Assessing Exposure in Epidemiologic Studies to Disinfection By-Products in Drinking Water: Report from an International Workshop

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The inability to accurately assess exposure has been one of the major shortcomings of epidemiologic studies of disinfection by-products (DBPs) in drinking water. A number of contributing factors include *a*) limited information on the identity, occurrence, toxicity, and pharmacokinetics of the many DBPs that can be formed from chlorine, chloramine, ozone, and chlorine dioxide disinfection; *b*) the complex chemical interrelationships between DBPs and other parameters within a municipal water distribution system; and *c*) difficulties obtaining accurate and reliable information on personal activity and water consumption patterns. In May 2000, an international workshop was held to bring together various disciplines to develop better approaches for measuring DBP exposure for epidemiologic studies. The workshop reached consensus about the clear need to involve relevant disciplines (e.g., chemists, engineers, toxicologists, biostatisticians and epidemiologists) as partners in developing epidemiologic studies of DBPs in drinking water. The workshop concluded that greater collaboration of epidemiologists with water utilities and regulators should be encouraged in order to make regulatory monitoring data more useful for epidemiologic studies. Similarly, exposure classification categories in epidemiologic studies should be chosen to make results useful for regulatory or policy decision making. *Key words:* disinfection by-products, epidemiologic methods, exposure assessment, haloacetic acids, trihalomethanes. *Environ Health Perspect* 110(suppl 1):53–60 (2002).
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The disinfection of potable waters has been a major public health initiative of the past century, drastically reducing waterborne diseases. However, epidemiologic studies found associations between elevated levels of disinfection by-products (DBPs) and increased risks of bladder, rectal, and/or colon cancers (*1–6*) and adverse pregnancy outcomes (*7–10*). A major criticism of these studies is the inadequate characterization of exposure (*11*). Many different indices are used to assign exposure, including surface water versus groundwater source; chloraminated versus chlorinated source; total or individual trihalomethanes (THMs); and haloacetic acid (HAA) concentrations. Generally, average DBP levels measured at the treatment plant or within the distribution system are assigned to all residents served by that treatment plant, which can result in DBP exposure misclassification.

To address DBP exposure assessment issues in epidemiologic studies, scientists from various disciplines (e.g., chemists, engineers, toxicologists, biostatisticians, epidemiologists) participated in a workshop in Ottawa, Canada, on 7–10 May 2000. The goals of the workshop were to develop better approaches in exposure assessment, provide insight on how to better interpret previously conducted studies, and promote more understanding among the disciplines of the need for more effective exposure assessment tools for epidemiologic studies.

The workshop was divided into four sessions with presentations and panel discussions. In this report, we review key elements of the problems discussed at each session of the workshop and summarize the major findings and recommendations. The Appendix lists the members of the panel.

Tap Water Sampling, Analysis, and Distribution System Modeling

The first session was concerned with drinking water sampling (timing, frequency, parameters to measure), factors affecting DBP formation, chemical analysis, and modeling of DBPs within the distribution system. Historical data on the occurrence of DBPs have been collected mostly in response to regulatory requirements. Consequently, the sampling strategies have not been designed to determine exposure for studies of adverse health effects. For example, in the United States, DBP concentrations are required to be reported only four times per year (quarterly basis) at four locations in the distribution system (three at average detention time and one at maximum detention time), with compliance based on a running annual average of these 16 samples. Smaller utilities may sample even less frequently.

DBP concentrations in a water distribution system can differ significantly from concentrations at the point of entry from the water treatment plant. Concentrations can increase or decrease because of biologic and chemical reactions within the distribution system and because of system hydraulics. For example, in a chlorinated system, THMs can

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increase in concentration with increasing distance from the plant, whereas some HAAs (e.g., dichloroacetic acid) are biodegraded at the end of a distribution system (locations with maximum retention time), where there is little or no chlorine residual. Other DBPs (e.g., chloral hydrate, haloacetonitriles, haloketones) may degrade in a distribution system maintained at an alkaline pH (e.g., ~pH 8–9) because of base-catalyzed hydrolysis. In fact, the hydrolysis by-products of some of these DBPs are other DBPs (e.g., chloral hydrate or 1,1,1-trichloropropanone are hydrolyzed to chloroform, one of the THMs). Hence, an individual's exposure from tap water may vary spatially (e.g., workplace vs. home) and temporally (depending on variations in water quality and/or treatment from season to season, day to day, and throughout the day) (*12*).

