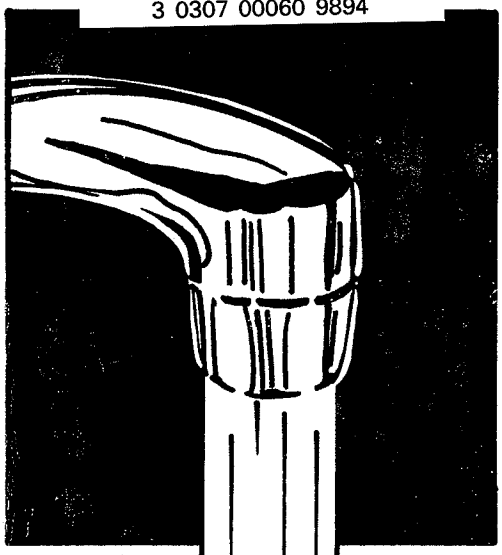

FEASIBILITY OF COMMUNITY-WIDE EPIDEMIOLOGIC STUDIES OF DRINKING WATER AND HEALTH: ST. LOUIS PARK & NEW BRIGHTON

FINAL REPORT TO THE MINNESOTA LEGISLATURE

DECEMBER 31, 1985

MINNESOTA DEPARTMENT OF HEALTH

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Minnesota Department Of Health

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FINAL REPORT TO THE MINNESOTA LEGISLATURE
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INTRODUCTION

Origin and Purpose of Study

In the spring of 1984, the Minnesota Legislature authorized funding for the Minnesota Department of Health (MDH) to evaluate the feasibility of conducting community-based epidemiologic studies in the cities of New Brighton and St. Louis Park (1984 Minnesota Session Laws, Chapter 654, Article 5, Section 4, and H.F. 1318). In St. Louis Park, six of fourteen municipal wells were removed from service between 1978 and 1981 due to trace levels of polynuclear aromatic hydrocarbons (PAHs). The contamination is believed to have originated from the former operation of a creosote and coal-tar distillation plant in St. Louis Park. In New Brighton, six of eight wells were modified or removed from service following the detection in 1981, of low levels of several volatile organic compounds (VOCs), primarily trichloroethylene (TCE) and trichloroethane (TCA). A major source of the contamination is believed to be the Twin Cities Army Ammunition Plant. Both sites have been ranked in the highest priority group of federal Superfund sites.

The discovery of contaminated municipal wells in these communities resulted in considerable concern among the residents that they may be at increased risk of adverse health effects, particularly cancers, as a result of their potential exposure to contaminated drinking water. Subsequently, several efforts were made to examine available disease statistics to determine whether a public health problem could be identified. These efforts were not able to resolve community or scientific concerns, and the possibility of large-scale community studies was considered. However, such

epidemiologic studies can pose serious technical difficulties, often require significant resources, and may be incapable of resolving specific concerns. In light of these issues, the MDH undertook an 18-month evaluation of the feasibility of conducting environmental epidemiologic studies in these communities that would address health outcomes that may be related to well water contamination. The goal of this study was to develop recommendations to the State concerning whether, or how, such studies should be conducted. It was also the goal of this study to provide a more general and socially useful assessment of the difficulties in evaluating the human health impacts of long-term exposure to low levels of chemicals present in community drinking water.

Some of the issues that were considered in this feasibility study include the following:

1. the availability and usefulness of existing morbidity and mortality data;
2. the ability to estimate individual exposure to drinking water contaminants (based on environmental and hydrologic data, biological markers, tissue burdens, residence history, etc.);
3. evidence on the biochemical, toxicological, and carcinogenic properties of identified contaminants;
4. existence of highly exposed subgroups within the communities that could serve as sentinel populations for the entire community;
5. the willingness of individuals, communities, industries, medical providers and other agencies to participate;
6. determination of potential epidemiologic study methods, their advantages, and their costs; and
7. determination of criteria by which to evaluate the feasibility of environmental epidemiologic studies of contaminated drinking water.

In July, 1984, the Chronic Disease and Environmental Epidemiology Section of the MDH, in consultation with faculty of the University of Minnesota School of Public Health, began the feasibility study with the goal of producing a final report with recommendations to the Legislature by January, 1986.

Approaches Used in the Study

Several approaches were taken to evaluate the feasibility of epidemiologic studies in the two communities.

1. A computerized literature search of appropriate biomedical and toxicological bibliographic databases was conducted to identify published reports pertaining to specific contaminant compounds, health effects related to drinking water, and environmental epidemiology in general;
2. Information relevant to this study was solicited from federal agencies, including the Environmental Protection Agency, the Centers for Disease Control, and the National Institute of Environmental Health Sciences;
3. Information was solicited from all fifty state epidemiologists concerning efforts in their states to address health effects related to waterborne environmental contaminants;
4. Other agencies within the state (local, state, and federal) were contacted to determine the availability and quality of various environmental, hydrogeologic, water supply and other engineering data;

5. All existing health-related information that had been generated as a consequence of the contamination problem was identified and reviewed;
6. A special two-day workshop with national experts was held to address issues related to development of a model of historical exposure to contaminants in drinking water. Many different areas of expertise were represented by workshop participants (see Appendix A);
7. Additional review of cancer incidence data for St. Louis Park was conducted, including a critical review by an outside expert in statistical epidemiology; and
8. Outside experts in epidemiology and toxicology were asked to review the final report.

Organization of the Report

This report consists of five sections which address the principles of epidemiology and their application to the study of potential health effects resulting from contamination of groundwater supplies. Section 1 provides a brief summary of epidemiologic methods, how epidemiologic associations are judged, and the kinds of data frequently used to describe health. A brief overview is provided of the methods and findings of studies that have examined water and health issues. Section 2 describes several non-epidemiologic approaches for assessing potential human health risks from environmental exposures. Section 3 outlines several major criteria for the conduct of meaningful community-based epidemiologic studies of environmental contaminants. Section 4 reviews available information regarding the well water contamination in St. Louis Park and in New Brighton. Information presented includes when contaminants were first

detected, the nature and magnitude of the contamination, the possible sources of contamination, various aspects of the municipal water supply that relate to potential community exposure, existing studies and available data that relate to community health, and the general environmental and toxicologic aspects of the contaminants. Section 5 outlines a series of epidemiologic options for addressing potential health effects as a result of well contamination in St. Louis Park and New Brighton. Proposals for studies or monitoring of both mortality and morbidity are provided, along with discussion of study strengths, limitations, costs, and recommendations.

FINDINGS AND CONCLUSIONS

Listed below is a summary of the major findings and conclusions of this feasibility study. General findings are presented first, followed by more specific findings for St. Louis Park and for New Brighton. Specific recommendations arising from these findings are presented elsewhere. The Section(s) of the full report that refer to a particular finding or conclusion are indicated in parentheses.

It is important to recognize that the findings and recommendations of this study, although of some applicability to other or future situations of water contamination, should not be interpreted as a statement of the appropriateness of water quality criteria, the type of remedial actions that should be taken to relieve water contamination problems, or the acceptability of particular levels of risk arising from such contamination. The scientific uncertainties in estimating human health risks, the nature of the risks (cancer risks or other risks, voluntary or involuntary, etc.) aesthetic values, public perceptions, and many other factors are extremely pertinent to the water quality issue. The right of a community to the best available water supply is a long established and accepted principle of public health and should be viewed separately from the issue of whether epidemiologic studies are warranted in particular instances of water contamination.

General

1. There have been many published epidemiologic studies that have attempted to examine cancer risks in relation to drinking water source. Most of these studies have serious design limitations that make interpretation of their findings very difficult. The major flaw has generally been the absence of individual measures of

exposure. Neither their findings nor their methodology serve as useful models for St. Louis Park or New Brighton. (Section 1)

2. Several studies have examined potential associations between particular health effects and contaminated well water. These studies have varied widely in their assessment of exposure, general study design, health outcomes examined, and many other factors. For a variety of reasons, these studies have not shown clear evidence of a causal association between water contamination and adverse health effects. Neither can these studies rule out such an association. (Section 1)

3. Major difficulties in almost all epidemiologic studies of environmental carcinogens include (a) long latency periods for most cancers; (b) lack of information on relevant exposures that may have occurred many years or decades ago; (c) the existence of multiple risk factors for most cancers; (d) multiple exposures to potential carcinogens; (e) population mobility; and, (f) the need for large study populations due to the relative infrequency of specific cancer types. (Sections 1, 3)

4. Quantitative risk assessment (bioassay) is a process for estimating human cancer risks based on animal experiments. The basic premise of this process is that substances that are carcinogenic in experimental animals may also be carcinogenic in humans. Mathematical models are used to extrapolate from high dose animal exposures to low dose human exposures. Although there are many assumptions and large uncertainties involved in this approach, bioassay offers a practical and objective means for identifying

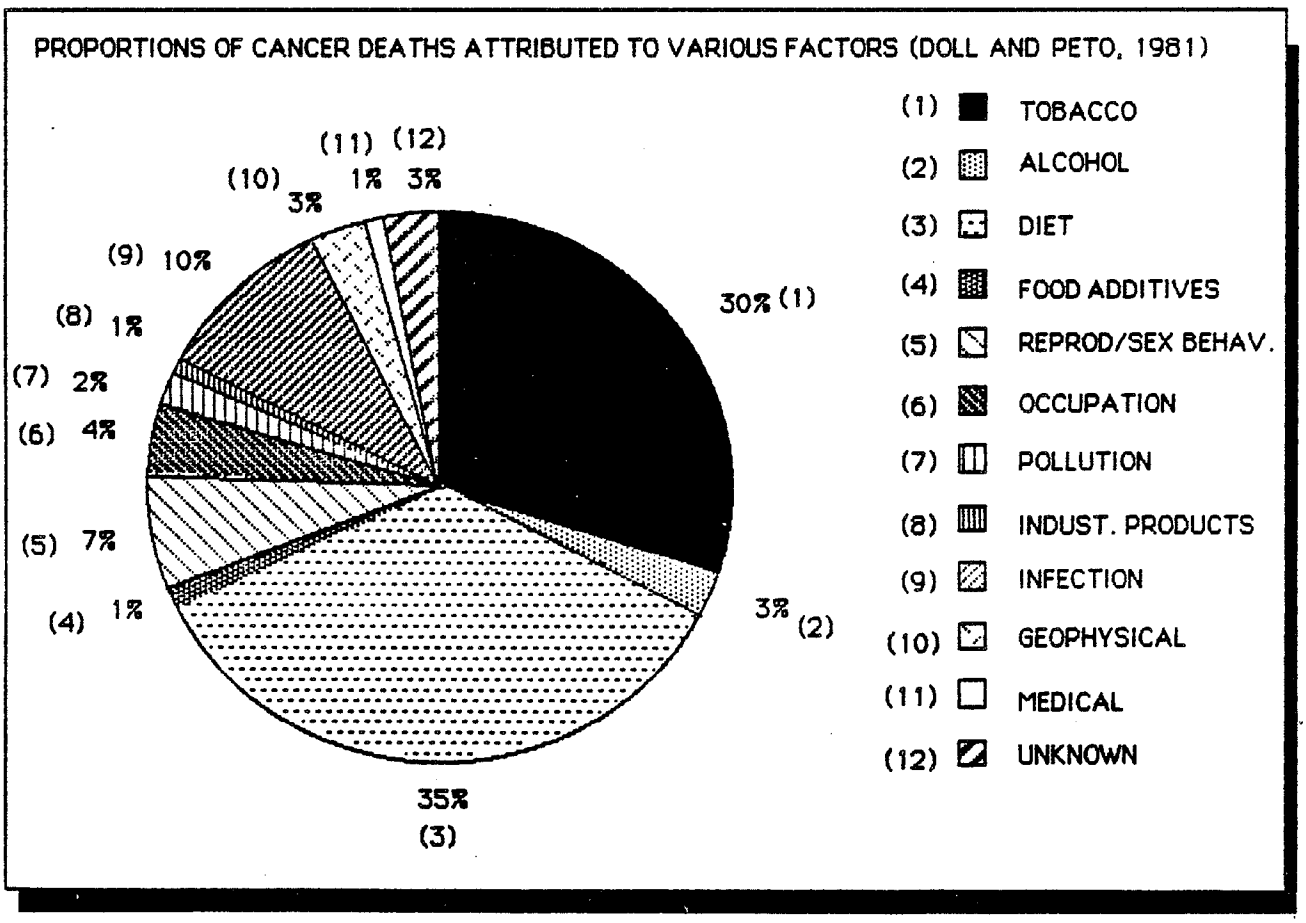
potential health risks. It is generally accepted that in the absence of direct epidemiologic evidence of a health risk, substances shown to be carcinogenic in experimental animals should be treated as if they represented a carcinogenic risk to humans. (Section 2)

5. Current epidemiologic methods are not generally capable of identifying or validating the excess cancer risks that are typically projected from animal bioassays for environmental exposure levels. These risks are commonly expressed in terms of the exposure level that would result in one additional cancer per 100,000 persons with lifetime exposure (10^{-5} risk level). Since the cumulative lifetime cancer risk in the population is approximately 30%, that one additional case would have to be detected among the 30,000 other cases. (Sections 1, 5)

6. There appears to be a growing concern among the public that cancer incidence is largely the result of chemical contaminants in drinking water, ambient air, or other environmental media. One factor that has probably contributed to this belief is a misunderstanding of statements made by scientists that a significant portion of cancer incidence is related to environmental factors. "Environment" in this sense should usually be interpreted to mean all non-genetic factors, and includes significant lifestyle characteristics such as smoking, alcohol consumption, type of diet, reproductive history, and occupation, in addition to ambient environmental exposures. The extent to which personal or lifestyle factors contribute to occurrence of a particular type of cancer varies, but may be extremely large (e.g., 90% of lung cancer and

30% of all cancer deaths are attributable to tobacco). An estimate of the proportions of all cancer deaths that are attributable to various factors is summarized in Figure E-1. It should be noted that these estimates have a large uncertainty and are intended to apply to the U.S. population in general. In particular subgroups of the population, these estimates would differ.

Figure E-1



The large contribution of "lifestyle" to many cancers does not imply that society should be less vigilant about reducing or eliminating exposures to identified environmental carcinogens (e.g., asbestos). Another factor that may contribute to public concerns regarding cancer and the environment is the lack of public knowledge regarding the natural history of cancers. For example, it is not always understood that cancer is not a single disease, but many different diseases with different risk factors and generally long latency periods. Continuing efforts are needed to inform the public of the many issues related to cancer and the environment, including information on the known or suspected causes of cancer, the magnitude of actual or potential cancer risks, and the methods used to identify cancer risks (e.g., animal bioassays, cytogenetic tests, and epidemiologic studies). (Section 1)

St. Louis Park

A substantial amount of information has been generated in relation to the water contamination that resulted in several well closings between 1978 and 1981 in St. Louis Park. This information includes environmental, hydrogeologic, water supply, and limited health data. In addition, much general information is available regarding the environmental and toxicological aspects of the contaminants found in the wells. The following findings and conclusions are based on review of this information.

1. A valid contaminant-exposure model for use in epidemiologic studies in St. Louis Park cannot be established. That is, it is not possible to classify individuals or residences within St. Louis Park according to their relative degree of historical exposure to PAH contaminants in drinking water. At the outset of this study, it had been thought that a crude surrogate for exposure might be

length of residency in St. Louis Park between 1947 and 1978. However, neither this nor any other approach would avoid the potential for serious misclassification of exposure. This conclusion is based on the following factors: (Section 4)

a. The pattern and history of municipal well contamination in St. Louis Park prior to 1978 are not known. The installation dates for contaminated municipal wells range from 1947 to 1969, long after the beginning of operation of Reilly Tar and Chemical Corporation (1917) and long after the first evidence of contamination of the major bedrock aquifer (early 1930s). Available information strongly suggests that the migration of groundwater contaminants has been complex. It is also possible, then, that the history of well contamination was complex, with some periods of well contamination and other periods with little or no contamination. The net effect of such variability, in addition to the effects of seasonal and long-term variations in well use, is that over different periods of time, it is possible that none, some, or most of the St. Louis Park water supply was provided by contaminated wells.

b. Additional insights into the history of contaminant migration (and well contamination) might be gained by further computer simulations using groundwater flow models developed for the St. Louis Park area by the U.S. Geological Survey. Such efforts might require several years, and it could not be known in advance whether these simulations would be capable of establishing time periods in which specific wells were likely to have been (or not have been) contaminated. The validity of computer groundwater flow models in predicting historical contaminant migration is unknown.

c. Contaminant levels were measured at the well head, and it is not known to what extent the usual water treatment, storage, and distribution processes would affect contaminant levels at the tap at various locations in the city.

d. Measurements of PAH residues in the water distribution system would not likely serve as a useful index of cumulative exposure. Much of the distribution system was installed many decades ago when the use of asphaltic or coal-tar liners in water mains was common in the U.S.

e. Polynuclear aromatic hydrocarbons (PAHs) are rapidly metabolized and eliminated from the body. They do not accumulate in human tissues; consequently, tissue residues cannot be used to estimate historical exposures.

2. It has long been established that certain PAHs and PAH-containing mixtures are potent animal carcinogens, capable of producing tumors in most animal species tested by most routes of exposure. Depending on the animal species used, the experimental conditions, and the specific PAH, tumors can be produced in many different tissues. Although PAHs commonly produce tumors in rodents at the site in which intake occurs (stomach, lungs, skin), some can also produce tumors at remote body sites, such as mammary glands. (Section 4)

3. PAHs are produced from most combustion processes and are ubiquitous in the environment. The general population is exposed to PAH in the air, in foods and beverages, and in drinking water. Smoking and certain occupational settings produce significant additional exposures. Estimates of PAH intake in the general population indicate that foods are the primary source of exposure to carcinogenic PAH. It is probable that exposures from food would significantly exceed exposures from contaminated St. Louis Park well water. Exposure to carcinogenic PAHs would also be much greater through smoking than through contaminated well water. For noncarcinogenic PAH, however, consumption of water with PAH levels found in the most highly contaminated wells could equal or exceed estimated intake from food sources. Since some noncarcinogenic PAH can act as "promoters" of carcinogenesis, while others have no effect or even act as inhibitors, the significance of increased exposure to noncarcinogenic PAH is not clear, but cannot be discounted. (Section 4)

4. Cancer incidence data for the Minneapolis-St. Paul metro area are available from a national survey conducted in 1969-71. Examination of these data in 1979 indicated that none of the forty-five types of cancer analyzed were elevated in men who resided in St. Louis Park at the time of diagnosis. Among women, however, elevated cancer incidence rates were found for several types of cancer, as well as for all cancers combined. The largest excess was for breast cancer (45% higher than the Metro area). The finding of elevated breast cancer in St. Louis Park in conjunction with the ability of several PAHs to induce mammary and other tumors in rodents raised both public and scientific concerns, and led to additional efforts to examine this issue. Evaluation of this issue requires recognition of the following factors:

   a. The specific PAHs that have been shown to induce mammary tumors in rodents were either not present in contaminated wells or were detected very rarely even in the most highly contaminated wells. In general, the level of carcinogenic PAH in contaminated wells was relatively low in relation to other environmental levels (atmospheric and dietary). These other sources of exposure to PAH would have to be estimated and taken into account before attributing effects to PAH in water. (Section 4)

   b. The many published case-control and cohort studies of breast cancer have not demonstrated clear evidence of an association between breast cancer and smoking (a substantial exposure to PAHs and other compounds occurs from smoking).

   c. Epidemiologic studies of breast cancer have identified a number of risk factors that account for some of the observed variations in rates among different groups of women. The population in St. Louis Park differs from that in the general Metro area with respect to several of the factors that are known to influence breast cancer rates. Previous efforts by the MDH to determine the extent to which these known risk factors account for the observed excess of breast cancer in St. Louis Park are not conclusive. (Sections 4, 5)

d. Epidemiologic evidence to date linking consumption of high-PAH foods with gastrointestinal cancer is weak. However, smoking and intense occupational exposures to PAH-containing mixtures have been strongly associated with a variety of human cancers, including lung, esophageal, kidney, bladder, and skin. (Section 4)

e. There are many known factors (e.g., selenium, certain vitamins and other dietary constituents) that are powerful inhibitors of PAH-induced carcinogenesis (including mammary carcinogenesis) in animals. The extent to which these factors might affect PAH-induced carcinogenesis in humans is unknown. (Section 4)

f. Although effects of mixtures of PAH compounds are generally assumed to be additive, synergistic or antagonistic effects cannot be ruled out. In experimental systems, co-carcinogenic, promotional, synergistic, additive, and antagonistic interactions have all been observed. (Section 4)

g. Studies of radiation exposure, an established initiator of breast cancer, suggest that there is a long latency period (at least 10 years) between onset of exposure and diagnosis of disease. Latency periods for most other cancers are also typically 10-30+ years. Thus, breast (and other) cancer cases observed in St. Louis Park in 1969-71 may be related to events that occurred several decades earlier. (Sections 1, 4)

In light of these and the other findings noted above, it does not appear likely that the observed excess of breast cancers in St. Louis Park in 1969-71 could be related to water contaminants. Nevertheless, further definition of this issue would be useful to determine whether this excess was a result of normal statistical variability; whether an excess rate still exists or has increased; whether any other cancer rates have increased or decreased; and, if an excess does exist, the portion of the excess that could be accounted for by known risk factors. Some of these important unknowns could be addressed by further study or epidemiologic monitoring; however, it is very unlikely that any type of study would be capable of directly addressing the health impact from contaminated wells.

5. Employee data provided by Reilly Tar and Chemical Corporation showed that the vast majority (>80%) of their St. Louis Park employees between 1950 and 1972 were employed for less than five years. The average duration of employment was slightly over three years. This observation, along with the small number of workers involved (<800) over this time period, suggests that a study of Reilly workers as a more highly exposed subgroup would have little power to detect important increases in cancer rates. Furthermore, it would not address the issue of breast cancer in women. (Sections 3, 4)

6. There appears to be little basis for expecting health effects other than cancers to result from low level environmental exposures to PAH. (Section 4)

New Brighton

There is a considerable and growing body of information concerning the well contamination problem in New Brighton. Information includes well monitoring, hydrogeologic, water supply, and some mortality data. There is also much available information regarding the general toxicological and environmental aspects of the contaminants. The findings and conclusions below are based on this information.

1. The development of a valid exposure model for epidemiologic studies in New Brighton is not currently possible. That is, it is not possible to classify individuals or residences on the basis of historical exposures to water contaminants. This conclusion is based on the following factors: (Section 4)

a. The history of municipal well contamination prior to 1981 is not known. Installation dates for contaminated wells range from 1955 to 1971. Available information suggests that many of the likely sources of contamination are located within the Twin Cities Army Ammunition Plant (TCAAP). This facility was put into operation in the early 1940s. The six municipal wells initially found to be contaminated are in close geographic proximity to each other, and (in 1981) were all drawing water from essentially the same bedrock aquifer. These six wells provided the vast bulk of the yearly municipal water pumpage in New Brighton back to at least 1971.

b. Additional insights into the history of contaminant migration (and the onset of well contamination) could probably be gained by further computer simulations of groundwater flow and contaminant transport using models developed for the New Brighton area by the Minnesota Pollution Control Agency. The validity of computer groundwater flow models and contaminant transport models in predicting details of historical contaminant migration is unknown.

c. Contaminant levels were only measured at the well head, and it is not known to what extent water treatment, storage, and distribution processes would affect contaminant levels at the consumer tap at various locations within the city.

d. Volatile organic compounds (VOCs) found in New Brighton wells are rapidly metabolized and eliminated from the body; they do not persist or accumulate in tissues. Consequently, tissue burdens cannot be used as a measure of historical exposure. (However, VOC levels in expired air or VOC metabolites in urine can be used to monitor current or very recent exposures.)

2. The contaminants found in New Brighton wells (TCE, TCA, among others) in 1981 are among the most commonly detected contaminants in ground water supplies in Minnesota as well as in the U.S. (Section 4)

3. Carcinogenic risks from exposure to environmental levels of the major contaminants in New Brighton wells (TCE, TCA) appear to be very slight. In contrast to several PAH compounds, studies to date have shown that these compounds are very limited in their ability to induce tumors in animals. Based on carcinogen bioassay data,

metabolic data, mutagenicity assays, and limited epidemiologic data, it appears unlikely that an observable increase in cancer would result from exposures to low (parts per billion) levels of these compounds in water. (Section 4)

4. Overall cancer mortality for New Brighton over the five-year period 1976-1980 did not differ from expected mortality, based on Metro area or statewide rates. (Sections 4, 5)

5. TCE, TCA and DCE (dichloroethylene) have not produced significant teratogenic or other reproductive effects in animal studies. (Section 4)

6. VOCs such as TCE and TCA are widely used in many industries, and are found in a number of consumer products. They have become widespread environmental contaminants and can be found in the air, water, and in some foods. In urban areas, atmospheric as well as indoor concentrations for individual VOCs are commonly in the microgram per cubic meter range, resulting in a daily uptake that may be comparable or greatly exceed uptake from consumption of contaminated well water. Occupational exposures can be many orders of magnitude greater than general population exposures. Thus, additional significant exposures, other than drinking water, would have to be evaluated in epidemiologic studies involving these compounds. (Section 4)

7. Levels of VOCs in several production wells at TCAAP were much higher (10-100 fold) than in New Brighton municipal wells. This suggested the possibility that employees at TCAAP might represent a subgroup with higher exposures. General information about the

number of employees, periods of employment, etc., were solicited from the two largest contractors at TCAAP -- Honeywell Corporation and Federal Cartridge Corporation. Discussions with Honeywell representatives suggested that it would be difficult to construct an occupational cohort with sufficient definition of exposures and with sufficient person-years of experience to allow reliable detection of increased mortality rates. Federal Cartridge Corporation did not provide any information concerning their employees during the time this study was conducted. Consequently, the suitability of this employee group as a useful sentinel population could not be assessed. However, it does not appear that a study of TCAAP employees would offer useful insights into potential community health issues due to the following factors: (a) occupational studies of other worker populations exposed to these VOCs have not to date shown increased health risks; (b) the TCAAP employee population would differ from the general New Brighton population in many important respects (e.g., age and sex distribution, general health status) that would make any findings difficult to extrapolate; and (c) the size of the employee population and the period(s) of employment would probably be too small to detect even modest elevations in risk. (Sections 3, 4)

RECOMMENDATIONS

Specific information is presented in this report concerning the feasibility of community-based epidemiologic studies in St. Louis Park and New Brighton. The finding of contaminated municipal wells in each of these communities raised public concerns over potential adverse health effects. Such studies would address the question of whether there is an excess risk of adverse health effects in these communities that could be attributed to contaminated drinking water. The following recommendations are based on an 18-month intensive review of available information regarding the contamination problem in these communities and on generally-recognized strengths and weaknesses of available epidemiologic methods.

General Recommendation

A statewide cancer surveillance system should be instituted to enable the systematic collection and analysis of cancer incidence data.

There is considerable societal concern over cancer, especially in relation to potential environmental factors. The water contamination problems and resulting public concerns in St. Louis Park and New Brighton are certainly not unique to these communities. Similar situations have occurred elsewhere in the state, and will continue to occur in the future. Public health agencies are increasingly being called upon to respond to the concerns of environmentally-related disease. The availability of statistical data on cancer incidence derived from a surveillance system, in addition to many other uses, would permit the state to respond to these issues more completely, efficiently, and in a more scientifically-useful manner. A cancer surveillance system would collect data on newly-diagnosed (incident)

cancer cases and would permit routine monitoring of the rate of cancer occurrence in the population. This information is quite different from cancer mortality and is of greater value when attempting to identify causative factors. (A feasibility study of a state cancer surveillance system was mandated by 1981 Session Laws, Chapter 340 and completed in December, 1985). Since it is not known how long wells were contaminated in these communities, or to what extent contaminants were present at the consumer tap, the monitoring of cancer incidence should continue for a sufficient period of time (many years and perhaps decades) to account for the long latency of many chronic diseases.

Recommendations - St. Louis Park

1. Existing state-collected mortality data should be monitored for possible excesses and/or time trends that are suggestive of an existing or emerging public health problem in this community.

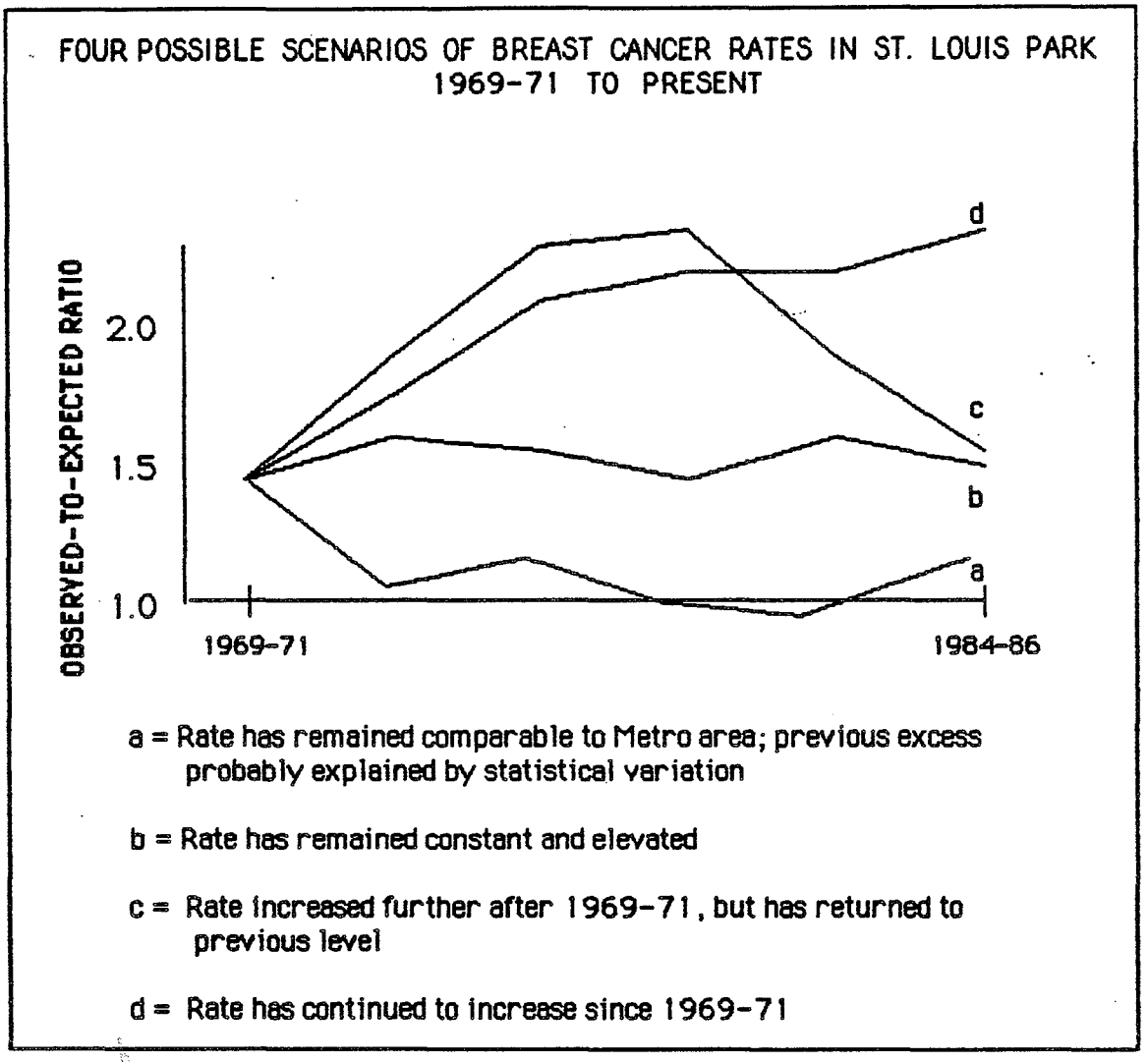
The State routinely collects mortality data and it would be relatively inexpensive to monitor these data for any excesses or trends in causes of death. Although there are limitations to mortality data, and their findings must be interpreted cautiously, they can provide useful insights into the mortality experience of a population. Analyses of mortality could identify, for example, unusual trends of disease, which would provide the focus for any future study. It should be noted that such analyses, in and of themselves, would not be able to identify the actual causes for observed patterns.

2. The need for additional epidemiologic monitoring or detailed studies will depend on the observed patterns of cancer mortality and on the implementation and findings of a statewide cancer surveillance program.

Data from the Third National Cancer Survey in 1969-71 indicated that the overall cancer rate was elevated in St. Louis Park women compared to the Metro area. The greatest excess was for breast cancer. No cancer sites were found to be elevated in men. Several interpretations of these findings are possible, including normal statistical variability and a higher prevalence of established cancer risk factors in the St. Louis Park population. It is not known if, or how, breast cancer or other cancer rates in St. Louis Park have changed since the time of the 1969-71 survey. As an example, several scenarios are possible with respect to breast cancer rates. Some of these possibilities are shown Figure E-2 below. These scenarios have different public health implications, and it is important to determine whether any changes in cancer incidence have occurred. Such information would be provided by a statewide cancer surveillance system. If such a statewide system is not implemented, a specific effort will be required to update the cancer incidence in St. Louis Park.

The need for, and the design of, additional analytic studies (case-control or cohort) will depend on trends or patterns observed from the monitoring of mortality and/or cancer incidence. This would apply to any population in which disease surveillance data were available. If, for example, breast cancer incidence in St. Louis Park has remained high or has increased, there would be substantial justification for undertaking further epidemiologic study to identify

Figure E-2



the factors associated with the increased risk. Since cases would already have been identified by cancer surveillance, a case-control study would represent the most cost-effective approach. Although it is unlikely that a case-control study could directly resolve the water contamination question (due to the lack of a valid exposure model), it could reveal the extent to which other known risk factors account for the breast cancer rate and would have considerable public health

value. Due to their enormous expense, time requirement, and social invasiveness, cohort studies of the entire community should not be considered unless the following conditions are satisfied:

a. There are unambiguous findings of a statistically significant excess of disease in the community;

b. Further information becomes available that permits assessment of individual exposures to water contaminants. This would involve additional efforts (i) to develop or refine computer models of groundwater flow, contaminant transport, and the water distribution system, and (ii) to define the relationship between contaminant levels at the well head and at the tap; and

c. Other significant sources of exposure to the contaminants (e.g., ambient atmosphere, foods, many workplace environments, various consumer products) can be assessed and taken into account.

Recommendation - New Brighton

Community-based epidemiologic studies in New Brighton are not justified at this time based on existing information.

In response to requests from state officials following identification of well contamination, the Minnesota Department of Health in 1983, conducted an analysis of cancer mortality in New Brighton for the five-year period 1976-1980. This study found that the number of observed cancer deaths among New Brighton residents was essentially identical to the number expected, based on Metro area or state rates. Specific types of cancer that are of conceivable interest (e.g., liver cancer) are exceedingly rare in the population

and cannot be meaningfully studied in populations of this size. The low and variable number of reproductive events (e.g., births, fetal deaths, infant deaths) in New Brighton, in addition to other technical difficulties, prohibits a meaningful examination and interpretation of adverse reproductive outcomes. Although scientific uncertainty still exists, the weight of the available evidence (toxicologic and epidemiologic) suggests that observable human risks of cancer or other adverse health outcomes are not likely to be associated with low-level environmental exposures to the major contaminants identified in New Brighton wells.

Finally, it is not currently possible to determine the magnitude or duration of actual exposure to water contaminants at the tap, or to distinguish these exposures from other major sources of individual exposure (outdoor air, indoor air, food, consumer products, and occupation).

In light of the available information and the costs, social intrusiveness, and probable yield of community-wide epidemiologic studies, such studies are not scientifically justified at this time and are not recommended. More intensive epidemiologic monitoring or special studies of mortality or cancer incidence is not required at this time. Routine monitoring of future cancer occurrence among New Brighton residents through a statewide cancer surveillance system, when available, will be sufficient.

1. EPIDEMIOLOGIC APPROACHES TO THE STUDY OF HEALTH EFFECTS OF CONTAMINATED DRINKING WATER

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BASIC PRINCIPLES OF EPIDEMIOLOGY

Epidemiology is the scientific discipline which examines the patterns of disease in human populations and attempts to identify etiologic (causative) factors associated with these patterns (Lilienfeld and Lilienfeld, 1980). Epidemiologic methods have been particularly effective in the description and subsequent identification of etiologic factors associated with infectious diseases. More recently, epidemiology has focused on non-infectious diseases, such as cancer and heart disease, that have become the major causes of death. Currently, much emphasis is being placed on epidemiology to provide answers regarding potential human health effects from environmental contamination. The strength of the epidemiologic method is that it is a means of directly assessing the risk of environmental agents to humans. The major weakness is the dearth of adequate exposure data through time from which estimates of risk are determined. Without adequate exposure data much reliance is placed upon animal experimentation and extrapolation to humans. This section provides a brief overview of epidemiologic principles and reviews the usefulness of mortality and morbidity data as measures of health.

There are two basic measures frequently used by epidemiologists to describe health (or disease); (1) mortality, and (2) morbidity. Indirect measures such as biochemical and chromosome tests have been proposed as potential indicators of human health, but, to date, these measures are not sufficiently predictive of subsequent adverse health outcomes to be useful in epidemiologic studies. As a result, most epidemiologic investigations

make use of morbidity and/or mortality data to determine associations between disease and putative risk factors.

It is important to note that correlational-type studies, which simply compare mortality or morbidity rates in populations where there are temporal or geographic differences in levels of environmental contaminants, do not provide information on causality. Epidemiologic studies using either the case-control or cohort techniques in which individual measures of exposure and disease are determined (to be discussed) provide better evidence for exposure/disease associations. Regardless of study type, an epidemiologic study cannot prove that an association between exposure and disease does not exist. The evaluation of negative findings from an epidemiolgic study requires consideration of many factors, such as statistical ability of the study to detect an association of a given magnitude (i.e., study power). Negative epidemiologic results are often considered applicable only to the population under study.

Scientific "proof" of a cause-and-effect relationship cannot be obtained from an epidemiologic study. However, as a practical matter, explicit or implicit judgments of causality are frequently derived from such studies, and strongly influence public health policy. Therefore, it is important to consider epidemiologic findings from a variety of perspectives. Epidemiologists have not established hard and fast rules for determining when a positive association should be considered a cause-and-effect relationship. Different experts stress different factors in evaluating associations and not all agree that certain items are indeed useful (Hill, 1965; Lilienfeld and Lilienfeld, 1980). However, certain guidelines do frequently appear in discussions of causal relationships, and these are discussed below.

(1) Strength of the association. The more strongly an exposure is associated with some disease, the more likely it is that the exposure causes the disease. The strength of the association is often expressed quantitatively as the "relative risk," which is defined as the ratio:

$$\frac{\text{Rate of disease among those exposed}}{\text{Rate of disease among those not exposed}}$$

As an example, smokers are ten times as likely to develop lung cancer than non-smokers (relative risk = 10). This greatly elevated relative risk makes it much less likely that some other variable (confounder) overlooked by the investigator is actually responsible for the association. A very low relative risk would have a greater probability of resulting from some study bias or confounding factor. Monson (1980) describes several categories of relative risks in the following terms.

Relative Risk	Strength of Association
1.0 - 1.2	None
1.2 - 1.5	Weak
1.5 - 3.0	Moderate
3.0 - 10.0	Strong
10.0	Infinite

Although a strong association is very suggestive of a causal relationship, a weak association is much less convincing evidence that the association is causal. However, weak associations do not necessarily argue against a causal relationship.

(2) Consistency. An association consistently found by different investigators, in different populations, and/or in different geographical areas is more likely to be causal. Although the many studies that have examined lung cancer and smoking have involved different investigators,

study populations, locations, and study designs, all have shown a very strong positive association. It is extremely unlikely that such a consistent finding can be the result of some overlooked bias. Some investigators attach special significance to consistent associations found as a result of different epidemiologic study techniques (e.g., case-control, cohort).

A recent example of inconsistent findings comes from the studies examining the relationship between coffee drinking and pancreatic cancer. At least five studies have explored this possible relationship. Two of the studies reported at least some association, while the three others found no association. There remains much doubt, therefore, whether coffee consumption is related to pancreatic cancer even in a non-causal manner.

(3) Temporal relationship. Obviously, an exposure must precede a disease if it is to be considered a possible causative agent. This time sequence is most firmly established in prospective cohort studies. In contrast, cross-sectional (prevalence) studies do not generally permit determination of whether exposures preceded disease development. It may also be difficult to establish the time sequence in some case-control studies in which, for example, a disease may have a very long preclinical (non-symptomatic) phase.

(4) Dose-response relationship. The existence of a dose-response relationship between exposure level and disease incidence supports a causal interpretation. In other words, those who have the highest exposures should also have the highest disease risks. It has been clearly demonstrated that the number of cigarettes smoked correlates directly with the degree of lung cancer risk. However, the absence of an apparent dose-response effect is not considered good evidence against causality. Exposures may not have been ascertained accurately enough in studies,

leading to misclassification and bias that can obscure a risk gradient. It is also possible that some threshold of exposure is necessary for a given agent before an effect is observed.

(5) Coherence. A causal hypothesis is supported when an association is consistent with or supported by other known facts and observations. For example, a causative hypothesis is favored if there is some demonstrated or potential biological mechanism by which the effect can be explained. The cellular effects of ionizing radiation have long been recognized and offer a clear explanation for the health hazards of radiation.

In the case of cigarette smoking, laboratory studies have identified a variety of organic compounds in inhaled smoke; a number of these compounds have been shown to cause cancer in animal studies. These findings are thus consistent with the human epidemiologic evidence.

