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RESEARCH ARTICLE

Maternal arsenic exposure and nonsyndromic orofacial clefts

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Background: Arsenic is widely distributed in the environment in both inorganic and organic forms. Evidence from animal studies suggests that maternal inorganic arsenic may lead to the development of orofacial clefts (OFC)s in offspring. This evidence, together with the limited epidemiologic data available, supports the need for a comprehensive examination of major sources of arsenic exposure and OFCs in humans.

Methods: Using interview data collected in the National Birth Defects Prevention Study, public and well water arsenic sampling data, and dietary arsenic estimates, we compared expert-rater assessed occupational arsenic exposure, individual-level exposure to arsenic through drinking water, and dietary arsenic exposure between mothers of OFC cases ($N = 435$) and unaffected controls ($N = 1267$). Associations for each source of exposure were estimated for cleft lip ± palate (CL/P) and cleft palate (CP) using unconditional logistic regression analyses.

Results: Associations for maternal drinking water arsenic exposure and CL/P were near or below unity, whereas those for dietary arsenic exposure tended to be positive. For CP, positive associations were observed for maternal occupational arsenic and inorganic arsenic exposures, with confidence intervals that excluded the null value, whereas those for drinking water or dietary arsenic exposures tended to be near or below unity.

Conclusions: Positive associations were observed for maternal occupational arsenic exposure and CP and for maternal dietary arsenic exposure and CL/P; the remainder of associations estimated tended to be near or below unity. Given the exploratory nature of our study, the results should be interpreted cautiously, and continued research using improved exposure assessment methodologies is recommended.

KEYWORDS

Arsenic, Cleft Lip, Cleft Palate, Metal, Pregnancy

1 | INTRODUCTION

Nonsyndromic orofacial clefts (OFC)s are common major birth defects (Genisca et al., 2009). Disruptions to the development of the lip and palate can produce multiple, distinct OFC phenotypes, which include cleft lip ± cleft palate (CL/P) and cleft palate only (CP) (Mossey, Little, Munger, Dixon, & Shaw, 2009). These disruptions likely occur from a combination of causal gene variants (reviewed in Jugessur, Farlie, & Kilpatrick, 2009) and environmental (broadly defined as non-inherited) exposures (reviewed in Mossey et al., 2009). Associations reported between OFCs and exposures, such as prenatal tobacco smoking (Kummet et al., 2016; Little, Cardy, & Munger, 2004) and maternal diabetes

(Aberg, Westbom, & Kallen, 2001; Becerra, Khoury, Cordero, & Erickson, 1990; Correa et al., 2008; Spilson, Kim, & Chung, 2001), have been rather consistent. Associations reported with other exposures, such as medications (reviewed in Hill, Wlodarczyk, Palacios, & Finnell, 2010), alcohol (reviewed in Bell et al., 2014), and folic acid supplementation (reviewed in Wehby & Murray, 2010), have been less consistent, and those reported for exposures, such as pesticides (Rappazzo et al., 2016; Romitti, Herring, Dennis, & Wong-Gibbons, 2007; Yang et al., 2014) or metals (Brender, Suarez, et al., 2006; Brender, Zhan, Suarez, Langlois, & Moody, 2006; Cordier et al., 2004; Irgens, Kruger, Skorve, & Irgens, 1998; Lorente et al., 2000; Nordstrom, Beckman, & Nordenson, 1979; Sanders et al., 2014; Suhl et al., 2018), have been largely equivocal. These latter exposures, in particular, can arise from multiple sources with variability in exposure levels across these sources. The lack of comprehensive investigation of multiple major exposure sources may have contributed to the equivocal reports.

Arsenic is a metal widely distributed throughout the environment (reviewed in Tchounwou, Yedjou, Patlolla, & Sutton, 2012) in both organic and inorganic forms, with inorganic arsenic considered to be most harmful to human health (reviewed in ATSDR, 2007). In the United States (US), arsenic exposure most commonly occurs via occupational, environmental, and dietary sources (reviewed in ATSDR, 2007), with occupational exposure potentially providing some of the highest levels (Vahter, 1986). Arsenic in US drinking water sources is predominately the inorganic form (reviewed in ATSDR, 2007) and commonly reported at low levels; however, some regions with higher levels of arsenic in rock, such as the Southwest, can have higher arsenic concentrations in water (Frey & Edwards, 1997). Diet also is a major source of arsenic exposure in the US (Xue, Zartarian, Wang, Liu, & Georgopoulos, 2010), having been reported in several food items (Capar & Cunningham, 2000), with some (e.g., rice, grains, vegetables, fruits) containing inorganic arsenic (MacIntosh et al., 1997; Schoof et al., 1999; Xue et al., 2010), and others (e.g., shellfish) containing organic arsenic (reviewed in ATSDR, 2007).

Although exposure to arsenic is of concern given its reported associations with several adverse pregnancy outcomes in humans (Quansah et al., 2015), epidemiologic evidence regarding associations between arsenic exposure and birth defects, particularly OFCs, is limited. We did not identify any studies that specifically examined occupational arsenic exposure during pregnancy and OFCs but did identify one study that examined birth defects among offspring of pregnant women employed at a smelter and potentially exposed to a combination of metals, including arsenic, compared to pregnant women not employed at the smelter. The authors reported a significant increase in the occurrence of any birth defect among offspring of exposed women, with OFCs among the most commonly reported defects (Nordstrom et al., 1979). Using these findings to ascribe the impact of arsenic exposure on OFC development, however, is limited by the use of smelter employment as a proxy for arsenic exposure rather than specific job tasks/duties and examination of multiple occupational metal exposures rather than arsenic exposure specifically.

In contrast to the literature on occupational arsenic exposures, several studies have examined the relations between maternal exposures to arsenic-contaminated drinking water and birth defects (Brender, Suarez, et al., 2006; Jin et al., 2016; Kwok, Kaufmann, & Jakariya, 2006; Mazumdar et al., 2015; Rudnai et al., 2014; Sanders et al., 2014; Zierler, Theodore, Cohen, & Rothman, 1988). Only one of these studies specifically examined OFCs (Sanders et al., 2014). The study examined arsenic levels in well water in North Carolina and reported a positive prevalence ratio for CL/P and an inverse prevalence ratio for CP; reported confidence intervals for each OFC subtype were consistent with the null. Applying an ecologic measure of arsenic exposure rather than individual-level water use and consumption limits the utility of these findings. No published studies of the effects of dietary arsenic exposure on birth defects were identified.

