human poisonings by ingestion cases) and occupational diseases (cases of workers made ill after inhalation or skin absorption). Therefore, chemicals are linked to the diseases "Asphyxiation, chemical" and "Hemolytic anemia" only if occupational cases (and not just ingestion cases) have been reported. Likewise, all chronic occupational diseases in Haz-Map are based on reports of occupational cases. (Brown, 2012d)

The www.haz-map.com website provides more information on some of the hazardous agent–occupational disease links in the database:

> The only exceptions to the rule that linkage indicates human disease known to be caused by the agent are the following diseases: Solvents, acute toxic effect (linked to all organic solvents); Encephalopathy, chronic solvent (linked to all organic solvents used in paints or varnishes); Encephalopathy, acute toxic effect (linked to other potential causes of acute encephalopathy excluding solvents, asphyxiants, fumigants, and insecticides); and Pneumonitis, toxic (caused by chemicals corrosive to the skin, eyes, and respiratory tract). The occupational disease "pneumonitis, toxic" is defined as noncardiogenic pulmonary edema induced by acute exposure to metal fumes or toxic gases and vapors after a spill or confined space accident. The "major irritant inhalants" are ammonia, bromine, chlorine, chlorine dioxide, diborane, ethylene oxide, formaldehyde, hydrogen chloride, hydrogen fluoride, methyl isocyanate, nitrogen dioxide, ozone, phosgene, and sulfur dioxide [LaDou, p. 523]. While human cases have been documented for the major irritant inhalants, there are many chemicals with similar properties that can cause acute lung injury. Haz-Map flags 560 chemicals that have the potential to cause toxic pneumonitis as an adverse effect in heavily exposed workers or in animal experiments. Of these 560 chemicals, 142 with the designation of "toxic inhalation hazard" by ERG 2008 are linked to the occupational disease "Pneumonitis, toxic." (Brown, 2012b)

More specifics on what constitutes a consensus, what evidence is reviewed in making the links, and how the Haz-Map developer determines that good industrial hygiene practices would prevent the disease are not provided on the database website.

Toxic substance–disease links are presented in the field "Diseases" under the

category "Related Information in Haz-Map" (see Table 2-1 and Box 2-1). The determination of what diseases are associated with the agent is based on a review of the literature by the developer, although much of the reviewed literature is of secondary sources rather than primary studies. Furthermore, the developer does not indicate the criteria he uses to determine "sufficient exposure," "increased risk," or a "causal relationship." The evidence used to determine associations or causal links is not provided for specific agents or generally for the database, so it is unclear how the developer made each determination and how robust the agent–disease link actually is. For example, it is unknown if the basis of a particular toxic substance–disease link is one well-conducted epidemiologic study, five adequate epidemiologic studies, three case studies, conflicting studies, or a lack of studies. For noncancer health endpoints, however, there is no evidence that the developer uses a weight-of-evidence approach for determining causality, such as that used by NTP or IOM.

The exception to this lack of specificity are those agents that are IARC Group 1 carcinogens (sufficient evidence in humans) as described in the chapter on occupation by Siemiatycki and colleagues in Schottenfeld and Fraumeni's *Cancer Epidemiology and Prevention*, *3rd ed*. (Brown, 2010; Schottenfeld and Fraumeni, 2006; Siemiatycki et al., 2006). This Haz-Map approach has recently been updated. Target site organs are determined by using IARC 2012 cancer site information. According to the developer,

> Prior to the 2012 IARC changes, the map of occupational cancer in Haz-Map was based on the "Occupation" chapter in *Cancer Epidemiology and Prevention*, 3rd Edition. New studies and new interpretations from IARC are now available. (Brown, 2012a)

STRENGTHS AND WEAKNESSES OF HAZ-MAP

Haz-Map has been favorably compared with other health information databases in terms of quality, number of chemicals, and usability (Laamanen et al., 2008). It has the advantage of providing basic health and safety information on more than 7,000 hazardous agents, and it can serve as a good initial resource for this type of information. There are important concerns, however, that preclude its use as a comprehensive resource for assessing the causal relationship between toxic substances and occupational diseases.

In this section, the committee comments on some of the problems in the hazardous agent-occupational disease links, that is the "Diseases" field. Although there are numerous other fields in the database (see Figure 2-1), the validity of the information in those fields, including the "Adverse Effects" category is beyond the scope of the committee's task and is not discussed in this report. In particular, the committee discusses the lack of transparency in how the links are established and the criteria used to select and weigh the evidence for each link.

Selection and Interpretation of Information Sources

There are several areas where Haz-Map lacks transparency. The most critical is the lack of formal criteria for determining the hazardous agent–occupational disease links. However, even before such criteria could be applied to the evidence selected by the developer, there is a lack of transparency about what information is reviewed, its sources, and how it is evaluated for each hazardous agent, with the exception of IARC classifications for carcinogens. For example, there are four noncancer diseases causally associated with formaldehyde—asthma, occupational; contact dermatitis, allergic; contact urticaria; and fumigants, acute toxic effect. The sources of the information for contact urticaria and fumigants, acute toxic effect are not given in the "Diseases" field, but rather must be deciphered from the earlier "Comment" field in the "Agent information" category. Further references can also be found by clicking on the specific disease link and reading the entry in the "Comment" field for that specific disease. Although sources for the information on asthma, contact urticaria, and allergic contact dermatitis are provided, the casual user would not easily find the supporting evidence for these agent–disease links in the database.

Criteria for Determining Agent–Disease Links

The rules and criteria used by the Haz-Map developer to determine whether the evidence is sufficient for a causal association between an agent and an occupational disease are not clear, with the exception of the very strict criteria of using only IARC Group 1 cancer designations. Furthermore, there appear to be discrepancies in using even this approach for carcinogens. Although IARC has designated asbestos as a known human carcinogen for ovarian cancer, this is not indicated in the asbestos record. However, cancer of the larynx, which was designated by IARC as caused by asbestos at the same time as ovarian cancer, is listed in the database as an asbestos-caused occupational disease.

For chronic noncancer occupational diseases, the database appears to favor evidence from epidemiological studies and reports of occupational illness. However, in the absence of human information, it does not consider other types of information (e.g., animal and mechanistic data) that may support a link between an agent and occupational disease. For acute occupational diseases, the developer states that

> animal data is sufficient if the routes of entry correspond. Examples of such acute occupational diseases include poisoning by pesticides, solvents, simple asphyxiation, hydrofluoric acid, and toxic pneumonitis. A special rule is applied to toxic pneumonitis. Any corrosive substance has the potential to produce toxic pneumonitis as an adverse effect. Any of these substances designated as "TIH" (Toxic Inhalation Hazards) in the 2008 Emergency Response Guidelines are also listed in Haz-Map as the occupational disease "Pneumonitis, toxic." Other

> acute diseases with special rules are "Asphyxiation, chemical" and "Hemolytic anemia." In Haz-Map, there is a distinction between adverse effects (includes animal toxicology and human poisonings by ingestion cases) and occupational diseases (cases of workers made ill after inhalation or skin absorption). Therefore, chemicals are linked to the diseases "Asphyxiation, chemical" and "Hemolytic anemia" only if occupational cases (and not just ingestion cases) have been reported. Likewise, all chronic occupational diseases in Haz-Map are based on reports of occupational cases. (Brown, 2012d)

The stringent criteria for establishing hazardous agent and cancer links and the uninterpretable criteria for establishing noncancer disease links present substantial obstacles for the effective use of Haz-Map as the sole source of toxic substance–occupational disease links in SEM as discussed in detail in Chapter 3.

Peer Review Concerns for Haz-Map

Peer review is a commonly used process for scientific and technical articles submitted to scholarly journals. The goal of peer review is to help ensure that the reviewed documents are accurate, comprehensive, and, in some cases, adhere to the authoring organization's policy guidelines. Peer review has been defined by the National Research Council as

> a documented, critical review performed by peers [defined in the U.S. Nuclear Regulatory Commission report as "a person having technical expertise in the subject matter to be reviewed (or a subset of the subject matter to be reviewed) to a degree at least equivalent to that needed for the original work"] who are independent of the work being reviewed. The peer's independence from the work being reviewed means that the peer, a) was not involved as a participant, supervisor, technical reviewer, or advisor in the work being reviewed, and b) to the extent practical, has sufficient freedom from funding considerations to assure the work is impartially reviewed. (NRC, 1997)

Typically, organizations have established criteria against which reviewers are asked to judge the document. Numerous organizations, including virtually all biomedical journals (e.g., *Journal of the American Medical Association*, the *Lancet*, *New England Journal of Medicine*), and other organizations such as the IOM and the National Research Council, NTP, ATSDR, EPA, IARC, and the Organisation for Economic Co-operation and Development, use peer review to ensure their documents meet scientific standards. Many government and other organizations have developed and documented their peer review process. Some organizations, such as NTP and IARC, publish their review guidelines so the public has an understanding of the level of rigor the organization has applied to its review process. For example, EPA has developed the *Peer Review Handbook* that provides guidance to EPA staff on how and when to conduct peer reviews of scientific documents and the types of peer review that are applicable to different documents (EPA, 2006). The Office of Management and Budget issued its "Final

Information Quality Bulletin for Peer Review" that established federal guidance for the peer review of government science documents (OMB, 2004). The peer reviewers' names are identified in many documents, although their reviews may be anonymous to the documents' authors during the review process.

Although the NLM publishes the database, Haz-Map lacks adequate oversight or content review by external, independent experts because the Haz-Map developer is solely responsible for its content. Furthermore, there is no disclaimer on the Haz-Map home page at NLM indicating that it is not peer-reviewed or that NLM is not responsible for its content. Thus, the user may be unaware that this database has not been peer-reviewed nor has it been reviewed by anyone at NLM for accuracy, bias, or comprehensiveness. In contrast, NLM's HSDB prominently displays a notice on its home page that the database has been peer-reviewed (NLM, 2011).

The current Haz-Map process for determining toxic substance–occupational disease links is based on the developer identifying "textbooks, journal articles, the Documentation of the Threshold Limit Values (published by ACGIH), and electronic databases such as NLM's Hazardous Substances Data Bank (HSDB)." The developer then "classifies, summarizes, and regularly updates the information found in the database" (http://hazmap.nlm.nih.gov/about-us; accessed January 2, 2013). The developer of Haz-Map extracts information from these sources and uses his own expertise and judgment to determine whether there is sufficient evidence from his sources to determine whether there is a causal link between a toxic substance and an occupational disease. The substance–disease links receive no further review for accuracy or comprehensiveness.

Ideally, appropriate review of a database such as Haz-Map would include both a technical review and a quality assurance component. A technical review would ensure that the correct information from each source was cited accurately. The quality assurance component would determine that all fields are complete, that the cited information is not taken out of context, and that all the relevant information is included. The failure to list asbestos as a cause of ovarian cancer is one of the examples that the committee was able to identify during the course of the study that show why technical and quality control reviews are needed. The reason for excluding this cancer from the asbestos record is unclear. With good technical review and quality assurance of the database entries, users can make informed judgments about the validity of the links between a toxic substance and an occupational disease.

Haz-Map relies heavily on textbooks and standardized reference books to determine agent–disease link. These books include *Cancer Epidemiology and Prevention* (Schottenfeld and Fraumei, 2006), the source of the database's references to Siemiatycki et al. (2006) reference in Haz-Map; *Textbook of Clinical Occupational and Environmental Medicine* (Rosenstock et al., 2004); and *Contact and Occupational Dermatology* (Marks et al., 1997). Databases such

as HSBD and REPROTOX are also used. Haz-Map cites only IARC for cancer designations.

Although some of the referenced databases, such as HSDB, are peer-reviewed, this is not necessarily true for textbooks and other information sources, including some databases. Textbooks are typically written as educational tools and are not designed to be either all-encompassing or used for compensation purposes. While subject to the scrutiny of editors, they are not peer-reviewed to determine if the authors' conclusions about the literature on a subject are accurate, comprehensive, or objective. Furthermore, although the information in many textbooks and, thus, in Haz-Map is presumably based on information from peer-reviewed and published documents, textbook chapters typically represent the interpretation of a limited number of authors who select which studies to review, evaluate, and summarize. Different conclusions about a chemical agent may be reached by different authors, depending on their purpose and their resources. Many of the references used for Haz-Map are not easily accessible to the general public either in hard copy or electronically, which makes it difficult to check the information from them to complete a quality assurance and technical review.

Updating Toxic Substance–Disease Links

Haz-Map is updated quarterly on the NLM website with some agents selected preferentially for review and updating (Brown, 2012d). Formal update information is not provided in the NLM version of Haz-Map making it impossible to ascertain which agents may be considered for review and updating and whether any changes have been made to the "Diseases" field. The developer provides some information on database updates at http://www.haz-map.com/wotsnu.htm, but this information can be difficult to interpret, such as the entry for January 7, 2013.

Updates to hazardous agent records in Haz-Map occur when a new edition of a textbook or other reference is published with revised information on that agent. In 2010, 2,400 substances listed in HSDB were added to Haz-Map, with another 600 chemicals and 10 diseases added in 2011 (Brown, 2012c). Further revisions to Haz-Map were made in December 2012. Hazardous agents may also be added to the database at the instigation of DOL. The SEM contractor is required to "develop a list of toxic substances whose Haz-Map profiles are to be prioritized for updating by the DOL Project Medical Consultant," subject to approval by the DOL (see Chapter 3). Although the committee was not informed as to the identity of the DOL project medical consultant, the DOL contractor stated that "funding is provided to Dr. Brown for research of toxic substances of interest to DOL" (Stalnaker, 2012). DOL refers substances on the SEM list to the Haz-Map developer for priority consideration. He also occasionally reviews proposed agent–disease links that have come to the attention of DEEOIC staff,

often from EEOICP claimants or their representatives (Karoline Anders, DOL DEEOIC, personal communication, October 9, 2012).

SUMMARY

In this chapter the committee has reviewed the approach by which Haz-Map links exposure to toxic substances to occupational diseases. Haz-Map was developed "for health and safety professionals and for consumers seeking information about the adverse effects of workplace exposures to chemical and biological agents." The committee restricted its review to the selection and evaluation of the information in the "Diseases" field, as that is the only field used by DOL to provide the substance–disease links in the SEM "Specific Health Effects" field. As of December 2012, there were more than 7,000 substances listed in Haz-Map.

The committee has not reviewed every substance–disease link in Haz-Map or all the links imported into SEM. However, the committee has attempted to highlight areas where the Haz-Map "Diseases" links are ambiguous and where the process for making those links is unclear. Although the committee appreciates the enormous amount of work that has gone into the development and maintenance of the database, the committee identified several limitations to the "Diseases" field as used by SEM in the context of the EEOICP compensation system. The limitations include the lack of transparency in data sources used for determining each toxic substance–occupational disease link and in the criteria for establishing these links, particularly in connection with noncancer diseases; the lack of a clear weight-of-evidence approach; the lack of peer review; the overreliance on textbooks such that information may be neither comprehensive nor up to date; and the lack of clarity on what toxic substances and fields have been updated by the Haz-Map database developer.

REFERENCES

Brown, J. A. 2008a. Haz-Map: A useful tool for SH&E professionals. *Professional Safety* 53(3):24-28.

Brown, J. A. 2008b. An internet database for the classification and dissemination of information about hazardous chemicals and occupational diseases. *American Journal of Industrial Medicine* 51(6):428-435.

Brown, J. A. 2010. *Database Overview*. http://www.haz-map.com/overview.htm (accessed February 15, 2012).

Brown, J. A. 2012a. *Causal Agent-Cancer Links in Haz-Map*. http://www.haz-map.com/cancer.htm (accessed October 11, 2012).

Brown, J. A. 2012b. *Database Overview*. http://www.haz-map.com/overview.htm (accessed December 5, 2012).

Brown, J. A. 2012c. *Haz-Map: A Process to Map Occupational Toxicology Information into a Relational Database*. Presentation at the First Committee Meeting, January 23, Washington, DC.

Brown, J. A. 2012d. Questions Posed by IOM Committee and Subsequent Answers from Dr. Brown, February 22, 2012. http://www.iom.edu/Activities/PublicHealth/SEMDatabaseReview/2012-MAR-16.aspx.

Cogliano, V. J. 2006. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. http://oehha.ca.gov/prop65/public_meetings/pdf/IARCVJCogliano121206.pdf (accessed March 18, 2012).

EPA (Environmental Protection Agency). 2006. *Peer Review Handbook, 3rd Ed.* Washington, DC. www.epa.gov/peerreview/pdfs/peer_review_handbook_2006.pdf (accessed January 23, 2013).

EPA. 2012. *A Chronological History of Causation for Environmental Scientists*. http://www.epa.gov/caddis/si_history.html (accessed July 27, 2012).

Hakkinen, P. 2012. *Presentation to the IOM Committee Covering NLM Databases and Review Processes for Haz-Map*. Presentation at the Second Committee Meeting, March 16, Washington, DC.

HHS (Department of Health and Human Services). 2012. *NTP Monograph on the Health Effects of Low-Level Lead Evaluation*. National Toxicology Program, Office of Health Assessment and Translation. http://ntp.niehs.nih.gov/NTP/ohat/Lead/Final/MonographHealthEffectsLowLevelLead_prepublication_508.pdf (accessed July 23, 2012).

Hill, A. B. 1965. The environment and disease: Association or causation? *Proceeding of the Royal Society of Medicine* 58:295-300.

IARC (International Agency for Research on Cancer). 2006. Preamble. *IARC Monographs on the Evaluation of Carcinogenis Risks to Humans: Preamble*. Lyon, France: World Health Organization.

IARC. 2012. *Chemical Agents and Related Occupations: A Review of Human Carcinogens, Volume 100F*. Lyon, France: World Health Organization.

IOM (Institute of Medicine). 2010. *Gulf War and Health. Volume 8, Update of Health Effects of Serving in the Gulf War*. Washington, DC: The National Academies Press.

Laamanen, I., J. Verbeek, G. Franco, M. Lehtola, and M. Luotamo. 2008. Finding toxicological information: An approach for occupational health professionals. *Journal of Occupational Medicine and Toxicology* 3:18.

Lewandowski, T. A., M. R. Seeley, and B. D. Beck. 2004. Interspecies differences in susceptibility to perturbation of thyroid homeostasis: A case study with perchlorate. *Regulatory Toxicology and Pharmacology* 39(3):348-362.

Marks, J. G., and V. A. DeLeo. 1997. *Contact and Occupational Dermatology.* 2nd ed. St. Louis: Mosby-Year Book.

Monson, R. 1990. *Occupational Epidemiology*. 2nd ed. Boca Raton, FL: CRC Press.

NLM (National Library of Medicine). 2011. *Hazardous Substances Data Bank (HSDB): Comprehensive, Peer-Reviewed Toxicology Data for about 5,000 Chemicals*. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (accessed February 15, 2012).

NRC (National Research Council). 1997. *Peer Review in the Department of Energy–Office of Science and Technology: Interim Report*. Washington, DC: National Academy Press.

OMB (Office of Management and Budget). 2004. *Final Information Quality Bulletin for Peer Review.* http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf (accessed January 23, 2013).

Rosenstock, L., and M. Cullen. 2004. *Textbook of Clinical Occupational and Environmental Medicine*. 2nd ed. London: Elsevier Inc.

Schottenfeld, D., and J. F. Fraumeni. 2006. *Cancer Epidemiology and Prevention*. 3rd ed. New York: Oxford University Press.

Siemiatycki, J., L. Richardson, and P. Boffetta. 2006. Occupation. In *Cancer Epidemiology and Prevention*. 3rd ed., edited by D. Schottenfeld and J. F. Fraumeni. New York: Oxford University Press. Pp. 322-354.

Stalnaker, K. 2012. *U.S. DOL Site Exposure Matrices, EEOICPA Part E*. Presentation at the First Committee Meeting, January 23, Washington, DC.

Wakefield, J. C. 2007. *Napthalene: Toxicological Overview*. Health Protection Agency. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203084377981 (accessed July 23, 2012).

3

Site Exposure Matrix Database

The Department of Labor's (DOL's) Site Exposure Matrix (SEM) database (www.sem.dol.gov) is an important tool in the claims adjudication process for workers and contactors covered by the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) Part E and the Radiation Exposure Compensation Act (RECA). SEM is a Web-accessible database of site-specific information, including a list of toxic substances that have been identified at Department of Energy (DOE) and RECA facilities and covered by EEOICPA Part E. In order to facilitate consolidation of information on DOE facilities, the DOL worked with a contractor to develop a database to store site-specific data, such as a list of DOE EEOICPA-covered facilities, an inventory of toxic substances present at each facility, job descriptions, and production processes. As of October 2012, there were 13,697 toxic substances listed in SEM (DOL, 2012e).

In this chapter, the committee discusses the development, content, structure, and updating of SEM, as well as its strengths and weaknesses. The committee recognizes that the database might be more accurately described as a "hazardous substance" rather than an "exposure" database. Exposure information—that is, the potential of a toxic substance to enter the body and cause harm—includes route (inhalation, dermal, oral), intensity (concentration, dose), duration, and frequency. Such information is not included in the database.

Although the majority of recommendations for improving SEM are provided in Chapter 4, specific suggestions are made in this chapter that could address some of the criticisms DOL has received from the Government Accountability Office (GAO), the DOL ombudsman, and the public. In accordance with its charge, the committee focused on the links between toxic substances and associ-

ated occupational diseases found in SEM. These links are imported solely from the "Diseases" field in the Haz-Map database (see Chapter 2).