The absence of a recognized biological mechanism is not necessarily contradictory to a causative interpretation. The lack of an apparent mechanism may only reflect an early stage of investigation. This situation is well illustrated by the recent outbreak of Toxic Shock Syndrome. Early epidemiolgic findings clearly indicated that the highest risk group consisted of young, menstruating females who used a high-absorbency brand of tampon. However, it was found that some non-menstruating females and some males were also disease victims. Thus, the use of high-absorbency tampons alone could not account for all cases, and there was considerable doubt by some (including the manufacturers) that the tampons could be causally related. However, the absence of an explanation or recognized mechanism did not prevent withdrawal of the tampons from the market. Some time later it was discovered that the disease was actually caused by a toxin from a common bacterium. The toxin is only produced under certain

physical and biolgical conditions, and these circumstances are more likely to occur in young women using high-absorbency tampons.

(6) Specificity. An interpretation of causation is favored when the association links the exposure to a single disease rather than some broad spectrum of diseases. An example of high specificity is the association between occupational exposure to vinyl chloride and angiosarcoma (a rare form of liver cancer). The high specificity, as well as the strength of this association leaves little doubt as to its causative nature.

A lack of specificity, however, does not necessarily argue against causality. For example, cigarette smoking has been associated with a wide range of diseases. In fact, the smoking history of study subjects is always considered in well-designed studies. This lack of specificity, although still sometimes raised in arguments by the tobacco industry, is not particularly troublesome to epidemiologists since a great many components have been identified in tobacco smoke, and many of these components can be transported through the body to different sites.

It is important to emphasize that none of the above factors is sufficient to either prove or disprove that an association represents a true cause-and-effect relationship. They do, however, offer some reasonable guidelines with which both epidemiologists and non-epidemiologists may judge whether a positive association is likely to represent a true cause-and-effect relationship.

MORTALITY DATA AS A HEALTH MEASURE

There are several mortality endpoints that can be used by the epidemiologist, each with its own advantages and limitations, depending on the study's objectives. An advantage of studying fetal and infant* deaths when assessing health implications of environmental contamination is that they represent an event closer in time to the exposure of interest. The major limitation is the very small number of events which normally occur. For example, in 1982 there was a total of 645 infant deaths in the State of Minnesota, which translates to an infant mortality rate of approximately 9.4 deaths per 1000 live births per year (MDH, 1982). Applying this rate to a community with a population of 25,000 generates an expected number of about 3 infant deaths per year, illustrating that these events are relatively rare, even on a community-wide basis. Consequently, the use of these data within the framework of small geographic areas or populations is severely limited, particularly if specific causes of death are defined as the endpoint of interest. Efficient application of these data requires large geographic areas (large populations) observed over extended periods of time. The exception, of course, is when the exposure of interest is stongly linked to a specific cause of infant mortality creating a large excess in a particular area.

The use of all-cause (general) mortality in a population as a measure of health does not suffer from insufficient numbers; however, all-cause mortality may mask relationships between exposure and specific causes of death. Cause-specific mortality data are, therefore, more meaningful and

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* infant deaths in this context include all deaths before one year (both neonatal and post-neonatal deaths).

yield greater insights into exposure/health outcome associations, especially when testing a priori hypotheses. Yet, the comparison of multiple, cause-specific mortality rates increases the probability of finding a "significant" difference that is due to chance alone.

The use of mortality data to examine chronic disease trends is not without limitations. Difficulties may arise due to the following factors. (1) Changes over time may occur in the methods of diagnosing disease. For example, the recent development of nuclear magnetic resonance has greatly improved diagnosis of certain diseases. More detailed and accurate diagnoses may produce artificial increases in cause-specific mortality. (2) Changes or inaccuracies in recording causes of death on death certificates. The accuracy of the death certificate depends, in part, on the diagnostic ability of the physician as well as historical information regarding the patient's medical history. This information is not always available at the time of death. (3) Changes occur in the classification of disease. Changes in the classification of disease have occurred approximately every ten years. Currently, diseases are classified according to the Ninth Revision of the International Classification of Disease. Comparisons of mortality trends over time must consider different disease classification schemes during the particular time period of interest. Failure to adjust for classification changes can produce artificial fluctuations in disease trends. For example, a comparison of mortality rates in 1978 with those in 1979 produced a 32% decrease in bone cancer and a sharp increase in malignant neoplasms of the connective tissue. These changes were entirely artifactual due to disease classification changes (Guinee et al., 1985). (4) Changes may occur in the age distribution of the population of interest. Changes in mortality

patterns may result from an aging population which would be expected to have different mortality characteristics than a younger population. Thus, stroke would be a more prominent cause of death in an elderly population while accidental deaths would be a more prominent cause in younger populations. (5) Changes may occur in survivorship attributable to improved treatment. Advances in the treatment of some diseases (e.g., cancer, heart disease) may prolong the life of some individuals and increase the chance of dying from other causes. For example, five year survival rates for acute lymphocytic leukemia in children less than 15 years of age have increased from 4% in 1960-63 to 56% in 1973-79 (Cancer Rates and Risks, 1985). Mortality data provide information only on those who die of a particular disease, not necessarily on those who have the disease. For example, not all people with cancer will die of cancer; some will die from other causes, such as a heart attack, stroke or car accident.

In general, mortality data are useful for formulating hypotheses about disease etiology rather than testing etiologic associations. They appear to be useful indicators of disease among those dying under the age of 65 (Moriyama et al., 1958) but are inconsistent predictors in older individuals where the influences of numerous conditions complicate death classification. This is particularly pronounced for a disease such as cancer where physicians tend to report non-specific cancer sites on the death certificate rather than the specific sites identified on the hospital discharge reports (Percy et al., 1981). However, many epidemiologists including Doll and Peto (1981) conclude that mortality data after 1950 are useful indicators of cancer trends. They contend that many people who died of cancer in the past (prior to 1950) never had their disease diagnosed or were certified as dying from another, more immediate cause. This has improved in recent decades such that, for most types of cancer, the

mortality trends since the 1950's reflect a reasonably accurate estimate of disease incidence rates. In addition, mortality data are readily available and inexpensive to use; however, costs increase with attempts to verify cause of death with information recorded in the medical records.

MORBIDITY DATA AS A HEALTH MEASURE

Morbidity is a measure of the frequency of illness within a population. Many institutions and programs may serve as sources of morbidity data including hospitals, clinics, and disease registries. The utility of these data depends upon the definition of disease and, more importantly, the composition of the population that served as the information source (Lilienfeld and Lilienfeld, 1980). For example, people admitted to a university hospital are demographically (e.g., age, race, sex) and medically different from those attending a neighborhood clinic.

The occurrence of disease in a population may vary considerably depending upon disease definition. Consider, for example, the definition and classification of birth defects. In general, these are relatively rare events with very poor mechanisms in place for monitoring changes in incidence. Only the most obvious (e.g., cleft palate, hip dysplasia) are identified at birth while subtle defects (e.g., cognitive function, heart anomalies) may not be identified until later in the child's life. Other factors such as variability of physician diagnoses and access to medical care may have a substantial impact on the identification and subsequent outcome of these events. Lumping all events into one category called birth defects does little in the way of identifying cause-specific associations. For example, gestational fever during the first trimester of pregnancy has been associated with neural tube defects but has not been associated with

Downs Syndrome or cleft palate. Thus, evaluating the effect of gestational fever on birth defects in general may miss a true association with neural tube defects (Bracken, 1984). In addition, disease patterns in select populations (e.g., hospitals) may be strongly associated with factors (e.g., socioeconomic status, physician referral patterns) independent of the exposure of interest such that extrapolation of findings to the general community is questionable. Berkson suggested the frequency of disease in a group of patients who have entered the hospital is biased when compared to the whole population (Berkson, 1946). He argued that the identification of risk factors for a particular disease can be strongly influenced by differential rates of hospitalization. Individuals with more than one disease have higher probabilities of hospitalization compared to those with a single disease. This may influence the distribution of risk factors and generate artifactual associations. This potential source of bias is not just of academic interest since it can completely distort the apparent natural history of a disease. An empirical demonstration of this bias was reported by Roberts and colleagues (1978).

There are two basic measures of morbidity -- disease prevalence and disease incidence. Prevalence is defined as the number of individuals with disease in a population divided by the total number of individuals in the population. Prevalence may be measured at a particular point in time or over a period of time. An increase in disease prevalence does not necessarily reflect an increase in disease risk; it may also result from such factors as better access to medical care or greater levels of patient awareness regarding health care (Lilienfeld and Lilienfeld, 1980). As a result, prevalence data may generate an inaccurate exposure/disease relationship distorted by the premature death of some cases and the extended survival of others through more effective treatment.

Incidence is defined as the number of new cases of disease occurring in a population during a specified time period divided by the number of persons at risk for developing the disease during that period of time. It provides an estimate of the probability of disease in relation to suspect etiologic agents and is a direct measure of disease risk. The use of prevalent cases may generate inaccurate risk estimates by failing to identify fatal or short episodes of disease (Sackett, 1979). Information gathered from prevalent cases (survivors) may be substantially different from information collected on those with fatal or short disease episodes. For this reason, incidence is preferable to prevalence for the identification and quantification of etiologic risk factors. However, incidence data are not usually available and they are expensive to collect. When available, they are restricted to specific health outcomes (e.g., cancer) and represent ill-defined geographic areas (e.g., hospital tumor registries).

Like mortality data, morbidity data are subject to changes in disease diagnoses and classification. It is often necessary to evaluate disease retrospectively to obtain a sufficient number of observations and identify changes which may have occurred. There are mechanisms in place such as the various revisions of the International Classification of Diseases which facilitate the evaluation of morbidity over time but this increases costs and complicates the interpretation of disease trends. In addition, cause-specific morbidity rate comparisions can yield "significant" results on the basis of chance alone if a large number of comparisons are made. Associations must be evaluated in terms of biologic plausibility and other criteria (as previously discussed) to avoid misinterpretation.

In summary, mortality data are readily available and inexpensive to use. They are useful for formulating disease hypotheses but are inadequate for testing etiologic associations. Two forms of morbidity data are commonly used in epidemiologic studies: (1) prevalence data, and (2) incidence data. Prevalence data are useful for program planning and are usually readily available. However, they are often inadequate for the evaluation of causal mechanisms of disease since selection and survivorship bias may mask etiologic associations. Incidence data are useful for testing causal relationships and are preferred for the identification and quantification of disease risk. However, they are usually unavailable and expensive to collect.

EPIDEMIOLOGIC METHODS APPLIED TO STUDIES OF DRINKING WATER

Introduction

Two types of carcinogenic hazards have been identified by Doll as being socially unacceptable: (1) iatrogenic hazards (those associated with medical treatment) particularly prescription pharmaceuticals (e.g., diethylstillbesterol (DES) and (2) occupational hazards (e.g., vinyl chloride or asbestos) (Doll, 1977). The public concern following incidents at Love Canal, Times Beach and Three Mile Island suggests that certain environmental hazards are also socially unacceptable.

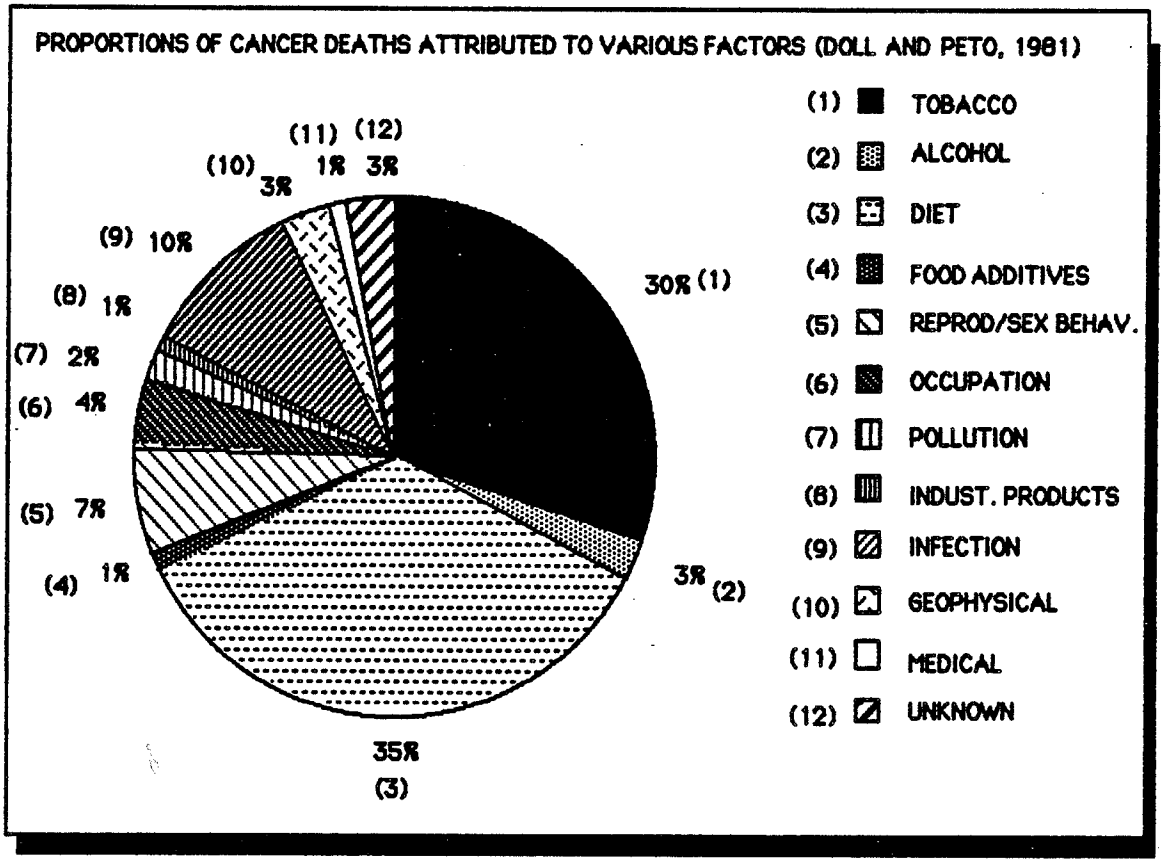
Continuing efforts to evaluate the impact of environmental contamination on human health have suffered from differing definitions of "environment." In 1964, the World Health Organization (WHO) estimated that as much as 75% of human cancers are influenced by "environmental factors." This statement has been misinterpreted by many people including some scientists to mean that malignancies are caused by man-made chemicals

entering the environment as by-products of manufacturing processes and inadequate waste disposal techniques. For example, in a special report, Bingham (1976), states that "as many as 90% of all cancers may be caused by environmental factors - a substantial portion of which are chemicals...". However, the WHO's definition of "environmental factors" included both natural and manmade carcinogens, viral infections, dietary deficiencies or excesses, reproductive abnormalities and a variety of other factors associated with personal behavior (Doll and Peto, 1981). In essence, "environmental" referred to any influence other than that of the genetic material inherited from an individual's parents (Maclure and MacMahon, 1980).

Several authors have attempted to refine the definition of "environment" to more accurately indicate its impact on disease. Higginson (1976) divided the term into two categories: (1) the macroenvironment (i.e., air, water, and general food supplies), characterized as those environmental factors beyond the individual's control (i.e., control is the responsibility of government); and (2) the microenvironment, which refers to the personal environment created by the individual. It includes cultural habits (e.g., diet, smoking, alcohol, sexual practices) and occupation. He proposed that 40% of human cancers are attributable to the cultural environment, 12-15% to iatrogenic hazards (e.g., prescription pharmaceuticals), 1-3% to occupation and 1% to hereditary factors. The remaining 40% of human cancers are idiopathic in nature (unknown cause) and are directly or indirectly related to the environment. Saracci (1978) defined environment as those material and social factors over which the individual has no direct control. Maclure and MacMahon (1980) identified two basic categories of environmental agents: (1) consumables, exposure to which is deliberate and (2) contaminants, exposure to which is inadvertant.

Another estimate of the proportions of all cancer deaths that are attributable to various factors is summarized below (Doll and Peto, 1981). It should be noted that these estimates have a large uncertainty and are intended to apply to the U.S. population in general. In particular subgroups of the population, these estimates would differ.

Figure 1-1



In this report, environment will be divided into three classes:

(1) the personal environment, characterized by those exposures which are controlled by individual choice (e.g., diet, smoking, alcohol);

(2) the occupational environment, characterized by those exposures over which the individual has indirect control (i.e., largely dependent upon industrial and local governmental policies); and

(3) the ambient environment, characterized by those exposures over which the individual has minimal control (e.g., contaminated air, water, land).

Attention will focus on the potential health effects associated with ambient environmental exposures, particularly as they relate to drinking water. The following section presents a brief literature review of the reported observations of drinking water and health. The primary purpose of this review is not to offer conclusions regarding the health impacts of drinking water or environmental contaminants, but to provide examples of the various types of studies which have attempted to address the potential health effects of contaminated drinking water.

Ecologic Studies

The single most crucial criterion for the conduct of environmental epidemiologic studies is a valid measure or index of individual exposure to the environmental agent of concern. Maclure and MacMahon (1980) have noted that epidemiology has failed to produce conclusive results regarding health effects of environmental contamination largely due to the operational definitions of exposure. For example, the county of residence is often used as a surrogate measure of "exposure". Such a scheme presupposes that this classification correlates with the quantities of contaminants available to communities and further assumes that community exposures correlate with those of the individual. The major problem with such an analytical scheme is the extrapolation of aggregate or group health observations to causal inferences of individual health, and is referred to as the "ecologic fallacy" (Morgenstern, 1982). For example, assume

"community A" has a higher mortality rate from bladder cancer than community B. Further assume community A utilizes surface waters for its public water supply whereas community B utilizes groundwater. This comparison might suggest that water source may be associated with bladder cancer. However, community A may differ from community B in a wide variety of factors such as socioeconomic status, demographic structure, or predominant industries. Thus, the association between bladder cancer and type of water supply may be explained by other factors.

In such ecologic-type studies, no information on individual risk factors (e.g. smoking, occupation) known to be associated with the disease(s) under study (e.g., bladder cancer) is evaluated. Another important factor not usually addressed in these studies is population mobility. This is a significant factor in contaminant-related cancer studies due to the long latency period between exposure and disease onset. Polissar (1980) demonstrated that the effect of migration on cancer incidence is a function of the latent period, cancer site, and the size and type of the geographic unit (e.g., city, county, state). As the size of the geographic unit decreases and the latency of cancer increases the accuracy of risk estimates decreases. Risk estimates of cancers which primarily affect young people are particularly susceptible to the effects of migration since younger people are much more likely to move; the result is to diminish any excess risk attributable to an exposure.

Several authors have explored the health effects of contaminants using a surface/ground water source dichotomy as an exposure index; the assumption is that surface waters contain more carcinogens than groundwater, and this difference may result in differences in cancer mortality rates. Page and colleagues (1976) examined site-specific cancer mortality data for Louisiana parishes that received their drinking water

from the Mississippi River. They demonstrated increased rates for cancers overall and for cancers of the gastrointestinal and urinary organs for various sex- and race-specific categories. The exact meaning of these findings is unclear since "related cancer sites were grouped" creating statistically significant associations with a cancer category containing several biologically distinct cancer sites. No relationships were found for site-specific categories suggesting that factors other than water may explain differences.

Cancer mortality in Ohio counties with surface water supplies was compared to those counties with ground water supplies. Rates for stomach, bladder and all cancers were higher for white males in those counties served by surface water. Rates for females were elevated for stomach cancer only. Since the overall rate of stomach cancer mortality is declining in the United States and may be asssociated with factors unaccounted for in this analysis, the significant correlation with surface water is biologically questionable (Kuzma et al., 1977). A similar study in St. Louis city and county reported an inverse association between surface water and cancer mortality. The population served by presumably less polluted water had a higher cancer mortality rate than that using the more polluted source. In addition, no differences were found in finished water mutagenicity as measured by the Ames test, suggesting that other factors may contribute to the high rates of cancer mortality in St. Louis city (Marienfeld et al., 1980).

Beresford (1981) examined the relationship between re-use of water and cancer mortality in 29 boroughs and districts in the London area. Parameters of re-use include concentrations of nitrates, chloride, phosphates and total nitrogen which were set to zero for groundwater

sources. No association between high levels of water re-use (i.e., surface waters) and cancers of the gastrointestinal and urinary tract was found when socioeconomic differences and variations in population size were taken into account.

The quality of water supply as measured by such parameters as asbestos or trihalomethane (THM) concentrations and their association with cancer mortality have been examined in several studies. The major limitation is the extrapolation of current measures of water quality to estimate historical quality. Data on contaminant levels, especially the organics, are only recently available (approximately 1975), and the use of current measurements to reflect previous levels is not appropriate and may lead to substantial misclassification error. Burton and Cornhill (1977) used general measures of water quality (e.g., conductivity, hardness, total dissolved solids) for which historical data are readily available and reported an inverse association between conductivity and cancer death rates. The reduction in cancer death rates in those cities with high conductivity measurements appears to be non-specific, making the biologic interpretation of the results most difficult. The authors speculate these parameters may influence acid/base balances in the body and subsequent cancer induction.

Cancer mortality in twenty-two Quebec municipalities was examined to determine possible health effects of asbestos exposure via water supplies. An excess of male stomach and lung and female pancreatic cancer mortality was reported in those communities with high concentrations of asbestos. However, no consistent trends were observed across exposure categories (i.e., high, possibly high, probably low) suggesting that misclassififcation may have attenuated any significant associations. Despite these findings the author concludes that observed excesses were

most likely explained by occupational differences since the percentage of the population employed in asbestos mining and quarrying was significantly higher among the community classified as having the highest exposure (Wigle, 1977).

Water samples from the city of Duluth contained trace amounts of asbestos-like fibers as early as 1939, prompting scientists to examine cancer incidence trends for potential adverse health effects. Duluth incidence rates from 1969-1980 were evaluated and compared to those from the Third National Cancer Survey (TNCS) and the State of Iowa. Significant differences for cancers of the peritoneum in both males and females were reported; however, rates were based on very small numbers (Sigurdson, 1983).

Several drinking water supplies serving the San Francisco Bay Area come from reservoirs that are contaminated with naturally occurring asbestos. This prompted a number of investigators to examine the possible association between cancer incidence and asbestos concentrations in the supply under the assumption that asbestos levels in 1978 reflect those over the past forty years. Census tracts with high exposure to asbestos were reported to have a higher incidence of various site-specific gastrointestinal cancers. Numerous rate comparisons were made in these studies, increasing the probability of finding a "statistically significant" difference by chance alone. However, consistent associations in both sexes for several sites (i.e., stomach, esophagus, pancreas) as well as a positive dose response suggest a potential relationship (Kanarek et al., 1980; Conforti et al., 1981). A similar study in the Puget Sound area, where asbestos also occurs naturally in the river watersheds, reported an increased cancer incidence in both sexes for the small

intestine in those areas with high asbestos concentrations. Since 332 comparisons were made, approximately 16 significant findings would be expected by chance alone. Therefore, chance is a likely explanation of this relationship (Polissar et al., 1982). To date, results of ecologic studies on asbestos exposure via drinking water are inconsistent and provide little evidence of an increased cancer risk (NAS, 1984a).

No association between the use of asbestos-cement pipe for carrying drinking water and deaths due to gastrointestinal, bladder, liver, lung and other cancers was reported in a study of Escambia County, Florida (Millette et al., 1983). There is some question, however, as to whether the number of cancer deaths in this study was sufficiently large. Inadequate sample size would decrease the probability or "power" of the study to detect an association if an association actually existed.

Cantor and his associates (1978) reported an association between bladder cancer mortality and trihalomethane (THM), a by-product of chlorination, in both sexes after controlling for social class, ethnicity, urbanicity and industrialization. Evidence of a dose-response relationship was observed providing further support for a real association.

Fluoride has been a controversial additive to public water supplies despite substantial evidence that it significantly reduces dental caries. The controversy stems in part from ecologic evidence claiming an association between fluoride and increased cancer mortality (Yiamouyiannis and Burk, 1977). Subsequent ecologic studies have not supported these findings (Cook-Mozaffari et al., 1981; Cook-Mozaffari and Doll, 1981; Kinlen and Doll, 1981; Chilvers, 1983). The major difference between these studies and those previously discussed is that mortality trends may be examined before and after the artificial introduction of fluoride to water supplies. Such analyses are impossible when the dates and concentrations

of contamination are unknown. The latter situation is frequently the norm in most community health studies of contaminated drinking water supplies.

The use of incidence data in ecologic studies is an improvement in study methodology in that survivorship bias associated with the use of prevalent cases is eliminated. The surface/ground water exposure dichotomy was used by Bean and colleagues (1982a) to identify potential differences in cancer incidence among Iowa municipalities. They reported a positive association between surface water use and increased incidence for cancers of the lung and rectum in both males and females. Of particular interest was the finding that the incidence rates decreased as well depth increased, suggesting that shallow wells may carry the same health risks as surface water. In a follow-up report using the same incidence data, historical measures of radioactivity were found to be associated with increases in lung and bladder cancer in males and breast and lung cancer in females (Bean et al., 1982b).

Beresford (1983) reported a positive association between the percentage of domestic sewage effluent in the water supply and the incidence of stomach and urinary cancer. These associations were reduced when social factors and borough size were taken into account. In addition, the incidence of stomach cancer has been decreasing while the re-use of polluted waters has been increasing suggesting the relationship, if any, is inconsequential.

An investigation by Carlo and Mettlin (1980) considered the possible relationship between cancer incidence rates and THM concentrations and reported a positive association for pancreatic cancer in white males only. They concluded this to be a spurious association since no correlations were found in other sex- or race-specific groups.

Zemla (1980) found a positive association between stomach cancer incidence and nitrate concentrations for males but the association was less clear for females. Water hardness was inversely associated with stomach cancer incidence.

Stomach cancer incidence was slightly higher in both males and females in the town of Aalborg, Denmark, where nitrate concentrations in the drinking water have been elevated for decades. Measurements of contaminant concentrations for extended periods of time provide better evidence for a true biologic relationship; however, the decline in stomach cancer incidence suggests that factors other than nitrate in drinking water may be more significant in its etiology (Jensen, 1982).

Thouez et al. (1981) explored the relationship between physicochemical water quality measures and cancer incidence in Quebec. A positive association was reported for several soft water parameters (e.g., nitrates, sodium) and the incidence of neoplasms of the rectum, prostate and other organs of the digestive system. No dose-response relationships were reported. In addition, the registry from which incidence cases were obtained is voluntary and verification of the reporting process indicated substantial underdeclaration (36%) for cancers of the intestine and rectum.

CASE-CONTROL STUDIES WITHOUT PERSONAL INTERVIEW

The basic method of the case-control study involves the comparison of patients (cases) with a group of controls who are free of the disease under study (Schlesselman, 1982). Information on past exposures and risk factors known to be associated with the disease in question is obtained from both cases and controls. Exposure frequencies of cases and controls are compared to determine if there is an excess of a particular exposure among the cases. The intent is to identify factors that differ between the groups and which may help to explain the occurrence of disease among the cases. This method provides an estimate of disease risk when the disease under study is rare and where exposure to the putative agent is common or accounts for a large proportion of the disease. It is a relatively quick and inexpensive way to test etiologic hypotheses. Despite the improved methodologic technique, the majority of case-control studies involving drinking water to date have used mortality data as the measure of health. Case-control studies based on mortality often suffer from a lack of information regarding three inter-related factors (1) population mobility, (2) length of exposure, and (3) latency period of site-specific cancers. In addition, these studies usually fail to account for the effects of extraneous variables (e.g., smoking, dietary practices) known to be associated with many cancers. Incidence data are, therefore, preferable to mortality data in a case-control study.

In a follow-up to the ecologic studies performed in Louisiana, Gottlieb et al. (1981) conducted a case-control study to further explore the relationship between drinking surface water and colon or rectal cancer mortality. Each colorectal cancer death was age-, sex- and race-matched to a non-cancer death within the same parish. A lifetime gradient of surface

water use (i.e., mostly surface, some surface, probable surface, least surface) was constructed based primarily on residence at birth and death for each study subject. A significant relationship between rectal cancer mortality and surface water consumption was reported which demonstrated an increasing risk with increasing proportion of surface water consumption. However, no information on the individual risk factors for disease, other than those available on the death certificate, was evaluated. No relationship was found for colon cancer mortality. A subsequent case-control study confirmed the association for rectal cancer mortality and suggested a possible association for breast cancer in white females (Gottlieb et al., 1982).

Several investigations have examined the health effects of water chlorination using THM concentrations or chlorine dosage as the index of exposure. Young et al. (1981) reported site-specific cancer mortality rates for white females using historical measures of chlorine usage to differentiate exposure status. Risk of cancer death was determined for those with high, medium, low and no chlorine-dosed water. Only colon cancer demonstrated a statistically significant association (although, due to multiple comparisons, this finding could be expected by chance alone). In addition, no consistent dose-response relationship was reported for any site nor were individual risk factors evaluated. Misclassification may have a serious impact in this study since exposure indices were based solely upon residence at death. To control for the effects of migration, analyses were restricted to those communities with the most stability, yet individual migration, especially among cases, may differ from that of the population as a whole (Kanarek and Young, 1982).

Lawrence et al. (1984) evaluated the relationship between chloroform concentrations and colorectal cancer deaths in white, female school

teachers. To reduce misclassification due to case mobility, cumulative chloroform exposure was estimated using historical records from water treatment facilities serving the homes and work addresses of study subjects 20 years prior to death. Cancer deaths were matched on age and year of death to non-cancer deaths. No evidence of an association between chloroform and colorectal cancer mortality was found.

A case-control study of gastrointestinal and urinary tract cancer mortality was conducted in Illinois to determine associations with groundwater chlorination practices. Both cases and controls were classified according to residence in chlorinated or non-chlorinated groundwater communities and controls were selected from a pool of non-cancer deaths. Females residing in urban communities demonstrated statistically significant differences in mortality while similar findings were not observed for males. Only the combined sites of large intestine and rectum were elevated. Despite the significance, excess risk was relatively small (approximately 19%) and no provisions were made for population mobility or control of extraneous factors (i.e., diet). It should be noted that the practice of water chlorination has been increasing while the incidence of those sites implicated in these studies (i.e., stomach, rectum, etc.) has been decreasing (Brenniman et al., 1978).

A similar study, (Alavanja et al. 1978) evaluated all gastrointestinal and urinary tract cancer deaths in seven New York state counties. Exposure to chlorinated vs. non-chlorinated water was determined using water chlorination maps. Cases and controls were matched on age, race, sex and county of usual residence. Living in a chlorinated water area was significantly associated with excess gastrointestinal and urinary tract mortality. This finding was due to an excess of all site specific cancers

in males. The only site significantly elevated for both males and females was stomach.

The use of cancer data to examine potential health effects of environmental contaminants in drinking water is particularly difficult due to the long latency periods (10-30+ years) for many types of cancer. Elwood and Coldman (1981) conducted a case-control study using infant mortality from anencephalus as the health outcome of interest. Only those localities for which water composition data were available were included in the study. The bias introduced from this exclusion is unknown. Univariate analysis indicated a positive association between anencephalus mortality and selenium, chromium and silver concentrations while a negative association was observed for mercury. In the logistic regression model the strongest associations were found for variables representing maternal factors (e.g, legitimacy, number of live births, stillbirths and child deaths). No significant residual associations between case or control status was found for any mineral.

CASE-CONTROL STUDIES WITH PERSONAL INTERVIEW

Despite the case-control format of the studies described above, no information was collected regarding individual confounders. Ecologic adjustments were made using population characteristics (e.g., census stability, urbanicity, industrialization, socioeconomic status) or the study was sex, race or occupation specific. The use of interview data in a case-control study facilitates control of the confounding effects of risk factors known to be associated with a disease. Newly diagnosed cancer cases may be interviewed to determine dietary patterns, smoking histories, water consumption practices and other factors known to be associated with

disease etiology. Thus, the effects of contaminant exposure may be estimated independent of other risk factors.

A case-control study of hospital-based incident cancer cases was conducted by Cuello et al. (1976) to determine geographic variation in stomach cancer risk. Patients were interviewed to obtain information on birthplace, current residence and history of use of water supplies. Samples of water were collected from several sources including wells, streams and aqueducts; the principal contaminant of interest was the naturally occurring levels of nitrates. Prevalence of intestinal metaplasia and chronic atrophic gastritis was determined by gastroscopic examination of individuals attending local medical centers. Samples of urine and saliva were obtained cross-sectionally to determine excreted levels of nitrates. Results indicated a positive association between geographic areas with high nitrate levels and gastric cancer risk, prevalence of intestinal metaplasia and chronic atrophic gastritis and urinary excretion of nitrates. The authors caution that water may be only one source of the nitrates in this area and the consumption of locally grown foods may also be a significant factor. Nevertheless, the consistent correlation between nitrates and various indicators of gastric insult support a causal association.

Polissar et al. (1984) conducted a case-control, interview-based study of cancer risk resulting from exposure to natually occurring asbestos in drinking water supplies. Estimates of asbestos exposure were based upon residence and work histories as well as individual water consumption practices. Incident cancer cases were ascertained through a population-based tumor registry and controls were selected from the same census tract. The study was restricted to those census tracts with lower than average

migration rates. The interview included questions on demographics, smoking and dietary histories, residence, occupation, alcohol consumption, education, religion, ethnicity, family history of cancer and sources and dates of water usage. No evidence of a significant excess cancer risk was reported and those sites which were elevated (i.e., male stomach and pharynx) suffered from very small numbers. The authors suggested that enormous sample sizes would be required to determine the relatively low risks associated with exposure to enviromental levels of asbestos in water.

The possible association between nitrates in drinking water and congenital malformations was investigated in a case-control study by Dorsch et al. (1984). Congenital malformations were defined as structural defects present at birth. Children with defects were individually matched to controls by hospital, maternal age, parity and date of birth. Exposure was based upon nitrate concentration at the current residence of the mother. Results suggested that consumption of contaminated water was associated with an increased risk of congenital malformations, especially neural tube defects. A positive dose-response relationship was evident; however, the number of cases and controls for specific categories of malformations may have been insufficient for meaningful conclusions.

COHORT STUDIES

In a cohort study, individuals, who are initially free of disease are selected for observation and followed over time. In most instances selection of the study cohort is such that individuals can be distinguished on the basis of some particular exposure(s) of interest. Cohort studies are further distinguished on the basis of the time at which the investigation begins. A concurrent cohort study involves the study of

individuals where the disease outcomes have not yet occurred. Biases associated with subjective recall of an event in a case-control format are minimized in a concurrent cohort study since information on exposure is collected prior to disease occurrence. A non-concurrent cohort study involves the study of individuals where disease outcomes have already occurred. Non-concurrent cohorts are usually constructed from historical records and do not require extensive periods of observation for health events to occur (Schlesselman, 1982). They utilize historical information on exposure and disease occurrence and compare rates of disease between the exposed cohort members and the non-exposed cohort (or the general population). This method assumes that, in the absence of a specific exposure, the study group would have the same probability of disease as the general population following adjustment for obvious differences in ethnicity, socioeconomic status and other variables which may influence disease rates among populations. However, the use of historical information to identify both the study cohort and exposure status could result in an incomplete cohort as well as misclassification of exposure status. For example, the records of certain occupational subgroups may be missing due to fire, loss or inadequate storage space and subsequent destruction. The exposure and/or disease histories of these subgroups may be completely different from those whose records were included in the study.

The cohort approach is applicable in instances where there has been heavy exposure in a defined population. It has been especially useful assessing risk in occupational environments or iatrogenic hazards (e.g., prescription pharmaceuticals). The major advantage to a cohort study is the capacity to calculate risk attributable to an exposure. In addition,

cohort studies provide the basis for studying multiple health outcomes and their relation to exposure.

Only one study has used this method to investigate the hypothesized relationship between cancer risk and the by-products of water chlorination. Source of drinking water at home was ascertained for each Washington county (Maryland) resident in a 1963 census. Additional information included demographics, smoking histories, education and religion. Incident cancers in the county were ascertained for the period July 1963 through July 1975. Three drinking water cohorts were developed to reflect the degree of exposure to trihalomethane based on a surface/ground water dichotomy with intermediate exposure a combination of both sources. Rates for cancer of the bladder and cancer of the liver among females were highest among persons using the chlorinated supplies; however, adjustment for the effects of variables (i.e., smoking) reduced the relative risk to less than two. There was an increasing rate with increasing duration of residence; however, this pattern was inconsistent. The findings provide little evidence of an association between chlorinated drinking water and cancer risk (Wilkins and Comstock, 1981).

STATE REPORTS

Health agencies in several states have investigated the potential health effects of contaminated drinking water. These investigations were stimulated, in part, by public concern over indiscriminant waste disposal practices and general environmental pollution. The majority of reports are cross-sectional or prevalence studies involving surveys of relatively small numbers of subjects. Cross-sectional studies are based on information collected at a particular point or period in time and include both

prevalent and incident cases of disease. The strength of a cross-sectional study is in its ease of conduct; the limitation is the effect of survivorship. Information obtained from prevalent cases of disease may not accurately reflect the true exposure/disease relationship since the exposure experience may differ between survivors and non-survivors.

Several other state reports are ecologic in design. For the most part, exposure indices are determined on the basis of proximity to the source of contamination. A variety of health endpoints have been used such as headaches, eye and skin irritations and many other self-reported symptoms and illnesses.

A large number of state studies have been undertaken in New Jersey. Concern over environmental contamination is not surprising since 95 of the EPA's National Priorities List of hazardous waste sites are found in New Jersey.

In general, data from a health survey of a population living near an area with suspected or proven ground water contamination were compared to similar data from a population residing in an uncontaminated area. Sample sizes were small and response rates were poor. Overall, the exposed population had more medical complaints than the unexposed population. It is not known whether these reported differences are attributable to exposure or in some cases whether exposure to any contaminant ever occurred. No differences were observed in the frequency of chronic health problems or adverse reproductive outcomes; however, the sample size and study design were such that even if an effect were present, it would not likely be found. The authors conclude that concern over contaminated water supplies may produce more health effects than the actual contamination itself (New Jersey, 1983a).

A similar survey was conducted in Jackson Township motivated in part by a class action lawsuit by the Concerned Citizen's Committee. Exposure estimates were largely ecologic, based on geologic data with no information on individual exposures. The frequency of a variety of medical symptoms was reported for the exposed community. Of the ten categories of skin complaints only "blisters" was statistically elevated among residents in the area presumed to be more highly contaminated. No differences were observed for systemic diseases or adverse reproductive outcomes. Although hospitalizations increased with years of well water use, this pattern was not apparent in the presumed high exposure area (New Jersey, 1983b).

At the request of the Hillsborough Township Health Department a survey of twelve households was initiated to gather information on symptoms and medical problems resulting from proximity to a dumpsite. A questionnaire was also administered to a control population living several miles from the landfill. In general, people living near the landfill reported more symptoms; however, significant differences were found for "tiredness" in females only. No differences in the frequency of medical problems or pregnancy problems were reported. Small numbers preclude meaningful interpretation of any of these results (New Jersey, 1984a).

Efforts to correlate environmental levels of benzene with urinary phenol, a metabolite of benzene, were attempted in a study of 153 residents of Pomona Oaks. Individuals were selected for study on the basis of water sampling data indicating benzene contamination. No evidence of a relationship was found. The frequency of skin rashes and complaints of poor water taste and smell were reported but no comparable populations were sampled (New Jersey, 1984b).

In Michigan, an investigation into reported health effects stemming from contaminated water in Saginaw county was conducted by the Michigan

Department of Health. An increased number of health complaints was noted for those with the greatest exposure potential to contaminated water. Complaints were non-specific and included skin rashes, numbness, arthritis, pains in arms, legs and lower back, dizziness, visual problems, nausea, injuries, thyroid problems and strokes. Surprisingly, no evidence of contamination in the water supplies was ever discovered and the difference in health complaints may be entirely attributable to the perception of contamination (Michigan, 1979).

A clinical study of individuals exposed to arsenic in drinking water was conducted in a mobile home court in Huron County, Michigan. Three indices of arsenic exposure were used including arsenic levels in the drinking water, arsenic levels and the amount of drinking water consumed and analysis of 24-hour urinary arsenic excretion. Reported cases of shingles were related in a dose-response manner to arsenic excretion; however, the small size of the study sample limited subgroup analysis. No information was available on the source of arsenic contamination (Williams and Lock, 1982).

Carbon tetrachloride (CCl_4) contamination was documented in groundwater adjacent to a Tennessee hazardous waste disposal site. A cross-sectional survey of 118 residents divided into exposure groups based upon CCl_4 concentrations in their water supplies indicated that those highly exposed had borderline liver enlargement. The health implications of liver enlargement are unknown but suggest potential adverse effects from CCl_4 exposure. A subsequent survey reported an unusually high frequency of nondescript medical symptoms ranging from headaches to sore eyes (Harris et al., 1979). No control population was sampled so the authors' conclusion that these symptoms were attributable to exposure to contaminated groundwater is difficult to evaluate.

Stimulated by a request by the local Waterford Village board members, the New York Department of Health conducted an ecologic study of cancer incidence. Residents were concerned about perceived excesses of cancer and the general state of the environment, especially the safety of the Hudson River as a drinking water source. Analysis of water supplies revealed no evidence of contamination. Overall cancer incidence was the same in Waterford Village as in other minor civil divisions in New York state. However, excesses were observed for cancer of the ovary, lymphoma in young men and pancreas in older men (New York, 1983). With the exception of pancreas, these sites have not been implicated with contaminated drinking water.