Similar to human studies for arsenic-contaminated drinking water, animal studies that examined the developmental toxicity of arsenic are equivocal. Several studies reported embryotoxic effects and occurrence of birth defects in offspring following maternal prenatal exposure to inorganic arsenic (Beaudoin, 1974; Burk & Beaudoin, 1977; Ferm, Saxon, & Smith, 1971; Hood & Bishop, 1972; Hood, Harrison, & Vedel, 1982; Morrissey & Mottet, 1983; Rogers, Chernoff, & Kavlock, 1981; B. Wlodarczyk et al., 2001; B. J. Wlodarczyk, Bennett, Calvin, & Finnell, 1996); others reported no teratogenesis (Holson, Stump, Ulrich, & Farr, 1999; Nemec, Holson, Farr, & Hood, 1998; Stump, Holson, Fleeman, Nemec, & Farr, 1999). Few studies reported OFCs among offspring (Burk & Beaudoin, 1977; Ferm et al., 1971; Hood et al., 1982; Rogers et al., 1981). More recently, two studies examined oral exposures to inorganic arsenic, with one study reporting mid-facial clefts in rats exposed to a combination of an organophosphate pesticide and sodium arsenate (Aggarwal et al., 2007), and the second study reporting craniofacial and neural tube abnormalities in chick embryos exposed to inorganic arsenic at levels under the current Safe Drinking Water Act (SDWA) maximum contaminant level (MCL) for arsenic (Ahir, Sanders, Rager, & Fry, 2013).

The limited evidence from human studies and the suggested evidence from animal studies of the effects of arsenic exposure, particularly inorganic arsenic exposure, on OFC development support the need to examine the relations between major sources of maternal arsenic exposure and OFCs in their offspring. To attempt to address this knowledge gap, we used data from Iowa participants in the National Birth Defects Prevention Study (NBDPS) to

develop exposure algorithms and explore relations between maternal arsenic exposure from occupation, drinking water, and diet, and OFCs in offspring.

2 | METHODS

2.1 | Study sample

The NBDPS was a population-based case–control study funded by the Centers for Disease Control and Prevention to investigate gene variants and environmental exposures for over 30 major structural birth defects among pregnancies with estimated dates of delivery (EDD)s during October 1997–December 2011. The NBDPS methods have been described elsewhere (Cogswell et al., 2009; Rasmussen et al., 2003; Reefhuis et al., 2015; Yoon et al., 2001). Briefly, the NBDPS was conducted at 10 US sites located in Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah. Cases were enumerated through active case finding and medical record abstraction at each site. All sites included live births, and all sites except New Jersey included stillbirths and elective terminations for all or part of the NBDPS study period; in Iowa, live births, stillbirths, and elective terminations were included for the duration of the study period. Abstracted data were reviewed by clinical geneticists at each site using predefined case definitions and exclusion criteria to confirm study eligibility, and each eligible case was further classified as isolated (no other major structural defect) or multiple (at least one additional major, unrelated structural defect). OFC cases diagnosed with a monogenic or chromosomal syndrome or an OFC secondary to other major structural birth defects were excluded. Controls were a random sample of livebirths without major defects delivered during the same time frame and in the same geographic catchment areas as cases selected from hospital delivery logs or birth certificate files; Iowa controls were selected from birth certificate files.

2.2 | Data collection

The NBDPS invited mothers of cases and controls to complete a telephone interview from 6 weeks to 24 months after their EDDs. Mothers were asked to provide information about their medical and prenatal care, lifestyle, family history of birth defects, sociodemographic characteristics, occupational information for jobs held for the period 3 months prior to conception through delivery (B3–P9), residential history during B3–P9, personal water use information during B3–P9 (for mothers with EDDs from 2000 to 2011), and dietary information during the year prior to pregnancy. Occupational information collected included the name and description of the product/service of each employer, job title with a description of each job and its associated activities/tasks, exposures associated with each job, hours and days worked per week, and the month and year employment began and ended (if applicable). Residential information included the full address of each residence and the month and year the mother started and stopped living at each residence. Drinking water information included personal water sources and daily consumption estimates. Dietary information included consumption patterns for food items for the year before pregnancy using a 58-item food frequency questionnaire (FFQ) adapted from the Willet FFQ (Willett, Reynolds, Cottrell-Hoehner, Sampson, & Browne, 1987). The NBDPS study protocol was approved by the institutional review board at the Centers for Disease Control and Prevention and at each participating NBDPS site.

2.3 | Arsenic exposure assessment

We developed algorithms for any and inorganic occupational and dietary arsenic exposures and for any drinking water arsenic exposure as described below. Due to cost considerations for occupational exposure assessment and potential data availability for arsenic sampling results of drinking water, we restricted application of these algorithms to data for OFC cases and controls from the Iowa NBDPS site and detail our experience herein.

2.3.1 | Occupational arsenic exposure assessment

Only OFC case and control mothers who were employed for at least 1 month during the year before their EDD were included in our occupational analyses. Using NBDPS interview data, each reported job for these mothers was assigned a 2007 North American Industrial Classification System code and a 2000 Standard Occupational Classification code. Using reports of maternal occupational history, arsenic exposure assessment for each reported maternal job was completed through review by an industrial hygienist blinded to case/control status. Our industrial hygienist has more than 30 years of experience conducting worksite inspections and health and safety consultations in Iowa and used this professional judgement and experience, along with relevant published literature, to manually review the provided occupational information and rate (yes, no) each reported job for any occupational arsenic exposure. Ratings for jobs with similar industry and occupation codes were manually reviewed for consistency in assigning occupational arsenic exposure ratings across jobs with similar worksites and work processes. Jobs rated as exposed to any arsenic also were rated (yes, no) for exposure to inorganic arsenic using similar methods. Jobs rated as exposed to any arsenic or inorganic arsenic were rated (yes, no) for each potential route of arsenic exposure (inhalation, dermal). Occupational exposure assessment was completed for jobs held at any time during pregnancy. Association analyses were restricted to jobs that overlapped all or part of the maternal critical exposure period (1 month before conception [B1] through the first

3 months of pregnancy [P1–P3]), because lip and palate development occurs during the first trimester of pregnancy (Mossey et al., 2009). The inclusion of the month before conception allowed for inclusion of potential prepregnancy exposures that may have extended into early pregnancy.

2.3.2 | Drinking water arsenic exposure assessment

We examined maternal arsenic exposure through drinking water for mothers who reported a residential history during B3–P9 and provided information on water source and consumption. Case and control mothers with EDDs before January 1, 2000 were asked only to report their drinking water source (tap water, bottled water, or both). Mothers with EDDs during 2000–2011 were asked to report additional detail on drinking water source (e.g. public water or well water) and consumption information; therefore, drinking water analyses were restricted to OFC case and control mothers with EDDs during 2000–2011.

Each reported maternal residence during B3–P9 was geocoded at the residence level. The geocoded residences were plotted in ArcGIS 10.5 (ESRI, 2011) for linkage to a public water supply or private well, as data permitted. Linkage of maternal residences to public water supplies followed a standardized protocol. Mothers were linked to 2010 census-designated places, which were assumed to represent public water supply service areas. For residences that were not located within a census-designated place, interactive methods were used to identify a public water supply, including manual review of water supplies for the city of reported residences and review of the Iowa Rural Water Association 2010 Membership directory (most recently available information relevant to the NBDPS study period). Wells identified in the Iowa Statewide Rural Well Water Survey Phase 2 (SWRL2) or the Iowa Community Private Well Study (ICPWS) were geocoded at the street level, and a one-mile radius buffer zone was placed around each well reported in either survey. Because the NBDPS interview did not ask mothers to report the location of wells used for drinking water, mothers could not be linked to their specific well. With arsenic concentrations assumed to be similar for wells within a one-mile radius of each other, mothers who reported using well water and were located within the one-mile radius buffer were linked to the respective SWRL2 or ICPWS respective well, which was used to estimate their arsenic concentration in well water. Overall, 431 of the 475 wells sampled in the SWRL2 study and 86 of the 236 sampled in the ICPWS were successfully geocoded at the street level.

