

ABSTRACT OF DISSERTATION

EXPOSURE TO DISINFECTION BY-PRODUCTS AND HYPOSPADIAS RISK: An Evaluation of Exposure Assessment Techniques

Epidemiologic studies have illustrated an association between disinfection by-products (DBP5) and increased risks of adverse reproductive outcomes, including birth defects. One of the largest constraints in these studies has been exposure misclassification. This dissertation presents the validation of an approach to link study participants to exposure data in such epidemiologic studies, evaluates and compares five techniques that have been proposed for reducing exposure misclassification in epidemiologic studies of DBPs, and presents the results of two population-based case-control studies of a genitourinary tract birth defect and DBP exposure during a critical period of gestation.

This study was designed to reduce exposure misclassification while testing the following hypothesis: women who give birth to infants with hypospadias are more likely to have been exposed to higher DBP concentrations than women that gave birth to infants without hypospadias. The specific aims of this study were as follows:

1. Develop a (315 for linking cases and controls to the water utility from which they receive their tap water during the vulnerable period of gestation for each birth or residence at time of birth;
2. Validate the (315 linking procedure by providing the residential addresses to the utilities to which they were linked to see if billing records and/or distribution boundaries include the subjects' addresses;
3. Compare different methods of assigning DBP exposure to study participants using routinely collected monitoring data and interview data from the NBDPS aimed

at reducing exposure misclassification

4. Determine whether exposure to DBPs increases the risk for development of hypospadias among ARHMS and NBDPS participants after accounting for potential interactions and confounding factors using linear regression models and routinely collected monitoring data;

5. Determine whether exposure to DBPs increases the risk for development of hypospadias among NBDPS participants after accounting for exposure via the ingestion, inhalation and dermal routes of exposure using interview data and routinely collected monitoring data.

Many epidemiologic studies concerning DBPs and adverse reproductive outcomes use community water system (CWS) monitoring data to estimate exposure. Use of such data requires linkage of residence location to a specific CWS and associated monitoring data during a given exposure period. The inability to perform this linkage successfully can lead to exposure misclassification and/or reduced sample size. We geocoded 3,886 residences obtained from the Arkansas Health Department and used boundary data from the 2000 U.S. Census Incorporated Place/Census Designated Places to link each of the residences included in the study to one or more CWS. In order to validate the linking procedure, we provided residential addresses to the CWS to which they were linked to see if billing records and/or distribution boundaries include the addresses. To explore potential bias, we compared demographic characteristics of participants linked to a U.S. Census Place name to participants not linked, and participants that were validated as linked to a specific CWS to those not validated. We successfully geocoded 97.2% of the addresses. The remaining 2.8% of addresses could not be

geocoded because they were listed as post office boxes or the addresses were incomplete. We linked 71.4% of the geocoded addresses to a U.S. Census Placename. Of those addresses linked to a Placename, we linked 97.4% to at least one CWS. We validated 81.4% of these addresses as being correctly linked to the CWS. We found no bias for age, education, or ethnicity between linked and unlinked participants. However, unlinked participants were more likely to be white and to live in a rural census block group. We found that the participants whose linkage we could not validate were more likely to be white and to live in a rural census block group. These results demonstrate that this method of assessing exposure to DBPs can be utilized in a large, population-based epidemiologic study.

Systematic reviews of the relationship between DBPs and adverse reproductive outcomes consistently identify exposure misclassification as an important limitation to accurate risk estimation. In the last few years researchers have developed exposure assessment metrics utilizing monitoring data while taking into consideration spatial variability, temporal variability, and personal water use into consideration. These metrics have been used with an expectation of decreasing exposure misclassification when compared to the use of quarterly CWS monitoring data alone. We compared five metrics used in assigning exposure to DBPs for a study of hypospadias in Arkansas. These included a weighting metric based on spatial variability of DBP concentrations throughout a water system, a threshold metric that excluded participants linked to a water utility classified as having high spatial variability, a spline regression technique that interpolated between sampling dates to account for temporal variability, the inclusion of water consumption data and an exposure index that included data on water consumption and shower and

bath duration. We compared each of these metrics to the use of routinely collected water utility monitoring data to assess exposure to DBPs using Pearson correlation coefficients, cross-classification of exposure quintiles, and risk estimation. Pearson correlation coefficients ranged from 0.36 when water consumption data was used to 0.97 when the spline regression technique was used. When we used a cross-classification technique to see if the different exposure metrics would cause participants to move from one exposure quintile to another, we found that the incorporation of water consumption data caused 75% of participants to change quintile while the use of the spline regression technique only caused 26% of participants to change quintile. Odds ratios (ORs) were computed for the study population using monitoring data and the 5 different metrics to assign exposure. There were no statistical differences between ORs calculated using monitoring data and ORs calculated using the 5 metrics, though this may be due to small sample size. We found that using spline regression had the least effect on exposure assessment, while the largest change in exposure assessment was observed when water consumption data was incorporated.

There is considerable evidence from both toxicological studies in animals and human epidemiology studies, to suggest that exposure to DBPs may be associated with genitourinary birth defects. Hypospadias is a birth defect in which the urethral opening occurs on the ventral side of the penis, as a result of abnormal urethral closure and is one of the most common congenital anomalies in the United States. We investigated the relationship of exposure to DBPs between gestational weeks 6 and 16 and risk of hypospadias. We obtained 651 cases from the Arkansas Reproductive Health Monitoring System and 1,277 controls from birth certificates

provided by the Arkansas Department of Health born between January 1, 1998 and December 31, 2002. We collected quarterly DBP concentrations from 263 CWS throughout Arkansas and used spline regression to estimate daily DBP concentrations for each CWS. Exposure estimates were obtained by averaging the daily DBP estimates between gestational weeks 6 and 16. We used logistic regression to obtain crude and adjusted ORs and 95% confidence intervals (CIs) for the relationship between DBPs and hypospadias. We examined exposure to total trihalomethanes (TTHMs), the sum of the 5 most prevalent haloacetic acids (HAAs) and 6 individual species of HAA5. None of the unadjusted or adjusted analyses produced statistically significant ORs. We conducted a subset analysis with 36 cases and 225 controls enrolled in the National Birth Defect Prevention Study that allowed us to refine our exposure assessment of fTHMs by including data on average volume of water ingested per day and average frequency and duration of bathing and showering per week. We found a statistically significant association for the highest tertile of exposure (OR 3.45 CI 1.05-11.35). A test for trend revealed a statistically significant dose-response relationship ($p < 0.05$). These results suggest that exposure to TTHMs during gestation may be related to hypospadias risk and emphasize the necessity of including water use data when assessing exposure to DBPs.

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