Trichloroethylene (TCE) contamination of drinking water in Montgomery and Bucks counties, Pennsylvania, prompted the Pennsylvania Health Department to examine mortality patterns of local residents during the period 1960-1978. Of particular interest were the deaths due to liver cancer. No statistically significant differences in liver cancer mortality were found for these two counties compared to the rest of Pennsylvania. Although some residents had measurable levels of TCE, none had observable health effects (CDC, 1980).

In response to citizens' concern over trichloroethane (TCA) contamination of the groundwater, pregnancy outcomes in Santa Clara County were evaluated by the California Health Department. The initial interview study did not have sufficient numbers to detect a 10-fold increase in major cardiac malformations in the exposed population so the study was modified to evaluate cardiac defects in a seven census tract area, which included the exposed census tract. Cardiac defect rates in these tracts were then compared to the rest of the county. The authors conclude that rates in

Santa Clara County were similar to rates reported elsewhere while those in the study area were higher than expected. Of interest was the fact that 75% of the cases within the study area came from non-contaminated census tracts (California, 1985). Thus, the association between excess cardiac defects and TCA exposure is questionable (California, 1985).

In Massachusetts, the discovery of organic chemicals in the drinking water wells of the city of Woburn and a perceived excess of childhood leukemia in local residents, prompted the State Health Department to conduct an investigation into the health status of Woburn's residents. Four disease endpoints were examined. The incidence of childhood leukemia and renal cancer was significantly higher than expected whereas the incidence of liver and bladder cancer was not significantly elevated. Results of a case-control interview study of childhood leukemia failed to identify any significant risk factors associated with this excess. Small numbers preclude any meaningful interpretation of these results. The authors concluded that information gathered to date failed to provide any evidence of an association between environmental contaminants and either childhood leukemia or renal cancer (Parker and Rosen, 1981).

SUMMARY OF THE LITERATURE

To date, reported studies have provided little evidence of a causal association between drinking water contaminated with non-infectious agents and cancer incidence or other health outcomes. Different methodologies, measures of health and measures of exposure have made it difficult to develop a consensus about these exposures and health outcomes. By far, the most limiting factor in all studies has been imprecise measures of exposure. The assumption that current measures reflect those in the past

is suspect. Thus, neither positive findings nor negative findings should be considered conclusive. The paradox is that negative studies are not always reassuring to the public, while positive studies are frequently alarming.

Ecologic studies are characterized by their ease of conduct and low cost. They are useful for qualitative statements of disease risk but they have serious limitations. Methodologic problems include (1) accounting for long latency periods of disease, (2) evaluating a mobile population, (3) historical extrapolation of contaminant indices, (4) assessing individual risk from population characteristics, and (5) assessing the impact of individual risk factors for disease. Thus, ecologic studies are useful for hypothesis formulation but more rigorous studies are required for testing etiologic associations.

Although case-control studies are methodologically more appropriate for testing etiologic hypotheses, the majority of studies in this area have used ecologic rather than individual measures for determining exposure and to adjust for the confounding effects of risk factors known to be associated with disease. This limits interpretation of their results. Cohort studies are expensive, time consuming and are not commonly used in studies of water contaminants. They are, however, a proven method for quantifying disease risk.

Cross-sectional prevalence surveys appear, for the most part, to be a limited approach. The frequency of non-specific medical complaints based upon small numbers, poor response rates and ill-defined exposures contributes little to the understanding of environmental contaminants on health. Indeed, a likely explanation for many of the differences in cross-sectional studies is the perception of contamination rather than contamination itself, suggesting that efforts directed toward community

education projects may be beneficial. However, this method will continue to be a part of a public health approach to perception of disease in a community for several reasons: (1) such studies are easy and inexpensive to conduct, (2) they provide evidence of an attempt to evaluate a perceived health problem which in and of itself is reassuring to the public, and (3) there are many instances where disease clusters in space and time were reported and specific etiologic agents were identified (e.g., angiosarcoma of the liver and polyvinyl chloride, analine dyes and bladder cancer, diethylstilbesterol and adenocarcinoma of the vagina). Although these diseases were subsequently linked to occupational or iatrogenic exposures, they support the concept of investigating reports of disease clusters.

2. OTHER METHODS FOR EVALUATING POTENTIAL HUMAN HEALTH EFFECTS

2. OTHER METHODS FOR EVALUATING POTENTIAL HUMAN HEALTH EFFECTS

Introduction

The role of epidemiology in modern society is the determination of the etiologies of various diseases of public health concern (Lilienfeld and Lilienfeld, 1980). It is generally recognized that epidemiologic studies provide the only direct evidence of human risk from environmental agents. In many instances, unfortunately, epidemiologic data for evaluating potential environmental carcinogens are either not available or are inadequate. As described in Section 1, difficulties in conducting epidemiologic studies of environmental exposures include such factors as the long latency periods for most cancers, the lack of information regarding exposures that occurred many years or decades earlier, the small size of exposed populations, and the existence of multiple risk factors for most cancers. While epidemiology can identify risks that have already occurred, current regulatory philosophy often aims at the prevention of disease in the population. Consequently, the estimation of potential cancer risks and other health risks must usually be made in the absence of epidemiologic data.

Several non-epidemiologic approaches are available for assessing the nature and likelihood of biological effects in humans arising from exposure to potentially hazardous substances or for estimating exposure to such substances. Perhaps the best known procedure is the animal bioassay, in which data from experiments involving high-dose exposures in laboratory animals are used to estimate the magnitude of risk in humans at markedly lower levels of exposure. The basic premise of this approach is that substances that can induce cancer in rodents or other laboratory animals may similarly affect humans. Other approaches being used by other workers

for identifying potential hazards or for determining biological exposures include a variety of short-term tests of mutagenicity in microorganisms, assays for residues of chemicals in body tissues, a variety of clinical measures, chromosome alterations or sister chromatid exchanges in lymphocytes, and chemical bonding to DNA.

These approaches play a significant role in the process referred to as quantitative risk assessment. The procedures, the assumptions, and the uncertainties used in quantitative risk assessment have been reviewed many times from a variety of perspectives (e.g., U.S. Office of Science and Technology Policy, 1984; Brown, 1985; Samuels and Adamson, 1985; Task Force on Risk Assessment, 1985; California, 1984).

The present emphasis on regulating exposure to potentially-carcinogenic substances requires estimation of the magnitude of associated risk, and the determination of a "safe dose" level. These estimates are then used to set priorities for environmental intervention, to focus further research, and for other purposes. The following discussion will provide a brief overview of quantitative risk assessment (or "health risk assessment") in the context of its application to identify and assess potential human cancer risks as a basis for setting regulatory priorities (risk management).

Risk assessment has been defined as:

"...The use of available information to evaluate and estimate exposure to a substance and its consequent adverse health effects. Risk assessment consists of the following four elements:

HAZARD IDENTIFICATION - The qualitative evaluation of available information on a substance's ability to produce toxic effects and the relevance of this information to humans.

EXPOSURE ASSESSMENT - The types (routes and media), magnitudes, and durations of actual anticipated exposures, and doses when known; and, when appropriate, the number of individuals who are likely to be exposed.

DOSE-RESPONSE ASSESSMENT - The process of estimating the relation between the dose of a substance and the incidence of an adverse health effect.

RISK CHARACTERIZATION - The process of estimating the incidence of a health effect under the various conditions of human exposure, including a characterization of the uncertainties involved." (Task Force on Risk Assessment, 1985).

Each of the above components of health risk assessment will be briefly described. This discussion does not provide a comprehensive or a critical review, but serves to highlight some of the steps that are used by federal agencies in assessing health risks.

HAZARD IDENTIFICATION

The demonstration in the 1950s and 1960s of environmental causes of cancer ("environmental" as opposed to "genetic") carried the attendant realization of a need to identify those environmental agents with a potential for producing human cancers and/or to determine the level of exposure for a human being at which they would be "safe" from the carcinogenic effects of that chemical (Schneiderman and Brown, 1978; Mantel and Schneiderman, 1975; National Academy of Sciences, 1980; Schneiderman et al., 1975; Cornfield, 1977; Rowe, 1983). It has been estimated that toxicity information is not available for over three-fourths of the approximately 50,000 compounds in commerical use (NAS, 1984b). Considering the enormous number of chemicals that have been, and

continue to be introduced into the marketplace, methods were needed to quickly identify potential hazards and establish regulatory priorities. The methods had to be low in cost, quick in execution, and technically simple (Tomatis et al., 1982; Mantel and Schneiderman, 1975; Kates, 1977; Schneiderman et al., 1975; Mantel and Bryan, 1961).

A number of different options have become available for testing chemical agents or environmental samples (air, water, soil) for biological activity, toxicity, or mutagencity. In general, the procedures recommended by federal agencies include bacterial mutagenesis assays, chromosomal studies using mammalian cells, and short-term animal toxicity assays involving 90-day exposures. The intent of these tests is simple: to identify the potential toxic effects of the tested material as part of the hazard identification process. The advantages of these systems include control of the experimental variables, possible assessment of complex mixtures, identification of a requirement for metabolic activation of the compound, rapid completion time, and determination of toxic interactions in tests of chemical mixtures. A major disadvantage of these short-term tests includes their possible misinterpretation. At present, these tests cannot be used to determine whether a compound or mixture is carcinogenic in man, or to predict the relative potencies of carcinogens in whole animals (IARC, 1985). Short-term tests should be viewed as one basis for determining if a substance warrants further examination as a health hazard. The main use for testing at this level is the rapid screening of a great number of chemicals or mixtures in order to form priorities in cancer research and to select substances for subsequent animal bioassays.

Hazard identification may also occur through other means, including: clinical reports, epidemiologic observations, comparative metabolism

studies, and data on chemical and physical properties of the substance of interest (Task Force on Risk Assessment, 1985).

EXPOSURE ASSESSMENT

Exposure assessment attempts to characterize the degree to which the population is exposed to a potential hazard. It attempts to estimate such parameters as the sources of exposure, the routes of exposure, the magnitude of exposure, factors that influence exposure, and characteristics of the exposed population. Many procedures are available for estimating exposures (OSTP, 1984). Theoretical or mathematical models may be used to supplement actual environmental measurements (Brown, 1985). Typically, exposure assessments have focused on "external" exposure levels, rather than the biologically effective dose (Task Force on Risk Assessment, 1985). More recently, a variety of biological measures have been proposed or utilized as measures of individual or population exposures. Some of these biological measures are described below.

One approach to estimating exposure is the analysis of biological specimens for the presence of chemicals or evidence of subclinical effects. Tissue sampling has long been used in the occupational setting as a means of monitoring workers' exposure to chemicals. Baseline levels of chemicals or biological effects of interest can be established in the worker prior to any occupational exposure, making it easier to detect changes in levels and the contribution job exposure may have made to these. Such information is usually missing or difficult to obtain in the general population. Workers are often aware of the identities of the chemicals to which they are exposed and they are usually exposed to higher levels than are found in the general environment. Finally, workers are more easily

ascertained as a group and may be more amenable to personal sampling than the general population (Sorsa et al., 1982).

One possible means of judging exposure objectively is to measure the amounts of the chemicals of interest or their metabolites in body tissues and fluids. For example, urinary excretion of the trichloroethylene metabolites, trichloroacetic acid and trichlorethanol, has been shown to be a useful index of exposure to trichlorethylene in the workplace (Doull et al., 1980). However, it is often difficult to relate their presence to a specific exposure source unless the exposure level was very high.

Once exposed to the chemical the body may react to it, affecting the fate of the chemical in the body. Important factors influencing the fate are the metabolism and tissue distribution. Some chemicals are rapidly metabolized and excreted by the body. Therefore, it is not practical to look for them except in instances of relatively recent or ongoing exposure, when they may be detected in body fluids such as blood and urine. Other chemicals are fat soluble, and they and their metabolites tend to accumulate in adipose tissue; they can also be found in the lipid portion of milk and serum. High concentrations of a variety of chemicals can be found in the liver and kidneys, possibly as a result of the role of these organs in eliminating toxicants from the body. Chemical residues sequestered in tissues such as bone and fat may remain for a long time, providing a continuous source of internal exposure after external exposure has ceased (Berlin et al., 1979; Doull et al., 1980; Murphy et al., 1983).

The rate at which the body is able to metabolize these chemicals is affected by many factors, including age, sex, and nutritional and

health status. Some chemicals (such as PAHs) may cause induction of the liver enzyme systems involved in their own metabolism, increasing the rate at which they and other chemicals undergo biotransformation (Doull et al., 1980).

In order to determine if tissue analysis for chemicals and their metabolites is warranted, the time since last exposure must be taken into consideration, along with the probability of detecting the compound. Additionally, detailed information from all specimen donors should be obtained regarding other factors which may affect the amount of chemicals found, including those variables which modify rate of metabolism. Phenobarbital is an example of a commonly-used drug which induces liver enzymes, resulting in an accelerated rate of metabolism of many other substances (Doull et al., 1980). Competing sources of chemical exposure should be ascertained. Donors should, therefore, be questioned concerning habits such as smoking cigarettes and drinking alcoholic beverages. Abnormalities in liver function tests, for example, may occur even with regular modest consumption of alcohol (Guzelian, 1983). The workplace is also frequently a source of exposure to chemicals (Berlin et al., 1979).

The exposure indices sought through biological sampling are those measurable but not clinically significant biochemical, functional or structural changes, either physiologic or pathologic, which result from the reaction of the body to exposure to environmental chemicals (Berlin et al., 1979).

Evidence of subclinical biological effects may be used to qualitatively and quantitatively estimate exposure. Limitations to this approach include the lack of appearance of the effect for some time following exposure, or the lack of specificity (i.e., have several

etiologies), making it difficult to attribute the effect to a specific cause. Unless the effect varies directly with the amount of exposure, the degree of exposure will be hard to ascertain. Additionally, minor effects may have already disappeared if exposure is not current, or at least relatively recent (Cralley et al., 1979).

In addition to being used as a measure of exposure, the presence of a subclinical biological effect has occasionally been used as an indication of a risk to health associated with the exposure. Currently, however, there are no subclinical markers with which we can precisely predict future development of disease in individuals chronically exposed to low levels of environmental chemicals (Heath, 1983). Reliable biochemical and morphological indicators of the earliest stages of the carcinogenic process have not been identified, precluding the use of subclinical markers as indicators of future disease. A recent advancement of note has been the development of a radioimmunoassay capable of detecting very small amounts of benzo(a)pyrene-DNA adducts in the host DNA. Further research will be required before this and similar assays can be related to carcinogenisis or other chronic effects (Guzelian, 1983).

The employment of cytogenetic markers (changes) as a biological monitoring tool has received much attention, both as a means of hazard identification and exposure assessment, and serves to illustrate more specifically the problems encountered when attempting to adapt tissue analysis techniques to environmental exposure situations.

One of the major mechanisms by which chemicals are believed to cause cancer is through the induction of mutations in the genetic material of somatic cells. Mutations in germ cells may lead to birth defects or

predispose future generations to the development of malignancies. Not all chemicals are mutagens, and not all mutations lead to cancer and birth defects. However, a significant number of chemicals which are believed to cause cancer and birth defects have been shown to induce genetic mutations in laboratory tests. Thus, chemically-exposed populations have been examined for genetic damage as evidence of exposure to mutagens (Doull, 1980).

Results of cytogenetic studies must be interpreted with caution. Though some types of defects are easier to recognize than others, there tends to be much intra- and interobserver variability. In addition, studies have shown that there can be great variability in the number of changes not only among individuals exposed to similar chemical doses, but also in repeated samples from the same individual. Many commonly-encountered agents have been shown to cause chromosomal aberrations, including viruses, medical x-rays and tobacco smoke. A further complicating matter is the fact that, over time, the number of aberrations may decrease due to the cells' ability to repair many types of genetic damage. Also, the sensitivity level of lymphocyte aberrations to all chemical mutagens has not been determined. Therefore, the absence of cytogenetic effects would not be evidence that there has been no exposure to carcinogenic agents (Hook, 1981; Maugh, 1982).

It is generally believed that many chromosomal abnormalities are sensitive biological indicators of exposure to chemical mutagens, but only in the population as a whole. They cannot be reliably used to estimate environmental exposures in the individual. Further, the biological consequences for the individual with chromosomal aberrations have not been established. For example, cytogenetic studies on survivors of Hiroshima and Nagasaki demonstrated that as the dosage of radiation

increased, the number of chromosomal aberrations increased, as did the incidence of cancer. However, those persons with the most aberrations were not necessarily the ones who developed the cancers (Kolata, 1980; Wolff, 1983).

Misuse of biological sampling techniques can lead to public misunderstanding and distrust such as occurred following the chromosome studies on residents of Love Canal (Kolata, 1980). When properly utilized in carefully selected exposure situations, these techniques can provide useful information, especially when used in conjunction with other methods, such as environmental sampling. Further research may lead to broader applications of this promising approach to the evaluation of long-term exposure to chemicals.

DOSE-RESPONSE ASSESSMENT

Dose-response assessment attempts to define the relationship between the level and duration of exposure to some agent and the incidence of the adverse effect (cancer), particularly in reference to humans. As with exposure assessment, dose-response assessment may involve measured information or a combination of measured and theoretical or mathematical responses (Brown, 1985). When adequate exposure data are available in epidemiologic studies, it may be possible to show directly the degree of risk at different levels of exposure. For example, it has been clearly demonstrated that the risk of lung cancer increases with the number of cigarettes smoked daily, as well as the number of years that smoking was practiced. As previously stated, however, epidemiologic information on environmental agents is frequently not available or is inadequate to judge cancer risks. Often the only information available comes from controlled animal experiments or bioassays.

In the bioassay technique, a small number (e.g., 50) of mice or rats or other appropriate laboratory animals are exposed to one of several doses of the chemical to be tested. The selection of appropriate doses is a critical aspect of the experiment. In order to obtain a maximum response, very high doses (just short of overt toxicity) are frequently employed. After a suitable time period (approaching the lifespan of the animal) the animals are sacrified and, through an autopsy on each animal, the frequency of tumors of various organs in the animals is determined. These frequencies are then tabulated along with the level at which they were observed. An equation relating dose and subsequent response (tumor development) is then derived. From this equation, an extrapolation would be made to a level of risk (e.g., one in a million) that was deemed acceptable or "safe", and the corresponding level of exposure should be the "virtually safe dose" (Rowe, 1983; Mantel and Schneiderman, 1975; Schneiderman and Brown, 1978; Haseman, 1984). However, the extrapolation of risks from a laboratory experiment to realistic conditions of human exposure involves many assumptions and uncertainties. A major problem is how to extrapolate a dose-response relationship observed at high doses to much lower dose levels where effects cannot actually be observed. A variety of statistical models have been developed in order to extrapolate from high doses to low doses. The rationale and limitations of some of these models are discussed below. Another issue of concern is how to extrapolate from animals to humans. There may be differences in the absorption, metabolism, and excretion of a compound in humans and animals, particularly between low and high doses. Another problem pertains to differences in the dose-time relationship, due to the differing life spans between rodents and humans. Some of these issues are also discussed below.

Statistical Methods of Extrapolation to a Safe Level of Risk

The development of statistical models for a safe dose estimation has been an active area of research during the past three decades. Initially, in the 1950s, investigators used linear models for the estimation of the safe level of exposure (Schneiderman et al., 1975; Mantel and Bryan, 1961; Ehrenberg and Holmberg, 1978; Guess and Crump, 1978; Hoel et al., 1975). These were simple approaches reflective of a lack of conceptualization concerning safe dose estimates (Rowe, 1983; Hoel et al., 1975). In the early 1960s, however, Mantel and Bryan noted that these approaches suffered from methodological weaknesses (Mantel and Bryan, 1961). A major weakness was a lack of discrimination between different estimates of a safe dose estimate, based upon the number of laboratory animals used (which was variable). They felt that laboratory workers should use a model which incorporated greater precision in the estimated safe dose resulting from the use of greater numbers of animals. An alternative formulation, the probit model, was offered by Mantel and Bryan (Mantel and Bryan, 1961). The Mantel-Bryan approach was the first method to use a tolerance distribution model. The use of these models is still controversial (Hunter and Crowley, 1979; Hogan, 1983; Hoel et al., 1975). Several of these models are discussed at greater length below.

Concurrent with the development of the Mantel-Bryan approach, Armitage and Doll began work on a theory of carcinogenisis which was based on the biological concept of "hits" (Armitage and Doll, 1961). A hit was defined as a single chemical interaction with a cell (usually the genome of the cell), which resulted in a carcinogenic transformation of that cell. Because of its biological basis, the "hit" model has

provided an additional area of study for safe-dose estimation. Also, its use in epidemiology by both Armitage and Doll, and others has provided an additional rationale for its use in safe-dose estimates.

An entirely different approach has been taken by the proponents of "time-to-occurrence" models. The basis for this class of models is that the latency or incubation period for a given tumor to develop is proportional to the dose of the etiologic agent (Drukery, 1967). Many of these models have been developed from a statistical point of view; much epidemiologic evidence suggests that this approach is unfounded (Schneiderman et al., 1979). Nonetheless, several adherents of the model have made use of it. They have argued that once a relationship between a dose and the time to occurrence (or latency or incubation period) for a tumor to develop is established, increasing this latency period beyond the life time of the species, would produce a dose corresponding safe level of exposure (Tomatis et al., 1982; Chand and Hoel, 1974). (There are also other, less well-studied statistical models.) These groups of models, however, constitute the major classes of the models in wide-spread use. They will be discussed presently, on a class-by-class basis.

Linear Models. The essence of the linear model is that for a given species, the frequency of tumor generation is directly proportional to the dose of the carcinogen. The simplicity of the linear model is that least squares regression and other statistical approaches that have been developed and tested over many years. They are well-accepted by the scientific community, may be used to fit the linear model to a given data set.

Although the linear model is the simplest class of models, it has many failings. As Hogan has noted, sufficient data from a given

experimental situation may not exist to justify its use, i.e., it may not "fit" the observed data (Hogan, 1983). Hence, it is possible that the linear model may seriously over-estimate the level of risk. There are several advantages to the use of the linear model. These include the stark simplicity of the relationship between dose and frequency of tumors, the wide variety of statistical methods for the estimation of its parameters which have been developed during the past century, and the ability of the public, particularly policy makers, to understand and accept the linear model. Once the parameters of the model are estimated, it is only necessary to specify the allowable (acceptable) level of tumor occurrence (i.e., one per million individuals exposed) in order to determine the safe level of exposure.

Tolerance Distribution Models. The tolerance distribution model is based upon the concept that each individual has a level of exposure to a chemical that can be tolerated, i.e., exposure without the production of a neoplasm (Hogan, 1983; Krewski and Van Ryzin, 1981). If an individual was exposed to a chemical above their tolerance level, then they will develop a neoplasm. Although the tolerance levels will vary from individual to individual, the levels can themselves be described by a statistical distribution. Hence, the name, "tolerance distribution model". There are several implications involved in the use of a tolerance distribution model, the most important of which is that there will always be a certain number of individuals for whom exposure to the chemical will result in the development of a neoplasm.

A major assumption in the tolerance distribution approach is the exact mathematical formulation specification of the distribution of an individual's tolerance level.

In the 1930s, Bliss worked with such tolerance distributions and found that if he used a normal distribution as a description of tolerance levels in the population, a cumulative normal distribution model would fit some observed toxicity data (Bliss, 1934; Bliss, 1935; Finney, 1965; Finney, 1947a; Finney, 1947b). Such a model is termed a "probit model". Among the reasons that Bliss presented for using the normal distribution at the time was that it was amenable to statistical/mathematical manipulation. Further work by Bliss, Finney, and others has resulted in statistical sophistication in estimating the parameters for a given probit model (Finney, 1965).

In the early 1960s, Mantel and Bryan pioneered the use of the probit model for determining safe levels of exposure (Mantel and Bryan, 1961; Schneiderman et al., 1979; Mantel et al., 1975). They argued that many of the then-existing statistical tools, particularly confidence interval calculation, for estimating the parameters of probit models should be used for the safe-dose estimation. One advantage to this approach would be that the number of animals used in the bioassay would be reflected in the estimates of a safe dose. The general approach of the Mantel-Bryan approach is straight-forward. The model parameters calculated for a given chemical and a given cancer would be linearly extrapolated (in "probit units") to the allowable level. The corresponding dose would be the safe dose estimate. Compared to other models, this approach tends to produce relatively high safe-dose estimates (OSTP, 1984). For this and other reasons, its use in quantitative risk assessment has greatly declined.

Other tolerance distribution models may be used in place of the probit model. Models such as the logistic have been, in fact, suggested for safe dose estimation. However, they are not widely

utilized and will not be discussed further (California, 1984).

"Hit" Models. The "hit" model can be traced to the development of the one-hit and multi-hit theories of carcinogenisis in the 1960s, pioneered by Armitage and Doll (Armitage and Doll, 1961). These theories accorded well with observed age-specific incidence rates for several cancer sites, which provided empirical evidence in favor of the model. Hence, it is not surprising that the models were also used shortly thereafter in the development of a method for safe-dose estimation.

The one-hit model is the simplest version of the "hit" family of models. However, it will not necessarily fit the observed experimental data. Like the linear model, the one-hit model has only one parameter with which the model may be fitted. Hence, it can not always accommodate a complex set of data. The multi-hit model, in contrast to the one-hit model, behaves like the linear model in the low-dose region. The multi-hit model also assumes that any background carcinogenic processes are independent (Hogan, 1983). This is not always a valid assumption.

A close cousin to the "hit" family, sharing the major advantages of the gamma multi-hit model, is the so-called "extreme value" model. Since this model can be recast in the form of a Weibull distribution, it is often referred to as the "Weibull model" (California, 1984; Krewski and Van Ryzin, 1981; Hunter and Crowley, 1979).

Multistage Models. The most frequently employed low dose extrapolation model in current use is the multistage model developed by Armitage and Doll (OSTP, 1984). This model reflects the observation that there are several stages in the development of clinically-detectable tumors

that may be affected by a carcinogen. This type of model has frequently been used by the U.S. EPA Carcinogen Assesesment Group (CAG) as the primary basis for risk extrapolation to low doses. Risk estimates made with this model are considered by the CAG to be conservative, representing a plausible upper limit for the risk (i.e., the actual risk is not likely to be higher, and could well be considerably lower) (EPA, 1985). This model can fit almost any monotonically increasing dose-response data, and allows estimates of the largest possible linear slope (upper 95% confidence level) at low extrapolated doses that are consistent with the experimental data (EPA, 1985). An example of a specific application of this model to low dose risk estimates can be found in a recent EPA Health Assessment Document for trichloroethylene (EPA, 1985).

Selection of Appropriate Dose-Response Models

From the previous discussions it is apparent that a number of different options are possible for interpreting bioassay results for positive animal carcinogen tests. Different models will produce different "virtually safe dose" estimates for the tested compound, which correspond to a socially acceptable level of risk. In general, the different models can usually be fitted to the observable results with equal validity. Unfortunately, none of the models can be validated by biological agruments alone. The choice among them is therefore made on the basis of supplementary information related to the action of the compound (mechanism) and the biological basis of the observed response, evaluated in concert with the empirical bioassay data.

The kinds of information used to augment the raw bioassay results include physiological functions, metabolic processes, physical attributes of the test compound, route of administration, and the mechanism of the

induced toxic response. For example, carcinogens that produce an active metabolite responsible for tumor-inducing activity may demonstrate non-linear kinetic behavior based on ingested dose (mg/day). However, metabolic testing in liver using experimentally-derived metabolic rate constants and tissue binding affinity can be used to supplement the bioassay dose estimate to attain linearity based on bioburden (the amount of compound actually in the animal multiplied by the duration of exposure). Conversely, alkylating carcinogens may follow first order linear kinetics, since they require no metabolic activation to produce carcinogenic effects. In the opinion of many toxicologists, the selection of an appropriate model should be done on a chemical-by-chemical basis, rather than selecting a "universal" model.

In the current process of risk assessment, the dose-response model selection process is usually simplified by federal agencies. In fact, the EPA uses the multistage model exclusively as a basis for carcinogenic risk assessment. This approach can be justified for a number of reasons. First, this model seems to provide a statistical method which best agrees with the process of cancer induction, as it is currently understood. Empirical observations indicate that tumor induction has more than one stage of expression (e.g., initiation and promotion), and that a single carcinogen may produce many active metabolites with differing carcinogenic potencies. Observations also show that for compounds inducing an increase in a spontaneous tumor background, tumor induction proceeds in a linear manner at low doses. Second, use of the multistage model provides a means for the determination of the comparative potency of carcinogenic substances, by using the slope of the dose-response observed in the bioassay tests. Third, and most importantly perhaps, use of the multistage

model will produce an upper limit of estimated risk in the low dose region, regardless of the actual dose-response pattern for any particular carcinogen. Thus, if use of the multistage model results in errors due to low dose extrapolation of the observed dose-response, these errors will be on the protective side. Use of the other models may underestimate the associated cancer risk if the model is not "ideally" fitted to the actual dose-response relationship (Krewski et al., 1984).

Considerable attention is often focused on comparisons of the variability of the various extrapolation models in the risk assessment process. The issue of model-fitting needs to be considered in light of the overall process of risk assessment. The National Academy of Sciences (1983c) recently issued a report identifying some 36 different components of the risk assessment process. Twenty-one components were allocated to the hazard identification step, used to determine if a substance may be carcinogenic. Dose-response assessment was assigned 10 components; exposure assessment, 2 components; and expression of overall results, 3 components. Of this total of 36 components in the risk assessment process, only one component can be attributed to the choice of model used in describing the bioassay dose-responses. The other assumptions and choices (mostly policy oriented, rather than scientific) have a far greater effect on the outcome than the choice of a mathematical model. This point is used to illustrate that model choice is important and it is only one of many judgments made during the risk assessment process. The complexity and assumptions of the process also indicate that determination of "safe dose" level will often change when any of these 36 components are modified by new information or policy changes.

A final point to consider regarding extrapolation models is the shape of the extrapolated dose-responses for the different models at the low-dose

region of response. The MDH currently uses a 1×10^{-5} risk level for environmental exposure. This means that the tolerated concentration for a carcinogenic environmental exposure is set so that the estimated cancer risk is less than one per hundred thousand persons with lifetime exposure. For some chemicals, at this level of risk, none of the conservative models differ significantly (Flamm and Winbush, 1984). For other chemicals this is not true (Krewski and Van Ryzin, 1981). The differences in risk estimation attributable to selection of the mathematical model must nonetheless be viewed in relation to the overall process and to the risks (or exposure) levels typically of concern in the regulatory process.

Species-to Species Extrapolation

Another major difficulty in cancer risk assessment is how to extrapolate findings from animals to humans. The area of species-to-species extrapolation has been dealt with by many workers in the context of safe dose estimation (Hoel et al., 1975; Goldberg, 1979; Schneiderman et al., 1975; Mantel and Schneiderman, 1975; National Academy of Sciences, 1980; Schneiderman and Brown, 1978; Rowe, 1983; OSTP, 1984).

Laboratory animal responses to toxicant exposure depend on physiological, anatomical, and biochemical attributes peculiar to the species tested. The metabolic processes of detoxification, biodistribution, and excretion all play an important part in the effects produced by the test chemical. In many cases, the native chemical is processed by the host to produce reaction products that are either more or less toxic than the parent compound. These factors contribute a level of uncertainity when animal bioassay results are used alone to estimate human risk from exposure to carcinogenic chemicals.

Besides the obvious reasons for using animals to test the carcinogenic potency of chemicals, there are some valid scientific reasons for this approach as well. The study of certain enzyme systems indicates that they frequently operate in the same way in both laboratory animals and humans and that the basic species difference is how much of a particular enzyme works in the case of xenobiotic chemical metabolism.

Since carcinogenesis can be thought of as just one type of toxic effect, some indications of the importance of species related to toxic chemical exposure can be derived from short-term bioassays. Weil (1972) compared 490 experiments measuring the acute toxicity of chemicals in many different test species and calculated interspecies adjustment factors. These data indicated that a response factor of 10 (or less) could be attributed to interspecies variability shown for acute toxicity tests. Most toxicologists would advocate use of a 10-fold safety factor only in the absence of direct interspecies comparisons, particularly for the carcinogenesis endpoint.

Empirical Methods. A number of approaches to extrapolating the dose in animal experiments to humans have been used, with varying degrees of success. One of the most common of these is the body surface area conversion:

$$\text{conversion} = (70/W)^{1/3}$$

where 70 is the body mass of a "standard" adult male in kg, and W is the experimental animal weight. This formula was derived from empirical data collected from studies of antineoplastic drug tests and observations on the action of drugs on human newborns and infants. Body weight comparisons have also been used, producing dose measurements of mg/kg/d as a means to apply data from animal tests to the human exposure condition. This

approach is based upon physiological parameters such as pulse, breathing rate, consumption of food, oxygen, and water, since these correlate linearly with body mass. Cruder estimates of dose conversion between species include direct food, air or water concentrations as exposure indices. In any case, the empirical approach always uses a relatively gross "factor" to account for the interspecies differences.

Pharmacokinetic Processes. Another approach to interspecies extrapolation is that based upon a quantitative estimate of the difference between animal species and man. In general, the mechanisms for adsorption and excretion of xenobiotic chemicals and their metabolites are the same in man as in conventional test animals. The site of action and toxic mechanisms are also more often similar than not. The greatest variation among species is the rate of metabolism, and it is this variable that pharmacokinetic models seek to measure. The use of this approach can be generalized as follows:

1. The major species difference is rate of elimination, which includes metabolism, distribution, and excretion;
2. Test animals can be manipulated to make these differences disappear, using multiple doses administered at the proper time and concentration. This is particularly true when the effect depends on plasma concentration over a long time period. In effect, this stabilizes the steady-state dose to overcome the species differences;
3. Where animals do not produce a metabolite active in man, these human matabolites should be administered to the test animal. This would facilitate extrapolation to man that would not be possible otherwise.

RISK CHARACTERIZATION

Risk characterization is the final step in the risk assessment process and usually involves the overall evaluation of the evidence to produce a quantitative estimate of the human cancer risk expected from known or anticipated human exposures. This evaluation includes qualitative and quantitative evidence relating to hazard identification, exposure assessment, dose-response and species extrapolation (Task Force on Risk Assessment, 1985). This process will necessarily involve a variety of assumptions and uncertainties which should be made explicit and quantitified whenever possible (OSTP, 1984; Task Force on Risk Assessment, 1985).

CONCLUSIONS

There is currently no single procedure or process that is capable of identifying all human carcinogens. The strongest evidence pertaining to carcinogenicity can be found when there is both epidemiologic data and bioassay data that are consistent. Because epidemiologic data are frequently not available, cancer risk assessments must be based primarily on results from long-term animal studies.

In examining the status of animal testing with respect to dose assessment determinations, a number of conclusions can be drawn. Animal models remain crude tools for assessing the risks associated with xenobiotic chemical exposure to man. The results must be interpreted cautiously and intelligently, so that the factors significant for man are also significant for the test species used in the dose response assessment. The reality of the situation necessitates testing carcinogenic potency by this method, regardless of the difficiencies. Experience is required for the prudent interpretation of the animal studies, since sophisticated biometric methods cannot compensate for inadequate experimental design or

for a lack of understanding of the biological principles involved. The erroneous application of statistical methods or disregard for the statistical limitations of the raw data set can lead to faulty conclusions.

Limitations of animal-derived carcinogenic dose response assessments include the basic assumption that animal experiments are relevant to human risk estimation. In addition, some conceptual problems exist with extrapolation from high-dose exposures to low-dose environmental levels. There is also no certainty that the tested species will be as sensitive as man to the tested toxicant with respect to tumor induction. Factors such as the genetic differences between animals and humans confuse the evaluation of individual exposure consequences, since the human population is far more heterogeneous than laboratory animal species.

Another difficulty with risk assessment based upon bioassay is the inability to verify the models or extrapolation techniques by direct observation of human populations. In situations involving exposures to substances with estimated risk levels of 1×10^{-5} or less, the chance of observing even a single "excess" case in a community is very remote. Even if an excess of cancer did occur, it could not be distinguished from the much larger number of cases arising from all other causes. Regulatory activity based upon risk assessments is intended to protect the public health by preventing potential situations in which excess cancer risks can actually be observed. The level of risk at which society is adequately protected depends on many factors, many of which have not been discussed in this section. Progress in the area of animal bioassay that reduces uncertainties inherent in the approach is proceeding, but concomitant efforts in the areas of hazard assessment and exposure assessment are needed to help reduce uncertainties relating to the entire policy making process.

3. PROPOSED CRITERIA FOR COMMUNITY HEALTH STUDIES

3. PROPOSED CRITERIA FOR COMMUNITY HEALTH STUDIES

Based on a literature review and the epidemiologic principles previously discussed, the following criteria are necessary for the proper conduct of epidemiologic studies to determine potential health effects from contaminated drinking water:

An Accurate Definition of Exposure

The most crucial element of any environmental epidemiologic study is the degree to which exposure can be measured on an individual basis. In general, evidence of an environmental hazard is usually provided through studies of persons with high exposures. Detecting causal relationships at low exposures is very difficult and is complicated by the interaction of many other factors which may not be adequately addressed by the study design. If exposure is low or rare, or if the excess risk posed by an exposure is small, then large numbers of individuals are required for a scientifically valid study. Often, information on the specific exposure of interest is unavailable; hence, surrogate measures are used, such as occupation or length of residence. Exposures are often determined on the basis of historical information or individual recollection, and such assessments are subject to bias from selective recall or missing records. Additional parameters will also influence the accuracy of any exposure model: (1) the nature and extent of environmental contamination; (2) the degree to which contaminants can be accurately measured and quantified; (3) the probable routes of human exposure; and (4) the duration, intensity and temporal variability of human exposure. Misclassification of exposure may result in inaccurate health risk estimates and seriously distort the perception of environment on health (Gladen and Rogan, 1978). Another

major problem in the evaluation of any environmental exposure is the difficulty in identifying excess risk in individuals due to one particular contaminant out of the many to which individuals are routinely exposed (Saracci, 1978). Shy (1985) concludes that "Further epidemiologic studies of cancer risk and water quality, in the absence of progress of exposure estimation, seems unlikely to advance our knowledge of the nature of this relationship."

Information on Confounding Variables

Confounding is defined as a situation in which the effects of two variables are not separated when evaluating their individual impact on health (Last, 1983). A confounding factor results in a distortion of the effect of exposure on disease risk. The most commonly considered confounding variable is age. Gender, race, religion, marital status, cigarette smoking, and alcohol consumption are also among the most common of many potential confounding factors. In addition, the apparent effect of an exposure may be masked due to the effect of other factors that are more strongly related to the etiology of the disease (effect modification). In order to adequately identify the health risks associated with environmental exposures, other factors known to be associated with disease must be evaluated in all individuals, whether exposed or unexposed.

The Use of Incidence Data

The incidence rate is defined as the number of newly-diagnosed cases during a specified time interval divided by the total number of individuals at risk of developing that disease during the same period of time. Incidence data provide a direct estimate of disease risk. This is in contrast to the prevalence rate which is the total number of cases of

disease (both new cases and old cases) in a population at a specified point in time divided by the number of individuals in that population at the same time. Prevalence is dependent on both the incidence rate of disease and the duration of the disease. Thus, differences in disease prevalence do not necessarily reflect differences in disease incidence; they may also reflect changes in disease duration. A study of prevalent cases would tend to include those who have higher survival rates; these cases may differ in several respects from non-survivors. A study of incident cases reduces the survivorship bias. Mortality data, although accessible and inexpensive, are subject to errors as previously described.

For several reasons then, incidence studies are preferable to prevalence or mortality studies for the identification of etiologic risk factors associated with adverse health effects.

Population-Basing

A "population-based" study examines disease incidence in a population in a defined geopolitical area. Population-at-risk is a term applied to all of those individuals in a population to whom an exposure could have occurred, whether it did or not. It is the denominator in rates of disease incidence. This is in contrast to studies which are confined to clinic or hospital settings. Data from such settings are often not representative of the community due to selection factors (e.g., services provided, costs and patient accessibility will affect who utilizes a particular clinic or hospital). Such studies may provide a biased perception of disease in the community. The use of population-based methodology allows a much better definition of the population-at-risk and the incidence of disease in that population. In addition, study results using population-based data are generalizable to the entire community.

Adequate Statistical Power for Study Endpoint

The "statistical power" of a given study refers to the probability that a disease risk of a particular magnitude would be detected. For example, a particular study may have a high probability (90%) of detecting a two-fold increased risk among the exposed. It would have less power to detect smaller increases in risk. Real differences in disease risk may go undetected in a study due to insufficient power. Power is associated with the size of the study population (the smaller the sample size the lower the power of the study), and is expressed in relation to a particular magnitude of risk (larger risks are easier to detect than smaller risks). A study with an inadequate sample size has less chance of detecting true differences. Typically, populations exposed to environmental contaminants are small and the statistical power of these studies is low. Landrigan (1983) has noted that negative data from environmental studies should be interpreted cautiously. He recommends that all negative studies include a clear statement as to the study's power to detect true differences in disease risk. On the other hand, a study with a very large sample size has the power to detect very small differences in risk (e.g., see Morin et al., 1985). However, such small differences are difficult to interpret biologically and the social implications are often unclear.