The Safe Drinking Water Act (SDWA) requires groundwater sourced public water supplies to sample for arsenic every 3 years, whereas surface water sourced public water supplies must sample annually (United States Environmental Protection Agency, 2001). The current SDWA MCL for arsenic, 10 μg/L, was adopted in 2001, covering all but one NBDPS study year (2000) included for drinking water analyses; prior to 2001, the SDWA MCL for arsenic was 50 μg/L. Iowa public water supply data, as well as data for some private wells in Iowa collected in the SWRL2 and ICPWS, are maintained by The University of Iowa Center for Health Effects of Environmental Contamination. Mothers were assigned arsenic concentrations based on historic water sampling data for public water supplies or private wells. Arsenic values from samples taken during the critical exposure period (B1–P3) were used when available. When arsenic values were not available within the critical exposure period, values for any samples taken in the 12 months before B1 (B13) through 12 months after the end of P3 (M15) were used (B13–M15). If multiple samples were taken either during B1–P3 or B13–M15, the mean of the arsenic values generated for the time period was used. When arsenic samples were not available within B1–P3 or B13–M15, values for the sample taken nearest the estimated date of conception, but outside B13–M15, were used. If a reported arsenic concentration during B1-P3 or the expanded time frames was below the limit of detection (LOD), the value of ½ the LOD was assigned. Samples with concentrations reported as 0 μg/L without reports of the LOD were assumed to be 0 μg/L.

The NBDPS drinking water module administered to mothers differed for those with EDDs during 2000–2005 and those with EDDs during 2006–2011; a revised version of the water module was used for mothers with EDDs during 2006–2011. Efforts to harmonize the two water modules resulted in several restrictions, with the final drinking water analyses restricted to mothers residing in Iowa during the time of conception who reported only a single residence during the B1–P3 period. Also, due to the differences in questions regarding drinking water usage, only cold-water and bottled water consumption at home were used in the main analysis.

Arsenic exposure in drinking water was examined for mothers of all OFC cases and controls with EDDs during 2000–2011 by combining measured arsenic concentrations in water with self-reported personal consumption information. Mothers who reported drinking no water during pregnancy were excluded. Total maternal water consumption at home during the critical exposure period was calculated as the sum of the number of 8-ounce glasses of cold tap water consumed/day and the number of 8-ounce glasses of bottled water consumed/day. The total number of 8-ounce glasses of cold tap water consumed/day, the number of 8-ounce glasses of bottled water consumed/day, and total maternal water consumption during the critical exposure period were converted to liters consumed/day (L/day). Daily arsenic consumption through drinking water (μg arsenic consumed/day) was estimated as the product of the concentration of arsenic in public water supplies or private wells (μg/L) and the number of 8-ounce glasses of cold tap water consumed/day at home (L/day); bottled water was assumed to contain 0 μg/L

of arsenic, as a previous study of arsenic in bottled water in Iowa did not report detectable arsenic in bottled water samples (Breuer, Friell, Moyer, & Ronald, 1990). For comparison with the MCL, ingestion of arsenic through drinking water (μg of arsenic/liter of water consumed) was estimated by dividing arsenic consumption through drinking water (μg arsenic consumed/day) by total maternal water consumption (L/day). Estimates of ingestion of arsenic through drinking water were categorized as unexposed, <½MCL, and ≥½MCL. Mothers who reported only drinking bottled water during pregnancy were considered unexposed to arsenic through drinking water.

2.3.3 | Dietary arsenic exposure assessment

We estimated maternal dietary arsenic exposure using self-reports of food consumption from the FFQ, mean arsenic concentrations reported in the US Food and Drug Administration Total Diet Study (United States Food and Drug Administration, 2007, 2017), and inorganic arsenic concentrations reported previously (Schoof et al., 1999). The Total Diet Study is a program that monitors contaminants in a variety of foods common to US diets. To determine arsenic concentrations (mg/kg), foods were sampled from retail outlets throughout four regions of the US (Northeast, North Central, South, West), prepared as they would generally be consumed, and analyzed using inductively coupled plasma-mass spectrometric analysis (United States Food and Drug Administration, 2018). To estimate the total arsenic consumed for each food item in the FFQ, we linked the arsenic concentrations reported by the Total Diet Study for 1991–2005 (United States Food and Drug Administration, 2007) and 2006–2013 (United States Food and Drug Administration, 2017) with the relevant NBDPS study periods. The NBDPS dietary assessment asked mothers to report dietary information for the year prior to pregnancy. To retain the same Total Diet Study arsenic estimates for case and control mothers with EDDs within the same calendar year, mothers with EDDs in 2006 were linked to the 1991–2005 Total Diet Study estimates and those with EDDs in 2007 were linked to the Total Diet Study estimates for 2006–2013.

For each version of the Total Diet Study (1991–2005 or 2006–2013), foods were matched to each line item in the FFQ; if more than one food reported in the Total Diet Study matched the description of an FFQ item, an overall mean arsenic concentration for that FFQ item (μg/g of food) was calculated using each relevant Total Diet Study value. In the Total Diet Study, samples that were <LOD were assigned a value of 0 μg/g. No LOD information was provided in the 1991–2005 Total Diet Study. As such, all estimates reported as <LOD, regardless of version of the Total Diet Study, were assumed to be 0 μg/g. Also, some individual food items used to estimate overall mean arsenic concentrations for an FFQ item were reported in only one version of the Total Diet Study; therefore, separate overall mean arsenic concentrations for each FFQ line item were calculated using estimates from each version of the Total Diet Study. For example, the FFQ collected information on maternal consumption of eggs. The 1991–2005 Total Diet Study provided arsenic estimates for fried eggs, scrambled eggs, and boiled eggs; however, the 2006–2013 Total Diet Study provided estimates for only scrambled and boiled eggs. As such, the arsenic estimate for eggs using the 1991–2005 Total Diet Study data incorporated all three egg dishes, whereas the estimate using the 2006–2013 Total Diet Study data incorporated only two egg dishes; comparison of arsenic estimates for FFQ items that differed in available data between Total Diet Study versions generally were observed to be similar (data not shown).