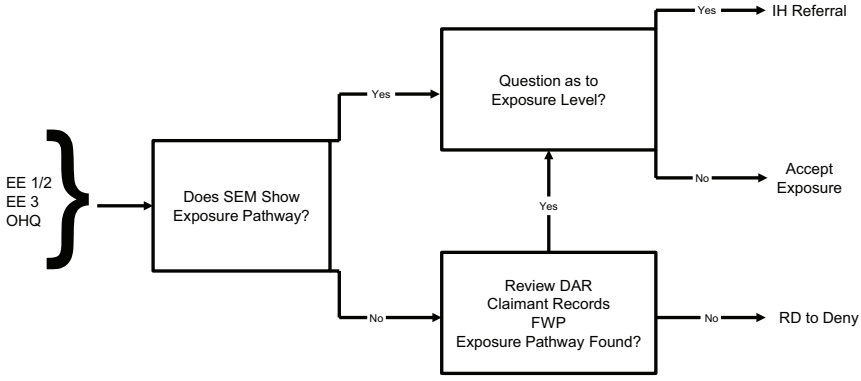
USE OF SEM IN THE EEOICPA CLAIMS PROCESS

For context on how SEM is used, DOL provided the committee with an overview of the EEOICP claims process (see Figure 3-1). Each pathway shows that information in the database is not the final determinant of either an exposure pathway (Figure 3-1a) or a toxic substance–disease link (Figure 3-1b). For example, a claims examiner uses the claimant's employment history to verify that the claimant was potentially exposed to a toxic substance based on location, job category, or process (Figure 3-1a). Based on a claimant's employment history and medical information, a claims examiner can also check to see whether a causal link between the claimant's disease and any toxic substance exists in SEM (Figure 3-1b). DOL appears to use "Exposure Pathway" to indicate the presence or absence of a substance at a DOE site. If a causal link is found in the database, the claims examiner can recommend that the claim be accepted if a well-rationalized link between the claimant's diagnosis and occupational exposure to a toxic substance is supplied by the treating physician and an exposure pathway is evident (Figure 3-1). If a link between a claimant's disease and exposure to a toxic substance is not given in the database, the claimant may provide additional supporting information and statements from the treating physician regarding the etiology of his or her disease. The claims examiner may further refer the claim to a toxicologist, a district medical consultant, or an industrial hygienist for further evaluation before a decision is made to accept or deny the claim (DOL, 2012e).

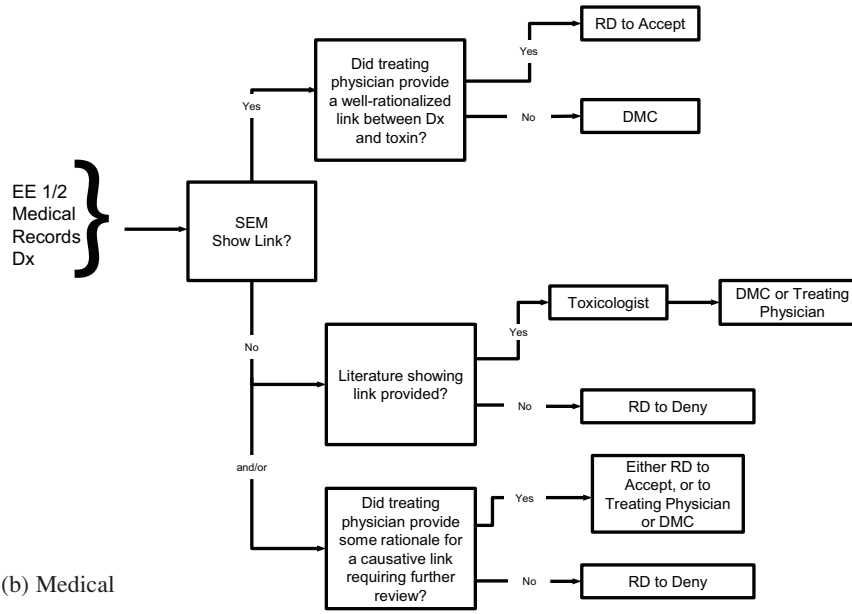
SEM is periodically updated. As the introductory website states:

> The exposure and diagnosed illness information provided on this website is not complete. Toxic substance use at each facility is continuously evaluated and new substances are added as their presence is discovered. DOL places SEM data on the Internet in an ongoing effort to obtain and organize exposure and disease information for all covered Part E facilities. The website was developed to support DOL Part E claims adjudication. The information presented is not an attempt to provide a complete history of any DOE or RECA facility. (http://www.sem.dol.gov; accessed January 24, 2013)

DOL states that "SEM represents the most current, accurate, and comprehensive information regarding toxic substances and their known health effects, and is updated regularly" (DOL, 2008). The current version of the database used by claims examiners and the version available to the public on the Internet contain the same information, although initially there were differences in the available information due to DOE security concerns. DOL asserts that the security concerns have been resolved and that there are no longer differences between the content of the public and the internal SEM databases (Anders, 2012a).



(a) Exposure



(b) Medical

FIGURE 3-1 The DEEOIC claims process for determining (a) exposure and (b) medical information. This flow diagram was created by DEEOIC staff to describe the use of SEM in the claims process.
NOTE: DAR = document acquisition request; DMC = district medical consultant; Dx = diagnosis; EE 1/2 = employee's claim form and survivor's claim form; EE 3 = employment history form; FWP = former worker program; IH = industrial hygiene; OHQ = occupational health questionnaire; RD = recommended decision; SEM = site exposure matrix.
SOURCE: Anders, 2012b.

Any judgment regarding whether exposure to a toxic substance causes a specific health effect requires a clear definition of the exposure of interest. SEM provides a set of indicators showing which exposures are presumed to occur in which occupations. The entries in the database indicate whether a worker in a specific job is considered potentially exposed to a given substance, but they contain no information on the probability of exposure, or the intensity, duration, or route of exposure. In order to assess the validity of links between an occupational exposure and disease, the committee recognized the need to consider the range of exposure scenarios involving concentrations, duration, and route of exposure to a toxic substance.

DEVELOPMENT OF SEM

Development of SEM began in early 2005 with database design criteria and a pilot project. It continues to expand as new information becomes available. DOL's goal is to identify all possible toxic substances that had been used at DOE sites. The database was populated with data from more than 11,000 documents collected from DOE sites and archives (Stalnaker, 2012). According to the DOL SEM contractor, sources of information included the following:

- worker and site interviews;
- record gathering on the substances used at major DOE facilities (e.g., work procedures, industrial hygiene reports, safety analysis reports, job hazard analyses);
- federal and state agencies (e.g., U.S. Environmental Protection Agency [EPA], State of Colorado);
- National Institute for Occupational Safety and Health (NIOSH) profiles;
- textbooks;
- former Worker Program documents; and
- other credible sources (as cited by the DOL contractor).

SEM does not indicate the actual source of any of the site-specific information. Therefore, the user is unable to ascertain whether all potential sources of information have been identified and used to develop the list of toxic substances present at a particular site. However, the public, including former workers, may submit both site-related and disease-related information directly to DOL on the database website (see discussion of external submissions to SEM) (http://www.sem.dol.gov/ComposeSubmittal.cfm).

Creating and updating SEM requires DOE cooperation because it must approve the declassification of any site information, including inventories of toxic substances. The database also contains information about occupational diseases that are associated with each toxic substance found at a site. DOL determined that an appropriate source for such associations was Haz-Map,which is published

online by the National Library of Medicine (NLM), and contains a variety of information about occupational exposures and diseases for more than 7,000 toxic substances (see Chapter 2).

The committee used the publicly available SEM database (http://www.sem.dol.gov/expanded; DOL, 2012e) for its review. The review is based on many hours of accessing the database and an overview of the database by its developer at the committee's first open session. The committee was not given specific information on the architecture of the database, although its structure affects how the database functions, including its search capabilities. An online user's guide is available for SEM that explains the database content, how to search for specific toxic chemicals, and how to filter the results (http://www.sem.dol.gov/expanded/help.cfm; DOL, 2012c).

CONTENT AND STRUCTURE OF SEM

SEM is a site exposure–driven database. To access information on toxic substances, the user must first choose a specific DOE site. Although this feature assists users by taking them immediately to a chosen site, the system may be cumbersome for those who worked at more than one site because each site must be searched independently and results cannot be electronically combined.

The database contains information in two general categories: site-specific exposure information for DOE facilities and universal information (all toxic substances and associated health effects) (see Figure 3-2). Each DOE site may be searched for information on site history, labor categories, processes that used toxic substances, areas and buildings where toxic substances were present, and incidents involving toxic substances. For example, a health physics technician at the Alba Craft site may have worked in four different buildings and performed concrete cutting, debris reduction operations, decontamination activities, decontamination and demolition activities, excavation and backfilling activities, and site waste packaging and shipment activities (see Figure 3-3). This worker may have been exposed to cement, diesel exhaust, gasoline, Hantavirus, *Histoplasma capsulatum*, kerosene, petroleum mid-distillate, and uranium.

Magnifying glass icons next to substances, buildings, and processes indicate that more information is available. In this example, by clicking on the icon next to kerosene, the user can view chemical information and properties for kerosene, the buildings, processes, and labor categories potentially exposed to kerosene at Alba Craft and specific health effects from the Haz-Map database (see Figure 3-3).

Specific Health Effects in SEM

DOL and its contractor control and choose what information from Haz-Map is used in SEM. The "Specific Health Effects" field for each toxic substance in SEM is populated directly from the Haz-Map "Diseases" field (see Chapter 2 and

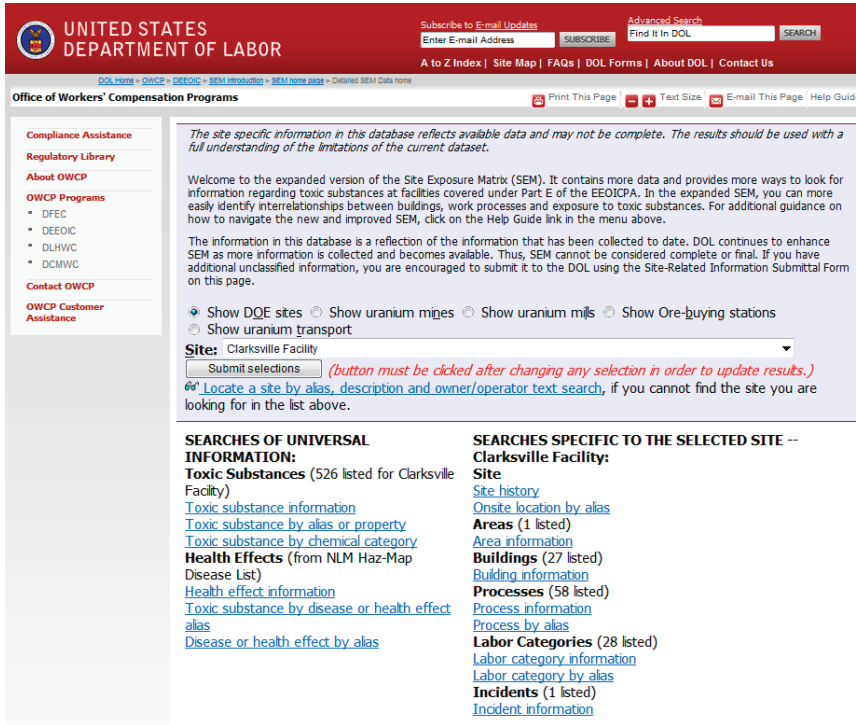


FIGURE 3-2 SEM search options for a specific DOE site. The Clarksville Facility is shown in this example.
SOURCE: DOL, 2012e.

Figure 3-3). The "Specific Health Effects" field contains health effects information based solely on "established relationships between toxic substance exposures and occupational diseases as reported by the National Library of Medicine (NLM) on its Haz-Map website (http://Haz-Map.nlm.nih.gov)" (DOL, 2012c). Although DOL relies on the NLM Haz-Map database for toxic substance–occupational disease links, NLM does not establish those causal associations as might be implied from that statement. As stated on the NLM website, "the views and opinions of authors expressed on NLM Web sites do not necessarily state or reflect those of the U.S. Government" (NLM, 2012).

No other health effects information from a Haz-Map toxic substance profile (see Chapter 2 for all the database fields) is included in SEM (Stalnaker, 2012). For example, in the kerosene profile, Haz-Map lists "CNS solvent syndrome" and "secondary hepatoxin" as adverse effects and "chronic solvent encephalopathy" and "solvents, acute toxic effect" as the occupational diseases that may result

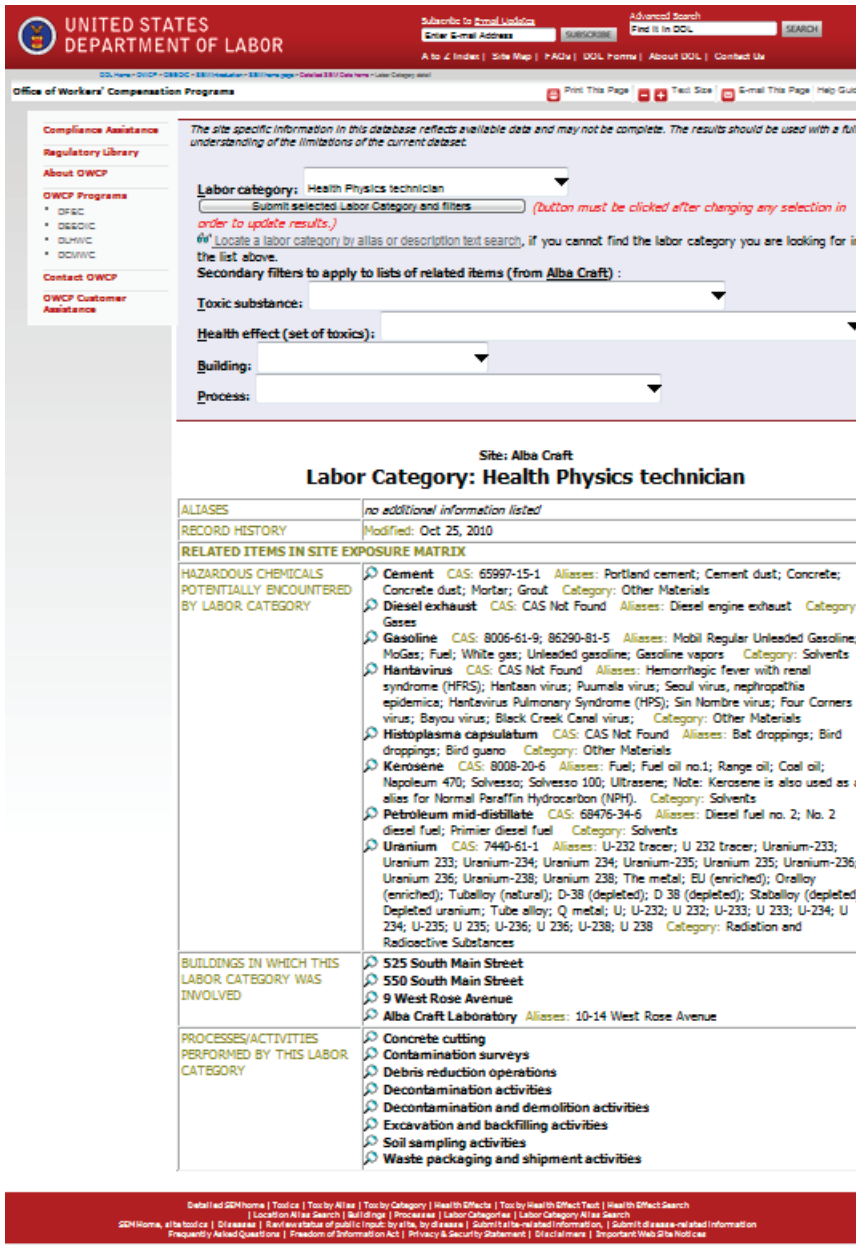


FIGURE 3-3 Example of SEM record for a health physics technician at the Alba Craft Facility.
SOURCE: DOL, 2012e.

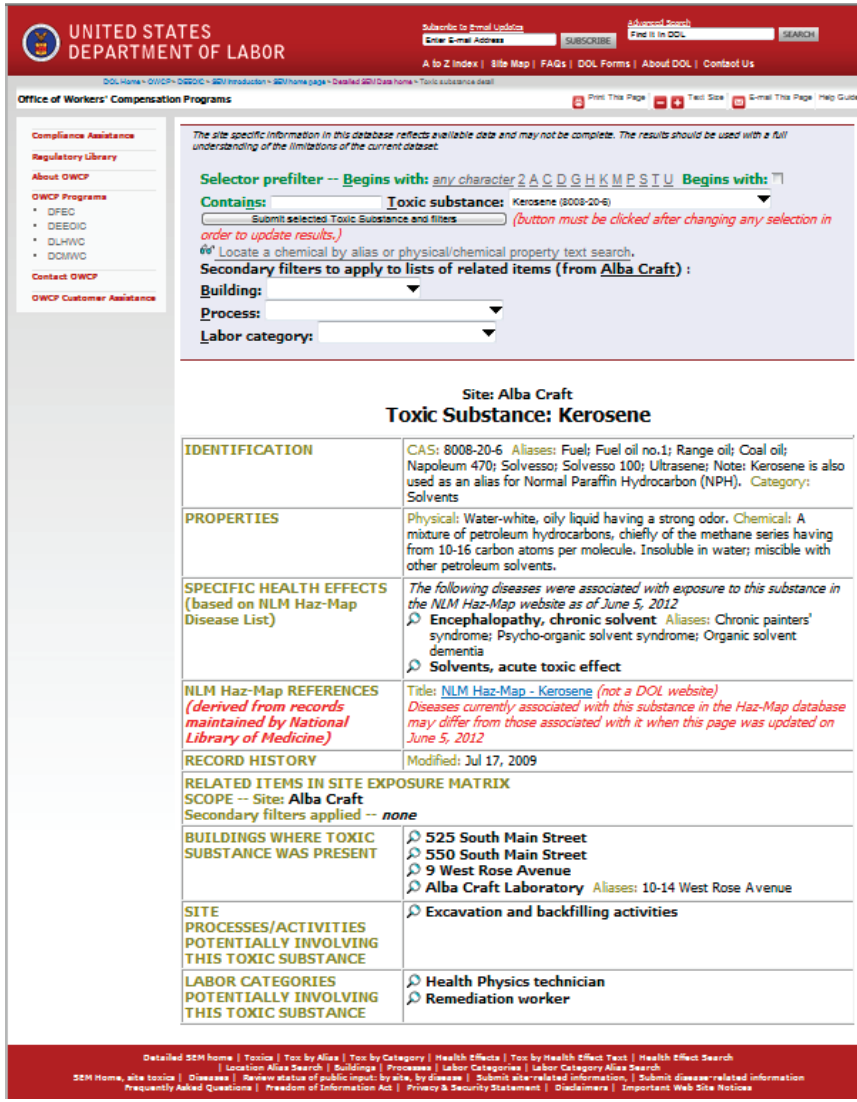


FIGURE 3-4 Example of SEM record for kerosene found at the Alba Craft site. SEM database queried on October 2, 2012.

from exposure to kerosene (see Box 2-1), but, only the latter two health effects are included in SEM (see Figure 3-4). Furthermore, SEM does not include any health effects that are not covered under Part E (e.g., birth defects), even if that health effect is included in Haz-Map, that is, it includes only those health effects that may be compensable under EEOICPA.

While more comprehensive information about the health effects associated with a toxic substance is available from Haz-Map (for example, skin designations), the DOL explicitly instructs its claims examiners to use only Haz-Map information that is included in SEM. The Claims Examiner Manual states:

> The occupational disease links in SEM are imported from the widely accepted and well rationalized medical science database called Haz-Map, a database of the National Library of Medicine (NLM). While the NLM database, Haz-Map, is often utilized in other circumstances as a resource, the claims examiner must never use Haz-Map as a development or adjudicatory tool. Only SEM is acceptable for use in case file development and adjudication. It is unacceptable to base a decision, particularly a remand order, on any information contained in Haz-Map beyond the established links populated directly into SEM. Haz-Map serves many purposes for the public and medical professional fields and will often cite suggestive research that it has not accepted as a basis for finding a demonstrable link between a given substance and an occupational illness. (DOL, 2012b)

Haz-Map, as noted in Chapter 2, contains more than 7,000 agents and 235 occupational diseases (Brown, 2012, 2013), whereas SEM contains 13,697 toxic substances as of October 2012 (DOL, 2012d) and more than 120 occupational diseases (Stalnaker, 2012). Many toxic substances in SEM, such as 1,5-cyclooctadiene platinum II chloride, are not included in Haz-Map and therefore, will have no health effects information available. DOL has developed its own internal guidance on a few occupational disease associations, such as DOL Bulletin No. 08-15, *Adjudication of Part E Claims for the Conditions of Parkinsonism and Parkinson's Disease, May 30, 2008*, but these bulletins are not included in SEM. SEM also contains many commercial products, mixtures, and compounds (e.g., 1 Shot Graphic Coat Enamel) that are or have been used at DOE sites, but these substances are not included in Haz-Map. Some substances in Haz-Map are not in SEM because they have not been identified or confirmed as being used at any DOE site, such as carob bean gum; however, these substances are included in Haz-Map because they have been found in other occupational settings. It should also be noted that not every toxic substance listed in Haz-Map has adverse health effects information. This may be because the agent has not been tested for toxicity or it may not be identified with any adverse effects, occupational or otherwise, in the medical, epidemiological, or industrial hygiene literature. Neither Haz-Map nor SEM, however, distinguishes between substance–disease links for which there is no evidence and those where the evidence that does not support a causal relationship between the substance and a disease. The committee believes this lack of clarity about the reason for no link may be confusing if the absence of a link in SEM is always interpreted to mean that the evidence does not support a link.

Updating SEM Content

Updating the SEM is a continuous process. Although there is no formal schedule for reviewing any specific components (Paragon Technical Services, 2012), DOL indicates that updates are made approximately every 6 months (Karoline Anders, DOL DEEOIC, personal communication, October 9, 2012). According to the DOL and its contractor, the SEM can be updated in three ways: external submissions from the public of site-related or disease-related information; incorporation of Haz-Map updates for health effects links; and receipt of new information from DOE. In the following sections, the committee discusses updates to the SEM based on external submissions of information and on revisions to Haz-Map. Because DOE does not provide health effects information to SEM, nor was the committee asked to comment on DOE activities with regard to it, updates to the database based on DOE information are not discussed further in this report. Regardless of the source of new information for SEM, for security reasons, DOE must approve all updates before they are publicly released.