Table 3-1 provides estimates of the minimum detectable relative risk of cancer as a function of the person-years of observation (PYO). This is defined as the size of the population multiplied by the duration of observation. In general, a large number of person-years of observation would be required to detect rather large relative risks for specific diseases (e.g., cancers of the urinary system). For example, a population of 1000 would have to be observed for ten years (10,000 person-years) to be

Table 3-1. RELATIONSHIP BETWEEN THE PERSON YEARS OF OBSERVATION (PYO) AND THE MINIMUM DETECTABLE RELATIVE RISK OF CANCER

Cancer Site	Person Years of Observation	Level of Significance	Baseline Rate of Disease	Power	Minimum Detectable Relative Risk
All Sites	1000	0.05	0.003	0.9	5.89
	10000	0.05	0.003	0.9	2.03
	100000	0.05	0.003	0.9	1.28
Digestive System	1000	0.05	0.0007	0.9	17.65
	10000	0.05	0.0007	0.9	3.64
	100000	0.05	0.0007	0.9	1.63
Urinary System	1000	0.05	0.0002	0.9	54.97
	10000	0.05	0.0002	0.9	7.80
	100000	0.05	0.0002	0.9	2.32

able to detect a two-fold increase of cancer (all sites). Smaller increases would require a greater length of observation or a larger study population. This same population would have to be observed for longer than 100 years to be able to detect a two-fold increase in the incidence of cancers of the urinary system.

Use of Appropriate Health Endpoints

Ideally, environmental epidemiologic studies would address any and all health (disease) endpoints that are of public or scientific concern. The identity of such endpoints may depend on public fears and perceptions as well as on scientific evidence. In some instances, social, political, legal, and/or scientific factors demand that many health endpoints be addressed simultaneously (e.g., from cancers to reproductive outcomes to skin rashes). However, to evaluate many different outcomes requires the use of large, costly, and socially-invasive cohort studies. Where an adequate exposure model cannot be developed for the environmental exposure of interest, such large-scale studies may not even be a viable option. As a practical matter then, it is usually necessary to determine which of an extremely large number of possible health endpoints are most appropriate for the focus of planned studies. Considerable care must be exercised in this process, since the selection of an inappropriate study endpoint may, in addition to its unproductive use of money and personnel, unnecessarily either alarm or reassure the community involved.

As indicated above, public perceptions, political, or legal factors may dictate the focus of an epidemiologic study arising from an environmental contamination problem. Even when not justified by scientific evidence, the social usefulness of such studies must be weighed. However,

aside from public or political factors, many scientific and technical issues come into play in selecting study endpoints.

Selection often involves a review of the published scientific literature regarding the contaminants of interest. Toxicological and epidemiologic data (if available) may identify specific health effects that should be examined. As Landrigan (1983) has pointed out, the evaluation of exposed populations should be directed toward health effects that are biologically plausible. Heath (1983) questioned the validity of subclinical markers such as cytogenetic or mutagenic tests as predictors of adverse health effects. He cites their inappropriate application during the Love Canal episode, and concludes that their use in epidemiologic studies is limited.

Another approach for identifying appropriate endpoints (particularly when other information is not available) is to examine available or readily obtained health data (such as mortality data) for the population. Although such data may not be useful in identifying effects related to the contamination exposure, they may be useful in identifying disease outcomes that should be the focus of analytic studies.

In summary, six criteria are considered essential for the conduct of environmental epidemiologic studies that have as their goal the identification and quantification of health risks that are attributable to environmental contaminants. These criteria are:

1) **an accurate definition of exposure,**
2) **information on confounding variables,**
3) **the use of incidence data,**
4) **population-basing,**
5) **adequate power for study endpoints, and**
6) **use of appropriate health endpoints.**

4. BACKGROUND ON DRINKING WATER CONTAMINATION: ST. LOUIS PARK AND NEW BRIGHTON

4. BACKGROUND ON DRINKING WATER CONTAMINATION - ST. LOUIS PARK AND NEW BRIGHTON

INTRODUCTION

In this section, brief and separate descriptions of the municipal well contamination that occurred in St. Louis Park and New Brighton will be given . Information presented includes the date(s) when contaminants were initially detected in municipal wells, the nature and magnitude of the contamination, the probable or known sources of contamination, aspects of the water supply that relate to community exposure potential, existing studies and available data pertaining to community health, and general environmental and toxicological aspects of the contaminants.

It might be noted at the outset that there are both similarities and major differences in the two situations that have implications regarding the feasibility of community health studies. Common to both communities, for example, is the involvement of a number of municipal wells that draw from the same water-bearing formation (aquifer). Both areas have been included in the highest priority group for eligibility for federal Superfund action. In both situations, computer groundwater flow models have been developed as aids in identifying sources of contamination and potential remedial actions. And in both communities, the number of people using potentially contaminated drinking water prior to detection of the contamination is well in excess of 10,000.

In contrast to these similarities are some very major differences. Some examples of the differences include the nature and magnitude of the contaminants and their potential for carcinogenic or other health effects, other sources of exposure to contaminants, the portion of the total water supply provided by contaminated wells at the time the contamination was

discovered, the potential period in which contamination of the water was possible or likely, the size and characteristics of the communities, and the extent to which the situations have been studied to date. These factors have obvious relevance to any consideration of community health studies, and will be emphasized in the following discussions.

BACKGROUND - ST. LOUIS PARK

As indicated in Section 1, a most important and problematic aspect of conducting environmental epidemiologic studies is the assessment of exposure. The following discussion summarizes what is known and what is not known about the nature, extent, duration, and magnitude of exposure to contaminants in St. Louis Park wells.

Nature and History of Contamination

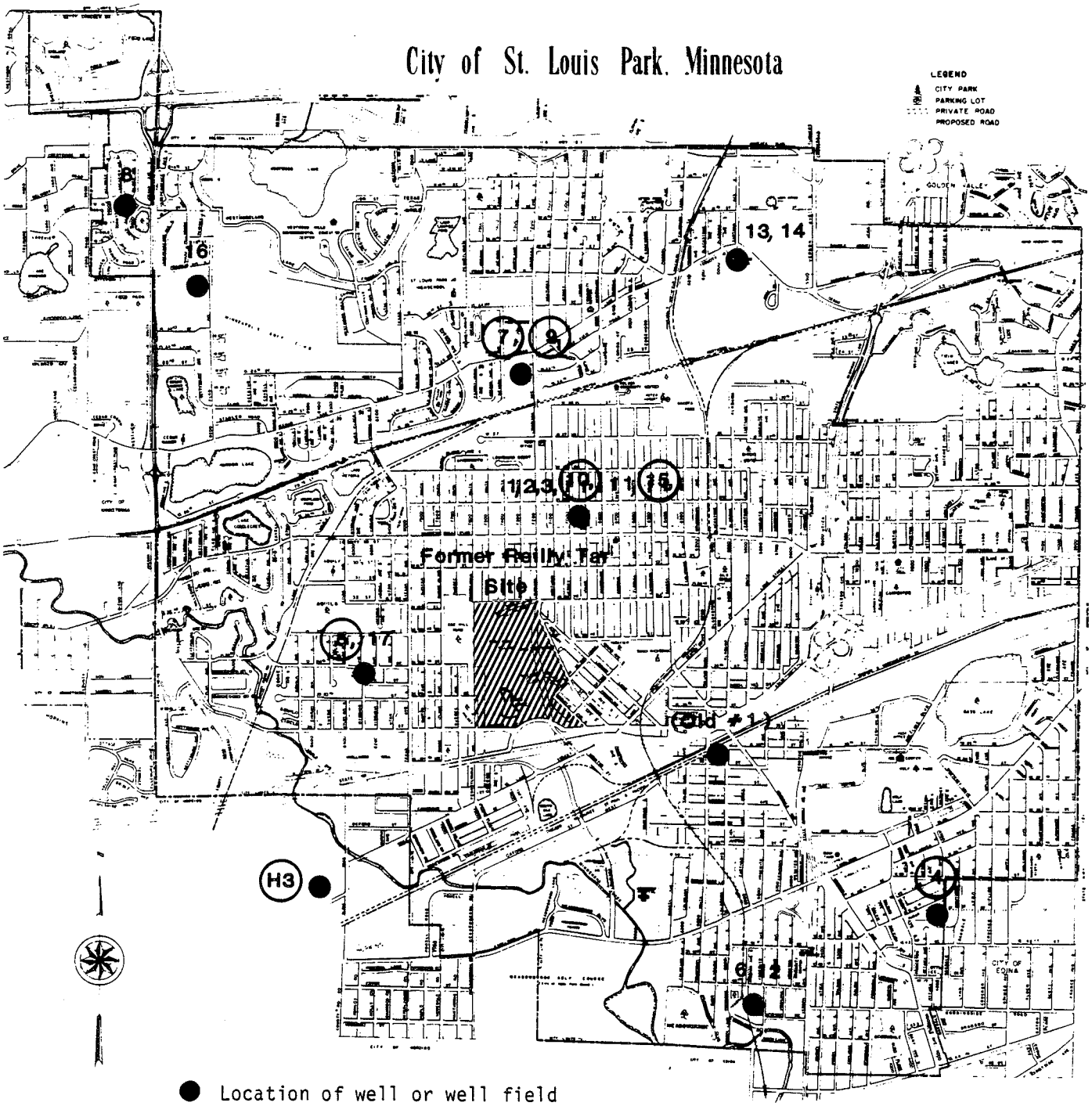
In 1978 four of the fourteen St. Louis Park municipal wells were taken out of service by the city after it was determined that the wells were contaminated with low levels of polynuclear aromatic hydrocarbons (PAHs). Some of these compounds are potent animal carcinogens (discussed later in this section). Between 1979 and 1981, two additional St. Louis Park wells and one Hopkins well became contaminated and were also removed from service. To date, these wells have remained out of service.

All of the contaminated municipal wells drew their water from the Prairie du Chien-Jordan aquifer -- the most utilized aquifer in the Twin Cities metro area. This bedrock aquifer is between 250 and 500 feet beneath the surface in the St. Louis Park area, and is generally considered to be well-protected from surface contamination due to a thick sequence of overlying materials including glacial drift, two bedrock aquifers, and two bedrock confining units (Stark and Hult, 1985).

The contamination has been clearly linked to a former coal-tar refinery and wood preservation treatment facility that had been operated by Reilly Tar and Chemical Corporation. This plant was located on an 80-acre site in St. Louis Park and was in operation between 1917 and 1972 (see Figure 4-1). The raw materials (coal-tars) and products (e.g., creosote) that were used in this facility are composed of hundreds, and probably many

Figure 4-1

LOCATION OF St. LOUIS PARK MUNICIPAL WELLS



● Location of well or well field

○ Circled numbers indicate wells found to be contaminated between 1978 and 1981

thousands of compounds, including the polynuclear aromatic hydrocarbons (PAHs). The Reilly site was among the earliest sites determined to be eligible for Federal Superfund remedial action (October, 1981). It has been ranked in the highest of eleven priority groups that include 786 current and proposed Superfund Sites (National Priorities List, Oct. 1984).

Contamination of the ground water probably resulted through several means (Hult and Schoenberg, 1984; Stark and Hult, 1985). Plant wastes were discharged with little or no treatment into a ditch that flowed to a bog or marshy area south of the plant. The soil and water beneath this bog were found to be very highly contaminated with coal-tar constituents such as the PAHs. Spills and drippings from various plant operations on-site would be another source. A third source of contamination was the direct entry of contaminated materials into the Prairie du Chien-Jordan aquifer through a deep (900-foot) multiaquifer well (W23) at the Reilly site. This well served as a water supply to the plant's operations since 1917 and was located near the refinery building in an area with potentially high contaminant loadings on the surface (ERT, 1983). There is anecdotal information suggesting other sources of contamination in W23 (e.g., a possible spill from a railroad tank car and the draining of creosote-contaminated process waters).

Whatever the sources, investigations between 1979 and 1982, along with historical information, have clearly indicated the significance of this well in introducing contaminants into the Prairie du Chien-Jordan aquifer. These investigations have revealed, for example, that the interior surfaces of this well were coated with coal-tar materials, and that water was flowing into the well through holes in the casing at about 215 feet (basal St. Peter aquifer) and out through holes at 264 feet into the

Prairie du Chien-Jordan aquifer. The flow rate was measured by the U.S.G.S. to be about 150 gallons per minute. Prior to 1930, the well was not cased between 65 and 80 feet, and thus would have permitted entry of water (and contaminants) from the shallow Drift-Platteville formations into the well. Furthermore, the construction of this well (ungrouted) was such that contaminated materials and waters near the surface could have flowed down the space around the outside of the well, entered through the breaks in the casing, and exited through the holes at the level of the Prairie du Chien-Jordan. It is significant to note that a plug of coal-tar material was found to exist in the well below a depth of about 595 feet. This plug was approximately 140 feet long and seven inches in diameter. Although providing a continuing source of contamination to adjacent aquifers, the plug may also have sealed off deeper aquifers from additional contamination after some point in time.

A number of additional multiaquifer wells have also been identified in the vicinity of the site and may also have contributed to the problem, although they are not believed to be as important as the Reilly well. (These interaquifer wells have been sealed or modified.)

Contamination of the Prairie du Chien-Jordan aquifer is likely to have occurred quite early. In 1932 St. Louis Park attempted to put into service its first municipal well. (Municipal water, where available at the time, was being provided by Minneapolis.) This well was over 500 feet deep and open to the Prairie du Chien-Jordan. It is located approximately 3500 feet east of the Reilly site (Figure 4-1, Old #1). Groundwater in the Prairie du Chien-Jordan in this area under natural gradient conditions flows towards the east and southeast to the Mississippi River; thus, water would have tended to flow from the Reilly site toward the well. Upon completion and after a short period of pumping, the well yielded water with a coal-tar

taste and odor and was not considered suitable as a public water supply. Documentation from the period (early 1930s) cited by the U.S.G.S. (Hult and Schoenberg, 1984) and Reilly (ERT, 1983) indicate that the Reilly plant was the suspected source of the contamination. In an apparent attempt to remedy the problem with the municipal well, additional casing was added to the Reilly well (W23) and another Reilly well (W105) was plugged with sand. The problem was not resolved, however, and the municipal well was not utilized. A number of other Prairie du Chien-Jordan wells completed in the 1930s were also reported to have coal-tar odors and tastes (Stark and Hult, 1985).

A second municipal well into the Prairie du Chien-Jordan aquifer (SLP 4) was drilled in 1946. (Three other municipal wells had been installed north of the Reilly site in 1938, all approximately 290 feet deep and drawing primarily from the St. Peter aquifer.) This well was 485 feet deep and was located at a site approximately 1-2/3 miles southeast of the Reilly facility and in the direction of groundwater flow. Phenol levels in this well in 1946 (the year of its installation) were reported to be 0.1 ppm initially, although these levels quickly declined (Hickok, 1969). Although not apparently contaminated in 1978 with PAH, this well was closed in 1979 due to PAH contamination.

Environmental Research and Technology, Inc. (ERT) notes Reilly correspondence in 1958 that refers to a problem with "tar" deposits on pump bearings in Well W23 one year after switching to a hydropneumatic pumping system in 1955 (ERT, 1983). This led to the installation of additional casing in this well.

The history of the Reilly operations, the experience with coal-tar tastes and odors in Prairie du Chien-Jordan wells in the 1930s, and the

hydrogeologic characteristics of the region suggest that significant contamination of this aquifer extending off-site may have occurred many decades ago. Six of the ten municipal wells open to this aquifer that were constructed between 1946 and 1969 were closed between 1978 and 1981 due to contamination. This raises the possibility that some of the wells that are currently closed were at least sporadically contaminated throughout much of the time they were in operation.

Magnitude of Contamination

Several problems arise in attempting to summarize contaminant levels in the municipal wells. First, several different laboratories have performed analyses, and have frequently analyzed for different compounds or different numbers of compounds. Even the same laboratory (e.g., MDH) has looked for different contaminants over time. Second, the methods and sensitivity of the analyses have varied over time and by laboratory. Third, the conditions under which samples were taken have varied or not been defined (e.g., how long the well was pumped prior to sample collection). Fourth, changes in contaminant flow due to altered pumping patterns in the aquifer would contribute to changes and variability in measured water quality. Fifth, there is the issue of quality control and other analytic variables that affect the reliability of measures, particularly in the nanogram per liter range. Finally, there is the problem of the sheer bulk of the data that have been acquired over the past seven years reflecting findings from many thousands of analyses. Several data bases have been compiled by participants in the Reilly investigation (e.g., MPCA, ERT). The most recent and comprehensive compilation of these data was prepared by the MPCA in early 1985, and it includes the data for almost every well water analysis.

In light of the difficulties mentioned above and the extremely large size of the database on well water quality, data on contaminant levels for specific compounds will not be presented. Instead, a more general presentation will be given in terms of order-of-magnitude ranges and typical values for total carcinogenic PAH concentrations and total non-carcinogenic PAH concentrations. PAH compounds that have been detected in analyses and that are included in these total PAH summaries are indicated in Table 4-1. (The Minnesota water quality standard for total carcinogenic PAH is 28 ng/l)

It should be pointed out at the outset that the reported concentrations for individual PAH compounds, as well as for total PAH, for a single well can show variations of up to 100-fold or more. Furthermore, this range almost always includes "less than" values (detection limits vary according to many factors).

As previously stated, it was initially determined that four of fourteen SLP municipal wells were contaminated (MDH, 1978). This was based on analyses of seven PAH compounds, including three carcinogens -- benzo(a)pyrene, benzo(ghi)perylene, and indeno(1,2,3-cd)pyrene. These initial analyses showed that low but detectable levels of PAH compounds were present in several St. Louis Park wells as well as in some other metro area water supplies. However, SLP Wells 10 and 15 clearly had the highest levels of contamination, while Wells 7 and 9 had lower, but still elevated PAH. Carcinogenic PAH were found only in Wells 10 and 15 at levels less than 10 ng/l (just in excess of detection limits at the time). Levels of non-carcinogenic PAH (anthracene, pyrene, fluoranthene, and naphthalene) in 10 and 15 were reported to be 100-1000 ng/l. In Wells 7 and 9, non-carcinogenic PAH levels were generally in the range of 10-100 ng/l.

Similarities in the measurements between Wells 10 and 15, and between Wells 7 and 9 could be expected since these wells are in very close proximity to each other.

Table 4-1

Carcinogenic and Noncarcinogenic PAH Included in Summaries of Total PAH

Carcinogenic PAH	Noncarcinogenic PAH
Benz(a)anthracene	Naphthalene
Chrysene	1-Methylnaphthalene
Benzo(b & k)flouranthene	2-Methylnaphthalene
Benzo(a)pyrene	Acenaphthylene
Benzo(j)flouranthene	Acenaphthene
Ideno(1,2,3-cd)pyrene	Anthracene
Dibenz(a,h)anthracene	Flourene
	Phenanthrene
	Pyrene
	Flouranthene
	Phenylnaphthalene
	1,2,6,7-Tetrahydropyrene
	9,10-Benzphenanthrene
	Benzo(e)pyrene
	Perylene
	Benzo(g,h,i)perylene

Many subsequent analyses, involving many additional PAH compounds, have been completed since these early samples. Many of the analyses have been performed long after wells were removed from service. These data have confirmed the relatively high contaminant levels in Wells 10 and 15. In Well 10, carcinogenic PAH have been detected up to 200 ng/l, while non-carcinogens have ranged up to 6000 ng/l. In Well 15, total carcinogens range to 100 ng/l, with typical values in the 10's of ng/l. Non-carcinogens have been detected in excess of 10,000 ng/l, with typical values in the 1000's of ng/l.

Wells 7 and 9 have averaged 1.0- 2.0 ng/l carcinogenic PAH, and slightly in excess of 100 ng/l non-carcinogenic PAH. Well 4 was closed in December 1979 due to rising levels of PAH. Carcinogenic PAH were typically around 2 ng/l, and non-carcinogens in the 100's of ng/l.

Well 5 was also not contaminated initially (i.e., 1978). However, by mid-1981, relatively high contaminant levels were being consistently found and the well was taken out of service. Once contaminated, levels of carcinogenic PAH were typically around 10 ng/l, and non-carcinogenic PAH were typically in the 1000's of ng/l. These values are similar to Well 15.

Overall in contaminated wells, the most frequently found carcinogenic PAH include benz(a)anthracene, chrysene, benzo(a)pyrene, and benzo(b)fluoranthene. The most frequently found noncarcinogenic PAH include anthracene, fluoranthene, acenaphthylene, phenanthrene, and pyrene. Many other PAH and other contaminants have been analyzed and detected at various times by various laboratories.

In summary, contaminated municipal wells are all in the Prairie du Chien-Jordan aquifer (although not all Prairie du Chien-Jordan wells are contaminated). Despite the fact that groundwater flow in this aquifer is generally towards the east-southeast, contaminants have reached wells

north, west, and southwest, as well as east of the Reilly site. Wells nearest to the site (5, 10, 15) appear to have the highest levels of contamination, typically at least an order of magnitude above levels found in wells farther from the site (4, 7, and 9). Levels of carcinogenic PAH in contaminated wells are generally quite low, typically less than 10 ng/l, except for wells 10 and 15, in which levels have frequently been in the 10-100's ng/l range. Levels of noncarcinogenic PAH are typically one to three orders of magnitude higher than carcinogenic PAH.

Potential Community Exposure to PAHs in Drinking Water

To relate potential health effects to consumption of contaminated drinking water in St. Louis Park, it is necessary to categorize or classify individuals on the basis of their exposure to contaminated water. Ideally, this classification would identify who was exposed to contaminated water, the duration and/or intensity of that exposure, and the timing of that exposure. At a minimum, individuals would be classified in broad categories such as "exposed" and "not exposed" or "highest exposure" and "lowest exposure." The degree and validity of the information required to classify individuals by ideal versus minimal standards would vary considerably; however, any classification scheme would require consideration of many factors. Some of these factors would include:

a. the identity and location of contaminated wells and the levels of the contaminants;

b. the likely time period when the contaminant plume first reached a given well or well field;

c. the portion of the water supply that was provided by contaminated wells over any given time period;

d. changes in the composition and the level of contaminants over time;

e. relation between contaminant levels at the well-head (where samples are almost always taken) and at the household tap;

f. the effects of typical water treatment processes (such as aeration, iron removal, chlorination, storage in reservoirs, etc.) on the nature and level of contaminants that reach the household tap;

g. characteristics of the water distribution system that may affect such factors as the pattern of distribution of contaminated waters, and the attenuation or the enhancement of contaminant levels (e.g., asbestos-cement vs. coal-tar linings);

h. the existence, if any, of contaminant residues in the water distribution system plumbing that could serve as an exposure index;

f. the existence and importance, if any, of pathways of exposure to water contaminants other than direct ingestion of water;

g. the existence, if any, of persistent tissue residues or other biological indices of chronic exposure to these contaminants;

h. the extent to which private wells or other water sources served as a drinking water supply to individuals.

Despite the extensive information base that has been developed in relation to the groundwater supply in St. Louis Park, many information deficiencies still exist that severely hinder development of a valid exposure classification model. Some of these problems and uncertainties will be identified and discussed below.

Historical Patterns of Well Contamination

Wells in St. Louis Park were not examined for PAH until 1978; consequently, it is not known which or for how long wells were contaminated with PAH before 1978. (For wells that showed contamination only after monitoring had been in effect for some time -- 4, 5, and Hopkins 3 -- it is quite possible that the start of contamination was detected, although other interpretations are also possible.) Although several types of historical water quality data do exist (e.g., phenols), there does not appear to be a reliable correlation between these parameters and PAH levels, based on current measurements. Several types of information may be considered in assessing historical patterns of well contamination such as when environmental contamination started, installation and pumping histories of city wells, properties of the contaminants, and hydrogeologic factors. Some of this information has previously been described; additional information is presented below.

Three-dimensional groundwater flow models for the St. Louis Park region have been developed by the U.S. Geological Survey (U.S.G.S.) (Stark and Hult, 1985) and by Reilly (ERT, 1983) as part of the remedial investigation. These computer models are useful in identifying strategies that may serve to reduce further spread of the contamination and in identifying (or ruling out) potential sources of contamination. Although not developed for this purpose, they may also have some potential value in establishing a time-frame in which groundwater (and/or contaminants) could reach wells from a given source.

Modeling efforts to date have indicated that, based on reasonable assumptions regarding interaquifer flow and other hydrogeologic parameters, the general easterly direction of groundwater flow in the area can be locally altered by heavy pumpage from large municipal and industrial wells.

These simulations show the possibility of flow from the Reilly site toward SLP Wells 10 and 15 (to the northeast), SLP Well 5 (to the west), and Hopkins 3 (to the southwest), given certain assumptions. These simulations do not show when contaminants might have reached specific wells, only that conditions could exist in which groundwater flow could be altered.

The potential ability of nearby, large-capacity wells to affect the direction of groundwater flow near the Reilly site would suggest that the contaminant history of the municipal wells could be complex and variable. Historical contamination of a well would depend not only on the pumping history of that well, but also on the history of the installation, pumping patterns, and abandonment of other large capacity municipal and industrial wells in the region. An illustration of this possibility can be seen in the post-1978 contaminant history. As previously noted, only Wells 7, 9, 10, and 15 showed clear evidence of contamination initially and were closed in late 1978. By late 1979, Well 4 became contaminated and was closed. Finally, in mid-1981, Well 5 began to show a rapid rise in contamination and was closed. The rise in contamination in "clean" wells following a period in which a number of large municipal and industrial wells were closed probably resulted from changes in local groundwater flow patterns. Such influences can readily be demonstrated by known computational methods and/or computer models of groundwater flow. It might be noted here that all proposed remedial plans in St. Louis Park involve the concept of "gradient control" wells whose pumpage would serve to capture or retard the spread of contamination (Hickcok, 1981; ERT, 1983; Stark and Hult, 1985).

It is reasonable to assume, therefore, that historical patterns of water and contaminant migration (and consequently well contamination) were also influenced by changing patterns of well usage in the Prairie du Chien-Jordan aquifer. As shown in Figure 4-2, new municipal wells were installed

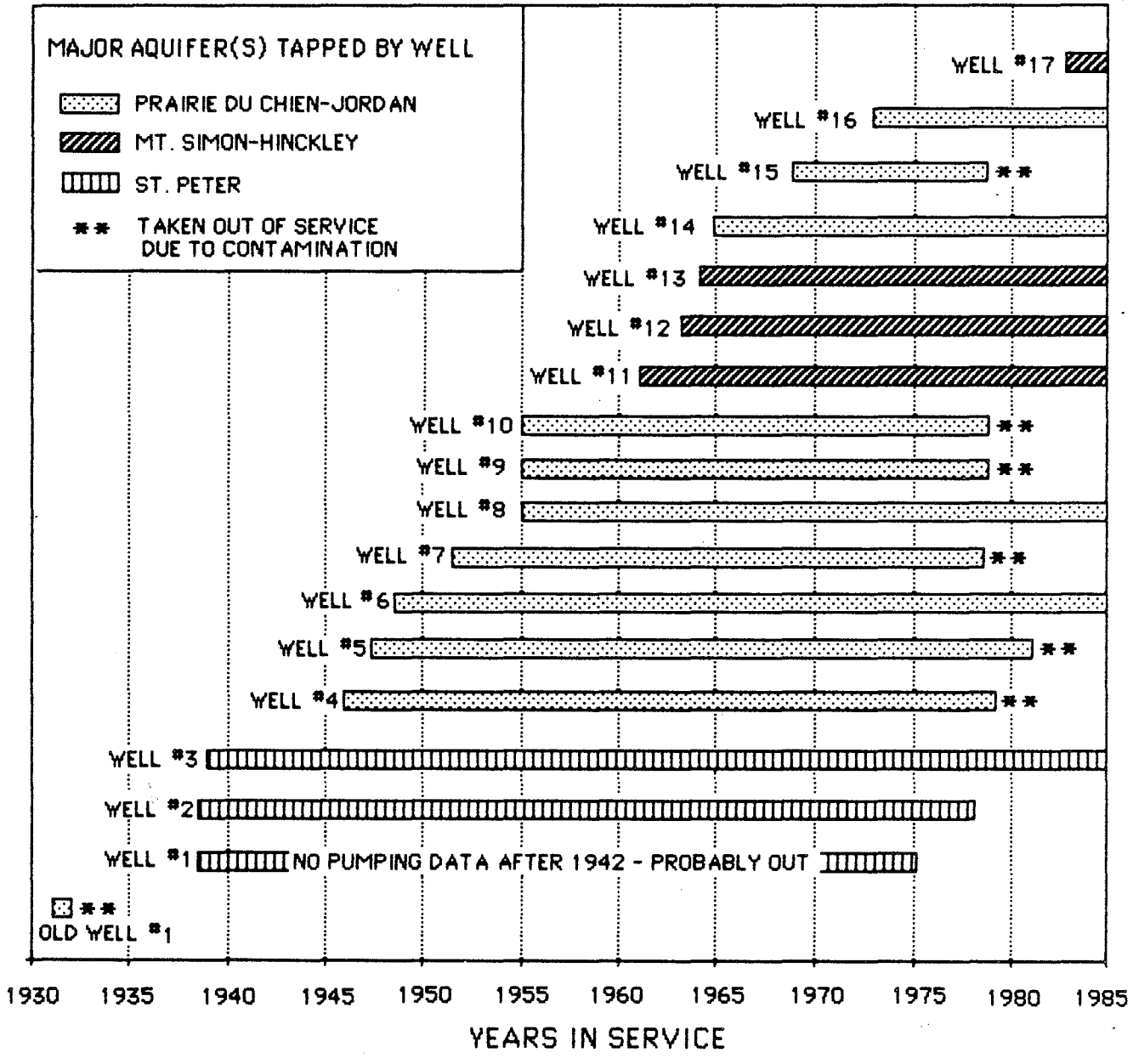
periodically since the late 1930s in St. Louis Park to meet the demands of the rapid population growth that occurred in the 1940s and 1950s. Not shown are the many industrial wells that were also installed during this period. Historical pumping data for SLP wells shows that large seasonal as well as long term changes have occurred in the patterns of pumpage from municipal wells (as well as for industrial wells).

The above information suggests that the pattern and extent of well contamination observed in 1978 or subsequent years does not necessarily reflect well contamination patterns and levels that existed during most of the history of the St. Louis Park municipal water supply. It seems likely, in fact, that a variable and complex history of contamination existed. However, the possibility that significant contamination did not reach municipal wells until comparatively recently cannot be disregarded.

Further insights into historical patterns of well contamination could possibly be gained through additional data collection and computer modeling with the U.S.G.S. groundwater flow model for St. Louis Park. It is believed by the U.S.G.S. (Stark, 1985) that, given adequate time and other resources, more specific and refined simulations (based, for example, on actual pumpage over short intervals of time) could be developed that might provide some insight into historical patterns of groundwater contamination. If such an effort were undertaken, costs of the project would be shared between state and federal agencies. It was roughly estimated that approximately two years would be required to complete the project at an approximate total cost of $140,000 (Stark, 1985).

Figure 4-2

Dates of Operation for St. Louis Park Municipal Wells



NOTES:

1. Chart indicates years in which wells were potentially in service. Individual pumping histories vary widely by season and year.
2. Old Well #1 was operated for less than several months due to a persistent phenolic taste and odor problem.
3. Wells 1, 2, and 3 are approx. 290 ft. deep; Wells 4, 5, 6, 7, 8, 9, 10, 14, 15, and 16 are approx. 450-500 ft; Wells 11, 12, 13, and 17 are over 1000 ft. deep.

Water Distribution and Treatment

Even if it were possible to establish the likely history of well contamination, there are many other components of the water supply and distribution system that could significantly affect exposure potential at individual residences. Prior to its arrival at the tap, drinking water may undergo a variety of chemical and physical treatments, remain in storage tanks or water mains for variable periods of time, and be mixed with waters from other wells. Each of these factors may have an impact on exposure potential.

Water that is pumped from wells typically undergoes several treatment processes before it enters the distribution system. In St. Louis Park, such processes commonly include aeration, iron removal, chlorination, and fluoridation. Water may be pumped into reservoirs and storage tanks or directly into the distribution system. In either case, water may or may not be mixed with water from other wells as it enters the system.

During these processes of treatment and storage, contaminants could be chemically or physically modified, resulting in a change in their concentrations and/or creation of chemical derivatives. In the case of surface water supplies, for example, in which most of the PAH is adsorbed to particulate matter, it has been shown that conventional water treatment generally eliminates well over 90% of the PAH present. In ground waters, where most PAH is not associated with particulates and where PAH concentrations are usually much lower, such large reductions have not been demonstrated. Reilly reports that an investigation of the iron removal system associated with Well 15 revealed that this process could cause some reduction in PAH, primarily carcinogenic PAH (ERT, 1983). It has been reported that chlorination can reduce high PAH levels, but is less effective with lower levels (EPA, 1980). The efficiency of this process

at the PAH levels, chlorination levels, and contact times typical of St. Louis Park has not been demonstrated. The effects, if any, of other treatment processes or the combination of processes used in St. Louis Park are also unknown.

If all operating wells in a water system were contaminated, it could be assumed that water quality at the tap would be essentially the same throughout the system (ignoring any treatment/storage differences). In St. Louis Park, however, most wells were not contaminated, and it is important to consider the implications on tap water quality. Mixing of waters from contaminated wells and uncontaminated wells can result in dilution of contaminants even before reaching the distribution system. For example, Wells 3, 10, 11, and 15 are all in close proximity and supply water to the same storage reservoir/distribution system point. Wells 3 and 11 are in different aquifers than 10 and 15 and have not been contaminated. It was common practice to operate Wells 11 and 15 together, and Wells 3 and 10 together (Tollefsrud, pers. comm., 1985).

In principle, and occasionally in practice, the water that is available at a given location in the distribution system (or at a given residence) could be derived from any one of the municipal wells. Typically, several wells are in service at a given time. Therefore, as a crude approximation of potential public exposure to water contaminants, an estimate could be made of the portion of the total yearly (monthly, daily, etc.) water pumpage that was produced by contaminated wells. This process was used, where individual well pumpage data were available, with respect to the water supply in St. Louis Park. Available records showed that the portion of the yearly water pumpage from wells 4, 5, 7, 9, 10, and 15 varied over time, accounting for as much as 60-90% of the supply during the 1950s to less than 20% during the mid-1970s. For individual wells or for

shorter periods of time, these percentages would of course be much more variable. For example, records show that Well 5 typically pumped between 250 and 450 million gallons/year during the 1950s, accounting for some 25-58% of the yearly total water supply. In the late 1970s, however, yearly pumpage from Well 5 was reduced approximately 10-fold, and represented less than 1.0 % of the yearly total.

These types of estimates do not reveal potential water quality at a given residence, in which the available water will represent some variable ratio of waters produced from wells currently or most recently in operation. Although it can often be assumed that residences located nearest to an operating well will obtain a higher ratio of their water from that well than from other operating wells that are more distant in the distribution system, the actual proportion of water at a residential tap produced from a given well would be highly variable, and could probably only be estimated with the aid of computer models of the distribution system.

It might be noted here that such an estimate of the proportion of water from contaminated wells at given locations in the distribution system has been attempted in at least one published report. In a study involving contaminated wells in Woburn, Massachusetts, the investigators estimated the yearly proportion of water available to each residence in the study that came from two contaminated wells (Lagakos et al, 1984). The basis for this numerical estimate was a distribution system model described in a draft report prepared for the Massachusetts Department of Environmental Quality and Engineering (Waldorf and Cleary, 1983). An attempt to obtain this report directly from this agency in September, 1984, was unsuccessful. According to the report's co-author, the draft report had not yet been sufficiently reviewed, and was not accepted as an official department

report at that time. A review of the report, to involve a new pressure-gradient model, was reported to be in progress (Cleary, 1984). Thus, the applicability of this distribution-model approach to St. Louis Park could not be evaluated. However, in light of the number of contaminated wells, the variability of contaminant levels over short periods of time, the influence of pumping patterns on groundwater and contaminant flow, the long and varied pumping histories of the municipal wells, and the lengthy history of potential contamination, it seems unlikely that such a distribution model, even if one could be constructed for St. Louis Park, would be of significant value or validity in distinguishing historical exposure levels at individual residences. As noted above, a major proportion of the total yearly water production in St. Louis Park in the 1950s (and possibly in the 1960s) was supplied by wells that were found to be contaminated. It would appear that a more significant unresolved issue in this situation is the timing and duration of the period(s) of contamination for each well.

Distribution System Liners and Sealers

Another aspect of the distribution system that relates to potential community exposure to PAHs is the nature of the lining of the water mains. Water mains and storage tanks in the U.S. have often been lined or sealed with coal-tar or asphaltic compounds (NAS, 1982). Much of the St. Louis Park distribution system was installed prior to 1950 when such liners were commonly used, and it is likely that much of the system has such lining materials. The Safe Drinking Water Committee of the NAS has summarized a variety of laboratory and field studies that have demonstrated that PAH constituents in such lining materials can be leached into the water depending on such factors as the composition and age of the lining, water

volume to surface area, contact time, and manner of application (NAS, 1982). It appears that there is potentially much greater leaching of PAH from coal-tar liners than asphaltic liners or sealers, reflecting the much higher concentration of PAH in coal-tar lining materials. Studies indicate that such liners can contribute a wide variety of PAHs and heterocyclics, including both carcinogenic and noncarcinogenic compounds, to waters in the distribution system. However, the greatest increases in PAH in distribution and/or storage tank waters have been reported for phenanthrene/anthracene, fluoranthene, chrysene, and naphthalene. PAH levels can be increased by several ng/l to several ug/l.

The impact of potential PAH leaching from the distribution system in St. Louis Park is very difficult to assess. Little seems to be known about the factors that affect the degree and duration of leaching in actual systems, and little is known in particular about lining materials in St. Louis Park. Although an enormous number of samples of water at the well head have been analyzed, almost no samples of tap or distribution water have been analyzed. A few tap samples were apparently taken from three or four residences between 1982 and 1984 under unknown conditions. Interestingly, ng/l quantities were reported in several samples for phenanthrene, anthracene, fluoranthene, fluorene, and pyrene. A much larger and better defined sampling program would be required to reveal the existence, patterns, and magnitude of distribution-system derived PAH in tap water. As with the raw water quality, it is quite likely that distribution water quality has varied, depending on when water mains were installed, the exact nature of the lining, the volume of water passing through sections of main over time, and many other factors.

In addition to its potential contribution to PAH levels in drinking water, the likely existence of coal-tar or asphaltic liners/sealers also

affects exposure assessments in another manner. It has occasionally been suggested that an approach to determining historical exposures might be to measure PAH residues that may have been deposited over time on the interior surfaces of the distribution system mains. It was previously noted that deposits of coal-tar materials were very evident in a well located on the Reilly site. However, this approach obviously would not appear to be feasible where mains have been lined with PAH-containing materials.

Conclusion

Despite the extensive information base that is available regarding contamination of groundwater and municipal wells in St. Louis Park, it is not presently possible to identify either the duration or the magnitude of community exposure to water contaminants. Although contamination of the major aquifer occurred by at least the 1930s, many scenarios are possible regarding the history of municipal well contamination and the extent to which contaminants would have reached consumers' taps.

Properties

Polynuclear aromatic hydrocarbons (PAHs) represent a very large group of compounds that are formed during most combustion and high temperature processes. They are ubiquitous in the environment from both natural and man-made sources. Chemically, they are composed of the elements of hydrogen and carbon with two or more fused aromatic rings. In alkyl-substituted PAH, one or more hydrogen atoms are replaced by an alkyl (e.g., methyl) group. Frequently included in discussions of PAH are those compounds in which a ring carbon atom has been replaced by a nitrogen, oxygen, or sulfur atom. Such analogs are referred to as heterocyclic PAH. The best known and most studied PAH is the carcinogen benzo(a)pyrene (BaP). Benzo(a)pyrene was one of the first pure chemical compounds demonstrated to be carcinogenic in an animal in the 1930s (IARC, 1985).

The structure and the chemical and physical properties of a wide variety of PAH are described in various review documents (e.g., EPA, 1980; Santodonato et al., 1981; NAS, 1983b; IARC, 1973; 1983) and will not be detailed here. In general, however, these compounds can be characterized as having high lipophilicity, extreme insolubility in water, low vapor pressure, and high melting and boiling points (IARC, 1983; NAS, 1983b). PAH also absorb ultraviolet light and fluoresce strongly.

Both in air and water, PAH are usually associated with or adsorbed to particulate matter. Although many PAH oxidize or photodegrade rapidly under atmospheric conditions, at least 20 PAHs are apparently stable enough when adsorbed to airborne particles to be transported long distances and may have lifetimes on the order of days (Santodonato et al., 1981; IARC, 1983).

In the aqueous environment, PAHs with three or more rings appear to be extremely stable compared to lower molecular weight PAH which can be rapidly biodegraded. Photodegradation appears to play little role in the aquatic environment. Lake and marine sediments may be regarded as an environmental sink for PAH (IARC, 1983).

As in aquatic environments, it has been shown that microorganisms in the soil can degrade PAH compounds, albeit slowly for higher molecular weight compounds such as BaP. Soil PAH is not transferred to a significant degree through root absorption to the consumed portions of crops (Santodonato et al., 1981).

Sources and Occurrence of PAHs

Polynuclear aromatic hydrocarbons result from essentially every combustion process. Some examples of important sources of emissions include the following (NAS, 1983b):

- Automobiles and trucks
- Other mobile sources (e.g., planes and ships)
- Fireplaces
- Wood-burning stoves
- Residential coal-fired heating
- Industrial coal-fired heating
- Coke production
- Industrial-commercial incinerators
- Agricultural open burning
- Land-clearing waste burning
- Prescribed burning of underbrush in forests
- Forest and prairie fires
- Structural fires
- Coal-refuse fires
- Volcanoes

It is well-established that these compounds are present in trace amounts, throughout the atmospheric, terrestrial, and aquatic environments. They are present in tobacco smoke, air (industrial and ambient), water, food, soil, sediments, aquatic organisms, mineral oils, and refined petroleum products (IARC, 1983). Thus, human exposures occur through

direct inhalation of tobacco smoke and polluted air, ingestion of contaminated and processed food and water, or by skin contact with soot, tar and oils (IARC, 1983).

