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SUMMARY AND ANALYSIS OF AVAILABLE AIR TOXICS HEALTH EFFECTS DATA

FINAL DRAFT

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ABSTRACT:

The purpose of this work assignment was to identify and review recent information regarding the qualitative relationship between exposure to toxic air pollutants and adverse human health effects. At the direction of USEPA OAQPS staff, ICF identified and contacted experts in air pollution epidemiology, and conducted limited computer searches to identify published literature and technical reports related to this issue. Two literature searches were performed, the first aimed at identifying recent (1993 to present) epidemiologic studies of air pollution adverse effects, and the second aimed at identifying studies by key researchers in the field identified through discussions with EPA and through the results of the first literature search. Each of the literature searches identified over 400 bibliographic citations; these lists were screened and those documents which were determined to be the most relevant were designated for procurement.

Among the articles and reports provided by EPA and those identified in the computer searches, over 165 were designated for procurement. In the time allocated to the project, about 125 documents were retrieved from libraries or other sources. These documents were further screened to identify those which provided information relevant to the elucidation of the relationships between air toxics exposures and adverse health effects. Thirty-four articles meeting this criterion were reviewed and their results and limitations briefly summarized. Detailed summaries were prepared of twelve of these studies which either described effects of ambient air toxics exposures which had not previously been documented, described effects in geographic regions or populations which had not previously been studied, or which employed novel approaches for assessing toxic air pollutant effects.

The studies which were identified included reports of adverse health effects of toxic air pollutant exposures in both U.S. (14 studies) and foreign populations (30 studies). Cancer and respiratory toxicity were the most commonly-studied effects; some studies addressed reproductive or neurological endpoints, or total and cause-specific mortality. Arsenic and metals were the most common pollutants addressed (primarily from metal smelting operations), followed by volatile organic chemicals and polynuclear aromatic hydrocarbons (PAHs). In a few cases, specific pollutants were not identified. Relatively few studies used both measured pollutant concentrations and observed health outcomes. Often exposures were estimated based on modeled air concentrations or using proxies for exposure measurements, such as residential location or duration. A number of studies used measured or modeled pollutant exposures as input to risk assessment calculations. Some of these risk assessment studies were reviewed, but the major focus of this report is on epidemiologic approaches to assessing air toxics risks.

The findings of health effects related to air toxics exposures near metals smelting operations generally confirm previously-identified relationships. Novel findings among the studies included neurobehavioral effects and elevated levels of chromosomal aberrations in populations living near uncontrolled hazardous waste disposal facilities, and a possible relationship between adverse respiratory effects and exposures to volatile organic pollutants at levels below those previously thought to be associated with such effects. In addition, several studies found relationships between "biomarkers" (measured tissue levels of pollutants or metabolites, or physiologic or biochemical changes due to chemicals) and emissions or exposures to toxic air pollutants. These studies included measurements of tissue levels of mercury, cadmium, and chlorinated pesticides, proteinuria resulting from cadmium exposure, and the quantification of DNA-pollutant chemical reaction products (adducts) due to PAH exposures.

1.0 INTRODUCTION

This Draft Report summarizes work done by ICF Kaiser International for the U.S. Environmental Protection Agency Office of Air Quality Planning and Standards, Program Review Group, under task 2-44 of EPA contract 68-D2-0189. The report provides a summary of recent evidence that links toxic air pollutant exposures to the occurrence of adverse human health effects. The study supports EPA's efforts to develop information for Congress, regarding "the public health significance of estimated remaining risks [associated with hazardous air pollution exposure]" and "concrete examples of populations that have experienced adverse health effects as a result of exposure to hazardous air pollutants.", which is required under the Clean Air Act, Section 112(f).

The scope of this project involved the following activities:

- Discussions with OAQPS project staff and ORD and regional EPA personnel to identify studies of air pollution health effects and populations exposed to toxic air pollutants;

- Discussions with ATSDR staff, experts at state and local regulatory and health agencies, and academic institutions, for the same purpose;

- Performance of computerized literature searches focusing on recent epidemiological studies related to air toxic health impacts and articles by key investigators in environmental epidemiology;

- Procurement, screening, and review of articles and other references identified by EPA, the air toxics experts, and through the computerized literature searches; and,

- Preparation of this draft report summarizing the results of the literature searches, identifying important data gaps, and suggesting directions for further research.

In keeping with direction from OAQPS, this effort has retained a narrow focus on recent studies of authenticated adverse human health effects of toxic air pollution exposures. Most of the information sources reviewed are articles published in refereed journals, although a number of technical reports prepared by or for EPA and other government agencies have also been reviewed. Resource limitations did not allow us to independently investigate reports of disease clusters, or to review raw data sources (disease registries, death certificates, or hospital records), except to the extent that these data had been independently evaluated by other investigators and reported in the published literature or technical reports.

Similarly, resource limitations did not allow us to provide detailed reviews of more than a representative portion of the large number of studies which were identified. (A complete listing of these studies is provided in Appendix A.) Instead, detailed reviews are provided (in Appendix B) of only a limited number of recent epidemiologic studies which provide novel or provocative findings, or which illustrate recently developed methods for investigating air pollutant-adverse effect relationships.

The remainder of this report is organized as follows:

- Section 2 provides a listing of the air toxics experts identified and contacted, and a detailed description of the literature search methods used to identify and obtain studies for review. The screening criteria used to select studies for detailed review, as well as the review procedure itself, are also described.

- Section 3 provides a review of background information related to the relationship between toxic air pollutant exposures and adverse health effects. This section explains the various techniques that have been used to establish a link between toxic air pollutant exposures and health effects, and provides a brief historical overview of past efforts to establish this linkage. This general information establishes the context for the focused discussion of the more recent studies that is provided in Section 4.

- Section 4 provides a summary of the results of the literature searches, screening, and review process. The most recent useful studies are broken down into categories related to types of adverse effect, the pollutants examined, and the state or country where the affected populations were located. Brief summaries are provided of a small number of studies, and general appraisal of other relevant studies is also given.

- Section 5 discusses the data gaps identified in our literature survey, and identifies a number of areas for further research to address the data gaps.

2.0 METHODS USED TO IDENTIFY AND REVIEW STUDIES OF AIR TOXIC IMPACTS

This section provides a brief summary of the procedures which were used to identify potentially relevant studies, to screen them, and to review them and summarize their results.

2.1 Discussions with EPA, Other Federal and State Agencies, and Academic Investigators

As noted in Section 1, many discussions of potentially useful studies were carried out with the EPA WAM and technical staff, and with experts from other EPA offices, other regulatory agencies, and academic experts in air toxics and epidemiology. In addition to the individuals identified through discussions with OAQPS, the literature searches discussed below also identified individuals actively working in the air toxics field.

EPA OAQPS staff provided a number of documents for review, as well as assistance in identifying and following up with experts inside and outside the agency. Table 2-1 provides a list of the individuals identified by ICF and OAQPS, indicating those who were successfully contacted and from whom information concerning the relationship between air toxics and adverse effects was obtained.

Contacts with experts were made both by ICF and OAQPS staff. Detailed interviews were not conducted with everyone on this list. In some instances, only exchanges of telephone messages were possible within the time frame of the study. When individuals were contacted, they were asked both for general insights and for specific studies concerning the relationship between air toxics and health in their geographical area or area of technical expertise.

2.2 Literature Search Methodology

In addition to the sources identified by the experts, several computer literature searches were also carried out to identify further studies for review. OAQPS provided the results of a February 1995 DIALOG literature survey on air toxics issues which served as a starting point for ICF's efforts.

2.2.1 Search Strategies and Data Bases Searched

Two distinct search strategies were employed. The first strategy was narrowly focused on the recent epidemiologic literature (1993 and later). The general intent of this search was to identify quite recent studies of air pollution effects that had not previously been reviewed by EPA. The focus was on studies which provided both exposure and effects data, although the initial search was broadly based, using a large number of key words to assure good coverage. A mixture of U.S. and a small number of major foreign data bases was searched, as listed in Table 2-2. Initial broad screening searches were performed by the ICF Information Services Group, and lists of titles were provided to technical staff for review. Based on this review, searches were fine-tuned, a final list of data bases was developed, and the final search was completed, providing full bibliographic information.

The second search strategy was intended to broaden the range of documents identified in the initial search, by looking further back in time. In addition, the search was keyed to the names of epidemiologists and scientists identified by EPA and ICF as being active in the field of air

TABLE 2-1 EPA, OTHER FEDERAL AND STATE AIR TOXICS CONTACTS AND ACADEMIC EXPERTS

USEPA-OAQPS

Julie Andresen(1,2)
Eric Ginsberg(1)
Margaret Round(1)
Dennis Pagano(1,2)

USEPA Other Offices

Ila Cote (ORD HERL)(1,2)
Joellyn Lewtas (ORD HERL)
Robert Fegley (ORD)
John Vandenberg (ORD HERL)(1)
Jane Metcalfe (ORD)
David Otto (HERL)(1)

USEPA Regional Offices

Linda Anderson-Carnahan (Region IV)
Bryan Bateman (Region IX) (1)

CDC

Godfrey Oakley (Analytical Epidemiology Division) (1)

ATSDR

Rick Canady (1)

State Regulatory Agencies

Joann Held NJDEQE (1)
Bliss Higgins LADEQ (1)

Academic Air Toxics Experts

Carl Shy (UNC SPH)
John Speizer (Harvard SPH)

Notes:
(1) Indicates individuals who provided studies or other information
(2) Reviewers of Draft of this Report

Table 2-2. LIST OF DATA BASES SEARCHED FOR AIR TOXICS-ADVERSE HEALTH EFFECTS INFORMATION

MEDLINE
Toxline
Cancerlit
Pascal
EMBASE
Env.Bib
Pollution Abs
Enviroline
NTIS
Energy SciTec
Ei Compendex*Plus
D-S/IAPV/INCIDENCE & PREVALENCE (IPD)

pollution adverse effects and epidemiology. The same databases were searched using this strategy as in the first search, omitting a few foreign sources which had not been productive.

2.2.2 Document Procurement

As noted previously, EPA OAQPS and other offices provided a number of documents to ICF for review. In addition, both of the computer literature searches identified very large numbers of documents (greater than 400 in each case) potentially related to toxic air pollution adverse effects. The results of the searches (study titles and abstracts) were reviewed by ICF technical staff and the studies which appeared to be relevant were identified for procurement. Articles were obtained from the ICF library, through interlibrary loans, or by sending runners to nearby libraries. A few government technical reports were ordered from NTIS. A complete list of documents which were identified for procurement is provided in Appendix A. This list also identifies articles that had been procured at the time this Draft Report was written. At that time, all but approximately 40 of over 165 requested articles and reports had been obtained.

2.3 Procedures for Screening Articles and Documents

When articles and other documents were obtained, each was screened by ICF staff to determine the level of review it would receive. After scanning the abstract and text of the article, we placed them into the following general categories:

Not Relevant. Studies in this category did not contain any significant information bearing on the relationship between air toxics exposures and adverse effects. Studies which fell into this category included those dealing with, for example, the environmental epidemiology of a specific adverse effect which did not address its relationship to air toxics exposures, or studies which were simply descriptions of air toxics exposure measuring methods, etc. These studies received no further review.

Background Studies. The studies which fell into this category were generally those which provided general background information on the relationship between air toxics and health effects, but which did not provide original exposure and effects data for any specific population. As discussed in Section 3, studies in this category included general historical reviews, pure methodology discussions, disease mapping studies which did not directly link observed patterns to air toxics, exposure evaluations, some biomarkers studies (if they were not accompanied by exposure or effects data), and risk assessments for air toxics exposures. These studies were reviewed in varying levels of detail (depending on their level of relevance), and provided reference material for the background discussion in Section 3.

Exposure-Effects Studies. Any study which provided information on both air toxics exposures and the occurrence of adverse effects in a specific population was included in this category. To "make the cut", the studies had to address specified "air toxics", as defined in Section 3.1. Studies of "criteria" pollutants (other than lead, and those studies which identified specific particulate toxic pollutants), and studies which did not identify specific pollutants also went into the "background" category. As noted in Section 2.1, the bias in identifying these studies was focused on recent articles, so some older epidemiologic studies with exposure and effects data were also used as background.

All recent exposure effects studies which we identified and obtained (about 40) were read and reviewed by ICF. The results of this review are summarized in Sections 4.1 and 4.2. A subset of these studies was selected for especially thorough review, and detailed-two page summaries (see Appendix B) were prepared for each of these studies. The criteria used to select studies for summarization included:

- The study provided information on a source category, pollutant, or effect not previously characterized;
- The study provided information on toxic air pollution adverse effects in a population or region not previously studied;
- The study employed novel or emerging methods for characterizing air pollutant-adverse effect relationships, or, in a few cases;
- The study illustrated key limitations and problems in evaluating the adverse effects of toxic air pollutants.

Limited reviews were performed of the remainder of the exposure-effects studies. Section 4.1 presents a tabular description of these studies, and a brief overview of their major findings.

2.4 Detailed Review Methods

The reviews of selected studies involved the development of detailed itemized summaries by senior technical personnel. A standardized format for the detailed summaries was developed, and is shown in Table 2-3. The areas addressed in the summaries include the identities of the pollutants studied, the exposure measures which were used, the study methods, the nature of the observed effects, and the overall study conclusions. At the end of each summary, the reviewers also provide comments on the methods, quality, and conclusions of the study. Striking findings in key studies are often the subject of debate or criticism by other workers in the field, and to the extent that the studies provoke comments or technical criticism, these are also addressed in this final summary section.

TABLE 2-3. FORMAT FOR DETAILED REVIEW OF AIR TOXICS HEALTH EFFECTS STUDIES

STUDY SUMMARY: (author, year)

CITATION:

SOURCES OF EXPOSURE:

HEALTH EFFECTS EVALUATED:

CHEMICALS EXPOSED TO:

EXPOSURE MEASURES:

CONFOUNDING FACTORS ASSESSED:

STUDY METHODS:

STUDY RESULTS:

AUTHOR'S CONCLUSIONS:

COMMENTS:

3.0 BACKGROUND

This section presents a brief discussion of the technical issues associated with establishing a qualitative relationship between exposure to toxic air pollutants and the development of adverse effects in humans. In section 3.1, historical background on the earliest efforts to establish air pollutant-adverse effects relationships is provided, and basic definitional issues are addressed (what is a "toxic air pollutant" for purposes of this assessment?). In addition, the major scientific approaches to evaluating the relationship between air toxics exposure and health effects (geographic pattern analysis, exposure/biomarker studies, risk assessment, and formal epidemiological analysis) are described. Section 3.2 provides a summary discussion of modern efforts to evaluate the effects of air toxics on human health, identifying the types of effects which have been evaluated, and placing in context past efforts at geographical pattern analysis, exposure and biomarker studies, and risk analysis. This discussion sets the stage for the treatment of the recent epidemiological studies of the relationship between air toxics exposure and adverse health effects which is presented in Section 4.

3.1 Approaches to Establishing a Qualitative Link Between Toxic Air Pollution and Health Effects.

The suspicion that man-made air pollution contributes to poor health is at least 300 years old[1]. However, the systematic investigation of the relationship between air pollution and ill health has only been undertaken in this century, primarily since 1950. The earliest efforts were focused on characterizing the relationship between obvious and acute effects (respiratory irritation, exacerbation of asthma, other respiratory and cardiovascular disease and death) and short-duration incidents ("air pollution episodes") of high exposures to combustion products, primarily coal smoke[2]. In air pollution episodes, the fact of high exposure was easy to establish (if only qualitatively), the spatial and temporal relationships between exposures and adverse effects were clear, and the nature of the adverse effects (serious incapacitation and mortality, in some cases) were easy to detect and quantify. Because of the clear relationship between exposures and effects, early attempts at controlling air pollution exposures were aimed primarily at these products of combustion, which in the U.S. are known for regulatory purposes as "criteria pollutants"[3]. With the exception of lead[4], the criteria pollutants have the common characteristics that their major, if not exclusive, adverse effects at near-normal ambient exposure concentrations are respiratory or ocular irritation, or exacerbation of

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[1] Suggestions of adverse effects air pollution associated with air pollution episodes in London were made as early as the 17th century.

[2] For example, an air pollution incident in Donora, PA, in 1948 resulted in an estimated 350 deaths from exposures to very high levels of mixed particulate, SO_2, CO, and other combustion products. Similar episodes of acute mortality in London, England (in 1952) and the Meuse Valley in Belgium (1930) have been recorded in this century.

[3] The criteria pollutants defined in the Clean Air Act are inhalable particulates (PM10), SO_2, nitrogen oxides (NO_x), carbon monoxide (CO), and lead.

[4] Lead is a criteria pollutant; "lead compounds" are HAPs. Thus lead falls on the borderline between the criteria and toxic pollutants. Studies of the adverse effects of lead exposure on human health are not included as a major focus of this study, however, because the relationship between lead exposures and adverse effects is so well-established, and because the literature on lead adverse effects is so large.

cardiovascular stress, and the technical basis for regulating these pollutants is primarily related to these effects[5].

The relationship between exposures to "toxic" air pollutants and adverse health effects is not so clear. Except for a few well-known cases (the sudden release of a large volume of methyl isocyanate in Bhopal, India, for example) where extremely high exposures to accidental releases of industrial chemicals resulted in severe acute health effects, the affects of adverse exposures to industrial chemicals are generally much harder to detect, for a number of reasons.

First, except in cases of accidental releases, exposure concentrations of toxic air pollutants in outdoor ambient air are generally much lower than exposure levels to the criteria pollutants in similar settings, since the criteria pollutants tend to be emitted in much larger amounts, at least in urban area. With the exception of those chemicals that have specific irritant properties, acute systemic effects such as are seen in occupational settings are less likely to be detected in the general population exposed to normally-occurring levels of "toxic" air pollutants, although as will be discussed later, at least one of the studies we reviewed shows evidence of adverse effects of toxics exposures (perhaps in especially sensitive individuals) at concentrations far below those previously thought to be hazardous. Often, the effects of the usually low chronic exposures to toxic air pollutants may be subtle, and may develop slowly over time in response to cumulative exposures (chronic effects), or may not develop until long after exposures occur (latent effects). The effects of exposure may include the same kinds of respiratory effects seen with exposure to criteria pollutants, or they may include effects on other organ systems in the body which are not so easily linked to inhalation exposures.

Thus it is not easy to directly characterize the risks associated with general population exposures to toxic air pollutants under conditions of chronic low-level exposures. Nonetheless, there is a high level of suspicion that such effects are occurring. The bases for this suspicion include the fact that many toxic air pollutants are suspected or known human carcinogens and even low levels of exposure could theoretically cause increased cancer risks. In a smaller number of cases, animal or controlled human studies indicate that noncarcinogenic effects might be expected to occur at exposures near ambient levels. In some instances, allergic sensitization may results in adverse effects in a small, especially sensitive subset of the exposed population. In addition, some toxicologists have also put forward theories that very low-level pollutant exposures (much lower than the no-effect levels indicated by laboratory studies) may cause subtle adverse effects by mechanisms which are not yet understood[6].

A final issue is the often-observed coincidence between exposures to criteria pollutants and exposures to toxic air pollutants. This phenomenon arises because both types of pollution are associated with areas of high population density and industrial development. As discussed below, many epidemiologic studies simply use measures of one or other of the criteria pollutants

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[5] Some criteria pollutants may cause chronic systemic effects in humans, however. Particulate pollutant exposures, SO_2, and acid aerosols have been linked to elevated cancer risks and other cause-specific mortality in some instances, and exposures to lead are regulated primarily based on its neurobehavioral effects.

[6] An example of such effects would include "multiple chemical sensitivity syndrome." The nature and causal mechanism of this syndrome has not been identified.

(particulates, usually) as the sole measure of exposure, and use it as a proxy for all "air pollution". Couple this with the fact that many of the toxic air pollutants (metals and low-volatility organics) are often present as part of particulate air pollution (especially near industrial point sources), and the issue of adequate exposure characterization becomes a key to evaluating potential relationships between air pollution and adverse health effects. The following sections discuss these various issues.

