

## *Epidemiological Studies to Estimate Effects of Low-level Exposures*

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### ABSTRACT

Low-level exposures to toxic agents usually confer relatively small increases in risk to individuals. If exposed populations are large, however, the public health impact may be substantial, and such exposure-disease links are therefore worthy of study. The epidemiological approach can provide useful information, provided the relative risk is at least in the neighbourhood of 1.4, but low risk levels impose significant constraints as regards methods and interpretation. This paper describes the strengths and weaknesses of various types of epidemiological studies, where data are collected from mortality records or from interviews. Several investigations of drinking water contaminants and cancer mortality or incidence are used to illustrate the major issues. Examination of the geographic correlation between environmental factors and cancer rates is an important first step in describing possible links and to suggest the particular cancer sites, types of exposure and geographic regions of greatest concern. Case-control studies that use mortality records are relatively inexpensive, and are used to refine hypotheses and to generate first quantitative estimates of the exposure-effect relationship. Subsequent case-control interview studies, in conjunction with clinical and laboratory investigations, can provide strong and convincing evidence for or against a causal relationship, and thus establish a firm scientific basis for effective preventive action.

### 1 INTRODUCTION

Epidemiological studies of effects of low-level chronic exposures are especially challenging because of the need to assess relatively small risk increases resulting from events that occurred many years ago. By low exposure levels we mean the concentrations of contaminants commonly found in the ambient air or in treated drinking water to which large numbers of people are regularly exposed over extended periods.

Small risk increases can have important public health impact if exposed populations are large. Cancer sites with suggested links to drinking water

contaminants are the large bowel, rectum and urinary bladder with approximately 134 000 total new cases diagnosed annually in the United States. If 20% of the US population were exposed to such water contaminants, and the relative risk for cancer of these sites were 1.2, 5000–6000 excess cases could be attributed to these exposures.

Several recent epidemiological studies of water quality will serve as examples highlighting the strengths, weaknesses and pitfalls of such endeavors. In 1974, when carcinogenic organohalides were first observed in drinking water supplies (Rook, 1974; Bellar *et al.*, 1974), studies were initiated to evaluate associations between one or more water supply characteristics and the occurrence of cancer. The first were ecological in design; that is, they examined associations between geographical distributions of water supply characteristics and site, sex and race-specific cancer mortality rates. Subsequently, case-control studies based also on mortality records were planned and executed. A third group of studies is now in progress: case-control studies of newly diagnosed patients, for which information on several risk factors is collected directly from the cases (or surrogates) and from matched controls. This paper will examine these methods, primarily using examples from the literature on water quality and human cancer, but drawing from other areas of epidemiology when warranted. The strengths and weaknesses of each approach will be described with reference to the appropriate use of results.

### 1.1 Environmental Background

The problem of estimating past exposures is common to most epidemiological studies of environmental contamination and cancer, regardless of design. In the case of studies of drinking water contaminants, historical records from water utilities can provide information on water sources used, chlorination and other treatment practices and distribution patterns, but not on historical levels of specific chemicals for which analytical methods have only recently become available. A conceptual scheme that ranks different types of water supplies by level of presumed carcinogenic potential can be applied to these historical data. The ranking scheme is based on recent measures of trihalomethanes and other low molecular weight compounds from a variety of water supplies, as well as on data from a growing body of toxicological and chemical information. Two general classes of compounds are of concern:

- (1) trace chemicals such as certain industrial solvents and process intermediates that enter a water distribution system unchanged by the treatment process, and
- (2) compounds produced during chlorine disinfection by interaction of chlorine with organic precursors (mostly naturally occurring humic and fulvic acids) in raw water.



For the purpose of defining historical exposures in epidemiological studies when quantitative measurements are not available, it is reasonable to assume that surface sources contaminated by upstream effluents have the highest level of toxic materials, followed by surface sources with protected watersheds and then chlorinated ground sources. Non-chlorinated ground sources, with little contamination, are expected to be associated with the lowest risk, and most studies place persons who habitually use these sources in a 'non-exposed' category.

Data on levels of trihalomethanes and other compounds in finished water that we recently collected from more than 800 US water supplies supports this assumption. The geometric mean chloroform level in samples from 72 unprotected surface sources was 60  $\mu\text{g/l}$ , from 122 protected surface sources 53  $\mu\text{g/l}$ , and from 627 (chlorinated) ground sources 0.8  $\mu\text{g/l}$ .

Surface waters generally have elevated levels of chlorination byproducts, including chloroform and other trihalomethanes (THMs). Chloroform is an animal carcinogen (Page and Saffiotti, 1976), and the brominated THMs are mutagenic in the Ames *Salmonella* testing system (McCann *et al.*, 1975; Simmon and Tardiff, 1979). In addition to low molecular weight volatiles, at least 40% of the organically bound halogen associated with chlorine disinfection is found among higher molecular weight non-volatile compounds (Glaze *et al.*, 1980). Concentrates of these chemicals from treated surface waters are mutagenic in the Ames *Salmonella* systems without S-9 activation (Loper, 1980). At least one direct acting mutagen of high potency, 2-chloropropenal, has been isolated from a non-volatile fraction of chlorinated water (Kringstad *et al.*, 1981). This compound is a proposed intermediate in the chemical reaction sequence leading to chloroform. Several other mutagens from concentrated drinking water samples have not yet been identified (Loper and Tabor, 1982). It is likely that chloroform levels bear some relation to the concentration of higher molecular weight non-volatiles and thus to the mutagenic/carcinogenic potential of finished drinking waters, but the exact relationship between chloroform content and mutagenic activity needs further elucidation. Given these data, there is a growing consensus that the THMs *per se* may not be of great concern, but that their levels indicate the presence of other, higher molecular weight compounds with carcinogenic activity.