Although a SEM record indicates when it was last updated, there is no indication as to what specific information or field was updated, added to, or revised. This lack of this information makes it extremely difficult for the user to know if the most current information has been incorporated. For example, the record for o-toluidine was last updated on November 14, 2011, according to the "Record History" field; however, the "Specific Health Effects" field states that "No diseases were listed in NLM Haz-Map (i.e., NLM had not identified any occupational disease related to exposure to this substance) as of June 5, 2012" and "Diseases currently associated with this substance in the Haz-Map database may differ from those associated with it when this page was updated on June 5, 2012," suggesting that the page had indeed been reviewed as of June 5, 2012 (accessed December 3, 2012). There is no explanation of why the review occurred or what information was being considered. Statements such as these can be confusing to the user.

The committee recognizes that the periodic updating of both Haz-Map and SEM as new information on toxic substances and occupations disease links become available is essential to assisting claimants and claims examiners. The committee encourages these ongoing updates to both Haz-Map and SEM and, therefore, has indicated in its report the dates a link was evaluated, recognizing that since then a link may have been added, revised, or deleted. The committee expects that between the time this report was written and when it is published, there may be additional changes to both databases and, thus, the committee's statements about a specific link may no longer be accurate. In fact, the committee was told that many revisions were made to SEM in December 2012 (Karoline Anders, DOL DEEOIC, personal communication, January 2, 2013); however, the committee was unable to review these revisions for its report.

External Submission of Content

External submissions may come directly from claimants, from their representatives or advocates, and from the general public (Stalnaker, 2012). On the SEM homepage, DOL provides a mechanism for public submission of site-related and disease-related information to be considered for addition to the database (see Figure 3-5) (http://www.sem.dol.gov). The SEM homepage states that "comments and documentation regarding the use of toxic substances at covered Part E facilities and documentation of established occupational illness links are welcome." The DOL contractor told the committee that there is a structured internal process for reviewing submitted information, but no formal external review process.

Another button on the SEM homepage labeled "Status of disease-related input" allows users to view the toxic substance–disease links that have been submitted and indicates whether the proposed link has been accepted by DOL and, therefore, is in the queue to be added to the SEM (see Figure 3-6). Before a toxic substance–disease link is added to SEM it is reviewed by the Haz-Map

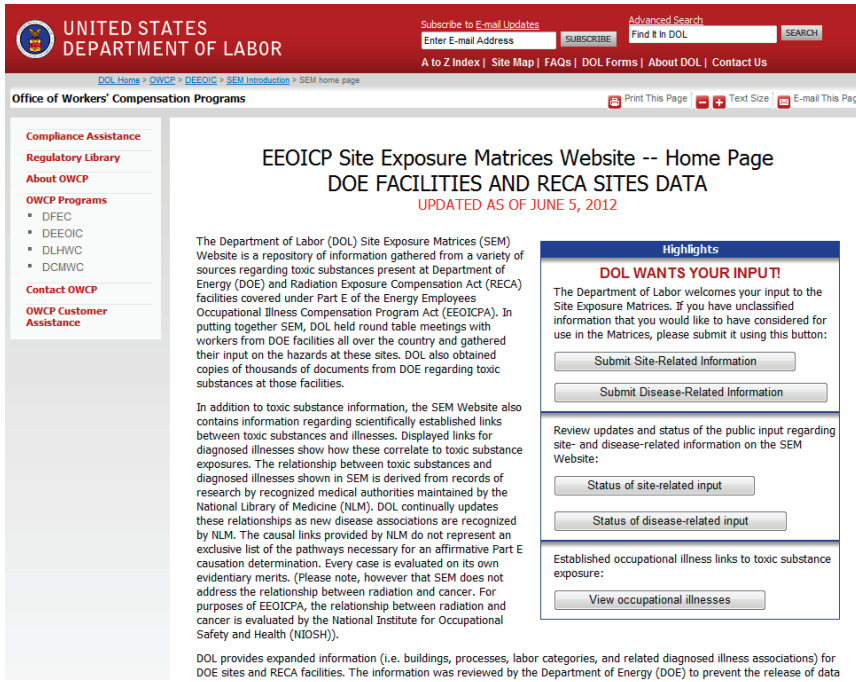


FIGURE 3-5 Screen capture of SEM homepage indicating highlights for public input. SOURCE: DOL, 2012d (accessed January 23, 2013).

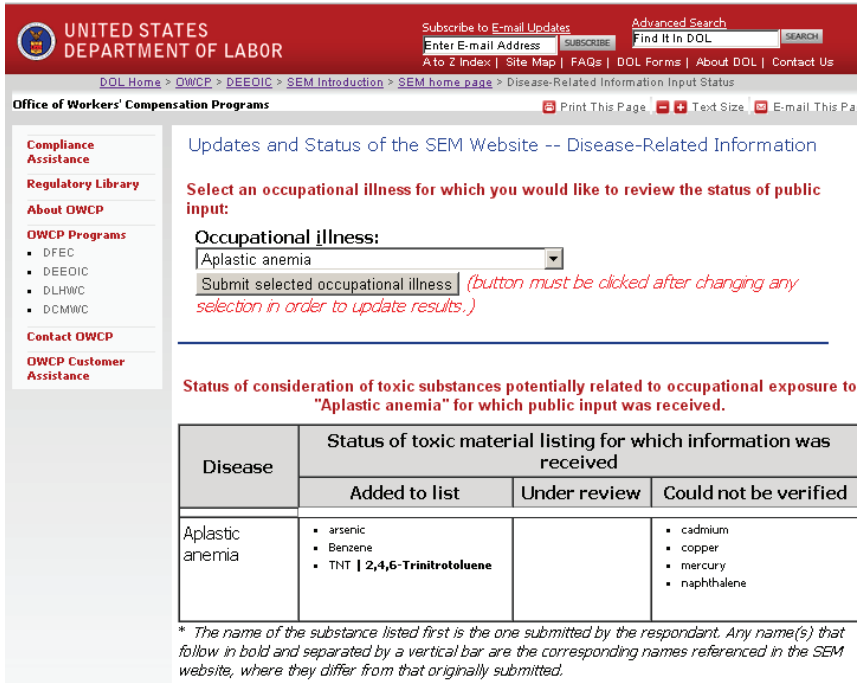


FIGURE 3-6 Screen capture on information on the status of SEM.
SOURCE: http://www.sem.dol.gov/Status.cfm for aplastic anemia (accessed January 22, 2013).

developer for inclusion in Haz-Map. If the Haz-Map developer accepts the link based on review of the evidence submitted by the public and other sources, the occupational disease is added to Haz-Map, and only then can it be added to the queue for a SEM update, pending review and approval by DOE. Clicking on the disease-related information button on the SEM homepage takes the user to a list of diseases. Once a disease is selected, the user sees a table (see Figure 3-6) that lists the toxic substances for which the disease link has been accepted, is under review, or has not been verified (and thus is no longer being considered for possible addition to SEM).

Updating Health Effects

The toxic substance–occupational disease links in SEM are updated after revisions are made to the occupational disease fields in Haz-Map, because the source of those links is Haz-Map. DOL can make ad hoc requests of the Haz-Map

developer to review or add substance profiles to Haz-Map to complement data needs in SEM. For example, such a request may be made if new external information is received on a substance or if DOE adds new chemicals for a site. The DOL SEM contractor is required "to ensure that the Haz-Map information used in support of the SEM project is properly managed, evaluated, and input into the system in a timely manner. Furthermore, the Contractor shall ensure that the SEM information is consistent with the information contained in the NLM Haz-Map database" (DOL, 2010). However, there are no contract specifications as to what is meant by "evaluated," nor is there a requirement that any of the information be formally or informally peer reviewed at any point in the update process.

NLM publishes quarterly updates to Haz-Map, as described in Chapter 2. Changes to the toxic substance–disease links in that database are then imported into SEM for all toxic substances common to both databases. The need for DOE review of each SEM update results in a lag between the availability of new information in Haz-Map and its incorporation into SEM. Given the update schedule for these databases, the committee believes that Haz-Map updates likely take less than a year to appear in SEM. The committee felt that compared with many organizations and governmental agencies, this is an acceptable time frame for updates.

GOVERNMENT ACCOUNTABILITY OFFICE REPORT

In 2008, a highly critical series of articles in the *Rocky Mountain News* (Denver, Colorado) highlighted many complaints from EEOICPA claimants who reported having difficulty navigating the program, years of delay in compensation, and perceived inconsistencies in how claims are adjudicated. The issue caught the attention of several members of Congress who criticized the program and requested that the Government Accountability Office (GAO) review the implementation of the EEOICPA by DOL. The consequent GAO report (2010) addressed four issues: (1) claim processing time; (2) costs of administering the program; (3) the extent to which there was quality control to ensure that claim determinations were supported with objective and scientific information; and (4) actions taken by DOE, NIOSH, and DOL to improve program transparency for claimants. The GAO "reviewed EEOICPA, relevant regulations, and agency technical and procedural guidance for EEOICPA; interviewed officials from the Department of Labor, Department of Energy, and NIOSH; and interviewed members of the Advisory Board on Radiation and Worker Health, the presidentially appointed board that oversees the scientific validity of NIOSH's work, and its contractor" (GAO, 2010).

The GAO report concluded that while independent review of Part B, in the form of its Advisory Board on Radiation and Worker Health, provided sufficient oversight for that section of the act, there was no oversight from outside independent reviewers to ensure the scientific soundness of various aspects of the implementation of Part E. Furthermore, the report specifically stated that "Labor

employs a contractor and a small team of internal experts to continuously update its site exposure matrix. However this effort is not supported by public, outside review to provide assurance that the matrix is comprehensive and scientifically sound" (GAO, 2010). In particular, the report cites the lack of independent review for "the detailed information in the site exposure matrix" (GAO, 2010). GAO had three major recommendations to enhance the oversight and transparency of EEOICPA Part E. First, DOL should strengthen the quality control measures in place for the Part E claims process. A technical review of detailed information in SEM was specifically encouraged. Second, DOE and DOL should formally partner to release more information to be included in the database to better facilitate public access and input. This recommendation also suggested actively seeking feedback from worker representatives and site experts. DOL acted in response to this second recommendation with the release of an expanded version of the SEM database website on January 11, 2011. The new version added six DOE work locations and provided more data for identifying interrelationships between DOE buildings, job categories, work processes, and toxic substances at all locations (DOL, 2011). Third, DOL should develop a formal action plan to respond to its Ombudsman's annual reports that contain major claimant criticisms (GAO, 2010). Subsequently, the DOL did respond publicly to the *Ombudsman's 2010 Annual Report to Congress* in a letter dated April 20, 2011 (Steinberg, 2011).

STRENGTHS OF SEM

The committee commends DOL for developing the SEM database to assist claims examiners and claimants to quickly determine the toxic substances to which a claimant may have been exposed during employment at a DOE EEOICPA-covered facility and the occupational diseases that are associated with exposure to those substances. The committee notes that some of the strengths of the database discussed below are a result of DOL's response to the issues identified in the 2010 GAO report. The SEM strengths include that it

- Contains occupational diseases that are linked to toxic substances found at DOE sites.
- Was developed in consultation with DOE experts and former facility workers. Data was gathered from DOE records at 43 DOE sites, 10 records archives, more than 100 meetings with more than 1,000 current or former DOE workers from 53 facilities, and 20 RECA sites (Anders, 2012a; Stalnaker, 2012).
- Attempts to be comprehensive for all toxic substances used at DOE sites. It includes more than 13,000 substances and trade name products (for example, WD-40) irrespective of their potential toxicity and the amount of exposure or health effects data available. Substances range from the

very toxic, such as chromium VI, to those that do not generally cause harm, such as walnut shells or vitamin B_{12}.

- Includes all DOE facilities covered by EEOICPA Part E, even those that are no longer in operation. The database lists 116 DOE sites and 4,122 RECA sites (DOL, 2012a; Stalnaker, 2012), including sites that have been closed for decades, such as Sacandaga Facility that was in use from 1947 to 1953 (DOE, 2012), sites that are currently being remediated under Superfund (Rocky Flats in Colorado and sites that are currently in operation such as Savannah River in South Carolina).
- Is publicly available on the Internet. Claimants, their families, or their representatives, and the general public can access the database at http://www.sem.dol.gov.
- Allows users to search for a variety of information once a specific DOE facility is chosen (see Figure 3-1) including health effects and toxic substances as well as details about the site itself, such as buildings, processes, labor categories, and site history. A user guide is accessible on the homepage that explains the search functions and fields (http://www.sem.dol.gov/expanded/help.cfm) and the Web interface allows users to drill down through the site-specific information.
- Is updated approximately every 6 months as new site or health information becomes available (Karoline Anders, DOL DEEOIC, personal communication, October 9, 2012).
- Provides a mechanism for the public to submit site-related and disease-related information. As discussed earlier, the database may be updated using information that is submitted by the public regarding substances that were present at sites or substance–disease links.

WEAKNESSES OF SEM

Although SEM has several strengths, there are several concerns that hinder its effective use by claims examiners and the public, and several information gaps that should be filled. Generally, these concerns and gaps are due to lack of information in or functionality of the database. The committee specifically found problems with accessing universal information (non-site-specific information); lack of exposure information; incomplete or inconsistent exposure profiles based on location and job; inability to handle complex exposures, including exposure to mixtures and radioactive substances; failure to consider epidemiologic studies of DOE workers; and the sole use of Haz-Map for the toxic substance–disease links. These problems are discussed in the following sections.

Difficulties in Accessing Information

Although major strengths of SEM are that it is accessible online, is publicly available, and can be searched to identify toxic substances that were present in a building or area at a DOE facility, the committee found that some information was difficult to access.

First, the SEM database is not directly accessible from the homepage (http://www.sem.dol.gov). To access the database, users must follow several steps. At the bottom of the homepage, users must select a facility type, (e.g., DOE facilities, uranium mines, uranium mills, ore-buying stations, or uranium transport) and then select a specific facility on the following page before any further information can be accessed. The user is shown a list of "Toxic substances verified as having been onsite and used at site," with a link to expanded data on the right-hand side of the website. This "expanded" link directs the user to the database where a different site can be selected. If the user selects no site (that is the blank row at the top of the list) access is given to universal information about toxic substances and health effects (see Figure 3-1). Several links are available that allow users to search and select a substance or health effect of interest. The committee finds that easier access to the database and a direct link to it from the homepage would improve use.

Requiring that a single site be selected initially prevents the user from finding universal information, such as all jobs linked to a specific toxic substance or all health effects in the SEM regardless of the site. While this restriction supports a site exposure matrix and limits searches to toxic substances and health effects for a particular site, it prevents the public from investigating exposures and health effects that may have occurred at more than one site or across sites, except for construction jobs (DOL, 2012c). Furthermore, the limited query and filter abilities of the database inhibit quality assurance or quality control review because access to the universal information on toxic substances and health effects is not direct or easy. Improved query operations to help users more effectively search the SEM would enhance its usability for both claims examiners and claimants.

DOL provides access to a list of occupational diseases on the SEM home page (accessible at http://www.sem.dol.gov/Dis.cfm) for "substances with an established causal link to the diagnosed illness as accepted by NLM." The descriptor for the list is misleading, however, because some the substances are commercial products and mixtures (such as BTEX) that are not in Haz-Map and, therefore, do not have the corresponding established disease links. The list of occupational diseases is external to SEM and is not harmonized with information found within the database itself (Karoline Anders, DOL DEEOIC, personal communication, October 9, 2012). Differences between this list and SEM are due to delays in updating. For example, in October 2012, 68 toxic substances are linked to aplastic anemia in the external list, but only 64 substances are listed as causing aplastic anemia using the "Universal Search" within the expanded SEM.

Likewise, 32 substances are linked to laryngeal cancer in the external list, but only 29 are listed in SEM (accessed October 4, 2012).

Lack of Exposure Information for Toxic Substances

SEM is used to confirm the potential presence of a toxic substance at a DOE facility and then to begin the process of determining whether a worker at that facility may have been exposed to the substance and whether his or her disease may be a consequence of that exposure. Generally, to conclude that a disease is caused by exposure to a toxic substance, an exposure assessment is conducted. For a toxic substance–disease link to be causal, the exposure must occur before the health effect, although some exposures may exacerbate existing diseases such as asthma. A formal exposure assessment is "the process of measuring or estimating the intensity, frequency, and duration of human exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new chemicals into the environment." In its most complete form, it describes the magnitude, duration, schedule, and route of exposure; the size, nature, and classes of the human populations exposed; and the uncertainties in all estimates (NRC, 1983). SEM does not contain qualitative or quantitative exposure data, such as air monitoring, or the concentrations (percent by weight) of components of trade name products.

The committee does not know whether or how DEEOIC claims examiners conduct quantitative exposure assessments for Part E and if the exposure assessments are similar to the radiation dose reconstructions developed by NIOSH in support of Part B claims. The committee also does not know how DOL assesses exposure pathways (see Figure 3-1) because assessment is conducted outside of SEM.

Incomplete Site Exposure Profiles

DOL acknowledges that SEM is incomplete. The committee found numerous examples where the lack of toxic substances information for a site could potentially impact claimants. There are several reasons why information may be missing in the database for example, DOL may never have received any documentation or confirmation from DOE that a substance was present at a site. For example, at the Ames National Laboratory, the database indicates that 33 of the 39 buildings contain toxic substances. Information on processes/activities performed in the buildings is available for 36 of the 39 buildings. However, the database identifies only 10 of the 39 buildings with labor categories that might potentially encounter toxic substances. Therefore, the labor categories are not linked to substances that were present based on process and building. Although toxic substances were found in 23 of the 53 buildings at the Albany Research Center, "remediation worker" is the only labor category listed as potentially

encountering those toxic substances. There is no information on labor categories, toxic substances, or processes or activities for the sheet metal, welding, paint, and electrical and electronics shops—areas where exposures to toxic substances would be expected. The extent to which other sites lack information on labor categories for processes or activities that potentially involve exposure to toxic substances is not clear, but should be assessed. These missing toxic substances for labor categories or processes were considered by the committee as a major weakness because links to associated diseases would be missed.

The committee suggests three methods to help identify missing information on substances present at the DOE facilities. First, DOL may draw on similarities between DOE sites where workers performed similar tasks or functions. For example, if there is a wealth of information about toxic substances at one site and a similar site has little information, DOL could reasonably make the assumption that exposures for comparable labor categories, processes, and so forth, would be the same for the second site until more site-specific information becomes available.

Second, some toxic substances are commonly used for a particular job or labor category regardless of the site at which the worker was employed. Therefore, it would be reasonable to expect that such exposures probably occurred even if the substance is not listed for the site (e.g., plumbers are commonly exposed to lead and asbestos regardless of the specific site). Some of this information is available from sources such as Haz-Map or NIOSH's National Occupational Exposure Survey Data for Potential Exposures to Agents by Occupation (NIOSH, 1990).

Third, diseases associated with certain occupations (labor categories), regardless of specific substance, could be added to SEM if those occupations are known to have been conducted at a site. For example, the International Agency for Research on Cancer (IARC) has evaluated the health effects associated with painting (a known carcinogen causing lung and urinary bladder cancer), firefighting (a possible carcinogen), and shift work (a probable carcinogen) without regard for exposure to specific toxic substances (IARC, 2010).

Inability to Assess Complex Exposures

DOL stated to the committee that "SEM handles all exposures individually and is not designed to gauge the effect of co-occurring exposures" (DOL, 2012f). However, most workers in industrial settings, including DOE facilities, would be expected to experience complex exposures to a single substance multiple times, to multiple substances a single time, or to a multitude of substances a multitude of times. Furthermore, the frequency, intensity, and duration of these exposures can vary widely from one time to the next and from substance to substance. In the following sections, the committee discusses the effects of mixtures and chemical

interactions, including chemical–radiation interactions, on the development of disease.

Mixtures

For some mixtures, SEM lists health effects that are associated with the components of a mixture, whereas for other mixtures the links are given for the mixture as a whole. For example, the health effects for diesel engine exhaust and coal tar pitch volatiles in the database are those associated with the mixture itself and not with the individual constituents. However, the following are examples of where the database has links for the individual components in a mixture but not for the mixture itself:

- Gasoline exhaust is associated with 29 possible diseases (e.g., aplastic anemia, bronchiolitis obliterans, male and female infertility) based on Haz-Map disease links to 38 individual toxic substances found in gasoline exhaust. However, Haz-Map does not have an agent profile specific to gasoline engine exhaust.
- Welding fumes are associated with 38 illnesses and diseases, including occupational asthma, bronchiolitis obliterans, acute toxic encephalopathy, spontaneous abortions, and metal fume fever based on Haz-Map links for 43 toxic substances. However, in it, exposure to "welding fumes, not otherwise specified (NOS)," is associated with "pulmonary disease, chronic obstructive" and "pneumonitis, toxic" only.

SEM includes a disclaimer that states "diseases presented for the individual components of the product may not necessarily be indicative of the health effect of the product." However, including information on the health effects of a mixture based on the components of the mixture, instead of using available health effects information on the whole mixture, is inconsistent with existing guidance for assessing the risk of chemical mixtures (ATSDR, 2012a; EPA, 1986, 2000) and can result in the omission of important toxic substance–disease links or erroneous inclusion of health effects for which there is no evidence.

Many of the mixtures used at DOE sites were trade name products, but SEM does not include the identity of the manufacturer, the dates of manufacture, or the component concentrations of these products. Product components and their concentrations can change over time for any number of reasons and therefore, it is important to capture the date of use of a product so that the component list is accurate and any conclusions about links between a given product and diseases are based on the correct product composition. For example, the database indicates that several products, including Pyromark Series 2500 Flat Black Paint, and Scotch-Grip Brand Contact Cement 1357, contain benzene (in addition to other toxic substances); therefore, these products are listed as causative for aplastic

anemia. The product dates, manufacturers, and benzene concentrations in these products are not provided. Material Safety Data Sheets (MSDSs) obtained online for Pyromark Series 2500 Flat Black Paint (dated June 12, 1990) and Scotch-Grip Brand Contact Cement 1357 (dated March 20, 2003) indicate that they do not contain benzene. The period during which these two products contained benzene, the amount of benzene they contained, and the time these products were used at any DOE site are not provided. Thus, the causal association in SEM between aplastic anemia and these two products, both assumed to contain benzene, may be inaccurate.

