PROJECT SUMMARY
MEASUREMENT ERROR ESTIMATION AND CORRECTION METHODS TO MINIMIZE EXPOSURE MISCLASSIFICATION IN EPIDEMIOLOGICAL STUDIES

September 2008

SUMMARY:

This project summary highlights recent findings from research undertaken to develop improved methods to assess potential human health risks related to drinking water disinfection byproduct (DBP) exposures. The primary objective of this research was to examine the utility of routinely collected monitoring data to estimate individual-level exposures in epidemiological studies. Another specific aim was to estimate the potential for exposure misclassification bias due to a variety of sources including (1) unmeasured spatial variability in town average surrogate measures and (2) lack of integration of individual water use practices data including exposure-modifying factors. In addition to quantifying potential exposure misclassification bias, we developed an approach to correct for measurement error that may cause this bias.

The citations for the publications that comprise this project include the following:

Bateson T.F. and J.M. Wright. 2007. Regression calibration to ameliorate classical measurement error bias in disinfection by-product studies. Am. J. Epidemiol. 165(Suppl):S37.

Wright J.M. and T.F. Bateson. 2005. A sensitivity analysis of bias in relative risk estimates due to disinfection by-product exposure misclassification. J. Expos. Anal. Environ. Epidem. 15:212–216.

Wright J.M., P.A. Murphy, M.J. Nieuwenhuijsen and D.A. Savitz. 2006. The impact of water consumption, point-of-use filtration and exposure categorization on exposure misclassification of ingested drinking water contaminants. Sci. Total Environ. 366:65–73.

Development of risk assessment methods is a major component of the work done by U.S. EPA's National Center for Environmental Assessment (NCEA), which provides guidance and risk assessments aimed at protecting human health and the environment. This research provides valuable information to the risk assessment community in their efforts to quantify the potential impact of using indirect exposure assessment metrics in epidemiologic studies. This has potential implications for U.S. EPA regulatory efforts—including DBP risk assessment research which will be considered in the 6-year review of the DBP Stage 2 Rule. Reduction of uncertainties in studies of drinking water contaminants will, in turn, help support U.S. EPA’s mission to protect human health and the environment.

BACKGROUND:

Disinfection of drinking water has been effective in combating illness related to microbial pathogens but can also result in the formation of DBPs. DBPs are formed in the presence of organic and inorganic precursors. Exposure to DBPs has been linked to adverse health outcomes including carcinogenic effects and adverse reproductive and developmental outcomes (Villanueva et al., 2006; Wright et al., 2004). More recent studies have attempted to refine exposure assessment and delineate critical periods of exposure (Savitz et al., 2006; Hinckley et al., 2005), but considerable uncertainty remains in quantifying exposures to human populations. The difficulties in characterizing variability in exposure and response across different populations add considerable uncertainty to estimating the true risk that DBPs may pose. This can impact weight-of-evidence considerations in risk assessments and has important public health implications given ubiquitous exposures to DBPs via disinfected drinking water.

Many epidemiologic studies of drinking water contaminants use surrogate ambient measures to estimate underlying town-level mean concentrations. These metrics are often used to estimate individual-level exposures for study participants. Using town-level ambient metrics to estimate individual-level exposures is a common source of measurement error in epidemiologic studies of DBPs because routinely collected monitoring data may not adequately characterize temporal and spatial variability in DBP concentrations experienced in many water systems or inter-individual differences in water use. The use of these surrogate measures can lead to two types of measurement error (Berkson error and classical error). Most DBP exposure metrics likely involve measurement error of both types, with an assumption that most of the error is non-differential in nature. Non-differential measurement error, including classical and Berkson error, can result in biased effect estimates due to misclassification of exposures and outcomes in epidemiologic studies. This can also lead to increased variability of standard errors of effect estimates, distortion of exposure-response relationships and reduced statistical power to detect associations that may be present. This can result in adverse health outcomes due to DBP exposures that may go undetected in epidemiologic studies.

Previous research has assessed the utility of using surrogate data (e.g., routinely collected monitoring data) to estimate individual-level exposures, including one epidemiologic study of DBPs showing consistent reductions in effect estimates due to misclassification of exposures based on unweighted utility averages (Waller et al., 2001). We conducted a sensitivity analysis to examine the adequacy of using town mean concentrations to estimate individual exposure (Wright and Bateson, 2005). Monte Carlo simulations were used to quantify the amount of bias due to non-differential exposure misclassification from the use of weighted and unweighted exposure metrics. Misclassification bias from the use of unweighted-town-mean exposures ranged from 19–39%, increasing in proportion to the size of the true effect estimates. Weighted town mean total THM exposures were less biased than the unweighted estimates of maternal exposure, with bias up to 23%. The weighted-town-mean analyses showed that

attenuation of the true effect of DBP exposure was diminished when town-mean concentrations with large variability were downweighted. We observed a trade-off between bias and precision in the weighted exposure analyses, with the least-biased effect estimates having the widest confidence intervals. We also found that effect attenuation due to intrasystem variability was most evident in absolute and relative terms for larger odds ratios. These findings may impact exposure assessment approaches used for a variety of drinking water contaminants and other environmental pollutants.