Current water utility sampling protocols for monitoring DBPs within the distribution system are generally inadequate for classifying an individual's exposure in reproductive/developmental epidemiologic studies. A grab sample represents only the DBP concentrations at that location and time. Fetal organ development occurs very early in gestation and over a relatively short time interval. During this period of organogenesis, the fetus is particularly sensitive to environmental exposures (*13*). Fetal growth mostly occurs during the last trimester of gestation. Therefore, the exposure during the time period (window) relevant to a specific outcome must be accurately characterized. Even quarterly sampling may not be suitable for reproductive studies because the samples may be taken as much as 5 months apart, and hence peak occurrences could be missed. Although the critical exposure window, if any, for DBPs remains unknown, the workshop recommended at least monthly sampling of several representative locations within the distribution system for exposure assessment in human reproductive/developmental studies. When data are not available for the time window of interest, one approach for reproductive studies has been to estimate DBP levels by sampling one year later (*9*). However, this may be problematic if there have been significant year-to-year variations in hydrology, climate, water quality, DBP precursor levels, treatment practices, and/or distribution-system hydraulics. The extent of the temporal differences will be system specific. A comparison of routinely collected parameters, such as total organic carbon (TOC), bromide, chlorine dose, chlorine residual, temperature, pH, and hydraulic parameters, from the two time periods could be used to assess the validity of reliance on the subsequent sampling period.

Quarterly monitoring was considered adequate for long-term chronic health effect studies (such as cancer). However, because of the long latency periods (decades) for cancer, historical exposure data are required. For cancer studies, the challenge is in predicting historical DBP exposure, especially if the etiologically relevant time period is prior to the implementation of current DBP monitoring programs and there have been significant changes in treatment practices (e.g., to meet current DBP regulations). Moreover, measures of DBP precursors (TOC, bromide) have been collected only in recent years. Historical DBP predictions may need to depend on collecting other water quality parameters (e.g., color, chloride) to estimate historical DBP precursor loadings.

Overall, a utility-specific (intrasystem) monitoring plan is needed to account for the degree of spatial and temporal variation in planning an epidemiologic study (*14*). Perhaps even more important, a determination must be made as to how much intrasystem variation in DBP concentrations is tolerable in the context of an epidemiologic study. Accurate assessment of DBP levels in an individual's water supply is important in calculating exposure because these levels are the basis for actual exposure due to water-use activities and consumption patterns (*7,15,16*). However, the degree of accuracy necessary for such studies has yet to be determined.

The recommended ideal set of parameters to adequately characterize DBP exposure is shown in Table 1. However, in most studies, it will be difficult or impossible to obtain data for all the parameters listed in this table. Therefore, researchers will need to prioritize which parameters to obtain to significantly improve exposure assessment for their study. The estimated costs for the suite of four THMs and nine HAAs is $400 (U.S.) per sample. The suggested level of precision for concentration of individual DBPs at the tap should be within 10–20%. Strict protocols must be followed to preserve the integrity of the sample and ensure that the DBP levels at the time of the analysis accurately reflect the levels at the time of sample collection. This is achieved by quenching the disinfectant residual and adjusting the pH of the sample. Analyses of polar DBPs, like the HAAs, have required expensive, complex, and time-consuming (about 20 samples/24 hr) preparative analytical procedures. Some promising new techniques such as electrospray ionization–mass spectrometry (ESI–MS) alone (*17*) or in combination with high-field asymmetric waveform ion mobility spectrometry (ESI–FAIMS–MS) (*18,19*) offer prospects for substantial improvements for polar DBPs like that seen with HAAs. ESI–MS and ESI–FAIMS–MS can reduce the time required for analysis to less than 5 min/sample.

Table 1. Ideal[a] set of tap water quality parameters to collect for each water treatment plant.