3.1.1 Definition of Toxic Air Pollutant

The primary focus of this report has been on locating and reviewing studies of exposures and adverse effects of substances which Congress has designated as "Hazardous Air Pollutants" (HAPs). The definition of "Hazardous Air Pollutant" (Clean Air Act Section 112(c)) includes 189 chemical compounds and families of compounds (Table 3.1). On the list are a wide range of organic compounds, the compounds of twelve metallic elements and metalloids, "all radionuclides" (including radon), and "fine mineral fibers". Included also are the broad categories of "coke oven emissions" and "polycyclic organic matter" (POMs), both of which include many high-molecular weight organic compounds, such as polycyclic aromatic hydrocarbons (PAHs).

This is an extremely inclusive list, covering the vast majority of the mass (greater than 99 percent) of all of the chemicals identified through Toxics Release Inventory (TRI) reporting as being released to air from industrial facilities in 1992. As part of this effort, we performed chemical-specific literature searches on the top 15 chemicals from the TRI list, but not on the other HAPs. No studies of any kind were found for most of the chemicals on the list; in fact, the great majority of the useful studies were limited to a relatively few (less than ten) pollutants, mostly metals. (See Section 4.) We did not specifically exclude studies of chemicals not on the list (except for criteria pollutants), but we identified no useful epidemiologic studies of non-occupational populations which related human health effects to any toxic chemicals which were not HAPs.

3.1.2 General Approaches to Establishing a Qualitative Relationship Between Air Toxics Exposures and Human Health Effects

At some level of certainty, no one seriously questions the fact that there is a relationship between exposures to toxic air pollutants and human health. The key questions are: At what levels of exposure do these affects occur, and what is their nature and magnitude? Thus, studies which attempt to establish a qualitative link between air toxics and adverse effects will inevitably involve, to some extent, quantitative measurement or estimation of both levels of exposure and the magnitude of effects. The level of certainty with which it can be ascertained that an effect is, in fact, due to an exposure is closely tied to the extent to which the relationship between exposures and effects can be established quantitatively (often through statistical hypothesis testing). Thus the qualitative and quantitative relationship between air toxics exposures and health effects are inextricably linked.

Table 3-1 HAZARDOUS AIR POLLUTANTS AS LISTED IN SECTION 112(b) OF THE CLEAN AIR ACT

Table 3-1 (continued)

Table 3-1 (continued)

Table 3-1 (continued)

There are five general types of approach that are employed to establish a relationship between air toxic exposures and health effects:

Studies of Laboratory or Occupational Exposures. Adverse health effects of exposures to specific pollutants are often first discovered through observations of adverse effects in workers exposed to high levels of the pollutants, or in laboratory studies of animal or human toxicity. These studies do not directly address the potential for adverse effects occurring in the general population at lower exposure levels.

Studies of Geographic Patterns of Disease Incidence or Mortality. It is often the case that studies of vital statistics, disease incidence, or mortality disclose geographic patterns of adverse health effects that are suggestive of a relationship to specific pollutants or pollutant sources (see section 3.2.2). Unfortunately, If such studies are not supplemented by exposure data, and are not controlled for confounding factors other than pollutant exposures, it is not possible to support inferences of causation associated with pollutant exposures.

Studies of General Population Exposures, Exposure Indices, and Biomarkers. There have been a number of environmental monitoring studies and data gathering exercises that have been used to estimate human exposures to pollutants and draw inferences about potential adverse effects (see Section 3.2.4). This information is often used, in conjunction with toxicity data, to conduct risk assessments. In some instances, measurable indices of exposures (biomarkers of exposures), such as body burdens or tissue concentrations of pollutants, can be used to document exposures and evaluate the potential for adverse effects. Other biomarkers (biomarkers of effects) can include altered enzyme or metabolite levels, DNA-chemical adducts, or chromosome abnormalities. Not all biomarkers are indicative of clinical effects (NAS/NRC 1989).

Risk Assessments. In a risk assessment, information about exposures (which may reflect actual measured exposures or exposures estimated using emissions and environmental models) is combined with toxicity information (from occupational or laboratory studies) to develop predictive estimates of the frequency or severity of occurrence of adverse effects in human populations. Risk assessment is a commonly used approach to evaluate the potential for adverse effects from air toxics exposure, but risk assessments may be subject to a high degree of uncertainty due to imprecision in exposure estimates, and uncertainties in dose-response information, especially at low doses, as discussed in section 3.2.5.

Formal Epidemiological Investigations. A "formal" epidemiological study involves systematic investigation of the relationship between an observed pattern of adverse health effects and exposures to one or more agents. The analysis of actual (as opposed to estimated) health outcome information is what distinguishes an epidemiological study from a risk assessment or a biomarkers study. Systematic efforts to control for confounding factors (factors other than toxics exposures which may be responsible for the observed effects) are what distinguish a formal ("analytical") epidemiologic study from a simple "descriptive" summary of geographic patterns of disease incidence. Recent epidemiological studies are the primary focus of our data gathering and review efforts, since they would provide the strongest direct evidence of air toxics-adverse effect associations. These studies are discussed in detail in Section 4.

Formal epidemiological studies, are the "gold standard" in establishing a relationship between air toxics exposures and adverse health effects. If adverse effects are unambiguously observed to occur in a distinctive pattern (in time or space, or in a given population), and this pattern can be shown to be significantly associated with estimated (or, preferentially, with measured) exposure patterns, and if other potential causes for the observed pattern in affects can be controlled for, then a strong inference can be drawn that the observed effect is associated with the agent in question. Support for a relationship between exposures and effect is further strengthened if the effect is consistent with the known toxic properties of the agent in question. Unfortunately, few studies measure up to this "gold standard". As will be seen in the following sections, many suggestive indications of possible relationships of air toxics exposures to health effects derived from geographic studies, exposure patterns, or risk assessment cannot be followed up due (most commonly) to a lack of comprehensive or reliable health outcome data, or due to a lack of exposure information. Many other suggestive findings from geographic studies do not stand up to detailed investigation; factors are found other than air toxics exposure which can adequately explain the observed patterns of health effects.

EPA has been investigating the relationship between air toxics and adverse health effects for many years, using all of the methodologies mentioned above. As will be discussed in more detail below, a major controversy currently surrounding the issue of air toxics health effects is the apparent inconsistency arising from the relatively high estimates of chronic health impacts which have been derived from exposure studies and risk assessments, compared to the relatively limited success that has been achieved in confirming the existence of these relationships through epidemiologic studies of exposed populations. This controversy has helped to focus our data gathering effort on the identification of recent epidemiological studies which can directly confirm the relationship between air toxics and adverse health effects. Our literature review also identified a number of risk assessment studies, but our major focus has been on epidemiological studies.

3.2 Past Efforts to Confirm the Relationship Between Air Toxics Exposures and Adverse Health Effect

In this section we provide a brief summary of major past efforts at characterizing the relationship between exposure to toxic air pollutants and adverse health effects. Included in this section are a discussion of the types of health effects which have been studied in conjunction with air toxics exposures, and summaries of how the current state of understanding of the major issues in the area has evolved over time in response to key findings from geographic studies, exposure studies, risk assessments, and epidemiologic investigations. The material in this section is intended to provide a brief historical overview, rather than a comprehensive treatment of the subject, and focuses on developments through approximately 1993; more recent studies are discussed in more detail in Section 4.

3.2.1 Types of Health Effects That Have Been Studied

Attempts to establish associations between air toxics exposures and health effects have focused on four major types of health effects: cancer, respiratory irritation and other respiratory

toxicity, neurobehavioral toxicity, and reproductive and developmental effects. Other effects are also occasionally studied, but much less frequently. Some of the toxic metals represent special cases, each having their own unique pattern of noncancer effects. The renal effects of cadmium exposures, neurodevelopmental impacts of lead, and the reproductive toxicity of mercury exposures are the most well-studied examples. In addition, a few studies use total mortality, or cause-specific mortality, as endpoints.

Among all of the data sources which we have examined, particularly the earlier studies, cancer is by far the most frequently-studied endpoint. Epidemiologic studies of air toxics have focused on cancer for two major reasons. First, there are established and easily accessible databases of cancer mortality and, to a lesser extent, incidence, at national and regional levels. In the U.S., the National Cancer Institute (NCI) has assembled and maintains a database of cancer mortality information at the county level starting from 1950, based on information provided by the National Center for Health Statistics (Fraumeni 1987). NCI also maintains a cancer incidence database covering a statistically representative weighted sample of about 12 percent of the U.S. population for the same period. Many states maintain similar cancer registries, as do many foreign countries. Another reason why cancer appears frequently as an epidemiological endpoint is its high mortality rate, so that studies can be based on analyses of death certificate files, which are also maintained by most states.

The second reason that cancer is a major focus of air toxics studies is that many toxic air pollutants, as noted previously, are suspect or confirmed human carcinogens[7]. Laboratory and occupational toxicity data suggest that many high-volume air toxics (metals, PAHs, benzene, some of the chlorinated solvents and organic monomers) can cause cancer at ambient exposures levels. This has been borne out by the results of a number of epidemiologic studies of populations exposed to metals and PAH air pollution from metal smelters and combustion sources. These carcinogenic pollutants also are convenient subjects for environmental studies because they are persistent in air and soil-water systems, and exposures can thus can be readily measured.

Respiratory toxicity[8] is a natural subject for epidemiologic investigation of airborne pollutants, since inhalation is the major route of exposure for these pollutants, and the respiratory tract is the initial site of pollutant contact and absorption. Also, inhalation endpoints have been the traditional subject of large-scale studies of the adverse effects of air toxics exposures to the criteria pollutants. Unlike cancer, however, there is no uniform national database or register of respiratory diseases, although national and state-level statistics on the incidence of some of the major noncancer respiratory diseases (asthma, emphysema, etc.) are available. This is partially because of the multiplicity of respiratory diseases, the difficulty of diagnosing them without physical examination and

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[7] In EPA's proposed rulemaking under Section 112(g) of the Clean Air Act, 120 of the 189 HAPs were classified as known, probable, or possible human carcinogens (59 Federal Register 15504 April 1, 1994)

[8] Folinsbee (1993) identifies the confirmed respiratory adverse effects of air pollution exposure as, "responses ranging from reversible changes in respiratory symptoms and lung function, changes in airway reactivity, and inflammation, structural remodeling of pulmonary airways, and impairment of pulmonary host defenses, to increased respiratory morbidity and mortality."

laboratory testing, and the wide range in severity of many of the disorders thought to be associated with exposure to toxic air pollutants.

Indications of the potential magnitude of adverse effects of toxic air pollutants can be found in numerous studies of the relationship between particulate exposures and acute and chronic health effects. In many of these studies, (usually where there is no clearly-identified dominant source of particulate air pollutants) it is not known which chemical constituents of particulates contribute to the observed increases in risk, and it is therefore difficult to attribute any given fraction of these effects to toxic air pollutants, as they are defined in this report. While toxic metals and organic pollutants may contribute significantly to these effects, acid aerosols and acid salts (which are not HAPs) bound to the particulates are thought to be major causative agents in the observed effects in many of the more recent studies.[9] Because of the known heterogeneity in particulate composition, studies of "particulate" air pollutants which do not identify specific toxic agents have not been a major focus of our effort. In addition to metals and PAHs, exposures to volatile organic HAPs have been implicated in a number of studies of adverse health effects[10].

As with respiratory effects, there are no national or regional registries of neurological disease. Also, the characteristics of many neurological disorders dictate the use of sophisticated testing and/or physiological monitoring methods to confirm diagnosis or evaluate the severity of impairments (Shy 1993). Thus, until recently, there have been relatively few studies of the association between neurological symptoms and exposure to toxic air pollutants. Exceptions include studies of Parkinson's disease, whose geographical patterns of mortality have been found to be correlated with specific industrial activities, but not specifically with air pollution (Rybicki et al 1993).

The existing literature on neurobehavioral effects of toxic air pollutants is dominated by discussions of the adverse effects of lead (which is a toxic criteria pollutant, as well as a "HAP") on intellectual and behavioral indices in children. These studies generally describe decrements in performance as a function of biomarkers of lead exposure, such as blood lead concentrations or heme metabolite levels. An important limitation of many of these studies is that there is often little information on the sources of lead exposures, and lead from deteriorating paint and in pipes and solders used for drinking water distribution can contribute significantly to total exposures. As noted above, one of the important characteristics of inorganic lead compounds is their persistence in the environment, which results in multi-pathway exposures to particulate materials deposited onto surface soil. Even this material could be counted as an impact of toxic air pollution, since the ultimate source of exposure was deposited air particulate.

Information related to the relationship of organic toxic air pollutant exposures to neurological effects is quite limited. Much of the effort in this area has been directed at characterizing the etiology

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[9] Recent reviews on this subject include Dockery and Pope (1993) on the acute effects of particulates, Folinsbee (1993) for a general overview of particulate health impacts, and Reichardt (1995) for an informal review of the health impacts of very fine particulates ($PM_{2.5}$).

[10] An example is the Kanawha Valley study (Ware et al 1993), reviewed in Section 4. Other instances where volatile organics have been implicated in the epidemiologic studies of respiratory toxicity include studies of populations near hazardous waste disposal facilities. Several of these studies are also discussed on Section 4.

of the physical and behavioral symptoms of "sick building syndrome" (Otto et al 1992), and investigating neurological impacts of exposures near toxic waste disposal sites. Some of these latter studies are discussed in Section 4.

The potential reproductive and developmental[11] impacts of exposure to air toxics have also been explored in a number of studies. The principal sources of data concerning the incidence and nature of reproductive effects include "state birth defects registries,....birth certificates, hospital and clinic records" (Shy 1993). There is, however, currently no comprehensive national registry of birth defects and other reproductive outcomes, and only about half of the states have birth defects registries[12]. Compared, however, to neurological disorders, data concerning major birth defects are relatively easy to obtain.

Epidemiologic studies of toxic air pollution impacts on reproduction in the U.S. have focused on a very few specific agents. Among these is vinyl chloride, whose teratogenic activity in animals prompted at least two epidemiological investigations of populations living near PVC manufacturing plants[13]. Another major toxic pollutant whose exposures have been strongly linked to adverse reproductive outcomes in mercury. The preponderance of the data concerning mercury is related to exposures to wastewater discharges rather than to mercury emitted into the air, however. Reproductive endpoints have also been investigated in populations residing near a number of hazardous wastes sites contaminated with volatile organic chemicals (Geschwind et al 1992). In some of these studies, air monitoring results support the possible relationship between inhalation exposures and the observed effects.

A few other endpoints have been used in attempts to link toxic air pollution to adverse health effects. One of the most important has been total and cause-specific mortality other than cancer. Many early studies of particulate air pollution impacts were based on developing statistical relationships between geographical exposure patterns and mortality. One of the most recent studies using this approach is the "Six Cities Study" (Dockery et al. 1993), although similar studies have been conducted of single cities in the U.S. and smaller geographical regions[14], and in eastern Europe

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[11] Note that reproductive and developmental toxicity are distinct types of adverse effect. They have been lumped together in this discussion in keeping with EPA's risk assessment guidelines.

[12] The Centers for Disease Control has operated the Birth Defects Monitoring Program (BDMP) since the 1970s. This registry of birth outcome data currently covers only about 12 percent of the live births in the U.S., and CDC is working with state registry systems to improve coverage (G. Oakley, CDC Analytical Epidemiology Division, telephone interview).

[13] Neither Edmonds et al. (1978), nor Rosenman et al. (1989) found evidence for an association between vinyl chloride emissions and the incidence of central nervous system malformations. Theriault et al. (1983), however found a consistent, but not statistically significant relationship between CNS birth defects and distance of residence from a PVC plant in New Jersey.

[14] Kaldor and Harris (1984), for example examined the relationship between air toxics exposure and major-cause mortality in an industrialized area near San Francisco. This study is discussed in more detail in Section 4. Schwartz and Dockery (1992) reported on the relationship between daily pollution levels and acute mortality in Philadelphia.

and the ex-Soviet Union[15]. Again, it is important to note that some or all of the effects of mortality seen in these studies may be associated with criteria air pollutants, rather than toxic air pollutants.

Finally, a number of studies which we identified have attempted to establish a relationship between exposure to toxic pollutant and cell mutations or chromosomal abnormalities (Klemens et al. 1995, Lakhanisky et al. 1993, Laurent et al. 1993). There have also been efforts to correlate air monitoring results for PAHs and levels of PAH-DNA adducts (biochemical reaction products of the PAH with DNA) in exposed populations (Binkova et al. 1995). These studies represent "biomarkers of effects", although the ultimates physiological and health significance of these endpoints is not clear.

3.2.2 Large-Scale Geographic Studies of Health Effects

Among the earliest studies in the attempt to link environmental factors (including toxic air pollution) to adverse health effects were a number of large-scale mapping studies of cancer mortality and incidence data in the United States. As noted above, these analyses were facilitated by the availability of national-level cancer mortality data which was evaluated and summarized by NCI starting in the early 1970s. This analysis culminated in the publication of a national atlas of county levels of organ-specific cancer mortality data.[16] Based on the maps produced during this efforts, NCI conducted a large number of epidemiological analyses of regional cancer hot-spots throughout the U.S.[17] These studies confirmed the existence of a gradient of increased cancer risk in cities compared to rural areas, associated primarily with differences in smoking habits and occupational chemical exposures. In addition, connections between observed cancer hot-spots were found to employment in World War II shipyards (associated with asbestos), to the textile and chemical industries, and to occupational exposures to pesticides in certain farming regions. Links to ethnicity, dietary habits, nutritional status, and to alcohol consumption were also found for a number of groups.

Two possible links to air pollution were also found in these followup studies; one was an increased incidence of lung cancer in residents of counties where metal smelting operations were located (Blot and Fraumeni 1975), and increased cancer incidence in counties (mostly in the gulf coast and New Jersey) with high concentrations of petrochemical and chemical industries. In neither case was a direct association with air toxics exposure established (cancer patterns on the gulf coast appear to be correlated with drinking water contamination, however), but the existence of such a linkage remains plausible. These findings spurred a number of studies of the relationship between residence near individual metal smelting operations and chemical plants and adverse health effects. Some of these studies are discussed in more detail in Section 4.

Similar large-scale mapping studies of geographic variations in cancer incidence have been conducted in Europe[18]. These studies generally confirm the urban-rural pattern of cancer incidence,

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[15] For a review, see Jedrychowski (1995)

[16] Pickle et al. (1987) provide county-level maps of cancer mortality for the period 1950-1980.

[17] For a summary of these studies, see Fraumeni (1987).

[18] For reviews, see Doll (1992), Tomatis (1991), and Hemminki and Pershagen (1995).

the strong dependence of cancer mortality on smoking habits and occupation, and suggested testable hypotheses regarding the relationship between toxic air pollution from industrial sources. A number of subsequent epidemiological investigations have been undertaken of the contribution of emissions from specific sources to cancer risks, as discussed in Section 4.

As noted previously, there are no readily accessible published data sources which provide comprehensive information on geographic variations in the incidence or mortality from diseases other than cancer, at the same level of detail as provided in the NCI cancer atlases[19]. Therefore, there has been only limited large-scale analysis of the geographic patterns of diseases other than cancer. One data source that has been used in the past is the Birth Defects Monitoring Program, which was an effort funded by the Centers for Disease Control in the 1970s, and which involved the collection of incidence data for major birth defects at a number of participating hospitals throughout the U.S. In recent years, the coverage of this program has declined so that is now no longer representative of overall U.S. patterns in birth defects[20]. In 1992, 25 states had active birth defects monitoring programs, which varied in degree of coverage and methods of data collection and organization (Greenwood 1993). Some states, including New Jersey, Louisiana, California, and Washington, have developed maps of birth defects incidence, and performed analyses of possible relationships between geographic patterns of birth defects and industrial facilities or hazardous waste disposal sites. Some of these studies are discussed in Section 4.