The serving size of each food item in the FFQ was converted to grams, using grams/serving information from the US Department of Agriculture Food Composition Database (United States Department of Agriculture, 2016). The reported number of servings consumed of each FFQ item (servings/month, servings/week, servings/day) was converted to servings/day and multiplied by grams/serving to estimate grams consumed of each FFQ item/day. Arsenic consumed per FFQ item (μg/day) was estimated as the product of the reported consumption of each FFQ item (g/day) and the corresponding Total Diet Study mean arsenic concentration estimate (μg/g). Total arsenic consumed through diet (μg/day) was estimated by summing across all FFQ items. In addition to total arsenic, daily inorganic arsenic consumption was estimated using published food inorganic arsenic estimates (Schoof et al., 1999). The reported inorganic arsenic estimates were calculated for foods that are considered to make up ≥90% of the US dietary intake of inorganic arsenic. Daily inorganic arsenic consumption was estimated in the same way as daily arsenic consumption. Total arsenic consumption and inorganic arsenic consumption through diet were categorized into tertiles based on the distribution of control mother estimates for total arsenic and inorganic arsenic. Case or control mothers who reported intakes of <500 day and were excluded. T/day or >5000 day and were excluded. T/day were excluded from analyses.

2.4 | Statistical analysis

We examined several child and maternal characteristics and maternal exposures as covariables based on previously reported associations with major structural birth defects or OFCs. Child characteristics were sex, plurality, and family history of a first-degree relative with an OFC. Self-reported maternal characteristics were race/ethnicity, age at delivery, education at delivery, parity, and prepregnancy Body Mass Index (BMI), as well as self-reported exposures to any folic acid-containing supplement, alcohol consumption, and cigarette smoke during the critical exposure period.

Our descriptive analyses compared OFC cases and controls on each selected characteristic and exposure using the

chi-square test of independence (or Fisher's exact test if at least one expected cell count was <5). Crude odds ratios (cOR)s and 95% confidence intervals (CI)s were estimated for the associations between each source of arsenic and inorganic arsenic during the critical exposure period and CL/P or CP. Referent groups for respective analyses were as follows: for occupational analyses—those unexposed to occupational arsenic in all jobs during the critical exposure period; for drinking water analyses—those unexposed to arsenic through drinking water; and for dietary analyses—the first tertile of dietary arsenic or inorganic arsenic consumption. Mothers who reported prepregnancy type 1 or 2 diabetes were excluded from all analyses, as prepregnancy diabetes is a well-known risk factor for birth defects, including OFCs (Aberg et al., 2001; Becerra et al., 1990; Correa et al., 2008; Spilson et al., 2001).

Adjusted odds ratios (aOR)s were estimated using multivariable logistic regression analysis applying a change-in-estimate procedure for each arsenic exposure and each OFC subtype; covariables associated with at least one source of exposure and an outcome were considered for inclusion in multivariable models for each source of arsenic exposure. For an exposure source-OFC outcome pairing, each individual covariable was entered into a model with the relevant arsenic exposure variable; if the covariable altered the cOR for the exposure by >10%, it was included in the multivariable model. To more completely characterize maternal arsenic exposure, these sources of arsenic exposure were considered for inclusion in multivariable models. Due to sparse data resulting from few case and control mothers rated as occupationally exposed to arsenic who also completed the drinking water and diet modules of the NBDPS interview (cases = 2, controls = 1), analyses for occupational arsenic did not consider other sources of arsenic exposure, nor did analyses for either drinking water or diet consider occupational arsenic exposure as a potential covariable. Drinking water analyses considered dietary arsenic consumption as a potential covariable, and dietary analyses considered arsenic ingestion through drinking water as a potential covariable. With drinking water analysis restricted to mothers with EDDs during 2000–2011, dietary arsenic analyses also were restricted to this time frame, because drinking water arsenic exposure was considered as a potential covariable. In addition to the previously mentioned covariables, total water consumption was considered as a potential covariable in drinking water analyses, and total caloric intake also was considered as a potential covariable in dietary analyses. Exact logistic regression analyses were used when at least one category of arsenic exposure included <5 case mothers.

We conducted sub-analyses where sample sizes permitted. Sub-analyses for child characteristics included analyzing cleft lip (CL) and cleft lip with cleft palate (CLP) separately, compared to all controls, as there may be etiologic differences between CL and CLP cases; analyzing only cases with isolated defects to disentangle OFC risk independent of that for other defects; and analyzing only cases and controls without a family history of a first-degree relative with an OFC to examine OFC risk independent of potential increased hereditary risk. Drinking water sub-analyses examined arsenic ingestion excluding well water users, as few mothers were successfully linked to SWRL2 or ICPWS wells with arsenic sampling information; consumption of cold, hot, and bottled water among mothers with EDDs during 2006–2011, as consumption information for hot water was only collected for mothers with EDDs during 2006–2011; and excluding mothers who reported drinking only bottled water, as arsenic in bottled water was not directly measured. Four additional drinking water sub-analyses examined the effect of the use of ½LOD for arsenic measurements <LOD in the main analyses. First, mothers with reported arsenic concentrations in drinking water of 0 μg/L were excluded from analyses, because LOD information was unavailable. Second, reported arsenic concentrations in drinking water of 0 μg/L were assigned the overall ½LOD median value. Third, analyses were restricted to mothers who reported drinking bottled water only or whose reported arsenic concentration in drinking water was >LOD, as these mothers represent those with the most complete data. Lastly, reported concentrations that were <LOD were assigned the reported LOD to assess the effect of the highest possible arsenic concentration for these mothers. All analyses were conducted using the Statistical Analysis System (SAS) version 9.4 statistical software (SAS Institute, Cary, NC).

3 | RESULTS

For the study period 1997–2011, 1764 (cases = 464, controls = 1300) Iowa mothers completed an interview for the NBDPS; 18 (cases = 12, controls = 6) of these mothers reported prepregnancy type 1 or type 2 diabetes and were excluded. Of the remainder, 1437 (cases = 370, controls = 1067) mothers with an EDD during 1997–2011 reported employment during the year before their EDD, 1451 (cases = 375, controls = 1076) reported a residential history during pregnancy for linkage to a public water supply or private well and had an EDD during 2000–2011, and 1449 (cases = 374, controls = 1075) reported on their diet prior to pregnancy and had an EDD during 2000–2011. Overall, 1702 (cases = 435, controls = 1267) mothers responded to at least one of the three interview modules (occupation, water, diet) and were available for analysis.

We observed statistical differences ($p < .05$) between CL/P cases and controls for child sex and family history of a first-degree relative with an OFC, as well as between mothers of CL/P cases and controls for age and education at delivery, parity, and cigarette smoking during the critical

TABLE 1 Selected characteristics of children and birth mothers for Iowa controls and orofacial cleft subtypes, National Birth Defects Prevention Study, 1997–2011