Lacking information on a product's components, its uses, the potential for exposure, and any additive, synergistic, or antagonistic reactions among components may result in the assumption that any amount of the product or its components can cause the diseases for which Haz-Map has established a link. This aspect of the product/disease association in SEM is overly broad, lacks scientific rationale, and may be misleading. Using only SEM links, it would be logical for a claims examiner or claimant to assume that the risks of developing any of the linked diseases is the same for all components of the mixture regardless of the actual product composition and how it is used. Without appropriate contextual information, the potential for misinterpreting the SEM toxic substance–disease links is substantial.

Chemical–Chemical Interactions

When individuals are exposed to multiple toxic substances, the nature of health effects resulting from exposure to any one of them is likely to be unchanged, although the magnitude of the effects may vary as a result of interactions among the substances. That is, if a mixture contains a component that individually acts as a neurotoxin and one that acts as a vasodilator, both of these components in the mixture are likely to continue to exert their peculiar effects, but the intensity (magnitude) of each of those effects may be greater, lesser, or unchanged because of the presence of the other components. This variation in health effects is knows as a chemical–chemical interaction and these interactions may be additive, synergistic, potentiative, or antagonistic, as described in Box 3-1. The committee has not provided a detailed description of synergism or the related concept of statistical interaction but, rather, refers to basic definitions of chemical–chemical interactions used in standard toxicological references. A more detailed discussion of the identification, estimation, and interpretation of the consequences of synergism would require addressing several complex issues, including the dependence of the identification of synergism on the selection of the statistical model (e.g., multiplicative versus additive), the failure of many methods of identifying synergism to adequately consider underlying biological mechanisms, and the slightly different terminology and perspective of different disciplines (e.g., toxicology, epidemiology, statistics). The committee considered

BOX 3-1
Types of Chemical Interactions and Examples

Additive: For a given effect, the combined magnitude of two or more chemicals is equal to the magnitude for the individual chemicals, i.e., 3 + 4 = 7

Cadmium, arsenic—kidney toxicity (ATSDR, 2004b; Mahaffey and Fowler, 1977; Mahaffey et al., 1981)

Synergistic: For a given effect, the combined magnitude is greater than the magnitude for the individual chemicals, i.e., 3 + 4 = 9

Asbestos, smoking—lung cancer (ATSDR, 2001; Erren et al., 1999)

Carbon tetrachloride, ethanol—liver effects (Eaton and Gilbert, 2008)

Potentiative: The chemical does not cause effects by itself, but increases the magnitude of effect for another chemical, i.e., 0 + 4 = 6

Isopropanol, carbon tetrachloride—liver toxicity (isopropanol does not cause liver toxicity, but can increase liver toxicity caused by carbon tetrachloride) (Eaton and Gilbert, 2008)

Antagonistic: For a given effect, the combined magnitude is less than the magnitude for the individual chemicals, i.e., 3 + 4 = 5

Cadmium, lead—renal toxicity (ATSDR, 2004b; Mahaffey and Fowler, 1977; Mahaffey et al., 1981)

Toluene, benzene—bone marrow toxicity (Plappert et al., 1994)

synergism as required by its the statement of task, but notes that synergism is just one of several types of chemical–chemical interactions that may occur from exposure to multiple chemicals at DOE sites.

Chemical interactions may occur because of toxicokinetic factors—for example, one chemical may enhance the dermal absorption of another chemical, or one chemical may alter the distribution and excretion of another chemical. Interactions can also occur because one substance modifies the metabolism of another—for example, by inducing or inhibiting metabolic enzymes, or by competitive inhibition (Eaton and Gilbert, 2008). Synergistic or potentiative interactions, for which toxicity of a chemical in a mixture is greater than when the chemical is present by itself, can occur if substances affect different components of the same physiological process, such as metabolic pathways or mechanisms that repair or protect cells from damage (European Commission, 2012).

To the extent that synergistic effects between toxic substances may occur, the majority of effects appear to be additive (Ikeda, 1988; Kortenkamp and Hass, 2009). For example, Ikeda (1988) found that of 62 cases of chemical–chemical and chemical–physical interactions reported in studies between 1981 and 1987, 42 resulted in effects that were either additive or less than additive. In cases where the effect was greater than additive (that is, synergistic), exposures were very high. The Agency for Toxic Substances and Disease Registry (ATSDR) has also evaluated interactions for groups of chemicals found at hazardous waste sites. Of 380 different binary combinations of chemicals, 41 percent of the interactions were additive, 15 percent were antagonistic, and 20 percent were synergistic (Pohl et al., 2009). Because the majority of chemical interactions are additive, scientific and regulatory agencies recommend assuming such interactions as a default approach for evaluating exposure to multiple toxic substances (e.g., ATSDR, 2004a; EPA, 2007a). However, because SEM does not include quantitative estimates of risk, the differences between additive and synergistic effects may be less important for mixtures cited in it.

Some of the most well-studied interactions are between occupational exposures and nonoccupational exposures, in particular, smoking and alcohol. Examples of these interactions are given in Box 3-2.

Synergy Between Radiation and Chemical Exposures

Chemical interactions may be particularly relevant for workers who are exposed to radiation—which can act as a tumor initiator by changing normal cells into cancerous cells—and to toxic substances—which can act as tumor promoters by encouraging the growth of cancerous cell. Such interactions may enhance the potency of radiation exposures (Little, 1990).

Evidence of synergism between radiation and toxic substance exposures in occupational settings is scarce although some evidence from nonoccupational settings is available. Synergism between radiation and toxic substances is discussed by Chen and McKone (2001) who note that the risk of secondary acute leukemia is significantly higher for patients treated with both chemotherapy and radiation compared with patients treated with radiation alone. Synergistic interactions between radiation and chemicals has also been observed in mice and rats for various tumor types, including lung (in mice treated with procarbazine and x-rays), mammary (in mice treated with 7,12-dimethylbenzanthracene and ionizing radiation and rats treated with diethylstilbestrol/estrogen and ionizing radiation), and liver (in mice treated with carbon tetrachloride and neutron irradiation). At present, however, there is insufficient evidence to determine whether synergistic interactions between radiation and chemicals would occur in humans (Chen and McKone, 2001).

BOX 3-2
Examples of Interaction Effects Between Occupational and Nonoccupational Exposures

Smoking:

Asbestos and smoking → Lung cancer (Frost et al., 2011; Reif, 1984)

Arsenic and smoking → Lung cancer (Hertz-Picciotto et al., 1992; Tapio and Grosche, 2006)

Cadmium and smoking → Kidney cancer (Reif, 1984)

Radon and smoking → Lung cancer (Mauderly, 1993)

Uranium and smoking → Lung cancer (Reif, 1984)

Vapors, gas, dust, or fumes and smoking → Chronic obstructive pulmonary disease (Blanc et al., 2009)

Alcohol:

TCE and alcohol → Upper gastrointestinal and liver tumors (Caldwell et al., 2008)

Vinyl chloride and alcohol → Hepatocellular carcinoma (Mastrangelo et al., 2004) [note: vinyl chloride is linked with hepatocellular carcinoma (listed as liver cancer) in Haz-Map and SEM]

Dealing with Multiple Exposures in SEM

Chemical–chemical and chemical–radiation interactions are not captured in SEM. DOL informed the committee that "in general, the concept of synergistic/additive effects is not widely accepted in the scientific literature, and for this reason, DEEOIC also does not recognize synergistic/additive effects per se" (DOL, 2012f). The committee disagrees with this assessment and finds that the potential for chemical interaction is widely recognized in the scientific literature, and regulatory agencies such as EPA and ATSDR have issued guidance on addressing combined exposures to multiple chemicals, including chemical interactions (ATSDR, 2004a; EPA, 2007a; European Commission, 2012). The committee also finds that the evidence for chemical–radiation interactions for substances in SEM is not strong enough to make conclusions about causal associations at this time, although research is ongoing. As new information becomes available, these issues should be reassessed.

Because toxic substances interactions are more likely to influence the magnitude rather than the nature of health effects (i.e., synergistic or potentiative

interactions would cause effects at lower exposure levels), assessing interactions for complex exposures to multiple substances requires knowledge of the amount of exposure to each substance. Because SEM does not include information on the duration, concentration, or route (inhalation, ingestion, skin contact) of exposure, it is unlikely that chemical interactions could be linked to specific health effects with accuracy and confidence. However, substances for which there is sufficient evidence of synergistic or potentiative interactions could be flagged or listed in a new field in SEM to trigger additional review by appropriate scientific staff.

Failure to Incorporate Epidemiologic Studies of DOE Workers

The committee asked DOL if and how epidemiologic studies of DOE workers are incorporated into SEM. DOL acknowledged the wealth of data on DOE workers but indicated that such studies were not useful because they pertained to radiation health effects, which is outside the scope of the database. For exposure information, DOL incorporated in it only one report that indicated that mercury[1] was used at Oak Ridge (DOL, 2012f).

Many studies have been conducted to assess health outcomes in DOE workers. Although most of them do in fact focus on radiation exposure, the committee found some studies of DOE workers with information on occupational exposures by specific jobs or aspects of employment (such as Kubale et al., 2008; Loomis and Wolf, 1996; Makie et al., 2005; Polednak and Hollis, 1985; Reyes et al., 1984; Richardson et al., 2007). There are fewer studies that estimate exposure to specific substances (Carpenter et al., 1988; Chan et al., 2010; Dement et al., 2003; Godbold and Tompkins, 1979; Ritz, 1999). For example, an analysis of data maintained by DOE's comprehensive epidemiologic data resource of 3,814 uranium processing workers at the Fernald Feed Materials Production Center specifically looked at cancer mortality associated with use of trichloroethylene, cutting fluids, and kerosene. Several cancer sites were significantly related to exposure to these substances (Ritz, 1999). The committee acknowledges that a scientifically rigorous causal relationship should not be based on one study alone and that additional evidence (such as animal or mechanistic studies, case reports) is needed to support the relationship. Nevertheless, studies such as that by Ritz (1999) might be useful because they are conducted in the population of interest—workers at DOE facilities—and provide specific site, job, process, and in particular, exposure information. The committee urges DOL to reconsider the epidemiologic and medical surveillance studies conducted on DOE workers to inform substance–disease links in SEM.

[1]"Mercury Releases from Lithium Enrichment at the Oak Ridge Y-12 Plant—A Reconstruction of Historical Releases and Off-Site Doses and Health Risks (January 7, 1999) (Anders, 2012a).

Use of Haz-Map for Causality in SEM

Haz-Map was developed to provide a causal link between a toxic substance and an occupational disease, information that is not provided as concisely or simply by other databases. Although the availability of toxic substance–disease links in SEM is a major strength of the overall database, the sole use of Haz-Map to provide those links is problematic for several reasons (also see Chapter 2). Because of SEM's reliance on only Haz-Map, its links lack

- external peer-review;
- transparent references and supporting documentation;
- explicit causal criteria for noncancer effects; and
- indication of weight-of-evidence evaluations.

As discussed in Chapter 2, the Haz-Map database was developed for a different purpose than SEM.

Interpretations of Causality

The DOL interpretation of the statutorily imposed causative burden in the claims process is not part of the committee's charge. However, the committee believes it is important to discuss SEM's reliance on the Haz-Map criteria for establishing toxic substance–disease links because these may affect the interpretation of what constitutes a causal link.

Haz-Map uses strict criteria for identifying toxic substances that cause cancer (IARC Group 1), but has ambiguous criteria for identifying toxic substances that cause noncancerous occupational diseases (see Chapter 2). EEOICPA states that an illness or disease may be compensable if "it is at least as likely as not that exposure to a toxic substance at a DOE facility was a significant factor in aggravating, contributing to, or causing the illness." The "Diseases" field of Haz-Map does not capture information on exposures that aggravate or contribute to diseases.

For EEOICPA Part B, quantitative risk assessment methods are used to estimate a claimant's ionizing radiation dose and the probability (or distribution of such probabilities) that their disease was caused by their occupational radiation exposure. Risk assessments may be conducted even under conditions of uncertainty regarding the strength of the association between an exposure and an outcome.

Unlike Part B, probability of causation calculations are not used for EEOICPA Part E. One reason is that such calculations require exposure information for chemicals and quantitative risk coefficients for each chemical exposure and outcome in order to calculate individual probabilities of causation; neither is available for the majority of scenarios encountered by claims examiners. Therefore,

for Part E, claims examiners make judgments about the etiology of a claimant's diseases on a case-by-case basis, using information on what toxic substances are accepted causes of the disease, the magnitudes of the claimant's exposures, and temporal characteristics, such as induction and latency periods. SEM serves as a guide to substances that are causes of specific diseases. However, it does not provide a framework, such as the one formalized for probability of causation calculations under Part B, for incorporating uncertainty into judgments on causation.

Information Sources for Evaluating Human Health Effects

Although the use of Haz-Map for toxic substance–disease links in SEM has advantages such as the relatively large number of substances in the former and the established links for those substances, the committee finds that Haz-Map should not be the sole source of such links for SEM and suggests that other databases and information sources should be considered by DOL. SEM would benefit from adding exposure and toxicological information, for example, the route and the levels of exposure. For example, the Haz-Map database includes information such as permissible exposure limits (PELs) and skin designations that are not imported into SEM. Exposure limits, such as PELs and threshold limit values (TLVs), are useful because they provide qualitative information about the potency of a substance. Substances with lower PELs or TLVs are more potent or toxic than ones with higher TLVs or PELs. Skin designations provide qualitative information on the potential for exposure. Substances that have skin designations can enter the body through skin absorption and inhalation, so the toxic effects are potentially increased. Incorporation of such additional information from Haz-Map or other sources may facilitate DEEOIC's ability to better evaluate the link between substance and disease for an individual.

The committee identified several databases and other resources that would populate health effects information in SEM. While some of these attributes are subjective, the committee considered them in the context of SEM and EEOICPA needs. These attributes include

- weight-of-evidence evaluations for occupational health effects and exposures,
- peer review,
- easy to use,
- transparent with methods clearly described,
- field contents appropriately referenced,
- communicative so that toxic substance–disease linkages are clear and accessible to nonexpert audiences,
- publicly available for free or minimal cost, and
- comprehensive.

There are many authoritative organizations that conduct evaluations of health effects of toxic substances, including occupational exposures and diseases, with the above-mentioned attributes. Table 3-1 lists some sources that the committee believes are particularly relevant and useful to augment the toxic substance–occupational disease links in SEM. Although many of these sources are in Haz-Map's reference list, it is not clear if they are regularly consulted or if the Haz-Map profiles are updated as new evaluations are made available. There is also additional detailed information available in these sources that Haz-Map does not incorporate.

Several of these information sources assess health effects primarily on the basis of human data; however, some also incorporate animal and mechanistic studies as supporting evidence (e.g., IARC monographs). These assessments generally follow a systematic methodology for collecting and analyzing data, are comprehensive, undergo extensive internal and/or external peer review, and are publicly available on the Internet free of charge, except for ACGIH TLV documentation, which has to be purchased and does not undergo external peer-review. Most importantly, these assessments are based on a weight-of-evidence approach and document the evidence used. Other databases are available that contain a wealth of data about health effects associated with toxic substances, such as the NIOSH Registry of Toxic Effects of Chemical Substances (RTECS; http://www.cdc.gov/niosh/rtecs); however, these databases vary by cost, extent of technical or peer review, and evaluation or synthesis of data.

Laamanen and colleagues (2008) reviewed more than 800 toxicological databases that might be used by occupational health professionals. To assess usefulness, content quality, and ease of use, each database was evaluated on the basis of the availability of a search engine, the factual information on toxic substances, and user costs. The authors found five databases to be particularly useful for occupational health professionals: GESTIS, an international database of occupational exposure limits (http://www.dguv.de/ifa/en/gestis/limit_values); ESIS, the European chemical Substances Information System that contains inventories of chemicals, their use, import and export, and associated hazards (http://esis.jrc.ec.europa.eu); the NLM Hazardous Substance Data Bank (HSDB) and TOXNET, a NLM search product that links to many databases (http://toxnet.nlm.nih.gov); and the NIOSH *Pocket Guide to Chemical Hazards* (http://www.cdc.gov/niosh/npg).

Bibliographic databases such as NLM's PubMed and TOXLINE are also potentially useful resources for information on toxic substances that have not been evaluated by any authoritative organizations. However, results from searches of bibliographic databases would require DOL to interpret the meaning, accuracy, and reliability of the data. Bibliographic databases are not included in Table 3-1 for this reason. HSDB is a unique resource because it contains actual quotes that are peer-reviewed by a panel of experts for more than 5,000 substances (HSDB, 2012). Although the experts do not synthesize the information in HSDB to make

TABLE 3-1 Additional Sources of Health Effects Information

Name	Authoring Authoritative Organization	Web Address
IARC Monographs*	World Health Organization	http://www.iarc.fr
Report on Carcinogens*	U.S. Department of Health and Human Services, National Toxicology Program	http://ntp.niehs.nih.gov
Health Assessment and Translation Evaluations	U.S. Department of Health and Human Services, National Toxicology Program	http://ntp.niehs.nih.gov/?objectid=4980AA81-E919-4E85-60B789CA36E59FA5
Integrated Risk Information System (IRIS) Summaries and Toxicological Reviews	U.S. Environmental Protection Agency	http://www.epa.gov/IRIS/
Toxicological and Interaction Profiles	U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry	http://www.atsdr.cdc.gov/toxprofiles/index.asp
Technical Support Documents for Describing Available Cancer Potency Factors*	California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	http://www.oehha.org/tcdb
Pocket Guide to Chemical Hazards	U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health	http://www.cdc.gov/niosh/npg/
Criteria Documents	U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health	http://www.cdc.gov/niosh/pubs/criteria_date_desc_nopubnumbers.html
Current Intelligence Bulletins	U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health	http://www.cdc.gov/niosh/pubs/cib_date_desc_nopubnumbers.html
Preambles to Final Rules	U.S. Department of Labor, Occupational Safety and Health Administration	http://www.osha.gov/pls/oshaweb/owasrch.search_form?p_doc_type=PREAMBLES&p_toc_level=0
Threshold Limit Values (TLVs®) Documentations	American Conference of Governmental Industrial Hygienists	http://www.acgih.org/TLV

TABLE 3-1 Continued

Name	Authoring Authoritative Organization	Web Address
Technical Support Documents for Describing Available Recommended Exposure Levels (for noncancer effects)	California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	http://www.oehha.ca.gov/air/allrels.html
Proposition 65 Hazard Identification Documents	California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	http://www.oehha.ca.gov/prop65/hazard_ident/hazard_id.html

*For cancer effects only.

toxic substance–disease associations, the database may be particularly helpful as a starting point for more information. Similarly, TOXNET (also available from NLM) is not a database itself but, rather, allows users to access and search multiple databases (ChemIDplus, TOXLINE, HSDB, CCRIS, DART, GENETOX, IRIS, ITER, TRI, Haz-Map, Household Products, TOXMAP, CPDB, CTD) (TOXNET, 2012; http://toxnet.nlm.nih.gov). TOXNET is also a useful resource for toxicologic and health effects data.

The committee did not consider MSDSs to be useful for providing additional health effects information on commercial products in SEM. The quality varies and the health effects information can be unreliable and outdated. However, manufacturers of commercial products must list all hazardous components and their percentages that compose more than 1 percent of a product;[2] therefore, the committee finds that MSDSs may be useful for augmenting exposure information in the database.

No database known to the committee provides indicators of causal relationships between substance and disease as does Haz-Map. Therefore, to capture the wealth of information provided by these bibliographic databases, trained and knowledgeable individuals would be needed to synthesize all the data and make judgments about causal substance–disease links. The committee noted that all of these information sources and databases would require some interpretation to distill and analyze the data to achieve the causal substance–disease links that the SEM currently contains.

[2]"[A] component present in the mixture in concentrations of less than one percent (or in the case of carcinogens, less than 0.1 percent) could be released in concentrations which would exceed an established OSHA permissible exposure limit or ACGIH Threshold Limit Value, or could present a health risk to employees in those concentrations, the mixture shall be assumed to present the same hazard." OSHA Hazard Communication 1910.1200(d)(6). http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10099 (accessed February 7, 2013).

TOXIC SUBSTANCE–DISEASE LINKS NOT IN SEM

In order to evaluate the potential for "missing" links between occupational diseases and toxic substances in SEM, as directed by its statement of task, the committee designed an exercise to evaluate some selected links. A nonrandom sample of 81 toxic substances was selected to identify cancer and noncancer disease links that are not in the database. Some of the sample substances were collected from information submitted by the public for DOL consideration and the substances were listed as "under review" or "not verified" on the SEM website (http://www.sem.dol.gov/StatusD.cfm, as of July 2012), other substances in the sample were brought to the attention of the committee by claimant representatives. The committee purposely selected substances that did not have disease links in SEM that claimants thought should be there, and for which they had submitted information to DOL to support the proposed links. Fifteen additional substances were identified by the committee from authoritative sources (e.g., IARC, ATSDR, EPA, and California Environmental Protection Agency [Cal/EPA]) using its expert judgment for a total sample of 96 substances (see Appendix B for the complete list of substances reviewed by the committee). The committee did not conduct a systematic or comprehensive assessment of all 13,697 substances and 129 occupational diseases in SEM. The committee's assessments of toxic substance–disease links that are not in SEM are shown in Tables 3-2 through 3-4.

The committee recognizes that SEM and Haz-Map are active databases that undergo frequent updates. However, the updates made it difficult to accurately describe the current status of links within both databases. The committee's review reflects the status of the databases as of October 1, 2012; however, during that month, Haz-Map substantially revised its description of how toxic substances are classified as carcinogens (haz-map.com, accessed October 30, 2012).