During the course of this project, we did not identify any other comprehensive national resources on geographic patterns of disease incidence which could be easily adapted for use in establishing the connection between toxic air pollution and cancer, nor did we review any mapping or geographic studies of other diseases. In theory, geographic patterns could be mapped and studied by using a sample of hospital admissions or discharge data, and many epidemiologic studies of potential air pollution affects have been conducted based on hospital data. We did not investigate the potential utility of this data source further.

3.2.3 Exposure Studies

A major limitation on the investigation of the relationship between air toxics exposure and adverse health effects is the shortage of air monitoring data for most toxic pollutants. In contrast to the situation for criteria pollutants, there is no national monitoring system for air toxics which can provide even general information on the urban and rural concentration patterns of these pollutants in ambient air. Epidemiological studies which seek to establish an association between air toxics exposure and health effects must therefore either include a monitoring program, find a local monitoring program which can provide data on the exposures of interest, or use some proxy for measured exposures. Such proxies may include modeled pollutant levels, pollutant emissions, or, as noted above, residential distance from an air pollution source. EPA and other organizations have

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[19] The National Center for Health Statistics maintain age-, sex-, and cause-specific mortality records at the county level for the entire U.S. As noted by Greenwood (1993), a number of academic institutions, including the University of North Carolina School of Public Health, are actively pursuing investigations of geographic patterns of disease mortality, including respiratory diseases, potentially related to toxic air pollutants.

[20] See note 12.

undertaken a number of efforts to fill the gap in knowledge concerning exposure levels to toxic air pollutants. These efforts have ranged from the establishment of centralized data bases of air toxics information to geographically focused efforts at exposure (and risk) estimation. The following paragraphs briefly review some of these efforts.

EPA currently has no comprehensive national monitoring system or data base of toxic air pollutant monitoring data[21]. The two national data bases on air pollutant levels, the Aerometric Information Retrieval System (AIRS) and the Air Pollution Enforcement Data System (APEDS) do not include information on toxic air pollutant levels other than lead, which is included by virtue of its status as a criteria pollutant (Greenwood 1993). These databases also contain information on particulate levels, but this is not speciated with regard to chemical composition.

During the 1980s, EPA attempted to investigate the connection between air toxics and adverse health effects by a number of local and regional exposure estimation, exposure modeling, and risk assessment studies. Some of these investigations were undertaken as part of the Integrated Environmental Management Program (IEMP). This program was initiated in 1985 in an attempt to characterize multipathway exposure to pollutants in a number of urban areas and to evaluate strategies for their control[22]. In almost all cases, the air toxics exposure estimates were developed based on emissions inventory information and air quality models, and only occasionally validated by air monitoring information (an exception is the Kanawha Valley, as discussed in Section 4). The estimated exposures were used, along with toxicological models, to estimate risk associated with toxics exposure, as will be discussed below.

During and after the IEMP, EPA made several attempts to characterize air toxics exposures at the regional[23] and national level through large air modeling studies based on emissions data. As early as 1985, EPA published a national exposure and cancer risk estimation study for air toxics (Haemisseger 1985). This and three other detailed exposure modeling and risk estimation exercises conducted by EPA are discussed in detail in Section 3.2.4.

For the most part, attempts to measure air toxics exposures to evaluate their relationship to spatial patterns in adverse health effects have been opportunistic and highly localized. Where monitoring data related to pollutant releases from specific sources are available, they have occasionally been used to support epidemiologic studies, as discussed in Section 4. By far the dominant approach to quantitatively estimating potential exposures to air toxics, however, is to use emissions information and air modeling data as was done by EPA in the IEMP discussed above. With the passage of Emergency Planning and Community Right-to-Know Act (EPCRA) and the

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[21] EPA developed a data base of modeled (not measured) air toxics concentrations for the IEMP cities and some other locations, and distributes it through the National Air Toxics Information Clearinghouse (Cote and Bayard 1988).

[22] The areas addressed were Baltimore, Philadelphia, the Santa Clara Valley, the Kanawha Valley, and Denver.

[23] Studies similar to the IEMP air modeling studies were performed in the San Francisco Bay Area (Kaldor and Harris 1984) and Chicago (USEPA 1989a).

promulgation of other requirements for pollution sources to provide emissions data, it has become easier to get emissions data for use in air modeling studies; in addition, exposure and risk characterization methods based on emissions modeling are required components of the permitting process for many industrial facilities.

A limited number of intensive efforts have been made, however, to comprehensively evaluate air toxics exposure patterns for small areas or narrowly defined populations. Among these have been EPA's TEAM (Total Exposure Assessment Methodology) studies of individuals daily patterns of indoor and outdoor air pollutant exposures, and the Airborne Toxic Element and Organic Substance (ATEOS) study in New Jersey. In the TEAM studies (Wallace 1991, Wallace et al. 1984a,b) EPA undertook to develop and employ personal monitoring technologies to evaluate patterns of exposure to toxics substances during the course of daily activities of study populations in a number of U.S. cities. The most important finding of these studies, for purposes of this effort, was that indoor air exposures appeared to contribute more to total air toxics exposures than did outdoor air. Often indoor air toxics concentrations were higher than outdoor exposures by a factor of ten or more. These studies did not, however, determine the specific sources of indoor (or outdoor) pollutant exposures, and the degree to which the findings of relative indoor-outdoor exposure relationships can be generalized to larger populations has not been established.

The ATEOS (Lioy and Daisey 1988) study evaluated exposures to airborne organic and inorganic pollutants at three urban and one suburban site in New Jersey for four 39-day periods during two consecutive summers and winters, and developed a detailed characterization of the temporal variability in pollutant levels during the sampling periods. In addition, detailed chemical speciation of the particulate air pollutants was performed, and source apportionment modeling was used to identify the contributions of major classes of pollutant sources to the observed exposures. The results of ATEOS were also used to develop quantitative risk estimates for exposure to air toxics at the various sites. A smaller scale effort, also in New Jersey (Butler et al. 1993), studied the relative contributions of ambient air pollution and other exposure pathways to the total intake of benzo(a)pyrene (a typical carcinogenic PAH compound) for typical exposed individuals.

3.2.4 Biomarker Studies

Biomarker studies attempt to evaluate and characterize exposures to pollutants through measuring changes in tissue levels or other indicators of exposure in exposed receptors (in this case, people). Biomarkers can range from tissue concentrations of pollutants and changes in enzyme or metabolite levels caused by pollutant exposures, to analyses of pollution-induced reaction products of genetic material. As noted previously, NAS/NRC (1989) divides biomarkers into two categories, "biomarkers of exposure" and "biomarkers of effect". The former term refers to tissue concentrations of pollutants and metabolites, while the latter terms refers to metabolic or physiologic changes that can be regarded as the first manifestation of adverse effects. (Some authors also view some of the subtle neurobehavioral effects of chemical exposures as "biomarkers", but we reserve this term for measurable changes in biochemical and physiological markers, consistent with the NAS definition.)

In the case of toxic air pollutants, biomarker studies have been used both to provide indices of the occurrence and severity of exposures, and as predictors of potential health risks. Among the most well-studied biomarkers of toxic pollutant exposures are the changes in blood lead concentrations,

tooth lead concentrations, and heme metabolites, associated with exposure to lead compounds in air, water, soil, and diet. Although such measurements can be used to reconstruct air exposure levels for the general population, it is almost always the case that direct air exposure contributes a relatively small fraction of total exposures compared to diet or exposures to contaminated soils or drinking water[24]. Where the indirect pathways are dominant, however, it is usually clear that the original source of these indirect exposures is air pollution. EPA uses children's blood lead concentrations as an indicator of potential adverse neurodevelopmental effects of lead exposures.

Blood or tissue concentrations of other metals are also occasionally used as indicators of exposure and potential adverse effects for airborne toxics. Among the studies that use biomarkers of exposures studies which we located through our search of recent literature are evaluations of tissue, hair, and urine cadmium levels in a population near heavily industrialized cities in the ex-Soviet Union (Busteva et al. 1994), and a study of arsenic concentrations in hair, urine and blood of children living near a smelter (Benko et al. 1977). Mercury is another metal whose concentrations in tissue or urine are often used as indices of exposure and potential adverse effects.

Recently, biomarkers which provide indices of exposure to mutagenic substances have become more prominent. In addition to the studies of chromosome aberrations (biomarkers of effects) around hazardous waste disposal sites which were noted previously, at least two other families of biomarker techniques have been increasingly applied to characterize potential exposures to mutagenic and possibly carcinogenic toxic air pollutants. The measurement and study of DNA adducts, or chemical reaction products of pollutants with the DNA (i.e., genetic material) is a techniques that has recently been used. Our survey of recent literature identified two studies (Binkova et al. 1995, Perera et al. 1990) of the relationship between DNA-PAH adducts and PAH exposures in ambient air. Both studies found strong relationships between measured PAH levels in ambient air and PAH adduct concentrations in peripheral leukocytes, suggesting that this method may be a useful indicator of recent exposure levels. In addition, because DNA adducts are premutagenic lesions, these data suggest that exposures to ambient levels of PAHs may lead to mutagenesis, and ultimately, to carcinogenesis. The results in both of these studies were not affected by confounding factors such as cigarette smoking.

All of these biomarker methodologies discussed above support, in one way or another, the qualitative relationship between air toxics exposures and adverse health effects. They can show, first of all, that exposures to given agents have occurred, and that sufficient amounts of the agents have been taken into the body to cause changes in tissue levels or metabolism, or to cause adverse health effects. They can also be correlated with exposure levels, to some extent, and can be used to document (as in the case of blood lead levels) when potentially harmful levels of exposure have occurred. Finally, some of the biomarkers can be considered precursors to clinically significant adverse effects.

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[24] In the commonly-occurring case of exposures resulting from metal smelting operations or waste disposal, the original source of exposure may have been air releases, although the actual exposure medium is soil or house dust. The other most common sources of lead exposure are particulates from automobile exhaust (less common in recent years, with the phase-out of lead in gasoline), leaching from pipes or solder in water distribution systems, and ingestion of lead paint.

3.2.5 Risk Assessment Studies of Toxic Air Pollutant Impacts

Because of the difficulty in detecting and measuring toxic air pollution effects, EPA has often relied on predictive risk assessment methods to estimate their magnitude, in the absence of actual health outcomes data. Risk assessment, in the context of this paper, means the development of quantitative estimates of the probability or severity of adverse effects using measured or estimated exposure information, and toxicological models and parameter values describing the relationship between exposures and effects[25].

The technical controversies surrounding the application of risk assessment methods constitute the main motivation for this study of recent epidemiologic studies. Risk assessment studies, cannot, in and of themselves, prove the existence of a relationship between air toxics exposures and adverse effects. If the exposure measures or estimates used as inputs to the risk estimate are incorrect, or if the postulated relationship between exposure levels and risk is incorrect, little confidence can be placed in the risk assessment results. Nonetheless, risk assessment provides a relatively inexpensive method for developing risk information in support of policy decisions, where direct measures of effects are not available. For this reason, EPA, and others have undertaken a number of risk assessment efforts to characterize the relationship between air toxics exposure and adverse effects.

As noted above, an early EPA effort to quantify the adverse effects of air toxic exposures on human health was a cancer risk assessment undertaken by Haemissegger et al. (1985). This analysis, which used emissions data, air quality models, and EPA cancer dose-response parameter estimates to evaluate risks from a relatively small number of pollutants, estimated that between 1,800 and 2,400 cases of cancer per year were caused by air toxics. The aggregate totals in this analysis were driven to a large extent by very high risks calculated for areas near a relatively few point sources.

EPA developed more refined estimates in the "Controllability Study" (1989b) and in the evaluation of Outdoor Exposure to Air Toxics (1990a). The first study, building on the results of the IEMP efforts discussed above, estimated cancer risks due to air pollutant exposures in the five IEMP cities. The total cancer risk from toxic air pollutants across all five cities was found to range from 2 to 10 cases per million individuals per year, implying comparable or somewhat lower national population cancer risks than the previous study. This study found that the chemicals which accounted for the greatest risk were POM (27 percent), 1,3-butadiene (19 percent), formaldehyde (18 percent), and hexavalent chromium (17 percent). The source categories which were associated with the greatest risks were vehicles (55 percent), chrome plating operations (9 percent), solvent use (7 percent), and wood smoke (6 percent). Emissions from chemical manufacturing accounted for approximately 1 percent of the total estimated risks. A subsequent review of these estimates (Portney 1991), used the same data derived by EPA to develop much lower estimates of nation-wide air toxics-related cancer risks.

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[25] In a typical risk assessment for toxic air pollutant, individual cancers risk are estimated by multiplying modeled or measured air concentrations of pollutants by the Unit Risk values for those pollutants. For noncarcinogens, air concentrations may be compared to, or divided, by Reference Concentrations, to generate an index of the potential for adverse noncancer effects.

EPA's 1990 study estimated the relative contribution of a number of chemicals to the total cancer risks due to air toxics. They estimated that the largest contributor to total cancer risks was PIC (products of incomplete combustion) at 35 percent, followed by 1,3-butadiene (12 percent), hexavalent chromium (9 percent), benzene (8 percent), and formaldehyde (6 percent). EPA (OPPE) is currently conducting a national air toxics exposure study, (as part of the "Cumulative Exposure Project") which will also be used to develop risk estimates to toxic air pollutant exposures. This project is still in its initial stages.

Similar efforts to use exposure and risk assessment methods to develop population cancer risk estimates due to toxic air pollutants have been performed in Sweden (Tornqvist and Ehrenberg 1994, Hemminki and Pershagen 1995). In one study, the lifetime cancer risks associated with exposures to typical urban air pollution levels was estimated to be on the order of 85 per 100,000, with the major contributors being POM (primarily from vehicle exhausts, about 58 percent), 1,3-butadiene (about 24 percent), and all radionuclides (about 15 percent). The other study estimated lower lifetime cancer risks, of about 17.5 per 100,000 at average swedish ambient exposure levels, with the major contributors being PAH, asbestos, benzene, and arsenic.

These estimates of cancer risks associated with toxic air pollutants remain extremely controversial. This is partly because of the uncertainty associated with the modeling procedures used to estimate exposures, and also because of the very large uncertainties associated with cancer dose-response estimation at very low dose levels. There are major controversies associated with low-dose cancer risk modeling for all of the major contributors to cancer risks which were identified in the above studies.

In addition to the risk assessments for cancer just discussed, EPA (1990b) has conducted a large-scale risk assessment study of the potential for adverse noncancer health effects of air toxics exposures. The approach taken in this study was to compare monitoring data or modeled pollutant concentrations to health reference levels (inhalation RfDs) or LOAELs (lowest observed adverse effect levels, usually from controlled laboratory studies in animals or occupational studies; they are almost always higher than reference doses). The analysis found that there were numerous instances where measured or modeled concentrations of pollutants exceeded reference concentrations. The concentrations of about one-third of all of the pollutants for which health reference levels were available exceeded the reference levels at 25 percent or more of the exposure locations. Concentrations for two percent of the pollutants examined exceeded LOAELs at one or more exposure locations. As was the case for the cancer risk assessment, these results are consistent with a high degree of suspicion that exposure to at least some toxic pollutants is resulting in adverse health effects. However, they do not provide any direct confirmation that adverse effects of the types modeled in the study actually are occurring.

4.0 SUMMARY AND RESULTS OF STUDY REVIEWS

This section summarizes the results of some recent epidemiology studies that we identified in our research that assessed both exposure to HAPs (or a surrogate of exposure, such as distance to a major emitter), along with observed health effects associated with the exposures. Section 4.1.1 provides an overview of the studies reviewed, the types of exposures that were evaluated by these studies, the types of endpoints that were evaluated, and the methodologies used. Section 4.1.2 provides more detailed descriptions of these studies and an evaluation of the overall knowledge base related to associations between exposures to HAPs and adverse health effects. Section 4.1.3 addresses the "bottom line" from these studies and their impact on establishing a link between air toxics exposure and adverse health effects. The reader is also referred to Appendix B for detailed reviews of selected studies.

4.1 Epidemiology Studies Evaluating the Link Between Exposure to HAPs and Adverse Health Effects

Based on the literature searches and interviews with experts described in Section 2, 34 studies were identified and obtained that attempted to associate some measure of exposure to HAPs with observed adverse health effects. As discussed in Section 2, although an attempt was made to cover the literature, the reviewed studies do not constitute an exhaustive list. For example, because the purpose of this study was to identify specific geographical areas where health effects may be occurring as a result of HAP exposure, negative studies were de-emphasized. Furthermore, a number of published and unpublished studies were identified, but could not be obtained and reviewed, due to time constraints. For certain well-studied classes of exposures and effects (most notably, exposure to arsenic from smelters and lung cancer), time constraints again prevented a thorough documentation of the available literature. Finally, due to the large number of reviews covering the scientific literature prior to 1990 (see Section 3), emphasis was placed on the literature since 1990.

4.1.1 Overview of Studies Evaluated

Table 4-1 summarizes the 34 retrieved studies evaluating health effects and using measurements and/or surrogate markers for levels of exposure to HAPs. It should be emphasized that the summaries provided in this table do not represent a detailed analysis of the methods, results, and limitations of each study. Instead, the table lists the key facts about the study, including the most important conclusions and main limitations. Additional limitations, including important confounders that were not accounted for, may also exist.