	Controls (n = 1267) N[b] (%)[c]	CL/P (n = 294)[a] N[b] (%)[c]	CP (n = 141) N[b] (%)[c]
Child Characteristics			
Phenotype			
Isolated	NA	265 (90.1)	121 (85.8)
Multiple	NA	29 (9.9)	20 (14.2)
Sex*			
Male	638 (50.4)	203 (69.0)	64 (45.4)
Female	629 (49.6)	91 (31.0)	77 (54.6)
Plurality			
Singleton	1218 (96.1)	287 (97.6)	139 (98.6)
Multiple	49 (3.9)	7 (2.4)	2 (1.4)
Family history of a first-degree relative with an OFC*·**			
Yes	4 (0.3)	24 (8.2)	9 (6.4)
No	1263 (99.7)	270 (91.8)	132 (93.6)
Maternal Characteristics			
Race/Ethnicity			
Non-Hispanic White	1125 (88.9)	266 (90.5)	128 (90.8)
Non-Hispanic Black	20 (1.6)	5 (1.7)	5 (3.5)
Hispanic	63 (5.0)	11 (3.7)	6 (4.3)
Other	57 (4.5)	12 (4.1)	2 (1.4)
Age at delivery (years)*			
<20	73 (5.8)	27 (9.2)	9 (6.4)
20–24	281 (22.2)	83 (28.2)	33 (23.4)
25–29	427 (33.7)	90 (30.6)	51 (36.2)
30–34	333 (26.3)	57 (19.4)	31 (22.0)
35–39	128 (10.1)	31 (10.5)	11 (7.8)
≥40	25 (2.0)	6 (2.0)	6 (4.3)
Education at delivery (years)*·**			
0–8	16 (1.3)	3 (1.0)	5 (3.6)
9–11	63 (5.0)	32 (11.0)	8 (5.7)
12	295 (23.4)	68 (23.3)	38 (27.1)
13–15	412 (32.7)	94 (32.2)	54 (38.6)
≥16	474 (37.6)	95 (32.5)	35 (25.0)
Parity*			
Nulliparous	497 (39.2)	137 (46.6)	57 (40.4)
Primiparous	413 (32.6)	95 (32.3)	45 (31.9)
Multiparous	357 (28.2)	62 (21.1)	39 (27.7)
Prepregnancy BMI (kg/m^2)			
Underweight (<18.5)	58 (4.7)	14 (4.8)	9 (6.5)
Normal weight (18.5–24.9)	625 (50.1)	155 (53.3)	63 (45.7)
Overweight (25.0–<30.0)	304 (24.4)	75 (25.8)	37 (26.8)
Obese (≥30.0)	260 (20.9)	47 (16.2)	29 (21.0)
Maternal Exposures[d]			
Folic acid-containing supplement			
Yes	1153 (91.9)	270 (92.5)	122 (87.1)
No	105 (8.1)	22 (7.5)	18 (12.9)
Alcohol consumption			
No drinking	653 (52.7)	147 (50.7)	70 (52.6)
Drinking but no binge events	271 (21.9)	67 (23.1)	34 (25.6)
Drinking and binge event (≥4 drinks)	314 (25.4)	76 (26.2)	29 (21.8)
Cigarette smoke*			
No active or passive smoking	805 (64.2)	159 (54.4)	81 (58.3)
Active smoking only	128 (10.2)	31 (10.6)	16 (11.5)
Passive smoking only	130 (10.4)	31 (10.6)	16 (11.5)
Active and passive smoking	190 (15.2)	71 (24.3)	26 (18.7)

CL/P = cleft lip with or without palate; CP = cleft palate; CL = cleft lip; CLP = cleft lip with palate; NA = not applicable; OFC = orofacial cleft; BMI = body mass index

[a] CL/P: 178 CL with CP cases; 116 CL without CP cases

[b] Numbers may vary due to incomplete or missing data

[c] Due to rounding, percentages may not total 100

[d] During the maternal critical exposure period (1 month before conception through the first 3 months of pregnancy)

*$p < .05$ for CL/P **$p < .05$ for CP

exposure period (Table 1). Comparing CP cases and controls, we observed statistical differences for family history of a first-degree relative with an OFC, along with maternal education at delivery (Table 1).

3.1 | Occupational exposure

Among the 1437 mothers who reported employment during the year before their EDD, 60 either did not report employment during the critical exposure period (cases = 20, controls = 37) or did not provide sufficient information to complete occupational arsenic exposure assessment (cases = 1, controls = 2). After these exclusions, 1377 (95.8% of employed mothers; cases = 349, controls = 1028) were available for occupational analyses.

No CL/P case, five (4.5%) CP case, and 10 (1.0%) control mothers were rated as exposed to any arsenic during the critical exposure period; three (2.7%) CP case and three (0.3%) control mothers were rated as exposed to inorganic arsenic during the critical exposure period (Table 2). All case and control mothers rated as exposed to inorganic arsenic were rated as exposed through dermal contact, whereas one case mother and three control mothers also were rated as exposed through inhalation. Case mothers rated as exposed to arsenic reported employment in agriculture or nursing. Control mothers rated as exposed to arsenic reported employment in agriculture, electronic industries, or in mechanical assembly (data not shown).

Analysis comparing CP cases and controls for any maternal occupational arsenic exposure produced a positive, but imprecise, association with a CI that excluded the null

TABLE 2 Maternal occupational arsenic exposure for Iowa controls and orofacial cleft subtypes, National Birth Defects Prevention Study, 1997–2011

	Controls (n = 1028)	CL/P (n = 239)		CP (n = 110)	
	N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Arsenic					
No arsenic exposure	1018 (99.0)	239 (100.0)	Ref	105 (95.5)	Ref
Exposed to any occupational arsenic	10 (1.0)	0 (0.0)	NC	5 (4.5)	4.8 (1.6, 14.5)[a]
Inorganic Arsenic					
No arsenic exposure	1018 (99.7)	239 (100.0)	NC	105 (97.2)	Ref
Exposed to occupational inorganic arsenic	3 (0.3)	0 (0.0)	NC	3 (2.8)	8.6 (1.1, 65.1)[b,c]

CL/P = cleft lip with or without palate; CP = cleft palate; OR = odds ratio; 95% CI = 95% confidence interval; Ref = reference; NC = not calculated
[a] crude estimate and 95% CI
[b] exact logistic regression analysis used
[c] adjusted for maternal education at delivery

value; because no covariables met the criteria for inclusion in a multivariable model, the cOR is reported (Table 2). Similarly, analysis comparing CP cases and controls for maternal occupational inorganic arsenic exposure produced a positive, but imprecise, association, adjusting for maternal education at delivery (Table 2).

3.2 | Drinking water exposure

Among the 1451 mothers with an EDD during 2000–2011 who reported a residential history during pregnancy, 1217 (83.9%; cases = 303, controls = 914) reported a single residence throughout B1–P3, and responded to the question on tap water source. Of these 1217 mothers, 1071 (cases = 260, controls = 811) reported a public water supply, 141 (cases = 41, controls = 100) reported a private well, and 5 (cases = 2, controls = 3) reported not knowing their tap water source. Among the 1071 mothers who reported a public water supply, 1032 (cases = 246, controls = 786) were linked to a public water supply, and of the 141 mothers who reported a private well, 10 (cases = 2, controls = 8) were linked to a well; in total, 1042 (85.6%) of the 1217 mothers were successfully linked to their respective tap water source. Of the 1042 mothers linked to a tap water source, 25 (cases = 4, controls = 21) were excluded due to reporting consumption of 0 glasses of water per day or having incomplete information on drinking water consumption, leaving 1017 mothers linked to a tap water source and reported water consumption information. Among mothers who were not successfully linked to a public water supply (cases = 14, controls = 25) or private well (cases = 39, controls = 92), or reported not knowing their source of tap water (cases = 2, controls = 3), 37 (cases = 15, controls = 22) reported drinking only bottled water during pregnancy and were subsequently included with 1017 mothers linked to a tap water source providing 1054 (cases = 259, controls = 795) mothers for drinking water analyses.