Chemical parameters
Total organic carbon
Ultraviolet absorbance at 254 nm
Specific ultraviolet absorbance
Bromide
Four THMs[b]
Nine HAAs[c]
Total organic halogen
Total organic chlorine
Total organic bromine
At least one from each class of priority DBPs (see Table 2)
Chlorine dose, demand, residual
Physical parameters
Conductivity[d]
Temperature
pH
Treatment practices
Primary and residual disinfection agents[e]
Filtration type
Types of coagulants
Advanced processes (e.g., granular activated carbon, membranes)
Others
Some measure of residence time in distribution system (e.g., water age)
Storage facilities in the distribution system
Water demand patterns of consumers
Hydraulic flow in distribution system
Use of EPANET software
Analytical methods used to measure various parameters[f]
Time, date, and location of samples within distribution system

[a]These recommendations are aspirational rather than mandatory. The resources or even feasibility to determine every item in this listing is not likely to be available for any one study, but each recommended parameter offers value added to the challenge of DBP exposure assessment. [b]Chloroform, bromodichloromethane, dibromochloromethane, bromoform. [c]Chloroacetic acid, dichloroacetic acid, trichloroacetic acid, bromoacetic acid, dibromoacetic acid, tribromoacetic acid, bromochloroacetic acid, dibromochloroacetic acid, and bromodichloroacetic acid. [d]As tracer of source waters in blended distribution systems. [e]Includes doses and points of application. [f]Detection limit, dechlorination agent, if any.

The focus of most of the data collection and research has been on the THMs and, to a lesser extent, on the HAAs. However, hundreds of other DBPs have been identified (*20,21*) in treated drinking water. Very little data exist on the occurrence or toxicity of these DBPs; however, new efforts are addressing certain priority DBPs (*21–23*). The workshop participants recommended specific DBPs to consider in future studies based on toxicologic considerations (Table 2).

Water quality simulation models can be used to estimate DBP levels at specific residences in a water distribution system. Most of the predictive equations for THM and HAA formation are empirical in nature, derived from multiple linear regression analysis of laboratory chlorination experiments conducted under controlled experimental conditions (*24,25*). Although these equations are typically based on experiments conducted

Table 2. Other specific disinfection by-products to be considered for future studies based on toxicologic considerations.

MX and analogs:
3-Chloro-4-(bromochloromethyl)-5-hydroxy-2(5*H*)-furanone (BMX-1)
3-Chloro-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (BMX-2)
3-Bromo-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (BMX-3)
3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX)
Haloacids
3,3-Dichloropropenoic acid
Halomethanes
Bromochloroiodomethane
Dibromoiodomethane
Dichloroiodomethane
Halonitromethanes
Dibromonitromethane
Haloacetonitriles
Bromochloroacetonitrile
Dibromoacetonitrile
Haloketones
1,3-Dichloropropanone
1,1,3-Trichloropropanone
1,1,3,3-Tetrachloropropanone
1,1-Dibromopropanone
1,1,3,3-Tetrabromopropanone
Haloaldehydes
Dichloroacetaldehyde
Bromochloroacetaldehyde
Haloacetates
Bromochloromethyl acetate
Haloamides
2,2-Dichloroacetamide
Aldehydes
2-Hexenal
Cyanoformaldehyde

on a wide range of waters, they yield a central tendency prediction that may not characterize variability in exposure at specific sites. In some cases, a central tendency model can be modified to improve the predictive capacity for site-specific uses. In other cases, a new model needs to be developed. However, linkage of predictive equations for DBP formation to epidemiologic studies is not a trivial endeavor. Important considerations are how well the models predict DBP concentrations at a set of predetermined node points such as those used in hydraulic performance models, and how well those node points represent hydraulic and water-quality conditions at individual residences. Evaluation of the predictive equations for THMs and HAAs in a simulated pipe environment has shown that the rate of THM formation from point-of-entry kinetic tests performed in clean bottles can be significantly different than the rate in an actual pipe system (*26*). This effect was not as pronounced for HAAs. A first-order DBP saturation growth model applied to a water distribution system by linking it with a hydraulic model found the results disappointing for predicting both THMs and HAAs (*27*).