It is also important to note that most study authors only assessed exposure (or measured an exposure surrogate) to one air pollutant or a small group of air pollutants. Exposure to many other air pollutants (and to pollutants in other environmental media) probably occurred in most of the study populations. The degree to which these other exposures may confound the study conclusions depends on the type of other pollutant and the endpoint evaluated. In situations where there may be confounding ambient exposure to HAPs other than the one measured, the observed effect may be erroneously attributed to a specific pollutant, but this will not affect the overall conclusion regarding an association between HAP exposure and adverse health effects.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Baker et al. 1994 Cross sectional	Health effects in 2 communities near NPL site. U.S.: Riverside County, California	Residence in communities at different distances from site	Interview on demographics, other exposures, variety of general health outcomes (respiratory, liver, skin); medical records	Increased prevalence of bronchitis, asthma, angina, skin rashes, ear infections. Possible recall bias, toxicological mechanism unclear.
Bencko et al. 1977 Cross sectional	Hearing loss in children near As-emitting coal power plant. Czechoslovakia	Residence in exposed area	Hearing test, clinical exam, questionnaire	Significant increase in hearing loss in exposed group.
Binkova et al. 1995 Prevalence	Effect of PAH exposure on DNA adducts in outdoors workers. EPA/HERL research. Czech republic	Personal exposure monitoring, ambient measure, DNA adducts	DNA adducts measured in white blood cells	Increased DNA adducts correlated significantly with increased exposure to PAHs. Well conducted, controlled for smoking.
*Brown et al. 1984 Case-control	Lung cancer near zinc smelter and steel plant. Exposure to As, Cd, Cu, Pb, other metals, SO_2. U.S.: Eastern Pennsylvania	Measure based on emissions, distance from plant, weighting based on soil samples. Air monitoring and soil sampling were also conducted.	Cancer mortality, interviews	Arsenic exposure resulted in significantly increased risk. Controlled for smoking and occupational exposure.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
*Bustueva et al. 1994 Cross sectional	Kidney function and Cd exposure near 3 Cd plants. Russia	Ambient Cd in air, urine and hair Cd levels	β-2-microglobulin (β-2m) excretion (kidney function)	Increased number exposed subjects with high β-2m, but too few affected for statistics. Smoking not addressed.
Cordier et al. 1983 Geographical correlation	Mortality in residents near a copper smelter. Canada	Residence near smelter. (Emissions also reported for SO_2, Zn, Pb, As, Cd, Hg)	Mortality, from population registry	Increased deaths from lung cancer, respiratory disease in men, corrected for occupational exposure and smoking. Increased deaths from respiratory and endocrine disease in women.
*Dayal et al. 1995 Cross sectional	Symptoms in predominantly African-American population near 2 Superfund NPL sites. U.S.: Houston, Texas	Measure based on distance to site ($1/d^2$) and estimated amount of toxic chemicals at that site	Symptom questionnaire	Excess of neurological symptoms in most-exposed 10% vs. bottom 30%. No control for confounders, all effect measures based on self-reporting, with no external control.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
*Edmonds et al. 1978. Cross sectional	Congenital CNS malformation near vinyl chloride plant. U.S.: Kanawha valley, West Virginia	Vinyl chloride monomer emissions, number of abnormal vinyl chloride emission incidents, distance/direction from plant	CNS birth defects from BDMP registry, interviews	Elevated rate, but decline in rate preceded decline in emissions. No control for smoking.
*Frost et al. 1987 Cross sectional, case-control	Lung cancer in women near arsenic-emitting smelter. U.S.: Tacoma, Washington	Cumulative exposure index based on distance from smelter, duration of residency, and weighting factor based on estimated emissions.	Lung cancer mortality from death certificates	No effect in observed vs. expected ratio; but significant effect seen in case-control study. No control for smoking.
Greaves et al. 1981 Case-control	Lung cancer near nonferrous smelters (potential As exposure). U.S.: Idaho, Montana, Arizona	Distance of residence from smelter	Lung cancer cases from cancer registry; controls were cases of cancers not associated with smelter effluent	No effect. Small sample, no measure that As was present. Controlled for age and sex.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Grimalt et al. 1994 Geographical correlation	Cancer incidence in residents near organo-chlorinated compounds factory. Spain	Ambient air monitoring, serum levels of organochlorine compounds	Cancer incidence registry, death records (age-standardized)	Significantly increased soft-tissue sarcoma and thyroid cancer in males, but no significant excess in females. Therefore, excess may be due to occupational exposure. No demographic information.
*Hallenborg et al. 1991 Prevalence	Respiratory function in residents near sugarcane factory. U.S.: Oahu, Hawaii	Residence near sugarcane factory. Suggested agent is silica fibers.	Questionnaire, physical exam (spirometry), chest radiograph	Decreased lung function. Small sample (14), no control; spirometry corrected for age and smoking.
Hertzman et al. 1987 Geographical correlation	Respiratory, skin, narcotic, mood disorders in residents near landfill. Canada	Distance of residence to landfill, length of residence	Questionnaire and interview, medical charts for respiratory, skin, narcotic, mood disorders	Trend with distance to landfill for all four types of effects. Possible oral exposure, risk perception confounding.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Kaldor et al. 1984 Geographical correlation	Cancer incidence, other causes of death related to industrial emissions of SO_2, NOx, hydrocarbons. U.S.: Contra Costa county, California	Pollution dispersion model for SO_2, NOx, and hydrocarbons, based on emissions, topography, meteorology; population-density weighted exposure	Cancer incidence surveillance and vital statistics (mortality causes)	Exposure-related trends in certain cancers, cardiovascular disease, and in cirrhosis in men. Possible occupational explanation or confounding from alcohol or smoking. Motor vehicles not included as a source. Subsequent review of exposure modeling has questioned the validity of exposure-effect relationship.
*Kilburn and Warshaw 1995 Matched cohort	Neurobehavioral effects of population near oil reprocessing plant and Superfund site. U.S.: Baton Rouge, Louisiana	Distance from site, duration of exposure	Battery of neurophysiological and psychological tests	Exposed group impaired compared to referent. No trend with exposure surrogate.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Kunst et al. 1993 Geographical correlation	Regional differences in lung cancer mortality. Netherlands	SO_2 levels (correlated with NO_2, PM, benzo(a)pyrene) as surrogate for all air pollution	Lung cancer deaths from national registry	Lung cancer mortality significantly correlated with degree of urbanization. In people $\geq$65 years old, significant correlation with SO_2 after controlled for smoking.
*Laurent et al. 1993 Cross sectional	Sister chromatid exchanges near industrial dump. Belgium	Measured air concentrations of volatile organic compounds at site and in village; emissions also measured	Sister chromatid exchanges	High quality, but SCEs indicate repair of damage, rather than persistent damage.
Matanoski et al. 1981 Geographical correlation	Cancer mortality near chemical plant. U.S.: Baltimore, Maryland	Residence near plant vs. census tracts matched for age, race, sex, socioeconomic status	Cancer deaths from death certificates, inspection of hospital records	Increased lung, pancreas, other cancers, controlled for occupational exposure Effect limited in time.
Nordstrom et al. 1978 Geographical correlation	Decreased birth weight near smelter emitting As, Pb, SO_2. Sweden	Residence in region at different distances from smelter	Birth weight from hospital records	Decreased birth weight at $\leq$10 km from smelter. Not due to difference in parity, but no control for smoking, occupational exposure.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Norseth 1994 Geographical correlation	Mortality near nickel smelters. Russia/Norway	Regional ambient air monitoring for SO_2, heavy metals; emissions data	Mortality and causes from death certificates, age standardized	Significantly increased cancer and cardiovascular disease. Attributed to SO_2 and nickel.
Otto et al. 1995 Cross sectional	Neurobehavioral performance in children in polluted area (documented air pollutants include SO_2, NOx, PM_{10}, PAHs) (EPA-HERL sponsored). Czech Republic	Hair and urine Hg levels; residence in polluted city	Battery of neurobehavioral tests	Decreased performance on objective tests (finger tapping, hand-eye coordination) with increased hair Hg. However, hair Hg higher in control area. Unpublished.
Ozonoff et al. 1994 Case-control	Cancer incidence near a Department of Defense Superfund site. U.S.: Upper Cape, Massachusetts	Air measure was based on distance and direction to source; drinking water contamination	Cancer incidence registry	Increased risk of lung and breast cancer, but increase was not significant. Confounders were addressed. Low statistical power.
*Pershagen 1985 Case-control	Lung cancer mortality near arsenic-emitting smelter. Sweden	Residence in exposed area; ambient levels measured	Lung cancer deaths from national registry	Significantly increased risk in exposed group. Controlled for occupational exposure, smoking.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Phillips 1992 Geographical correlation	Relationship between toxic releases and biomarkers of human exposure to organic pollutants (tissue levels). U.S. regions	Toxic releases to all media based on the Toxics Release Inventory (TRI), STORET database (water monitoring data)	Biomarker of exposure (chemical levels in adipose tissue)	Significant correlation for all exposure pathways between exposure and tissue levels. Exposure only; no effect measure
Revich 1995 Geographic correlational/ prevalence	Health effects in a region with metallurgy and pulp and paper industry, with emphasis on children and women. Russia	Residence in region. Measured ambient levels at various distances from plants and emissions were also reported.	Developmental (premature delivery, birth defects), infant morbidity, cancer, growth of children.	Review. Respiratory and neurologic diseases were increased, and physical development of children was slowed in the exposed region. Increased gastric cancer attributed to ingestion of food contaminated by radioactive fallout. No control for confounders. No statistical analysis.
*Rosenman et al. 1989 Modified case-control	Central nervous system birth defects related to vinyl chloride exposure from industry. U.S.: Burlington County, New Jersey	Distance from polyvinyl chloride plant, emissions	CNS birth defects from hospital records	Increased odds ratio near plant, but not significant. Low statistical power, no control for smoking or drinking

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Swaen and Slangen 1995 Geographical correlation	Leukemia and gasoline consumption. Western and Eastern Europe (19 countries)	Gasoline consumption as surrogate for benzene exposure	Leukemia incidence and mortality	No association found
Theriault et al. 1983 cross sectional, case-control	Birth defects near vinyl chloride plant. Canada	Ambient air monitoring, dispersion modeling	Birth defects and types in exposed town and 2 referents, interviews	Increase in multiple types of birth defects, correlated with seasonal variation but not with distance to plant. Well-controlled.
*Ware et al. 1993 Cross sectional	Respiratory and irritant effects of volatile organic compounds in children. Kanawha Valley, West Virginia	Ambient air monitoring for 15 volatile organic compounds at schools	Symptom questionnaire	Increased asthma and respiratory effects. Effects correlated with living in/out of valley, but not with proximity to industry. Indoor air not assessed. Question of criteria pollutant confounding.
Williams et al. 1995 Geographical correlation	Mortality and sex ratio of births near point sources of industrial pollution. Scotland	Residence near major sources of metals and organic air pollutants	Vital statistics data from national register	Increased SMR, no effect on sex ratio, almost significant increase in lung cancer.

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
*Woodall et al. 1992 Prevalence, cross sectional	Health effects in polluted area (EPA-region sponsored). Kentucky/Ohio/West Virginia	Days of increased emissions from refinery complex (largely criteria pollutants), taking wind direction into account; residence in polluted area	Review of hospital records, official complaints of adverse effects, random survey of health complaints, comparison of symptoms reported in interviews	Only criteria pollutants mentioned with regard to emissions, although monitoring also suggested for H_2S. Increased emergency room visits on high exposure days. Increased respiratory effects in exposed area.
Yansheva et al. 1993 Geographical correlation	Lung cancer in polluted region. Ukraine	Ambient concentration of benzo(a)pyrene (BAP). (Article is unclear, concentration may be estimated.)	Lung cancer incidence	Correlation of BAP with lung cancer. Poor quality, little methodology information.
Zhao et al. 1994 Cross sectional	Chromosomal changes in workers and population related to vinyl chloride. China	Measured vinyl chloride concentration in air	Serum lysozyme, markers of genetic changes (e.g., chromosome aberrations, sister chromatid exchanges)	Ambient exposure affected only serum lysozyme; occupational exposure increased genetic changes

Table 4-1 Exposures and Effects for Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study/Type	Topic	Exposure Measure	Effects Measure/Source	Comments
Zmirou et al. 1994 Cross sectional	Health effects near toxic waste landfill emitting VOCs. France	Measured ambient levels, dispersion model, taking into account daily activity	Drug prescriptions as surrogate	Very slight, nonsignificant trend with distance to site. No decrease after site closed (national consumption increased).

Key:

* Study also analyzed in Appendix B

As=arsenic; β-2m=beta-2-microglobulin; BAP=benzo(a)pyrene; BDMP=Birth Defects Monitoring Program; Cd=cadmium; CNS=central nervous system; Cu=copper; DNA=deoxyribonucleic acid; H_2S=hydrogen sulfide; Hg=mercury; NOx=nitrogen oxides; NPL=national priorities list; PAHs=polycyclic aromatic hydrocarbons; Pb=lead; PM=particulate matter; SO_2=sulfur dioxide; SCE=sister chromatid exchange; SMR=standard mortality ratio; TRI=Toxic Release Inventory; VOC=volatile organic compound; Zn=zinc

Because high exposure to HAPs is generally limited to a localized area around point sources, such situations would generally be limited to studies conducted in highly industrialized areas, such as the Kanawha valley, with several different industries emitting different HAPs in a localized area.

Exposure to HAPs in indoor air presents a special case of potential confounding. Most of the population spends a majority of the time indoors, and personal exposure monitoring data indicate that HAP concentrations in indoor air can be much higher than those outside (Wallace 1991, Wallace et al 1984a,b). Very few of the studies that we evaluated used personal exposure monitoring or controlled for indoor air exposure to HAPs. Due to the wide variation in indoor exposure, it is difficult to design studies that assess the effects of HAPs in ambient air, while effectively controlling for indoor exposures.

When the confounding exposure is to criteria pollutants, the potential for confounding depends on the endpoint being studied. If the exposure to criteria pollutants is sufficiently high, it may be impossible to determine whether certain effects (e.g., acute respiratory effects, eye irritation) resulted from exposure to criteria pollutants or HAPs. By contrast, other effects, such as objective neurological deficits, are rarely attributed to criteria pollutants, except for lead. Thus, if exposure to lead is low, exposure to criteria pollutants is less likely to confound any observed association between neurological effects and HAP exposure.

Table 4-2 categorizes the studies screened by study type, the type of pollutant that was evaluated (keeping in mind that other exposures may have occurred), the exposure measure or surrogate used, the endpoints that were evaluated, and the location of the study. As shown, cancer was the most commonly evaluated endpoint, accounting for 14 studies. General systemic effects, including overall mortality, were evaluated in 11 studies, while neurological endpoints were evaluated in 9 studies and reproductive/developmental endpoints were evaluated in 7 studies. Noncancer respiratory effects were assessed in 7 studies, and 3 studies considered genotoxicity endpoints. (Because several studies evaluated multiple endpoints, the breakdowns discussed here do not add up to the total of 34 studies reviewed.)

A variety of different exposure measures or surrogates was used in the reviewed studies. Measured ambient outdoor levels were used in 8 studies. The most common measure (9 studies) was simply whether or not the subject lived in the exposed area (indicated as "residence" in Table 4-2). An additional 8 studies used distance (or inverse distance) from a source as a surrogate for exposure, often in an attempt to establish a dose-response relationship. Dispersion models that took into account such factors as wind speed and direction, topography, and distance to emitters were also used to estimate exposure levels in 3 studies. Eight studies used other exposure surrogates, often an exposure index that combined such factors as distance to the emitter, duration of exposure, and amount of exposure during different time periods. Biomarkers of exposure and/or effect were used in 4 studies. Several studies also reported ambient pollutant concentrations or emission levels, but did not use these data to evaluate the epidemiological data or in a dose-response analysis.

The most common type of study design (13 studies) was the geographical correlation study, which simply compares the incidence of an effect in an exposed area (or areas with different degrees of exposure) with that in the control area. Cross sectional studies accounted for 12 studies. In these studies, a selected group of the exposed population was matched or

Table 4-2 Categorization of Studies Investigating Health Effects of Ambient Exposure to Air Toxics

Study	Study type	Pollutant type Evaluated	Exposure Measure	Endpoint	Location
Baker et al. 1994	Cross sectional	Multiple (Metals, organics, not further specified)	Residence	Cancer, reproductive, mortality, respiratory, CNS, general (other systemic)	U.S.: Riverside County, California
Binkova et al. 1995	Prevalence	Organic (PAHs)	Personal exposure monitoring, ambient measure, DNA adduct levels	Biomarker (DNA adducts)	Czech republic
Brown et al. 1984	Case-control	Metals (arsenic, cadmium, lead, manganese, zinc), SO_2	Other (measure based on emissions, distance from plant, weighting based on soil samples)	Cancer mortality	U.S.: Eastern Pennsylvania
Bustueva et al. 1994	Cross sectional	Metal (cadmium)	Ambient measure, biomarker (urinary and hair cadmium levels)	Systemic (kidney function, as measured by β-2-microglobulin excretion)	Russia
Cordier et al. 1983	Geographical correlation	Metal (Arsenic, others) also SO_2	Residence (emissions were reported)	Mortality (all types)	Canada
Dayal et al. 1995	Cross sectional	Organics (benzene, toluene, tetrachloro-ethylene, others)	Distance, other (measure based on distance to site ($1/d^2$) and concentration of chemicals at that site)	Respiratory, neurological, general (cardiovascular, gastrointestinal)	U.S.: Houston, Texas

Table 4-2 Categorization of Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study	Study type	Pollutant type Evaluated	Exposure Measure	Endpoint	Location
Edmonds et al. 1978	Cross sectional	Vinyl chloride	Distance/direction from plant, emissions, number of abnormal emission incidents	Developmental, neurological (CNS birth defects)	U.S.: Kanawha valley, West Virginia
Frost et al. 1987	Cross sectional, case-control	Metal (arsenic)	Distance, duration of residency	Lung cancer mortality	U.S.: Tacoma, Washington
Greaves et al. 1981	Case-control	Metals (arsenic)	Distance	Lung cancer	U.S.: Kellogg, Idaho; Anaconda, Montana; Hurley, New Mexico; Salt Lake City, Utah; Ajo, Arizona; Douglas, Arizona; Hayden, Arizona; Miami, Arizona; Morenci, Arizona; San Manuel, Arizona.

Table 4-2 Categorization of Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study	Study type	Pollutant type Evaluated	Exposure Measure	Endpoint	Location
Grimalt et al. 1994	Geographical correlation	Organic (hexachloro-benzene)	Ambient air monitoring, other (biomarker--serum levels of organochlorine compounds)	Cancer incidence, mortality (general)	Spain
Hallenborg et al. 1991	Prevalence	Silica fibers	Residence	Respiratory (symptoms, function tests, chest radiograph)	U.S.: Oahu, Hawaii
Hertzman et al. 1987	Geographical correlation	Multiple, not specified	Distance, duration of residence	Respiratory, CNS symptoms, general symptoms (skin disorders)	Canada
Kaldor et al. 1984	Geographical correlation	Multiple (SO_2, hydrocarbons, nitrogen oxides)	Pollution dispersion model	Cancer incidence, mortality (general)	U.S.: Contra Costa County, California
Kilburn and Warshaw 1995	Cross sectional	Organics (toluene, benzene, possibly others), lead	Other (exposure metric based on distance from site, duration of exposure, wind conditions)	Neurotoxicity	U.S.: Baton Rouge, Louisiana
Kunst et al. 1993	Geographical correlation	Multiple (SO_2, NO_2, particulates, benzo(a)pyrene)	Other: SO_2 levels (correlated with NO_2, PM, benzo(a)pyrene) as surrogate for all air pollution	Lung cancer deaths	Holland

Table 4-2 Categorization of Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study	Study type	Pollutant type Evaluated	Exposure Measure	Endpoint	Location
Laurent et al. 1993	Cross sectional	Organics (primarily benzene, toluene, vinyl chloride, trichloroethylene)	Ambient measures	Genotoxicity (sister chromatid exchanges)	Belgium
Matanoski et al. 1981	Geographical correlation	Metal (arsenic)	Residence	Cancer deaths (general)	U.S.: Baltimore, Maryland
Nordstrom et al. 1978	Geographical correlation	Metals (arsenic, lead), SO_2	Residence, distance	Developmental (birth weight)	Western Europe (Sweden)
Norseth 1994	Geographical correlation	Metals (arsenic, nickel, chromium, cobalt, copper), SO_2	Ambient air monitoring, emissions data	Mortality (general)	Russia/Norway
Otto et al. 1995	Cross sectional	Metal (mercury)	Residence, biomarker (hair and urine Hg levels)	Neurobehavioral	Czech Republic
Ozonoff et al. 1994	Case-control	Organics, metals	Distance, other (metric based on distance, direction, and years of exposure)	Cancer incidence	U.S.: Upper Cape, Massachusetts
Pershagen 1985	Case-control	Metal (arsenic)	Residence; ambient levels measured	Lung cancer deaths	Sweden

Table 4-2 Categorization of Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study	Study type	Pollutant type Evaluated	Exposure Measure	Endpoint	Location
Phillips 1992	Geographical correlation	Organics (multiple, including pesticides, PCBs, dioxins, semi-volatiles, volatiles)	Emissions, biomarker (levels of chemicals in adipose tissue)	Exposure biomarker only (no effect biomarker)	U.S. by region
Revich 1995	Geographic correlational, prevalence	Metals (copper, nickel) fluoride, criteria pollutants (SO_2, NOx, CO), radionuclides	Residence; some ambient levels and emissions also measured	Developmental (premature delivery, birth defects, child growth), respiratory and neurologic disease, cancer, general morbidity	Russia
Rosenman et al. 1989	Modified case-control	VOC (vinyl chloride)	Distance	CNS birth defects	U.S.: Burlington County, New Jersey
Swaen and Slangen 1995	Geographical correlation	Organics (benzene)	Other (Gasoline consumption as surrogate)	Cancer (Leukemia incidence and mortality)	Western and Eastern Europe (19 countries)
Theriault et al. 1983	Cross sectional, case-control	Organics (vinyl chloride)	Ambient air monitoring, dispersion modeling	Developmental (birth defects)	Canada

Table 4-2 Categorization of Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Study	Study type	Pollutant type Evaluated	Exposure Measure	Endpoint	Location
Ware et al. 1993	Cross sectional	VOCs (toluene, xylene, others)	Ambient measure	Respiratory and irritative symptoms	U.S.: Kanawha County, West Virginia
Williams et al. 1995	Geographical correlation	Multiple (metals, such as arsenic, lead, nickel, organics such as PAHs, PCBs, dioxins)	Residence	Lung cancer, mortality (general), developmental (sex ratio)	Scotland
Woodall et al. 1992	Prevalence	Multiple, largely criteria pollutants	Emissions	Respiratory, neurotoxicity, general	U.S.: Kentucky/ Ohio/West Virginia
Yansheva et al. 1993	Geographical correlation	Organic (benzo(a)pyrene, PAHs)	Ambient measure, possibly estimated	Lung cancer	Ukraine
Zhao et al. 1994	Cross sectional	VOC (vinyl chloride)	Measured ambient levels	Genotoxicity (e.g., chromosome aberrations, sister chromatid exchanges), other (serum lysozyme)	China
Zmirou et al. 1994	Cross sectional	VOCs (classified by type, not identified)	Measured ambient levels, dispersion model	Other (drug prescriptions as surrogate for general health effects)	France

Table 4-2 Categorization of Studies Investigating Health Effects of Ambient Exposure to Air Toxics (continued)

Key:
As=arsenic; Cd=cadmium; CNS=central nervous system; PAH=polycyclic aromatic hydrocarbons; VOC=volatile organic compounds

otherwise compared with a comparable group in an unexposed area, and the prevalence of adverse effect was compared between the two groups. This type of study is more rigorous than geographical correlation studies, because it is possible to control for confounding factors, such as age, ethnicity, income, and smoking habits. We evaluated 7 case-control studies; these are considered the most rigorous of the study types evaluated. Case-control studies identify a group of people with the disease or effect of interest (the cases) with a comparable group that does not have the effect (controls), and then compare the exposure histories of the two groups. Four prevalence studies (which only reported an effect, and did not include control groups) were also included. Several studies included multiple phases, with different types of studies methodologies applied in the different phases.