For the 1042 mothers successfully linked to a public water supply or private well, relevant results for 1708 Iowa arsenic water samples were provided by the Center for Health Effects of Environmental Contamination. Of these samples, 1208 (70.1%) were reported as <LOD, and 467 (38.7%) were reported to have 0 μg/L. For the 1032 mothers linked to a public water supply, 208 (cases = 57, controls = 151) were linked to arsenic sampling results for B1–P3, 434 (cases = 111, controls = 323) to sampling results for B13–M15, and 390 (cases = 78, controls = 312) to sampling results outside B13–M15. For the 10 mothers linked to a private well, no arsenic sampling results were available within the B1–P3 or B13–M15 periods.

Estimates of arsenic drinking water exposure for the 1042 mothers linked to a tap water source were based on values <LOD for 723 (69.4%; cases = 242, controls = 554) mothers; arsenic concentration was reported as 0 μg/L for 139 (19.2%; cases = 31, controls = 108) of these 723 mothers. Of the 1042 mothers linked to a tap water source, 175 (16.8%; cases = 47, controls = 128) reported drinking only bottled water and were assigned an arsenic ingestion from drinking water of 0 μg/L water consumed regardless of arsenic sampling result obtained. Estimates of mean and median maternal arsenic ingestion from drinking water (μg/L of water consumed) were similar between CL/P or CP and controls (Table 3). Adjusted (CL/P) or crude (CP) associations between maternal arsenic ingestion <½MCL or ≥½MCL through drinking water compared to no exposure tended to be near unity, and the CIs included the null value (Table 3).

3.3 | Dietary exposure

Of the 1449 (cases = 374, controls = 1075) mothers who had an EDD during 2000–2011 and completed the NBDPS FFQ, 83 (5.7%; cases = 20, controls = 63) reported consuming <500 or >5000 calories/day and were excluded. Total arsenic estimates from the Total Diet Study were available for 55 of the 58 food items in the FFQ. The mean and median dietary arsenic consumption estimates (μg/day) were modestly higher for mothers of CL/P cases and modestly lower for mothers of CP cases compared to mothers of controls (Table 4). Inorganic arsenic estimates were available for 24 of the 58 food items in the FFQ. The mean and median dietary inorganic arsenic

TABLE 3 Maternal arsenic exposure through drinking water for Iowa controls and orofacial cleft subtypes, National Birth Defects Prevention Study, 2000–2011

	Controls ($n = 795$)	CL/P ($n = 169$)		CP ($n = 90$)	
Arsenic Ingestion from Drinking Water					
Mean ± SD (μg/L)	1.0 ± 2.5	0.8 ± 1.6		1.0 ± 2.1	
Median (μg/L)	0.5	0.4		0.5	
	N (%)	**N (%)**	**OR (95% CI)**	**N (%)**	**OR (95% CI)**
0	258 (32.5)	62 (36.7)	Ref	31 (34.4)	Ref
<½MCL	508 (63.9)	100 (59.2)	0.9 (0.6, 1.3)[a]	56 (62.2)	0.9 (0.6, 1.5)[b,c]
≥½MCL	29 (3.6)	7 (4.1)	0.9 (0.4, 2.3)[a]	3 (3.3)	0.9 (0.2, 3.0)[b,c]

CL/P = cleft lip with or without palate; CP = cleft palate; SD = standard deviation; OR = odds ratio; 95% CI = 95% confidence interval; Ref = reference; MCL = maximum contaminant level SDWA MCL for arsenic = 10 μg/L
[a] adjusted for dietary arsenic consumption
[b] crude estimate and 95% CI
[c] exact logistic regression analysis used

consumption estimates (μg/day) were similar between mothers of CL/P cases or CP cases and controls (Table 4).

Compared to the lowest tertile of exposure, adjusted estimates for associations between maternal dietary arsenic consumption and CL/P were near or above unity, and those for CP were near or modestly below unity; the CIs for all estimates included the null value (Table 4). Crude estimates for associations between dietary inorganic arsenic and CL/P were near unity, whereas adjusted estimates for associations between maternal dietary inorganic arsenic consumption and CP were near unity; the CIs for either the crude or adjusted estimates included the null value (Table 4).

3.4 | Sub-analyses

Sub-analyses examining CL and CLP separately compared to controls, only isolated CL/P or CP cases compared to controls, and cases and controls without a first-degree relative with an OFC tended to be similar to the main analyses. Analyses excluding maternal well water users, those excluding mothers who reported drinking only bottled water, and those including information about hot water consumption from mothers with an EDD during 2006–2011 tended to be similar to the respective main analyses. Lastly, all analyses examining the effects of the ½LOD substitution method were similar to the main analyses (data not shown).

4 | DISCUSSION

We developed exposure algorithms and explored relations between maternal arsenic exposure and OFCs in offspring. For CL/P, no case mother was rated with occupational

TABLE 4 Maternal dietary arsenic exposure for Iowa controls and orofacial cleft subtypes, National Birth Defects Prevention Study, 2000–2011

	Controls ($n = 1012$)	CL/P ($n = 237$)		CP ($n = 117$)	
Dietary Arsenic Consumption (μg/day)					
Arsenic					
Mean ± SD	11.4 ± 27.1	12.1 ± 17.6		9.0 ± 11.0	
Median	5.8	6.8		4.7	
Inorganic Arsenic					
Mean ± SD	4.6 ± 3.5	4.2 ± 2.4		4.3 ± 3.1	
Median	3.7	3.8		3.6	
	N (%)	**N (%)**	**OR (95% CI)**	**N (%)**	**OR (95% CI)**
Arsenic					
Tertile 1 (<2.7 μg/day)	333 (32.9)	75 (31.6)	Ref	46 (39.3)	Ref
Tertile 2 (2.7–9.4 μg/day)	345 (34.1)	68 (28.7)	1.0 (0.6, 1.6)[a]	34 (29.1)	0.8 (0.5, 1.3)[b]
Tertile 3 (>9.4 μg/day)	334 (33.0)	94 (39.7)	1.6 (1.0, 2.5)[a]	37 (31.6)	0.9 (0.6, 1.4)[b]
Inorganic Arsenic					
Tertile 1 (<2.6 μg/day)	333 (32.9)	75 (31.6)	Ref	44 (37.6)	Ref
Tertile 2 (2.6–5.0 μg/day)	346 (34.2)	89 (37.6)	1.1 (0.8, 1.6)[c]	39 (33.3)	1.0 (0.6, 1.8)[d]
Tertile 3 (>5.0 μg/day)	333 (32.9)	73 (30.8)	1.0 (0.7, 1.4)[c]	34 (29.1)	0.8 (0.4, 1.5)[d]

CL/P = cleft lip with or without palate; CP = cleft palate; SD = standard deviation; OR = odds ratio; 95% CI = 95% confidence interval; Ref = reference
[a] adjusted for maternal age at delivery, ingestion of arsenic through drinking water
[b] adjusted for maternal education at delivery
[c] crude estimate and 95% CI
[d] adjusted for total daily caloric intake, ingestion of arsenic through drinking water

arsenic exposure precluding association analyses. Associations observed for maternal drinking water arsenic exposure and CL/P were near or below unity with CIs for these associations that included the null value. Those observed for dietary arsenic exposures and CL/P were near or above unity, with corresponding CIs that included the null value. For CP, associations observed with maternal occupational arsenic and inorganic arsenic exposures were positive, albeit imprecise, with CIs that excluded the null value; the modest number of mothers rated with occupational arsenic exposure may have led to chance positive findings. Associations observed between drinking water or dietary arsenic exposures and CP tended to be near unity with CIs that included the null value.