Table 3. Tap water sampling, analysis and distribution modeling: research needs.

More and better data on occurrence and toxicity for
Chlorine DBPs—both halogenated and nonhalogenated (e.g., aldehydes)
Ozone DBPs
Chlorine dioxide DBPs
Chloramine DBPs
Exposure reconstruction by exploiting site-specific correlations among
Trihalomethanes, haloacetic acids, and other DBPs
Brominated species and bromide
Potential surrogate measure for bromide (e.g., chloride)
DBPs and other measures (chlorine demand, specific ultraviolet absorbance)
New identifications of
Polar and nonvolatile DBPs
Thermally labile DBPs
Higher-molecular-weight DBPs
Standards and standardized analytical methods for DBPs that are not routinely analyzed
Models to predict historic DBP formation in treatment plants and distribution systems: factors that should be considered in model development are the capability to
Represent variability in raw water sources
Utilize historically available water quality parameters
Estimate specific DBPs
Incorporate changes in treatment practices over time
Measure residence time by location in distribution system better than has been possible to date
Deal with the reality that some historic DBP monitoring data were collected without the use of dechlorination agents
Deal with improvements in analytical detection limits over time
Kinetic models interfaced with hydraulic network models to describe DBP behavior: factors that should be considered in model development are
Parameters need to be site specific
Models must be calibrated and validated and
Represent sufficient time frame for exposure analysis
Address diurnal variations in water demands and pumping/distribution practices
Address blending issues
Surface and groundwater sources
Water from different treatment plants
Water from different systems (wholesaler vs. retailer)
Improved methods for water sample collection
To arrest (quench) reactions to form additional DBPs
Choice of dechlorination (quenching) agent and preservation pH[a]
Improved methods for determining chlorine dose in treatment plant
Considering that chlorine dose can vary significantly during the course of the day[b]
Identification of chemical reactions occurring in hot water tanks and during boiling of water
Considering that increases in temperature and other storage conditions affect formation and stability of DBPs
Evaluation of the effectiveness of surrogates for improving DBP data exposure estimates
Ultraviolet absorbance[c]
Conductivity[d]
Adaption of monitoring protocols to collect data more useful for future epidemiologic studies

[a]Some DBPs, if not properly preserved, will degrade during sample storage; in some cases, the degradation by-products are other DBPs, such as the trihalomethanes. [b]Sunlight-catalyzed destruction of chlorine in open treatment basins requires adjustments in the dose during the daylight hours. [c]Indicator of reactivity of total organic carbon to form DBPs. [d]Used as a tracer of source waters in blended distribution systems.

The panel identified a number of research needs for sampling, analysis, and modeling of DBPs (Table 3). Evidence is mounting that knowledge about exposure to specific DBPs within a given class (e.g., brominated vs. total THMs) is likely to be as important or more important than total DBP class exposure levels. Improved techniques and standardization of methods are needed for water sample collection and measuring residence time in the system (e.g., "water age"). Effective collaboration is required among analytical chemists, water quality specialists, and epidemiologists to develop monitoring programs that will achieve the exposure assessment objectives.

Surrogate Measures of Exposure

The discussion in this session focused on features of epidemiologic study design and questionnaire content (and other surrogate measures of exposure) that affect the quality of DBP exposure assessment. Water utility personnel and other professionals (e.g., chemists, engineers, and toxicologists) should be involved as collaborators early in the design of epidemiologic studies. Strategies for measuring DBP exposure will differ among studies of cancer and reproductive outcomes. Cancer studies present unique challenges by requiring estimates of

exposure data from the distant past usually without relevant exposure measurements. Most of the discussion at the workshop was related to exposure assessment for reproductive studies, which focus on relatively recent exposures. Table 4 is a summary of the panel's recommendations on minimum exposure information to collect for reproductive outcome studies.