As shown in Table 4-2, we located similar numbers of studies evaluating exposure to metals and to organic compounds. There were 14 studies in the former category and 17 studies in the latter category. Several of these were studies that evaluated exposure to both metals and organic compounds; 7 studies evaluated both organic and inorganic HAPs or did not specify the exposure type. An additional study attributed the observed effects to silica fibers. We did not review any studies that specifically evaluated effects of ambient exposure to radionuclides, although radiation exposure also occurred in the study of Revich (1995).

In our identification of articles to review, we emphasized literature focusing on the U.S.; 14 of the studies evaluated U.S. populations. Since air quality standards in Canada and western Europe are generally comparable to those of the U.S., results from the 11 studies of populations in those countries are also likely to be applicable to the U.S. population. Due to the relatively high level of air pollution in eastern european countries and parts of China, much recent research has focused on these countries. However, because of the likelihood of concomitant exposure from contamination of water or food, and the high level of criteria pollutants in many of these areas, it is often more difficult to attribute any observed effects reliably to HAP exposure. In addition, HAP exposure levels may be higher than those observed in the U.S. We reviewed 5 studies from Eastern Europe and one study from China.

4.1.2 Evaluation of Data Relating Adverse Health Effects and Exposure to HAPs

This section provides brief summaries of the results of the studies of greatest interest, emphasizing novel exposures and endpoints, and studies that lend themselves to generalization of exposure-affects relationships for HAPs. Detailed summaries of selected studies and evaluations of the study conclusions are provided in Appendix B. In preparing this Appendix, we have not only summarized the key findings reported by the study authors, but also provided an independent analysis of the degree to which the data which are presented support the authors' conclusions regarding adverse effect-exposure relationships.

Key factors in such an analysis are the qualitative and quantitative biological plausibility of the reported effect. Qualitative plausibility addresses whether the reported effects are consistent with the known toxic endpoints of the chemical(s) to which the population was exposed, based on data from laboratory animals and occupational studies at higher exposure levels. Quantitative plausibility addresses whether exposure level at which the effect is observed is consistent with concentration-response relationships from other sources. Studies that do not meet the test of qualitative plausibility should be viewed with suspicion, because it is very unusual for an organ or system that is a target at low exposure concentrations to not be a target at higher levels. Addressing the issue of quantitative

plausibility is more complicated, because concentration-response data may not be available for human exposure to the chemical of interest. While extrapolation from animal data is routinely conducted for risk assessment purposes, such extrapolations are conducted using methods that generally err on the side of conservatism, and which may be accurate only within a very broad range of uncertainty (perhaps spanning two or more orders of magnitude). However, because most epidemiological studies of air toxics have been conducted with high-volume chemicals, occupational exposure has also usually been elevated. Thus, at least some human dose-response data usually exists for the endpoint of interest, although no-effect levels may not always have been determined.

Generally it is difficult to interpret studies that do not meet the test of biological plausibility in terms of establishing a simple relationship between exposure to the agent being studied and the occurrence of the observed adverse effects. Very often the explanation for the observed association must be sought in the presences of some confounding factor that has not been included in the analysis. Occasionally, the additional factor may be an unknown biological mechanism of the agent being studies. However, strong data are needed in order to support the proposal of a new mechanism, and such data are rarely available from epidemiological investigations.[26] The following discussions address these issues in evaluating the results of the epidemiologic studies.

One of the most extensively investigated connections between exposure to HAPs and health effects is that between lung cancer and exposure of populations near smelters to arsenic. Several studies addressing this relationship are summarized in Table 4-1 and 4-2 (Brown et al. 1984, Frost et al. 1987, Pershagen 1985). These studies tend to show increased risk associated with exposure (or exposure surrogates, such as distance), although the apparent increase is not statistically significant in all cases. For example, Frost et al. (1987) found increased risk of lung cancer (of borderline statistical significance) in a case-control study of a population near an arsenic-emitting smelter that was conducted with women only in order to reduce confounding from occupational exposure. However, there was no control for smoking and no effect was seen in the cross-sectional phase of their study. Pershagen (1985) analyzed lung cancer data in residents near an arsenic-emitting smelter, controlling for smoking status and occupational exposure. In the group that was not occupationally exposed, there was an increased relative risk for both nonsmokers and smokers, but the increase reached statistical significance only among the smokers. Hughes et al. (1988) reviewed over 10 studies investigating health effects (primarily lung cancer) in communities near arsenic-emitting industries. They noted that about half of the studies reported significant adverse effects, while about half of them reported no effect or decreased risk in the exposed populations. However, they noted that many of the studies (particularly those that observed no effect) lacked sufficient statistical power to detect the small increases in risk that would be expected, and they suggested that some small increase in risk is likely. An association between inhalation-pathway arsenic exposure and lung cancer meets the criterion for biological plausibility, in light of the carcinogenic activity of arsenic demonstrated in occupational studies.

Nordstrom et al. (1978) found decreased birth weight in babies born to mothers who lived close to an arsenic-emitting smelter. However, it is unclear if the magnitude of the decrease was

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[26] An occasional exception to this rule is in the case of very rare (low-probability) effects of toxic pollutant exposures. In such cases, large-population epidemiologic studies may be the only way to detect adverse effects that are not apparent in animal or occupational studies.

clinically significant (Hughes et al. 1988). It appears likely that some increased risk of lung cancer occurs near arsenic-emitting smelters, but the size of the increased risk remains unclear.

Several studies investigated a possible association between vinyl chloride emissions and central nervous system birth defects (Edmonds et al. 1978, Rosenman et al. 1989, Theriault et al. 1983). While all three studies reported some positive result, each is limited by internal inconsistencies or potential confounding that precludes strong inferences about causality from being drawn. Two of the studies (Edmonds et al. 1978, Rosenman et al. 1989) did not control for the mother's (or father's) smoking or drinking habits, exposures that increase the risk of birth defects. Edmonds et al. (1978) observed a significant decrease in birth defects incidence in populations near a PVC factory during a period of generally decreasing emissions, but the decrease in incidence preceded the actual decrease in emissions from the plant being studied. Theriault et al. (1983) found that the increased incidence of birth defects correlated with seasonal variation in exposures, but not with distance to the plant. Rosenman et al. (1989) reported increased birth defects at exposure levels several orders of magnitude lower than those reported to cause developmental toxicity in mice (John et al. 1981), raising questions about the biological plausibility of the observation, or possibly about the reported exposure levels. Overall, these studies provide insufficient data to conclude that there is a relationship between ambient exposure to vinyl chloride and central nervous system birth defects[27].

Several other studies were reviewed that investigated the relationship between ambient HAP exposures and neurological or neurobehavioral symptoms. The most notable of these were two recent studies conducted of populations exposed near Superfund sites (Dayal et al. 1995, Kilburn and Warshaw 1995). In a well-controlled cross-sectional study, Kilburn and Warshaw (1995) found lower scores on objective neurophysiological tests related to balance and response to visual stimuli, and on neuropsychological tests related to pattern recognition and manual skill tasks. They were unable to establish an exposure-response relationship, but this may have been due to uncharacterized variability in the meteorological conditions which affected the relationship between distance from the site and exposure. A variety of organic chemicals was reported at the site, including aromatics, aliphatics, chlorinated compounds, and PCBs. Dayal et al. (1995) evaluated the self-reported incidence of symptoms in a population near a Superfund site, comparing the incidence in the most-exposed groups with the incidence in the least-exposed group. There was no objective assessment of health effects and no control for confounding factors. Nonetheless, significant differences were observed between the two exposure extremes, most notably in the prevalence of learning difficulties, unusual fatigue, nervousness, and numbness in extremities. Exposure to chemicals that migrated off-site into drinking water may also have occurred in both of these studies.

In an example of the state of the art in exposure monitoring and the use of biomarkers, Binkova et al. (1995) measured PAH DNA adducts in a group of women in the Czech Republic who worked outdoors for about 8 hours per day. Personal exposure monitoring was used, allowing both indoor and outdoor exposure to be evaluated; exposures to both respirable particles (<2.5 μm) and to PAHs were measured. Levels of DNA adducts in white blood cells were increased immediately after days of high measured PAH exposure. This study demonstrated that DNA adducts can be used as biomarkers of exposure, reflecting short-term exposure levels. In addition, DNA adducts can be used as biomarkers of effect, because, if unrepaired, they can lead to gene mutations, which can ultimately

[27] It should be noted, however, that these studies by no means rule out to possibility of such a relationship.

lead to cancer. However, due to the multiple steps from gene mutation to tumor development, DNA adducts and gene mutations are best viewed as indicating carcinogenic potential, rather than indicating actual risk of cancer. As discussed in Section 3.2.4, biomarker studies, especially of DNA adducts, are a fertile current field of research. Only a few primary studies on this topic were obtained and reviewed for this project.

In another biomarker study, Bustueva et al. (1994) measured ambient exposure to airborne cadmium in three Russian cities, as well as using hair and urinary cadmium levels as biomarkers of exposure. Urinary cadmium is a reliable indicator of recent cadmium exposure, as shown by several occupational studies. The presence of β-2-microglobulin in urine (termed proteinuria) was used as a biomarker of effect, indicating impaired kidney function. Although no significant effect was seen in the general population, this was probably due to the small sample size and resulting low statistical power of the study. Proteinuria (β-2-microglobulin levels above 250 μg/L) was observed only in the exposed population. Collecting biological samples and conducting laboratory testing, as in this study, is more labor-intensive than doing epidemiological investigations using disease registries. However, because proteinuria is a well-characterized effect of cadmium exposure, and both exposure and effect biomarkers can be monitored by urinalysis, this is an area of potentially fertile future investigation where high exposure to cadmium is expected.

4.1.3 Directions of Recent and Ongoing Studies

As discussed in the preceding sections, studies of the relationship between toxic air pollution exposure and adverse health effects are proceeding on a number of fronts. In section 3, we discussed how the earlier efforts to address this question employed techniques such as follow-up studies of geographic patterns of disease (particularly cancer), emissions inventories, exposure and risk assessment studies, biomarkers studies of selected pollutants, and focused studies of particular classes of toxic air pollutant sources. Much attention was paid initially to the well-studied and common metallic pollutants cadmium, mercury, and to lead and the other criteria pollutants, or other general indicators of air quality. In addition, U.S. studies are being followed up by similar risk assessments in Europe, particularly in Sweden, Denmark, and in eastern Europe and the ex-Soviet Union. Individually, these various studies have provided data which contribute to the growing understanding of the relationship between air pollution exposure and adverse affects, on both the qualitative and quantitative level.

Classes of Sources Being Studied

Recently, the pattern of investigations of adverse effects of air toxics have taken a slightly different course than earlier studies, and new avenues of investigation have been pursued. As noted in Sections 4.1.1 and 4.1.2, studies of disease patterns around metals smelting operations are still being performed, both because the association between these sources and adverse effects has been well-established, and because of the relative ease with which metals pollution can be measured in air and soils. Recent advances in this area have included, for example, the detection of adverse reproductive outcomes (Nordstrom et al. 1978), and elevated cancer risks (Frost et al. 1987), among women living near smelters. These findings help to rule out occupational exposures as the sole determining factor in the occurrence of adverse effects. Also, studies of metals processing operations (and other pollutant sources) are coming out of eastern Europe and the ex-Soviet Union (Mizernitskiy et al. 1993, Norseth 1994, Bustueva 1994), helping to broaden the geographic base of these findings.

The other major class of sources which is showing up frequently in the recent literature is hazardous waste disposal sites. Beginning in the late 1980's, studies of adverse health effects near such sites began to appear, including U.S. studies conducted by ATSDR and others, as well as a number of foreign studies. In many instances, the major classes of pollutants present at the sites are volatile organic chemicals, and in some cases these studies include data on both adverse health outcomes and air concentrations of pollutants. Several of these studies, which were reviewed in Section 4.1.1, have found an association between measures of air pollutant exposures and health outcomes of various types.

Surprisingly, the amount of epidemiological information available concerning the relationship between air toxics releases from chemical and petrochemical industry operations and adverse health effects is not very great, in relation to the number of such facilities which are operating in the U.S. Attempts to confirm the relatively high risks predicted to be associated with emissions from these sites using epidemiologic studies have generally not been successful. One of the most well-studied examples is PVC polymerization plants, where three studies have all found only equivocal evidence of a connection between vinyl chloride releases and increased incidence of birth defects (Rosenmann et al. 1989, Theriault et al 1983, and Edmonds et al. 1978). Similarly, Zhao et al. (1994) found biomarkers of exposures (altered enzyme levels) in populations exposed to vinyl chloride in China, but no other adverse effects. The positive results of two other studies of the relationship between industrial chemical emissions and adverse effects from multiple sources (the Kanawha Valley study of Ware et al. (1993) and the mortality study of an industrialized area near San Francisco by Kaldor et al. (1984)), have been seriously questioned by other investigators (Collins et al. 1994, and Wong and Bailey 1993, respectively). Two additional studies of potential health effects near petrochemical facilities are included in Appendix B. The first, by Kilburn and Warshaw (1995) quantifies the neurobehavioral deficits found in a population living near an oil reprocessing facility which is also a Superfund site. There is no indication in this study whether emissions were due to plant operations or to improper waste disposal. The other study, by Woodall et al. (1992) documents increases in the frequency of emergency room visits in a hospital near a petrochemical facility on days when "upsets" (increased emissions) occurred, but there are no measured pollutant levels to support this finding, and the major pollutants emitted from the facility are "criteria" pollutants and not HAPs.

Emissions from mobile sources have also been evaluated as a potential cause of adverse health effects, primarily from a risk assessment perspective. Releases of POMs and 1,3-butadiene from mobile sources have contributed significantly to the aggregate cancer risks in EPA's major risk assessment studies, as discussed in Section 3.2.

Another source of toxic air pollutant exposure which has been subject to a large amount of research effort recently is domestic wood smoke. Efforts have been directed both at characterizing exposures (Larson and Koenig 1994) and at evaluating the toxic and mutagenic potential of this source class (Lewtas and Lewis 1992, Cupitt et al. 1994), which is a major contributor to the total mass of air pollutants generated in some airsheds. Evaluation of this source class is still apparently at the exposure and risk assessment stage, however, and we were not able to find any published studies which contained both exposure data and information on adverse effects.

Types of Effects Being Studied

As noted in section 4.1.1, a number of studies have recently been published in two areas which had not previously been addressed. In the area of neurobehavioral assessment, a number of newly developed and previously standardized techniques for assessing neurological and psychological impairment have been applied to the issue of air toxics. Previously, these methods were used mostly in the clinical or occupational setting. More recently, the results of a number of these studies, for example Kilburn and Warshaw (1995) and Dayal et al. (1995), have suggested that adverse neurological effects of toxic air pollutant exposures are occurring in populations residing near some toxic waste disposal sites.

The other types of effects which are becoming more widely studied are cytogenetic and mutagenic impacts. The studies we have identified include the use of mutagenesis screening tests to characterize the mutagenic activity of particulate air pollutants, measurement of DNA-pollutant adducts in populations exposed to toxic air pollutants, and the measurement of chromosomal aberrations in populations exposed to volatile organic pollutants. None of these efforts has yet formally linked genetic damage to clinically detectable adverse effects, such as increased cancer risks or reproductive effects, so these studies still fall into the category of "biomarkers".

4.2 Summary: Impact of Recent Studies on Establishing the "Qualitative Relationship"

None of the studies reviewed during this effort significantly changes the general picture of the relationship between exposure to toxic air pollutants and the occurrence of adverse human health effects. None of the recent epidemiologic studies provides a comprehensive picture of population risks on the national level, even for one pollutant, let alone for all pollutants. Rather, the epidemiologic studies which were reviewed focus on individual aspects of the problem (one or a few pollutants, effects in relatively small regions or populations) and, like the earlier studies, contribute incrementally to a broader understanding of air toxics health effects. Aggregate estimates of population risk must continue to rely on the relatively early national studies of cancer incidence patterns, and on risk assessment-based estimation procedures, as discussed in Section 3.2

The studies we have reviewed, however, do shed additional light on the qualitative relationship between air toxics exposures and adverse health effects by (1) providing confirmatory examples of adverse effects of pollutants and sources previously identified, (2) by characterizing some new effects of air toxics exposure which had not previously be measured, and (3) by identifying some source classes which had not previously been associated with confirmed adverse effects. Perhaps the most significant impact of the studies which we reviewed has been to provide additional support for the idea that certain types of noncancer adverse effect (e.g. neurological and behavioral impairment, cytogenetic damage), previously seen only in occupational studies, also could be measured in the general population following exposures to lower levels of toxic pollutants, primarily volatile organics.

The studies reviewed also provided an additional information related to air toxics adverse effects, particularly on the international level. Some of the important findings of our reviews of these studies include:

- The most successful recent attempts to document the relationship between HAP exposures and adverse health effects in the U.S. and western Europe have generally been either case-control studies, or cross-sectional studies focused on smaller populations near discrete air pollution sources. Studies of geographic patterns of

disease incidence over large areas are becoming less common, both because of the unavailability of disease incidence data and because of the lack of HAP exposure data for large areas. Studies of larger areas may be of limited value in most instances because the increased statistical power gained from evaluation large populations is offset by reduced ability to detect very low response rates in the less-exposed segments of the population. Regional studies in the U.S. (the IEMP studies, including the Kanawha Valley Study), have had only limited success in demonstrating exposure-effect relationships, primarily because of a lack of exposure data.

- In eastern Europe and the ex-Soviet Union, by contrast, large population and regional studies are still being undertaken. The comparative success of these studies often reflects the higher levels of pollutants in these areas, and the correspondingly higher levels of adverse effects. While these studies help to confirm general air pollution-disease relationships, the relatively high pollution levels studied, and the highly variable quality of the studies themselves, has limited their generalizability to U.S. populations.

- On the whole, the epidemiologic case for a relationship between measurable adverse effects and exposures to HAPs has been made more successfully for toxic inorganic pollutants than for organic pollutants. This situation arises both out of the comparative ease in measuring exposure levels to the inorganic pollutants, and from the fact that arsenic and cadmium (which are among the metals most frequently studied) cause cancer, the incidence of which in a given population can be followed relatively easily through tumor registries and death certificates[28]. This situation has been changing recently, through the development of refined exposure measurement techniques for organics, the measurement of biomarkers of organic exposures, and through the application of testing methods which address neurobehavioral effects of exposures to organic chemicals which had not previously been measurable.

