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Editorials

Water Chlorination, Mutagenicity, and Cancer Epidemiology

Nineteen ninety-four marks the 20th anniversary of the discovery of chlorination by-products in drinking water[1,2] and the 86th year since chlorine was first used as a drinking water disinfectant in the United States. Chlorine (hypochlorite) was first added to drinking water to assist the Boonton, NJ, waterworks in meeting its contractual obligation to supply Jersey City with pure drinking water.[3] The bacteriological quality of the treated water was much improved, and in 1910 a court examiner found that (1) hypochlorite was effective "in removing . . . dangerous germs, (2) the water [was] . . . pure and wholesome," and (3) chlorination left "no deleterious substances in the water."[3] Population surveys over the next decade documented dramatic decreases in the rates of typhoid fever and other waterborne enteric diseases in communities with chlorinated drinking water.[4] Although we now know that some enteric infections transmitted by cysts, such as *Cryptosporidium* and *Giardia lamblia,* must be controlled by other treatment measures such as filtration, chlorine remains the disinfectant of choice in US public water supplies, doubtlessly preventing widespread illness and death.

This backdrop of an enormously successful preventive health measure needs to be kept in mind in assessing subsequent developments. When chloroform and other trihalomethanes were discovered in chlorinated water in 1974, a controversy arose immediately around the court examiner's conclusion that chlorination left "no deleterious substances." Are trihalomethanes and other chlorination by-products deleterious to human health, and if so, what level of risk do they pose?

Chemical analyses of chlorinated water samples have since detected hundreds of nonvolatile chlorinated hydrocarbons of higher molecular weight, including chlorinated ketones, aldehydes, carboxylic acids, and alcohols.[5] These measurements also established that the trihalomethanes, the most readily measured part of the mixture, account for less than half of the organically bound halogen.[6] There is increasing evidence that the major part of the toxicity of the mixture resides in the nonvolatile fraction. This dilute chemical soup is generated by the interaction of chlorine with organic matter (mostly naturally occurring humic and fulvic acids) in the untreated water. With the exception of the trihalomethanes and chlorinated acetic acids, most of the compounds occur at trace levels, well below 1 ppb. However, their presence has both increased the level of concern and greatly raised the complexity of assessing potential health risks.

As soon as epidemiological investigation of chlorination and cancer began, it encountered three hurdles: determining which organs might be affected, developing acceptably precise estimates of what is likely a low-level effect, and accurately estimating exposure. In the 20 years since, we have made great strides in refining the hypotheses. Investigators have tried various approaches, including ecological analyses (geographic comparison), cohort studies, and case-control studies (based on both death certificates and interviews). There has been a general convergence of findings in that cancers of the bladder, colon, and rectum have been associated with various measures of chlorination by-product contamination far more often than have cancers of other sites, although

Editor's Note. See related article by Koivusalo et al. (p 1223) in this issue.

other sites have not been ruled out.[7] We argue below that only data from carefully conducted case-control interview studies or cohort studies are appropriate for quantitative assessment of risk, although the findings from other study designs are certainly important in making qualitative risk assessments and in guiding research priorities. At present, only a small number of such studies have been completed.

We have not yet achieved precise risk estimates. Indeed, a recent meta-analysis aimed at increasing precision by combining studies has probably confused the situation.[8] This exercise may have been premature since most of the input data came from studies with (1) inadequate control for confounding and other sources of bias, and (2) highly limited estimates of historical exposure to drinking water contaminants. For example, the data for rectal cancer risk and drinking water exposures came from case-control studies that used death certificates as the primary source of outcome and exposure information. These studies are subject to many types of biases. With minor exception in these studies, the residential water source at the time of death was used as a surrogate of exposure level, and exposures earlier in life were not ascertained and assumed to be similar. Patient mortality from rectal cancer (and others) may have been related to medical care access that differed in places with different types of water supplies, leading to selection bias for cases. In addition, there was little ability to control for other risk factors that may have confounded the association with water quality measures.

An especially challenging aspect of studying environmental contamination and disease is to define and then estimate exposure at the relevant time in a person's life. Retrospective studies of cancer risk pose special challenges in that exposures of interest usually occurred many decades in the past, given the long latency period for most chemically induced malignancies. The observation that, owing to higher levels of organic precursors, chlorination by-products are 10- to 100-fold higher in surface than in groundwaters has provided a basis for exposure estimates in many epidemiologic studies. Past exposures have been expressed as (1) type of water source (surface or groundwater) and its treatment (chlorinated or not) as categorical variables; or (2) estimated levels of a chemical measure, such as chloroform or total trihalomethanes, that are related to total levels of chlorination by-products. In the few interview studies available, one or both of these measures were combined with information on the level of reported water intake. Water intake was not considered in ecologic and case–control studies that used death certificates.

The article by Koivusalo et al. in this issue takes a new approach to assessing exposure by using estimates of a waterborne marker of genotoxic activity: mutagenicity in a tester strain of *Salmonella typhimurium* (TA100).[9] Because historical water samples were not available for direct measurement, exposure estimates were based on mathematical models developed by Koivusalo's colleague Vartiainen, who measured mutagenicity of recent drinking water samples and successfully modeled the levels on several water treatment parameters (permanganate consumption, pH, color, and ammonium and iron content) and chemical additions (pre- and postchlorination dose).[10] Finnish water authorities apparently maintain thorough records, and adequate historical information was available to apply this mathematical model to past information from municipal water supplies. Estimates of mutagenicity in 1955 and 1970 were associated with the incidence of several cancers, including those of the kidney, stomach, and urinary bladder. A confusing aspect of these findings is that one would expect the strength of most associations to be greater when communities without mutagenic water are included in the calculation; yet the opposite was found for kidney cancer, and risk estimates remained approximately the same for bladder and stomach cancers.