For the purpose of the exercise, the committee consulted evaluations of the 96 toxic substances conducted by authoritative sources. The committee considered an authoritative organization to be a government or nongovernment entity whose scientific findings on the health hazards of toxic substances are relied upon by governments and their supporting public health entities in regulating or otherwise protecting public health. In addition to providing evaluations of toxicological information on the basis of the weight of scientific evidence, the organizations also include citations to the specific studies upon which the evaluations are based. The evaluated information also has undergone peer review, and in many cases, public review, except for ACGIH TLV documentations. ACGIH was included as an authoritative organization for this exercise because ACGIH TLVs are the basis for most of the current OSHA PELs (Rappaport, 1993) and many of the NIOSH Recommended Exposure Limits (NIOSH, 2005).

Links not listed in SEM are referred to as "missing," however, this should be interpreted with caution as the committee recognized that

- any examination of "missing" toxic substance–disease links in SEM would not be comprehensive because it currently contains more than 13,000 substances and 129 diseases;
- the identification of links as "missing" may not be accurate because the toxic substance–disease links in the database are periodically updated; and
- describing links as "missing" also may be subject to interpretation because the criteria used to establish the noncancer disease links in SEM are not fully described in Haz-Map, from which the information is taken.

The committee sought to evaluate the scientific rigor of the links, without consideration of possible use of the links for compensation or other DEEOIC purposes. The committee recognized that such applications were beyond its scope. The links in Tables 3-2, 3-3, and 3-4 are for information purposes only and should not be considered as definitive for EEOICPA claims without further review (see Chapter 4).

Cancer Links

Table 3-2 shows 15 substances for which there are no cancer links in SEM. With the exception of trichloroethylene, which is classified by EPA as being carcinogenic to humans by EPA (EPA, 2011), all the other toxic substance–cancer links are based classified by IARC as Group 1, sufficient evidence of cancer in humans (Cogliano et al., 2011; IARC, 2012)—the only criterion that Haz-Map uses to designate a link between cancer and a toxic substance (www.haz-map.com). The committee relied on human data to identify substance-cancer links for this exercise because animal and mechanistic cancer data may not accurately reflect the potential cancer sites in humans.

Some cancer links are missing from SEM for unknown reasons. Although there are possible explanations for why some of the cancer links in Table 3-2 are not in the database, it is not apparent why the cancer links shown for arsenic and bladder cancer, asbestos and ovarian cancer, and hepatitis B virus and liver cancer are not in the database. The links are based on cancer sites that IARC identifies as having sufficient evidence of cancer in humans (Cogliano et al., 2011; IARC, 2012), and they meet the Haz-Map criterion of a toxic substance–cancer causal relationship. However, the cancer links are not in Haz-Map either, and unlike the cancer links for diesel exhaust and coal tar pitch volatiles discussed earlier, they are not scheduled to be added to Haz-Map in the future (www.haz-map.com). Additional, but unspecified, criteria or rationales, other than IARC classifications of sufficient evidence in humans appear to be used for some toxic substance–cancer links in SEM. DOL should provide a rationale for not adding the cancer

TABLE 3-2 Selected Missing Links for Toxic Substance–Cancer Based on Sufficient Evidence of Cancer in Humans[a]

SEM Substance	Cancer Site
Arsenic	Urinary Bladder
Asbestos	Ovary
1,3-Butadiene	Hematolymphatic Organs[b]
Coal Tar Pitch Volatiles	Lung[c]
Diesel Exhaust	Lung[d]
Formaldehyde	Leukemia[d]
Hepatitis B Virus	Liver (hepatocellular carcinoma)
Iodine 131	Thyroid
Plutonium	Bone[e]; Liver
Radium	Bone[d]; Mastoid Process; Paranasal Sinus[d]
Radon	Lung[d]
Strontium 90	Leukemia; Solid Cancers
Thorium	Bile Duct, extrahepatic; Gall Bladder; Leukemia (excluding chronic lymphocytic leukemia); Liver (including hemangiosarcoma)
o-Toluidine	Urinary Bladder[d]
Trichloroethylene	Kidney[e]

[a]Except as noted (see footnote d), identified by IARC as sufficient evidence of cancer in humans as described in Cogliano et al. (2011) and IARC (2011). IARC (2012) reclassified diesel exhaust as sufficient evidence of cancer in humans.

[b]Haz-Map identifies "Leukemia" and "Lymphoma, Non-Hodgkin" as the cancer sites linked to 1,3-butadiene.

[c]Scheduled to be added to Haz-Map at the end of 2012 (www.Haz-Map.com). Presumably will be added to SEM when the database is updated.

[d]Listed in Haz-Map. Presumably will be added to SEM when the database is updated.

[e]Identified by EPA as sufficient evidence of cancer in humans by all routes of exposure (EPA, 2011).

links shown in Table 3-2 for arsenic, asbestos, and hepatitis B virus to SEM so that it is transparent to SEM users.

The rationale for not including in SEM the trichloroethylene–kidney cancer link established by EPA may be due to the fact that trichloroethylene has not been identified as a Group 1 carcinogen by IARC (IARC, 1995).[3] As a result, the trichloroethylene-cancer link does not meet the Haz-Map criterion for cancer causality. EPA classified trichloroethylene as carcinogenic in humans by all routes of exposure based on the results of a meta-analysis that included occupational

[3]In December 2012, a news item was published in the *Lancet* describing IARC's recent reclassification of trichloroethylene as a Group 1 carcinogen with sufficient evidence of carcinogenicity in humans for kidney cancer (Guha et al., 2012).

TABLE 3-3 Selected Missing Toxic Substance–Cancer Links Based on Limited Evidence in Humans[a]

SEM Substance	IARC Group	Cancer Site (IARC Group)
Arsenic	1	Kidney; Liver; Prostate
Asbestos	1	Colorectum; Pharynx; Stomach
Benzene	1	Multiple myeloma and Non-Hodgkin Lymphoma[b]
Cadmium	1	Kidney; Prostate
Chloramphenicol	2A	Leukemia
Chlorodiphenyl (Polychlorinated Biphenyls)	2A	Hepatobiliary Tract
Chromium VI	1	Nasal Cavity and Paranasal Sinus
Coal Tar Pitch Volatiles	1	Urinary Bladder
Cobalt Metal with Tungsten Carbide	2A	Lung
Diesel Exhaust	1	Urinary Bladder
Ethylene Oxide	1	Breast; Non-Hodgkin Lymphoma and Multiple Myeloma[b]
Formaldehyde	1	Nasal Cavity and Paranasal Sinus
Hepatitis B Virus	1	Liver (cholangiocarcinoma); non-Hodgkin lymphoma
Iodine-131	1	Bone and Soft Tissue; Digestive Tract; Leukemia; Salivary Gland
Lead	2A	Stomach
Plutonium	1	Solid Tumors (other than bone, liver, and lung)
Radon	1	Leukemia
Styrene	2B	Lymphatic and Hematopoietic Neoplasms
Sulfuric Acid	1	Lung
Tetrachloroethylene (Perchloroethylene)	2A	Cervix; Non-Hodgkin Lymphoma; Esophagus
Thorium	1	Pancreas; Prostate
Trichloroethylene	2A	Non-Hodgkin Lymphoma[c]; Liver and Biliary Tract[c]
Welding Fumes	2B	Lung

[a]Identified by IARC as limited evidence of cancer in humans as described in Cogliano et al. (2011).

[b]IARC also identifies chronic lymphocytic leukemia and acute lymphocytic leukemia as being linked to benzene and ethylene oxide exposure based on limited evidence in humans. However, SEM lists "Leukemia," which includes chronic lymphocytic leukemia and acute lymphocytic leukemia, as being linked to benzene and ethylene oxide, so it is not included in the table.

[c]Also identified by EPA (2011).

TABLE 3-4 Selected Missing Toxic Substance–Noncancer Disease Links Based on Evaluations by Authoritative Organizations[a]

SEM Substance	Human Disease/Illness	Authoritative Organization
Antimony	Cardiovascular (deaths; increased blood pressure; EKG changes from occupational exposures)	ACGIH, 2001; ATSDR, 1992; NIOSH, 1978
Carbon Disulfide	Cardiovascular (increase in mortality due to ischemic heart disease in several occupational studies)	Cal/EPA, 2002
Carbon Monoxide	Cardiovascular (workers at significantly increased risk of death from atherosclerotic disease; deaths of workers with existing cardiovascular disease)	ACGIH, 2001; Cal/EPA, 1999
Chromium VI	Male Reproduction (infertility, decreased fecundability, other effects in exposed workers)	Cal/EPA, 2009
Dibutyl Phthalate	Male Reproduction (decreased testosterone levels in occupationally exposed men)	Cal/EPA, 2007
2,4- and 2,6-Dinitrotoluene	Cardiovascular (significant increase in heart disease mortality in occupational cohort study)	ACGIH, 2001; ATSDR, 1998
Hydrogen Cyanide	Central Nervous System Endocrine System (nervous system effects and thyroid enlargement in workers chronically exposed to low levels)	ACGIH, 2001; Cal/EPA, 2000
Methylene Chloride (Dichloromethane)	Cardiovascular (OSHA standard based in part on protecting against effects on the heart)	Cal/EPA, 1999; DOL, 1997
Rotenone	Peripheral Nervous System (a few reported cases of peripheral neuropathy)	EPA, 2007b
Tetrachloroethylene (Perchloroethylene)	Central Nervous System (visual changes, increased reaction time, decrements in cognition from low level occupational exposures)	EPA, 2012; NRC, 2010

TABLE 3-4 Continued

SEM Substance	Human Disease/Illness	Authoritative Organization
Toluene	Central Nervous System (altered color vision; decreased performance in neurobehavioral tests from low level occupational exposures)	EPA, 2005b
Welding Fumes	Metal Fume Fever[b]	DOL, 1989; IARC, 1990; NIOSH, 1988

[a]The process the committee used to identify the toxic substance–disease links and the definition of authoritative organizations are provided in the text.

[b]Based on the complex mixture. Metal fume fever is also listed in SEM; however, it is listed as a potential disease link based on one of the 43 chemical constituents of welding fumes.

NOTE: EKG = electrocardiogram; OSHA = Occupational Safety and Health Administration.

epidemiological studies (EPA, 2011). EPA's criteria for "carcinogenic in humans" (EPA, 2005a) are not substantially different from IARC's criteria for "sufficient evidence of cancer in humans" (IARC, 2006). Since the IARC evaluation was published in 1995, IARC's classification of trichloroethylene as a Group 2A or probable carcinogen does not take into account the more recent cancer evidence for trichloroethylene in the EPA meta-analysis. From a scientific perspective, the committee does not believe that the omission of the trichloroethylene-kidney cancer link from SEM is valid.

Some of the links in Table 3-2 (formaldehyde and leukemia, o-toluidine and bladder cancer, 1,3-butadiene and cancer of the hematolymphatic organs) are in Haz-Map but not in SEM presumably due to a time lag in importing the Haz-Map links into SEM (i.e., the links are currently in the former, but have not yet been added to the latter). This is described further in the section on updating SEM.

Additionally, the lung cancer links for diesel exhaust and coal tar pitch volatiles presumably also will be added to SEM, although the links are not in Haz-Map. As a part of the revisions to Haz-Map, based on the 2012 IARC cancer evaluation (Cogliano et al., 2011; IARC, 2012), the lung cancer links for diesel exhaust and coal tar pitch volatiles are scheduled to be added to it by the end of 2012 (http://www.haz-map.com/cancer.htm). DOL has also concluded that the diesel exhaust cancer link could be verified and would be added to SEM (http://www.sem.dol.gov/StatusD.cfm).

SEM does not include links between radioactive substances and cancers. The reason for not including cancer links for the six radioactive substances (iodide-131, plutonium, radium, radon, strontium-90, and thorium) in Table 3-2 is not clear. It may be because DOL does not evaluate claims involving radiation and cancer under Part E. Radiogenic cancers, including thyroid, bone, liver, lung, leukemia, and gall bladder cancers, are covered under Part B which does not use

SEM. According to the SEM website, SEM does not address the relationship between radiation and cancer. For purposes of EEOICP, the relationship between radiation and cancer is evaluated by the NIOSH (http://www.sem.dol.gov). However, if this is the reason, it does not appear to be consistent with information in the SEM profiles for the substances. They state that "no diseases were listed in NLM Haz-Map (i.e., NLM had not identified any occupational disease related to exposure to this substance) as of June 5, 2012." The statement, which is used generically in the database when there is no disease information, implies that if or when disease information for the radioactive substances is added to Haz-Map, it will be subsequently added to SEM. The committee found this generic language misleading for radioactive substances.

Regardless of SEM's inclusion or exclusion of radiogenic cancers, the committee found discrepancies in the cancers linked to radioactive substances in the Haz-Map and SEM databases. As shown in Table 3-2, cancer links for plutonium, radon, and radium are currently in Haz-Map. Since some information for these substances is listed in SEM, it is not clear if the Haz-Map cancer links eventually will be added to SEM. Currently, Haz-Map does not have links for iodine-131 and thyroid cancer; plutonium and liver cancer; strontium and leukemia and solid cancers; thorium and bile duct, gall bladder, or leukemia; and radium and the mastoid process (see Table 3-2). It is unclear if they will be added to Haz-Map (and eventually to SEM), even though they are IARC Group 1 carcinogens. These cancer links are not scheduled to be added to Haz-Map, although they are in the 2012 IARC cancer monograph (http://www.haz-map.com/cancer.htm). The DOL notation of "could not be verified" (http://www.sem.dol.gov/StatusD.cfm) for the publicly submitted link between iodine-131 and thyroid cancer suggests that the cancer link will not be added to SEM. It also suggests that additional criteria (other than the IARC designation of sufficient evidence of cancer in humans) are used to identify cancer links for radioactive substances. Given these inconsistencies and the lack of transparency, DOL should clarify whether Haz-Map cancer links for radioactive substances are included in specific SEM substance profiles. If the cancer links are included in SEM, DOL should provide the complete criteria that are used to identify which cancer links are imported into the database.

To assess how criteria for substance–disease links may affect SEM, the committee looked for cancers associated with substances in SEM using a less strict criterion than the IARC Group 1 classification currently used by Haz-Map. Table 3-3 shows cancer links for 23 substances that are not in SEM because the epidemiological studies on which the links are based are classified by IARC as "limited" evidence of cancer in humans (Group 2) rather than "sufficient" (Cogliano et al., 2011; IARC, 2012). As a result, the links do not meet the Haz-Map criteria for cancer causality and are not included in either Haz-Map or SEM. The toxic substance–cancer links include 11 cancers—prostate, colorectum, pharynx, multiple myeloma, breast, digestive tract, salivary gland, hepatobiliary tract, cervix, esophagus, and pancreas—that were not listed in Haz-Map.

Deciding whether only the IARC classification of sufficient evidence of cancer in humans or whether the IARC classifications of both sufficient and limited evidence of cancer in humans most appropriately reflect the intent of EEOICPA is a DOL policy decision on the application of scientific information, not a scientific decision.

Noncancer Links

Table 3-4 shows 13 substances for which noncancer disease links are not in SEM. Diseases or health effects identified include cardiovascular, male reproductive, central and peripheral nervous system, and endocrine effects. All of the disease links are based on human case reports or epidemiological studies. As a result, according to the limited information available in Haz-Map, the links appear to be consistent with its criteria for determining noncancer disease causality. Regarding noncancer disease links, Haz-Map states that "for chronic diseases, linkage between an agent and a disease means that a causal relationship has been determined based on human case reports or epidemiological studies" (www.hazmap.com; accessed January 22, 2013).

Some authoritative organizations, for example, OSHA and EPA, also use disease or health effect endpoints to derive exposure limits for regulatory or preventative purposes. Such use indicates that the toxic substance–disease associations are strong, and that the disease is the most sensitive health endpoint for the toxic substance. EPA and Cal/EPA prioritize human studies of sufficient quality over animal studies (EPA, 2002). The diseases in Table 3-4 are all based on occupational health studies.

Effects on the cardiovascular system resulting from occupational exposures were identified as the most sensitive health endpoint and are the basis for the NIOSH recommended exposure limit for antimony (NIOSH, 1978), the Cal/EPA acute reference exposure level for carbon monoxide (Cal/EPA, 1999), and the Cal/EPA chronic noncancer reference exposure level for methylene chloride (Cal/EPA, 1999) (see Table 3-4). Cardiovascular effects are also the basis for the OSHA methylene chloride standard, due to metabolism of methylene chloride to carboxyhemoglobin (DOL, 1997). The OSHA standard includes medical surveillance requirements that are intended to provide specific protections for workers with existing cardiovascular disease. As of October 1, 2012, however, cardiovascular disease is not included in Haz-Map as an occupational disease, and is listed in the "More Research Needed" category (http://hazmap.nlm.nih.gov). The criteria used to determine whether cardiovascular disease is an occupational disease and the basis for adding toxic substance–cardiovascular links to SEM, are not clear in Haz-Map. To ensure transparency, these criteria should be made available to SEM users.

Chronic central nervous system (CNS) effects are linked to tetrachloroethylene and toluene (see Table 3-4) on the basis of chronic low-level, occupational

exposures resulting in such effects such as visual deficits (EPA, 2012). These CNS effects are different from "encephalopathy, chronic solvent," which is found in both Haz-Map and SEM databases, and is caused by chronic high exposures to solvents. This health effect is listed for all organic solvents used in paints and varnishes in both databases (www.haz-map.com/overview.htm; accessed January 22, 2013). These CNS effects at low exposures are the basis for EPA's reference concentrations for tetrachloroethylene (EPA, 2011) and toluene (EPA, 2005b), but neither are in either database. Since the EPA IRIS database is one of the information sources Haz-Map identifies in its references, it is not clear why the disease links for tetrachloroethylene and toluene are not in Haz-Map or SEM.

Male reproductive effects have been associated with chromium VI and dibutyl phthalate (Cal/EPA, 2007, 2009) but these associations are not listed in either the SEM or Haz-Map. Furthermore, neither database has a chemical profile for chromium VI alone, but rather include it with other forms of chromium in a profile for "Chromium and Chromium Compounds." The Haz-Map profile for chromium and compounds is a mix of data pertaining to chromium III, a relatively benign compound and essential nutrient, and chromium VI, a highly-toxic substance known to cause lung cancer (ATSDR, 2012b). Because the toxicity of chromium III and chromium VI differ substantially, the distinction between the two chemicals should be made clear in both databases. A further complication is that the CAS (or Chemical Astract Service) registry number used for chromium and chromium compounds in both databases is 7440-47-3, the number usually associated with chromium metal. The CAS number used typically for chromium VI is 18540-29-9. However, the occupational diseases listed for the CAS number 7440-47-3 are specific to chromium IV (ATSDR, 2012b), which is included in chromium compounds in both databases. This method of combining substance profiles may lead to inaccurate conclusions; in this case, that chromium III causes lung cancer. Despite this flaw, the substance–disease links for chromium and compounds (if interpreted as being chromium VI) are correct except for the lack of male reproductive effects. In cases where the effects of a specific form of a compound differ greatly from the group of compounds, a separate profile or distinct notation should reflect the differences in toxicity among them.

The link between welding fumes and metal fume fever is captured in SEM, but it is missing in the Haz-Map database. This is because SEM lists toxic substance–disease links for the constituents of mixtures as opposed to the mixture as a whole. Metal fume fever can result from exposure to welding fumes (DOL, 1989; IARC, 1990; NIOSH, 1988) and should be captured in SEM. However, this link in SEM is based on the diseases associated with the two of the constituents of welding fumes, zinc and copper, both of which are linked to metal fume fever in Haz-Map. In Haz-Map, welding fumes are linked to toxic pneumonitis and chronic obstructive pulmonary disease.

In summary, the committee determined that there are missing links between substances potentially present at DOE sites and cancers and noncancer diseases in

SEM as of October 1, 2012. Links may be missing due to human error, ambiguous criteria for establishing links in Haz-Map, lack of consistency between the "Diseases" field in Haz-Map and the "Specific Health Effects" field in SEM, or because of delays in updating both databases.

SUMMARY

SEM provides a key function in the EEOICPA Part E compensation system and is one tool by which claims examiners assess whether occupational exposure to a toxic substance at a DOE facility is associated with an occupational disease. In its evaluation of this database, the committee identified several strengths, including its development with consultation from DOE experts and former workers and its attempt to comprehensively list all toxic substances used at DOE facilities. However, the committee also identified several major weaknesses in SEM, specifically the difficulty in accessing some information in the database, lack of detailed exposure information; inability to handle complex exposures, including exposure to mixtures, chemical compounds, and radioactive substances; ambiguity in why certain links are not listed; incomplete or inconsistent exposure profiles based on location and job; disregard of epidemiologic studies in DOE workers; and the sole use of Haz-Map for substance–disease links.

In particular, the sole use of Haz-Map for disease causation was problematic for several reasons, and the committee conducted an exercise that illustrated examples of toxic substance–disease links that are not currently in SEM. The exercise was extensive, but not comprehensive. However, based on it, the committee identified cancer links that are missing in SEM that have been categorized by IARC as having sufficient evidence in humans (see Table 3-2) or limited evidence in humans (see Table 3-3), as well as missing links in the database for noncancer diseases based on evaluations by other authoritative organizations (see Table 3-4). The exercise also identified noncancer disease links that are missing from SEM. Overall, the committee noted that links may be missing due to human error, ambiguous criteria for determining or excluding links in Haz-Map, lack of exposure information in SEM, or because of delays in updating links in both databases. To address the weaknesses in SEM, and particularly to strengthen the toxic substance–disease links in SEM, the committee proposes a number of recommendations to DOL. These recommendations are discussed in detail in the next chapter.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. *Documentation of the Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs): Antimony and Compounds*.

Anders, K. 2012a. *Energy Employees Occupational Illness Compensation Program Overview*. Presentation at the First Committee Meeting, January 23, Washington, DC.

Anders, K. 2012b. DEEOIC Claims Process Flow Charts for the Committee on Review of the Department of Labor's Site Exposure Matrix (SEM) Database. March 15, 2012.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. *Toxicological Profile for Antimony and Compounds.* Washington, DC: U.S. Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp23.pdf (accessed December 11, 2012).

ATSDR. 1998. *Toxicological Profile for 2,4- and 2,6-Dinitrotoluene.* Washington, DC: U.S. Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp109.pdf (accessed December 11, 2012).