Levels and Sources in Air

Non-occupational exposures to PAH via inhalation result primarily from smoking and from urban air polluted with emissions from coal combustion (industry and power plants), waste incinerators, domestic heating, and vehicles powered by gasoline or diesel fuels (IARC, 1983).

A large number of PAH compounds have been firmly identified in tobacco smoke and many more probably exist in trace amounts. Some of these compounds are quantified in Table 4-2. It is estimated that BaP intake from smoking alone is approximately 400 ng/day.

The levels and ratios of PAH compounds produced from combustion of fossil fuels can vary by several orders of magnitude depending on the fuel source and the conditions of combustion. Most studies of atmospheric PAH have used BaP levels as a surrogate for total PAH or for carcinogenic PAH, although it is generally recognized that BaP does not exist in a constant ratio to other PAHs. EPA estimates cited in Santodonato et al. (1981) of total BaP emissions from different sources for 1985 are shown in Table 4-3.

The National Academy of Sciences (1983b) estimates of total BaP emissions for 1975 and 1985 are as follows:

	BaP Emission, Metric Tons	
Estimate	1975	1985
Minimum	346	67
Intermediate	588	358
Maximum	1676	885

Table 4-2

Concentrations of Some PAH Compounds in Tobacco Smoke[a]

Compound	Cigarette Main Stream Smoke (µg/100 cigarettes)	Smoke Polluted Environment (ng/cubic meter)
Anthanthrene	0.2-2.2	0.5-3
Anthracene	2.3-23.5	
Benz(a)anthracene	0.4-7.6	
Benzo(b)fluoranthene	0.4-2.2	
Benzo(j)fluoranthene	0.6-2.1	
Benzo(k)fluoranthene	0.6-1.2	
Benzo(g,h,i)fluoranthene	0.1-0.4	
Benzo(a)fluorene	4.1-18.4	39
Benzo(b)fluorene	2	
Benzo(g,h,i)perylene	0.3-3.9	5.9-17
Benzo(c)phenanthrene	present	
Benzo(a)pyrene	0.5-7.8	2.8-760
Benzo(e)pyrene	0.2-2.5	3-18
Chrysene	0.6-9.6	
Coronene	0.1	0.5-2.8
Dibenz(a,c)anthracene	present	
Dibenz(a,h)anthracene	0.4	
Dibenz(a,h)anthracene	1.1	6
Dibenzo(a,e)pyrene	present	
Dibenzo(a,h)pyrene	present	
Dibenzo(a,i)pyrene	0.17-0.32	
Dibenzo(a,l)pyrene	present	
Fluoranthene	1-27.2	99
Fluorene	present	
Ideno(1,2,3-cd)pyrene	0.4-2.0	
1-Methylchrysene	0.3	
2-Methylchrysene	0.12	
3-Methylchrysene	0.61	
4-Methylchrysene	present	
5-Methylchrysene	0.06	
6-Methylchrysene	0.7	
2-Methylfluoranthene	present	
3-Methylfluoranthene	present	
Perylene	0.3-0.5	0.1-11
Phenanthrene	8.5-62.4	
Pyrene	5-27	2-66
Triphenylene	present	

[a] Modified from IARC (1983). See IARC for original references.

Table 4-3

Estimates of Benzo(a)pyrene Emissions, Metric Tons/Year[a]

Source	Intermediate Estimate for 1985
Coal-Fired Power Plant	1.1
Coal-Fired Industrial Boiler	0.1
Coal-Fired Residential Furnaces	26
Residential Fireplaces	77
Oil-Fired Industrial Boilers	1.8
Oil-Fired Commercial/Institutional Boilers	24
Oil-Fired Residential Boilers	1.2
Gas-Fired Industrial Boilers	0.025
Gas-Fired Commercial/Institutional Boilers	0.71
Gas-Fired Residential Furnaces	0.43
Coke Production	21
Alphalt Production	0.0126
Other Industrial Processes	0.74
Incinerators	2.127
Open Burning	~0
Agricultural & Forest Fires[b]	9.5-127
Burning Coal Refuse Banks[b]	280-310
Auto (gasoline)	0.21
Auto (diesel)	5.4
Trucks (diesel)	0.21
Rubber Tire Wear[b]	0-11
Motorcycles	5.4

[a] Modified from Santodonato et al. (1981), based on 1978 EPA estimates.
[b] Values represent estimated range for 1978.

BaP concentrations in 34 urban areas in the U.S. showed a steady and significant decrease over the period 1966 to 1975, with the median of average annual concentrations falling from 3.2 ng/m^3 to 0.5 ng/m^3 (Santodonato et al., 1981). This decline, as well as the reduction in seasonal variation in BaP levels, has been attributed primarily to the reduced use of coal as a fuel in residential heating units. The average daily BaP concentration in the urban atmosphere in 1979 was calculated to be 1.3 ng/m^3 (NAS, 1983b). However, urban BaP concentrations as high as 74 ng/m^3 have been reported in the U.S. Within an urban area "hot spots" of BaP concentrations can occur in such locations as roadway tunnels with heavy traffic congestion (50 ng/m^3) or along heavily congested freeways (10 ng/m^3). Exposures in such situations are usually relatively brief.

The general contribution of auto emissions to BaP or other PAH levels varies in urban areas. In Los Angeles, for example, it was estimated that at least 60% of PAH was contributed by automotive emissions (NAS, 1983b). In contrast, in Detroit, in which there is extensive use of coal, oil, and wood combustion, it was estimated that only 5-42% of ambient BaP was contributed by auto emissions. It was also noted that typical BaP levels were several times higher in Detroit than in Los Angeles. Recent studies in New Jersey indicated that PAH levels were 3-5 times higher in urban locations than in rural locations, and that winter levels were 4-6 times higher than summer levels (Greenberg et al., 1985). It was estimated that 98% of summer emissions were due to motor vehicles, while 98% of winter emissions were due to residential wood combustion.

As noted above, a major and increasing contributor to local PAH emissions is wood-burning, through stoves or fireplaces. PAH or BaP emissions from wood-burning, whether measured per kilogram of fuel burned or per unit of heat produced, is several orders of magnitude greater than

that for coal, oil or gas (NAS, 1983b). The NAS cites a number of studies and reports that indicate that wood burning stoves and fireplaces are the single largest source of polycyclic organic matter, emitting almost 4000 metric tons annually, or about one-third of total emissions. It has also been shown that indoor BaP concentrations over 24 hours were five times greater when wood stoves were in use (NAS, 1983b).

A summary of the large number of PAHs that have been detected and quantified in urban air by various investigators is given in the reviews by Santodonato et al. (1981) and the NAS (1983b). Although not all have been quantified, approximately one hundred compounds have been detected in urban air, and many more are probably present. Finally, it should be noted that significant exposures to PAH-containing mixtures can occur in the workplace environment. For example, coke-oven workers in the U.S. may be exposed to BaP concentrations on the order of ten thousand ng/m^3, and even higher levels may be found associated with pavement tarring, roof tarring and coal-tar pitch working areas (IARC, 1985).

The total human intake of PAH through inhalation will depend on many factors, such as geographic location, smoking habits, occupation, use of fireplace, etc. However, Santodonato et al. (1981) have provided an estimated range of inhalation intake due to ambient air concentrations. These estimates are given below. They do not take into account personal factors such as occupation and smoking, which can significantly modify individual exposure.

	BaP	Carcinogenic PAH	Total PAH
Ambient Air Concentration, ng/m^3	0.5-2.9	2.0	10.9
Inhalation Intake*, ng/day	9.5-43.5	38	207

* Assumes 19 m^3 of air breathed per day (ave. of adult and children)

Levels and Sources in Water

Reviews by the National Academy of Sciences (1982; 1983b) and the International Agency for Research on Cancer (1983) indicate that there are a number of sources of PAH in the aquatic environment:

- industrial and domestic sewage effluent
- surface runoff from land (soil, roads, etc.)
- atmospheric fallout and precipitation
- spillage of petroleum and petroleum products

The immediate source of PAH in a given body of water will vary and may be any of the above (e.g., municipal sewage, street runoff). In general, however, several lines of evidence indicate that anthropogenic combustion is the major ultimate source of PAH in surface waters and sediments (Santodonato et al., 1981). In fact, PAH levels in sediments closely reflect the extent and proximity of industrial emission sources, and sediments may be considered an environmental sink (IARC, 1983).

In ground waters, PAH contamination is related to leaching from contaminated soils. Reported BaP levels in soil (most soil data are for BaP) show great variation but are commonly in the mg/kg (ppm) range. Where obvious contamination has occurred by coal-tar, BaP levels as high as 650 ppm in soil have been reported (Santodonato et al., 1981).

In tap waters, an additional source of PAH can arise in situations where the distribution mains and/or storage tanks are lined with coal tar or asphalt materials (NAS, 1982). Depending on a variety of factors (such as the age of the lining, type of lining, contact time, etc.), it has been demonstrated that PAHs can leach from these linings resulting in higher PAH levels at the consumer tap than in the raw or finished waters. In Portland, Oregon, for example, the level of phenanthrene in water at the end of a 2.4 mile coal-tar lined pipe was 3225 ng/liter compared to 3 ng/liter at the source. Several other PAHs were also increased by several

orders of magnitude. In another example, Alben (1980) reported a significant increase in PAH levels in a water storage tank that had a five-year old coal-tar coating. The PAH level at the tank outlet was 410 ng/l while water at the inlet had a level of 29 ng/l. Concrete-lined pipes, on the other hand, may reduce PAH levels in the water (NAS, 1982).

The BaP and total PAH concentration in U.S. surface waters are reported to range from 0.6 to 350 ng/l and 140 to 2500 ng/l, respectively (NAS, 1982). Conventional water treatment processes in the U.S. reduce PAH levels significantly from surface water sources. PAH concentrations in finished surface water supplies are reported to range from 3- 138 ng/l for total PAH and 0.1 to 2 ng/l for BaP (NAS, 1982). Santodonato et al. (1981) cite studies as showing average concentrations in U.S. drinking waters as follows: BaP, 0.55 ng/l; the sum of three carcinogenic PAH (BaP, benzo(j)fluoranthene, indeno(1,2,3-cd)pyrene, 2.1 ng/l; and total PAH, 13.5 ng/l. Somewhat higher values have been reported in European drinking waters -- 3-5 ng/l carcinogenic PAH and 40-60 ng/l total PAH.

In a recent study, aggregate PAH levels in twelve Great Lakes finished water supplies were reported to range from about 8 to 3000 ng/l (Williams et al., 1982). Most supplies fell in the range of 10-200 ng/l, with summer values usually much lower than winter values.

Reported levels of PAH in surface, tap, and ground waters in the U.S. and Europe have been summarized in recent reviews (IARC, 1983; Santodonato et al., 1981; NAS, 1982). Table 4-4 presents some of the water PAH data summarized by IARC (1983).

These data reveal that wide variations can occur in the PAH levels in various waters, that raw surface waters generally have much higher PAH levels than raw ground waters (in contrast to the situation with volatile organics), and that conventional water treatment processes significantly

Table 4-4

Concentration Range of Some PAHs in Water (ng/liter)[a]

PAH Compound	Surface	Ground	Tap	Rainfall
Anthanthrene	0.2-10.9			
Anthracene	1000		1.1-59.7	
Benz(a)anthracene	1.9-30.6	0-1.3	0.4-10.7	3.2-12.3
Benzo(b)fluoranthene	0-320	0.5-9.0	0.6-45	4.4-840
Benzo(j)fluoranthene	0.6-1.2	0.6-1.3		2.6-11.1
Benzo(k)fluoranthene	0-400	0.2-3.5	0.9-0.8	1.6-450
Benzo(g,h,i)fluoranthene	1.0-11.2			
Benzo(g,h,i)perylene	0-390	0.3-5	0.8-130	0-275
Benzo(c)phenanthrene	1.0-9.1			
Benzo(a)pyrene	0-13000	0.1-6	0-1000	10-1000
Benzo(e)pyrene	3.4-30.8			
Chrysene	7.6-62.0			
Fluoranthene	4.7-1200	3.5-100	7.2-132.6	5.6-1460
Fluorene	3000		4-16	
Ideno(1,2,3-cd)pyrene	0-350	0.2-5.0	0.3-75	0-1020
Perylene	0.2-520	0-0.2	0.1-1.4	0-1.0
Phenanthrene	0-1300		24-90	
Pyrene	2.0-530	1.6-2.5		5.8-27.8

[a] Modified from IARC, 1983. Presumably values are for European waters.

reduce PAH levels found in surface waters. Based on calculated average values, Santodonato et al. (1981) developed the following estimates of average daily PAH intake from drinking water:

	BaP	Carcinogenic PAH	Total PAH
Ave. Water Concentration, ng/l	0.55	2.1	13.5
Drinking Intake*, ng/day	1.1	4.2	27

* Assumes 2 liters of water consumed per day

Levels and Sources in Food

A large number of studies since the early 1960s have demonstrated that a wide variety of foods are contaminated with small amounts of PAHs. PAHs have been found in broiled and smoked fish and meat, smoked cheese, roasted coffee, seafood, vegetables, vegetable oils, margarine, grains, fruits, sugar, whiskey, rum, and a number of other food products (Santodonato et al., 1981; IARC, 1983). Some of the BaP levels reported in various foods are indicated in Table 4-5.

The sources and levels of PAH in food are related to the type of food and its method of preparation. Atmospheric deposition may be a major source for many surface crops, whereas absorption of PAH from soil may be important for root crops such as carrots and potatoes. (As noted above, soil PAH levels are frequently in the ppm range, and are believed to be related to atmospheric fallout or contamination.) Food and beverage containers are another source. Although raw meats generally do not contain PAH, the smoking and/or cooking of meats (and fish) can be a significant source of PAH in these foods. Table 4-6 shows PAH levels in charcoal-broiled steaks as determined in one of the earliest studies (1964) of PAHs in foods.

Table 4-5

Reported Concentrations of Benzo(a)pyrene in Some Foods and Beverages, g/kg (ppb)[a]

Food	Concentration[b]
Smoked ham	0.5-14.6
Smoked bacon	0.16-0.25
Smoked sausages	0.05-0.08
Various smoked meats	33.5
Smoked fish	0.2-6.6
Broiled meats	0.17-0.63
and sausages	3.7-50
Charcoal-broiled fish	0.2-0.9
Charcoal-broiled steak	4.4-50.4
Barbecued ribs	10.5
Cereals	0.2-4.1
Potatoes (peelings)	0.36
(tubers)	0.09
Grain	0.73-2.3
Flour, untreated	0.73
Flour, dried	4.4
Bread	0.23
Bread, toasted	0.39-0.56
Lettuce	2.8-12.8
Tomatoes	0.2
Spinach	7.4
Fruits	0.02-30
Chocolate	0.2-1.7
Margarine	0.9-36
Coconut oil	0.3-8.2
Sunflower oil	0.2-62
Coffee, roasted	0.3-15.8
Tea leaves	3.9-21.3
Dark rum	1.0
Whiskey	0.04

[a] From data cited in Santondonato et al. (1981) and IARC (1983).

[b] Only includes detected values; for many food products, particularly vegetables, the actual range of values in cited reports includes "not detected", although detection limits are not specified.

Table 4-6

Some PAH Compounds in Charcoal-Broiled Steaks, μg/kg (ppb)[a]

Compound	Reported Concentrations	
Anthanthrene	2	
Anthracene	4.5	
Benz(a)anthracene	4.5	1.4
Benzo(g,h,i)perylene	4.5	6.7
Benzo(a)pyrene	8	5.8
Benzo(e)pyrene	6	5.5
Chrysene	1.4	
Coronene	2.3	
Dibenz(a,h)anthracene	0.2	
Fluoranthene	20	43.0
Perylene	2	
Phenanthrene	11	21.0
Pyrene	18	35.0

[a] Data from Lininsky and colleagues cited in Santodonato et al. (1981) and IARC (1983).

The amount of BaP formed depends on the cooking temperature, type of fuel used, the fat content of the meat, and other cooking conditions (such as whether the heat source is above or below the food). Most of the BaP found in smoked foods is in the superficial layer of meat. The presence of PAH in cooked or smoked meats is not fully understood, but PAH is probably formed during combustion, and is then deposited on the food. No information appears to be available on the PAH levels in many common foods (such as dairy products) or on the stability of PAHs in foods (Santodonato et al., 1981).

Estimates of average daily PAH intake from food have been made by Santodonato et al. (1981). These estimates must be considered in light of the large uncertainties about PAH levels in many common foods and the variability in personal diet and food preparation methods. The above authors believe, however, that the estimates given below are likely to be accurate to within an order of magnitude:

	BaP	Carcinogenic PAH	Total PAH
Typical Concen. Range in Food, ng/kg	100-1000	-------	1000-10,000
Dietary Intake*, ng/day	160-1600	-------	1600-16,000

* Assumes 1600 g/day total food intake

Other Potential Sources of Exposure to PAH

Although significant skin contact with PAHs occurs mainly in several occupational groups, exposure can also occur in the general population. Cosmetic and medicinal products containing mineral oils, coal-tars, and refined petroleum products may contain PAH compounds (IARC, 1983; 1985). Examples of cosmetic preparations that may contain refined petroleum products include cold creams, cleansing creams, suntan oils, baby lotions or creams and lipsticks. Pharmaceutical coal-tar ointments (which usually

contain 1-10% coal-tar) and shampoos have long been used in the treatment of various skin conditions such as psoriasis. PAH levels in pharmaceutical-grade coal-tars are reported to be in the mg/kg (ppm) range (IARC, 1985).

Summary of Population PAH Intake

Recent reviews indicate that, mainly as a result of anthropogenic combustion, PAH compounds are ubiquitous in the environment and essentially the entire population is continuously exposed to trace amounts of PAH through food, water, and air. Except for those with specific occupational exposures (such as coke-oven workers, foundry workers, roofers, creosote workers, and many others), the greatest degree of exposure in the population occurs through ingestion of food rather than through inhalation of ambient air or ingestion of water. Estimates by Santodonato et al. (1981) of average daily intake for BaP, carcinogenic PAH, and total PAH are given below:

	Average Daily Intake, ng/day		
Source	BaP	Carcinogenic PAH	Total PAH
Air	9.5-43.5	38	207
Water	1.1	4.2	27.0
Food	160-1600		1600-16,000
Smoking	400		

Absorption, Distribution, Metabolism, and Excretion

Due to their chemical properties, PAHs are rapidly absorbed through the respiratory tract, the gut, and the skin. Respiratory absorption is dependent not only on the characteristics of the PAH, but also on the properties of the carrier particles to which the PAHs are usually adsorbed. PAH is eluted from particles deposited in the lung and can then interact with respiratory tissues or enter the systemic circulation. Mucociliary clearance and subsequent swallowing of respired particles results in additional absorption of PAH via the gastrointestinal tract.

However absorbed, PAHs are quickly distributed to a wide variety of tissues. The level of PAH observed in any given tissue is dependent on factors such as the particular PAH administered, the route and vehicle of administration, and the presence of inducers of PAH metabolism (IARC, 1983). Relative to other tissues, unmetabolized PAH may be extensively localized in mammary and other fat tissues where it is more slowly released.

It has long been recognized that regardless of the route of administration, PAHs are primarily removed from the body by hepatobiliary excretion and elimination through the feces. A relatively small amount is eliminated through the urine. The route of administration may, however, have an important effect on the rate of elimination of PAH. Xenobiotics, such as PAHs, that are absorbed from the gastrointestinal tract reach the liver via the portal circulation before reaching the systemic circulation. PAHs absorbed through the skin or respiratory tract reach the systemic circulation without a "first-pass" through the liver. The importance of hepatobiliary metabolism and excretion suggests that orally administered

PAH would have higher rates of elimination and lower tissue levels relative to other routes of administration; this is supported by experimental data (IARC, 1983) Thus, it has been postulated that the first-pass liver metabolism, as well as biotransformation by enzymes of the intestinal mucosa, could represent an effective mechanism for handling ingested PAH (Santodonato et al., 1981).

IARC (1983) notes that there is an enormous and exponentially growing literature on PAH metabolism, in contrast to the relatively scant literature on absorption and distribution. Recent reviews of the literature on PAH metabolism indicate that the following aspects of PAH metabolism have generally been established:

(1) PAH are metabolized by the cytochrome P-450 dependent mixed-function oxidase system, often designated aryl hyrodrocarbon hydroxylase (AHH).

(2) This enzyme system is readily inducible by exposure to PAH (and certain other compounds) and is present in most tissues in humans and other mammals, particularly in the liver.

(3) Carcinogenic properties of PAH are derived from electrophilic metabolites, and it is one (or more) of these metabolites that is believed to be the "ultimate" carcinogen.

(4) To date, mutagenicity, DNA binding, cell transformation, metabolism and tumorgenicity studies have indicated that the so-called "bay region" diol epoxide metabolites of about a dozen PAHs are the ultimate carcinogenic chemical forms.

(5) Great variation exists among individuals, and tissues within an individual, in ability to induce the AHH enzyme system.

(6) The similarities in metabolic profiles of PAH in different tissues and different species appear much more dramatic than the differences;

however, there are numerous studies that show both quantitative differences and qualitative differences in PAH metabolism depending on such factors as target species and tissues, sex, diet, exposures to other chemical agents, and the specific PAH compound. Higher primates and human tissues appear to produce a more complex pattern of PAH metabolites (Leber et al., 1976; Selkirk et al., 1976).

(7) Because PAHs are generally rapidly metabolized by a variety of tissues, there appears to be little tendency for PAHs to bioaccumulate in the fatty tissue of people or animals or to be magnified through the food chain. Several marine organisms, however, may effectively concentrate PAH and represent an important exposure if consumed.

(8) PAH metabolites can form covalent bonds with cellular macromolecules including DNA, RNA and proteins. The PAH-nucleic acid adducts found in human tissues are essentially the same as those found in animal tissues [it is believed by many scientists that the binding of a foreign compound to DNA is the essential initial event leading to mutagenicity or carcinogenicity].

In sum, the enzyme system that metabolizes PAH compounds can be found in most mammalian tissues and is rapidly induced by the presence of PAH. Metabolism of PAH compounds serves at the same time to detoxify and eliminate them from the body as well as to produce activated derivatives that possess the mutagenic and carcinogenic activity. Once absorbed, PAH compounds can become rapidly and widely distributed through the body. Elimination occurs mostly through the feces.

Non-carcinogenic Effects

Most of the research on health effects of PAH exposure has focused on their carcinogenic potential. Carcinogenic effects occur at exposure

levels much lower than those needed to produce other types of toxic effects. However, other toxic effects have been recognized with several PAH. In general, normally proliferating tissues (intestinal epithelium, bone marrow, lymphoid organs, testis) are the major targets of PAH toxicity (Santodonato et al., 1981). In the skin, sebaceous glands are the most sensitive structure. Chronic intratracheal exposure in hamsters to certain PAH resulted in acute pneumonia and chronic pneumonitis as well as significant mortality. Epithelial proliferation and cell hyperplasia is a common observation in the tracheobronchial mucosa of animals directly exposed to carcinogenic PAH. Carcinogenic PAH can also produce an immunosuppressive effect, although the importance of this effect to carcinogenesis is unclear (Santodonato et al., 1981).

Reproductive and teratogenic effects have been studied in relatively few PAH. Studies cited by Santodonato et al. (1981) and NAS (1983b) indicate that the feeding of large doses of BaP (up to 1.0 mg/g of food) to rats or mice had no impact on various reproductive variables and generally produced no abnormalities, despite the fact that BaP can cross the placenta. However, it has been shown that prenatal treatment of pregnant mice with large doses of BaP can enhance tumor development in both the lung and skin of offspring during the postnatal period. A large intravenous dose of DMBA can produce significant teratogenic effects.

Carcinogenic Effects

PAH were the first class of compounds shown to be carcinogenic in animal experiments. In fact, as early as 1918 it was shown by Japanese investigators that coal-tar (which contains many PAH in addition to other organics) could cause skin tumors when applied to the skin of animals (IARC, 1985). BaP and dibenz(a,h) anthracene were shown to produce skin

cancer in mice approximately fifty years ago. Since that time, a large body of research has shown that many other individual PAH compounds and PAH-containing mixtures (such as coal-tars, asphalts, creosotes, coke oven emissions, and auto exhausts) are carcinogenic in a variety of animal species and by different routes of administration (Santodonato et al., 1981; NAS, 1983b; IARC, 1983; 1985). As described by Santodonato et al. (1981), carcinogenic PAH are distinctive in that "(1) several PAH are among the most potent carcinogens known to exist, producing tumors by single exposures to microgram quantities, (2) they act both at the site of application and at organs distant to the site of absorption, and (3) their effects have been demonstrated in nearly every tissue and species tested, regardless of the route of administration."

Oral administration of certain PAH to rodents can produce tumors of the forestomach, mammary gland, ovary, lung, liver, and lymphoid and hematopoetic tissues (Santodonato et al., 1981). Intratracheal or direct pulmonary exposure to very small doses can produce tumors of the respiratory tract. In addition, as previously mentioned, application of a variety of PAH to the skin can produce skin tumors.

Interestingly, it has proven extremely difficult to induce malignant tumors with PAH in certain higher primates despite several attempts to do so. Various PAHs that produce tumors in rodents have not produced tumors under similar experimental conditions in rhesus, cynomologus, and squirrel monkeys (Adamson et al., 1970).

In short-term *in vitro* cell tests (bacterial mutation, mammalian cell transformation, etc.), many PAH have shown activity. In addition, some PAH are positive in *in vivo* tests for genetic or chromosomal effects such as sister chromatic exchange (NAS, 1983b). No correlation has been found, however, between the quantitative aspects of sister chromatic exchange and

carcinogenicity of PAH. Reviews of the findings from a large battery of short-term tests for various PAH can be found in Santodonato et al. (1981), NAS (1983b), IARC (1983), and IARC (1985).

As previously noted, it has been demonstrated in many tissues and species (including humans) that certain PAH metabolites can bind at specific locations on DNA, RNA, and proteins. The PAH metabolite-DNA adducts are of particular interest in that it is currently believed by most researchers that this interaction is the essential first step in PAH-induced carcinogenesis (NAS, 1983b). Numerous studies have examined various qualitative and quantitative aspects of the formation and the elimination of these adducts and their relation to carcinogenesis. It has been shown that administration of AHH inducers to animals prior to BaP exposure reduces BaP metabolite-DNA adduct formation *in vivo*, although the opposite effect occurs *in vitro*. These same AHH inducers also sharply inhibit BaP carcinogenesis in animals. A consistent correlation does not exist, however, between the ability of a tissue to form adducts and its sensitivity to carcinogenesis (NAS, 1983b). It has been shown in several studies that a dose-response relationship appears to exist between formation of PAH metabolite-DNA adducts and PAH exposure dose, and that there is no observed threshold. Based on these and other aspects of adduct formation, a committee of the NAS concluded that specific PAH metabolite-DNA adduct amounts are clearly a good measure of effective biologic dose that could be used for "low-dose extrapolation of carcinogenic data, for the ranking of a series of similar carcinogens, and for determining the effect on neoplasia of pretreatments that alter the metabolism of a carcinogen" (NAS, 1983b).

Numerous studies have shown that, in addition to AHH inducers, antioxidants and certain other compounds are effective inhibitors of PAH-

induced carcinogenesis. Among other compounds, this action has been demonstrated with selenium, alpha-tocopherol (Vitamin E), ascorbic acid, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), flavones, Vitamin A, and benzyl isothiocyanate and phenethyl isothiocyanate (both the latter found in cruciferous plants) Santodonato et al. (1981).

Environmental exposures to PAH almost always involve a complex mixture of PAHs (along with other compounds), and a few studies have examined the carcinogenic effects of mixtures of PAH. Such mixtures offer the potential for various types of interactions such as synergism or antagonism. Studies reviewed by Santodonato et al. (1981) and NAS (1983b) indicate that such mixtures are frequently either inhibitory or have no effect on the activity of the carcinogenic PAH present in the mixture. For example, NAS (1983b) cites data from Misfield that show that a mixture of 13 PAH in proportions that simulate auto exhaust condensate, most of which were carcinogenic, was essentially similar to the BaP fraction alone in inducing skin tumors in mice. Data of Falk et al. cited by Santodonato et al. (1981) showed that when BaP was administered to mice together with various non-carcinogenic PAH commonly found in polluted atmospheres, a marked inhibition of carcinogenesis was observed in all cases. Early studies of the effects of simple pairs of PAH, however, show all possible interactions - no effect, additive, antagonistic, and synergistic. In addition, it has been shown that the timing and sequence of application of the pair affects the outcome, further complicating the situation. It should be noted that none of the cited studies on mixtures involved oral exposures.

There is convincing evidence that heavy exposures to PAH-containing materials in humans is etiologically associated with an excess of lung cancer. The best known and most common source of exposure is, of course, smoking. Although there remains little doubt that smoking is the

overwhelming cause of lung cancer, it is less clear to what degree the PAHs in cigarette smoke contribute to the risk. There have been a number of occupational epidemiologic studies that clearly demonstrate that very high workplace exposures to such PAH-containing mixtures as coal gas, tars, soot, and coke-oven emissions confers an elevated lung cancer risk (see Santodonato et al., 1981; NAS, 1983b; EPA, 1980, 1983, 1984a; IARC, 1985). Individual PAH levels in such workplace environments show enormous variability but are frequently in the microgram/m^3 range or higher, and human exposure can thus be several orders of magnitude higher than from smoking (IARC, 1985). As in the case with smoking, it is difficult to determine to what degree the PAH component of the workplace air contributes to the risk.

In addition to lung cancer, several other cancer sites may be associated with occupational exposures to PAH-containing compounds. Among coke plant workers, excess cancers have also been reported for the pancreas, kidney, buccal cavity, pharynx, and intestine. A greater than expected frequency of cancer of the skin (scrotum), esophagus, and liver and leukemia has been reported for chimney sweeps (IARC, 1985). The association between scrotal cancer and the occupation of chimney sweeps has been recognized for over 200 years (IARC, 1985). Among U.S. roofers, who have exposure to both coal tar and asphaltic materials, an increased risk has been found for cancers of the oral cavity, larynx, esophagus, stomach, skin, bladder, and for leukemia. Many case reports exist of skin cancer among workers exposed to creosote and among users of pharmaceutical coal-tar preparations (EPA, 1984a; IARC, 1985).

Few epidemiologic studies are available which directly consider the impact of ingested PAH through food and water, despite the fact that diet accounts for the greatest degree of PAH exposure in the general population.

Several studies have suggested some association between intake of certain smoked foods (which contain high levels of PAH and which may contain high levels of nitrosamines) and gastrointestinal malignancies in selected populations (NAS, 1983b). However, the NAS (1983b) suggests that the gastrointestinal system including the liver may be relatively resistant to ingested PAH:

> "The remarkably large amounts of PAHs that are ingested, compared with those to which the pulmonary system is exposed (even in heavy smokers), makes it clear that there must be tissue-specific factors related to the disposition or metabolic responses to PAHs that protect the gut from the deleterious impact that might be anticipated from such exposure. The possibility of detrimental effects of diet-derived PAHs on the gastrointestinal system will not be so amenable to quantitation as has been the case with respect to smoking and the development of lung pathology."

Although the nature of this apparent resistance is not known, Santodonato et al. (1981) point out that the combination of first-pass liver metabolism and biotransformation by the intestinal mucosa could represent an effective mechanism for handling ingested PAH.

A number of reviews, studies, analyses and assessments of potential health impacts of PAH-contaminated water (or other media) in St. Louis Park have been undertaken over the past eight years. The majority of these analyses have concluded that contaminated drinking water (or other PAH-contaminated media) poses an additional and unacceptable risk of cancer or other adverse health effects in the community. Most of these analyses were based on findings in the scientific literature that demonstrate the carcinogenic potential of PAH-containing mixtures (such as creosote) or specific PAH compounds; some of the analyses also considered estimated or measured PAH levels in contaminated well water.

Some data on cancer incidence have also been collected and analyzed. Several of the analyses (or re-analyses) of these data were conducted as part of this feasibility study to better define limitations and implications of earlier data. Some of the major existing health-related documents and analyses are described below. They are loosely grouped into two categories according to the general approach or type of information; these categories are (1) risk assessment, and (2) epidemiologic data and analyses related to cancer incidence in St. Louis Park.

Risk Assessments

A number of reports have utilized a qualitative or a quantitative risk assessment approach to assess potential health impacts of PAH contaminants. (A general discussion of quantitative risk assessment procedures is presented in Section 2 of this report.) Two quantitative assessments were prepared by the MDH during early phases of the well-contamination investigation when relatively little information was available on the actual extent and magnitude of the contamination. Over a dozen assessments

or statements have been prepared by scientific consultants to Reilly Tar & Chemical and to the State as part of the litigation effort. Only two of these latter assessments will be discussed, one of which was prepared by scientific consultants to Reilly, and the other prepared by a consultant to the State.

1. "Assessment of Possible Health Effects Resulting from the Contamination of the Former Republic Creosote Site" (MDH, 1977).

Two reports were prepared by the Section of Health Risk Assessment, MDH, in 1977 and 1978. The earlier report was intended as an initial step in an ongoing process of risk assessment and was prepared before any data were available on PAH levels in well water. Following an extensive review of the literature on the properties, occurrence, and carcinogenicity of PAH compounds and mixtures, a quantitative risk assessment procedure was used to calculate an acceptable exposure level to BaP based on animal data. BaP levels were then estimated for water in St. Louis Park, and the two estimates were compared. Using a worst-case scenario, this showed that estimated water levels were several orders of magnitude in excess of acceptable values. However, as pointed out in the report, this assessment was made without the benefit of monitoring data on actual PAH levels, extent of contamination, or other essential information. Later data showed that BaP and other carcinogenic PAH levels were much lower than estimated. Furthermore, the level of acceptable risk used (10^{-8}) was much lower than the level commonly employed by MDH today (10^{-5}). The study made numerous recommendations for further investigation including epidemiologic studies. Many of the recommendations were ultimately implemented.

2. "Health Implications of Polynuclear Aromatic Hydrocarbons in St. Louis Park Drinking Water," (Gray and Scruton, 1978).

Approximately one year after the first assessment, a second risk assessment was performed by MDH. This assessment was prepared after the initial sampling for PAH levels in well waters. The report notes that the sampling showed the unequivocal presence of four PAH compounds in several St. Louis Park wells. These compounds were pyrene, fluoranthene, anthracene, and naphthalene. Levels of these compounds in the most contaminated wells (10 and 15) were compared to existing WHO recommendations, and estimates of daily intake from water were compared to estimates of intake from food sources. It was found that levels in wells 10 and 15 exceeded WHO recommendations, and that daily intake from water was comparable to dietary intake plus or minus a factor of ten. It is noted that although these specific PAH are not generally regarded as carcinogens, they have potential cocarcinogenic effects or share certain properties with the carcinogens. It was concluded that use of wells 10, 15, 7, and 9 posed "a potential hazard to the public's health" and it was recommended that these wells be removed from service or that the water be treated. The above wells were taken out of service at that time.

3. "Scientific Basis for Recommended Criteria for PAH and Heterocyclic PAH in Potable Water with Reference to the St. Louis Park, Minnesota Ground-Water Supply" (Andelman and Santodonato, 1983).

In 1983, a consultant to Reilly Tar & Chemical prepared a multi-volume report entitled "Recommended Plan for a Comprehensive Solution of the Polynuclear Aromatic Hydrocarbon Contamination Problem in the St. Louis Park Area" (Environmental Research & Technology, 1983). Although many sections of this report are related to health, Appendix I focuses most directly on human health impacts of PAH in drinking water. This section, cited above, was prepared for ERT by Julian Andelman, Ph.D., and Joseph

Santodonato, Ph.D. In contrast to the earlier MDH reports, this report could draw upon a substantial data base of PAH levels in St. Louis Park wells. In addition, more information was then available on PAH levels generally found in water supplies and on possible human intake of PAHs through various environmental pathways - air, water, and food.

The report appears to present essentially the same risk assessment data used by the EPA in 1980 to establish water quality criteria for PAH. Benzo(a)pyrene and dibenz(a,h)anthracene were the only two carcinogenic PAH considered. Based on oral administration studies in animals, a linear, non-threshold extrapolation model was used to assess cancer risk in humans (this is the same model used by MDH). Using the upper 95% confidence level for the estimated dose, it was estimated that consumption of drinking water with a BaP concentration of 28 ng/l would produce one additional cancer for every 100,000 persons with lifetime exposures. A slightly higher level (43 ng/l) was calculated for dibenz(a,h)anthracene. It was noted that the BaP criteria has been applied by the EPA to all carcinogenic PAH as a class (i.e., the sum of all carcinogenic PAH should not exceed this limit).

The report also considers risk assessment for noncarcinogenic PAH. These assessments are generally based on exposure levels in chronic feeding studies that produce no observable adverse effect. These levels are then divided by some safety factor (10-1000) to estimate an acceptable daily intake. After noting the limitations of the available data, several acceptable water levels are given for specific PAH; all are approximately in the 100 ug/l order-of-magnitude range. Taste and odor (organoleptic) effects are also considered, and the level for such effects is reported to range from 4-6800 ug/l, depending on the compound or mixture.

The report then compares estimated daily intake of carcinogenic and noncarcinogenic PAH from food, air, and water (generally) to estimated

intake from Well 15 (average levels). This comparison indicated that intake of carcinogenic PAH from untreated water from Well 15 would be similar in magnitude to intake from air, and much less than intake from food. However, for noncarcinogenic PAH, intake from Well 15 water could equal or greatly exceed intake from food. The authors also note that finished waters from closed wells do not exceed stated or proposed health-related water criteria for carcinogenic or noncarcinogenic PAH, although levels are abnormally high in comparison to other finished waters. No recommendations are made on the use of contaminated wells; several factors are noted that must be considered in any such decision, including the "likely perception of the public in being exposed to unusual concentrations of trace chemicals, even when an assessment of health impacts does not identify a significant risk."

4. "Potential Health Hazard in the St. Louis Park Drinking Water" (Selkirk, 1984).

This was one of three health hazard assessments prepared by consultants to the State as part of the lawsuit. This document was prepared by James K. Selkirk, Ph.D., and is dated December 6, 1984. This document presents a more general and qualitative assessment, rather than a quantitative analysis of potential health impacts. The report is organized as a series of numbered items or statements that offer information or challenge statements made by Reilly's consultants. Some of the major points developed in this report include the following: (a) many components of creosote have been identified in St. Louis Park samples; (b) PAH containing mixtures such as creosote have been shown to be carcinogenic in animals and in humans who have certain occupational exposures; (c) the metabolism of PAH is the same in all tissues and species; (d) that

significant cancer promoting effects could be expected from the presence of noncarcinogenic PAH in St. Louis Park water; (e) an accurate approximation of acceptable daily exposure to carcinogens is impossible; (f) people consuming contaminated water will likely have a constantly elevated state of drug metabolizing enzymes; and (g) that noncarcinogenic PAH present in mixtures with carcinogenic PAH are not inhibitory, but additive or synergistic in their effect. In his conclusions, Selkirk states that historical and current information unequivocally implicates creosote in cancer initiation and promotion, and that "in effect, we could have a rather large initiation/promotion experiment ongoing" in St. Louis Park. He suggests that the distribution of "cancer or mutation or other maladies (e.g. spontaneous abortion)," may be related to distance from the Reilly site. Finally, he proposes that exposure to carcinogenic and promoter chemicals in St. Louis Park should be restricted to levels no greater than in a "control population in a similar environment."

Epidemiologic and Statistical Analyses

Subsequent to the identification of PAH compounds in several St. Louis Park Wells in 1978, an analysis was made of cancer rates as determined in 1969-1971 in the five county Minneapolis-St. Paul metro area which included St. Louis Park and other suburbs. The findings of this analysis were initially reported in 1979 and published in 1980. It showed that compared to metro area rates, there was no increase for any cancer site or for cancers overall for men in St. Louis Park. However, for women there was approximately a 33% excess for cancers overall in St. Louis Park, a statistically significant difference. The only specific sites that were elevated were breast, gastrointestinal, and corpus uteri. The greatest excess was for breast cancer, with approximately a 45% elevation. By early

1981, additional data had been collected on breast cancer, and a second analysis was reported. This suggested that the excess in breast cancer might be explained by established risk factors, such as age at menarche, religion, and age at first birth . Because of the many unresolved issues involved in both the preceding analyses, further review of these studies has been conducted as part of this feasibility study. Each of these efforts is described below.

1. "Epidemiologic Investigation of Third National Cancer Survey Data for St. Louis Park, Edina, Richfield, and the Minneapolis-St. Paul Standard Metropolitan Statistical Area with a Historical Review of St. Louis Park's Water Supply" (Dusich, 1979). A shortened version of this study was later published as, "Cancer Rates in a Community Exposed to Low Levels of Creosote Components in Municipal Water", (Dusich et al., 1980).

The (then) five-county Minneapolis-St. Paul metro area was one of the study sites in the Third National Cancer Survey (TNCS) in which all newly-diagnosed cancer cases were identified during the three year period 1969-71. Following confirmation of PAH compounds in well water in St. Louis Park, it was decided to examine these TNCS records (stored on computer tapes) for geographic differences in cancer incidence. Using these data, it was possible to compare rates of newly-diagnosed cancer cases in St. Louis Park, Edina, Richfield, and the whole metro area. For each area, crude and age-adjusted rates and standardized morbidity ratios (observed cases/expected cases) were calculated for each sex for 45 individual sites or types of cancer. In addition, rates for organ systems and for all sites combined were also calculated and compared statistically. This study found that none of the rates were statistically elevated for white males living in St. Louis Park at the time of diagnosis. However, for white females in

St. Louis Park, several rates were found to be statistically elevated. Overall cancer incidence in females was approximately 33% higher than in the metro area; it was also higher than in Richfield and Edina (all p values <0.0005). The greatest excess was found for breast cancer, in which a 45% elevation was found compared to the metro area ($p<0.0005$). Breast cancer rates were also statistically elevated when compared to Richfield. Other marginally significant and less sharply elevated rates were found for cancers of the colon, rectum and corpus uteri and for cancers of the gastrointestinal system overall.