The approach to exposure estimation using mutagenicity appears promising and deserves validation. In particular, more work is needed to assess its applicability in other settings. In our experience, assessment of historical mutagenicity levels may be difficult in the United States because the required historical information is usually not available from US water utilities or regulatory authorities. In addition, both the quality of surface waters and drinking water treatment practices appear to differ significantly between the United States and Finland. A potent bacterial mutagen in the byproduct mix, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX),[11,12] is reported to occur at much higher levels in Finnish drinking water than elsewhere.[13]

Quantitative estimates of cancer risk owing to water chlorination by-products are highly uncertain. However, the growing body of toxicological and epidemiological data suggests that risk is likely to be elevated and near or above the level at which a meaningful association can be detected by carefully conducted case-control interview studies or cohort studies (i.e., relative risks of 1.5 to 2 for one or more cancer sites). Rectal and bladder cancers have been identified as those most likely to be associated with long-term consumption of chlorinated surface water. If excess risks are in the measurable range for these sites, several thousand excess cases each year may be linked to consumption of chlorination by-products from surface water sources in the United States.

Some steps have been taken to reduce exposure to chlorination by-products. However, the paucity of sound, quantitative information about risk has apparently made regulatory agencies and utility operators reluctant to take aggressive action. In 1979, the US Environmental Protection Agency (EPA) promulgated regulations to limit total trihalomethane levels to 100 μg/L (ppb). This requirement was already being observed by most utilities that obtained water from surface sources. Relatively minor engineering controls, such as changing the point of chlorination, were usually effective in reducing trihalomethane levels among the small proportion of water purveyors that did not meet the requirement.

For many utilities, further limitation of trihalomethane levels to 80 ppb or 40 ppb would require major shifts in treatment practices and substantial capital investment. The EPA recently released negotiated rules for disinfectants and disinfectant by-products that will have this effect, and has set limits for haloacetic acids and total organic carbon.[14] The available information supports the concern over an elevated carcinogenic risk, and is more than adequate to motivate water utility operators to minimize exposure to chlorination by-products while maintaining control of microbiologic contamination. In addition, it is incumbent on the public health research community, and on epidemiologists in particular, to continue development of the database to improve the precision of quantitative assessment of health risks from chlorination by-products in drinking water. □

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Making Aging a Public Health Priority

It is high time that public health took a serious interest in the problems of aging. That this issue of the Journal focuses on aging is an acknowledgment of this subject's timeliness. The topics in this issue reflect a range of public health concerns about older persons. Many of the articles address how aging and the treatment of diseases affect the functioning of older persons. As with other public health activities, efforts are being directed toward prevention and improved treatment, and toward assessing the effects of that care in terms of both health status and expenditures.

Whereas public health has used age-based criteria actively in the past to identify special populations of concern, the emphasis has traditionally been on children, who were viewed as especially vulnerable and exploited. Some might argue today that older persons present a similar picture of vulnerability, although others might suggest that older people are favored, at least with respect to health insurance coverage.[1]

There are similarities between the plight of children and that of older persons, but there are also important differences. Both populations are more likely to be influenced by their environment than to influence it, but it would be a serious mistake to expect that all older persons are dependent. Indeed, many continue to lead productive lives, contributing much to the generations that follow them, up to the time of their death. The general social debate that has pitted one generation against another is often framed in terms of investment versus payback. Older persons deserve some reward for their years of social contribution, whereas children represent the future. Both can make compelling cases. The choice between them may prove an artificial dichotomy.

Do older persons warrant special attention? At least two disciplines have evolved to address the special problems of aging: geriatrics and gerontology. The latter is inclined to study the aging process in biological, social, and psychological terms, whereas the former is concerned with rendering older persons specialized medical assistance. However, the distinctions are not so clear in practice, and both disciplines are relatively new.

Gerontology has no specific date of birth, but its serious origins are usually traced back to research on the biology of aging early in this century.[2,3] The first White House Conference on Aging in 1961 laid the groundwork for the establishment of the National Institute on Aging within the National Institutes of Health in 1974. In the following year, Butler and Van Nostrand's book on the plight of older persons attracted national attention.[4]

Although the term *geriatrics* was used in the early part of this century,[5] practical programs that offer specialized services for older persons are a new phenomenon in the United States. Effectively, geriatric programs began in earnest in the late 1970s and early 1980s with active federal and foundation support for training programs.[6] In 1988, nearly 4300 physicians took the first national examination to certify physicians as having special competence in geriatrics. Similar certification programs are available in other health professions. The recent past has seen considerable progress and change in both the biological understanding and care of older people.[7]

Both geriatrics and gerontology owe their rationale to a belief that there is a body of knowledge unique to older persons. From the perspective of clinical care, older persons present a higher risk of frailty, a greater likelihood of having chronic diseases, and a consequent probability that their status will reflect the interaction of multiple problems rather than a single condition. Clinical conditions may present with symptoms different from those seen in younger patients, and the relative benefits and risks of therapy may differ from those that are appropriate to younger patients. However, it is as difficult to express precisely when aging begins as it is to know for sure when youth ends. Likewise, one of the most difficult differential diagnoses is distinguishing processes attributable to aging from those attributable to disease. It is recommended that aging research em-