ATSDR. 2001. *Toxicological Profile for Asbestos*. Washington, DC: U.S. Public Health Service. http://www.atsdr.cdc.gov/ToxProfiles/tp61.pdf (accessed January 23, 2013).

ATSDR. 2004a. *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures*. Washington, DC: U.S. Public Health Service Division of Toxicology. http://www.atsdr.cdc.gov/interactionprofiles/IP-ga/ipga-p.pdf (accessed December 11, 2012).

ATSDR. 2004b. *Interaction Profile for: Arsenic, Cadmium, Chromium, and Lead.* Washington, DC: U.S. Public Health Service. http://www.atsdr.cdc.gov/interactionprofiles/IP-metals1/ip04.pdf (accessed January 23, 2013).

ATSDR. 2012a. *About the Chemical Mixtures Program*. Division of Toxicology and Environmental Medicine. http://www.atsdr.cdc.gov/mixtures/index.html (accessed December 11, 2012).

ATSDR. 2012b. *Toxicological Profile for Chromium.* Washington, DC: U.S. Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp7.pdf (accessed January 23, 2013).

Blanc, P. D., M. D. Eisner, G. Earnest, L. Trupin, J. R. Balmes, E. H. Yelin, S. E. Gregorich, and P. P. Katz. 2009. Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. *Journal of Occupational and Environmental Medicine* 51(7):804-810.

Brown, J. A. 2012. Haz-Map: A Process to Map Occupational Toxicology Information into a Relational Database. Presentation at First Committee Meeting, January 23, Washington, DC.

Brown, J. A. 2013. *What's New?* Web Changes and Database Updates. http://www.haz-map.com/wotsnu.htm (accessed January 23, 2013).

Caldwell, J. C., N. Keshava, and M. V. Evans. 2008. Difficulty of mode of action determination for trichloroethylene: An example of complex interactions of metabolites and other chemical exposures. *Environmental and Molecular Mutagenesis* 49(2):142-154.

Cal/EPA (California Environmental Protection Agency). 1999. *Air Toxics Hot Spots Program Risk Assessment Guidelines. Part 1: The Determination of Acute Reference Exposure Levels for Airborne Toxicants.* http://oehha.ca.gov/air/pdf/acuterel.pdf (accessed January 23, 2013).

Cal/EPA. 2000. *Chronic Toxicity Summary: Hydrogen Cyanide*. CAS Registry Number 74-90-8. In *Appendix D.3, Chronic RELs and Toxicity Summaries Using the Previous Version of the Hot Spots Risk Assessment Guidelines.* Pp. 313-320. http://oehha.ca.gov/air/hot_spots/2008/AppendixD3_final.pdf#page=313 (accessed January 23, 2013).

Cal/EPA. 2002. *Chronic Toxicity Summary: Carbon Disulfide*. CAS Registry Number 75-15-0. http://www.oehha.org/air/chronic_rels/pdf/sum111401.pdf (accessed January 23, 2013).

Cal/EPA. 2007. *Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Di(n-butyl)phthalate (DBP)*. Office of Environmental Health Hazard Assessment (OEHHA) Reproductive and Cancer Hazard Assessment Section. http://oehha.ca.gov/prop65/law/pdf_zip/DBP%20MADL%20062907.pdf (accessed January 23, 2013).

Cal/EPA. 2009. *Evidence on the Developmental and Reproductive Toxicity of Chromium (Hexavalent Compounds)*. Office of Environmental Health Hazard Assessment Reproductive and Cancer Hazard Assessment Section. http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/chrome0908.pdf (accessed January 23, 2013).

Carpenter, A. V., W. D. Flanders, E. L. Frome, W. G. Tankersley, and S. A. Fry. 1988. Chemical exposures and central nervous-system cancers. A case-control study among workers at 2 nuclear-facilities. *American Journal of Industrial Medicine* 13(3):351-362.

Chan, C., T. S. Hughes, S. Muldoon, T. Aldrich, C. Rice, R. Hornung, G. Brion, and D. J. Tollerud. 2010. Mortality patterns among Paducah gaseous diffusion plant workers. *Journal of Occupational and Environmental Medicine* 52(7):725-732.

Chen, W.-c. G., and T. E. McKone. 2001. Chronic health risks from aggregate exposures to ionizing radiation and chemicals: Scientific basis for an assessment framework. *Risk Analysis* 21(1):25-42.

Cogliano, V. J., R. Baan, K. Straif, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, C. Freeman, L. Galichet, and C. P. Wild. 2011. Preventable exposures associated with human cancers. *Journal of the National Cancer Institute* 103(24):1827-1839.

Dement, J. M., L. Welch, E. Bingham, B. Cameron, C. Rice, P. Quinn, and K. Ringen. 2003. Surveillance of respiratory diseases among construction and trade workers at Department of Energy nuclear sites. *American Journal of Industrial Medicine* 43(6):559-573.

DOE (Department of Energy). 2012. *Find Facilities*. http://www.hss.doe.gov/healthsafety/fwsp/advocacy/faclist/findfacility.cfm (accessed October 6, 2012). Office of Health, Safety, and Security. http://www.hss.doe.gov/healthsafety/fwsp/advocacy/faclist/findfacility.cfm.

DOL (Department of Labor). 1989. *Occupational Safety and Health Guideline for Welding Fumes*. http://www.osha.gov/SLTC/healthguidelines/weldingfumes/recognition.html (accessed October 6, 2012).

DOL. 1997. *Occupational Exposure to Methylene Chloride*. RIN 1218-AA98. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=PREAMBLES&p_id=998 (accessed January 23, 2013).

DOL. 2008. EEOICPA Bulletin No. 08-38 (replacing Bulletin Nos. 06-10 and 06-14). http://www.dol.gov/owcp/energy/regs/compliance/PolicyandProcedures/finalbulletinshtml/EEOICPABulletin08-38.htm (accessed January 23, 2013).

DOL. 2010. *Presolicitation for Site Exposure Matrices for DOL/DEEOIC*. Solicitation Number DOL011RP20896. https://www.fbo.gov/index?s=opportunity&mode=form&id=c70989c92ca49c5679ad783067dbbe97&tab=core&_cview=1 (accessed January 23, 2013).

DOL. 2011. *US Department of Labor Completes Expansion of Site Exposure Matrices Website*. http://www.dol.gov/opa/media/press/OWCP/OWCP20110041.htm (accessed September 10, 2012).

DOL. 2012a. 116 DOE Fcilities available on Public SEM. Division of Energy Employees Occupational Illness Compensation (DEEOIC). http://www.dol.gov/owcp/energy/regs/compliance/DOEPublicSEM_list.htm (accessed October 9, 2012).

DOL. 2012b. Establishing Toxic Substance Exposure. In *The Federal (EEOICPA) Procedural Manual*. http://www.dol.gov/owcp/energy/regs/compliance/PolicyandProcedures/UnifiedProcedureManual.htm (accessed February 6, 2013).

DOL. 2012c. *Site Exposure Matrices Website Help Guide*. http://www.sem.dol.gov/expanded/help.cfm (accessed January 16, 2012).

DOL. 2012d. EEOICP Site Exposure Matrices Website—Homepage, DOE facilities and RECA Sites Data. Updated June 5, 2012. http://www.sem.dol.gov/index.cfm (accessed February 6, 2013).

DOL. 2012e. Office of Workers' Compensation Program Site Exposure Matrix (SEM) Expanded. http://www.sem.dol.gov/expanded (accessed February 6, 2012).

DOL. 2012f. Questions posed by IOM committee and subsequent answers from DOL. Committee on Review of the Department of Labor's Site Exposure Matrix (SEM) Database.

Eaton, D. L., and S. G. Gilbert. 2007. Principles of toxicology. In *Casarett and Doull's Toxicology: The Basic Science of Poisons*. 7th ed, Klaasen, C. New York: McGraw-Hill Publishers. Pp. 11-44.

EPA (Environmental Protection Agency). 1986. *Guidelines for the Health Risk Assessment of Chemical Mixtures. Federal Register* 51(185):34014-34025. EPA/630/R-98/002. Washington, DC: EPA Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22567 (accessed February 9, 2012).

EPA. 2000. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*. EPA/630/R-00/002. Washington, DC: Risk Assessment Forum, EPA. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533 (accessed February 9, 2012).

EPA. 2002. *A Review of the Reference Dose and Reference Concentration Processes*. EPA/630/P-02/002F. Washington, DC: EPA Risk Assessment Forum. http://www.epa.gov/raf/publications/pdfs/rfd-final.pdf (accessed February 9, 2012).

EPA. 2005a. *Guidelines for Carcinogenic Risk Assessment*. EPA/630/P-03/001F. Washington, DC: EPA Risk Assessment Forum. http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF (accessed February 9, 2012).

EPA. 2005b. *Toxicological Review of Toluene (CAS No. 108-88-3).* EPA/635/R-05/004. Washington, DC: EPA. http://www.epa.gov/iris/toxreviews/0118tr.pdf (accessed February 6, 2012).

EPA. 2007a. *Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (Final Report)*. Cincinnati, OH: Office of Research and Development, National Center for Environmental Assessment. EPA/600/R-06/013f. Washington, DC: EPA. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190187 (accessed February 6, 2013).

EPA. 2007b. *Reregistration Eligibility Decision for Rotenone, List A, Case No. 0255*. EPA 738-R-07-005. Washington, DC: EPA. http://www.epa.gov/oppsrrd1/REDs/rotenone_red.pdf (accessed February 9, 2012).

EPA. 2011. *Trichloroethylene Toxicological Review and Appendices.* http://www.epa.gov/iris/supdocs/0199index.html (accessed February 9, 2012).

EPA. 2012. *Toxicological Review of Tetrachloroethylene (Prchloroethylene), CAS No. 127-18-4).* EPA/635/R-080/011F. Washington, DC: EPA. http://www.epa.gov/iris/toxreviews/0106tr.pdf (accessed February 9, 2012).

Erren, T. C., M. Jacobsen, and C. Piekarski. 1999. Synergy between asbestos and smoking on lung cancer risks. *Epidemiology* 10(4):405-411.

European Commission. 2012. *Toxicity and Assessment of Chemical Mixtures*. http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf (accessed January 23, 2013).

Frost, G., A. Darnton, and A–H. Harding. 2011. The effect of smoking on the risk of lung cancer mortality for asbestos workers in Great Britain (1971-2005). *Annals of Occupational Hygiene* 55(3):239-247.

GAO (Government Accountability Office). 2010. *Energy Employees Compensation: Additional Independent Oversight and Transparency Would Improve Program's Credibility.* GAO 10-302. Washington, DC. http://www.gao.gov/assets/310/302183.pdf (accessed January 23, 2013).

Godbold, J. H., and E. A. Tompkins. 1979. A long-term mortality study of workers occupationally exposed to metallic nickel at the Oak Ridge Gaseous Diffusion Plant. *Journal of Occupational and Environmental Medicine* 21(12):799-806.

Guha, N., D. Loomis, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, L. Benbrahim-Tallaa, R. Baan, H. Mattock, and K. Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group. 2012. Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites. *The Lancet Oncology* 13(12):1192-1193.

Hertz-Picciotto, I., A. H. Smith, D. Holtzman, M. Lipsett, and G. Alexeeff. 1992. Synergism between occupational arsenic exposure and smoking in the induction of lung cancer. *Epidemiology* 3(1):23-31.

HSDB (Hazardous Substances Data Bank). 2012. TOXNET (Toxicology Data Network) Hazardous Substances Data Bank (HSDB). Bethesda, MD: Division of Specialized Information Services, National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (accessed January 23, 2013).

IARC (International Agency for Research on Cancer). 1990. Chromium, Nickel and Welding. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 49. Lyon, France: World Health Organization.

IARC. 1995. Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 63. Lyon, France: World Health Organization.

IARC. 2006. Preamble. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon, France: World Health Organization.

IARC. 2010. Painting, Firefighting, and Shiftwork. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 98. Lyon, France: World Health Organization.

IARC. 2012. Chemical Agents and Related Occupations. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 100F. Lyon, France: World Health Organization.

Ikeda, M. 1988. Multiple exposure to chemicals. *Regulatory Toxicology and Pharmacology* 8(4):414-421.

Kortenkamp, A., and U. Hass. 2009. *Expert Workshop on Combination Effects of Chemicals, 28–30: Workshop Report.* January, Hornbæk, Denmark. http://www.mim.dk/NR/rdonlyres/C59693B7-2421-4748-89F0-5937496E0A28/0/BILAG_2_Expertworkshop.pdf (accessed January 23, 2012).

Kubale, T., S. Hiratzka, S. Henn, A. Markey, R. Daniels, D. Utterback, K. Waters, S. Silver, C. Robinson, G. Macievic, and J. Lodwick. 2008. A cohort mortality study of chemical laboratory workers at Department of Energy nuclear plants. *American Journal of Industrial Medicine* 51(9):656-667.

Laamanen, I., J. Verbeek, G. Franco, M. Lehtola, and M. Luotamo. 2008. Finding toxicological information: An approach for occupational health professionals. *Journal of Occupational Medicine and Toxicology* 3:18.

Little, J. B. 1990. Low-dose radiation effects—Interactions and synergism. *Health Physics* 59(1):49-55.

Loomis, D. P., and S. H. Wolf. 1996. Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947-1990. *American Journal of Industrial Medicine* 29(2):131-141.

Mahaffey, K. R., and B. A. Fowler. 1977. Effects of concurrent administration of lead, cadmium, and arsenic in the rat. *Environmental Health Perspectives* 19:165-171.

Mahaffey, K. R., S. G. Capar, B. C. Gladen, and B. A. Fowler. 1981. Concurrent exposure to lead, cadmium, and arsenic: Effects of toxicity and tissue metal concentrations in the rat. *Journal of Laboratory and Clinical Medicine* 98:463-481.

Makie, T., D. Adcock, D. T. Lackland, and D. G. Hoel. 2005. Pulmonary abnormalities associated with occupational exposures at the Savannah River Site. *American Journal of Industrial Medicine* 48(5):365-372.

Mastrangelo, G., U. Fedeli, E. Fadda, F. Valentini, R. Agnesi, G. Magarotto, T. Marchi, A. Buda, M. Pinzani, and D. Martines. 2004. Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: Synergistic effect of occupational exposure with alcohol intake. *Environmental Health Perspectives* 112(11):1188-1192.

Mauderly, J. L. 1993. Toxicological approaches to complex mixtures. *Environmental Health Perspectives* 101:155-165.

NIOSH (National Institute for Occupational Safety and Health). 1978. *Criteria for a Recommended Standard: Occupational Exposure to Antimony.* Centers for Disease Control. Washington, DC: U.S. Government Printing Office. http://www.cdc.gov/niosh/pdfs/78-216a.pdf (accessed January 23, 2013).

NIOSH. 1988. *1988 OSHA PEL Project Documentation: Welding Fumes*. http://www.cdc.gov/niosh/pel88/welding.html (accessed January 23, 2013).

NIOSH. 1990. Potential Exposures to Agents by Occupation. *National Occupational Exposure Survey Conducted from 1981 to 1983*. http://www.cdc.gov/noes/noes2/occs0000.html (accessed October 11, 2012).

NIOSH. 2005. *Pocket Guide to Chemical Hazards*. http://www.cdc.gov/niosh/npg/ (accessed January 22, 2013).

NLM (National Library of Medicine). 2012. *NLM Copyright Information*. http://www.nlm.nih.gov/copyright.html (accessed February 24, 2012).

NRC (National Research Council). 1983. *Risk Assessment in the Federal Government: Managing the Process.* Washington, DC: National Academy Press.

NRC. 2010. *Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene.* Washington, DC: The National Academies Press.

Paragon Technical Services. 2012. Questions Posed by IOM Committee and Subsequent Answers from Paragon Technical Services, February 22. http://www.iom.edu/Activities/PublicHealth/SEMDatabaseReview/2012-MAR-16.aspx (accessed February 6, 2013)..

Plappert, U., E. Barthel, and H. J. Seidel. 1994. Reduction of benzene toxicity by toluene. *Environmental and Molecular Mutagenesis* 24:283-292.

Pohl, H. R., M. M. Mumtaz, F. Scinicariello, and H. Hansen. 2009. Binary weight-of-evidence evaluations of chemical interactions—15 years of experience. *Regulatory Toxicology Pharmacology* 54(3):264-271.

Polednak, A. P., and D. R. Hollis. 1985. Mortality and causes of death among workers exposed to phosgene in 1943–45. *Toxicology and Industrial Health* 1(2):137-151.

Rappaport, S. M. 1993. Threshold limit values, permissible exposure limits, and feasibility—The bases for exposure limits in the United States. *American Journal of Industrial Medicine* 23(5):683-694.

Reif, A. E. 1984. Synergism in carcinogenesis. *Journal of the National Cancer Institute* 73(1):25-39.

Reyes, M., G. S. Wilkinson, G. Tietjen, G. L. Voelz, J. F. Acquavella, and R. Bistline. 1984. Brain tumors at a nuclear facility. *Journal of Occupational and Environmental Medicine* 26(10):721-724.

Richardson, D. B., S. Wing, and S. Wolf. 2007. Mortality among workers at the Savannah River Site. *American Journal of Industrial Medicine* 50(12):881-891.

Ritz, B. 1999. Cancer mortality among workers exposed to chemicals during uranium processing. *Journal of Occupational and Environmental Medicine* 41(7):556-566.

Stalnaker, K. 2012. *U.S. DOL Site Exposure Matrices, EEOICPA Part E*. Presentation at the First Committee Meeting, January 23, Washington, DC.

Steinberg, G. A. 2011. *Response by the Office of Workers' Compensation Programs to the Ombudsman's 2010 Annual Report to Congress*. http://www.dol.gov/owcp/energy/regs/compliance/news/640907-1.pdf (accessed September 10, 2012).

Tapio, S., and B. Grosche. 2006. Arsenic in the aetiology of cancer. *Mutation Research–Reviews in Mutation Research* 612(3):215-246.

TOXNET. 2012. Toxicology Data Network. Bethesda MD: National Library of Medicine, Division of Specialized Information Services. http://toxnet.nlm.nih.gov (accessed January 23, 2013).

4

Findings and Recommendations

This Institute of Medicine (IOM) committee was asked by the Department of Labor (DOL) to review and critique the scientific rigor of the Site Exposure Matrix (SEM) database used by DOL as one of many tools that support the claims process for Energy Employee Occupational Illness Compensation Program Act (EEOICPA) Part E (Public Law 106-398, Title XXXVI). The committee was specifically tasked with assessing the strengths and weaknesses of SEM with particular reference to the links between the toxic substances found at Department of Energy (DOE) nuclear facilities and occupational diseases that may result from exposure to them. Where possible, the committee was to identify any toxic substance–disease links missing from the database, to highlight other databases that might be used to supplement it, to comment on the review process for Haz-Map, and finally, to evaluate the National Library of Medicine's peer-review process for the Haz-Map database, which is the sole source of the toxic substance–disease links in SEM.

Initially, the committee thought it would be a relatively straightforward process to review the links in Haz-Map and their incorporation into SEM, but this was not the case. The process by which toxic substances are determined to be the cause of an occupational disease in Haz-Map was not straightforward and the committee spent many hours attempting to identify the specific sources of the toxic substance–occupational disease links in Haz-Map. Furthermore, the information in only one of its fields, "Diseases" is imported into SEM, which contains more than 13,500 toxic substances, Haz-Map has more than 7,000—and not all of its substances are in SEM and vice versa. Therefore, much of the committee's deliberations centered around whether to focus on the information in the Haz-Map, SEM, or both. The committee was also cognizant that it had not been

asked to comment on any aspect of the EEOICPA claims process other than the toxic substance–occupational disease information in SEM. The committee was also aware that approval of an EEOICPA claim is based on more than information in the SEM "Specific Health Effects" field and that each claim is considered on a case by case basis.

HAZ-MAP FINDINGS

In Chapter 2, the committee reviewed the approach used by the Haz-Map developer for linking toxic substances to occupational diseases. This approach was compared with those used by other authoritative organizations including the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences and the International Agency for Research on Cancer (IARC). These organizations also attempt to determine what, if any, diseases may be associated with exposure to toxic substances. The committee did not review every substance–disease link in Haz-Map or even all of the links that are imported into the DOL SEM. However, the committee has attempted to highlight areas where the Haz-Map "Disease" links are ambiguous or where the process for making those links is unclear.

Although the committee is appreciative of the enormous amount of work that has gone into the development and maintenance of Haz-Map to assist health providers in identifying and possibly preventing occupational disease, the committee identified several limitations to the database links in the Haz-Map "Diseases" field that is imported into SEM. These include the lack of transparency in data sources used for determining each toxic substance–occupational disease link and the criteria for establishing those links, particularly for noncancer endpoints; the lack of a clear weight-of-the-evidence approach; the lack of peer review; overreliance on textbooks such that information may be neither comprehensive nor up-to-date; and the lack of clarity on which toxic substances and fields have been updated by the Haz-Map database developer. The committee finds that there is no formal oversight or review process for the Haz-Map "Disease" links and that such review is critical for ensuring the scientific rigor of and user confidence in the database, irrespective of its use in SEM. In particular, the committee finds that the scientific evidence base used for the Haz-Map toxic substance–disease links should be documented so that a user can verify the information and determine its accuracy, validity, and credibility, and its use of the most comprehensive and current information. Without identification of all sources of the underlying information, the accuracy and timeliness of the links cannot be determined.

SEM FINDINGS

SEM serves a key function in the EEOICPA Part E claims process. It is one of many tools used by DOL claims examiners to assess whether exposure to a

toxic substance at a DOE facility caused an occupational disease. In its evaluation of the database, the committee noted several strengths, including its development in consultation with DOE experts and former workers and its attempt to comprehensively list all toxic substances found at DOE sites. However, the committee also identified major weaknesses in SEM, including difficulties in accessing information; the lack of detailed exposure information; poor handling of complex exposures, e.g., exposures to mixtures; the lack of clarity for why certain links are missing; incomplete or inconsistent exposure profiles for particular locations and jobs; disregard of epidemiologic studies of DOE workers; and the sole use of Haz-Map for toxic substance–occupational disease links as discussed in Chapter 3.