Groundwaters that are chlorinated usually have measurable levels of THMs, and often traces of low molecular weight volatiles such as perchloroethylene and trichloroethylene at levels below 5 parts per billion. The presence of these latter compounds is worrisome because it suggests widespread contamination of groundwater resources. Water from private community wells that are not chlorinated generally has low levels of most organics. Most water supplies of this type serve small populations (< 5000) in non-industrial areas, and their water sources therefore may be expected to have minimal contamination from industrial solvents or chlorination byproducts.

## 2 ECOLOGICAL STUDIES

The 'ecological' or geographical correlation approach implies comparison of geographic patterns of disease occurrence with the distribution of environmental factors, occupations, sociodemographic characteristics or other intrinsic features of populations, their activities or their surroundings. Most ecological studies of air or water quality in the US use the county as the unit of measure, due in part to the publication in 1974 of age-adjusted sex-, race-, and site-specific county cancer mortality rates for 1950–69 (Mason and McKay, 1974). Two exceptions that made use of incidence data are an analysis of cancer incidence rates and asbestos in the drinking water of census tracts of the San Francisco Bay area (Kanarek *et al.*, 1980) and on-going studies of cancer incidence and water quality in Iowa towns (Bean *et al.*, 1982a,b; Isacson *et al.*, 1983). These take advantage of regional tumor registries, permitting analysis of data from geopolitical units smaller than the county. Results can be more meaningful because populations from these smaller places are likely to be more homogeneous than county populations with respect to disease rates, environmental exposures and many other demographic and socioeconomic factors.

When evaluating ecological studies, one must consider the strength, direction and consistency of associations as well as the homogeneity of exposures and disease rates within the unit areas of measurement. Other items to consider are the dilution of populations or exposure misclassification within areas by unexposed individuals or through in- or out-migration, the presence of a dose-response relationship, and the potential influence of causal factors for which data are not available, or the inclusion in statistical models of extraneous factors not in the causal chain. In addition, some statistical issues deserve attention, such as the type of weighting applied to multivariate equations.

### 2.1 The Formal Model

Ecological studies typically use a variation of the standard multiple linear regression model:

$$E(y_i) = \beta_0 + \beta_e X_{ei} + \beta_1 X_{1i} + \beta_2 X_{2i} \dots + \beta_n X_{ni}$$

where:

$y_i$  = age-adjusted sex-, site-, and race-specific county cancer mortality rate;

$X_{ei}$  = 'exposure' variable (see discussion);

$X_{1i}$  to  $X_{ni}$  = a series of variables directly or indirectly in the causal sequence influencing cancer rates, such as population density, percentage foreign born, dummy variables denoting the region of the county's



location, percentage of county population employed in each of several manufacturing industries, etc.;

$i = 1, 2, \dots, n$  is a subscript denoting the county.

This model assumes that the disease (or mortality) rates can be represented by a linear combination of county-level factors, including environmental exposures. The linear model assumes additivity of risk, whereas the interaction for several known etiological factors appears to be multiplicative. A logarithmic or other transformation of the dependent variable (cancer rate) may be more appropriate in some situations, but this has not been done.

## 2.2 Weighting the Regression

The precision of cancer mortality rates from places of different size, as estimated by the variance, is proportional to population size. Most ecological studies of water or air quality have weighted the rates in regression models directly by population size or its square root (proportional to the standard deviation).

Some ecological studies report the effects of different weighting procedures on study results. Hogan *et al.* (1979) reported important and variable differences in patterns of association in weighted versus unweighted models. They developed a weighting scheme:

$$W_i = (10^{-6} + n_i^{-1})^{-1}$$

Cantor *et al.* (1978), in a study of trihalomethanes in drinking water and county cancer mortality, used regression models weighted by the square root of the county population. In subsidiary analyses, rates were weighted directly by population size. Results from the two weighting schemes generally followed the same patterns, with some differences in the level of significance of regression coefficients. Page *et al.* (1976) studied associations between cancer rates in Louisiana parishes and drinking Mississippi River water. Most of the analyses used unweighted models (i.e., weighting factor = 1). They report that subsequent weighting 'left the (regression) coefficients for drinking water roughly the same but raised the values of  $t$  by about 50% on average, leading to a large increase in the level of significance'.

On theoretical grounds, weighting of multivariate regressions by a factor that adjusts for differences in precision of rate estimates is the preferred approach. There is probably no one 'best' weighting method for all applications, but it may not greatly matter, so long as the more stable rates from places with large populations are given more weight in regressions than rates from smaller places. In our experience, a strong and consistent association usually retains its statistical significance under several different weighting schemes.

### 2.3 Variables in the Regression Model

The regression model should include as many 'independent' variables as are reasonably related (even indirectly) to the disease, but no more. Inclusion of extraneous factors or exclusion of important causal variables may lead to misleading associations.