Interindividual variability in water use practices can dramatically affect exposures to drinking water contaminants such as DBPs (Forssén et al., 2007). More recent epidemiologic studies of DBPs have begun to collect individual-level exposure information including residential tap measurements to reduce measurement error from reliance on ambient monitoring data to estimate exposures. One limitation is that most studies integrating individual-level exposure information only collect water use data at one time period that may not represent exposures during the critical period of exposure. This is of increasing importance since some studies have demonstrated behavioral changes in water use practices over short time periods such as during pregnancy (Forssén et al., 2008). Individual-level exposures to DBPs are modified due to various factors including point-of-use treatment of water (e.g., filtration or boiling prior to consumption), ventilation use during showering/bathing and swimming activities, etc. Previous research also suggests that some exposure modifying assumptions used in epidemiologic studies may not be warranted such as DBP group-level assumptions regarding point-of-use treatment effectiveness. For example, we previously examined within- and between-group differences in DBP concentrations, such as the volatile trihalomethanes (THMs) and non-volatile haloacetic acids (HAAs), upon boiling of drinking water (Krasner and Wright, 2005). We found that THM concentrations were largely reduced in chloraminated and chlorinated water upon boiling, but some variability was detected depending on length of boiling and availability of free chlorine. Considerable variability was detected among the HAAs with some increasing in concentration upon boiling while others decreased. Other studies have demonstrated efficient DBP removal upon filtration although this can be influenced by filter type and amount of water filtered (Weinberg et al., 2006; Egorov et al., 2003). These studies highlight the need to accurately quantify the impact of exposure modifying factors in exposure assessment efforts. We further examined the impact of DBP exposure assessment approaches that do not incorporate data on modifying factors (Wright et al., 2006). In this study, data were simulated to examine exposure misclassification resulting from the use of system average DBP concentrations to estimate individual-level exposures based on a variety of assumptions including variable filtration removal efficiency for DBPs and variable intake of bottled and filtered water. Compared to estimates of DBP ingestion that considered daily consumption, source type (i.e., unfiltered tap, filtered tap, and bottled water), and filter efficiency (with 90% DBP removal), 48–62% of subjects were misclassified across one category based on system average concentrations. Average misclassification across at least two exposure categories (e.g., from high to low) ranged from 4–14%. These data illustrate the importance of individual water-use information in minimizing exposure misclassification in epidemiologic studies of drinking water contaminants.

Although measurement error is known to occur through use of ambient surrogate measures such as town-level DBP concentrations, minimal research has been conducted on separating out the types of measurement error that may occur and developing methods to correct for this error. We examined two types of non-differential exposure measurement error that result from the use of these surrogate ambient measures to estimate individual exposure levels. This included use of simulated data to quantify exposure misclassification bias and application of bias correction methods to relative risk estimates typically found in environmental epidemiologic studies. We simulated subjects' "true" DBP exposures, as well as their indirect surrogate exposure metric based on the mean of several local area water samples and examined the magnitude of bias attributable to classical measurement error on the odds ratio assuming a logistic function of true exposure. We assessed the performance of the regression calibration in the absence and presence of additional Berkson-type error. We found that classical-type measurement error, which resulted in as much as 50% bias towards the null in naïve regression estimates, can be completely corrected for using this regression calibration method. Berkson-type error did not meaningfully alter the ability of the regression calibration to correct for classical measurement error. The strength of this methodology is that is does not require a supplemental validation study to compute the attenuation factor for the regression calibration. This methodology should allow for certain investigations of environmental exposure based on local area means of several samples to be calibrated for this bias thereby providing effect estimates that are less biased and less uncertain. While this method may be most useful in primary data analyses to show the extent of the magnitude of bias from measurement error, previously published results may be amenable to calibration if estimates of the within- and between-locality variances are known.

For purposes of hazard identification, risk characterization and the pursuit of the most rigorous science, it is important to make more accurate quantitative estimates of the true effects of environmental exposures. As part of this effort, we examined the utility of using town-level measures to estimate individual-level exposures in epidemiologic studies. This included assessing the impact of poorly characterized spatial and temporal variability and interindividual variability (largely due to exposure modifying factors) on DBP exposure assessment. We have also quantified the potential bias that may occur from these sources of measurement error in epidemiologic studies of DBPs and have demonstrated the use of regression calibration methods to correct for some of the error that may be present in these studies.

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RELATED LINKS AND DOWNLOADS:

U.S. EPA (Environmental Protection Agency). 2006. Stage 2 Disinfectants and Disinfection Byproducts Rule; Final Rule. Federal Register, 71(2):388-493. Available at: http://www.epa.gov/fedrgstr/EPA-WATER/2006/January/Day-04/w03.pdf

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