One promising study design is for the investigator to select study sites that maximize contrasts in potential DBP exposure among populations while minimizing variability of DBP exposures within sites. Sites that are consistently in the low or high tails of the distribution for the DBPs of interest, and that have low temporal and spatial variation within their distribution systems, offer the best prospects, provided the population base is sufficiently large for the health outcomes under study. Within a site chosen for its DBP level, variations in exposure will occur, particularly if individuals do not live and work in the same area or use filters or bottled water. When comparing different geographical areas with differing DBPs, however, investigators must understand that underlying differences among the sites could bias results (e.g., access to prenatal screening or abortion clinics [in studies of reproductive outcomes], other environmental exposures, lifestyle factors, and risk-taking behaviors).

When analyzing the data, investigators should select exposure categories that, when possible, are relevant to regulatory and policy decisions. For example, researchers could use cut-points for assigning exposure categories that include current and proposed maximum contaminant levels.

The current state of knowledge is sufficiently limited that some studies are still needed to generate viable hypotheses about DBPs (hazard identification), whereas other studies are needed to test hypotheses (e.g., whether brominated DBPs are a greater health risk than chlorinated DBPs). In exploratory types of studies, researchers should avoid restricting data collection to only one exposure window of interest. Deferring this restriction to the analysis phase of the study will allow greater flexibility in exploring several hypotheses regarding the critical exposure period for the health outcomes under study.

Ecologic study designs (where information on the exposure and disease is an overall index available for a group of people rather than for the individual) may be attractive for interesting natural experiments such as before-and-after studies evaluating changes in treatment practices over time in the same geographical area. For the ecologic design, problems with selection bias, recall errors, and missing data on individual exposure or outcome may be less important. Of course, analytic study designs will ultimately be needed to test hypotheses that have been generated by effective ecologic study designs.

The panel identified a number of areas needing further research (Table 5), such as developing, testing, standardizing, and validating questions on water consumption and use patterns. The common view held by members of the panel is that our estimates of recent DBP personal exposure are likely in error by well over a factor of 2 (i.e., quantitative estimates of individual DBP exposure from all routes likely range from 0.5 to 2 times the true value for any individual). Further research is needed to determine how much exposure misclassification is tolerable and what level of accuracy is needed to achieve that tolerable level. Finely characterizing answers to questions on activity patterns may provide more detailed information, but the value of incremental detail needs to be judged according to its ability to reduce errors in exposure misclassification. Resources may be better spent increasing the number of tap water samples collected. Future epidemiologic research needs to reflect the inevitable diversity of DBP exposures and emerging insights from toxicology studies about DBP exposure routes, metabolic pathways, and toxicity mechanisms.

Table 4. Recommended information to collect by questionnaire for recent disinfectant by-product exposure assessment (relevant to reproductive outcome studies).

Water consumption characteristics and water use activities diary for critical exposure period
Type of activity (e.g., showering, bathing, operation of dishwashers and washing machines, use of swimming pools and hot tubs)
Source of water
Tap or bottled
Home or other location
Ground or surface (river or lake)
Hot or cold tap or boiled water
Supplier (e.g., name of utility, private well)
Volume consumed (ingestion), duration of shower/bath (inhalation or dermal exposure)
Water temperature
Air circulation level (e.g., in bathroom)
Factors potentially modifying concentration
Water filters[a]
Boiling of water[b]
Use of bottled water[c]
Allowing water to stand (stored vs. directly from tap)
Time of day, season
Other sources of exposure
Foods and beverages[d]
Pharmaceuticals (direct agents and metabolites)
Occupation and full range of workplace activities

[a]Type, location, maintenance schedule. [b]Do not assume that all DBPs are volatilized off; moreover, some may form during the boiling process as residual chlorine reacts at an elevated temperature with DBP precursors in the water. [c]Do not assume to be free of DBPs. [d]Including those prepared with tap water having disinfectant residual.

Table 5. Epidemiologic study design: research needs.