#### 2.3.1 Misspecification

Inclusion of irrelevant variables in the model can decrease the precision of correlations and, to the extent that such variables are statistically associated with both exposure and effect, can also diminish the strength of associations (overspecification). Failure to include important exposures as explanatory variables can lead to spurious associations. Table 1 presents data we developed in analyzing associations between trihalomethanes in drinking water and cancer mortality (Cantor *et al.*, 1978). Shown are correlation coefficients for males between county cancer rates and trihalomethane levels, after the rates had been adjusted, in two separate models, for several demographic factors. Model I included variables for county 'percentage foreign stock' for each of 10 ethnic groups. In model II, these 10 foreign stock variables were excluded, resulting in important differences in correlation coefficients. The differences for stomach cancer, with notably different patterns among certain foreign born and US ethnic groups (Haenszel, 1961), are understandable, but not the differences for lung and colon cancers. It is not known, in the case of the colon and lung cancer correlations, whether the foreign stock variables masked a real association, or if they were good surrogates for dietary patterns. A growing body of evidence points to a real link between drinking water contaminants and colon/rectum cancer risk (Crump and Guess, 1982), suggesting in this case that ecological associations may have been obscured by our inclusion of extraneous variables. Others hold an opposing view, i.e., that there is no underlying association and that control for ethnicity introduces proper adjustment for social factors, presumably

Table 1 Correlation coefficients between residual mortality rates in white males and total trihalomethane levels in drinking water in 76 US counties

	Residuals calculated with:		
	I Ethnicity variables included in the regression model		
	II These variables excluded from the model		
	Anatomic site		
	Stomach	Colon	Lung
MODEL I	-0.02	0.14	0.07
MODEL II	-0.12	0.20	0.16



related to dietary patterns (Tuthill and Moore, 1980). Resolution of this issue cannot be provided by ecological studies, but awaits results from case-control studies in which information on diet and drinking water source (from residential histories) is collected directly from patients and controls.

Ecological associations may result from statistical links with causal factors that are incidentally associated with the exposure variable but whose levels are unknown and therefore cannot be included in the regression model. Among the known or suspected causal factors not considered in ecological studies of air or water quality are cigarette smoking and dietary patterns. These deficits in the information base severely compromise the specificity of results, especially in ecological studies examining smoking-related diseases such as cancers of the bladder or pancreas, or cancers of respiratory sites. If county smoking rates are statistically related to county measures of water or air exposures, the causal associations with smoking could mistakenly be attributed to ambient environmental factors.

#### **2.4 Exposure Estimates**

Most cancers show a long latent period between exposure and diagnosis, ranging up to several decades. In etiological studies, we are therefore not concerned about current levels of ingested drinking water contaminants, but rather the exposures of several decades ago. This poses special problems in ecological studies because of the opportunity for exposure misclassification due to migration, and problems in estimating area-wide exposures of many years ago. This issue was discussed, in part, in section 1.1 above. Between 1955 and 1960, 17% of the US population moved between counties, ranging from 10 to 36% in different states (U.S. Bureau of the Census, 1961). Migration is expected to diminish the strength of ecological associations, because new migrants to study areas are, on the average, randomly distributed with regard to past exposures (Polissar, 1980).

Estimates of exposure to air or water pollutants of many years ago are derived in ecological studies from industrial surveys, census information or are reconstructed from knowledge of past engineering or water treatment practices. Many ecological studies of cancer mortality and water quality rely on data from a 1963 inventory of municipal water supplies (U.S. Public Health Service, 1964) to calculate the percentage of a county's population served by surface or ground sources, by chlorinated or non-chlorinated sources, or by sources treated by prechlorination. Thus, Salg (1977) examined the association between water quality factors and cancer mortality in 346 counties of the Ohio River drainage basin, using as exposure variables are percentage of population in each county (1) served by surface water and (2) served by prechlorinated water. Page *et al.* (1976) used the percentage of population of Louisiana parishes drinking water from the Mississippi River. Kuzma *et al.* (1977), studying associations of water quality and cancer rates in Ohio counties, used a dichotomous exposure variable indicating

the type of source (surface or ground) used by the majority of a county's population. Simplifying the exposure variable to this degree may unnecessarily obscure gradients of exposure. Other studies used as exposure trihalomethane levels derived from U.S. Environmental Protection Agency surveys or special state surveys (Cantor *et al.*, 1978; Hogan *et al.*, 1979; Tuthill and Moore, 1980).

In seeking to evaluate the correlation between current and past contaminant levels, we compared levels of chloroform in 42 supplies sampled by the EPA in 1975 with levels from the same supplies a year later. There was a strong year-to-year correlation ( $r = 0.73$ , Cantor, 1977). Hogan *et al.* (1979) reported consistency in the rank order of THM levels among 12 supplies sampled in two surveys, but the absolute values of the THMs varied considerably.

Most ecological studies use mortality rates from 1950 to 1969, so that meaningful exposures took place 25–30 years earlier, between 1920 and 1945. Although some changes in water treatment practices have occurred since, relative patterns of chlorination among different source types have been stable. In my judgement, migration is a much more important source of exposure misclassification than changes in water source or treatment.

## 2.5 Measures of Outcome

The underlying purpose of ecological studies is the measurement of the effects of exposure on disease frequency (incidence). Mortality rates are used because they are readily available, whereas incidence data usually are not. Mortality can be an inappropriate and inadequate measure of incidence for cancers with long survival that are responsive to therapy. Geographical variations in such cancer rates may indirectly provide as much information about local medical care systems or the socioeconomic status of patients as differences in environmental characteristics. Mortality statistics are appropriate measures for malignancies with a high fatality rate or regional consistency in diagnosis and treatment. When they are available, incidence data are preferable to mortality statistics.

The most refined ecological studies of water quality are those of Isacson and co-workers who have used incidence data from the Iowa state tumor registry to calculate age-adjusted cancer incidence rates for Iowa towns, most of which have well-characterized water supplies. Cancer cases and populations from towns with similar exposure and demographic characteristics are aggregated, expressed as a rate, and evaluated for associations with drinking water characteristics.