No previous epidemiologic studies were identified that examined the role of arsenic exposures from occupation, drinking water, and diet in the etiology of OFCs. Although, one previous occupational study reported an increase in the occurrence of birth defects among mothers potentially occupationally exposed to arsenic, with OFCs among the most common defects reported (Nordstrom et al., 1979); however, these results are not directly comparable with our study.

Although we observed mostly null associations between arsenic exposures and OFCs, some animal studies reported OFCs (Burk & Beaudoin, 1977; Ferm et al., 1971; Hood et al., 1982; Rogers et al., 1981) and other craniofacial defects (Aggarwal et al., 2007; Ahir et al., 2013) following maternal inorganic arsenic administration during pregnancy. It should be noted that the arsenic doses expected to produce birth defects in animals are likely higher than those typically experienced in human populations, which may account for differences between our results, particularly for drinking water and dietary arsenic exposure, and results from animal studies. Also, the potential mechanisms by which inorganic arsenic may influence OFC development are unclear; some potential mechanisms include downregulation of Msh Homeobox 1 (McCoy, Stadelman, Brumaghim, Liu, & Bain, 2015), alterations to glucocorticoid pathway signaling (Ahir et al., 2013), oxidative stress (Han, Song, Cui, Xia, & Ma, 2011), and alterations to placental DNA methylation (Green et al., 2016).

4.1 | Strengths

We used data from Iowa participants in the NBDPS, one of the largest population-based case–control studies of birth defects. Clinical geneticist review of medical record data for cases in the NBDPS helped to reduce the potential for case misclassification, and NBDPS controls were observed to be similar to all live births in the corresponding NBDPS areas on several maternal characteristics (Cogswell et al., 2009), which may have reduced the potential for selection bias. Additionally, inclusion of information on occupational history, water source and consumption, and diet in the NBDPS interview allowed for a more comprehensive assessment of major sources of arsenic exposure than has been conducted in previous studies of birth defects.

Other methodologic strengths of our study were the use of industrial hygienist review of maternal job histories to assess maternal occupational arsenic and inorganic arsenic exposure, potentially reducing exposure misclassification compared to use of less comprehensive methods (Rybicki, Johnson, Peterson, Kortsha, & Gorell, 1997). Job information in the NBDPS also allowed for the exclusion of nonworking mothers, helping to reduce the potential for confounding through factors related to employment status (Rocheleau et al., 2017). We characterized environmental arsenic exposure by incorporating information on arsenic sampling in public water supplies and private wells and information on maternal water consumption from the NBDPS interview, rather than relying on ecologic measures, such as residence as a proxy measure for exposure. Related to this, the NBDPS water module asked about the tap water source (e.g., public water, private well water) and arsenic sampling data for Iowa wells from two independent well surveys were used to estimate arsenic consumption for well water users. Lastly, use of maternal NBDPS FFQ responses and arsenic concentrations in food from the Total Diet Study and published by Schoof et al. (1999) allowed us to examine arsenic and inorganic arsenic exposures from diet, which has not been conducted in previous studies of OFCs.

4.2 | Limitations

Although NBDPS data were used, we restricted analyses to Iowa participants to facilitate examining multiple sources of arsenic exposure by conducting assessment for occupational exposures and accessing public and private water sampling results; thus, our sample sizes were modest for some analyses, which produced imprecise estimates or the inability to examine some arsenic exposures. As funding permits, algorithms applied to Iowa NBDPS data will be used in analyses of NBDPS data from other sites.

A potential limitation of our occupational exposure assessment was having a single industrial hygienist rate maternal arsenic exposures, which limited evaluating the reliability of exposure ratings generated. Our use of a yes/no exposure rating for occupational exposure assessment may have diluted the effects of high-dose or high-intensity exposures, although this limitation was probably attenuated by the small number of mothers rated with occupational arsenic exposure. With occupational arsenic levels and thus, risk, likely differing among the routes of exposure (inhalation, dermal absorption), our small number of occupationally exposed mothers precluded analysis of risk by route of exposure. We also lacked data on factors that may have modified maternal occupational arsenic exposure, such as use of personal protective equipment. Additionally, the small numbers of mothers occupationally exposed to arsenic who also supplied drinking water or dietary information (cases = 2, controls = 1) limited our ability to examine the effects of

occupational exposure jointly with these other sources of arsenic exposure.

In our assessment of drinking water arsenic, most women who reported using public water supplies were linked to arsenic sampling data, but few mothers who reported using well water were able to be linked to well water arsenic sampling data; private well users may experience higher levels of arsenic exposure than public water supply users (reviewed in ATSDR, 2007). Despite this limitation, only a small proportion (13%) of Iowa mothers reported using well water. Also, most mothers were linked to arsenic sampling data outside the critical exposure period, which may not reflect the actual concentration of arsenic in drinking water during the critical period of lip and palate development. Similarly, bottled water was assumed to contain 0 μg/L of arsenic, which may not reflect actual arsenic concentrations in bottled water, but a previous Iowa study did not report detectable concentrations of arsenic in the samples of bottled water (Breuer et al., 1990). Further, results of analyses excluding mothers who reported only drinking bottled water reflected those from the main analyses. Additionally, it should be noted that a substantial proportion of the estimates of arsenic ingestion through drinking water used arsenic sampling values that were reported as <LOD. Although application of ½LOD may result in biased estimates (Hewett & Ganser, 2007), the results of the sub-analyses examining this limitation were similar to the main analyses. Lastly, information on water source and amounts used for cooking was not available, which may have underestimated arsenic exposure from water.

Our reliance on maternal retrospective self-reports may have introduced differences in recall of water use and consumption between case and control mothers; however, a previous study reported good agreement between recall for recent and past water use in a sample of pregnant women (Shimokura, Savitz, & Symanski, 1998). With our main analyses restricted to cold water consumption due to differences in items included in different interview versions, water consumption and drinking water arsenic exposure were potentially underestimated; however, results from a sub-analysis examining hot and cold water consumption in mothers with EDDs during 2006–2011 were similar to those from the main analysis. Differences in items asked for water use and consumption away from home between interview versions restricted our main analyses to home water consumption only, again, potentially underestimating water consumption and arsenic exposure.