2. "High Breast Cancer Rates in St. Louis Park Explained" (MDH, 1981).

In light of the high level of community concern regarding the TNCS data indicating an elevated breast cancer rate in St. Louis Park and experimental data that have demonstrated that several PAH can induce mammary cancer in selected rodent strains, the MDH sought to evaluate the extent to which known risk factors for breast cancer might explain the observed excess. It was known, for example, that a significant percentage of the St. Louis Park population was Jewish and that several epidemiologic studies have shown Jewish women have a higher risk of breast cancer. To obtain further information, an interview study was conducted of 75 of the 95 St. Louis Park breast cancer cases (or surrogates) and an equal number of randomly-selected metro area breast cancer cases (frequency matched for age). This study showed a higher prevalence of risk factors such as higher income, Jewish background, and family history of breast cancer or fibrocystic disease in St. Louis Park cases compared to metro area cases. This information, in combination with published relative risks from other studies, was used to calculate "attributable risk factors". Using this method, it was determined that the higher breast cancer rates in St. Louis

Park could be explained on the basis of known risk factors, and that no excess remained that might be attributed to PAH in drinking water. The study concludes that these findings do not establish that PAH levels found in St. Louis Park wells are "safe," only that these findings offer an explanation for the elevated 1969-71 breast cancer rates.

3. Additional analyses and reviews conducted as part of this feasibility study.

Several analyses and reviews of the above studies have recently been conducted by (or for) the Chronic Disease and Environmental Epidemiology Section, MDH. These are briefly described below.

Residence History of Interviewed St. Louis Park Breast Cancer Cases. Reviews of the epidemiology of breast cancer indicate that a latency period (i.e., period from initial exposure to manifestation of disease) of at least ten years exists between exposure to radiation and increased risk of breast cancer (Thomas, 1980; Moore et al., 1983; Rico, 1984). Latency periods of ten to thirty years have also been demonstrated for many other cancers that are associated with chemical exposures. It seemed useful therefore to review the residential histories of the St. Louis Park breast cancer cases that were obtained during the interview study to ascertain how long the cases resided in St. Louis Park prior to their diagnosis. This information is shown in Table 4-7. It can be seen that 12 of the 75 interviewed cases had resided in St. Louis Park less than five years before their diagnosis, while 29 of the 75 cases (39%) resided there less than ten years before diagnosis. For some portion of these cases, then, it might be argued that they did not reside in St. Louis Park a sufficient period to time to attribute their cancers to water contaminants or other ambient environmental factors in that city.

It should be noted here that no effort was made to confirm residential histories or to ascertain histories of those 20 cases who could not be interviewed.

Although the above discussion indicates the need to consider in-migration in evaluating cancer rates in St. Louis Park, it does not address the equally important issue of out-migration. It is certainly the case that some individuals who had resided in St. Louis Park for a period of time and were thus "exposed" to the drinking water had moved from the city prior to any cancer diagnosis. These cases would not be included in the St. Louis Park rates. The relative magnitude of in- and out-migration in St. Louis Park is not known. The 1970 census data showed that only 55% of the population in St. Louis Park lived in the same house five years earlier. Similar residency patterns were observed for other cities in the metro area. As discussed elsewhere in this report, the effect of migration on comparisons of disease rates in geographic areas can be significant, particularly when considering diseases with long latency periods (Polissar, 1980). The general effect is to reduce any true differences in observed rates.

Estimate of Breast Cancer Incidence in non-Jewish Population. It was recognized at the outset of the epidemiologic studies that the substantial Jewish population in St. Louis Park could be an important factor in the observed breast cancer rates. Various epidemiologic studies have suggested that Jewish women have higher breast cancer rates which may reflect such factors as socioeconomic status, age at marriage and first pregnancy, etc. The interview study revealed, in fact, that 19 of the 75 interviewed cases (25%) in St. Louis Park were Jewish compared to 1 of 75 metro area cases. To evaluate the impact of the Jewish population in St. Louis Park, an effort was made to calculate the standardized morbidity ratios

Table 4-7

Residence History of Interviewed Breast Cancer Cases

LENGTH OF RESIDENCY IN ST. LOUIS PARK PRIOR TO DIAGNOSIS	YEARS 0-4	5-10	10+
Number of Cases	12	17	46
Percent of Total (75)	16%	23%	61%

NOTES:

1. MDH interviewed 75 of the 95 observed breast cancer cases (or their surrogates) identified from the 1969-1971 TNCS data tapes.

2. Based on five-county metro area rates, 65 caases were expected.

3. 19 (25%) of 75 cases interviewed were Jewish.

(observed/expected ratios) separately for the Jewish and non-Jewish populations in St. Louis Park. This calculation required estimates of the the number of Jewish women and their ages among the cases and in the general population of St. Louis Park. Interview data were available for 75 of the 95 (79%) total cases, indicating that 19 of the 75 (25%) were Jewish. Although this percentage could have been applied to the non-interviewed cases, an additional attempt was made to identify the religious affiliation of the remaining 20 cases. This was accomplished by use of death certificates, Jewish Federation membership lists, and hospital or physician records. This indicated that 10 (50 %) of the remaining 20 cases were probably Jewish.

Jewish population estimates were derived from a study conducted by Erickson and Lazarus in 1971 and are presented in Table 4-8. Estimates of the female population for St. Louis Park, 1969-71, are shown in Table 4-9. Incidence rates from the Third National Cancer Survey (1969-71) for the Metro area were used to calculate the "expected" numbers of breast cancer cases among both Jewish and non-Jewish women in St. Louis Park. Table 4-10 presents the standardized morbidity ratios (SMRs) for the total female population, and separately for the Jewish and the non-Jewish populations. This calculation shows that based on metro area rates, 48 cases would be expected among the non-Jewish population while 66 cases were observed. The non-Jewish SMR of 1.35 is marginally significant. For Jewish women only, 15 cases would be expected based on metro area rates, while 29 cases were observed, for a statistically significant SMR of 1.88.

The above analysis would suggest that some, but not all, of the observed excess in breast cancer could be explained by the large Jewish population in the community. This is in agreement with the initial interpretation of Dusich et al (1980) that the observed excess of breast

Table 4-8

Jewish Population Estimates for St. Louis Park, Minnesota - 1971[1]

Age Category	% of Total Jewish Population Living in SLP	Total No. of Jewish People in SLP	Total No. of Jewish Females in SLP**
0-4	4.9	507.3	255.9
5-9	6.2	641.9	323.8
10-14	9.5	983.6	496.2
15-19	12.1	1252.8	632.1
20-24	7.0	724.8	365.8
25-29	3.9	403.8	203.8
30-34	4.3	445.2	224.6
35-39	3.8	393.4	198.5
40-44	7.0	724.8	365.7
45-49	7.6	786.9	397.0
50-54	7.6	786.9	397.0
55-59	6.3	652.3	329.1
60-64	7.1	735.1	370.9
65-69	4.6	476.3	240.3
70-74	2.7	279.6	141.1
75+	3.6	372.7	188.0
		10168	
NOT REPORTED	1.8	186	
		10354*	

1 From Population Study 1971-1972 the Jewish Community of Greater Minneapolis by J.B. Erickson and M.J. Lazarus

* Number of Jewish people living in St. Louis Park/Morningside in 1971.

** Assumes 50.45% of the total Jewish population in the greater Minneapolis area is female and applying this percentage to each age group.

Table 4-9

Female Population Estimates and Person-Years of Observation:
St. Louis Park - 1969-1971

Age Category	Non-Jewish		Jewish*		Total**	
	No.	PYO***	No.	PYO	No.	PYO
0-14	5221	15663	1076	3228	6297	18891
15-24	3523	10569	998	2994	4521	13563
25-34	3205	9615	428	1284	3634	10902
35-44	2163	6498	564	1692	2728	8184
45-54	2467	7401	794	2382	3261	9783
55-64	1789	5367	700	2100	2490	7470
65-74	1181	3543	381	1143	1562	4686
75+	743	2229	188	564	931	2793
TOTAL	20292	60876	5129	15387	25424	76272

* Derived from: Population Study 1971-1972 The Jewish Community of Greater Minneapolis.

** Derived from 1970 Census Data.

*** PYO (Person-Years of Observation) = No. of persons in age category X 3 years of observation.

Table 4-10

Observed and Expected Breast Cancer Incidence in Jewish, Non-Jewish and Total Female Populations in St. Louis Park, Minnesota

Population	Expected	Observed	O/E Ratio	95% CI for O/E Ratio*
Non-Jewish	48.82	66	1.35	(1.05-1.72)
Jewish	15.42	29	1.88	(1.26-2.69)
Total	64.25	95	1.48	(1.19-1.80)

*Probable (95 percent) upper and lower limits for the O/E ratio estimate.

cancer would not be entirely explained by the presence of the Jewish population (estimated at 20%) even if it were assumed that the Jewish population had a two-fold risk.

Critical Review of Case-Case Study Approach and Findings. Because of the importance of the findings and the unique case-case study approach taken by the MDH in 1980-81 to determine whether the excess breast cancer cases could be explained by known risk factors, it was decided that this study should be further reviewed. This critical review included analyses and comments by an internationally recognized expert in statistical epidemiology and attributable risk (Stephen D. Walter, Ph.D., Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada).

This review pointed to several aspects of this study that weakened its conclusions. The major problem was found to be in the application of the attributable risk proportions to the entire population rather than to individuals "exposed" to a given risk factor. It was noted that the consequence of this error was that the percentages of disease estimated to be attributable to the factors studied are overestimates for both St. Louis Park and the Metro area. Whether or not this error would make a substantial difference to the conclusions was not possible to determine from the data provided. Other methodological issues that were considered in this review included the problem of multiple comparisons, reliability of the interview data, non-response bias, the basis for relative risk estimates, the completeness of the risk factors considered, interactions between risk factors, and effects of migration.

The Chronic Disease and Environmental Epidemiology Section generally agrees with the findings of this review that several unresolved issues in the case-case study approach previously taken by the MDH weaken the

conclusions that can be drawn. Accordingly, the extent to which the observed breast cancer rate in St. Louis Park can be explained on the basis of known risk factors remains unclear.

Nature and History of Contamination

While investigating a suspected sewer break or spill at the Twin Cities Army Ammunition Plant (TCAAP) in 1981, the Minnesota Pollution Control Agency (MPCA) became aware of an Army document (U.S. Army, 1978) that described the disposal practices for chemical wastes at the arsenal. The TCAAP facility has been in existence since 1941 and has been operated during most of its history for the Army by Federal Cartridge Corporation. Because of the potential of the described disposal practices to have introduced contaminants into the groundwater, the MPCA analyzed water samples from private wells located near TCAAP. These analyses showed that the well water was contaminated with several volatile organic compounds (VOCs), primarily trichloroethylene. Subsequent analyses by the MDH of municipal and other public water supply wells in communities surrounding TCAAP revealed that VOC contamination existed in six of eight municipal wells serving New Brighton. New Brighton, a community of about 23,000 population, is located immediately southwest of the TCAAP site and northeast of Minneapolis. It was also found that a number of large production wells within TCAAP had much higher levels of contamination. As a result of these findings, a number of wells were closed, modified, or taken out of routine service, and investigations were launched by state agencies and the U.S. Army to identify the extent and the sources of the contamination, and appropriate remedial actions. The Phase I Final Report of the Remedial Investigation was completed by the MPCA in May 1985 (CDM, 1985).

Source(s) of Contamination

An investigation of potential sources of the contamination was undertaken by the MPCA with funding provided by the U.S. Environmental Protection Agency (under the federal Superfund provisions). Based on new information developed during this investigation and review and analysis of existing information, it was concluded that four significant source areas of contamination may exist within the New Brighton/Arden Hills study area. These general source areas are located on or near the TCAAP and are as follows:

1. An industrial area along Old Highway 8 north of Interstate 694;
2. A commercial/industrial area to the north of Rush Lake;
3. Sites located within TCAAP that lie above the Twin Cities till;
4. Sites located on TCAAP that are situated within the Kame deposit (below which no till is present).

This investigation showed that the direction of groundwater flow in the contaminated Prairie du Chien-Jordan aquifer is toward the southwest, while flow in the shallower contaminated Hillside Sand aquifer is generally toward the west-southwest. The study also indicated that contamination in the New Brighton area is comprised of separate eastern and western plumes.

Magnitude of Contamination

A large number of water samples have been analyzed for a wide variety of compounds since the contamination was first detected. This has provided an extensive database of qualitative and quantitative aspects of the contamination, and has enabled preliminary definition of the horizontal and vertical spread of the contaminant plume(s). Major contaminants (and their corresponding Minnesota water quality standard) that have been identified in municipal wells since 1981 are:

1,1,2-trichloroethylene (TCE, 31.2 µg/l)
1,1,1-trichloroethane (TCA, 200 µg/l)
1,1-dichloroethylene (DCE, 0.3 µg/l)
1,1-dichloroethane

Other contaminants that were sporadically identified in some wells include:

cis-1,2-dichloroethylene
trans-1,2-dichloroethylene
chloroform
1,2-dichloroethane
1,1,2-trichloroethane
1,1,2,2-tetrachloroethylene

As in the case with St. Louis Park wells, substantial variations are evident in the detected contaminant levels for a given well. Contaminant concentrations reported for a single well commonly vary by as much as one or two orders of magnitude, with the lower end of the range often at "less than" (detectable) levels. Sources of this variation may be attributed to such factors as local changes in hydogeologic patterns due to changed pumping stresses, sampling procedure variations, analytic variability, and changes in the migration of the contaminant plume.

Mean concentrations of contaminants from analyses conducted between 1981 and 1984 were available from the MPCA and are presented in Table 4-11 for the three major contaminant compounds (TCE, TCA, DCE) in municipal wells. These data show that mean TCE levels among the six wells initially contaminated ranged from about 12 to 150 µg/l. Mean TCA levels were approximately 5 to 40 ug/l, and mean DCE levels were from less than 1 to 7 µg/l. For all three contaminants, levels were slightly higher in wells 3, 4 and 8 which are located just slightly northeast of wells 5, 6 and 9 (Figure 4-3).

The variability of the data is indicated in Figure 4-4 which shows mean TCE values and the standard deviations for each well from the analyses conducted between 1981 and 1984 (1981-1982 for wells 8 & 9). It should be noted that TCE levels in wells 2 and 7 were near or below detection limits

Table 4-11

Mean Concentrations of Trichloroethylene (TCE), Trichloroethane (TCA), and Dichloroethylene (DCE) in New Brighton Municipal Wells: Analyses from 1981-1984[a]

Well Number	Mean Concentration (µg/l) TCE	TCA	DCE
2	4.7	1.1	0.1
3	83.6	24.7	3.8
4	70.5	22.0	3.2
5	24.5	7.5	0.9
6	11.9	4.8	0.9
7	0.33	0.14	0.01
8[b]	153	43.4	7.2
9[b]	57.6	15.8	2.5

[a] Data from Phase I Remedial Investigation Final Report (CDM, 1985).

[b] Excludes analyses taken after wells were deepened in 1982.

Figure 4-3

Location of New Brighton Municipal Wells

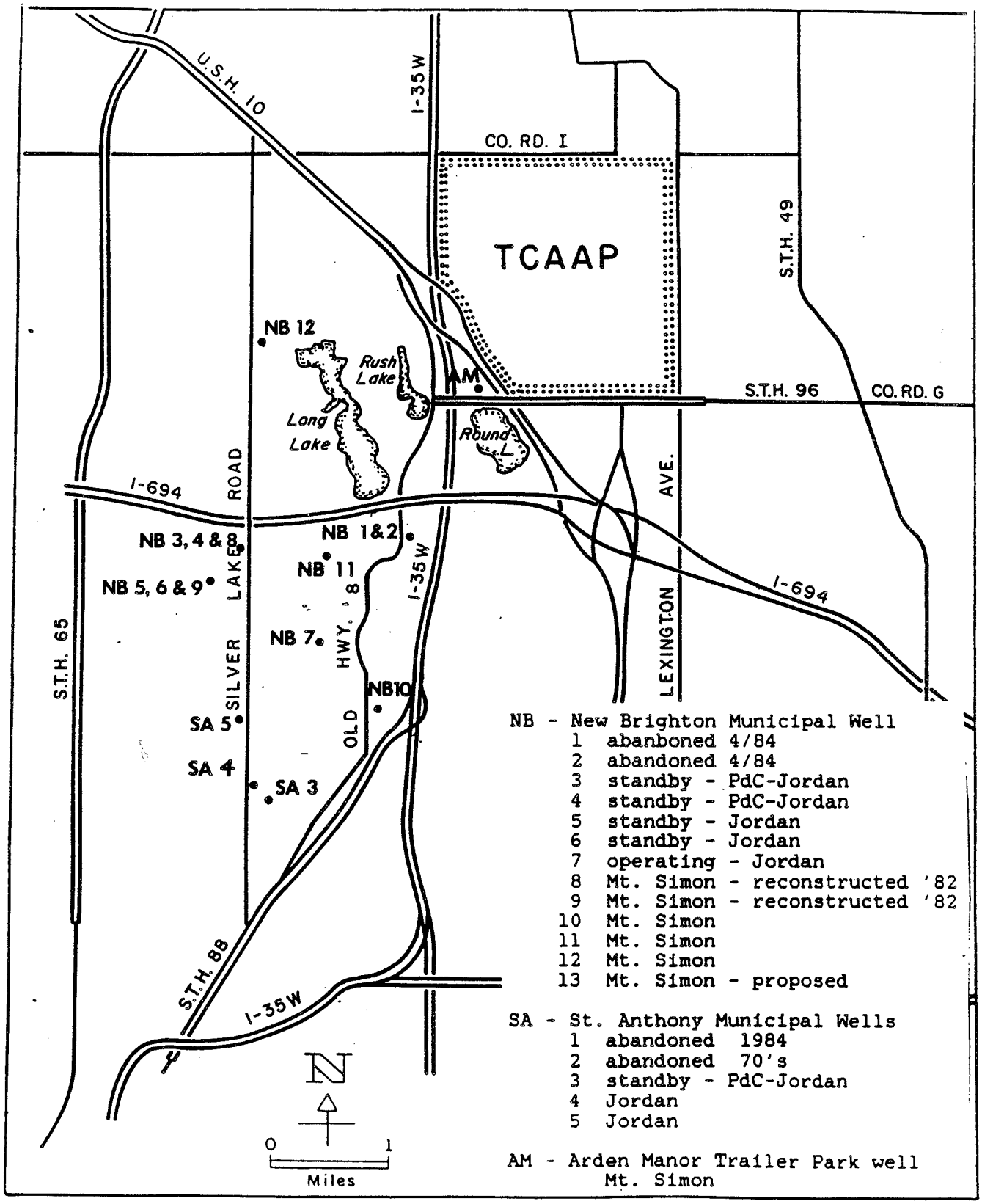
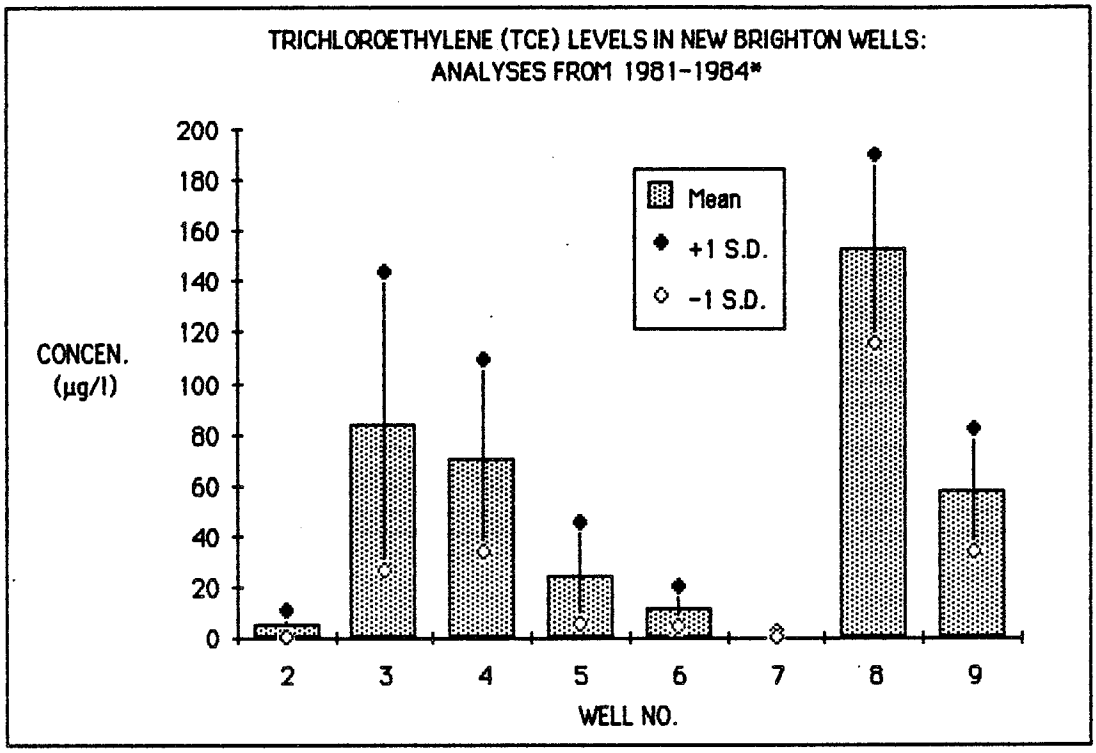


FIGURE 4-4. TCE LEVELS IN MUNICIPAL WELLS



*Excludes analyses from Wells 8 and 9 after they were deepened in 1982

when initially sampled. After closure of several wells, these two wells were put into more active service, after which time low but rising contamination was seen.

Contamination levels in a well serving a trailer park located immediately southwest of the arsenal were comparable to levels in municipal wells. Several private residential wells located in this same area had somewhat higher levels. Contaminant levels in three of six active TCAAP production wells were much higher than in municipal wells or other wells off TCAAP. Average TCE concentrations in the three most contaminated wells were near 2000 µg/l, while average TCA and DCE levels in these three wells were approximately 800 µg/l and 100 µg/l, respectively.

Potential Community Exposure to Water Contaminants

As outlined in the earlier discussion on St. Louis Park, a critical question in considering the feasibility of environmental epidemiologic studies is whether individuals can be categorized on the basis of intensity and/or duration of exposure. In the case of contaminated municipal water supplies, some of the specific issues that need to be addressed in developing an exposure model were listed previously in the discussion of St. Louis Park. Factors such as the number and location of contaminated wells, the levels of contaminants, well history, effect of water treatment, aspects of the distribution system, period of contamination, and personal consumption patterns must clearly be taken into consideration. Exposure-related factors are considered below with respect to the New Brighton municipal water supply.

In 1981 the New Brighton municipal water was obtained from eight wells, all approximately 420-520 feet deep. (A ninth well, Well # 1, had been disconnected from the distribution system in the 1960s.) The

locations and operating histories of the New Brighton wells are shown in Figures 4-3 and 4-5. It can be seen that the six New Brighton wells initially found to be contaminated (3, 4, 5, 6, 8, and 9) are all in close geographic proximity to each other and were then all open to the Jordan or Prairie du Chien-Jordan bedrock aquifers.

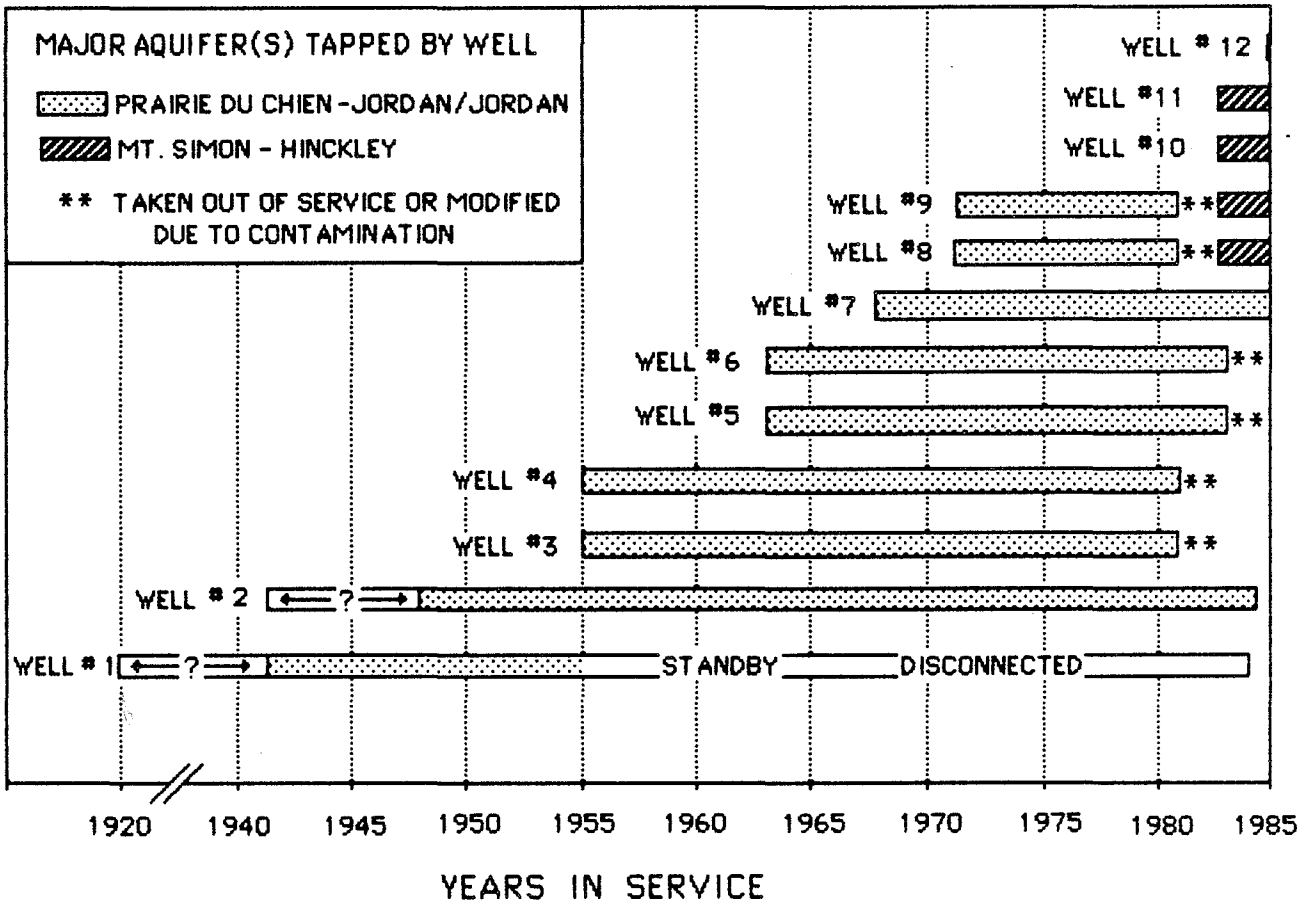
Well pumping data from the City of New Brighton and the Department of Natural Resources provide an indication of the relative contribution of the wells found to be contaminated in 1981 to the total water supply. As shown in Figure 4-6, it is apparent that wells 3, 4, 5, 6, 8, and 9 accounted for almost all (90-99%) of the city's yearly water pumpage from 1971 until the contamination was detected in 1981. Prior to 1971, pumping records are incomplete. However, limited pumpage data and the installation dates of the above wells suggest that they provided a significant portion of the water supply during the 1960s as well. In light of the above information, it may reasonably be assumed that the water available at the tap in essentially all service areas of New Brighton throughout the 1970s and probably throughout the 1960s was mostly or entirely produced by some combination of wells 3, 4, 5, 6, 8, and 9 (wells 8 and 9 were not placed into service until 1971).

The above information does not indicate the magnitude or duration of actual exposure to water contaminants; it does indicate that chronic and community-wide exposure can not be ruled out on the basis of well usage. Additional factors must be considered in assessing the actual likelihood and/or magnitude of exposure.

As with St. Louis Park, little or no data are available concerning actual contaminant levels at the consumer's tap. (A possible exception here would be analyses taken from the small number of residential wells located

Figure 4-5

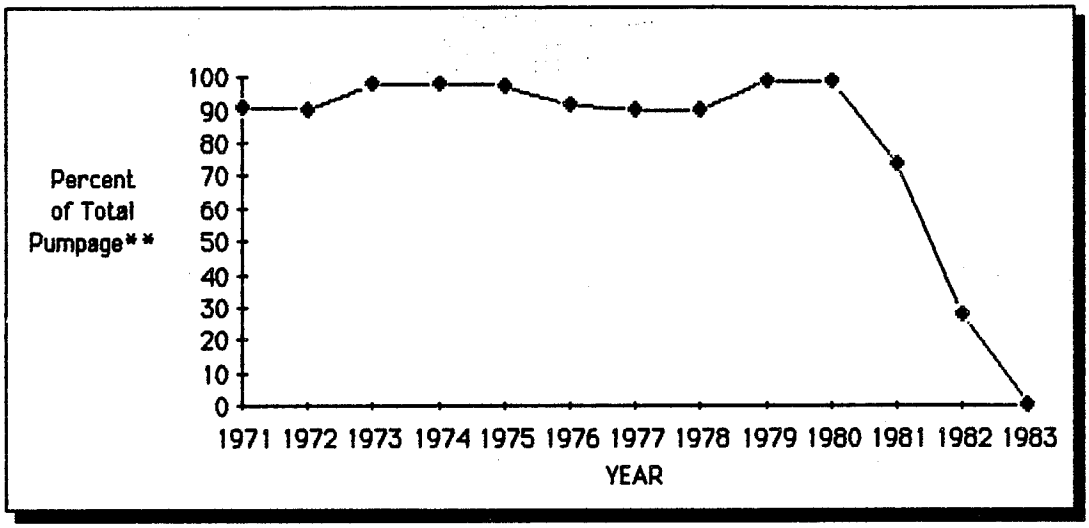
Dates of Operation for New Brighton Municipal Wells



NOTES:

1. Chart indicates years in which wells were potentially in service. Individual pumping histories vary widely by month and year.
2. Wells 1 and 2 were abandoned in 1984.
3. Wells 2, 3, 4, 5, 6, and 7 are 420-520 feet deep and are open to the Jordan (5, 6, 7) or Prairie du Chien - Jordan (2, 3, 4).
4. Wells 8 and 9 were approx. 480 feet deep prior to 1982; subsequently they were deepened to the Mt. Simon - Hinckley and returned to service.
5. A carbon filtration unit was added to Wells 5 and 6 in mid-1983, and they remained in service for approximately 3 months.

FIGURE 4-6. PROPORTION OF TOTAL ANNUAL PUMPAGE FROM NEW BRIGHTON WELLS 3, 4, 5, 6, 8 & 9: 1971-1983*



* These six wells were found to be contaminated when initially analyzed in 1981.

** Pumpage from wells 8 & 9 not included after wells were deepened in 1982; pumpage from wells 5 & 6 not included after carbon filtration added in 1983.

just southwest of TCAAP.) Tap levels could differ, perhaps substantially, from well head levels as a consequence of water treatment, storage, distribution, and other factors. For example, in some water supply systems in the state, it has been observed that iron removal processes (involving aeration of the water) can significantly reduce certain volatile organics. (Note, however, that iron removal was not a treatment process used in conjunction with any of the contaminated wells in New Brighton prior to 1981.)

Another major question is when the water supply initially became contaminated (or how rapidly contamination reached present levels). Several types of information may be considered in relation to this issue, such as when environmental contamination started, installation and pumping histories of the city wells, estimated contaminant travel times and dispersion, and other hydrogeologic factors. Some of this information is available and is briefly summarized below.

Estimates of when operations started at suspected source sites and when "breakthrough" of contaminants from underlying till into aquifers may have occurred (assuming contamination started at the beginning of operations) were developed during the MPCA Phase I Remedial Investigation. For the sources of contamination considered to be the most significant, these dates generally extend back to the early 1940s-1950. It is not generally known, however, when contamination actually started at most of these sites, whether it was continuous or sporadic, the quantities of materials involved, and in some cases, whether chlorinated solvents were even used.

A second type of information that may set limits to the onset of contamination is the history of the installation of the municipal wells. MDH sanitary survey records indicate that New Brighton wells 1 and 2 were

in service by at least the late 1940s. However, well 1 was on standby or was disconnected from the distribution system for possibly 20 years or more. Well 2 showed little contamination prior to its abandonment in 1984, and it generally provided little contribution to the municipal water supply between the early 1960s and 1981. Wells 3 and 4 were installed in about 1955, and wells 5 and 6 in about 1963. These dates might indicate the earliest potential dates in which contaminated municipal water may have been provided, under a worst-case scenario. At the other end of the range, laboratory analyses demonstrated that well contamination existed in mid-1981.

Another source of information that was considered of possible value in estimating the onset of contamination comes from 3-dimensional computer models of groundwater flow and contaminant transport. Such models were developed for the MPCA by CDM as part of the Phase I Remedial Investigation to better understand the hydrogeologic characteristics of the region and as a tool to screen the large number of potential contaminant sources that had been identified from previous investigations. It should be noted that these models were not developed to estimate the duration or magnitude of well contamination. A detailed description of these two models, their derivations, inherent assumptions, applications, calibration, and other features is presented in the Phase I Final Report (CDM, 1985).

These models have been of considerable value in screening potential sites by demonstrating whether the hydrogeologic characteristics of a site would enable it to be a source of groundwater contamination in New Brighton and St. Anthony. Further investigation of possible solvent use is then focused on those sites found to possess particular hydrogeologic characteristics. As of the time of the Phase I Report (May, 1985), actual

chlorinated solvent use had been documented for approximately 15 of the 65 sites that fell within the appropriate hydrogeologic framework.

Since most of the sites identified to date with known solvent use and appropriate hydrogeologic aspects are within the TCAAP facility, a model simulation of particular interest was one that looked at one of the TCAAP sites. This simulation took into account the greatly increased pumpage of TCAAP wells during the period 1968-1973. (Other simulations were based on pumping levels of wells as they existed only during 1979, which were thought to be representative of conditions in which TCAAP production well pumpage was at a minimum and New Brighton municipal well pumpage was at a maximum.) Assuming a continuous source of contamination since 1950 at this particular site within TCAAP, the model simulated the extent of the contaminant plume originating from this site as of 1968, 1973, and 1984. It was seen that the increased pumpage of TCAAP wells did not prevent migration of the contaminant plume off the arsenal; however, it did suggest that heavy TCAAP well pumpage would have slowed the migration of the plume during that period. Unfortunately, this simulation was limited to only one potential contaminant site within TCAAP, and it is currently unknown which of the potential contaminant sources are the most significant.

Despite the apparent usefulness of the groundwater flow and contaminant transport models in the remedial investigation, it does not appear that the CDM models utilizing currently available data can offer significant insights with respect to the arrival times of contaminants at particular well fields. Whether further modeling efforts devoted to this issue could better characterize historical patterns of contamination is not clear; it is likely that any such characterization would have a significant, and possibly unquantifiable, degree of uncertainty. In sum,

currently-available information cannot establish whether contamination in the western New Brighton wells was present several years or several decades prior to detection.

Other Exposure Considerations

Even assuming that VOCs are present at the consumer tap, individual exposure will depend on many factors. An obvious factor is how much tap water is consumed. However, the presence of VOCs in drinking water can result in exposure through means other than the direct consumption of water. Exposure to VOCs could also occur, for example, by inhalation and skin absorption, such as when showering. Although the data are very limited, such additional pathways of exposure may be significant and need to be considered in evaluating individual exposure levels (Brown et al., 1984). As discussed elsewhere in this Section, the VOCs found in New Brighton water are widely-used chemicals that have become dispersed throughout the environment. The sum total of these other environmental exposures is not well-established, but could be of comparable or greater magnitude to exposures derived from New Brighton well water.

The primary contaminants that were found in New Brighton municipal wells are trichloroethylene (TCE) and 1,1,1-trichloroethane (TCA). Lower concentrations of several other VOCs, primarily 1,1-dichloroethylene (DCE), were also detected. The following discussion provides brief overviews of the uses, environmental exposures, and the toxicology of TCE, TCA and DCE. A number of comprehensive review documents and articles on these compounds (particularly, TCE) have been prepared by various individuals and agencies during the past several years. These reviews provide the basis for the following summaries.

Trichloroethylene

Occurrence and Exposure. TCE is a colorless, nonflammable solvent that has been produced commercially in the U.S. since 1925. U.S. production in 1977 was 132,000 metric tons, down from 277,000 metric tons in 1970 (IARC, 1979).

The major use (82% of 1977 production) is in the vapor degreasing of metal parts. It is also used as a solvent in the textile industry; as a solvent for adhesives and lubricants; and, as a low-temperature heat transfer fluid. It has been used in such consumer products as spot removers and rug cleaning fluids. A pharmaceutical grade of TCE has been used as a general anesthetic in surgical, dental, and obstetrical procedures and in veterinary practice. For many years, it was used as an extraction solvent in foods (such as in the manufacture of decaffeinated coffee); the FDA has since prohibited many such uses.

Although TCE is not known to occur naturally, it has become widespread in the environment. The EPA has estimated that 60% of the total world

production is released to the environment. Annual emissions in the U.S. alone were estimated (in 1976) to be 193,000 metric tons. TCE is not expected to persist in the environment due to its photooxidation, low water solubility, and volatility (EPA, 1980b). Nevertheless, TCE has been detected in air, water, soils, some food products, marine organisms, and human tissues (IARC, 1979).

Some reported ambient air concentrations in the U.S. are as follows: 1 $\mu g/m^3$ in urban areas in the northeast; 0.1 $\mu g/m^3$ in rural areas; 0.15-0.5 $\mu g/m^3$ in Michigan; and 0.08-1.7 $\mu g/m^3$ at sites in California. In Tokyo, average levels were reported to be 6.4 ug/m^3, and in Manchester, U.K., 5-343 $\mu g/m^3$ were reported. Wallace et al. (1985) reported that personal exposure levels to TCE (and other organics) were consistently higher than outdoor concentrations. Geometric mean levels of TCE in personal air were 2.6-3.0 $\mu g/m^3$. It was estimated that an average daily dose of 19.7-75.6 μg/day is inhaled in three urban locations in the U.S. (Singh et al., 1981). The greatest inhalation exposure generally occurs in certain occupational settings, primarily in hospitals, in the aircraft manufacturing industry, in blast furnaces and in steel mills. It was estimated by NIOSH in 1975 that approximately 290,000 U.S. workers were potentially exposed to TCE (CDC, 1985).

TCE has been detected with some frequency in raw surface waters, ground waters, sewage, and finished tap waters. A recent EPA survey of 29 VOCs in randomly-selected finished ground water supplies showed that TCE, tetrachloroethylene, and TCA were the three most frequently detected compounds (Westrick et al., 1983). TCE was detected in 11% of systems serving populations of over 10,000. Levels exceeded 5 $\mu g/l$ in 3% of the systems. In a recently completed state survey of 1801 community water

supply wells in Minnesota, TCE was the most frequently identified contaminant, found in 42 samples (MDH, 1985).

TCE has been reported in foodstuffs in the U.K. as follows: dairy products (0.3-10 ppt), meat (12-22 ppt), oils and fats (0-19 ppt), beverages (0-60 ppt), and fruits and vegetables ($<$ 5 ppt) (IARC, 1979). Packets of tea were found to contain 60 ppt. Little TCE would be expected in other foodstuffs except where TCE is used as an extractive solvent (EPA, 1980b).

In human tissue samples at autopsy, TCE has been detected at levels of $<$1-32 ppt (wet tissue) (EPA, 1980b). As expected from its physical and chemical properties, TCE has a greater affinity for body fat than other tissues, both in humans and animals.

Toxicology. Many articles and comprehensive reviews have been prepared in recent years on the absorption, metabolism, and elimination of TCE in humans and animals, and on the potential health effects of TCE (e.g., IARC, 1979; EPA, 1980b, 1984b, 1985; NAS, 1977, 1983a; Kimbrough et al., 1985; Prout et al., 1985; Elcombe et al., 1985; D'Souza et al., 1985). Some general conclusions that can be drawn from these reviews are presented below.

TCE is readily absorbed through all routes of exposure - inhalation, ingestion, and dermal. However, quantitative data on oral absorption are lacking. Once absorbed, TCE enters the blood and is distributed to various tissues and organs. Data on distribution are mainly from inhalation studies. From studies of human patients under TCE anaesthesia, it has been shown that TCE crosses the placental barrier.

TCE is metabolized to a qualitatively similar set of products in various species, including humans. Some of the identified metabolites

include trichloroacetic acid, trichloroethanol, trichloroacetaldehyde, monochloroacetic acid, and trichloroethanol glucuronide. An important intermediary metabolite is chloral hydrate. TCE and its metabolites are eliminated in urine, by exhalation, and to a lesser degree in sweat, feces, and saliva. Recent studies have indicated that several aspects of TCE metabolism vary substantially depending on the species and the dosage. It has been proposed that these differences (which include such factors as the rate of TCE metabolism, metabolic saturation, blood levels of key metabolites, and hepatic peroxisome proliferation) may explain the observed species differences in sensitivity to TCE hepatotoxicity and carcinogenesis and may have public health implications (Kimbrough et al., 1985; Prout et al., 1985; Elcombe et al., 1985; D'Souza et al., 1985).