For most cancers, there is a good correspondence between underlying cause from the death certificate and the hospital diagnosis (Percy *et al.*, 1981). Colon and rectum cancers are unusual in this respect, in that colon cancer is over-reported and rectum cancer under-reported on death certificates. These sites have been linked with indicators of water contaminants in many epidemiological studies, and the misclassification of rectal as colon cancer must be considered when evaluating the results.



## **2.6 Strengths and Weaknesses of Ecological Studies and Implications for Risk Assessment**

Epidemiological studies serve several purposes, such as generation of new hypotheses, elaboration and specification of existing ideas and hypothesis testing. Ecological studies of low-dose exposures to environmental contaminants have made important contributions to hypothesis generation and elaboration. When it was recognized that human populations have long been exposed to contaminants in drinking water, and that some compounds are carcinogens or mutagens in laboratory tests, epidemiological risk assessment was appropriate. Several problems arose in the planning of such studies, such as choosing the anatomical sites and types of exposure that deserve most attention. Ecological studies were designed to address these issues and have successfully served their purpose.

Ecological studies have several features that make them well-suited for this role. They are usually rapidly performed, make use of available data and thus are relatively inexpensive. The relative speed and ease of conducting ecological studies are somewhat offset by their lack of sensitivity in detecting real associations and the possibility that positive results can arise from associations with factors that were not ascertained nor used in the regression model.

Despite these weaknesses, hypotheses generated in the correlational studies were strengthened when similar patterns of association emerged from independent studies conducted in different populations by several investigators, and when the associations appeared to have biological plausibility. Thus the suggestion of a link between low levels of carcinogens in drinking water and elevated risk of bladder, colon and rectum cancers was placed on a sounder footing by observations from ecological studies in several settings, as well as by the continuing elaboration of the chemistry and chronic toxicity of suspected compounds.

It is tempting to go beyond hypothesis elaboration and to apply results of ecological studies to risk assessment. This may be appropriate if the risk assessment is qualitative and if statements of possible association are framed in the context of limitations in the ecological study design. The probability that ecological associations are grounded in causal relationships is enhanced when several independent studies show similar results. The larger the number of parallel independent observations, the lower the probability that the associations are due to chance alone or to a common confounding factor, although these possibilities cannot be excluded.

Quantitative estimations of risk from ecological studies are not appropriate. Estimates, based on ecological data, of the number of excess deaths in Louisiana due to drinking contaminated water from the Mississippi River (Harris *et al.*, 1974) met with criticism from epidemiologists and statisticians (DeRouen and Diem, 1975).

In 1979, the US Environmental Protection Agency issued regulations setting

an upper limit of 100  $\mu\text{g/l}$  for total trihalomethanes in US drinking water supplies (EPA, 1979). The scientific rationale is instructive. In addition to citing the available laboratory evidence for carcinogenicity, it was stated:

'EPA has also concluded that the available epidemiological evidence . . . has not been conclusive but is hypothesis generating and at least suggestive of a health risk.'

A National Academy of Sciences review of epidemiological data was also mentioned (NAS, 1980):

'They (NAS) pointed out the lack of sensitivity of (these) epidemiological procedures due to a lack of exposure data for individuals, population diversity and mobility, inability to control for all known contributing variables such as smoking, occupational exposures, diet, alcohol consumption, socioeconomic and urbanization factors, and the usual 20–40 year latency period. . . . Since epidemiology per se cannot "prove" causality, and because it may well be impossible to epidemiologically (sic) establish a strong causal linkage . . . EPA extrapolated from the results of animal studies to assess the risk posed by THMs to humans.'

The 'epidemiological procedures' referred to were mostly ecological studies, as all but one of the studies reviewed by the NAS followed this design. The scientific basis for rule-making properly considered these results to be 'suggestive', and looked to animal studies for data on which to base a numerical standard for a maximum contaminant level for THMs.

### 3 ANALYTICAL STUDIES

In contrast to ecological studies, the unit of measure in analytical studies is the individual, not the group. Links are sought between exposures of individuals and their subsequent disease status. The use of data from individuals makes the analytical study a more powerful and focused instrument than the ecological study. Associations between exposure and disease in analytical studies are commonly expressed as relative risks, the probability of disease among exposed persons relative to the unexposed. Analytical studies thus directly furnish quantitative estimates of risk. The retrospective cohort study and the case-control study are the approaches most commonly used.

#### 3.1 Retrospective Cohort Studies

Although the cohort design is not the most efficient design to evaluate effects of low-level exposures, it deserves brief mention. Entry of subjects into a retrospective cohort study is based on past exposures, for example, to occupational or environmental agents or therapeutic treatments (X-rays, specific



pharmaceuticals), or on shared host characteristics. Cohort members are followed over time, and the frequency of disease occurrence within the group is measured and compared with the frequency of like conditions in other populations that are presumably not exposed. The cohort study usually finds productive application in assessment of risks from exposures that are relatively rare in the overall population but common in the study population, such as selected occupational exposures. The cohort approach is generally inefficient in studying the relationship between low level chronic exposures and risk of rare diseases (such as most cancers) because of the need to gather exposure information for many thousands of individuals to evaluate risk in relatively few persons. For this reason, the method is not often chosen to evaluate exposures to ambient environmental contaminants. One cohort study of cancer risk as related to water quality has been reported from a Maryland county where a population-based registry of exposures and cancer cases had been created for other purposes many years before the water quality exposures were evaluated (Wilkins and Comstock, 1981). In this case, it was not necessary to gather additional information about other individual exposures to evaluate the hypothesis.

### **3.2 Case-control Mortality Studies**

In contrast to the cohort design, entry into a case-control study is governed by disease status, and exposures are determined retrospectively. In the case of a relatively rare disease such as site-specific cancer, the case-control study has many advantages. The level of association of a disease with a factor is based on a high or low frequency of that factor among diseased persons (cases) relative to its frequency among healthy individuals (controls).