In particular, the committee found that the use of Haz-Map as the sole source of disease causation in SEM to be problematic. The committee conducted an extensive exercise to identify examples of toxic substance–disease links that are not currently in SEM. The results of the exercise identified substances categorized by IARC as having sufficient evidence in humans for cancers and these links were not listed in it. In addition, the exercise identified agents considered by IARC to have "limited" evidence for cancer in humans, based on epidemiologic studies. These links are also not listed in SEM, although the committee recognizes that, given the Haz-Map criterion of including only IARC Group 1 substances for cancer links, substances with limited evidence of carcinogenicity would not be included in Haz-Map and, therefore, would also not be in SEM. The exercise also identified links between toxic agents and noncancer health effects that were missing in SEM. Overall, the committee found that links may be missing in SEM for several reasons, including ambiguous criteria for establishing the links in Haz-Map (the source of the SEM links); lack of consistency between the Haz-Map "Diseases" field and the SEM "Specific Health Effects" field for some substances; an inability to deal with complex exposures, e.g., exposures to mixtures; and delays in updating links in Haz-Map and, thus, in SEM. There are no explanations for why some links are excluded from SEM. Many, if not all, of these weaknesses could be addressed with modifications to this database as discussed in the following sections.

RECOMMENDATIONS TO IMPROVE SEM

After its review of Haz-Map and SEM, the committee has several recommendations that should help ensure that the toxic substance–occupational disease links in SEM are current, comprehensive, and transparent. The committee notes that these recommendations focus only on changes to SEM, and can be implemented even if no changes are made to the Haz-Map database. The reasons for this are several:

- Haz-Map is an independently developed database that was developed prior to SEM and for purposes unrelated to SEM.
- Haz-Map has other users outside of DOL, and the integrity of the information for those users should not be compromised.
- Although Haz-Map is published by the National Library of Medicine (NLM); neither NLM nor DOL is responsible for its content. Ultimately, the developer is responsible for its content.
- Only one field ("Diseases") from Haz-Map is imported into SEM and is used by DOL claims examiners.

The committee found that focusing on only the "Specific Health Effects" field in SEM as imported from the Haz-Map database field "Diseases," without consideration of the EEOICP claims process, was difficult because its review lacked context. Furthermore, the focus on the "Specific Health Effects" field precluded consideration of many other aspects of occupational health such as the potential for exposure (concentration, frequency, duration), strength of association between exposures and health effects, and exposure to more than one chemical at a time. Nevertheless, the committee came to three overarching recommendations for DOL to improve the toxic substance–disease links in SEM.

1. Add supplemental information sources to the health effects information imported from Haz-Map.
2. Improve the structure and function of SEM, including the addition of available exposure information.
3. Use an external advisory panel to review the health effects information in SEM.

Although those three recommendations focus on improving SEM, recommendations 1 and 3 and portions of recommendation 2 are also applicable to Haz-Map. The committee believes that establishing a formal oversight and review process for the Haz-Map database and using a weight-of-evidence approach are critical for both maintaining and expanding the Haz-Map database and for its use in SEM. Expansion of the information used in Haz-Map and inclusion of citations for all the information in each of its fields would greatly enhance its utility not only for SEM but also for other users. Peer review of the database would also increase public confidence in its accuracy and comprehensiveness and help ensure that it contains the most current information available, irrespective of its use for SEM.

Each of these recommendations is discussed in greater detail in the following sections.

RECOMMENDATION 1: Use supplemental information sources for the Site Exposure Matrix database.

To improve SEM, the committee found that supplemental data sources, in addition to the health effects links imported from Haz-Map, are necessary to provide a more comprehensive picture of the adverse effects that may be associated with exposure to the toxic substances found at DOE sites. Many information sources are used by Haz-Map to support the toxic substance–occupational disease links, as discussed in Chapter 2. However, the evidence used to support each link is not cited, nor are all available sources of information on adverse effects associated with a toxic substance necessarily used. Furthermore, because Haz-Map, for the most part, lacks transparency as to the criteria used to establish the causal links, it may be overly conservative in making the links for cancers by using only IARC Group 1 designations. The committee recommends that additional IARC classifications (e.g., IARC 2A "probably carcinogenic to humans" and 2B "possibly carcinogenic to humans") and additional information on noncancer effects of agents be considered for inclusion in SEM in separate fields. These fields may be structured as text fields that could capture the variety of adverse effects for each substance. This supplemental information should also be cited and referenced specifically in each SEM field. For example, IARC has determined that for some substances there is "limited evidence of cancer in humans" at specific organ sites. These designations might meet the statutory requirement that a toxic substance be more than likely than not to cause an occupational disease. See Chapter 2 for a more detailed discussion of the IARC cancer classifications. The committee emphasizes that any supplemental information in SEM should include appropriate references; such references will enhance the rigor, robustness, and transparency of each link.

The committee suggests that there are two types of information that might be used to supplement the "Specific Health Effects" field in SEM—bibliographic information sources (e.g., PubMed and TOXLINE), and evaluative information sources, such as those found in the Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) database and the NTP Office of Health Assessment and Translation (OHAT) toxicology reports. Bibliographic sources are typically databases such as those mentioned above that provide references that must be screened and assessed by the user (e.g., case reports, cohort studies, mechanistic studies). While helpful in collating large numbers of publications and indentifying new studies, bibliographic databases are labor intensive to use for tools such as SEM database because they require knowledgeable staff to screen, retrieve, and assess the references before they are added. Therefore, although the committee finds that the use of such databases and the references they contain may be helpful in supplementing the information in SEM, but they are not the ideal sources for readily available information.

Evaluative information is a more likely source of supplemental information

for SEM. The committee acknowledges that some sources of evaluative information are already used to make the toxic substance–disease links in Haz-Map and are cited in its reference list. However, the use of these sources does not appear to be consistent and, in some cases (such as the use of NTP OHAT toxicology reports), is missing entirely. The advantage of using these evaluative databases and documents is that they typically use a weight-of-evidence approach to reach conclusions about the strength of association between exposure to a toxic substance and a health effect. They also have a defined methodology, describe the evidence base for their conclusions and, for the most part, are periodically updated with new evidence used and documentation of any changes to the conclusions. Among the databases and documents that evaluate health effects for individual toxic substances or groups of related chemicals is the EPA's IRIS database and background documents, the Agency for Toxic Substances and Disease Registry's (ATSDR's) toxicological profiles, NTP OHAT toxicology reports, the background document preamble for the Occupational Safety and Health Administration permissible exposure limits, IARC monographs, the California Environmental Protection Agency's (Cal/EPA's) toxicity criteria database and staff reports, documentation for the American Conference of Government Industrial Hygienists (ACGIH) threshold limit values (TLVs), documentation for the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits, and the NIOSH *Pocket Guide to Chemical Hazards*. For virtually all these information sources, a group of experts reaches a conclusion on a substance's toxicity by using established criteria and a weight-of-evidence approach.

The inclusion of supplemental materials in SEM may be done by listing each source in an individual data field (e.g., separate fields for ACGIH, EPA, NTP) that would then be available to the claims examiner and the general public. This supplemental information might include descriptions of synergistic and other chemical–chemical interactions, as well as data from other sources, for example, additional IARC designations, NTP documents, and epidemiologic studies on DOE workers. However, it might be preferable to include a comment or text field where all the supplemental information could be given in paragraph form, similar to the format used by the Hazardous Substances Data Bank (HSDB). In either case, all sources of information (i.e., specific citations) and the conclusion reached by each source should be included so the user can find it in the original documentation. The committee appreciates that claims examiners should not be required to synthesize the supplemental information to reach a nuanced conclusion about the strength of the association between exposure to a toxic substance and a possible health effect. The committee recommends that such syntheses be done by an expert advisory panel, as discussed later in this chapter.

The committee recognizes that the causal links between toxic substances and diseases in Haz-Map, as currently imported into SEM, are established in the absence of site-specific exposure information. These links are not representative of any judgment about whether an individual's disease was caused by the toxic

substance, or whether any site-specific factors contributed to his or her disease. Including site-specific exposure information in SEM such as the dates a toxic substance was used at a site, would increase its transparency. However, such information is not equivalent to conducting a site-specific exposure assessment for an individual or a group of workers or to determining the likelihood that an individual developed a disease as a result of his or her workplace exposures. Such exposure-outcomes determinations are made by DOL on a case-by-case basis.

RECOMMENDATION 2: Improve the structure and function of the Site Exposure Matrix database.

The committee has a number of specific recommendations that it believes will help both the public and claims examiners to navigate the SEM database and more effectively retrieve information. The committee has tried to be realistic about making modifications to the database and limited the number of suggested changes. Nevertheless, it firmly believes that such changes will not only greatly improve the usability of the database, but also the strength of the associations between exposures to toxic substances and possible health effects.

First, the committee believes that the current links between a toxic substance and an occupational disease must be appropriately referenced whether in SEM, Haz-Map, or, preferably both databases. The committee spent considerable time in attempting to determine the sources and specific evidence used to make the links in Haz-Map, and therefore in SEM, and in many cases was largely unable to do so. The Haz-Map "Diseases" field does not indicate specific documentation on which the disease link was based, although some documentation is presented in its "Comments" field for a substance and by clicking on the specific disease and reading the explanation of that disease. There is no reason why SEM cannot contain such references. Including appropriate citations in it would increase user confidence that the links were accurate, up-to-date, and scientifically rigorous. Because the toxic substance–disease links in SEM are imported from Haz-Map it might be easier to modify the latter rather than ask DOL staff to research the evidence base for the imported Haz-Map database links. Alternatively, the Haz-Map author could provide the documentation to the DOL for uploading to SEM.

The committee found several statements about NLM involvement in SEM to be misleading and recommends that they be corrected. First, the database homepage states

> The relationship between toxic substances and diagnosed illnesses shown in SEM is derived from records of research by recognized medical authorities maintained by the National Library of Medicine. DOL continually updates these relationships as new disease associations are recognized by NLM. The causal links provided by NLM do not represent an exclusive list of the pathways necessary for an affirmative Part E causation determination. (http://www.sem.dol.gov; accessed December 7, 2012)

The NLM publishes the Haz-Map database on its website, but other than copyediting the agent profile fields, including the chemical identification field and physical properties, and making the links to other NLM databases such as the HSDB, the NLM does not review the other Haz-Map fields for content. DOL also states on its page for "Occupational illnesses and toxic substances" that it includes "Toxic substances with an established causal link to the diagnosed illness as accepted by NLM." NLM does not "recognize" or "accept" any of the links in Haz-Map nor does it make any judgments on the accuracy of its "Diseases" field; rather, the toxic substance–disease links are made solely by the developer. If the implication is that the links come from evidence in NLM MEDLINE database, then this also is not accurate, as many of the information sources cited in Haz-Map are not in any NLM database (e.g., textbooks).

Second, the committee was initially confounded in its attempts to retrieve from SEM a comprehensive list of all toxic substances identified at more than one DOE site. SEM search capabilities could be improved by providing a direct link on its homepage (http://www.sem.dol.gov) to the database (http://www.sem.dol.gov/expanded), without first requiring that a specific DOE site be chosen. The expanded database allows users to see a list of all the toxic substances and all the health effects in it, but this option is not immediately evident on the SEM homepage. The committee also notes that it is difficult to find toxic substances or diseases in the database if the user misspells a word or does not know the correct terminology, and possible alternatives are not suggested to help the user.

Although records in SEM indicate when a record was last updated, there is no specification as to what information or which field was updated, added to, or revised. The lack of such information makes it extremely difficult for the user to know if and when the most current information has been incorporated into the database.

The committee also notes other areas where an improved SEM search function would be helpful. The user cannot generate a list of toxic substances that have been used at more than one site or that are associated with a general job category (e.g., plumber). This makes it difficult for workers who may have been at more than one site to identify all toxic substances to which they may have been exposed without cross referencing each substance individually and compiling an external list. This is also true for health effects. The committee suggests that the search capabilities of SEM be expanded so that the user could enter a job description (e.g., plumber), site (e.g., Hanford), and a disease (e.g., lung cancer), and retrieve a list of toxic substances that were used at that site, in that job category, and that might cause that disease.

The committee was asked to comment on the Haz-Map review process conducted by National Institutes of Health (NIH)/NLM and the Haz-Map developer. The committee finds that there are several levels of review that should be applied

to both Haz-Map and SEM. The peer-review process is discussed in the following section on the external advisory panel but a quality control review of both databases is critical to ensuring their accuracy. The IOM committee recommends that DOL or its contractor conduct a quality control review of all records to ensure that the data abstracted from each information source are correctly cited, have no typographic errors, and are complete (that is, no important information has been omitted and the information is not taken out of context). Although NLM performs a quality control review of a portion of each Haz-Map record, it reviews only the chemical identification information. The NIH/NLM review might be expanded to include the entire Haz-Map record.

Finally, the committee notes that although SEM is considered to be a site exposure matrix, information on possible exposures to toxic substances at each DOE site is incomplete. To help evaluate whether an individual's disease might result from his or her occupational exposures requires information on the duration, intensity, frequency, and route of exposure. None of this exposure information, such as air monitoring data, is currently in SEM, however, inclusion of such information, if available, would enhance the utility of the database for both claimants and claims examiners. The committee suggests that the DOL give consideration to conducting a feasibility study to determine if and what exposure information could be included in SEM.

RECOMMENDATION 3: Establish an expert advisory panel for the Site Exposure Matrix database.

To accomplish the two major recommendations given above, the committee recommends that DOL establish an expert advisory panel. This is not the first time that such a panel has been suggested (e.g., 2010 GAO report; H.R. 1030), and there is a precedent for such a panel as required for EEOICPA Part B, that is, the Advisory Board on Radiation and Worker Health (see Chapter 3). The proposed EEOICPA Amendment Act of 2011 (H.R. 1030) would have required the president to establish an Advisory Board on Toxic Substances and Worker Health to review and approve the SEM.

An expert advisory panel could perform several important functions with regard to SEM, but the committee believes that the primary function of the advisory panel would be a peer review of its toxic substance–occupational disease links. The expert advisory panel should be broad based, external to DOL and its current SEM contractor, and its membership should include such expertise as epidemiology, occupational medicine, toxicology, and industrial hygiene. The committee also recommends that the advisory panel include claimants and advocacy organization representation.

The expert advisory panel would have several immediate tasks:

- Establish the criteria for the evidence base for causal links between exposure to a toxic substance and an occupational disease; criteria might be expanded to include a category of "evidence of no association" as is used by IOM and IARC.
- Determine the information sources that might be reviewed to identify information on possible links.
- Develop a worksheet or other documentation to capture the evidence taken from each information source, including Haz-Map.
- Oversee revisions of SEM to add appropriate fields for capturing supplemental information (such as, chemical interactions, route of exposure, and IARC 2A designations), supplemental information sources (such as NTP, ATSDR toxicological profiles, and IRIS), and update information (such as the date of the last revision of the record and the fields revised).

Whatever criteria are established by the expert panel, this committee suggests that the criteria be expanded to include a category to capture "evidence of no association," as done by IOM and IARC. The committee recognizes that the expert advisory panel may be the most appropriate body to decide whether the criteria for making toxic substance–cancer links in SEM should be expanded to include substances considered by IARC as having limited evidence of cancer in humans (Group 2), and whether information on possible structure-activity relationships might be useful. Inclusion of such information would not necessarily require a change in Haz-Map but might require an additional field in SEM.

The expert advisory panel would also have several ongoing responsibilities in support of EEOICPA Part E:

- Peer review of all new links in SEM that are based on both Haz-Map and the supplemental information described earlier. This might include determining whether the appropriate references are screened and the data are accurately cited.
- Assessment of occupational diseases that might result from complex exposures.
- Identification of potential new links and tracking them for possible future inclusion in SEM, including those suggested by external sources.
- As time permits, review of existing causal links in SEM that are based solely on Haz-Map.
- Periodic review of a sample of the toxic substance–disease links from both accepted and rejected claims to determine whether SEM links are actually assisting in the claims process and, if not, what improvements could be made in the toxic substance–disease links or what other information might be added to the SEM that would help claimants and claims examiners, such as available monitoring information, disease terminology, or results of cohort studies of DOE workers.

The committee recognizes that peer review is not a simple task nor is the recommended expert advisory panel likely to solve the complex problem of providing clear-cut links between every toxic substance in SEM and occupational diseases. Nevertheless, the committee believes that such a panel is essential if the database is to meet the scientific standards needed to ensure that both the DOL claims examiners and claimants have access to balanced, comprehensive, accurate, and understandable information. DOL need not develop its peer review process de novo. Other federal agencies (EPA in 2006 and the Office of Management and Budget in 2004) have prepared guidance on the peer review process for scientific documents. DOL may use this guidance for the SEM or require that Haz-Map use a similar process before the agency can import Haz-Map information into SEM.

The committee also acknowledges that there are several approaches that may be used to institute a peer review process for SEM, all of which have advantages and disadvantages. However, a major feature of each option is that all information and actions would be documented so that the evidence base used to make decisions on toxic substances–occupational disease links could be reviewed by others and would be easy to understand. Each of these options is discussed below:

1. DOL may use an expert advisory panel to review only the evidence used for those Haz-Map links that are incorporated into the SEM "Specific Health Effects" field. The expert advisory panel could review the references used for each Haz-Map record and direct the DOL SEM contractor to make any changes as necessary. No changes would be required for Haz-Map although the IOM committee believes that such changes would strengthen it as well.
2. A DOL contractor would prepare a comprehensive profile for each toxic substance in SEM. The profile would include the Haz-Map information and any supplemental health effects information deemed appropriate by the expert advisory panel (e.g., other database profiles or documents, such as NTP toxicological reports). The contractor might then make an initial recommendation regarding the toxic substance–disease links that should be included in SEM. The expert advisory panel would review all the information in the substance profile, along with the contractor's recommendation and either approve the recommendation or modify it as necessary. This final recommendation on the appropriate toxic substance–disease link would then be entered into SEM by the contractor.
3. A DOL contractor would prepare a profile for each toxic substance as described in Option 2, but would not make any recommendations regarding a plausible toxic substance–disease link. The expert advisory panel would review each profile and using a weight-of-evidence approach,

comes to a conclusion about to the strength of the association between exposure to a toxic substance and the development of an occupational disease. This toxic substance profile and the conclusions reached by the expert advisory panel would then be reviewed by one or more outside peer reviewers. Outside peer review comments would be considered by the expert advisory panel and responses to them would be incorporated into the profile. The revised (if necessary) conclusions of the expert advisory panel would then be included in SEM.

An expert advisory panel will increase claims examiner and claimant confidence in the toxic substance–disease links in the SEM database. Given the wealth of health effects information available on toxic substances, the IOM committee believes that a transparent process for identifying, screening, and evaluating this information must be done by a group of experts using a weight-of-evidence approach. The expert advisory panel would also be ideally situated to review the public submissions of disease-related information (and exposure-related if the panel has appropriate expertise) and could provide detailed responses to public submissions requesting that a link be added to SEM.

The IOM committee finds that there are excellent prototypes that DOL might consider for establishing its expert advisory panel. First, in support of EEOICPA Part B, the law mandates that a review panel oversee the NIOSH radiation dose–reconstruction process, determine whether there should be additional special exposure cohorts, and develop guidelines to assess the likelihood that an employee's cancer was caused by his or her work at a covered site. This Advisory Board on Radiation and Worker Health may provide the most relevant prototype for an expert advisory panel for Part E. Other federal agencies also use advisory panels. For example, the EPA Toxic Substances Control Act Interagency Testing Committee reviews toxicity and exposure information on numerous substances for possible inclusion on the EPA's Priority Testing List. NIH has several study groups that review numerous grant applications. NLM also has a group of experts that periodically reviews information for HSDB records. Several of these panels are responsible for reviewing a wealth of information on a volume of substances in a timely manner, typically with contractor support to gather and abstract relevant information.

In summary, the committee appreciates the need for and the utility of SEM as well as the urgency with which it was developed. However, as the EEOICP claims process has evolved and new claims continue to be submitted to DOL, the need for peer review of SEM (and Haz-Map) has increased. The committee believes that with implementation of its recommendations, DOL will improve its claims process for both claims examiners and claimants.

STATEMENT OF TASK QUESTIONS AND RESPONSES

In addition to offering recommendations to improve SEM, the committee provides here concise responses to the eight questions in its Statement of Task.

1. **What, if any, occupational diseases that might have affected the DOE contractor workforce are missing from SEM?**
   The committee examined the list of diseases in SEM and found that some diseases such as those of the cardiovascular system and ovarian cancer are not listed in it. Occupational diseases are listed in SEM only if they are associated with exposure to a toxic substance, so diseases associated with a particular job or worker population may not be included. Such organizations as IARC also look at associations between specific occupations (including painters and welders) and diseases in those workers without reference to exposure to specific toxic substances. DOL should consider those types of associations to identify other occupational diseases that may affect the DOE contractor workforce. Furthermore, epidemiology studies conducted on DOE worker cohorts are not included in SEM. Given the opportunity to assess effects in the population of interest, results of those studies should be carefully considered by DOL and the recommended expert advisory panel.

2. **What, if any, links between occupational diseases and toxic substances present at DOE sites are missing from SEM?**
   The committee notes that some links between toxic substances found at DOE sites and diseases associated with them are not in SEM, such as the link between asbestos and ovarian cancer. The committee notes, however, that given the lack of exposure information in SEM—including period of use and intensity and frequency of exposure—it is difficult to ascertain whether occupational exposures were acute or chronic and were sufficient to result in chronic occupational disease. The committee did not conduct a systematic review of all the substance–disease links in SEM, which includes more than 13,000 substances and more than 120 occupational diseases.