- The studies reviewed vary in the extent to which they address potential confounding factors, such as lifestyle (smoking, drinking), occupation, socioeconomic factors, sensitive populations, and exposures to multiple pollutants. The quality of the best studies (of which there are only a few) is such that they can usually make a strong case by themselves for air pollution-adverse effect relationships, where such relationships are found. In addition, a few agents (toxic metals) have been subject to multiple studies which together show a generally consistent relationship. Indoor air pollution is a major confounding factor which is rarely addressed in studies of the adverse effects of ambient air toxics exposures. As noted previously, indoor exposures have been shown to contribute a large proportion of the total air toxics exposures for typical individuals, and they could thus potentially obscure or distort apparent relationships between ambient air toxics exposures and adverse effects.

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[28] While risk assessment studies (Section 3.2.5) have predicted that a substantial proportion of all of the cancer risks associated with HAP emissions (particularly from mobile sources) can be attributed to organic pollutants, so far epidemiologic studies have not been able to confirm this prediction in the general population.

Taken together, these observations point to a gradually changing paradigm for epidemiological studies of the relationships between air pollution-adverse effects and adverse health effects. If recent trends continue, studies in the future will tend to be focused on small exposed populations or geographical areas, and on single sources or small numbers of sources. Case-control studies may become more prominent than in the past as a tool for following up suggestions of causality, and more studies may incorporate personal monitoring or microenvironmental modeling of exposures to account for indoor and outdoor exposures. Exposure studies may be supported to a greater extent by the measurement of biomarkers in the exposed populations. Studies incorporating these features would seem to have the most promise in elucidating the relationships between hazardous air pollutant exposures and adverse effects for individual sources or populations.

Whatever the methodologies which are employed, an integrative framework will be needed that incorporates the existing knowledge base into a comprehensive picture of the relationship between air toxics exposures and adverse effects. The elements of this integrative approach will continue to include direct epidemiologic studies of populations exposed to air toxics (the subject of this report), as well as toxicologic and dose-response considerations from animal and occupational studies, refinements in exposure assessment and modeling methods, and risk assessment methods for extrapolating the results of individual studies to larger populations.

5. MAJOR DATA GAPS AND OPPORTUNITIES FOR FURTHER RESEARCH

This section summarizes what we found to be some the major data gaps associated with characterizing the relationship between air toxic air pollutant exposures and human health effects, and suggests approaches to filling these gaps.

5.1 Major Data Gaps

As discussed throughout this report, the ability to document and characterize the relationship between air toxic exposures has always been limited by shortages of certain kinds of information and limitations on our understanding of the physiochemical and biological mechanisms through which air toxic adversely affect human health. Our review of recent studies sheds light on the potential for addressing some of these data gaps, which have historically limited our ability to evaluate air toxics-adverse effect relationships, including the following:

Lack of Integrated Exposure and Health Data

As noted in Section 3.0, both exposure data and health data status or outcome are needed to support epidemiologic studies of the relationship between air toxics exposures and adverse health effects. The shortage of exposure data and health data in general are both major obstacles to such studies on the national level. There are no national data bases of HAP monitoring data (Section 3.2.3) nor are there any comprehensive national data bases on the potential non-cancer health impacts (Section 3.2.2 and see below). Thus, for investigators without the resources to gather health or ambient concentration data, studies of the health impacts of HAP exposure are limited to those pollutants, areas and populations for which health status, biomarkers or exposure data are fortuitously available, or for which they can be obtained cheaply. The recent studies in the literature for the most part reflect this pattern, with most of the recent studies being limited to single exposure sources, or to relatively small exposed populations.

The lack of integrated exposure and effects data will continue to be a major limitation of the ability to identify adverse effects of HAPs for the foreseeable future. The reasons for this include both the cost and difficulty of tracking the health status of large populations, and the difficulty and costs of evaluating exposures to the large number of HAPs. This difficulty can only be overcome to some extent by the biomarker techniques which are beginning to be applied to studies of HAP-health effect relationships.

Lack of Indoor Air Pollutant Exposure Information

Another key data gap limiting the ability to relate air toxics exposures to health effects is the lack of indoor exposure data in most cases. Since the majority of individuals spend most of their time (usually 80 percent or more) indoors, and since pollutant concentrations in indoor air tend to be quite different from (and higher than) those outdoors, studies which do not take indoor air quality into account will have difficulty in elucidating the true relationship between air toxics exposures and effects. It is not clear that there is a simple general solution to this problem. Instead, indoor-outdoor pollutant relationships need to be addressed in the context of individual health effects studies.

Lack of Non-Cancer Disease Registries

The most important data gap repeatedly identified in the literature, and obvious from the nature of the studies which were reviewed, is the lack of nationally-standardized and comprehensive disease registries for adverse effects of toxics exposures other than cancer. Particularly mentioned as key data gaps are the lack of information on birth defects and reproductive outcomes (Shy 1993). Currently, studies of these impacts require investigators to obtain access to local or state health status information, whose availability is highly variable from state to state, or to obtain information from hospital or other medical records. This difficulty is less of a concern for case-control studies, but can severely limit the ability to do large-population cohort analyses or cross-sectional studies.

For some diseases (neurological and behavioral disorders, and less severe acute effects such as respiratory irritation), it is unlikely that any kind of nationally standardized registry will ever be practical, and thus other approaches to addressing these impacts must be found. Some of the studies reviewed described approaches to addressing these issues, but most require some form of survey or testing approach to support each study of adverse effects.

Data Gaps Related to Exposure-Response Relationships and Toxicological Mechanisms

There are a number of other "data gaps," which are more gaps in mechanistic knowledge than gaps in information. These include the uncertainties related to potential adverse effects of organic pollutant exposures in very sensitive individuals (Neutra et al. 1991), and whether adverse effects occur in "normal" individuals at exposures below generally accepted "safe" levels, as suggested by at least one of the studies reviewed (Ware et al. 1993). If low-exposure effects turn out to be a general phenomenon, and the biochemical mechanism for such effects can be found, then the case for the occurrence of adverse effects at observed ambient pollutant concentrations becomes much stronger, and potential routes to avoidance of adverse effects in sensitive individuals may be identified.

Another technical issue which can only be addressed by fundamental advances in scientific knowledge is the nature of the relationship between specific cytogenetic biomarkers (DNA adduct formation, for example) and clinical adverse effects (for example, increased cancer risks). The potential utility of genotoxic endpoints (e.g. chromosome abnormalities) as predictors of cancer risks also needs to be explored. If such relationships can be established, then the biomarkers studies become much more convincing as indicators of adverse health effects. The same is true of any studies which advance the state of knowledge concerning dose-response relationships at low exposures levels for carcinogenic and noncarcinogenic chemicals. Uncertainty in this area is a major reason why risk assessment studies of air toxics adverse effects are subject to question.

5.2 Potential Opportunities for Additional Research

This section identifies a number of practical steps for improving the nature of the information available related to toxic air pollutant adverse health effects. The topics discussed below are limited to issues that can be addressed by OAQPS without substantial additional commitment of resources. They are aimed primarily at continued exploration of easily-accessible information, and not at the actual performance of epidemiological, monitoring, or laboratory studies. The latter types of investigation may be desirable in and of themselves, but recommending priorities in these areas are beyond the scope of this review. The following activities may be fruitful.

Complete the Review of Previously Identified Literature Studies. The limited resources available for this study did not allow all of the sources of information which were identified to be fully reviewed, or, in some cases, even to be procured. There are a number of additional studies that could be obtained and reviewed:

- Additional ATSDR documents related to health effects from hazardous wastes sites;
- A number of recent studies of neurobehavioral and cytogenetic impacts of air toxics that were identified as secondary references in the existing bibliography;
- A number of other studies in various areas identified late in the effort.

Procuring and reviewing these studies, and incorporating them into the report as appropriate, would improve the overall coverage and completeness of our effort.

Finish Efforts to Interview Government and Academic Experts. As pointed out in Section 2, in the limited time allocated to this project, we were not able to contact all of the Federal and State regulatory personnel who were identified as experts, and we talked to only a small proportion of the academic experts identified. The individuals who we were able to contact generally supplied us with useful information on local efforts, and unpublished and ongoing studies of air pollution adverse effects. Continuing this effort could provide a more comprehensive picture of current research.

Identify and Review Potential Health Outcome Data From NCHS. The National Center for Health Statistics (NCHS) has provided data to support a number of efforts to characterize the relationship between air toxics exposures and adverse health outcomes, notably the NCI cancer mapping efforts. Information from previous EPA studies (primarily the 1990 Screening Evaluation) indicated that NCHS has made some efforts in the past, on an ad hoc basis, to develop detailed information on the geographic patterns of respiratory disease and mortality, and on other air toxics-related adverse effects. It might be worthwhile to get more information on these and more current NCHS efforts which could provide useful information on air toxics-disease relationships.

Follow-Up of Birth Defects and Reproductive Outcomes Data Sources. We did not systematically evaluate the quality of national and state data sources related to birth defects reproductive outcomes. Getting more information on the states who have birth defects registries, could greatly improve our coverage of this issue. This would fit in with the strategy of continuing to pursue academic data sources, as the UNC - School of Public Health group (Professor Shy) is reportedly quite active in this area, and may have developed or used some of these data bases.

Review Literature and Databases Related to Health Outcomes from Hospitals, HMOs, Insurers, and Other Health Care Providers. We did not systematically investigate these potential data sources. It would probably be useful to do a more focused literature survey in the public health databases, and to contact industry groups, such as the American Hospital Association, insurance groups, and other health care organizations. This effort would help to greatly expand our knowledge of past efforts to link data from these sources to environmental factors, and potential data sources for doing so in the future.

Review Selected Studies of Indoor Air Toxics and Indoor-Outdoor Air Pollutant Relationships. The current study has touched only indirectly on indoor-outdoor air pollutant relationships, and how they bear on the issue of establishing the relationship between air toxics exposures and adverse health effects. A modest effort could help firm up our understanding in two key areas; first, how studies of "sick building syndrome" and related health issues has affected the understanding of the toxicology of toxic air pollutants and second, how studies of indoor air quality can clarify the relationship between outdoor ambient exposures and health effects.

Conduct a Symposium on the State of Knowledge Regarding the Adverse Effects of Toxic Air Pollutants. When this report is finalized it could serve as discussion document for academic, government and industry professionals who are studying air toxics-adverse effects relationships. A symposium built around response to this report could address topics such as how the recent studies change the prevailing view of the nature or magnitude of the health impacts of air toxics exposures, and how the relationships could best be further elucidated and how data gaps could be addressed.

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APPENDIX A

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RELATING TO AIR TOXICS EXPOSURE

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APPENDIX B

SUMMARIES AND ANALYSES

OF SELECTED STUDIES

STUDY SUMMARY: Brown et al. 1984

CITATION:

Brown, LM, LM Pottern, and WJ Blot. 1984. Lung cancer in relation to environmental pollutants emitted from industrial sources. *Environ. Res.* 34:250-261.

SOURCES OF EXPOSURE:

Zinc smelter and steel plant in eastern Pennsylvania

HEALTH EFFECTS EVALUATED:

Lung cancer mortality

CHEMICALS EXPOSED TO:

Arsenic, cadmium, copper, lead, manganese, zinc

EXPOSURE MEASURES:

Air monitoring of metals and sulfur dioxide, soil samples for metals provided general information. An exposure surrogate was also used in the analysis, which was based on residential distance to the smelter or steel plant, weighted by emissions data.

CONFOUNDING FACTORS ASSESSED:

Occupational exposure, smoking, amount of smoking, age

STUDY METHODS:

This was a case-control study of 335 white male lung cancer deaths in 1974-1977 and 332 white male control deaths in eastern Pennsylvania. Cases and controls were identified from state mortality records, and next of kin were interviewed with the interviewers blinded as to whether they were interviewing case or control relatives. As an exposure measure, maps were divided into 1 km^2 grids, which were classified as "heavy" or "light" exposure based on soil and air sampling and prevailing wind direction. The surrogate individual exposure measure was based on distance of residence to the plants and an emissions weighting for the grid of residence.

STUDY RESULTS:

Increased relative risks of lung cancer were reported for heavy versus light exposure areas for arsenic and cadmium. When cases and controls were broken down by proximity to the zinc smelter (taking into account the prevailing wind direction), there was a significantly increased relative risk, adjusted for smoking and usual employment in the steel or zinc industries, based on residence in 1950. There was also an apparent trend with distance, although no trend test was conducted. Based on usual residence, relative risk was increased in those near the zinc

smelter (with or without adjustment for smoking and occupation), but the increase was not significant.

AUTHOR'S CONCLUSIONS:

The study authors concluded that the results suggest an increased lung cancer risk associated with ambient exposure to heavy metals, including arsenic and cadmium. However, they noted that the small sample size and limited exposure data preclude a causal conclusion.

COMMENTS:

The study was well-conducted and controlled for the major confounding factors of smoking habits, occupational exposure, and age. The data suggest increased risk of lung cancer following environmental exposure to inhaled arsenic or cadmium. It is limited by the lack of detailed exposure data and the small number cases and controls in the "near" proximity group (< 10-16 km).

STUDY SUMMARY: Bustueva et al. 1994

CITATION:

Bustueva, KA, BA Revich, and LE Bezpalko. 1994. Cadmium in the environment of three Russian cities and in human hair and urine. *Arch. Environ. Health* (USA). 49(4): 284-288.

SOURCES OF EXPOSURE:

Alkaline storage battery factory, cadmium production plant, cadmium-dye plant (each in a separate city)

HEALTH EFFECTS EVALUATED:

Beta-2-microglobulin (β-2m) excretion in urine (proteinuria) as an indicator of kidney function

CHEMICALS EXPOSED TO:

Cadmium

EXPOSURE MEASURES:

Ambient exposure measure of cadmium in air. Levels of cadmium in hair and urine were also used as biomarkers of exposure. Soil levels of cadmium were also measured.

CONFOUNDING FACTORS ASSESSED:

None

STUDY METHODS:

The study included 153 adult women and 430 children exposed to atmospheric cadmium. However, not all assays were conducted with all subjects. The total number of controls is unclear, but 34 adults were used as controls for the determination of β-2m. For the children, only levels of cadmium in urine and hair were reported. The cadmium concentration in air was measured at various distances from the cadmium plant, and urinary β-2m was reported for the corresponding group of subjects. Levels of β-2-microglobulin in urine were measured as an indicator of kidney function. A separate study was conducted on the effects of occupational exposure in the cadmium plants.

STUDY RESULTS:

Although average levels of β-2m were not elevated compared to controls in the population exposed to environmental cadmium, the maximum levels were generally higher. In addition, only the groups exposed to environmental cadmium had individuals with β-2m levels above 250 μg/L. However, only a total of 4 subjects had this level of increased β-2m excretion, and no statistical tests were conducted. None of the children had elevated β-2m excretion (defined as >250 μg/L). Daily cadmium intake from air was estimated at 0.0035 μg,

compared with daily intake from water of 0.0001 μg and intake from food of 0.113 μg. However, absorption appeared to have been taken into account only for the calculation of air and water intake, but not for the calculation of food intake. Cadmium levels in food were elevated, presumably due to air deposition. In the occupational study, the concentration of cadmium in air correlated with the percent of subjects with proteinuria.

AUTHOR'S CONCLUSIONS:

The study authors concluded that the observed cadmium levels in air resulted in elevated cadmium levels in hair and urine of exposed children and adults. They also suggested that cadmium exposure from air, together with cadmium intake in food, can result in proteinuria, which is indicative of diminished kidney function.

COMMENTS:

A major strength of this study is that it measured exposure and effect in the same population. In addition, the study authors attempted to determine total cadmium intake from air, food, and water, to determine the degree to which the observed effect was from inhalation exposure. However, the small size of the control group makes it difficult to determine the background level of proteinuria in the control population. The observed endpoint is plausible, since cadmium is a known kidney toxin, and proteinuria occurs after several years of occupational exposure leads to the accumulation of cadmium in the kidney. However, the cumulative exposure necessary to result in proteinuria above background levels is generally reported at much higher levels. For example, Jarup et al. (1988) reported proteinuria at a cumulative exposure of 691 yr x $\mu g/m^3$, while the highest ambient exposure reported in this study was 0.085 $\mu g/m^3$. This suggests three possible explanations for the observed findings: (1) Increased proteinuria did occur as a result of cadmium exposure, and a major source of cadmium intake was food contaminated with cadmium from air deposition. (2) Increased proteinuria did occur, and this study population is more sensitive than that studied by Jarup et al. (3) There was no cadmium-related effect on the incidence of proteinuria, and the observed deviations result from statistical fluctuations. The available data are insufficient to differentiate among these possibilities.

Reference:

Jarup, L., C.G. Elinder and G. Spang. 1988. Cumulative blood-cadmium and tubular proteinuria: a dose-response relationship. Int Arch Occup Environ Health 60: 223-229.

STUDY SUMMARY: Dayal et al. 1995

CITATION:

Dayal, H and S Gupta. 1995. Symptom clusters in a community with chronic exposure to chemicals in two superfund sites. *Arch. Environ. Health* 50(2): 108-11.

SOURCES OF EXPOSURE:

Two National Priority List sites located east of Houston, Texas

HEALTH EFFECTS EVALUATED:

Neurological, respiratory, cardiovascular, gastrointestinal, and miscellaneous symptoms

CHEMICALS EXPOSED TO:

Potential exposure to: benzene, toluene, naphthalene, tetrachloroethylene, trichloroethylene, polychlorinated biphenyls, dichlorodiphenyltrichloroethane, 1,1,2-trichloroethane, 1,2-dichloroethane, heptachlor, fluorene, pyrene, benzo(a)anthracene, benzo(a)pyrene, chrysene, lead, copper, chromium, nickel, and zinc.

EXPOSURE MEASURES:

An exposure measure was calculated by calculating (c/d^2) for each residence of the test subject (where c is the estimated amount of chemicals present at the site at the time of residence and d is the distance to the site), and weighting by the duration of residence at that location. For each test subject, this value was calculated for both sites and the two exposure ratings were added together. Amounts of chemicals present at the two sites were determined for period from August 1962 to February 1990.

CONFOUNDING FACTORS ASSESSED:

None.

STUDY METHODS:

Health effects and residence data for 6209 African-American residents of a community near two Superfund sites were gathered by a mail-in questionnaire. The response rate was 73%. The questionnaire also evaluated smoking and drinking history, but data supplied on these factors were limited. Cumulative exposures for study participants were calculated from the residence and chemical site data. Reported symptoms in the subjects from the top 10% of the exposure distribution (321 subjects) were compared with reported symptoms in the bottom 30% of the exposure distribution (351 subjects).

STUDY RESULTS:

There were significant increases in the prevalence of several of the symptoms, especially those affecting the nervous system. Significant increases of at least 50% between the low- and high-exposure groups were observed in prevalence of learning difficulties, unusual fatigue, decreased sense of smell, and peculiar odor/taste. Significant increases were also observed for several other symptoms, including nervousness, numbness in fingers/toes, chest pains, irregular heartbeat, and skin rashes. The individuals in the high-exposure group were also twice as likely to report five or more neurological symptoms than individuals in the limited exposure group.

AUTHOR'S CONCLUSIONS:

The authors noted the following study limitations: possible self-selection, response, and differential recall biases, subjective symptom data, no chemical analysis of site wastes, no evaluation of probable exposure route(s), the lack of determination of actual exposure based on prevailing wind information, and the lack of evaluation of confounding factors, such as occupational exposure, smoking, and drinking. However, the reporting of effects on mostly one system (the nervous system) supports the apparent relationship between exposure and effects. Study results are also supported by the fact that the chemicals to which residents would be exposed are known from animal studies to cause neurological effects. The study authors concluded that their study indicates that an analytical epidemiological investigation of this population is warranted.