The completed case-control studies of drinking water quality and cancer risk derive most of their data from death records, selecting cases and controls from computerized listings of State bureaus of vital statistics. These studies have some of the same weaknesses as the ecological studies that use mortality statistics, among them the potential for exposure misclassification and the inability to account for many other exposures or risk factors that can confound relationships with water contaminants or interact with them. A major strength resides in the ability to study large numbers of cases and controls drawn from the digitized state mortality files. Given the marginal excess risks expected from low-level exposures, inclusion of large numbers of cases and controls is desirable to ensure statistical stability of risk estimates.

In these case-control studies, cases are those who died of the disease of interest. Controls are selected randomly from among other causes of death (in some cases, only non-cancer causes), matching to cases on demographic characteristics such as sex and age. Measures of past exposure are categorical descriptions of source type (for example, surface or groundwater) and treatment (for example, chlorinated or not chlorinated), sometimes modified by information on up-

stream contamination (for surface sources) or by chlorination levels. A single exposure category for each decedent is obtained by linking the residence address as listed on the death certificate with local water utility information. Underlying this method is the assumption that study subjects have had the same address and water source for a period at least as long as the latent period of the cancer under study. This assumption is not always valid, and serious errors of exposure misclassification can occur if there was much immigration into the study area (Polissar, 1980). Table 2 shows the correlation between a person's 1975 water source and the usual water source of adult respondents in a large case-control interview study of bladder cancer (methods explained in section 3.3.5). It shows that between 14 and 39% of study subjects would have been misclassified as to water source had the definition of exposure been based solely on recent address as in the case-control mortality studies (Barron, 1981). A simple calculation shows that if the 'true' relative risk in a case-control study were 2.0 and misclassification were at this level, the observed relative risk would be 1.4. To decrease the possibility of exposure misclassification in case-control studies, the investigators have:

- (1) limited studies to places (for example, counties) with low rates of immigration (Young *et al.*, 1981);
- (2) stratified by the number of years prior to death that the decedent was served by the same water source, as documented by water company records (Gottlieb *et al.*, 1981); and
- (3) stratified and independently computed relative risks for study subjects (a) born in the same county as listed on the death certificate, (b) born in the same state but a different county, and (c) born in a different state (Struba, 1979).

Table 2 Usual adult water source compared with the 1975 water source of 8764 study respondents. Column percentages are in parenthesis

1975 water source	Usual adult water source					Total
	Ground not chl.	Ground chl.	Protected surface	Unprot. surface	Other	
Ground not chl.	817 (60.5)	16 (2.2)	106 (4.0)	106 (4.8)	149 (8.3)	1194
Ground chl.	246 (18.2)	600 (82.9)	129 (4.8)	128 (5.8)	253 (14.1)	1356
Prot. sur.	61 (4.5)	9 (1.2)	2186 (81.9)	11 (0.5)	340 (18.9)	2607
Unprot. sur.	111 (8.2)	76 (10.5)	167 (6.3)	1922 (86.3)	285 (15.9)	2561
Other	115 (8.5)	23 (3.2)	81 (3.0)	59 (2.7)	768 (42.8)	1046
TOTAL	1350	724	2669	2226	1795	8764



The last approach assumes that decedents with the same residence county at the beginning and end of life are more likely to have had longer exposures to their last source than those with different counties.

### *3.2.1 Confounding, Bias, and Effect Modification*

**Confounding** Positive associations in a case-control study may not signal a causal relationship but rather a statistical association of the putative cause with a real cause (the confounder). The error arises from attributing causality to a factor which is not itself a risk factor, but is associated with a causal factor. When this link is unknown, the disease can mistakenly be associated with the unrelated factor. If, for example, cigarette smoking rates were elevated in geographical areas with poor drinking water quality but there was no information on smoking levels, elevated bladder cancer due to cigarette smoking might falsely be attributed to drinking water contaminants. When no information on the suspected confounder is available, as with smoking levels in the completed case-control mortality studies, there is no simple way to distinguish between the influence of confounders and other putative risk factors. In some cases, confounding goes unnoticed because the confounder is not recognized as a causal factor and is therefore not assessed nor used in the analysis. In addition to creating false links, confounding can also mask real ones. If the hypothetical association above between smoking and water quality were inverted (that is, if smoking were more prevalent in places with clean water) and water quality were a real risk factor, the elevated risk from water contaminants could be obscured by the confounder. To reduce the possibility that associations are due to confounding, results from several independent studies should be evaluated. Similar patterns of association from many independent sources diminish the likelihood that confounding is responsible.

Confounding from an unknown factor has been suggested as responsible for the link between coffee consumption and bladder cancer noted in some case-control studies, after control for smoking. Experimental evidence for DNA repair inhibition by caffeine supports a causal interpretation (Maher *et al.*, 1975), but epidemiological studies reveal no dose-related gradient, the association is weak and some studies are negative. Given these inconsistencies, some analysts think the link is due to confounding (Simon *et al.*, 1975). They suggest that the life-style of people who do not drink coffee places them at a low risk for bladder cancer. The etiological agent may not be coffee *per se*, but some other feature of the coffee drinkers' habits or life patterns that has not yet been identified.

Careful control for confounding becomes especially important in studies of low-dose exposures, where low increases of risk are expected. Case-control interview studies, where much information on potential confounders is gathered,

provide a greater opportunity than case-control mortality studies to control confounding.