Improved methods for measuring water consumption and use patterns
Standardized questions that are
Valid and reliable (accurate recall)
Tested in different geographical areas
Development of a "gold standard" to test against
Further testing on usefulness of water meter data loggers
Strategies to accurately estimate past activities (e.g., look at differences in population activity patterns by age and locale)
Development of perspectives on
How much exposure misclassification is tolerable?
What level of accuracy is needed to achieve that tolerable level?
Direction on valid means of combining exposure data based on such factors as
Diversity of individual DBPs
Metabolic pathways
Toxicity mechanisms
Routes of exposure
New cancer studies that can exploit emerging biomarkers of susceptibility to relevant cancer sites

Biomarkers of Exposure

Biomarkers have been classified into biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility. The primary concern of this session was biomarkers of exposure, but some insights about the utility for exposure assessment of biomarkers of effect and of susceptibility also emerged.

Optimally, DBP biomarkers should be sensitive and specific to the exposure of

interest, readily accessible, inexpensive to measure, and technically feasible to measure; have an elimination half-life appropriate to the exposure window of interest; be indicative of exposure duration, intensity, and pattern; and be consistently and quantitatively related to exposure.

Biomarkers of exposure can be used to refine exposure assessment (i.e., establish that exposure has occurred with some measure of the extent of exposure), reconstruct exposure from all routes, evaluate effectiveness of interventions (e.g., changes in treatment practices or regulations), identify important data gaps for questionnaires, and identify susceptible populations. Some work has been done in developing biomarkers for THMs in blood (*28–30*) and exhaled breath (*31–33*) and HAAs in urine (*33–35*). The studies on HAAs in urine (*33–35*) involved a cross-sectional sampling design that precluded evaluation of intraindividual variability and limited the assessment of interindividual variability. Recent research from a longitudinal exposure trial to evaluate trichloroacetic acid (the most promising HAA biomarker) indicated that both of these sources of variability are important (*36*). DBP biomarker research has developed sufficiently to discriminate population average exposure differences, but more research is needed to interpret individual differences in biomarker levels and to validate what the measured biomarker levels actually represent in terms of DBP exposure. In particular, the contribution to biomarker levels of sources other than drinking water must be better understood. Knowledge of DBP toxicokinetics, which continues to be developed for HAAs and THMs (*37,38*), and human physiologically based toxicokinetic models, which will soon be available for bromodichloromethane (*39*), should prove valuable in using biomarker data to ascertain DBP exposure.

The practicality of using biomarkers in epidemiologic studies should be considered. Standard methods for a biomarker such as trichloroacetic acid in urine are very labor intensive and susceptible to analyte loss. Estimated costs for a study population of 2,000 couples, with two urine samples per person and associated residential and workplace tap water samples, would be more than $1.5 million over a 2-year period. New methods may substantially reduce the cost and time required to measure biomarkers [e.g., solid-phase microextraction followed by fast gas chromatography with either electron capture detection or mass spectometry can substantially reduce sample volume requirements and analysis time for biological samples (*40*)]. The emerging technology of ESI–MS and ESI–FAIMS–MS shows early promise for rapid analyses of HAAs (*18,19*), which may eventually make such biomarkers more feasible, although considerable method development and validation are required.

Collecting and analyzing biomarkers at very low concentrations require rigorous protocols. Commercial vacutainer rubber stoppers contain volatile compounds (e.g., bromoform), which can severely interfere with accurate measurements of THMs in blood (*41*). These compounds must be removed by heating the stoppers under vacuum prior to use. Current detection limits for THMs in blood are below 1 pg/mL (*42*), which is sufficient to provide quantitative levels of THMs in the blood of most users of chlorine- or chloramine-treated water. Blood samples can be stored under refrigeration for up to 10 weeks before analysis. Less progress has been made in measuring HAAs in blood. Currently, HAAs have a considerably higher detection limit in blood (at least 1,000 times greater) and improved detection methods are needed.

Preliminary measurements on a series of large, differentially exposed populations indicate that blood levels are responsive to concentrations and species of THMs found in household water (*30*). Measurements of blood levels after exposure through specific routes indicate that internal dose levels of THMs increase to a much greater extent from inhalation or dermal exposure compared with dose levels from ingestion (*30,43*). However, because the putative etiologic agent(s) in disinfected drinking water has not yet been identified, we cannot discount the role of the ingestion route or any metabolites of the parent compounds in causing any observed health effect.