3. **Is there additional literature (preferably human epidemiological in nature) that might be incorporated into SEM to strengthen or add to the existing links between toxic substances and occupational diseases? Are the existing links sufficiently robust?**
   Because SEM incorporates toxic substance–occupational disease links only from Haz-Map, any information missing from Haz-Map is necessarily missing from SEM. Because Haz-Map does not adequately reference the evidence used to establish each toxic substance–disease

link (except for cancer), the committee was unable to determine what additional literature might make the Haz-Map links more robust. The committee strongly recommends that evidence used to establish the Haz-Map links be clearly referenced in the Haz-Map "Diseases" field. Furthermore, the committee has commented on the information sources used for Haz-Map (see Chapter 2) and on the use of additional epidemiologic information in SEM (see Chapter 3), particularly the use of DOE worker cohort studies. Better and more comprehensive use of the existing data sources, such as IARC and ATSDR, and new ones—such as Cal/EPA OEHHA background documents, NTP, and IRIS—would substantially improve the robustness of the links in both Haz-Map and SEM. The recommended expert advisory panel could provide advice on the best way to incorporate the epidemiologic studies conducted in DOE worker populations; the exposures of these workers are directly relevant to the claimant populations.

4. **What, if any, other occupational disease databases might be used to supplement the Haz-Map information in SEM?**
Haz-Map is used for SEM because it provides causal toxic substance–occupational disease links in an easily captured field. Haz-Map is a unique database, and the committee was unable to identify any other databases that explicitly link occupational exposures to toxic substances to occupational diseases. However, the committee does not believe that lack of such databases means that other sources of information might not be used to supplement either Haz-Map or SEM. The committee emphasizes that databases alone, whether occupational or other, are not sufficient resources to supplement Haz-Map information in SEM, and it recommends that such documents as ATSDR toxicological profiles, NTP reports, and EPA background documents be reviewed by the proposed expert advisory panel. Many of those documents contain information on health effects seen in worker populations that have been exposed to the substances of interest. Another database that might be used is EPA's IRIS, which has clear documentation of the evidence on which EPA's conclusions are based.

5. **How scientifically rigorous are the disease links contained in SEM and Haz-Map?**
The toxic substance–disease links in Haz-Map, and thus in the SEM, for cancer are scientifically rigorous inasmuch as they are based solely on IARC's determination that there is sufficient evidence that a given substance is carcinogenic in humans (Group 1). However, for noncancer health effects in Haz-Map and SEM, it is difficult to determine the evidence base for some of the links. Therefore, the committee is unable

to state with certainty how rigorous the links are and finds that the rigor of links varies. In some cases disease links are based on one case report and in others on a substantial body of evidence. Furthermore, the links for mixtures are not robust.

6. **What are the strengths and weaknesses of the NIH/NLM peer review process with regard to Haz-Map? How might this process be improved?**
   There is no NIH or NLM peer review process for Haz-Map. The committee finds that that is a critical weakness for the database. NLM indicated that its staff copyedits the toxic substance profiles for Haz-Map and makes the links to other NLM databases, such as the Hazardous Substances Data Bank (HSDB), but NLM does not conduct any peer review of the substance–disease links determined by the Haz-Map developer. NLM also does not conduct peer review of any of the publications listed in PubMed; that is the responsibility of each journal. NLM does not conduct peer reviews of any external publications, even manuscripts. It is merely a platform for Haz-Map, and has little involvement in content. NLM does facilitate the peer review process for the HSDB, a database cited in Haz-Map, using an external group of experts. There are several options for a peer review process for both Haz-Map and SEM.

7. **Can any known (epidemiologically significant) synergistic effects between chemicals/chemicals or chemicals/radiation be placed in SEM? If so, what are the sources of these links and are they occupational in nature?**
   Research on synergism underscores that this type of chemical–chemical interaction is a valid scientific phenomenon. Such interactions, some of which are occupational, could be flagged in SEM for evaluation case by case. ATSDR and EPA conduct health assessments of chemical interactions, and these could be included in SEM in a new field as supplemental information. The evidence base on chemical–radiation interactions is less robust, especially in humans. However, as more information becomes available, the proposed expert advisory panel could revisit this topic and determine whether such interactions should be flagged in SEM.

8. **What consistent process or approach could be used to consider a disease or cancer established when studies are inconclusive, inconsistent, or conflicted in some way?**
   As discussed above, the committee strongly recommends that an expert advisory panel be established to review the evidence on any potential toxic substance–disease link. Such a panel, using a weight-of-evidence

approach, could determine how to assess inconclusive, inconsistent, or conflicted studies for purposes of evaluating whether there is a causal link. The panel may wish to develop its own criteria for weighing evidence or use criteria established by other authoritative organizations, such as IARC, NTP, and IOM.

Appendix A

Biosketches of Committee Members

Mark J. Utell, M.D. (*Chair*), is a professor of medicine and environmental medicine and the Director of Occupational and Environmental Medicine at the University of Rochester School of Medicine and Dentistry, and former director of Pulmonary and Critical Care Medicine at the University of Rochester Medical Center. His research interests have centered on the effects of environmental toxicants on the human respiratory tract. Dr. Utell has published extensively on the health effects of inhaled gases, particles, and fibers in the workplace and other indoor and outdoor environments. He is the co-principal investigator of an Environmental Protection Agency (EPA) Particulate Matter Center. He has served as chair of the Health Effects Institute's Research Committee, chair of EPA's Environmental Health Committee and on the executive committee of the EPA Science Advisory Board. He is a former recipient of the National Institute of Environmental Health Sciences (NIEHS) Academic Award in Environmental and Occupational Medicine. Dr. Utell is currently a member of the National Research Council's (NRC's) Committee to Develop a Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials. He previously served as chair of the NRC Committee to Review the NIOSH Respiratory Disease Research Program and the Committee to Review the Department of Defense Enhanced Particulate Matter Surveillance Program Report; as a member of the NRC Board on Environmental Studies and Toxicology; as a member of the NRC Committee on Research Priorities for Airborne Particulate Matter; and as a member of the Institute of Medicine (IOM) Committee to Review the Health Consequences of Service During the Persian Gulf War. He received his M.D. from Tufts University School of Medicine.

John R. Balmes, M.D., is a professor of medicine at the University of California, San Francisco, and the chief of the Division of Occupational and Environmental Medicine at San Francisco General Hospital. He is also a professor of environmental health sciences at the University of California, Berkeley, and the director of the Northern California Center for Occupational and Environmental Health. Dr. Balmes studies the respiratory health effects of various air pollutants, with a particular interest in occupational respiratory disease. He has investigated the acute effects of inhalation exposures to ambient air pollutants, the chronic effects of such exposures in epidemiological studies, and genetic determinants of responses to air pollutants. Dr. Balmes has led research to assist in the development of a national program to link environmental hazards with health outcome data to improve the tracking of diseases potentially related to environmental exposures. He is also the physician member of the California Air Resources Board. He served on the NRC's Committee for the Review of the Army's Enhanced Particulate Matter Surveillance Project Report, and on the IOM Committee on the Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan. Dr. Balmes received his M.D. from the Mt. Sinai School of Medicine.

Stanley C. Haimes, M.D., M.P.H., CIH, FACOEM, has spent 20 years in the occupational medicine field and his career encompasses the governmental, academic, private, and public sectors of occupational health programs. Dr. Haimes has experience with workers compensation programs, medical surveillance programs, and occupational medicine clinics. He is the medical director of the Center for Occupational and Environmental Health, the associate medical director for Seminole County Emergency Medical Services, and a medical review physician for Medical Audit Resource Services, Inc., all near Orlando, Florida. He has served as the director of Medical and Health Services for Lockheed Martin; as an environmental physician at the Veterans Administration Medical Center of Bay Pines, Florida; and Assistant Professor at the University of South Florida College of Medicine. Dr. Haimes has served on committees and panels for the National Institutes of Health (NIH) National Library of Medicine, the American Conference of Governmental Industrial Hygienists (ACGIH), and the American Industrial Hygiene Association (AIHA). He is a board certified physician in occupational medicine and is a certified industrial hygienist (CIH). He is a fellow of the American College of Occupational and Environmental Medicine. He received his M.D. from the University of South Florida and his M.P.H. from the Johns Hopkins School of Hygiene and Public Health.

William E. Halperin, M.D., Dr.P.H., is the chair of the Department of Preventive Medicine, New Jersey Medical School, and the interim associate dean for the Newark Campus of the School of Public Health, University of Medicine and Dentistry of New Jersey. His experience in epidemiology ranges from field

investigations of disease outbreaks (such as anthrax), to more subtle investigations of the association of chemical exposures with a variety of outcomes (such as dioxin and soft tissue sarcoma), as well as occupational injuries. Dr. Halperin has served on numerous NRC committees, including as Chair of the Committee on Toxicology and as a member of the Committee on Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations, and he is a member of the Board on Environmental Studies and Toxicology. He is board certified by both the American Board of Preventive Medicine and the American Board of Occupational Medicine. Dr. Halperin received his Dr.P.H. and his M.D. from Harvard University.

Philip Harber, M.D., M.P.H., is a professor of public health in the Mel and Enid Zuckerman College of Public Health, University of Arizona, and professor emeritus at the David Geffen School of Medicine at the University of California, Los Angeles. Dr. Harber's research focuses in occupational respiratory diseases, occupational health services assessment, and computer applications in occupational health. He is board certified in occupational (preventive) medicine, pulmonary diseases, and internal medicine. Dr. Harber served on the IOM Committee on Gulf War and Health: Updated Literature Review of Depleted Uranium. He received his M.P.H. from the Johns Hopkins University School of Hygiene and Public Health and his M.D. from the University of Pennsylvania School of Medicine.

Francine Laden, Sc.D., is the Mark and Catherine Winkler Associate Professor of Environmental Epidemiology at the Harvard School of Public Health. She is also an associate professor in the Department of Medicine, Harvard Medical School and Brigham and Women's Hospital. Dr. Laden's research focuses on environmental risk factors of cardiovascular disease and cancer, specifically breast cancer, non-Hodgkin's lymphoma (NHL), and lung cancer. She studies the relationship of exposure to organochlorine chemicals with both breast cancer and NHL and the association of diesel exhaust and other sources of fine particulate matter with lung cancer mortality. She has served on two IOM committees on the Gulf War and Health and on the NRC Committee on Contaminated Drinking Water at Camp Lejeune. Dr. Laden received her Sc.D. from the Harvard School of Public Health.

Ephraim Massawe, Sc.D., is an assistant professor in the Department of Computer Science and Industrial Technology at Southeastern Louisiana University. His research focuses on environmental and occupational health, nanoinformatics for health and safety of nanomaterials, and assessment and management of alternative substitutes to toxic chemicals. Dr. Massawe directs the EPA-funded Indoor Air Quality Assessment Project and the Modeling Exposures and Health Risks of Nanomaterials. He has experience in global environmental health issues and has

worked for the United Nations in Australia, Holland, Kenya, Tanzania, and the United States. Dr. Massawe is a member of AIHA, ACGIH, and the American Public Health Association, among many other related professional organizations. He earned his Sc.D. in environmental health and industrial hygiene from the University of Massachusetts.

Julia B. Quint, Ph.D., is a retired research scientist and section chief of the Hazard Evaluation System and Information Service in the Occupational Health Branch of the California Department of Public Health. She was involved in indentifying and evaluating reproductive toxicants, carcinogens, and other workplace chemical hazards, and in developing research protocols and other strategies to protect workers, communities, and the environment from the hazards of toxic chemicals. Dr. Quint is a member of the California Environmental Contaminant Biomonitoring Program Scientific Guidance Panel, the California Environmental Protection Agency's Green Ribbon Science Panel, and the National Institute for Occupational Safety and Health World Trade Center Scientific and Technical Advisory Committee. She was a member of the NRC Committee on Tetrachloroethylene and the Committee on Health Impact Assessment. Dr. Quint received her Ph.D. in biochemistry from the University of Southern California.

David Richardson, Ph.D., M.S.P.H., is an associate professor of epidemiology in the School of Public Health at the University of North Carolina at Chapel Hill. His research focuses on the health effects of exposure to ionizing radiation. Dr. Richardson has conducted studies of cancer among nuclear workers at several U.S. Department of Energy facilities, as well as studied cancer among the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki. He has served as a visiting scientist at the World Health Organization's International Agency for Research on Cancer in Lyon, France, and at the Radiation Effects Research Foundation in Hiroshima, Japan. Dr. Richardson is an associate editor of the journals *Occupational and Environmental Medicine* and *Environmental Health Perspectives* and a member of the President's Advisory Board on Radiation and Worker Health. He received his Ph.D. and his M.S.P.H., both in epidemiology, from the University of North Carolina at Chapel Hill.

Howard E. Rockette, Ph.D., M.A., is professor emeritus of biostatistics at the University of Pittsburgh School of Public Health. His primary research focuses on the development and application of statistical methods for problems in the areas of clinical trials, and in occupational and environmental epidemiology, and on the evaluation of radiological imaging systems. Research in occupational and environmental health has included estimation of cancer risk for various occupational groups including coal miners, steelworkers, and aluminum reduction plant workers. Dr. Rockette completed his Ph.D. and his M.A. degrees at the

Pennsylvania State University. He remains active on review committees, student committees, and NIH grants.

Mara Seeley, Ph.D., DABT, is a senior toxicologist at Gradient with experience in the areas of human health risk assessment, exposure assessment, and regulatory comment. She performs critical reviews of animal toxicology and human epidemiology studies, conducts multi-pathway human health risk assessments, develops toxicity criteria and health-based exposure levels, and evaluates exposures for non-standard exposure scenarios. Before joining Gradient, Dr. Seeley worked as an NIEHS research fellow at the University of Washington, where she studied the health effects of air pollution. She has authored or co-authored peer-reviewed articles and book chapters on a variety of topics, including risk assessment, health effects of perchlorate and nitrogen dioxide, endocrine disruptors, and developmental toxicity. Dr. Seeley has served on the IOM Committee to Review ATSDR's Great Lakes Reports. She received her Ph.D. in environmental health and toxicology from the University of Washington and is a diplomat of the American Board of Toxicology.

Rosemary K. Sokas, M.D., M.Sc., M.O.H., is a professor and the chair of Human Science at the Georgetown University School of Nursing and Health Studies. Her research interests include applied intervention effectiveness studies targeting occupational safety and health needs of vulnerable working populations. Dr. Sokas previously served on the faculties of the University of Illinois at Chicago School of Public Health, the University of Pennsylvania School of Medicine, and George Washington University. She also directed the Occupational Safety Health Administration's Office of Occupational Medicine and served as associate director for science at NIOSH. Dr. Sokas has served on the National Academies' Committee on the Review of NIOSH Research Programs, the Committee on Persian Gulf Syndrome Comprehensive Clinical Evaluation Program, and the Committee to Review the Worker and Public Health Activities Program administered by the Department of Energy and the Department of Health and Human Services. She has an M.D. from the Boston University School of Medicine and an M.Sc. and an M.O.H. from the Harvard School of Public Health (occupational physiology and occupational health, respectively).

Appendix B

Substances Evaluated by the Committee to Identify Toxic Substance–Occupational Disease Links Not Found in SEM

The following substances were evaluated by the Institute of Medicine's Committee on the Review of the Department of Labor's Site Exposure Matrix (SEM) Database to identify toxic substance–occupational disease links that were not found in SEM (see discussion in Chapter 3).

81 substances (and CAS [Chemical Abstracts Service] numbers) for which public inquiries were made:

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine/MPTP (28289-54-5)
1,2-Benzisothiazoline-3-one (2634-33-5)
1,3-Butadiene (106-99-0)
1,4-Phenylenediamine (106-50-3)
2-Aminophenol (95-55-6)
2-Butanone/MEK (78-93-3)
2-Naphthylamine (91-59-8)
2,4,6-Trinitrotoluene (118-96-7)
4,4´-Methylenedianiline/MDA (101-77-9)
5-Chloro-2-methyl-4-isothiazolin-3-one (26172-55-4)
Acetic acid (64-19-7)
Acetone (67-64-1)
Aluminum (7429-90-5)
Arsenic (7440-38-2)
Asbestos (1332-21-4)
Benzene (71-43-2)
Beryllium (7440-41-7)

Cadmium (7440-43-9)
Carbon disulfide (75-15-0)
Chromic acid cleaning solution/Chromic sulfuric acid (14489-25-9)
Chromium (7440-47-3)
Cobalt (7440-48-4)
Copper (7440-50-8)
Cutting oils/Tap Magic Original Formula
Cyanide (57-12-5)
Di-2-Ethyl Hexyl Phosphoric Acid (298-07-7)
Edetic acid/Versene (60-00-4)
Engine exhaust
Epoxy resins/Bisphenol A diglycidylether (1675-54-3)
Ether/Diethyl ether (60-29-7)
Euxenite
Fiberglass/Borosilicate (12676-29-8)
Formaldehyde (50-00-0)
Hard metals/Stainless steel (7440-44-0; 7440-47-3; 7439-89-6; 7439-98-7; 7440-02-0; 7440-03-1; 7440-32-6)
Hexane/n-Hexane (110-54-3)
Hydrogen Fluoride/Hydrofluoric acid (7664-39-3)
Iodine 131 (10043-66-0)
Isodecanol (25339-17-7)
Kerosene (8008-20-6)
Lead (7439-92-1)
Lead chromate (7758-97-6)
Lithium deuteride (13587-16-1)
Lithium hydride (7580-67-8)
Maneb (12427-38-2)
Mercury (7439-97-6)
Metal Working Fluids/Mineral Oil (8020-83-5)
Methylene bisphenyl diisocyanate/MDI (101-68-8)
Methylene Chloride/Dichloromethane (75-09-2)
Monel/nickel alloys (11105-19-4)
Naphthalene (91-20-3)
Nickel (metal dusts) (7440-02-0)
Niobium (7440-03-1)
Nitric acid (7697-37-2)
Paraquat (4685-14-7)
Perchloric acid (7601-90-3)
Phosphoric acid (7664-38-2)
Plutonium (7440-07-5)
Polychlorinated Biphenyls/PCBs (1336-36-3)
Polyvinyl chloride/PVC (9002-86-2)

Potassium hydroxide (1310-58-3)
Pyridine (110-86-1)
Radon (10043-92-2)
Rotenone (83-79-4)
Silicon (7440-21-3)
Sodium bicarbonate (144-55-8)
Sodium chlorate (7775-09-9)
Sulfuric acid (7664-93-9)
Tantalum (7440-25-7)
Titanium (7440-32-6)
Toluene (08-88-3)
Tool steel/carbon and steel alloys
Tri-Butyl Phosphate (126-73-8)
Trichloroethylene/TCE (79-01-6)
Trifluoroacetic anhydride (407-25-0)
Uranium (7440-61-1)
Uranium hexafluoride (7783-81-5)
Vinyl chloride (75-01-4)
Welding fumes
Zinc chloride (7646-85-7)
Zinc chromate (13530-65-9)
Zinc chromate hydroxide (15930-94-6)

15 substances identified by the committee:

2,4- and 2,6-Dinitrotoluene (121-14-2; 606-20-2)
Antimony (7440-36-0)
Chloramphenicol (56-75-7)
Coal Tar Pitch Volatiles (65996-93-2)
Cobalt Tungsten Carbide (60674-89-7)
Dibutyl Phthalate (84-74-2)
Diesel Exhaust
Ethylene Oxide (75-21-8)
Hepatitis B
o-Toluidine (95-53-4)
Radium (7440-14-4)
Strontium 90 (10098-97-2)
Styrene (100-42-5)
Tetrachloroethylene (127-18-4)
Thorium (7440-29-1)

Appendix C

Individuals Who Made Presentations to the Committee

The following individuals made presentations to the Institute of Medicine's Committee on the Review of the Department of Labor's Site Exposure Matrix (SEM) Database at open session:

January 23, 2012
Keck Center of the National Academies

Overview of Energy Employees Occupational Illness Compensation Program
Rachel Leiton, Director, Division of Energy Employee Occupational Illness Compensation, U.S. Department of Labor

Energy Employees Occupational Illness Compensation Program: Presentation on EEOICPA Law
Karoline Anders, Policy Analyst, Policy, Regulations, and Procedures Unit, U.S. Department of Labor, Division of Energy Employees Occupational Illness Compensation

U.S. DOL Site Exposure Matrices EEOICPA Part E
Keith Stalnaker, Project Manager, Paragon Technical Services, Inc.

Haz-Map: A Project to Map Occupational Toxicology Information into a Relational Database
Jay A. Brown, Haz-Map Developer and Consultant to the National Library of Medicine and to the U.S. Department of Labor

Comments on SEM

Terrie Barrie, co-founder, Alliance of Nuclear Worker Advocacy Groups
Laurence Fuortes, Professor of Occupational and Environmental Health and Internal Medicine, University of Iowa

March 16, 2012
Keck Center of the National Academies

Discussion with the Study Sponsor

Karoline Anders, Policy Analyst, Division of Energy Employees Occupational Illness Compensation, U.S. Department of Labor
Rachel Leiton, Director, Division of Energy Employees Occupational Illness Compensation, U.S. Department of Labor
Michael Chance, Chief, Policy Branch, Division of Energy Employees Occupational Illness Compensation, U.S. Department of Labor

Also in attendance:
Jay Brown, Haz-Map Developer and Consultant to the National Library of Medicine and to the U.S. Department of Labor
Carol Campbell, Chief, Policy Unit Division of Energy Employees Occupational Illness Compensation, U.S. Department of Labor
Jeffrey Kotsch, CHP, Acting Chief, Policy Branch
Wayne Knox
Christy Long, Deputy Director Division of Energy Employees Occupational Illness Compensation, U.S. Department of Labor
Trese Louie
Keith Stalnaker, Project Manager, Paragon Technical Services, Inc.
John Vance, Chief, Policy Unit, Division of Energy Employees Occupational Illness Compensation, U.S. Department of Labor

NLM Databases and NLM Review Process for Haz-Map

Pertti (Bert) J. Hakkinen, Senior Toxicologist and Toxicology and Environmental Health Science Advisor (to the Director), Specialized Information Services, National Library of Medicine.

NOTE: Dr. Hakkinen participated via teleconference. His presentation was given in person by his colleagues *Florence Chang,* Chief of the Biomedical Files Implementation Branch, Specialized Information Service, and *Lucie S. Chen,* Technical Information Specialist.