*Bias* Bias in case-control mortality studies can arise if controls died of causes related to the exposure of interest. Evidence from ecological studies suggests that coronary heart disease mortality may be higher in places served by soft water than in hard water locales (Comstock, 1979; Sharrett, 1979), and deaths from heart disease often comprise a large proportion of mortality study control series. If there were an association between hardness of drinking water and organic levels, the relative risk associated with exposure to organics would be elevated in case-control mortality studies simply because of greater probability of selecting a non-cancer control from a soft-water area.

Bias can also occur if digitized records of death are grouped by town or by village, and potential controls are not randomized before selection into the study. When controls are selected by the method of next best 'match' (on age, race, sex) in the same sequence, chances will be enhanced that the control will reside in the same place as the case, and thereby be overmatched on drinking water source. Overmatching obscures real risk differences, because it reduces the basis for distinguishing exposure differences.

*Effect modification by age, sex and race* Age, sex, and race are not causal in the same sense as external 'exposures' may be, but they do influence disease probability. In most studies, the influence of age, sex, and race on disease probability is designed out by matching controls to cases on these characteristics. Age, sex, and race can be effect modifiers altering the interaction of etiological factors with the organism.

### *3.2.2 Strengths and Weaknesses of Case-control Mortality Studies and Implications for Risk Analysis*

In 1980, the Safe Drinking Water Committee of the U.S. National Research Council, National Academy of Sciences, reviewed the then available data from ecological studies of water quality and cancer risk, and suggested further, more precise studies (NAS, 1980). Case-control mortality studies were the next step in this direction. Five have been completed and provide direct estimates of relative risk. Their strengths derive primarily from analyses of individual records, in contrast to ecological studies, but their interpretation must be tempered by several considerations, including:

- (1) exposure ascertainment for the last residence only, with no information on other water sources earlier in life;
- (2) a limited ability to control for many potential confounders, such as diet, smoking, alcohol and occupational exposures;



- (3) the use of death records as surrogates for incidence information, with the possibility of error in cause-of-death classification, and underascertainment for malignancies with good survival;
- (4) possible bias resulting from the method of selecting the control group.

The five completed studies are reviewed in a report to the President's Council on Environmental Quality, now published (Crump and Guess, 1982). The studies were consistent in their findings of elevated risk for rectal cancer, for the exposure chlorinated versus non-chlorinated waters, with odds ratios in the range 1.22–1.53. Results for colon and bladder cancers were less consistent; three of the five showed positive associations for colon cancer and two for bladder. Most risk ratios were below 2.0, small risk increases by traditional epidemiological standards. Two studies attempted to estimate the 'dose' of past exposures, in one case by the presence or absence of contamination from rural run-off (Young *et al.*, 1981), and in another by noting the distance of intakes from the mouth of the Mississippi River (Gottlieb *et al.*, 1981). Translation of the 'quantitative' findings of these studies into true estimates of risk is difficult because exposures and dose gradients were expressed in categorical, not numerical terms.

These results extend the findings of ecological studies by providing first approximations for risk ratios, and confirming the choice of colon, rectal, and bladder cancers as the sites most deserving of further study. Among other conclusions, Crump and Guess (1982) write:

'The . . . case control studies have strengthened the evidence for an association between rectal, colon, and bladder cancer and drinking water quality . . . . the epidemiologic studies . . . are not sufficient to establish a causal relationship . . . but they do contain evidence that supports such a relationship for rectal cancer, and to a lesser extent, for bladder and colon cancer.

(The) increases in cancer risks . . . lie near the lower limit of what can be detected and separated from other environmental risks by large, well-designed case control studies involving over a thousand cases.'

The quantitative estimates of risk provided by these studies could be used in formal risk assessments that also explain the weaknesses of the methodology and its potential for erroneous findings. As with ecological studies, similar findings by several investigators strengthen the argument that causal links underlie statistical associations of exposure and disease.

### **3.3 Case-control Interview Studies**

The most important contributions of epidemiology to risk assessment and ultimately prevention of disease associated with low-level exposures will come from large population-based case-control interview studies. Most drawbacks of

ecological and case-control mortality studies are overcome in this design. Information on a large number of host and environmental factors is gathered by interview directly from individuals with the disease of interest and from a matched series of randomly selected controls without the condition.

Case-control interview studies to low-level exposures are no different, in principle, than case-control studies of other types of exposures, but the small excess risks expected and the types of exposures demand that special care be taken in study design and execution to minimize bias and confounding and to maximize the possibility of discovering risk elevations, if present. Among the more important design considerations are:

- (1) size of study population;
- (2) hospital-based versus population-based study;
- (3) the choice of study population(s);
- (4) questionnaire design and interview procedures;
- (5) exposure assessment.

These issues will be discussed, using as examples features of a large bladder cancer study recently conducted by the National Cancer Institute (NCI) in collaboration with the U.S. Food and Drug Administration, the U.S. Environmental Protection Agency, and ten regional tumor registries supported by the NCI (Hoover and Strasser, 1979). Dr Robert Hoover designed and initiated the study and Ms Patricia Hartge was the study coordinator. Its primary purpose was to fill an urgent need for reliable human data on saccharin, that had been shown to be a carcinogen in animal studies (Arnold *et al.*, 1980). The case-control design also permitted evaluation of several other exposures, such as exposure to chronic low levels of water-borne chemicals.

### *3.3.1 Size of the Study Population*

The smallest odds ratio detectable in a case-control study depends on the sample size, the number of controls per case and the proportion of exposed in the control group. Due to the small excess risk expected, studies of ambient air and water contaminants require large numbers of respondents. From calculations assuming a desired statistical significance of 0.05, with 80% probability of detecting an association if present, and an assumed exposure rate among controls of 20%, detection of an odds ratio of 1.2 requires 2203 cases, with one control per case (Rothman and Boice, 1979). Detection of an odds ratio of 1.5 requires at least 419 cases.