COMMENTS:

Although there are several limitations to the study, as identified by the study authors, this study does provide suggestive evidence that neurotoxic effects resulted from exposure to chemicals at the NPL site. Because no information on exposure route was available, it is unclear whether the predominant exposure was oral (presumably from drinking water contamination) or via inhalation. However, the evidence is sufficient to warrant better characterization of actual exposures and exposure route(s).

STUDY SUMMARY: Edmonds et al. 1978

CITATION:

Edmonds, LD, CE Anderson, JW Flynt Jr., and LM James. 1978. Congenital central nervous system malformations and vinyl chloride monomer exposure: a community study. *Teratology* 17: 137-142.

SOURCES OF EXPOSURE:

Polyvinyl chloride polymerization plant, other chemical plants in the Kanawha valley

HEALTH EFFECTS EVALUATED:

Central nervous system (CNS) birth defects

CHEMICALS EXPOSED TO:

Vinyl chloride, 100 other compounds emitted by chemical plants in the Kanawha valley

EXPOSURE MEASURES:

Mean hourly vinyl chloride monomer emissions, number of abnormal vinyl chloride emission incidents, distance/direction from plant

CONFOUNDING FACTORS ASSESSED:

Maternal age, parental occupation, history of previous pregnancies and birth defects, education, socioeconomic status

STUDY METHODS:

Due to concerns about occupational exposure to vinyl chloride being linked to birth defects, CNS birth defects were evaluated in U.S. counties with polyvinyl chloride polymerization (PVC) plants. A detailed study was conducted in the Kanawha valley, West Virginia, which had a CNS birth defect rate above the national average during the early 1970s. All infants (n=47) with central nervous system (CNS) defects born in Kanawha County in 1970-1974 were identified using the national Birth Defects Monitoring Program (BDMP), which contained data on 95% of all reported births in the county, and state vital statistics records noting CNS defects recorded on birth or death certificates. Controls were matched for race, paternal education, maternal age within 2 years, and parental residence in the county at the time of conception. Families of 46 cases and the corresponding controls were interviewed to determine the previous pregnancy, miscarriage, and birth defect history, and occupational history of both parents. The study authors did not control for smoking or alcohol use.

STUDY RESULTS:

CNS birth defect incidence rates for Kanawha County in 1970-1972 were found to be 1.5-2 times higher than the national average, based on the BDMP data. There was no significant difference between cases and controls with regard to previous reproductive experience of the parents, occupational parental exposures to VC, or any of the other control variables. Using the matched-pairs, signed-ranks test, there was no significant difference between cases and controls with regard to distance of residence from the plant. There was apparent clustering of cases living less than three miles from the plant in the direction to the northeast of the plant. However, analyses of the locations of cases and controls, when grouped by distance from the plant, found no consistent differences between the geographical distribution of case residences and control residences.

The total number of cases of CNS defects were relatively constant in 1970-1972 (14, 15, and 12 cases, respectively), but decreased to 5 cases in 1973 and 1 case in 1974. Emissions data indicated that average emissions in the years 1967-1973 were relatively stable at 235-270 pounds/hour, decreasing to 180 pounds/hour in 1974; the number of large releases also decreased during this period. Exposure monitoring was limited to a single release incident, when vinyl chloride monomer concentrations were 0.1-0.2 ppm downwind (to the northeast) of the plant. The decrease in the reported incidence of CNS defects did not coincide with the decrease in average emissions.

AUTHOR'S CONCLUSIONS:

The study authors stated that the data did not allow any conclusions to be drawn regarding the relationship between air pollution and birth defects in the community. They noted that if there were such an association for vinyl chloride, decreased birth defect rates would be expected to follow decreased atmospheric vinyl chloride levels after an ~9-month lag. However, the largest decrease in birth defect rates preceded the decline in vinyl chloride emissions. Similarly, the lack of a strong geographic pattern of cases relative to the plant, and the presence of numerous other sources of chemical emissions were identified as weakening the possible relationship between the plant VC emissions and CNS defects.

COMMENTS:

The study authors have drawn appropriately conservative conclusions based on the data quality and small study size. The data in this study, in and of themselves, cannot explain the elevated rate of CNS birth defects in this county compared to the national average as being related to vinyl chloride monomer exposure. Similarly, however, exposures to vinyl chloride, or the combined effects of the numerous HAPs present in the air in the valley, cannot be ruled out as a factor contributing to birth defects incidence in the study area.

This study is limited by two major factors. First, the small sample size and short duration make it very susceptible to statistical fluctuations. For example, the CNS birth defect rate (per 10,000 births) dropped from about 43 in 1971 to about 3 in 1974. There was no similar decrease in vinyl chloride emissions preceding this drop; emissions dropped slightly from 1973 to 1974, and more strongly in 1975. It is difficult to evaluate the significance of these data without emissions and birth defect data from 1975 and later years. This study is also limited by the failure of the authors to assess or control for smoking and drinking among cases and control parents, both of which could affect the incidence of birth defects.

STUDY SUMMARY: Frost et al. 1987

CITATION:

Frost, F, L Harter, S Milham, R Royce, A Smith, J Hartley, and P Enterline. 1987. Lung cancer among women residing close to an arsenic emitting copper smelter. *Arch. Environ. Health* 42: 148-152.

SOURCES OF EXPOSURE:

Copper smelter and arsenic refinery in Tacoma, Washington

HEALTH EFFECTS EVALUATED:

Lung cancer mortality

CHEMICALS EXPOSED TO:

Arsenic

EXPOSURE MEASURES:

Distance from smelter (cross-sectional study). For the case-control study, a cumulative exposure index was used, based on years × 1/distance, multiplied by a weighting factor that accounted for varying estimated emissions levels.

CONFOUNDING FACTORS ASSESSED:

Age, race

STUDY METHODS:

Two study methods were employed to evaluate the possible increase in lung cancer deaths in women from 1935 to 1969 due to arsenic exposure from the copper smelter and arsenic refinery. In the cross-sectional study, three exposure groups were defined. The first group resided within a 3-mile radius of the facility, the second group resided between 3 and 9 miles from the site, and the third group resided between 6 and 40 miles from the plant. The expected numbers of lung cancer deaths were calculated and the observed rates of lung cancer deaths were determined from death certificate information. The second investigation was a case-control study. Each lung cancer death case was matched to a female control according to age and year of death. A total of 156 pairs were used in the analysis.

STUDY RESULTS:

In the first investigation, the total numbers of observed lung cancer deaths did not exceed the expected numbers of lung cancer deaths. In fact, the relative risk (observed/expected, O/E) was < 1 in all groups, with risk significantly lower than expected in the lowest exposure group. This decrease was attributed to the lower level of urbanization in this group. In the

case-control study, the cumulative exposure index was 27% higher for cases than for controls ($p=0.10$); the p value dropped to 0.07 after adjusting for a 20-year latency. When the exposure levels were divided into quintiles of exposure, the odds ratios ranged from 1 to 1.6, and a trend test fell just short of significance ($p=0.07$).

AUTHOR'S CONCLUSIONS:

The study authors offered several explanations for the mixed results. They suggested that the national rates used to calculate the number of expected deaths due to lung cancer may not be valid for the study area. Inverse distance was used as part of a surrogate measure of exposure, but the measure used may not give an accurate picture of exposure. The unknown period of latency may prevent detection of significant trends in increased risk of lung cancer from low-level arsenic exposure. Confounding factors, such as movement of residence, socioeconomic status, and smoking habits, were not considered. Because the observed increases were so small, the study authors concluded that the data indicate that any increased risk would be small and limited to those who lived very close to the smelter for over 20 years. They also noted that the community 24-hour average ambient arsenic level during 1980-1985 exceeded the 8-hour workplace standard of 10 $\mu g/m^3$. (The source of this statement is unclear, since the mean ambient level reported for 1969-1980 ("the only period for which such data are available") was 0.8 $\mu g/m^3$ at 2100 feet from the smelter.)

COMMENTS:

This study indicated that any increased risks resulting from arsenic exposure near this smelter are likely to be small. All increases in relative risk were small, and no statistical test was significant at a p value of 0.05. However, increased risk of lung cancer is plausible in light of the unit risk for inhaled inorganic arsenic (4.3E-3 per $\mu g/m^3$). The lack of control for smoking makes the results of this study very hard to interpret.

STUDY SUMMARY: Hallenborg et al. 1991

CITATION:

Hallenborg, CP and N Marsh. 1991. Toxic substances in the environment affecting respiratory function of people in Hawaii. *Hawaii Med J* 50(3): 101-7.

SOURCES OF EXPOSURE:

Air emissions from sugar cane factory

HEALTH EFFECTS EVALUATED:

Standard pulmonary function variables

CHEMICALS EXPOSED TO:

Particulate emissions from sugar cane burning and processing; evidence is presented that fine silicate particles are a key pollutant contributing to health effects

EXPOSURE MEASURES:

Residential distance from factory, duration of residence (no direct measurements)

CONFOUNDING FACTORS ASSESSED:

Pulmonary function was compared to literature control values matched for age, weight, and sex

STUDY METHODS:

Spirometry and diffusing capacity measurements were performed on 14 adult residents who have lived near the plant for 4 to 40 years. Histories were taken and physical examinations were also performed.

STUDY RESULTS:

A high proportion of all of the residents had reduced diffusing capacity (79 percent), forced expiratory volume (14 percent), forced expiratory fraction measures (93-100 percent), total lung capacity (83 percent), vital capacity (43 percent) or elevated residual volume (93 percent). Self-reporting and physical examinations also disclosed a high frequency of respiratory symptoms, but no radiological or other evidence of asbestosis or other frank disease related to inorganic fiber exposures. Decreased diffusing capacity was found to be strongly related to length of residence near the plant, but the other symptoms were not.

AUTHOR'S CONCLUSIONS:

The authors conclude that the findings in this study are consistent with "the presence of some lung disease in this population." They recommend long-term studies to confirm whether sugar cane burning and processing are adversely affecting the respiratory health of nearby residents.

COMMENTS:

The lack of actual exposure measurements make it hard to determine whether the observed respiratory symptoms were related to sugar cane processing, and there is no information on occupational exposure histories or how "normal" control values of the various pulmonary function measures were derived. A matched control group would have been desirable. The hypothesis that the silicate component of air emissions may be responsible for the observed effects is plausible, and supported by other studies of sugar cane processing emissions and health impacts, but not directly confirmed by this study. These results illustrate the need for better characterization of unconventional sources of toxic air pollution.

STUDY SUMMARY: Kilburn and Warshaw 1995

CITATION:

Kilburn, KH, and RL Warshaw. 1995. Neurotoxic Effects From Residential Exposure to Chemicals from and Oil Reprocessing Facility and Superfund Site. *Neurotoxicology and Teratology*. 17(2): 89-102.

SOURCES OF EXPOSURE:

Emissions from an oil and chemical reprocessing facility and superfund site in Louisiana

HEALTH EFFECTS EVALUATED:

Self-reported neurological/psychological symptoms, mood indices from questionnaire, results from objective neurophysiological and neuropsychological testing

CHEMICALS EXPOSED TO:

Primarily organic chemicals (aliphatic, aromatic and chlorinated, including PCBs) and some metals; major site operations were poorly-controlled burning and distillation of wastes

EXPOSURE MEASURES:

Length of residence in area affected by air emissions (based on screening-level models), distance from residence to site (no direct measurements of exposure)

CONFOUNDING FACTORS ASSESSED:

Control groups from a distant location were compared in terms of age, sex, race, education, occupational chemical exposures, smoking status, drug use, trauma, history of neurological, psychological disease

STUDY METHODS:

The study population consisted of 77 women and 55 men living within 2.4 kilometers of the site, including both self-selected and randomly-selected individuals. The control group was randomly selected from a town 35 kilometers away from the site. Questionnaires related to physical and psychological symptoms and mood variables were administered to the study group and to the control population, along with a battery of neurophysiological and neuropsychological tests. Questionnaire and test results were compared between the control and study groups, between the self-selected and randomly-selected individuals in the study group, and as a function of residential distance from the site and residential duration.

STUDY RESULTS:

The exposed group scored significantly lower on four of the neurophysiological tests (related to balance and response to visual stimuli), and showed a significant impairment in several of the neuropsychological tests (pattern recognition and manual skill tasks), compared to the control group. The exposed group also scored higher than did the control groups on indices of mood disturbance consistent with depression. There was no difference in symptoms as a function of distance from the site or length of residence, nor between self-selected and randomly-selected subjects.

AUTHOR'S CONCLUSIONS:

The authors conclude, "Subjects exposed residentially for up to 17 years to chemicals dispersed from a waste oil reprocessing plant showed neurophysiological and neuropsychological impairment."

COMMENTS:

This is generally a well-controlled study that takes great care to control for major confounding factors. While the control and study populations did vary on a few variables (level of education, for instance), there is no evidence that these differences accounted for the observed differences in test results. The lack of an apparent relationship between exposure measures and response within the exposed group somewhat weakens support for a link between chemical exposures and adverse effects, but plausible explanations for this phenomenon (nonuniform prevailing winds for lack of correlation with distance, short latency period for lack of correlation with duration of exposure) are advanced. In light of the reported off-site migration of chemicals in water, exposure in drinking water may also have occurred. This study provides a good illustration of the current state of the art in the epidemiological investigation of neurophysiological and neuropsychological effects of chemical exposures.

STUDY SUMMARY: Laurent et al. 1993

CITATION:

Laurent, C, T Lakhanisky, P Jadot, I Joris, M Ottogali, C Planard, D Bazzoni, JM Foidart, and Y Ros. 1993. Increased sister chromatid exchange frequencies observed in a cohort of inhabitants of a village located at the boundary of an industrial dumping ground: phase I. *Cancer Epidemiol Biomarkers Prev* 2(4): 355-62.

SOURCES OF EXPOSURE:

Industrial chemical disposal site near a village in Belgium, which released chemicals into the air due to containment failure

HEALTH EFFECTS EVALUATED:

The frequency of sister chromatid exchanges (SCEs) in peripheral white blood cells of village residents

CHEMICALS EXPOSED TO:

Aliphatic, aromatic, and chlorinated hydrocarbons, including the known carcinogens/mutagens benzene, vinyl chloride, vinylidene chloride, trichloroethylene (TCE), tetrachloroethylene (perchloroethylene, PCE)

EXPOSURE MEASURES:

Analyses of gases released from landfill, short-terms measurements of ambient air concentrations at several locations in the village

CONFOUNDING FACTORS ASSESSED:

Control groups were matched for age, sex, and smoking habits

STUDY METHODS:

SCE levels in lymphocytes were assayed using standard cytogenetic methods in 51 village residents (11 children, 30 nonsmoking adults, and 10 smoking adults), randomly selected from a group of volunteers. A control group was selected from a village 400 kilometers away where chemical exposures were not thought to have occurred. SCE frequencies were also compared to literature values.

STUDY RESULTS:

All three groups (children, nonsmokers, smokers) from the village next to the disposal site had significantly elevated frequencies of SCE compared to the corresponding control groups. SCE levels were elevated approximately two-fold in exposed children, and slightly less in

both adult smokers and nonsmokers, compared to the control groups. SCE frequencies in the control groups were within the normal range expected from previous studies.

AUTHOR'S CONCLUSIONS:

The authors concluded that there is an association between residence in the village and elevated frequencies of SCEs. They infer that the observed increase is related to chemical exposures, and point out that, despite the relatively low levels of exposure measured in ambient air, the SCE frequencies in residents are comparable to those seen in occupational groups receiving much higher exposures. They are cautious to point out that no firm conclusions can be drawn regarding the relationships between elevated SCE rates and increased risk of cancer or genetic defects, and elect to characterize the observed SCE increase merely as an indicator of exposures.

COMMENTS:

This study seems to have been very well-designed and executed, and the relatively sudden failure of the containment at the dump site, with the corresponding rapid release of large volumes of volatile contaminants to the air near a village, provided an excellent opportunity to investigate the relationship between volatile chemical exposures and cytogenetic abnormalities. The use of both literature controls and a separate control group strengthens the conclusion that SCE levels were abnormally elevated in the exposed village residents. The significance of SCE frequency elevation, in terms of increased cancer or other health risks, remains unresolved at this time, as appropriately noted by the authors. However, it should be noted that, unlike gene mutations, which are passed on in later cell divisions, SCEs are indicative of repair of damage to DNA, and thus are not directly passed on in later cell divisions.

STUDY SUMMARY: Pershagen 1985

CITATION:

Pershagen, G. 1985. Lung cancer mortality among men living near an arsenic-emitting smelter. *Am J. Epidem.* 122: 684-694.

SOURCES OF EXPOSURE:

Arsenic-emitting smelter in northern Sweden

HEALTH EFFECTS EVALUATED:

Lung cancer deaths

CHEMICALS EXPOSED TO:

Arsenic, various metals (e.g., copper, lead, zinc), sulfur dioxide

EXPOSURE MEASURES:

Limited measurements of arsenic concentrations in ambient air and soils. Residence in exposed areas was used as an exposure surrogate.

CONFOUNDING FACTORS ASSESSED:

Occupational exposure, smoking, indoor radon exposure (based on housing type), age

STUDY METHODS:

This was a case-control study of 212 men with pulmonary carcinoma and 424 matched controls in northern Sweden. Cases were identified in the county containing the exposed and reference areas from cancer registries. Ambient air levels were measured at distances up to 7 km from the smelter. Controls were extracted from a national death register and had died in the study area during the same time period, but without a diagnosis of lung carcinoma. Data on occupation, smoking and residence were obtained by questionnaire and interviews of next of kin.

STUDY RESULTS:

Although ambient air concentrations of metals in suspended dust were measured for several years, only highly summarized data were presented. Monthly average arsenic and lead concentrations were mostly $<0.5\ \mu g/m^3$ and a few measurements exceeded $1\ \mu g/m^3$. However, no data were available for earlier periods when emissions were substantially higher.

Excluding smelter workers and miners, the relative risk for lung cancer was 2.2 for nonsmokers in the exposed area versus nonsmokers in the reference area, and 2.3 for smokers in the exposed area versus smokers in the references area. The increase observed for smokers

was statistically significant, but increase for nonsmokers was not. Most of the difference in occupational distribution between the exposed and referent populations was accounted for by increased employment at the smelter in the exposed area and increased farming, forestry, and fishing work in the referent area. The age- and smoking-standardized relative risk was 2.0 for residents in the exposed area (95% confidence interval 1.2-3.4). Significant increases in age- and smoking-standardized relative risk were also observed in miners and smelter workers. Daily tobacco consumption of the cases in the reference area tended to be higher than among cases in the exposed area; no information was available on age at start of smoking. Analysis of housing characteristics for associations with increased levels of indoor radon did not explain the increased risk.

AUTHOR'S CONCLUSIONS:

There was an increased relative risk for lung cancer in the exposed area that remained after standardization for age, smoking habits, and occupation. The increased risk could also not be explained by differences in tobacco consumption or in housing characteristics. The study authors also noted that additional studies were conducted based on duration of residence in the exposed area. These studies tended to show increased risk with longer residence in the exposed area, but the numbers were too small for meaningful conclusions.

COMMENTS:

This was a well-conducted and well-controlled study that provides strong suggestive evidence of an association of increased lung cancer deaths with exposure to emissions from a smelter. The significantly increased relative risk remained after control for the major likely confounding factors. While it would be useful to have more quantitative exposure-response information and data on exposure levels when emissions were higher, an effect is plausible in light of the unit risk for inhaled inorganic arsenic (4.3E-3 per $\mu g/m^3$) and the higher emissions that occurred prior to monitoring. Information on other exposures (criteria pollutants and other metals) would have been helpful.

STUDY SUMMARY: Rosenman et al. 1989

CITATION:

Rosenman, KD, JE Rizzo, MG Conomos, and GJ Halpin. 1989. Central nervous system malformations in relation to polyvinyl chloride production facilities. *Arch Environ Health* 44(5): 279-82.