The research needs in DBP biomarker development are detailed in Table 6. Possible biomarkers of susceptibility include DBP-metabolizing enzymes that are polymorphically expressed in people. For example, glutathione *S*-transferase theta, can catalyze the activation of brominated THMs to mutagenic intermediates (*44,45*).

Because currently unknown biomarkers of effect or of genetic susceptibility may be discovered in the future, investigators in human studies should explore the possibility of collecting and storing appropriate tissue samples (e.g., blood, exfoliated bladder epithelial cells, buccal epithelial cells) for future biomarker research. The challenges in obtaining ethics approval and informed consent in human studies to allow for subsequent genetic analysis were discussed but not resolved.

Exposure Modeling and Uncertainty Analysis

This session focused on the impact and interpretation of exposure misclassification, methods and approaches to model personal exposure to specific DBPs, and uncertainty analysis of the parameters of these models.

A "closest-site" method has been proposed and developed as a way to possibly reduce exposure misclassification created by using utilitywide average exposure assessment methods. However, reliance on the proximity of a subject's residence to the closest utility sampling site can produce

Table 6. Biomarkers of DBP exposure: research needs.

Better understanding of absorption, distribution, metabolism and excretion of specific DBPs and how these are affected by
Chemistry of compound
Route of exposure
Prior or continuous exposure
Metabolic precursors of DBPs
Information on population differences in
Biomarker production by metabolism
Biological residence time (elimination and excretion half-life)
Indicators of susceptibility (e.g., genetic markers, presence/absence of specific enzymes such as glutathione *S*-transferases)
Physiologically based toxicokinetic models for humans for the most relevant DBPs
Toxicity of DBPs and metabolites
Need to know which agents are of toxicologic concern so can focus efforts (i.e., rapid screening tests)
Markers of longer-term exposure such as DNA or protein adducts
Possible integrated surrogate measures of exposure to multiple DBPs (e.g., analogous to total organic halogen tests on urine)
Valid and reliable instructions for participants on biomarker sample collection
Population baseline data on occurrence of DBPs in biologic fluids/media
Identification of other appropriate biologic media to sample (e.g., saliva, sweat)
Identification of important biomarkers of susceptibility
Need to examine many candidate genes to see how these polymorphisms affect risk when taken into consideration with exposure
Collection and archiving of human tissue samples for future biomarker development needs
Protocols on collection and storage of such samples
Development of the basis to include such plans into approvals for studying human subjects

exposure misclassification. The magnitude of the error will depend on how the distribution system is configured. For example, nearby or even adjacent residences may be served by different segments of a distribution system, which could result in substantially different DBP levels. Errors may also occur if study subjects reside in undersampled areas of the distribution system.

Misclassification of exposure can also occur because of difficulty in recalling and reporting drinking water activities and consumption. Number preferences by subjects in response to questions about time spent in an activity or volume consumed may also contribute to misclassification errors (e.g., rounding estimates to common increments, such as 5 or 10 vs. 7 min of showering time). Whether such errors matter in the context of actual dose needs to be assessed. In a preliminary study of the effect of showering on predicted dose of chloroform, two factors had a significant impact—time in the shower and amount of time spent in the bathroom after the shower (*46*).

Assumptions about drinking water source also need to be verified, as illustrated by a convenience sample of 114 women that found 26% used bottled or filtered water, 50% worked outside the home, and 80% of those working outside the home used the workplace water supply as one of their drinking water sources (*47*).

Some evaluation of the nature and direction of the exposure measurement error (misclassification) is required, including whether the error is similar in all study groups. For dichotomous exposure variables, methods are available to estimate the impact of misclassification errors that use sensitivity (probability that someone who is truly exposed will be classified as exposed) and specificity (probability that someone who is truly unexposed will be classified as unexposed) (*48*).