In in vitro mutagenic tests, TCE has been found to be weakly mutagenic or nonmutagenic. In vivo, TCE does not bind with DNA as do many other carcinogens. TCE does not appear to be teratogenic or fetotoxic in rodents.

A number of studies have examined the carcinogenicity of TCE in rodents. These studies are summarized in the previously cited review documents. These studies show that TCE significantly increases the incidence of hepatocellular carcinomas in some rodent strains and species (B6C3F1 mice), but not in others (rats and hamsters). As noted above, species differences in the metabolism of TCE, particularly at the high doses used in these studies, may account for differences in the sensitivity to carcinogenesis. Based on the results of the study with B6C3F1 mice, a mathematical model was used to determine the upper 95% confidence limit on cancer risk associated with low level exposure (NAS, 1983a). This risk was estimated to be 3.3 x 10-7 per 1 µg/liter of water for lifetime exposure.

A limited number of occupational epidemiologic studies have been conducted on workers potentially exposed to TCE. These studies have involved relatively few workers to date. At an exposure to 50 or 100 ppm in the workplace air, a worker would receive a dose approximately 10,000 times higher than the dose that would be received from consumption of water with a TCE level of 100 ppb. These studies have not demonstrated increased cancer mortality among these workers. Based on metabolic factors and occupational experience, Kimbrough et al. (1985) conclude that the theoretical cancer risks attributed to TCE are extremely questionable, and that the "risk associated with exposure to trace amount (ppb) concentrations of TCE in water appear to be minimal or perhaps negligible."

Acute and chronic toxicity from TCE exposure has long been known. The effects of TCE mainly involve the central nervous system and the periferal nervous system, although other organ systems can also be affected. Several deaths have been reported following extremely high exposures. Exposures which may produce acute or chronic effects are much higher (ppm) than those associated with extrapolated cancer risks (ppb).

Based on recent reviews of the carcinogenic, metabolic, and limited epidemiologic data regarding TCE, there is currently little evidence that TCE poses a significant human risk of cancer or other adverse effects at environmental exposure levels.

Trichloroethane

Occurrence and Exposure. Trichloroethane (TCA) is a colorless, nonflammable solvent that was introduced commercially in 1946 (IARC, 1979). It has been used increasingly as an industrial solvent and in consumer products. U.S. production of TCA was estimated at 289,000 metric tons in 1977 and 315,000 metric tons in 1980 (EPA, 1984c).

The major uses of TCA are cold cleaning of metal and electrical materials and vapor degreasing. These uses accounted for some 75% of total usage in 1975. Approximately 12% was used in the synthesis of vinylidene chloride (1,1-dichloroethylene). The largest other use is in aerosols as a vapor-pressure depressant and as a solvent and carrier for active ingredients. Other uses include the development of printed circuit boards; as a solvent in adhesives, spot removers, and printing inks; as a motion picture film cleaner; and, as an additive in cutting oils. Vapor degreasing grades of TCA contain several percent stabilizers and additives (EPA, 1984c).

Most of the world production is eventually released to the atmosphere. Estimates of yearly global emissions during the late 1970s range from 300,000 to 500,000 metric tons. In the U.S. emissions have been estimated at 214,000 and 245,000 metric tons (EPA, 1984c). An additional 29,000 metric tons are released to the environment via solid waste and water. It has been estimated that TCA has a residence time of 5-10 years in the atmosphere, which suggests that some fraction will reach the stratosphere. Some models indicate that photodestruction of TCA in the stratosphere could accelerate ozone destruction.

As with TCE and other chlorinated solvents, TCA is widespread in the environment, although it is not known to occur naturally. Typical ambient levels of TCA in the atmosphere are in the 0.1 to 1 ppb (0.54 to 5.4 ug/m^3) range, but levels as high as 64 ppb (346 $\mu g/m^3$) have been reported in urban areas (EPA, 1984c). Wallace et al. (1985) reported that geometric mean TCA levels in personal air samples were much higher than in outdoor air, 19 $\mu g/m^3$ versus 4 $\mu g/m^3$. It was estimated by Singh et al. (1981) that the average daily adult dose in several urban locations was 38-133 μg.

TCA has been detected in finished drinking water, ground water, surface water, sea water, rain water, and in raw and treated sewage (IARC, 1979). As previously noted, TCA was one of the three most commonly detected VOCs in finished groundwater supplies in the U.S. In the random survey, TCA was detected in 8.1% of the water supplies serving populations of over 10,000 (Westrick et al., 1983). The median of positive values was 1.0 µg/l. In the survey of VOCs in Minnesota water supplies, TCA was detected in 0.9% of the 1801 community supply wells, with a median of positive values of 0.5 µg/l.

TCA residues were found in a U.K. study of twelve food items: meat (3-6 ppb), oils and fats (5-10 ppb), tea (7 ppb), fruits and vegetables (1-4 ppb), and fresh bread (2 ppb) (IARC, 1979).

Toxicology. Recent comprehensive reviews of TCA have been conducted by EPA (1984c), NAS (1983a) and IARC (1979). These reviews indicate that TCA has considerably less potential for toxicity than other chlorinated solvents such as TCE. Some general observations on TCA from these reviews are presented below.

TCA can be absorbed through the lungs, through the gastrointestinal tract, and through the skin. After absorption, it is widely distributed into various body tissues, particularly those high in lipid content. However, in contrast to TCE, very little of the absorbed dose ($\leq$ 6% in man) is estimated to be metabolized. Most of the TCA is eliminated from the body unchanged through the lungs. Metabolites are excreted mainly in the urine. The only identified urinary metabolites are trichloroethanol and trichloroacetic acid.

Physical and chemical properties would indicate that TCA can cross membrane barriers in the body. Thus, it can cross the blood-brain barrier,

and can probably reach the fetus during pregnancy. TCA has not shown any teratogenic potential in the studies conducted to date in rodent species involving either short- or long-term exposures.

TCA has been subjected to a wide variety of mutagenic assays. Although generally negative, reviewers indicate that the conventional protocols used in these tests are inadequate in the case of TCA. Under specialized treatment conditions (to overcome solubility and volatility properties), commercially available samples of TCA (i.e., containing stabilizers) are weakly mutagenic or genotoxic in several *in vitro* tests. It is not established whether these effects are due to TCA, stabilizers, or contaminants. One stabilizing compound (1,4-dioxane) shows evidence of being an animal carcinogen.

Effects have not been observed for short-term exposures to air concentrations in the range of 350-500 ppm (it can be estimated that an eight-hour exposure to 350 ppm will result in about 10 grams of TCA absorbed into the body of a 70-kg man). High exposures in humans produces effects mainly in the central nervous system. A threshold for these effects may occur around 1000 ppm (5400 mg/m^3). At much higher exposures ($>$5000 ppm) death can occur due to anesthesia and/or cardiac toxicity. Unlike other chlorinated compounds, TCA has not been associated with clearly evident liver or kidney damage.

Three carcinogen bioassays have been completed in rats and two in mice. Two of the rat studies were negative, but are not considered conclusive due to various inadequacies. Conclusions from a third rat study (and one mouse study) are under re-review by the National Toxicology Program. The other mouse study was negative, but was also considered inadequate to judge carcinogenicity.

The weight of the evidence to date does not suggest that TCA is a human carcinogen or is likely to be associated with adverse reproductive outcomes at environmental exposure levels. However, further studies are needed to better define any possible risks.

Dichloroethylene

Occurrence and Exposure. Dichloroethylene (1,1-dichloroethylene, also called vinylidene chloride) is a colorless, highly reactive, and flammable liquid. U.S. production capacity is approximately 120,000 metric tons, most of which is used in the production of copolymers with vinyl chloride or acrylonitrile (EPA, 1983).

A small portion is used in the synthesis of trichloroethane. Losses to the environment during manufacturing processes are estimated at 580 metric tons.

Median ambient air levels of DCE was estimated to be 20 ng/m^3 in urban/suburban areas of the U.S., resulting in an estimated daily inhalation intake of 0.4 µg (EPA, 1983). Singh et al. (1981) estimated average daily adult intakes of 0.4-2.5 µg in three urban locations. Near point sources of emission, these values can be approximately 1000-fold higher.

In the EPA survey of groundwater supplies, DCE was found in approximately 3% of the supplies serving populations of over 10,000. The median of positive values was about 0.3 ug/l. In the Minnesota survey, DCE was found in 0.4% of the wells sampled, with a median concentration of 1.2 µg/l for positive values. There are insufficient data to estimate DCE levels or exposures related to food.

Toxicology. DCE is readily absorbed in rats and mice through ingestion or inhalation, and is rapidly distributed in the body. DCE is metabolized in the liver producing a number of possible reactive intermediates, including an epoxide. These intermediates may bind with macromolecules, such as DNA, producing toxic effects. Excretion of metabolites and parent compound occurs primarily through the urine and through exhaled air and is dependent on dose; at higher doses, more of the compound is eliminated unchanged through exhalation. Primary metabolites found in urine include thiodiglycolic acid and an N-acetyl-S-cysteinyl derivative. There does not appear to be an accumulation of DCE in body tissues.

Much information exists on the toxicity of DCE in experimental animals. Toxicity varies with age, sex, species, and fasting-state. The kidney and liver are the target organs affected by both acute and chronic exposures through either inhalation or ingestion. Reproduction and teratogenic effects have not generally been observed in studies involving several species and different routes of exposure, including a three generation study in rats involving DCE in drinking water (up to 200 ppm). Where pregnancy outcomes were effected, doses were high enough to produce maternal toxicity (EPA, 1983).

DCE is mutagenic in several bacterial assays, when metabolic activation is employed. DCE may react *in vivo* with DNA of mouse kidney. However, other *in vitro* and *in vivo* assays have not shown mutagenic activity (EPA, 1983).

According to the recent review by EPA (1983), there have been eight cancer bioassay studies in which DCE has been administered to rats, mice, or hamsters orally or through inhalation. Seven of these studies failed to find a significant carcinogenic response. In one inhalation study,

significant elevation of kidney tumors was found only in male Swiss mice. It has been suggested that this may be a species- and strain-specific response, resulting from severe kidney toxicity. Very limited epidemiologic data from an occupationally-exposed cohort revealed no significant clinical differences compared to matched controls (EPA, 1983).

Based on noncarcinogenic effects, the suggested no-adverse response level (SNARL) for chronic toxicity for DCE in drinking water was calculated to be 100 µg/l (NAS, 1983a).

EXISTING HEALTH INFORMATION - NEW BRIGHTON

There is little existing health information which permits identification of any excess of adverse health effects in New Brighton that could be related to well water contaminants. The limited information that is available is described below.

Some data are available on cancer mortality in New Brighton. This information was prepared by the MDH in response to information requests in 1983 by State Senator Steve Novak and Representative Dan Knuth. The number of cancer deaths among New Brighton residents over a five-year period (1976-1980) was compared to the number of "expected" deaths using Metro area or state mortality rates as a reference. The "expected" numbers take into account age and sex differences, but do not reflect many other factors that influence cancer mortality rates (such as smoking habits, occupation, and socioeconomic factors). As shown in Table 4-12, application of Metro area rates (which are slightly higher than statewide rates) to the population of New Brighton indicates that 121 cancer deaths would have been expected over the five-year period, while 114 cancer deaths were observed. This is not a statistically significant difference. For specific types of cancer, observed and expected numbers were also very similar. However, the small number of deaths due to any particular cancer limits the possibility for finding small differences. The advantages and limitations of cancer mortality data in assessing potential risks from environmental exposures are discussed elsewhere in this report.

As part of this feasibility study, existing vital statistics were examined to determine whether it would be possible to detect differences in fetal, neonatal, or infant deaths in New Brighton over time or in comparison to other communities. However, the small number of yearly

Table 4-12

Observed and Expected Cancer Mortality in New Brighton: 1976-1980

Observed Deaths	Expected Deaths[a]	O/E Ratio	95% Confidence Interval
114	121	0.94	0.77-1.13

[a] Expected deaths based on mortality rates for Minneapolis-St. Paul Standard Metropolitan Statistical Area (excluding data from New Brighton and several surrounding communities). New Brighton population data from 1980 census. Expected number adjusted for sex and age.

Table 4-13

Vital Statistics for New Brighton and Other Areas

	New Brighton	Roseville	New Hope	Ramsey County*	
1977					
Live Births	389	327	307	6096	
Fetal Deaths	3	1	4	34	(5.6)
Neonatal Deaths	7	3	3	42	(6.9)
Infant Deaths	9	3	4	62	(10.2)
1978					
Live Births	402	359	333	6081	
Fetal Deaths	2	2	2	51	(8.4)
Neonatal Deaths	1	5	4	50	(8.2)
Infant Deaths	3	6	6	79	(13.0)
1979					
Live Births	387	366	304	6454	
Fetal Deaths	4	2	2	49	(7.6)
Neonatal Deaths	-	4	1	33	(5.1)
Infant Deaths	2	4	3	53	(8.2)
1980					
Live Births	353	357	333	6641	
Fetal Deaths	3	1	3	37	(5.6)
Neonatal Deaths	3	-	1	47	(7.1)
Infant Deaths	3	-	2	65	(9.8)
1981					
Live Births	388	382	301	6686	
Fetal Deaths	2	4	1	40	(6.0)
Neonatal Deaths	4	1	1	39	(5.8)
Infant Deaths	5	2	2	57	(8.5)
1982					
Live Births	365	383	322	6634	
Fetal Deaths	2	1	3	43	(6.5)
Neonatal Deaths	6	1	-	38	(5.7)
Infant Deaths	8	2	4	71	(10.7)
1983					
Live Births	304	350	317	6533	
Fetal Deaths	1	7	-	50	(7.7)
Neonatal Deaths	1	4	2	48	(7.3)
Infant Deaths	4	8	2	82	(12.6)

* Ramsey County data are for whites only; numbers in parentheses show rates (events per 1000 live births).

births (300-400) in New Brighton coupled with the low rate of fetal and neonatal deaths (Table 4-13) produced large variability in the observed yearly rates. Thus, although no trends were observed (compared to Ramsey County), only large differences in rates (almost two-fold) could have been detected statistically. It should also be noted that such crude comparisons do not take into account any community differences in known maternal risk factors, such as maternal age, maternal smoking, diseases during pregnancy, prenatal care, and many other factors.

No other health-related information pertaining to well contamination in New Brighton is believed to exist. (However, a number of epidemiologic studies have considered health effects in other community or occupational populations exposed to VOCs; findings from these studies are presented elsewhere in this Section.)

5. EPIDEMIOLOGIC STUDY OPTIONS: ST. LOUIS PARK AND NEW BRIGHTON

5. EPIDEMIOLOGIC STUDY OPTIONS: ST. LOUIS PARK AND NEW BRIGHTON

As described in Section 1, several different epidemiologic methods and several types of health outcomes can be utilized in studies to identify potential relationships between chemical exposures and adverse health effects. Possible study options range from simple tabulations and comparisons of mortality rates in "exposed" and "nonexposed" populations to analytic studies using case-control or cohort study methods. Selection of appropriate methods and health endpoints will depend on many factors, and each approach will have particular advantages and disadvantages. In the following discussion, various study options are presented for St. Louis Park and New Brighton. Each option is briefly outlined in terms of its general approach, advantages, limitations, and costs. Based on these considerations, a recommendation is made as to the usefulness of each option.

DESCRIPTIVE MORTALITY STUDIES

Mortality studies are relatively inexpensive and may indicate if a problem exists that warrants further investigation. A mortality study can also be used as a first step in looking for adverse health effects associated with exposures whose specific health effects, if any, are not known (Lilienfeld, 1983).

As previously described, there are several limitations associated with mortality studies including changes in disease diagnosis, classification and survivorship (Lilienfeld and Lilienfeld, 1980). Advancements in diagnostic technique have improved the clinician's ability to accurately diagnose disease. In some instances an improvement in the differential diagnosis of a disease has affected the number of cases recorded. Improved

treatment regimens have increased survivorship for certain diseases resulting in a decrease in mortality even though the incidence may be quite stable. In addition, the International Classification of Disease (ICD) code, used to code causes of death, has gone through several major revisions, each one incorporating greater detail and specificity in disease classification. These revisions have affected the numbers of cases assigned to certain disease codes. The significance of these limitations varies depending upon the time period and cause of death under study. Several other factors such as community characteristics and information available on the exposure also determine the feasibility of doing these studies.

A mortality study can be conducted using data recorded on death certificates. Because contact with individuals is not necessary, this study is noninvasive to the community and would be much less expensive than a study requiring community contact.

The number of deaths in the community of interest (St. Louis Park or New Brighton) could be compared to the number of deaths in a similar population. There are several criteria for the selection of an appropriate comparison community. The community should not have the same "exposure" to the factor of interest (e.g., comparison communities for St. Louis Park and New Brighton should not have contaminated well water). A comparison community should also be similar to the community of interest in several major demographic characteristics (Edmonds, 1981). This reduces the possibility of a factor other than the exposure of interest (i.e., well water contamination) causing an observed difference in mortality (ecologic fallacy). These characteristics may include race, socioeconomic status, urban/rural status and community size. It is possible to select more than one comparison group when no single group is an entirely satisfactory

comparison (MacMahon and Pugh, 1970). Multiple comparison communities may give additional insight into any observed differences in mortality. Several communities that may be appropriate to use as comparisons for St. Louis Park are Edina and Richfield; comparison groups for New Brighton may include Roseville and New Hope. These are neighboring communities in which the water supply has not been known to be contaminated. The populations' size, median income, racial distribution, and educational status are also generally comparable. Comparison of mortality rates in St. Louis Park and New Brighton to general Twin Cities area or statewide rates could also be made. The use of such a large reference population would serve to reduce the effects of statistical variability.

Mortality rates can also be examined in the same community over time. This analysis can reveal changes in a community's cancer mortality experience. Its primary use is to generate hypotheses or to suggest appropriate study endpoints; it does not address changes in mortality due to specific exposures. Many other factors, either real or artifactual (e.g., changes in ICD coding, improvements in disease diagnosis and survival, the presence of other unmeasured risk factors) other than the exposure of interest can cause changes in mortality over time (Lilienfeld and Lilienfeld, 1980).

There are several ways in which death certificate data could be analyzed. Age-, sex-, and cause-specific mortality rates could be examined. In addition, both direct and indirect standardized rates could be calculated to compare the mortality experience in the community of interest relative to the comparison community. Age- and sex-standardization eliminates the effect of differences in the age and sex structure of the populations being compared (Shryock et al., 1976). Crude

or unadjusted rates from different populations can be misleading if compared (Pike, 1978). For example, a crude death rate is likely to be high in a population with a large number of elderly relative to a population composed primarily of young adults, even if their age-specific mortality experience is identical. Standardized rates can control for these differences.

Direct standardization applies the age- and sex-specific death rates in the population of interest to the number of the same age and sex in the standard population. The comparison community's age- and sex-specific death rates are also applied to the standard population. The resultant summary statistics can be directly compared and differences in the communities' mortality experience can be determined (Shryock et al., 1976).

Standardized mortality ratios (also called indirect standardization) can also be calculated. A standardized mortality ratio (SMR) is the ratio of the observed number of deaths in the population of interest to the number expected if the population of interest were to have the same mortality rates as the comparison population (Shryock et al., 1976). An SMR of 1.0 indicates that the observed number of deaths is identical to the expected number. An SMR greater than 1.0 implies an excess number of deaths in the population of interest, while an SMR less than 1.0 implies fewer deaths than expected in the population of interest.

Several different mortality endpoints can be examined including fetal, neonatal or infant deaths, and cancer deaths. The advantages and disadvantages of doing a study of infant, neonatal or fetal deaths are similar for St. Louis Park and New Brighton and therefore will be discussed jointly. The advantages and disadvantages of conducting a cancer mortality study are sufficiently different in St. Louis Park and New Brighton that they will be described separately.

Infant/Fetal Mortality

An advantage of studying events such as infant, neonatal, or fetal deaths is that they occur much closer in time to potential exposures of interest; a long latency period is not involved. Although it is not known when wells in St. Louis Park and New Brighton were first contaminated, it is known when contaminated wells were removed from service. A study could be conducted to examine and compare infant mortality several years before and several years after closure of contaminated wells. The most highly contaminated wells in New Brighton were taken out of regular service in 1981. A "before and after" study could compare mortality several years prior to 1981 to mortality after the wells were closed. In St. Louis Park the first wells were closed in 1978 (several additional wells were closed between 1979 and 1981, soon after contamination was first detected; thus, there was probably little exposure potential after 1978). Here the same type study could be done before and after 1978.

There are several major limitations to the study of acute events (i.e., infant/fetal mortality) in these communities. First, as described in Section 4, there is no evidence to date which suggests that low-dose exposure to the contaminants found in either community is associated with an increase in any of these events. Certain PAH's are known carcinogens but they are not known to be teratogens. The available evidence does not suggest that the contaminants found in the New Brigthton water supply are associated with measureable adverse human health outcomes at environmental exposure levels.

An additional difficulty in doing this type of study is the small number of these acute events which occur and are recorded. Since 1977, 500-650 live births per year have been recorded in St. Louis Park, and 300-400 live births per year have been recorded in New Brighton (Minnesota

Health Statistics, 1977-1982). Fewer than 10 fetal, neonatal, or infant deaths occurred each year in either community (Minnesota Health Statistics, 1977-1982). If these acute events were accumulated from 1977-1980 and assuming a power of 80%, the relative risk for overall mortality would need to be between 2.2 and 2.5 in order to be detected (Table 5-1). A study's ability to detect a relative risk of this magnitude for fetal and neonatal deaths would be less than 80% because these events occur less frequently than infant deaths.

Examining the overall infant or neonatal mortality rate (vs. cause-specific mortality), however, gives little insight into changes in a community's mortality experience due to specific exposures. There are many categories of infant death (e.g., accidents, congenital defects, and Sudden Infant Death Syndrome), each of which may be associated with a particular set of risk factors (Edmonds, 1981). It may not be possible to identify the risk associated with a specific exposure by examining overall rates; if a specific cause were truly elevated, its existence might well be masked by other causes of death and would not be apparent from a comparison of overall mortality.

An alternative to studying overall rates is to compare various cause-specific mortality rates in the community of interest at different periods of time or between the community of interest and one or more control communities. By looking at specific causes of death, it is less likely that an increase in one cause of mortality will be missed. However, this approach also has limitations. Any specific cause of death occurs very infrequently and the examination of these events would be severely limited by small numbers. A very large increase in the number of cause-specific deaths would have to occur for a statistically significant elevation to be

Table 5-1

Lowest Detectable Relative Risk for a Specified Power (alpha = .05, 2-Sided)*

	Power		
Infant Mortality (1977-80)	.90	.80	.50
St. Louis Park	2.83	2.51	1.97
New Brighton	2.46	2.22	1.79

* Walter, S.D., Determination of Significant Relative Risks and Optimal Sampling Procedures in Prospective and Retrospective Comparative Studies of Various Sizes. Am. J. Epi. 105: 387-397 (1977).

Note: Calculations based upon 17 infant deaths and 1531 live births in New Brighton from 1977 through 1980. St. Louis Park calculations based upon 12 infant deaths and 2103 live births in this community from 1977 through 1980.

found. Results, even if significant, would be very difficult to interpret. If a large number of comparisons are made it is likely that one or more rates will be found elevated by chance alone (Snedecor and Cochran, 1976). If the specific rate found to be elevated is biologically plausible and is confirmed by additional studies, then it is not likely to be a result of normal random variation. Until these types of validating data are available, however, conclusions can not be drawn.

A disadvantage specific to the study of fetal deaths is the data source itself -- fetal death certificates. In Minnesota, reporting of fetal deaths prior to 20 weeks gestation is not required by state law; therefore, fetal death certificates document only the deaths which occurred at 20 or more weeks gestation (M.S. 144-222, MN Rule 4600.1800). There are several other sources of data on fetal deaths prior to 20 weeks. Medical and physician's records document fetal deaths that occur in the hospital or physician's office. Even these data are not complete, however, as not all spontaneous abortions (and therefore early fetal deaths) come to medical attention. In a study of New York women known to have had first trimester spontaneous abortions, 40% of them did not seek medical attention (Edmonds, 1981). These data could also be obtained by personal interview, although the accuracy of this information may vary (Edmonds, 1981). Obtaining data from these sources (i.e., physician and hospital records, personal interview) would be time consuming and would increase the cost of a study.

In sum, a study of infant, neonatal, or fetal deaths could be done in either St. Louis Park or New Brighton. The accessibility of the data, the relatively low cost (Table 5-2) and the general lack of knowledge regarding the causes of these events are factors that would support the conduct of such studies. On the other hand, there would be serious difficulties and

Table 5-2

Study Budget: Infant Mortality in St. Louis Park and New Brighton

Personnel	Effort	Dollar Amount	
Title of Position	% (months)	Salary	Total
Epidemiologist I	50 (4)	28,000	4,667
Computer Progammer	10 (4)	32,000	1,067
Health Program Aide	10 (4)	20,000	667
	Personnel Subtotal		6,401
	Fringe (18%)		1,152
	Personnel Total		7,553
Computer Expenses			2,000
		Total	$ 9,553

Note: This is the cost of doing an infant mortality study in one community. The cost of doing a study in each community would be $19,106.

limitations to the conduct or interpretation of these studies. At this time there is no evidence that low exposures to any of these contaminants would result in an increased rate of these events (i.e., a lack of biologic plausibility). In addition, the number of these events is very small and data available on fetal deaths is incomplete. Because of the small number of acute events which occur, only a considerably elevated risk could be detected. This is especially true if examining cause-specific mortality. Therefore it is not likely that this type of study would offer new insights into possible adverse health effects associated with water contamination in either St. Louis Park or New Brighton.

Cancer Mortality - St. Louis Park

A mortality study examining cancer deaths in these two communities could also be conducted. In St. Louis Park, cancer mortality over time and in comparison to similar communities and to the Metro area could be examined. Specifically, cancer rates from approximately 1948-1952, 1958-1962, 1968-1972, and 1978-1982 could be calculated. These time periods surround the census years for which accurate population data are available, a necessity when determining rates. Wells that were contaminated between 1978-81 were installed between approximately 1947 and 1969. It might be assumed then that 1950 (and probably 1960) rates would represent cancer mortality before any possible effects from the contaminants would occur. The 1970 and 1980 rates could represent the community's mortality experience several decades following possible onset of exposure. (This is speculative since it is not actually known when wells became contaminated or to what extent contaminants were actually present in tap water.) Calculating rates over 5-year periods in lieu of annual rates, increases the person-years of observation and therefore increases the chance of

detecting a true elevation in mortality. The St. Louis Park mortality rates would need to be compared to those in similar communities (e.g., Edina and Richfield), as well as to the Metro area during the same period.

In St. Louis Park, this type of study has several advantages. Data on causes of death are readily available on computer tapes dating back to 1944. The records are each 80 characters in length (see record layout in Table 5-3). The city code for St. Louis Park has been recorded on the tapes since at least 1948, allowing easy identification of St. Louis Park residents. Street address is not coded on the tapes and therefore, if in the future, areas of exposure within St. Louis Park could be identified, the certificates would have to be accessed in order to determine exposure status of the residents.

Although present at extremely low levels, certain of the water contaminants in St. Louis Park wells are known animal carcinogens. Exposure to certain PAH-containing mixtures (such as cigarette smoke and coke oven emissions) has been associated with an increased risk for several cancers, e.g., lung, (NAS, 1983b). In addition, the cancer incidence study done in this community, based on data from the Third National Cancer Survey (1969-1971), demonstrated an increase in several cancers in women. The incidence of breast cancer was found to be elevated, as was the incidence of colon and rectal cancers, cancer of the corpus uteri, and cancer of the digestive system as a whole. Several of these findings were based upon a small number of cases and were of marginal significance (Dusich, 1979). In a study of St. Louis Park mortality it would be possible to reexamine those cancers previously found to be elevated and to examine additional cause-specific rates to look for any other elevations. This study would be used to generate hypotheses and would not address the etiology of any elevations

Table 5-3

Coding Scheme for Death Tapes

Variable	Columns
Name	6-31
Sex	32
Date of death	33-38
Age	39-40
Race	41
Place of death - county	42-43
Place of death - hospital	44-47
Marital status	48
Place of residence - county	49-52
Census tract	53-57
Cause of death (ICD code)	58-61
Autopsy (Yes/No)	62
Attendant	63
*Cancer (Yes/No)	64
*Accident type	65-66
*Accident age	67
*Accident place	68-71
*Place of death	72-77
*Veteran status	78
*Birthplace (State/county)	79-80

*Available only for certain years. When available, entered only if applicable.

found. Again, the probability of finding an increase due to chance alone is greatly increased with this approach and the results would have to be interpreted with caution.

There is a long latency period associated with many cancers (i.e., the cancer does not develop until many years after initiation of the exposure). Municipal well water contamination in St. Louis Park could conceivably have begun anytime between the late 1940s and the late 1970s. If it is assumed that well contamination occurred quite early, then a sufficient period of time since initial exposure has passed to allow for the 10-30 year latency period for most cancers.

A mortality study could detect relatively small increases in overall cancer mortality because of the size of the population in St. Louis Park. The population has been between 42,000 and 49,000 since 1960 (Table 5-4). Thus, a sufficient number of cancer deaths during 5 year intervals from 1960-1980 will have occurred, enabling the detection of a 20-30% increase in overall cancer mortality (this assumes power of .80-.90 and level of significance of 0.05). A 50-100% increase in mortality from any of the major cancer groups (e.g., breast, digestive) could also be detected (Table 5-5). Accumulating cases over a longer period of time might allow the detection of similar increases in more specific cancer types or detection of smaller increases in the major cancer groups.

The limitations of doing a mortality study in St. Louis Park are primarily those commonly associated with mortality studies where death certificate data are used (see Section 1). These limitations include changes in disease diagnosis, classification, and survivorship.

Another limitation to this study is the degree of population migration (or mobility) which has occurred in St. Louis Park since 1950. Migration may occur in two directions: (1) exposed persons may move to another

Table 5-4

St. Louis Park and New Brighton: Population Census

1950 - 1980

	Census Year			
	1950	1960	1970	1980
St. Louis Park Population	22644	43310	48883	42931
New Brighton Population	2218	6448	19517	23269

Table 5-5

St. Louis Park: Lowest Detectable Relative Risk for a Specified Power**

	Year					
	1980*			1970+		
	Power			Power		
Cause of Death	0.90	0.80	0.50	0.90	0.80	0.50
all cancers	1.27	1.23	1.16	1.24	1.21	1.14
digestive cancers	1.51	1.44	1.30	1.46	1.39	1.27
breast cancer	1.97	1.82	1.54	1.94	1.79	1.52
respiratory cancer	1.59	1.50	1.34	1.65	1.55	1.37
leukemia	2.38	2.15	1.75	2.28	2.07	1.70
uterine and cervical cancer	3.33	2.92	2.22	3.14	2.76	2.12

** Walter, S.D., Determination of Significant Relative Risks and Optimal Sampling Procedures in Prospective and Retrospective Comparative Studies of Various Sizes. Am. J. Epi. 105: 387-397 (1977).
* Calculations based upon cancer rates for state of Minnesota, 1980.
+ Calculations based upon cancer rates for state of Minnesota, 1970.

Note: Person years of observation accumulated over 5 years and based upon St. Louis Park population in 1980 for 1980 risks and 1970 population for 1970 risks.

geographic area (possibly to one of the comparison communities) and therefore their death will not be included in the exposed group, or (2) previously unexposed persons may move into the exposed community. In either event, the ability to detect differences in mortality between the exposed and unexposed area is decreased because the two groups become intermixed (Polissar, 1980). Population migration or mobility is of special concern in a study where the diseases of interest, e.g. cancer, have a long latency period (Polissar, 1980). The longer the latency period the more likely it becomes that some exposed people will have left before disease develops. Data from the 1980 Minnesota census indicate that only 53% of the residents in 1980 resided in St. Louis Park in 1970. This degree of mobility may affect the ability of the study to detect differences in mortality.

It is feasible to conduct epidemiologic monitoring of mortality in St. Louis Park. In this community there are several specific cancers of interest, the data are available on computer tapes, and the population is large enough to detect reasonable elevations in cancer mortality. Epidemiologic monitoring of cancer mortality rates over time and relative to several comparison populations will be useful. These mortality data, together with data from a statewide cancer surveillance system (see below), will be important to addressing the concern in St. Louis Park about the current health implications of the 1969-1971 finding of increased breast cancers. An important step in interpreting this observation is the development of historical (pre-1967) and subsequent (post-1971) cancer rates for St. Louis Park.

Cancer Mortality - New Brighton

A study of cancer mortality rates is also an option in New Brighton. In fact, a study of overall cancer mortality rates has already been completed. In 1983, the MDH examined cancer mortality in New Brighton for the period 1976-1980 in response to a request by State Senator Steve Novak and Representative Dan Knuth. The number of observed cancer deaths in New Brighton was compared to the number expected, based on state and metro area rates and adjusting for age and sex differences. Results indicated that cancer mortality in New Brighton over the five-year period was slightly less than that in the metro area.

The year that the New Brighton municipal water supply first became contaminated is unknown. Use and/or disposal of contaminants began in the early 1940's. Wells found to be contaminated in 1981 had been installed between 1955 and 1971. It might be assumed that municipal wells became contaminated some time between 1955 and 1981. Consequently, exposure could have started from less than 5 years ago to almost 30 years ago. A latency period of 10-30 years after exposure to an environmental carcinogen is generally required for the development of cancer (Shy and Struba, 1978). Therefore, it is uncertain, although possible, that there has been a sufficient time period since onset of exposure to allow for a cancer mortality study.

A mortality study in New Brighton could update the 1976-1980 data as well as include data prior to 1976. The rates from 1948-1952, 1958-1962, 1968-1972 and 1978-1982 can be calculated. Comparisons can be made over time and relative to another community. The New Brighton population in 1950 was only 2,218 and therefore the rates must be viewed with caution during this period. When examining mortality in a small population, cause-

specific death rates are quite unstable (i.e., can vary from year to year normally) (Mantel, 1967). Rates from 1950-1980 will presumably represent the community's mortality experience both in the period before effects from the exposure could be expected and the period when effects (if any) might be expected. The New Brighton rates could also be compared to those in several other communities (e.g., Roseville and New Hope) and to the Metro area during the same period of time.

New Brighton is a fairly small community (Table 5-4) and therefore a mortality study will not be able to detect as small an increase in cancer mortality as is possible in St. Louis Park. For the population size during 1970-1980, a mortality study would be able to detect a 30-40% increase in all cancers combined if cases are accumulated over 5 years. A 60-200% increase could be detected in some of the major cancer groups (Table 5-5). The population was considerably smaller in the 1950s and 1960s and therefore a mortality study would be much less likely to detect an increase during these periods. The ability to detect a small increase in a specific cancer in New Brighton is extremely poor.

The death certificate data for New Brighton are also available on computer tapes. However, information on residence is not as readily available for persons residing in this community. Until 1961, New Brighton was coded as Rural Ramsey County on the death certificate tapes, along with several others communities (e.g., Shoreview and Maplewood). To determine which deaths occurred in New Brighton residents, the original death certificates from all persons residing in Rural Ramsey County prior to 1961 would have to be examined.

Population mobility is also a concern in New Brighton. According to the 1980 Minnesota census, only 42% of the 1980 population had been living in New Brighton since at least 1970. Therefore, some persons considered

exposed (as determined by the residence listed on their death certificate) may have only recently moved to New Brighton. Alternatively, New Brighton residents who moved to another community and then died will be missed.

Another factor to consider in relation to mortality (or other) studies in New Brighton is the available evidence regarding health effects of the contaminant compounds. There are presently no epidemiologic data which suggest that the substances found in the New Brighton water supply pose an observable cancer risk in humans. TCE is known to cause hepatocellular carcinoma in a strain of mice, although there appears to be dose-related and metabolic differences that may account for the sensitivity of this strain (see Section 4). A potential endpoint of interest then is liver cancer. As mentioned above, the small population size in New Brighton would prohibit detection of even modest increases in specific types of cancer. For liver cancer, which is very rare, the minimum detectable risk is about 6 (Table 5-6).

In summary, an expanded cancer mortality study in New Brighton is clearly possible. It would have some advantages and many limitations. The study would be quite inexpensive and could be done in a short period of time. It would update and expand upon the data presently available. The limitations of this study include the lack of suspected human health effects upon which to focus (other than liver cancer, based on animal data), the difficulty in obtaining mortality data prior to 1961 and the size of the community, especially prior to 1970. To have adequate power to detect an elevation in mortality, deaths will have to be accumulated over at least 5 years and only the major categories of cancer could be examined. Furthermore, the previous mortality study did not show any significant elevations in cancer mortality for the period 1976-80. For these reasons

another mortality study of cancer in New Brighton is not recommended at this time. In addition, the institution of a statewide cancer surveillance system (see below) would provide adequate surveillance of future cancer experience for New Brighton.

The primary expense associated with mortality studies in either community would be personnel and computer time. A mortality study could be completed in approximately six months. A study in St. Louis Park would cost approximately $21,000 (Table 5-7). A study in New Brighton would be more expensive (approximately $23,000; Table 5-7) because of the need to review every death certificate from Rural Ramsey County prior to 1961 to identify the New Brighton residents.

Table 5-6

New Brighton: Lowest Detectable Relative Risk for a Specified Power**

	Year					
	1980*			1970+		
	Power			Power		
Cause of Death	0.90	0.80	0.50	0.90	0.80	0.50
all cancers	1.38	1.32	1.22	1.40	1.34	1.23
digestive cancers	1.73	1.61	1.41	1.80	1.68	1.45
breast cancer	2.41	2.17	1.77	2.65	2.37	1.89
respiratory cancer	1.83	1.70	1.47	2.12	1.94	1.62
leukemia	3.05	2.69	2.08	3.31	2.90	2.20
liver cancer	6.48	5.37	3.60	7.31	6.00	3.94

** Walter, S.D., Determination of Significant Relative Risks and Optimal Sampling Procedures in Prospective and Retrospective Comparative Studies of Various Sizes. Am. J. Epi. 105: 387-397 (1977).
* Calculations based upon cancer rates for state of Minnesota, 1980.
+ Calculations based upon cancer rates for state of Minnesota, 1970.

Note: Person years of observation accumulated over 5 years and based upon New Brighton population in 1980 for 1980 risks and 1970 population for 1970 risks.

Table 5-7

Mortality Study Budget: St. Louis Park and New Brighton

Personnel	Effort	Dollar Amount	
Title of Position	% (months)	Salary	Total
Epidemiologist I	50 (6)	28,000	7,000
Computer Programmer	25 (4)	32,000	2,667
Health Program Aide	50 (3)	20,000	2,500
	Personnel Subtotal		12,167
	Fringe (18%)		2,190
	Personnel Total		14,357
Computer Expenses (computer time, tape)			7,000
		Total	$ 21,357

Note: The cost of doing the St. Louis Park Study is $21,357. The New Brighton Study would cost $22,832 because the Health Program Aide would be needed at 75% time for 3 months (all other costs would be the same). This would allow the Health Program Aide to review each Rural Ramsey County death certificate prior to 1961 to identify New Brighton residents. The total cost of the two studies would be $44,189.

DESCRIPTIVE CANCER MORBIDITY STUDIES

Statewide Cancer Surveillance System

The advantages of using cancer morbidity (vs. cancer mortality) in epidemiologic studies were described previously in Section 1 of this report. However, Minnesota does not now routinely collect cancer incidence (morbidity) data. The feasibility of a statewide cancer surveillance system has been exhaustively studied by the MDH at the request of the Legislature (1981 Session Laws, Chapter 340). The proposed pathology-based statewide cancer surveillance system was found to be scientifically valid, cost-effective, technically feasible and is being recommended for implementation in Minnesota. One of the important uses of the system will be to monitor cancer incidence trends in order to detect potential problems that may have public health significance or to indicate that no additional investigations are necessary. The proposed system will collect the amount of cancer information on each Minnesota resident with cancer necessary for the computation of incidence rates by age, sex, cancer and geographic area of the state, including St. Louis Park and New Brighton. Detailed information on the feasibility study results, patient confidentiality, needs, uses and costs of the proposed system are contained in the MDH report entitled, "Feasibility Study of a Statewide Pathology-Based Cancer Surveillance System in Minnesota: Final Report."

The following discussions outline additional cancer incidence studies that may, depending on the data from the cancer surveillance system and mortality data, be required to interpret the observations about cancer occurrence in St. Louis Park or New Brighton.