SOURCES OF EXPOSURE:

Two polyvinyl chloride production facilities in New Jersey. Additional potential exposure sources in the area that were not evaluated included foundries, an industrial gas manufacturer, an acrylate manufacturer, a plastics manufacturer, and an electrical generation plant.

HEALTH EFFECTS EVALUATED:

Birth defects, central nervous system (CNS) birth defects

CHEMICALS EXPOSED TO:

Vinyl chloride

EXPOSURE MEASURES:

Distance from plant. In addition, annual stack and fugitive emissions were reported.

CONFOUNDING FACTORS ASSESSED:

Parental occupation, maternal age

STUDY METHODS:

This was a modified case-control study of the relationship between birth defects in the years 1977-1980 and distance from two polyvinyl chloride (PVC) production facilities in New Jersey. Birth defect information was taken from Burlington County's and adjoining counties' delivery room hospital logs. Residence information was taken from birth certificates. For New Jersey residents who delivered in Pennsylvania, birth defect and residence data were taken from computer printouts of birth certificate information. In general, 3 controls were matched to each CNS birth defect case according to maternal age, month and year of birth, race, and sex of child. Parents were interviewed to confirm the presence of the birth defect and to determine whether the parents worked in the PVC facilities; only CNS birth defect cases in which the parents could be interviewed were included in the analysis. Odds ratios were calculated for birth defects and, specifically, for CNS birth defects.

STUDY RESULTS:

The odds ratio for CNS birth defects showed a trend of increasing odds ratio with increasing proximity to the higher-emitting plant. Although the odds ratio never achieved statistical

significance, an odds ratio >1 (indicating increased risk) was observed at all distance intervals where cases were observed. No statistical analysis for trend was conducted. A weaker trend was seen in analysis of the second facility; again, all odds ratios were >1. When the data was adjusted for the elevated trend in CNS birth defects, no correlation was seen between birth defects and distance from the facilities. The CNS birth defects could not be attributed to occupational exposure to vinyl chloride or ethylene oxide.

AUTHOR'S CONCLUSIONS:

The study authors concluded that the data suggest an increased probability of CNS birth defects with exposure to vinyl chloride. They noted that, due to the small sample size, the study has only a 54% statistical chance of detecting a 4-fold increased risk. Therefore, the lack of statistical significance of the observed increases is not surprising. However, the highest ambient exposure to vinyl chloride reported by the EPA (actual value was not reported) is much lower than the 2500 ppm reported by John et al. (1981) to cause skeletal and urethral effects in rats. No comparison was made to the vinyl chloride concentration found to cause fetotoxicity in mice (500 ppm), but vinyl chloride levels near PVC facilities tend to be <10 ppm.

COMMENTS:

This study did not consider many potential confounding factors, such as pregnancy and birth defect history, smoking, drinking, education, or socioeconomic status. Although the observed trend with distance is suggestive, the conflict with animal toxicity data on the levels at which vinyl chloride is teratogenic increases the likelihood that the observed effect may be due to a confounding factor. Because of the strong drop-off of apparent effect with distance from the plant, this study could not be expanded by increasing the size of the study population. However, it could be expanded by studying CNS birth defects over a longer time period.

Reference:

John, J.A., Smith, F.A., Schwetz, B.A. 1981. Vinyl chloride: inhalation teratology study in mice, rats, and rabbits. Environ. Health Perspect. 41: 171-177

STUDY SUMMARY: Ware et al. 1993

CITATION:

Ware, JH, JD Spengler, LM Neas, JM Samet, GR Wagner, D Coultas, H Ozkayanak, and M Schwab. 1993. Respiratory and irritant health effects of ambient volatile organic compounds : the Kanawha county health study. *American Journal of Epidemiology* 137(12): 1287-1301.

SOURCES OF EXPOSURE:

11 chemical manufacturing plants in the Kanawha valley

HEALTH EFFECTS EVALUATED:

Chronic respiratory symptoms (wheezing, cough, asthma, bronchitis) and acute irritation of eyes, nose, throat, or chest in elementary school children grades 3-5

CHEMICALS EXPOSED TO:

Outdoor vapor badge samples of 15 volatile organic compounds (VOCs) were taken at fixed locations (schools). Substances analyzed for included toluene, xylenes, benzene, decane, 1,1,1-trichloroethane, carbon tetrachloride, chloroform, and 1-butanol. Subjects were also exposed to other air pollutants.

EXPOSURE MEASURES:

Continuous sampling for 15 VOCs at 75 elementary schools; maximum, median, mean, and standard deviation were reported. Criteria pollutants were also measured and reported in separate studies.

CONFOUNDING FACTORS ASSESSED:

Parental smoking, socioeconomic status, age, criteria pollutants, air moisture in homes

STUDY METHODS:

Health questionnaires were completed for 8,549 children, a 97% return rate. Because children in special instruction units were excluded, data from 7,796 children were analyzed. Schools were categorized by proximity to chemical industry complexes into four groups: in valley, near industry; in valley, far from industry; outside of valley, but near valley; outside of valley, and far from valley. The incidence of health outcomes was adjusted for parental smoking and socioeconomic status. Dampness of homes was strongly related to outcomes, but was not related to proximity to industry, so no adjustment was made for this variable.

STUDY RESULTS:

There was a significant trend with increasing proximity in the adjusted health measures for persistent wheezing, asthma, and acute eye irritation. The strongest difference was between

children attending school in the valley and those attending school outside the valley. However, there was little correlation between incidence of effect and proximity to industry within the valley. For asthma, the odds ratio (OR) was 1.27 (95% confidence interval 1.09-1.48), and for the composite indicator of chronic lower respiratory effects, the OR was 1.17 (confidence interval 1.04-1.31). A correlation between concentration of VOCs and several of the health effects was also observed.

AUTHOR'S CONCLUSIONS:

The study authors concluded that children attending schools closer to chemical plants and schools with higher measured concentrations of VOCs were more likely to report respiratory symptoms and eye irritation. They further stated that regional air pollutants, such as particulates, nitrogen dioxide, and sulfuric acid, were not potential confounders, although the possibility remains that the VOCs were a marker for other pollutants (likely HAPs). The study authors noted that the monitoring method used (vapor monitoring badges) may have underestimated exposure, compared to levels measured using an active monitoring method.

COMMENTS:

The authors of this study draw a strong inference that exposures to VOCs from industrial sources are causally associated with the observed gradients in respiratory symptoms in children, even though the measured levels of volatile organics are far lower (in some cases by many orders of magnitude) than levels which have been shown to be associated irritant effects in laboratory and occupational studies. A subsequent review of this study (Collins, et. al 1994) questioned the grounds for postulating a relationship between outdoor VOC exposures and symptoms, pointing out the low levels of measured VOCs in ambient air, the failure to include consideration of indoor air exposures and other confounding factors, and methodological concerns regarding the way the epidemiological data were analyzed. In response to these comments, the authors of the original study agreed that it would have been very desirable to have indoor air monitoring data, since a pilot study of homes in the region indicated that indoor organic exposures were often higher than outdoor exposures. In light of these factors, it does not appear that a clear causal relationship between exposures to ambient VOC pollutants and respiratory symptoms has been demonstrated.

Reference:

Collin, J.J., J.M. Ramlow, and M.J. Teta. 1994. Respiratory and Irritant Health Effects of Ambient Volatile Organic Compounds: The Kanawha Valley Study (letter). *American Journal of Epidemiology*, 140: 72-75.

STUDY SUMMARY: Woodall et al. 1992

CITATION:

Woodall, G, Jr., L.H. Kuller, E.O. Talbott, J. Ramlow and B. Salthouse. 1992. Epidemiological study for the Kenova and Ceredo, West Virginia and Catlettsburg, Kentucky area, (Phase II). Final Report. Prepared for USEPA Region IV, Air Compliance Branch. March 1992.

SOURCES OF EXPOSURE:

Oil refinery complex

HEALTH EFFECTS EVALUATED:

General health symptoms, including respiratory, cardiovascular, dermatological, and affective (e.g., anxiety) disorders

CHEMICALS EXPOSED TO:

Not reported, except that the oil refinery is a major point source of criteria pollutants

EXPOSURE MEASURES:

Days of high emissions (>10% higher than baseline for historically similar operating conditions for any pollutant) from oil refinery complex. These were defined as "upset days." Wind direction on upset days was also taken into account in a reanalysis of the data.

CONFOUNDING FACTORS ASSESSED:

Pre-existing chronic conditions (e.g., bronchitis, stroke, allergy, asthma) and smoking status were reported, but not included in the analysis for the first phase of the study. In the cross-sectional study, confounding factors assessed were smoking, age, sex, education level, and residence in an air-conditioned home.

STUDY METHODS:

The study was initiated as a result of public complaints about air pollution and related health problems (cancer, skin irritation, lethargy, memory loss, joint pain, and breathing difficulties) in the area. The first part of the study compared the number of visits to health care facilities during 30 "upset days" (defined as emissions >10% higher than baseline for any pollutant) with visits during non-upset days. A total of 636 emergency room and urgent care facility visits were examined, excluding those unlikely to be related to air quality, such as trauma, laboratory test requests, and worker's compensation releases. In the reanalysis, upset days included only those days on which the prevailing wind direction was from the refinery toward the study area; 20 upset days were identified and compared with 40 non-upset days. In the second part of the study, 50 randomly selected complainants were interviewed regarding the observed health symptoms, the types of observed pollution, and any non-health effects (e.g.,

effects on plants). An attempt was made to verify reported symptoms by comparison with medical records, but an insufficient number of consent forms were obtained. In the third part of the study, 67 people in the exposed area and 66 people in a control unexposed area were interviewed regarding the frequency and severity of specific symptoms.

STUDY RESULTS:

In the first phase of the study, there were a total of 337 visits that met that inclusion criteria on upset days, compared with 299 on the non-upset days. The difference was borderline significant only for those seen in the emergency room and discharged ($p=0.06$). There was no significant difference between upset and non-upset days in the distribution of symptoms or in the initial diagnosis. In the reanalysis (taking into account wind direction), there was a significant increase in emergency room visits resulting in discharge on upset days compared to nonupset days ($p=0.031$). There were no significant differences in reported symptomology or initial diagnosis, but the statistical power of the study was reduced by the reduced number of upset days. In the second phase of the study, respiratory complaints were most common, followed by skin and eye irritation and neurologic complaints, primarily headaches and fatigue. The major types of pollution reported were dust fallout and odor. In the third part of the study, analysis of underlying chronic medical conditions showed there was a borderline significantly higher prevalence of nervous disorders ($p=0.06$) and a significantly higher prevalence of "other conditions" in the exposed area. The reported incidence of chronic lung disease was nonsignificantly increased. However, several persistent respiratory and other symptoms, including cough, breathing difficulties, headache, sore throat, and sinusitis, were significantly increased in the exposed area. There were no significant differences between the exposed and unexposed areas in demographics, cigarette smoking, or percent of population with an air-conditioned home.

AUTHOR'S CONCLUSIONS:

The study authors concluded that "there is sufficient presumptive evidence of significant health effects occurring in the Kenova/Ceredo area to warrant further prospective study," including ambient air monitoring and prospective surveillance of respiratory disease. The study authors suggested that levels of specific pollutants, including hydrogen sulfide, sulfur dioxide, and carbon monoxide, be monitored. They also suggested that objective medical examination, including pulmonary function testing, could be conducted to reduce the subjective nature of the data.

COMMENTS:

The study was well-designed and used two different study designs to determine whether acute symptoms were correlated with pollutant exposure. In the first phase of the study, the study population served as its own control. Therefore, control for confounding factors was not necessary. The cross-sectional study was appropriately controlled and indicated that respiratory symptoms and headache are more common in the exposed area, suggesting a connection to air pollutant exposure. A major limitation of this study is the lack of any monitoring data or reporting of the air pollutants to which the population was exposed. The respiratory and irritative symptoms reported in the cross-sectional study are consistent with exposure to criteria pollutants, the only pollutants specifically mentioned as being released.

However, the study authors also suggest that levels of hydrogen sulfide, a HAP, be monitored. Thus, although it would be difficult (even with monitoring data) to determine the degree to which the observed effects can be attributed to HAP exposure, it is possible that HAP exposure makes a contribution to the observed effect.

TABLE 3-1. HAZARDOUS AIR POLLUTANTS DEFINED BY THE CLEAN AIR ACT SECTION 112(b)

000050000	Formaldehyde	000106445	p-Cresol
000051285	2,4-Dinitrophenol	000106467	1,4-Dichlorobenzene
000051796	Ethyl carbamate	000106503	p-Phenylenediamine
000053963	2-Acetylaminofluorene	000106514	Quinone
000056235	Carbon tetrachloride	000106887	1,2-Epoxybutane
000056382	Parathion	000106898	Epichlorohydrin
000057147	1,1-Dimethyl hydrazine	000106934	Ethylene dibromide
000057578	beta-Propiolactone	000106990	1,3-Butadiene
000057749	Chlordane	000107028	Acrolein
000058899	Lindane	000107051	Allyl chloride
000059892	N-Nitrosomorpholine	000107062	1,2-Dichloroethane
000060117	Dimethyl aminoazobenzene	000107131	Acrylonitrile
000060344	Methyl hydrazine	000107211	Ethylene glycol
000060355	Acetamide	000107302	Chloromethyl methyl ether
000062533	Aniline	000108054	Vinyl acetate
000062737	Dichlorvos	000108101	Methyl isobutyl ketone
000062759	N-Nitrosodimethylamine	000108316	Maleic anhydride
000063252	Carbaryl	000108383	m-Xylene
000064675	Diethyl sulfate	000108394	m-Cresol
000067561	Methanol	000108883	Toluene
000067663	Chloroform	000108907	Chlorobenzene
000067721	Hexachloroethane	000108952	Phenol
000068122	Dimethyl formamide	000110543	Hexane
000071432	Benzene	000111422	Diethanolamine
000071556	1,1,1-Trichloroethane	000111444	Bis(2-chloroethyl)ether

000050000	Formaldehyde	000106445	p-Cresol
000072435	Methoxychlor	000114261	Baygon
000072559	p,p'-DDE	000117817	Bis(2-ethylhexyl)phthalate
000074839	Bromomethane	000118741	Hexachlorobenzene
000074873	Chloromethane	000119904	3,3-Dimethoxybenzidine
000074884	Iodomethane	000119937	3,3'-Dimethyl benzidine
000075003	Ethyl chloride	000120809	Catechol
000075014	Vinyl chloride	000120821	1,2,4-Trichlorobenzene
000075058	Acetonitrile	000121142	2,4-Dinitrotoluene
000075070	Acetaldehyde	000121448	Triethylamine
000075092	Dichloromethane	000121697	N,N-Dimethylaniline
000075150	Carbon disulfide	000122667	1,2-Diphenylhydrazine
000075218	Ethylene oxide	000123319	Hydroquinone
000075252	Bromoform	000123386	Propionaldehye
000075343	1,1-Dichloroethane	000123911	1,4-Dioxane
000075354	Vinylidene chloride	000126998	Chloroprene
000075445	Phosgene	000127184	Tetrachloroethylene
000075558	2-Methyl aziridine	000131113	Dimethyl phthalate
000075569	Propylene oxide	000132649	Dibenzofurans
000076448	Heptachlor	000133062	Captan
000077474	Hexachlorocyclopentadiene	000133904	Chloramben
000077781	Dimethyl sulfate	000140885	Ethyl acrylate
000078591	Isophorone	000151564	Ethylene imine (aziridine)
000078875	1,2-Dichloropropane	000156627	Calcium cyanamide
000078933	Methyl ethyl ketone	000302012	Hydrazine
000079005	1,1,2-Trichloroethane	000334883	Diazomethane

000050000	Formaldehyde	000106445	p-Cresol
000079016	Trichloroethylene	000463581	Carbonyl sulfide
000079061	Acrylamide	000510156	Chlorobenzilate
000079107	Acrylic acid	000532274	2-Chloroacetophenone
000079118	Chloroacetic acid	000534521	4,6-Dinitro-o-cresol
000079345	1,1,2,2-Tetrachloroethane	000540841	2,2,4-Trimethylpentane
000079447	Dimethyl carbamoyl chloride	000542756	1,3-Dichloropropene
000079469	2-Nitropropane	000542881	Bis(chloromethyl)ether
000080626	Methyl methacrylate	000584849	2,4-Toluene diisocyanate
000082688	Pentachloronitrobenzene	000593602	Vinyl bromide
000084742	Dibutyl phthalate	000624839	Methyl isocyanate
000085449	Phthalic anhydride	000680319	Hexamethylphosphoramide
000087683	Hexachlorobutadiene	000684935	N-Nitroso-N-methylurea
000087865	Pentachlorophenol	000822060	Hexamethylene-1,6-diisocyanate
000088062	2,4,6-Trichlorophenol	001120714	1,3-Propane sultone
000090040	o-Anisidine	001319773	Cresol
000091203	Naphthalene	001330207	Xylenes
000091225	Quinoline	001332214	Asbestos
000091941	3,3'-Dichlorobenzidene	001336363	Polychlorinated biphenyls (a) 4-chlorobiphenyl (b) decachlorobiphenyl
000092524	Biphenyl	001582098	Trifluralin
000092671	4-Aminobiphenyl	001634044	Methyl tert butyl ether
000092875	Benzidine	001746016	2,3,7,8-Tetrachlorodibenzo-p-dioxin
000092933	4-Nitrobiphenyl	007550450	Titanium tetrachloride
000094757	2,4-D	007647010	Hydrochloric acid

000050000	Formaldehyde	000106445	p-Cresol
000095476	o-Xylene	007664393	Hydrogen fluoride
000095487	o-Cresol	007723140	Phosphorus
000095534	o-Toluidine	007782505	Chlorine
000095807	2,4-Toluene diamine	007803512	Phosphine
000095954	2,4,5-Trichlorophenol	008001352	Toxaphene
000096093	Styrene oxide	000000000	Antimony Compounds
000096128	1,2-Dibromo-3-chloropropane	000000000	Arsenic Compounds
000096457	Ethylene thiourea	000000000	Beryllium Compounds
000098077	Benzotrichloride	000000000	Cadmium Compounds
000098828	Cumene	000000000	Chromium Compounds
000098862	Acetophenone	000000000	Cobalt Compounds
000098953	Nitrobenzene	000000000	Coke Oven Emissions
000100027	4-Nitrophenol	000000000	Cyanide Compounds
000100414	Ethylbenzene	000000000	Glycol ethers
000100425	Styrene	000000000	Lead Compounds
000100447	Benzyl chloride	000000000	Manganese Compounds
000101144	4,4-Methylene bis(2-chloroaniline)	000000000	Mercury Compounds
000101688	Methylene diphenyl diisocyanate	000000000	Fine mineral fibers
000101779	4,4'Methylenedianiline	000000000	Nickel Compounds
000105602	Caprolactam	000000000	Polycyclic Organic Matter
000106423	p-Xylene	000000000	Radionuclides
		000000000	Selenium Compounds

TECHNICAL REPORT DATA

(PLEASE READ INSTRUCTIONS ON THE REVERSE BEFORE COMPLETING)

1. REPORT NO. EPA-456/R-97-001	2.	3. RECIPIENT'S ACCESSION NO.
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15. SUPPLEMENTARY NOTES		

16. ABSTRACT

THIS REPORT REVIEWS AND ANALYZES RECENT INFORMATION REGARDING THE QUALITATIVE LINK BETWEEN EXPOSURE TO TOXICS AIR POLLUTANTS AND ADVERSE HUMAN HEALTH EFFECTS. IT DESCRIBES THE TYPES OF HEALTH EFFECTS, SUMMARIZES FINDINGS ON THE MOST IMPORTANT STUDIES, AND POINTS OUT MAJOR DATA GAPS AND NEEDS FOR ADDITIONAL RESEARCH.

17. KEY WORDS AND DOCUMENT ANALYSIS

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