When nondifferential misclassification is assumed, the same values of sensitivity and specificity apply to both cases and noncases. This assumption may be less reasonable in case–control studies if, for example, cases are more likely to recall exposures (correctly or incorrectly) than are controls. When the exposure variable has more than two categories, nondifferential misclassification can lead to bias away from the null value. For example, in a case–control study, if 20% of the observations in each exposure category were incorrectly classified into the lowest exposure category and all observations in the lowest category were classified correctly, depending on the sample size within each category and disease status, the expected odds ratios could be approximately one half of what they would have been if no misclassification had occurred (*49*).

Misclassification measures such as sensitivity and specificity should be treated as probabilities. This will create a recognition and quantification of the fact that, if the expected bias (i.e., the bias on average) from misclassification is in one direction (e.g., toward the null), there is always a nonzero probability that the misclassification in a given study will cause that study's results to be distorted in the opposite direction (e.g., away from the null). This probability can be appreciable in some circumstances. In addition, measures of random variability (e.g., estimated standard errors) of estimated misclassification probabilities from exposure assessment validation studies need to be propagated throughout any correction, adjustment, or sensitivity analyses of exposure misclassification bias in which those estimates are employed.

The detailed personal DBP exposure models are driven by human activities. Information on what activities are undertaken, when, and for how long must be collected. Any exposure model developed must account for all relevant exposure pathways and routes of uptake. The research needs in this area are listed in Table 7.

Conclusions

An accurate characterization of DBP exposure (from all sources and routes) for all individuals in the study population is required for valid risk assessment of the potentially associated adverse health effects. The complexity of issues requires an interdisciplinary approach.

Current information on DBP exposures is largely determined by monitoring results that are driven by regulatory requirements. Meanwhile, regulators look to epidemiologic evidence to justify regulatory levels. Despite this obvious interconnection, the workshop panel found that regulatory monitoring for DBPs was of limited value for improving individual classification of exposure to DBPs, particularly for acute health effects investigations such as reproductive studies. The value of performing new epidemiologic studies using inadequate DBP exposure data sources is questionable.

The workshop panel concluded that greater collaboration with water utilities and regulators should be encouraged for future epidemiologic studies. Likewise, exposure scales, categories, and contrasts analyzed in future epidemiologic studies should be chosen to make study results useful for regulatory or policy decision makers. For example, if municipal water authorities are faced with the choice between different methods for disinfecting water from a given source, with little or no option to change the water source itself, they will need epidemiologic evidence that compares different disinfection methods applied to similar source waters. In these circumstances, studies comparing different source waters (e.g., surface water vs. groundwater) are of limited value for making informed choices among disinfection alternatives.

Overall, improving the quality of individual DBP exposure assessments will improve the quality of evidence that can be generated through epidemiologic studies. Achieving these improvements will require an interdisciplinary approach to the problem.

Table 7. Disinfectant by-product personal exposure modeling and uncertainty analysis: research needs.

Valid human exposure models
Many individual components have been evaluated; however, most models have not been evaluated when these components are aggregated
Results of simulation models can be used to improve epidemiologic questionnaires by pinpointing the most important environmental and water use activities affecting DBP exposure
Methods to evaluate contribution to exposure from various sources and routes of exposure
Will vary by type of DBP (e.g., volatile vs. nonvolatile)
Currently chloroform model used, but validity for other DBPs is unknown
What is effect of home treatment devices on total DBP exposure?
How much do DBP exposures occurring outside the home contribute to total exposure?
Models to predict historical exposure from decades ago
Specific for individual DBPs
Represent variability in personal exposures, considering all relevant routes
Sensitivity and uncertainty analysis should be done to
Determine exposure to individual DBPs (e.g., brominated species) as adverse health effects are likely caused by particular species or combinations thereof rather than total exposure to all DBPs
Identify activities that will differentiate individuals for exposures of interest versus activities that vary little among individuals
Exposure models for mixtures of DBPs
Better understanding of the relationship between water concentration and actual DBP uptake
Should resources be expended on collecting more and better data on personal habits or on increasing number of participants in study?
What is the relative contribution of tap water compared to all other possible sources of exposure to specific DBPs (e.g., bottled water, other beverages, and foods)?
Development of integrated exposure models with physiologically based pharmacokinetic models

Appendix. Panel Members of the Disinfectant By-Product Exposure Assessment Workshop

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