Cancer-Incidence Study - St. Louis Park

As described previously in this report, much of the public concern in St. Louis Park was precipitated by the findings of a study of cancer incidence rates in St. Louis Park in comparison to rates in several similar communities and to rates for the Minneapolis-St. Paul metro area (Dusich, 1979; Dusich et al., 1980). This study was based on data from the Third National Cancer Survey for newly-diagnosed (incident) cancers, 1969-1971. None of the rates for the 45 cancer sites analyzed was found to be elevated in men who had a St. Louis Park address at the time of diagnosis. Among women, however, greater than expected rates were found for cancers of the breast, corpus uteri, digestive system and for cancers overall. The greatest excess (45% higher than in the Metro area) was for breast cancer. Efforts to determine the extent to which known risk factors account for this excess have not been conclusive. Several interpretations of this observed excess in 1969-71 remain possible: it could be explained, for example, in terms of normal statistical variation, known risk factors, and/or environmental exposures. Based on available evidence, it appears unlikely that the observed excess is related to well contamination. Regardless of the potential explanations, a significant elevation in cancer rates in a community will be of public health concern. To further define this issue, cancer incidence in St. Louis Park could be monitored for the period 1972 to 1986 to determine whether the previous excesses still exist or other cancer rates have increased or decreased in women or men. In addition to providing information on trends in cancer incidence and resolving some of the above questions, case identification for further studies, if warranted, would be greatly facilitated. This cancer incidence data would be particularly valuable if a statewide cancer surveillance

program were not initiated or if findings from this surveillance were unclear.

i. Case Ascertainment

Cases would be identified by reviewing pathology reports in metropolitan area hospitals for individuals with a diagnosis of cancer between 1972-1986. All incident cases would be checked with hospital lists to obtain residential information and eliminate all non-St. Louis Park residents. To ensure maximum case ascertainment records from the University of Minnesota Hospitals, Mayo Clinic, physician reports, outpatient information from pathology labs and radiotherapy facilities serving St. Louis Park residents would also need to be reviewed. Case identification would begin by using the TUMORS hospital-based cancer registry system which collects information regarding cancer diagnosis from almost all of the metro area hospitals. Since this registry is incomplete for all hospitals during this time period (1972-1986), additional cases would have to be identified by reviewing individual hospital records. Access to medical records would be arranged by the Minnesota Department of Health pursuant to Minnesota Statute 144.67-144.69. This statute assures access to medical records for cancer research and protects patient confidentiality. The protocol and methods employed during the Third National Cancer Survey would be followed to ensure comparability and minimize development costs. (An example of the abstract form for cancer ascertainment can be found in Table 5-8).

ii. Analysis

All abstracted information would be entered onto computer tape by the data entry personnel at the Minnesota Department of Health. Data would be verified for accuracy and uploaded without personal identifiers to the

University of Minnesota's Cyber Computer for subsequent analysis. Cancer incidence rates would be calculated by age, sex, race, primary site and histology (if available). In addition, cancer incidence rates would be examined for trends by comparing site-specific rates at three year intervals (i.e., 69-71; 72-74; 75-77; 78-80 etc.). Since the State of Minnesota had no population-based cancer incidence data for this time period, site-specific rates could be compared with those of the State of Iowa. Time trends will also be compared to those of St. Louis Park after the statewide cancer surveillance system is implemented.

iii. Cost Estimates

The cost estimate for updating cancer incidence in St. Louis Park for the years 1972-1986 is shown in Table 5-9. Overall costs would be approximately $250,000. This cost could be reduced to approximately $205,000 if no St. Paul area hospitals were included in the abstracting process. The approximate duration of this study would be two years. The first year would involve case ascertainment and medical records abstracting while the second year would involve data analysis and report generation.

Table 5-8

Hospital and Clinic Abstract Form

Budget Bureau No. 68-S68086: Approval expires 12/31/72

NIH-1430-3 Rev. 12-69

THIRD NATIONAL CANCER SURVEY

HOSPITAL AND CLINIC ABSTRACT

1. DOCUMENT IDENTIFICATION NUMBER: Area | RT (1) | Year | Julian Date | Doc. Number

2. CASE NUMBER

SECTION I - PATIENT INFORMATION

PATIENT'S NAME: 3. LAST | 4. FIRST | 5. MIDDLE (Maiden) | 6. SPOUSE'S FIRST NAME

ADDRESS OF PATIENT: 7. HOUSE NO. | 8. STREET NAME OR NUMBER | 9. APT. NO. | 10. TOWN OR CITY | 11. STATE

12. ZIP CODE | 13. COUNTY | 14. If patient's usual address is a hospital, nursing home, hotel, etc., give NAME | NAME OF INSTITUTION

15. Date of Birth — Month / Day / Year

16. Age at Admission

17. Sex
○ 1-Male ○ 2-Female ○ 3-Unknown

18. Present Marital Status
○ 1-Married ○ 4-Divorced
○ 2-Widowed ○ 5-Single (Never married)
○ 3-Separated ○ 6-Unknown

19. Race
○ 1-Caucasian ○ 5-American Indian
○ 2-Negro ○ 6-Other (Specify) _____
○ 3-Chinese
○ 4-Japanese ○ 7-Unknown

20. Birthplace (State or country) _____

21. Social Security Number ___-___-____

22. Hospital History Number

SECTION II - HOSPITAL AND MEDICAL INFORMATION

23. Is this the first admission to this hospital for this cancer?
○ 1-Yes ○ 2-No ○ 3-Unknown

24. Was this cancer diagnosed before this admission?
○ 1-Yes ○ 2-No ○ 3-Unknown

25. If "Yes", please specify:
NAME
(Doct. or Inst.) _____
ADDRESS _____
CITY _____ STATE _____

26. Date of first diagnosis of this cancer. — Month / Day / Year

27. Date of this admission

28. Date of discharge

29. Referral Source
○ 1-Doctor* ○ 5-Statutory authority
○ 2-Other hospital* ○ 6-Other*
○ 3-Nursing home* ○ 7-Unknown
○ 4-Self

30. *If "1, 2, 3, or 6 above", please specify:
NAME
(Doct. or Inst.) _____
ADDRESS _____
CITY _____ STATE _____

31. Primary site AT THIS CONTACT _____

32. Histologic type AT THIS CONTACT

33. Method of Diagnosis

MICROSCOPICALLY CONFIRMED
○ 1-Autopsy
○ 2-Tissue from primary site under direct or indirect vision
○ 3-Blind biopsy or tissue not from primary site
○ 4-Cytology or Hematology
○ 0-Micro, tissue source of method not known

NOT MICROSCOPICALLY CONFIRMED
○ 5-Gross Specimen only
○ 6-X-Ray
○ 7-Clinical
○ 8-Other (specify) _____
○ 9-Unknown

34. How many other independent cancers has this patient ever had?
○ 0-None ○ 3-Three or more
○ 1-One ○ 4-An unknown number
○ 2-Two ○ 5-Don't know

For most recent ind. cancer, please specify:

35. PRIMARY SITE _____

36. HISTOLOGIC TYPE _____

37. DATE OF DIAGNOSIS — Month / Year

NOTE: For any additional independent cancers, specify in the Comments section below, primary site, histologic type, and month and year of diagnosis.

38. Follow-up after discharge by:
○ 1-Doctor* ○ 5-Died in hospital (Give cause) _____
○ 2-Hospital* ○ 6-Other*
○ 3-Nursing home* ○ 7-Unknown
○ 4-None

39. *If "1, 2, 3, or 6 above", please specify:
NAME
(Doct. or Inst.) _____
ADDRESS _____
CITY _____ STATE _____

40. NAME OF HOSPITAL

COMMENTS: Refer to Question No. when making comments

SECTION III - SURVEY INFORMATION

SOURCES CHECKED
○ Discharge summary
○ Progress notes
○ Pathology report
○ Discharge diagnosis
○ Operative notes
○ Radiology reports
○ Autopsy report

DATE OF ABSTRACT

41. ABSTRACTOR ID

42. ☐ 43. ☐ 44. ☐ 45. ☐ 46. ☐ 47. ☐ 48. ☐ 49. ☐ 50. ☐ 51. ☐ 52. ☐ 53. ☐ 54. ☐ 55. ☐ 56. ☐

Table 5-9

Cost Estimates for Cancer Incidence Study in St. Louis Park

POSITION	ANNUAL SALARY	NUMBER OF MONTHS	% OF TIME	TOTAL COST REQUIRED
Record abstractors (7)	$15,000	12	100	105,000
Programmer	31,000	24	25	15,500
Clerical	15,800	24	100	31,600
Epidemiologist I	28,000	24	100	56,000
Epidemiologist II	45,000	24	10	9,000
			subtotal	217,000
			fringe at 18%	20,178
				237,178
Supplies				
travel				2,000
printing				2,000
computer processing				10,000
			TOTAL	$ 251,178

Overall study design and methods would be the responsibility of the Epidemiologist II. Day-to-day supervisory tasks would be the responsibility of the Epidemiologist I. Seven record abstractors, supervised by the Epidemiologist I would be responsible for the identification and abstraction of all incident cancer cases living in St. Louis Park anytime between 1972-1986. A clerk typist, under the supervision of the Epidemiologist I would be responsible for the typing of all correspondence, study instruments, protocols and reports as well as ensuring communication between all staff members on project schedules. A computer programmer, working in concert with the epidemiologists, would be responsible for data management including abstracting schedules, coding, data entry and the generation of computer files for data analysis. Data analysis and report generation would be the primary responsibility of the epidemiologists.

iv. Discussion and Recommendation

To gain further insights into the previously-observed elevations in female cancer rates the city of St. Louis Park, it would be beneficial to examine cancer incidence trends since the conduct of the Third National Cancer Survey in 1969-71. A statewide cancer surveillance system, once implemented, will provide future cancer incidence data for St. Louis Park. If these data are inconsistent with the 1969-1971 findings then additional historical epidemiologic monitoring of cancer incidence will be necessary. This information would provide a means to assess whether the previous cancer rates were increasing, decreasing or remaining the same. Site- and age-specific rates should be evaluated for trends as well as compared to other cancer incidence data to assist in the interpretation of previous observations of the 1969-1971 population. Decisions about the need for

more sophisticated studies (i.e., case-control) must await the collection and analysis of the descriptive cancer incidence and mortality data. These data may indicate that the 1969-1971 increase was not consistent with a potential public health problem or they may indicate that more work is necessary to resolve their public health significance. If a case-control study is needed it could be conducted with relative ease since the cases would already be identified. It is recommended, therefore, that if a statewide cancer surveillance system is not implemented or if the findings from the statewide cancer surveillance system do not clarify the 1969-1971 findings, then the cancer incidence data should be updated in St. Louis Park to include individuals diagnosed between the years 1972-1986.

Cancer Incidence in New Brighton

Although there is still scientific uncertainty about the health risks associated with exposure to low levels of the volatile organic compounds found in New Brighton city wells (TCE, TCA and DCE), available evidence does not suggest that these contaminants pose an observable human cancer risk. The specific type of cancer (i.e., liver cancer) which has been implicated in mice studies as being associated with TCE exposure is exceedingly rare in humans; the population size in New Brighton precludes the investigation of this potential relationship. Therefore, it is not recommended that retrospective cancer incidence studies be conducted in New Brighton. However, if the statewide cancer surveillance system is implemented, data from this system should be used to monitor future cancer incidence in New Brighton, as well as in other communities which have experienced environmental contamination.

CASE-CONTROL STUDY - ST. LOUIS PARK

Several methodologic approaches could be used, in principle, to test the hypothesis that contaminated drinking water in St. Louis Park is associated with an excess cancer risk. Before discussing these approaches, two major points need to be noted. The first is that regardless of the approach, it does not appear possible to define or even approximate individual exposure to PAH contaminants in drinking water (Section 4). Even if water exposures could be estimated, there would be the serious problem of distinguishing water exposures from the potentially much greater cumulative exposures to PAH from food and air. The potentially large errors in the classification of exposure to water contaminants could result in inaccurate and misleading risk estimates. Consequently, it is unlikely that more sophisticated epidemiologic studies would be able to directly address the relationship between PAH contaminants in water and human health.

The second point is that, as previously noted, several interpretations are possible regarding the elevations in cancer rates (particularly breast cancer) in St. Louis Park women in the period 1969-71, and it is not known whether the earlier rates have persisted, increased or decreased. Therefore, new analytic studies should not be undertaken unless health monitoring of past or future cancer incidence shows continued elevations or significant trends.

Should monitoring data indicate a significant elevation or persistent high trend, a likely analytic study design to assess possible causes (other than water contaminants) is a case-control study. In the following discussion the protocol for a case-control study of breast cancer is outlined as an example. If some other cancer site were to be studied, the general approach would be the same.

Case-Control Study of Breast Cancer

The basic concept of case-control methodology and its application in environmental epidemiology has been previously described (Section 1). Briefly, individuals with disease are compared to individuals without disease to identify factors that differ between groups. In a case-control study, all incident breast cancer cases in St. Louis Park residents would be ascertained within a specified time period and their exposure histories compared to those of a group of controls. Several issues including definition of exposure, sample size required, case ascertainment, control selection and study instruments will be addressed.

i. Exposure

As previously noted, it remains unclear when contaminants reached public water systems in St. Louis Park, and it does not appear possible to estimate individual exposures to water contaminants. Therefore, an arbitrary assessment of exposure could be defined such as length of residence. Those individuals residing in St. Louis Park longer than 10 years could be considered exposed while those residing less than 10 years could be considered unexposed. Data from the 1980 Minnesota Detailed Housing Characteristics indicate that approximately 53% of the population has lived in the same residence for 10 years or more. Assume therefore, that the proportion of the population "exposed" to water for at least 10 years is 0.53.

ii. Sample Size Considerations

Using incidence data from the 1978-81 Iowa SEER registry and applying these rates to the population of St. Louis Park, the expected number of breast cancers per year is 21. Table 5-10 outlines the number of cases and controls required for detecting a specified relative risk. Numbers vary

slightly according to the case-control design (unmatched, matched, multiple matching). Cancer risk associated with environmental contaminant exposure is small, especially when known risk factors are evaluated simultaneously. Therefore, sample size estimates using the smallest detectable relative risk would be the most appropriate in this instance. For example, an unmatched case-control study of breast cancer with 509 cases and 509 controls would be able to detect a relative risk of 1.5 (i.e., a fifty percent excess of breast cancer) among those exposed. To be able to detect smaller risk differences would require a larger study population.

iii. Case Assertainment

If the expected number of breast cancer cases in St. Louis Park is 21 per year, then cases would need to be accumulated over approximately a 24-year period to be able to detect a relative risk of 1.5. The assembly of cases retrospectively, (i.e., identify all incident cases occurring from 1960 to 1985) could be done through chart review of all hospitals serving the St. Louis Park community.

Cases would be identified by reviewing records in the Minneapolis area hospitals that have treated breast cancer patients with a St. Louis Park residence. Records from the Mayo Clinic would also be reviewed to insure maximum case ascertainment. Abstracting would begin by identifying the cases of breast cancer most recently diagnosed and continue backward in one year intervals until a sufficient number of incident cases had been identified. This process would minimize problems associated with follow-up, such as missing records, subject migration and subject death.

Table 5.10

Number of Cases and Controls Required to Detect A Specified Relative Risk

study design	relative-risk to be detected	alpha level	power level	number of cases required	number of controls required
1:1 unmatched	1.5	0.05	0.90	509	509
1:2 unmatched	1.5	0.05	0.90	383	766
1:1 matched	1.5	0.05	0.90	478	478
1:1 unmatched	2.0	0.05	0.90	193	193
1:2 unmatched	2.0	0.05	0.90	145	290
1:1 matched	2.0	0.05	0.90	177	177
1:1 unmatched	2.5	0.05	0.90	109	109
1:2 unmatched	2.5	0.05	0.90	82	163
1:1 matched	2.5	0.05	0.90	108	108

Since the population in St. Louis Park is primarily white, the study would be restricted to white females only. Access to medical records would be arranged by the Minnesota Department of Health pursuant to the guidelines set forth by Minnesota statute 144.67-144.69. This statute assures access to medical records for cancer research as well as protects patient confidentiality. Information to be abstracted would include name, birthdate, last known address and phone, date of diagnosis, stage, grade and histological type of tumor and social security number. Any additional information regarding risk factors known to be associated with breast cancer would be recorded if available in the medical record.

iv. Control Selection

Following case ascertainment, one control subject for each case, matched on age, would be identified using random digit dialing according to the method of Waksberg (1978). Not all telephone exchanges in St. Louis Park are unique to St. Louis Park; therefore, the address of the randomly selected numbers would have to be verified as a St. Louis Park residence. It would be expected that randomly selected phone numbers would result in some residences in which cases were present, no eligible controls were present, females were present who do not wish to participate, or several eligible controls were present. In the first three instances another random number would be selected until the required number of controls is obtained. In the last instance, the first eligible control to respond to the study participation request would be selected. It would also be expected that some of the cases will have died necessitating proxy interviews. In those instances where a proxy interview would be conducted for a case, both the selected control for that case and a proxy interview

for that control would be conducted. The purpose of this procedure would be to ensure comparability between proxy case and control interviews.

v. Interview Methods and Study Instrument Considerations

All individuals identified as cases would be contacted, first by letter and then by telephone and asked to participate in the study. Those agreeing to participate would be asked to sign and return a study consent form. Physician approval for patient contact would be obtained prior to this effort.

All cases or their proxies would be interviewed by telephone using a detailed study questionnaire. Controls and their proxies would be interviewed in the same manner. Every effort would be made to ensure that the interviewers are unaware of the exact nature of the study as well as the case/control status of the interviewee.

The study questionnaire would include questions regarding demographic information (i.e., age, height, weight, marital status and sex), employment history, residential history, family history of disease (e.g., cancer, fibrocystic disease), religion, smoking history, reproductive history, water source and consumption history, education and dietary history including alcohol and coffee consumption practices and other elements of lifestyle. Table 5-11 shows some of the factors reported to be associated with an increased risk of breast cancer.

vi. Analysis

All completed questionnaires would be entered onto computer tape by the data entry personnel of the Minnesota Department of Health. Data would be verified and uploaded to the University of Minnesota's Cyber computer for subsequent analysis. Risk estimates for matched data sets would be generated using the method described in Schlesselman (1982). Thus, the

risk of breast cancer as a function of length of residence in St. Louis Park adjusted for the effects of all variables known to be associated with breast cancer would be determined.

Table 5-11

Factors Reported to be Associated with an Increased Risk of Breast Cancer*

- History of breast cancer in mother and/or sister
- History of breast surgery for a nonmalignant breast condition
- Jewish Religion
- Menopause at age 50 or older
- Menarche before age 12
- Never married
- First live birth at 30 years of age or older, or no live birth
- College graduate
- Daily alcohol consumption (wine, beer, or hard liquor)
- Relative weight index 110 or more

* Taken from Seidman et al. (1982).

vii. Cost Considerations

The cost estimates for a case-control study of breast cancer in St. Louis Park with sufficient numbers to be able to detect a relative risk of 1.5 may be found in Table 5-12. The approximate duration of the study would be three years. The first two years would involve study protocol and instrument development, (prevalent and incident) case identification, and control selection, as well as the interviewing of cases and controls or their proxies. The third year would involve completion of interviewing, data processing, analysis and preparation of the final report.

Study design and conduct would be under the direction of the Epidemiologist III with the day-to-day supervisory tasks under the direction of the Epidemiologist I. All study protocols and instruments would be the joint responsibility of the two epidemiologists. A clerk typist, under the supervision of the Epidemiologist I, would be responsible for all the typing of materials and instruments as well as to ensure communication between all staff members on project schedules. A record abstractor, supervised by the Epidemiologist I, would be responsible for case ascertainment and record abstraction. Selection of controls would be the responsibility of the Epidemiologist I with assistance from staff members. Interviewers, supervised by the Epidemiologist I, would be responsible for the collection of data from all study participants. A computer programmer, working in concert with the epidemiologists, would be responsible for data management including interview schedules, coding, data entry and the generation of computer files for data analysis. Data analysis and report generation would be the primary responsibility of the epidemiologists.

Table 5-12

Cost Estimates for Breast Cancer Case-Control Study.

Position	Annual Salary	# of months	Time	Amount Requested
record abstractor	20,800	18	100%	31,200
Interviewer(s) (1000 interviews at 3 hrs per interview/$7.00 per hr)	21,000	24	100%	42,000
programmer	31,000	36	50%	46,500
clerical	15,800	36	100%	47,400
Epidemiologist I	28,000	36	100%	84,000
				251,100
			Fringe at 18%	45,198
				296,298
Supplies				
telephone				2,000
printing and postage				5,000
computer processing (including data entry)				10,000
			Total	$313,298

viii. Discussion and Recommendation

There are several factors regarding the conduct of a case-control study of breast cancer (or other cancer site) in St. Louis Park which must be considered. First, the measure of exposure is extremely poor. The assumption that individual exposure can be expressed as a function of the length of residence (i.e., the greater the length of residence, the greater the exposure, the greater the risk of breast cancer) may generate substantial misclassification resulting in inaccurate risk estimates. It is possible, for example, that well contamination patterns changed over time as different demands were placed on the system, producing a situation in which exposure to contaminants was sporadic. Thus, there may have been short periods with some exposure and long periods with no exposure. Misclassification could occur in those instances where a breast cancer case resided in St. Louis Park for a short period of time during which there was actual exposure or when a control resided in St. Louis Park for a long period of time during which there was no exposure. Such misclassification could, in principle, cause length of residence to appear to be a protective factor for breast cancer. The general result of misclassification is to weaken any real association that might exist. Second, the effect of migration is not well controlled. Individuals with long residence histories in St. Louis Park may have moved prior to their disease diagnosis. These individuals would not be identified in a case-control study. On the other hand, there will be individuals who migrated into the city just shortly before their disease is diagnosed. The relative impact of such in and out migration is difficult to determine. Cases and controls selected for study may not be an accurate representation of the true population at risk. Third, the use of proxy respondents could result in inaccurate and incorrect information. Combining case and proxy responses

may weaken etiologic associations. Fourth, all information obtained in the interview of cases and controls would have to be verified through medical record review. This may decrease the participation rates when people refuse to permit access to medical records. In addition, access to records may be complicated by the fact that many may have been lost over time. Fifth, the study protocol and instruments would have to be pilot tested to determine effectiveness, accuracy and ease of use.

A case-control study of breast cancer (or other cancer) in St. Louis Park would provide limited insights into the impact of drinking water contaminants. Given the ubiquitous nature of PAH compounds in the environment and the inability to determine historical exposures to PAH contaminants in drinking water, it is highly unlikely that a case-control study could detect any excess cancer risks attributable to contaminated drinking water. Such a study would, however, yield valuable information regarding other risk factors for the disease and could have considerable public health importance. In light of these considerations, especially the inadequate information on exposure, a case-control study to evaluate the contribution of contaminated drinking water on breast cancer risk in St. Louis Park is not recommended at this time.

COHORT STUDY - ST. LOUIS PARK

The basic concept of a cohort study has been previously described. As applied to the situation in St. Louis Park, a cohort study would involve the identification and subsequent follow-up of all individuals residing in St. Louis Park as of some historical date. Cohort members or their proxies would be interviewed to determine disease patterns and identify risk factors associated with those disease patterns. Both mortality and incidence rates of disease in the exposed community of St. Louis Park could be compared to those of a similar but non-exposed community, adjusted for differences in the frequency of risk factors between communities (e.g., family history of disease, smoking behavior, length of residence, etc.) An advantage of a cohort study is that a variety of disease entities may be evaluated. It would also satisfy the criteria proposed in Section 3 for environmental epidemiologic studies. Inherent problems involve the completeness of cohort ascertainment and follow-up, the selection, ascertainment and follow-up of a suitable control (non-exposed) population and the overall costs.

i. Exposure

It remains unclear when and to what degree exposure to waterborne contaminants began in St. Louis Park. Historical information suggests aquifer contamination as early as the 1930s. Municipal wells found to be contaminated in 1978-81 were installed between about 1947-1969. To ensure some degree of exposure and adequate lag time for disease occurrence, especially cancer, an arbitrary date for the identification and follow-up of St. Louis Park residents would be January 1, 1960. This assumes that water supplies were contaminated for approximately 10 to 15 years prior to

1960 and the follow-up of all residents to 1985 would allow sufficient time (i.e., 25 years) to elaspe for disease induction. It further assumes that all residents were exposed to some degree, the magnitude of which would be dependent upon the length of residence. These exposure assumptions are completely speculative (Section 4).

ii. Sample Size Considerations

The proposed non-concurrent cohort method for the study of health effects in St. Louis Park would generate approximately 1,200,000 person years of observation (i.e., a population of approximately 48,000 observed for 25 years), providing sufficient power to examine a variety of disease entities including cancer. For example, the expected number of incident cancers within the twenty-five year follow-up period would be breast (525), colon (450), rectum (175), bladder (175) and stomach (75).

iii. Cohort Ascertainment and Follow-up

The use of the 1960 census information would greatly facilitate case ascertainment and decrease study costs; however, this information is confidential and available only in summary form. Thus, all St. Louis Park residents as of January 1, 1960 would be identified using a variety of ascertainment methods, including telephone and reverse directory listings, utility bill listings (e.g., gas, electric, water), taxation rosters and drivers license registration lists. In addition, membership lists of various community organizations (e.g., VFW's, churches, synagogues, schools, nursing homes) would be reviewed. Information to be collected during cohort ascertainment should include, at a minimum, the name, address, sex, birth date, and social security number of the individual. Additional information such as marital status, religion and occupation would greatly facilitate tracing efforts during the follow-up process.

Subsequent interview of St. Louis Park residents would generate information on the names of family members, neighbors and friends which would be added to the cohort. The objective of this process would be the identification of all individuals residing in St. Louis Park as of January 1, 1960.

Following ascertainment, all residents of St. Louis Park in 1960 would be traced to determine their present day status (i.e., alive vs. deceased). Some overlap of cohort ascertainment and tracing efforts would be expected since the interview of successfully traced cohort members may generate information on additional cohort members (e.g., family members, neighbors, friends).

Initial tracing efforts would involve the review of current telephone and reverse directory listings, utility bill listings, taxation rosters and membership lists of community organizations to identify all those individuals still residing in St. Louis Park. Driver registration lists could be used to identify individuals still residing within the state of Minnesota, as well as provide information on where individuals may have moved. Additional sources of information that could facilitate tracing efforts include the post office, social security administration and the National Death Index. Death certificates would be reviewed to determine those who had died during the twenty-five year period. Marriage certificates would be reviewed to facilitate tracing of female residents who may have changed names following marriage. All tracing efforts would be conducted by phone, and subsequent contact with next of kin, neighbors and family friends would provide information on those cohort members currently residing outside the St. Louis Park area. Current residents may provide information on past owners, and realty companies may have information regarding title and address changes of cohort members. The

objective of the follow-up process would be the successful determination of the present health and vital status of all individuals who resided in St. Louis Park in 1960.

iv. Control Community

It does not appear possible to estimate individual exposures to drinking water contaminants. It is possible that all, some, or few residents were exposed to varying degrees of contaminated drinking water over time. The follow-up of St. Louis Park residents would provide information regarding health patterns among a population with potential but unknown exposure to contaminated drinking water. Since it is not possible to distinguish exposure potential among residents, population information from St. Louis Park must be compared to information derived from a similar population without potential exposure to these contaminants in drinking water. Thus, rates of disease in the "exposed" population of St. Louis Park could be compared to rates in a non-exposed population to determine potential differences which may be attributable to contaminated drinking water. This necessitates the ascertainment and follow-up of a control community. For example, the city of Richfield is similar to St. Louis Park in size and certain other characteristics and might serve as a control community. (The selection of an appropriate control community would require very careful evaluation.) Thus, all residents of Richfield (for example) as of January 1, 1960, would be identified and traced to their present day status using the same methods and techniques previously described.

v. Interview Methods and Study Instrument Considerations

All individuals identified as residents of St. Louis Park and Richfield (if determined to be the most appropriate comparison community)

in 1960 would be asked to participate in the study. Those agreeing to participate would be asked to sign a study consent form and complete a detailed study questionnaire by telephone. Proxy interviews (e.g., next-of-kin) would be conducted in those instances where the individual has died. All death certificates for individuals who died during the twenty-five year period would be requested and cause of death determined.

The study instrument would include questions regarding demographic information (e.g., age, height, weight, sex, marital status), employment history, residential history, reproductive history, medical history (including all diagnosed diseases and the name and address of the physician who diagnosed the disease), family history of disease and dietary history including water consumption practices. All diseases and conditions reported by the interviewer would be verified through physician contact and medical records requests.

vi. Analysis

All completed questionnaires would be entered into a data base such as System 2000 and placed in the University of Minnesota's Cyber computer for subsequent analysis. Cause- and sex-specific mortality rates would be calculated by obtaining all death certificates of deceased individuals in the St. Louis Park and Richfield cohorts. Excess mortality would be evaluated by comparing rates in St. Louis Park and those in Richfield. Incidence rates of disease would be determined by using the verified questionnaire information. Risk of disease would be calculated by comparing disease rates in St. Louis Park with Richfield adjusted for the effects of variables known to be associated with the disease under evaluation (e.g., lung cancer ---- smoking).

In addition, a case-control study within the cohort could be conducted in those instances where excesses in disease incidence or mortality are discovered. For example, if an excess incidence of breast cancer were found in the St. Louis Park cohort compared to the Richfield cohort, breast cancer cases and suitably matched controls from St. Louis Park and Richfield could be enrolled in a case-control to further identify etiologic factors associated with that excess. All apparent disease excesses could be further evaluated in this manner. Thus, the cohort approach to the study of disease provides the opportunity to identify various health outcomes that can then be further explored, if necessary, by case-control methodology.

vii. Cost Considerations

The cost estimate for a non-concurrent cohort study of St. Louis Park is approximately $3,000,000; details may be found in Table 5-13. The approximate duration of such an effort would be five years. The first year would involve study protocol and instrument development, as well as the initiation of cohort identification and follow-up. The next three years would involve the completion of cohort interviews. The last year would involve data analysis including cause-specific mortality and incidence rate calculations. However, without the additional information obtained from a non-exposed community, rate comparisions cannot be made. Thus, the risk of disease associated with residing in St. Louis Park independent of other known risk factors could not be determined. It is important therefore, that information from both exposed and non-exposed populations be collected. The effect of collecting cohort information on a control

Table 5-13. Cost Estimates for a Cohort Study in St. Louis Park.

	Annual Salary	Number of Months	Time	Amount Required
Epidemiologist III	$45,000	60	25%	56,310
Epidemiologist II	35,000	60	100%	175,000
Epidemiologist I	28,000	60	100%	140,000
Project Coordinator	24,000	60	100%	120,000
*Tracers (48,000 @ 1 hr/7 per hr)	--	--	--	336,000
**Interviewers (48,000 @ 3 hrs/7 per hr)	--	--	--	1,008,000
Computer Programmer	31,000	60	100%	155,000
Clerical Support	15,800	60	100%	79,000
				2,069,310
			Fringe at 18%	130,556
				2,199,866
Printing, Postage, and Telephone @ $15.00 per study subject				720,000
Computer				
Data Entry				25,000
Tapes				5,000
Analysis, Computer Time				25,000
			TOTAL	$2,974,866***

* To trace 48,000 people will average approximately one hour per person at a cost of $7.00/hr.

** To interview 48,000 people will average approximately three hours per interview at a cost of $7.00/hr.

***The inclusion of a control community will effectively double the costs.

community (e.g., Richfield) would effectively double the costs. Thus, costs for a cohort study of both exposed and non-exposed communities would total approximately $6,000,000.

Study design and conduct would be under the direction of the Epidemiologist III with the day-to-day supervisory tasks the responsibility of the Epidemiologist II. The Epidemiologist I would be responsible for the hiring and training of a project coordinator, trainers and interviewers. Study protocol and instruments would be the joint responsibility of the Epidemiologists. A clerk typist, under the supervision of the Epidemiologist I would be responsible for the typing of all materials and study instruments and ensure proper communication between all staff members regarding project schedules. The project coordinator, under the supervision of the Epidemiologist I, would be responsible for the day-to-day supervision of tracers and interviewers whose main responsibilities would involve cohort ascertainment, follow-up and interview. The computer programmer, under the supervision of the Epidemiologist I would be responsible for data management, including the construct of a data base for cohort ascertainment, tracing efforts and interviewing schedules. In addition, the programmer would generate computer files for data analysis. Data analysis and report generation would be the primary responsibility of the Epidemiologist II working in concert with the Epidemiologist III.

viii. Discussion and Recommendations

A cohort study would be an enormous undertaking and encroach upon all individuals in both St. Louis Park and a control community (e.g., Richfield). The lack of adequate exposure data raises serious questions about the conduct of such a costly study. The use of proxy respondents in

those instances where individuals have passed away would result in less accurate and less complete information. Verification of medical information obtained in the interview process of study subjects may be very difficult with aged members of this cohort. Development, pilot testing of study protocol and instruments would, in and of itself, be very costly. Except for inadequate exposure data relating to water contaminants, a study of this nature satisfies the criteria set forth in Section 3 and would provide information regarding disease/exposure relationships for an entire generation. Issues surrounding the association between health and diet, smoking, excercise, genetics, occupation and environment would be addressed simultaneously and provide useful information for a variety of public health concerns. However, in light of the absence of a valid model of individual exposure to water contaminants and the absence of a documented public health problem, a cohort study of this magnitude is <u>not</u> recommended, nor is it needed at this time.

A cohort study should be considered only if descriptive (cancer surveillance or mortality) and subsequent case-control studies provide unequivocal evidence of the need for such a study. In addition, if historically contaminated water is to be evaluated as a risk factor for any disease then further information that permits assessment of individual exposures to water contaminants is required before a cohort study can be recommended.

CASE-CONTROL STUDY-NEW BRIGHTON

There is currently no scientific basis for conducting a case-control study in New Brighton in relation to contaminated municipal wells. First, it is not known when wells first became contaminated or to what extent contaminants were present at the tap. Contaminated wells were installed between 1955 and 1971, and contamination could conceivably have occurred anytime between 1955 and 1981 (date of detection). Thus, even assuming that contaminants were present at the tap, there may or may not have been a sufficient period of time for induction of chronic diseases (e.g., cancer). Second, it is unclear what health endpoint should be studied. Specific health effects have not been identified in published epidemiologic studies. Animal experiments suggest that high exposures to TCE are associated with excess liver cancer in mice. According to the Iowa SEER estimates, the annual incidence of liver cancer in humans is 1.2 per 100,000. Thus, the expected number of liver cancers in New Brighton is 0.3 per year. The time required to assemble enough incident cases retrospectively to conduct a study would span the century. Thus, it is not possible to use liver cancer as a health endpoint. In addition, no excess cancer mortality was apparent in New Brighton during the five year period 1976-1980 (see above). Current literature suggests that human cancer risks associated with low level exposures to TCE are probably very small (Section 4). There is little, if any, evidence to date that TCA and DCE are human carcinogens. Thus, a case-control study with cancer as an endpoint is not recommended. Third, the use of congenital anomalies as a health endpoint would be limited due to the small number of these events. The State rate of congenital anomalies is 1.2% and approximately 5 congenital anomalies per year would be expected in New Brighton. The length of time required to generate

sufficient cases for study is prohibitive. The major contaminants identified in New Brighton wells have not produced reproductive effects in animal studies. In addition, findings from the State of California do not suggest that exposure to TCA via contaminated ground water is associated with excess risk of congenital malformations. Thus, the use of a case-control approach in New Brighton is extremely limited and cannot be recommended at this time.

COHORT STUDY-NEW BRIGHTON

The concurrent cohort study method would be the most appropriate cohort method in New Brighton. This would involve the identification of all current residents in New Brighton. Cohort members would be interviewed to collect baseline information and to identify potential risk factors. These individuals would be followed forward through time to identify disease mortality and incidence patterns. Similar efforts would be undertaken in a suitable control community comparable to New Brighton, but where the water supply is not known to have been contaminated. A comparison of rate differences and ratios would provide estimates of risk associated with living in New Brighton, which may or may not serve as an index of exposure to contaminants in drinking water.

i. Cohort Ascertainment

All current residents of New Brighton would be identified through a census. Complete enumeration of the population would involve door-to-door interviews of all residents in New Brighton collecting, at a minimum, the name, address, sex, birthdate, social security number, and occupation of all members of the household. The willingness of the individuals to participate in a community health study could also be determined at this point.

ii. Control Community

For purposes of comparison, information from a similar community without a history of public water contamination would have to be collected as well. The selection of an appropriate control community would require careful evaluation. As an example, a possible comparison community is the city of New Hope. It is similar to New Brighton in size and socioeconomic status, and has not experienced known contamination of the municipal water supply. All current residents of New Hope would be identified through a census which would involve door-to-door interviews. Information identical to that collected for New Brighton would be collected for New Hope as well as an indication as to whether these individuals desired to participate in a community health study.

iii. Interview Methods and Study Instrument Considerations

All individuals identified as current residents of New Brighton or New Hope would be asked to participate in the study. Those agreeing to participate would be asked to sign a consent form (at the time of enumeration) and complete a detailed telephone questionnaire. Both cohorts would be asked to repeat the telephone questionnaire every three to five years to collect information on disease incidence and mortality, as well as to determine changes in behavior and risk factors. Baseline clinical information (e.g., blood pressure, blood profiles, etc.) on a subset of this cohort should be considered. All death certificates for individuals dying during the follow-up period would be requested and cause of death determined.

The study instrument would include questions regarding demographic information (i.e., age, sex, height, weight, marital status) employment history, residential history, reproductive history, medical history

including all diagnosed diseases and the name and address of the attending physician, family history of disease, educational history and dietary history. All diseases and conditions reported by the interviews would be verified through medical records.

iv. Analysis

All enumerated cohort members would be entered into a computer data base for purposes of follow-up. Vital status of these individuals could be updated every year. Questionnaire information would be entered into another data base which could be linked to subsequent information obtained on follow-up every three to five years. Incidence rates of disease in the "exposed" and "unexposed" communities could be compared to determine any excess risk associated with residence in New Brighton, adjusted for the effects of variables known to be associated with disease. The accuracy and reliability of analytical results would improve with increasing duration of follow-up. Thus, more reliable risk estimates would be achieved with increasing duration of population follow-up.

v. Cost Considerations

The cost estimates for a concurrent cohort study of New Brighton residents may be found in Table 5-14. These are estimates for the first two years which would include population enumeration and collection of baseline data. Subsequent costs associated with follow-up and reinterview of the cohort would involve similar amounts every three to five years. Thus, the average cost per year following the establishment and interview of the cohort would be approximately $250,000. Both time and cost considerations should be doubled with the addition of a cohort of control subjects in New Hope.

Table 5-14. Cost Estimates for Prospective Cohort Study in New Brighton.

Position	Annual salary	Number of months	% of time	total cost requested
Epidemiologist II	35,000	24	50	35,000
Epidemiologist I	28,000	24	100	56,000
Tracers (5) at $7 per hour for 60 days				16,800
Interviewers $7 per hour/ 3 hours per interview				504,000
Clerk	15,800	24	100	31,600
Computer programmer	31,000	24	75	46,500
				689,900
			Fringe at 18%	30,438
				720,338
Printing, postage and telephone $5.00 per person				120,000
Computers				
data entry				15,000
tapes				2,500
analysis				15,000
			Total	$872,838*

*Inclusion of control community would effectively double costs.

Study design and conduct would be under the supervision of the Epidemiologist II with the day-to-day supervisory tasks being the responsibility of the Epidemiologist I. All study protocols and instruments would be the joint responsibility of the two epidemiologists. A clerk typist would be responsible for the typing of all materials and instruments as well as for insuring communication between all staff members. A group of five individuals, under the supervision of the Epidemiologist I, would be responsible for the complete enumeration of the population of New Brighton and New Hope. It would be expected that both populations could be enumerated within a period of six months. A team of interviewers under the supervision of the Epidemiologist I would be responsible for the collection of information from all cohort members in both communities. It would be expected that a team of twenty interviewers would complete all interviews within a period of two and a half years. A computer programmer, working in concert with the epidemiologists would be responsible for data management including interview scheduling, coding, data entry and generation of computer files for data analysis. Data analysis and report generation would be the responsibility of the epidemiologists.

vi. Discussion and Recommendations

The conduct of a cohort study in New Brighton and a control community (e.g., New Hope) would be an enormous undertaking. The approximate costs associated with the identification of all current residents of New Brighton and a suitable control community amount to 1.7 million dollars (i.e., $800,000.00 for each community). Follow-up of these cohorts would cost approximately 0.5 million per year (i.e., $250,000 for each community). To gain insights into disease/exposure relationships the cohorts should be

followed for a minimum of ten years. It should be noted that the ten years of follow-up may be an insufficient period of time of observation for some diseases of long latency (e.g., cancer). Thus, 20 years of follow-up may be required to be able to detect changes in disease rates especially if well contaminations had not occurred until relatively recent years (e.g. 1970's).

In the absence of evidence of significant health risks from low level exposures to the contaminant compounds, and for reasons similar to those set forth previously regarding a cohort study in St. Louis Park (e.g., lack of adequate exposure data coupled with the social invasiveness and magnitude of costs), the conduct of a cohort study to evaluate potential health effects associated with contaminated drinking water in New Brighton is not recommended, nor is it needed at this time.

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APPENDICES

APPENDIX A

WORKSHOP ON EPIDEMIOLOGIC EXPOSURE MODELS: ST. LOUIS PARK/NEW BRIGHTON FEASIBILITY STUDY

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APPENDIX B

LIST OF ABBREVIATIONS

BaP	Benzo(a)pyrene
CDM	Camp, Dresser & McKee
DMBA	7,12-Dimethylbenz(a)anthracene (not an environmental PAH)
DCE	1,1-Dichloroethylene (vinylidene chloride)
EPA	United States Environmental Protection Agency
MDH	Minnesota Department of Health
MPCA	Minnesota Pollution Control Agency
NAS	National Academy of Sciences
NB	City of New Brighton
PAH	Polynuclear (polycyclic) aromatic hydrocarbon
SLP	City of St. Louis Park
SMR	Standardized Morbidity (Mortality) Ratio
TCA	1,1,1-Trichloroethane (methyl chloroform)
TCAAP	Twin Cities Army Ammunition Plant
TCE	1,1,2-Trichloroethylene
USGS	United States Geological Survey
VOCs	Volatile Organic Compounds
µg	microgram (1/1,000,000 of a gram)
ng	nanogram (1/1,000,000,000 of a gram)
l	liter
ppm	parts per million
ppb	parts per billion
ppt	parts per trillion