In general, the largest study population that is logistically and economically feasible should be planned. A large study population serves several other purposes that recommend it. It is desirable that major study subgroups (by age, sex, cigarette smoking status, etc.) be large enough in themselves to permit



relatively stable risk estimates, since consistency of risk patterns across subgroups bolsters confidence in overall estimates. If there are adequate numbers of respondents in different 'dose categories', dose-response gradients can also be determined with some confidence. Cases in the NCI bladder cancer study included all residents of ten US geographical areas diagnosed with bladder cancer in 1978. Approximately 3000 cases and 6000 controls were interviewed.

### *3.3.2 Hospital-based Versus Population-based Studies*

In hospital-based studies, cases include patients newly diagnosed in one or more institutions during a defined period. Controls are usually matched to cases on hospital of diagnosis, as well as demographic characteristics (sex, age, race). Controls are randomly selected from a range of diagnoses other than the disease of interest or related conditions. Population-based studies draw cases from the general population, usually all cases (or a fixed proportion thereof) with the study diagnosis from one or more well-defined geographic locations. Controls are also drawn from the general population, randomly selecting individuals and matching on sex, age, and race. Several methods for selecting controls are available. The NCI bladder cancer study was population-based. Controls less than 65 years of age were selected by a random digit dialing approach (Waksberg, 1978) and those 65 and over from a random 1% listing of the over-65 population from the U.S. Health Care Financing Agency.

Population-based studies enjoy numerous advantages over hospital-based designs, especially for studies in which low increases of risk are expected. The source (denominator) population in the population-based design is unambiguous—the total population of the study area. In hospital-based studies, the source population is never as clearly defined. Extrapolation of results to the general population is therefore on less secure grounds than with a population-based study.

Population-based case control studies provide more opportunity to control for bias and confounding than hospital-based studies, an important factor in detecting small increases in risk. While hospital-based studies have logistical advantages over population-based studies, such as simpler case ascertainment and access, they can be compromised by biases inherent in the type of available controls. A hospital-based study of bladder cancer observed comparable saccharin use in cases and controls (Kessler and Clark, 1978). This finding was questioned because many conditions leading to hospitalization are linked to obesity, and it is likely that the obese consume greater than average levels of saccharin. Use of this control group might have biased the result by obscuring a real association, if present, between saccharin ingestion and bladder cancer (Goldsmith, 1982). A large number of such biases are possible when using hospital-based control series.

Hospital patients are usually drawn from a restricted geographical area with

limited variation in levels of air and water contaminants. If controls are matched to cases by hospital, as is customary, there will likely be overmatching on pollutant exposure, decreasing the possibility of detecting an effect. Because population-based studies seek to include all cases in a region, estimates of absolute risk are facilitated, as are the estimates of exposure frequency in the general population, inferred from the experience of control groups.

### *3.3.3 Choice of the Study Population*

Geographic areas appropriate for population-based case-control studies are those where a significant number of persons may be found at each of several exposure levels. It is also helpful if places are chosen so that a large majority of the source population has had limited migration into the area(s), because characterization of past exposures can require linking past residential locations with information on the geographical distribution of environmental contaminants. Study populations must be large enough to assure availability of the desired number of newly diagnosed cases over the study time period.

Having been designed for other primary purposes, the NCI study did not use all of the above criteria in the selection of source populations. Nevertheless, at least three of the five states that were included (Iowa, New Jersey, and Connecticut), with more than half the total study population, satisfy the requirements for numbers, exposure variety, and limited immigration.

### *3.3.4 Questionnaire Design and Interviews*

The questionnaire should seek information on as many known and suspected risk factors, effect modifiers and confounders as possible while keeping the interview to a reasonable length. Interviewers must be carefully selected and trained to avoid the possibility of introducing bias by approaching cases and controls differently, by seeking to collect more information from one group or the other, or by asking leading questions. In the ideal study, the interviewer would be ignorant of the respondent's status as case or control, but this is usually not possible. A form of bias that is difficult to eliminate may arise when cases, in seeking reasons for their disease, remember past events differently than controls.

In the NCI bladder cancer study, we obtained demographic background, detailed smoking and occupational histories, information on relevant medical conditions, and a history of artificial sweetener use. The interview also covered coffee drinking habits, hair dye use, and fluid ingestion patterns. With regard to water quality as a risk factor, a lifetime residential history was recorded, and for each residence, the respondent was asked if the primary drinking water source was the community supply, a private well, bottled water, or another source. The



residential/water source history was subsequently linked to historical water supply information.

### *3.3.5 Exposure Assessment*

The ultimate success of low-level exposure studies rests in large part on the accuracy of estimates of past exposures. Because direct environmental measurements are usually not available for the exposure periods of greatest interest, we must rely on other types of information sources that permit modelling of past environmental conditions.

In air quality studies, the exposure modelling might integrate several types of information: wind patterns and air mixing zones; inventories of past industrial patterns and fuel consumption; and locations of the residence and workplace of respondents relative to known air pollution sources. Residence location has been used to divide populations into groups likely to have had different exposure to air pollutants.

The quality of drinking water in the past may be modelled with somewhat more confidence. Section 1.1 outlined the major differences in water quality among various types of water supplies. Because water source and treatment practices have not changed over the years, because distribution systems represent large fixed investments and because past changes in sources, treatments and distribution are well documented, it is possible to estimate accurately many aspects of drinking water quality delivered to residences of study respondents in the past.

In our experience, most respondents know if their primary water source at each residence was a private well or spring or the local community supply. Thus it is feasible to gather individual residence histories, and to link these data with historical information from the water utilities likely to have served most of the study population, matched by year and geographical area. This is aided by the fact that distribution zones for most water utilities follow the geopolitical boundaries that also define the residence towns or cities of respondents. In the NCI bladder study we linked past residence and water supply records to construct a year-by-year lifetime water quality profile for each of the approximately 9000 study participants, going back to 1900 or the year of birth, whichever was the more recent. Using this method, water supply source and treatment for 75% of all the years lived by study respondents was successfully defined. Figure 1 shows the year-by-year distribution of water sources for men in the control population whose water sources are known. Shown are the proportions of controls using each of four source types. Most unknowns occurred when respondents lived outside of the ten study areas and used drinking water from a community source not included in the water supply survey.

These data permit the identification of persons with one water source for most of their lives, as well as the definition for most study participants of the 'usual

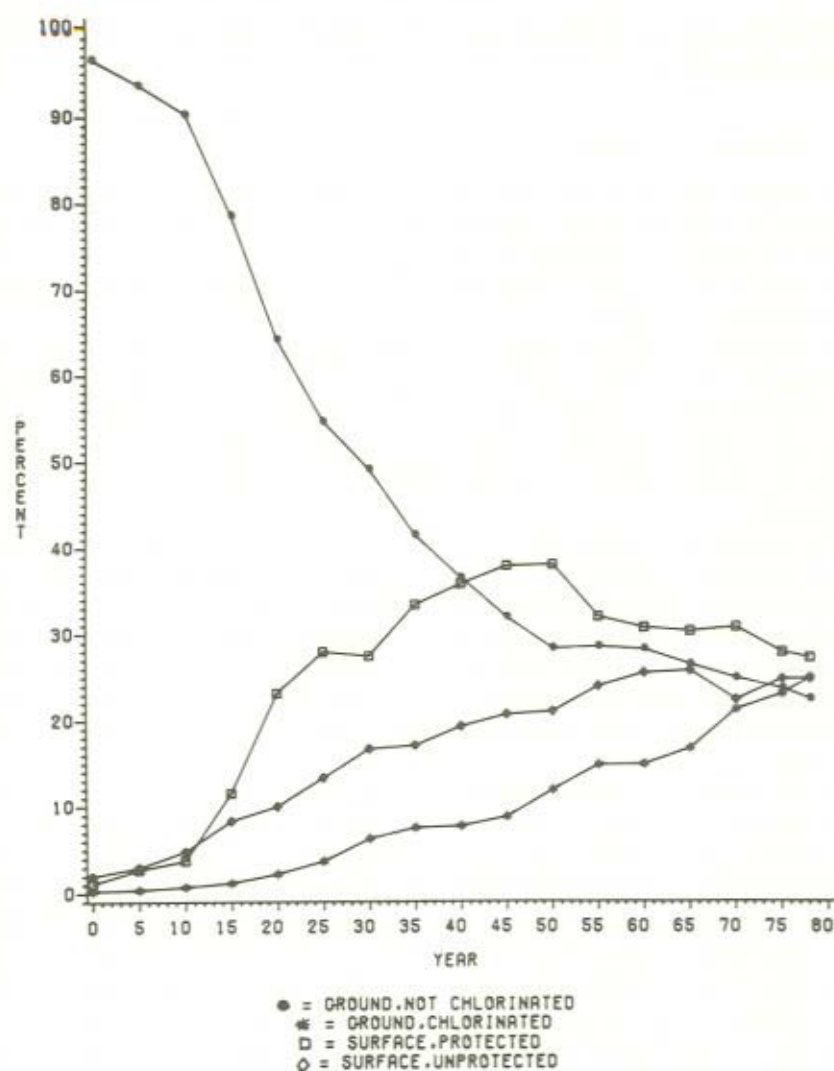


Figure 1 The percentage of male controls using various water sources, 1900–1978, from an NCI national study of bladder cancer

source' over defined time periods. As mentioned above (3.2), Table 2 shows a comparison of 'usual adult source' with the 1975 water source for the 8764 bladder cancer respondents. 'Usual adult water source' is defined as the type of source used for more years than any other between age 18 and the year 1978. Persons with mixed sources were placed in the category of presumed poorer water quality for the appropriate time period. The magnitude of misclassification



errors possibly created by using only exposures of recent years, such as in the completed ecological or case-control mortality studies, can be gleaned from this table. The net effect of such misclassification in risk analyses would be a considerable dilution of the apparent effect and reduction of risk measures. When possible, year-by-year information should be developed and used in the analysis.

### 3.3.6 Summary of Case-control Interview Studies

Case-control interview studies provide an efficient way of evaluating effects of long-term low-dose exposures so long as the risk ratio is at least 1.4 or 1.5. Even if the study population is large enough so that risk ratios of this magnitude are statistically significant, the results might be questionable because low relative risks can arise from bias in selection of controls, interview procedures or selective memory of respondents. Carefully designed population-based case-control studies decrease the possibility of most types of bias. They are preferable to hospital-based studies.

A retrospective study cannot by itself establish or disprove a causal association between exposure and disease, because the possibility of confounding, however remote, always exists. Case-control studies, however, in conjunction with other epidemiological, clinical, and laboratory investigations, can provide strong and convincing evidence for, or against, causal patterns, and thus establish the basis for effective preventive measures. If adverse effects can in fact be measured, the case-control study is one of the best tools to obtain risk estimates directly from human experience.

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