Our assessment of any dietary arsenic exposure using the NBDPS FFQ may not have captured all sources of arsenic through diet. In particular, some items considered to be common sources of organic arsenic and inorganic arsenic exposure, such as shrimp (reviewed in ATSDR, 2007) and rice (reviewed in ATSDR, 2007), respectively, were not included as independent food items in the FFQ; instead, reports for combined rice and pasta consumption were requested. Additionally, the use of fixed values (mean arsenic concentrations from the Total Diet Study) as an estimate of arsenic concentrations in food may not account for the variability and uncertainty in the measured concentrations of arsenic in food. Also, Total Diet Study arsenic estimates were not available for all items reported in the FFQ, which may have underestimated dietary arsenic consumption; inorganic arsenic estimates were available for fewer than one-half of FFQ items and did not include rice. To assess inorganic arsenic exposure, we used estimates from a market-based study of two communities in Texas (Schoof et al., 1999), which may not be representative of estimates of foods consumed in Iowa. Lastly, we lacked data on other possible sources of environmental exposure to arsenic.

In summary, our study is the first to examine the relations between maternal arsenic exposures during pregnancy and OFCs in their offspring using a comprehensive approach incorporating occupational, drinking water, and dietary sources of arsenic exposure. Our analyses did not suggest an increase in risk for CL/P with any source of maternal arsenic exposure. We observed an increased, but imprecise risk for maternal occupational arsenic or inorganic arsenic exposure and CP; however, these estimates did not account for other sources of arsenic exposure, such as exposures related to residing near hazardous waste facilities. Future studies should attempt to improve upon the limitations in our study to better elucidate the role of arsenic and inorganic arsenic in OFC etiology. Specifically, information about factors that could modify occupational exposures should be considered in occupational exposure assessment, as well as more detailed measures of exposure to examine the effects of high-intensity or high-dose exposures. In assessing maternal arsenic exposure from drinking water, future studies should improve upon arsenic sampling methodologies, to better characterize arsenic exposures during the critical exposure period, with particular attention to the handling of large proportions of samples <LOD. Increased information on well water also should be incorporated to better estimate exposures among well water users. Along with improving water sampling methodologies, additional information on all sources of water consumption should be considered to more completely characterize maternal water consumption during pregnancy. Lastly, further sampling of foods for both total arsenic and inorganic arsenic should be attempted to more completely characterize dietary arsenic exposures, with particular emphasis on foods known to contribute to human inorganic arsenic burden.

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REFERENCES

Aberg, A., Westbom, L., & Kallen, B. (2001). Congenital malformations among infants whose mothers had gestational diabetes or preexisting diabetes. *Early Human Development, 61*(2), 85–95.

Aggarwal, M., Wangikar, P. B., Sarkar, S. N., Rao, G. S., Kumar, D., Dwivedi, P., & Malik, J. K. (2007). Effects of low-level arsenic exposure on the developmental toxicity of anilofos in rats. *Journal of Applied Toxicology, 27*(3), 255–261. doi:https://doi.org/10.1002/jat.1203

Ahir, B. K., Sanders, A. P., Rager, J. E., & Fry, R. C. (2013). Systems biology and birth defects prevention: blockade of the glucocorticoid receptor prevents arsenic-induced birth defects. *Environmental Health Perspectives, 121*(3), 332–338. doi:https://doi.org/10.1289/ehp.1205659

ATSDR. (2007). *Toxicological Profile for Arsenic*. Atlanta, GA Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp2.pdf.

Beaudoin, A. R. (1974). Teratogenicity of sodium arsenate in rats. *Teratology, 10*(2), 153–157. doi:https://doi.org/10.1002/tera.1420100211

Becerra, J. E., Khoury, M. J., Cordero, J. F., & Erickson, J. D. (1990). Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics, 85*(1), 1–9.

Bell, J. C., Raynes-Greenow, C., Turner, R. M., Bower, C., Nassar, N., & O'Leary, C. M. (2014). Maternal alcohol consumption during pregnancy and the risk of orofacial clefts in infants: a systematic review and meta-analysis. *Paediatric and Perinatal Epidemiology, 28*(4), 322–332. doi:https://doi.org/10.1111/ppe.12131

Brender, J. D., Suarez, L., Felkner, M., Gilani, Z., Stinchcomb, D., Moody, K., … Hendricks, K. (2006). Maternal exposure to arsenic, cadmium, lead, and mercury and neural tube defects in offspring. *Environmental Research, 101*(1), 132–139. doi:https://doi.org/10.1016/j.envres.2005.08.003

Brender, J. D., Zhan, F. B., Suarez, L., Langlois, P. H., & Moody, K. (2006). Maternal residential proximity to waste sites and industrial facilities and oral clefts in offspring. *Journal of Occupational and Environmental Medicine, 48*(6), 565–572. doi:https://doi.org/10.1097/01.jom.0000214466.06076.07

Breuer, G. M., Friell, L. A., Moyer, N. P., & Ronald, G. W. (1990). *Testing of Bottled Waters Sold in Iowa*. (90-1). The University of Iowa: University Hygienic Lab.

Burk, D., & Beaudoin, A. R. (1977). Arsenate-induced renal agenesis in rats. *Teratology, 16*(3), 247–259. doi:https://doi.org/10.1002/tera.1420160303

Capar, S. G., & Cunningham, W. C. (2000). Element and radionuclide concentrations in food: FDA Total Diet Study 1991-1996. *Journal of AOAC International, 83*(1), 157–177.

Cogswell, M. E., Bitsko, R. H., Anderka, M., Caton, A. R., Feldkamp, M. L., Hockett Sherlock, S. M., … National Birth Defects Prevention Study. (2009). Control selection and participation in an ongoing, population-based, case-control study of birth defects: the National Birth Defects Prevention Study. *American Journal of Epidemiology, 170*(8), 975–985. doi:https://doi.org/10.1093/aje/kwp226

Cordier, S., Chevrier, C., Robert-Gnansia, E., Lorente, C., Brula, P., & Hours, M. (2004). Risk of congenital anomalies in the vicinity of municipal solid waste incinerators. *Occupational and Environmental Medicine, 61*(1), 8–15.

Correa, A., Gilboa, S. M., Besser, L. M., Botto, L. D., Moore, C. A., Hobbs, C. A., … Reece, E. A. (2008). Diabetes mellitus and birth defects. *American Journal of Obstetrics and Gynecology, 199*(3), 237 e231-239. doi:https://doi.org/10.1016/j.ajog.2008.06.028

ESRI. (2011). *ArcGIS Desktop: Release 10 (Version 10.5)*. Redlands, CA: Environmental Systems Research Institute.

Ferm, V. H., Saxon, A., & Smith, B. M. (1971). The teratogenic profile of sodium arsenate in the golden hamster. *Archives of Environmental Health, 22*(5), 557–560.

Frey, M. M., & Edwards, M. A. (1997). Surveying arsenic occurrence. *Journal American Water Works Association, 89*(3), 105–117.

Genisca, A. E., Frias, J. L., Broussard, C. S., Honein, M. A., Lammer, E. J., Moore, C. A., … National Birth Defects Prevention Study. (2009). Orofacial clefts in the National Birth Defects Prevention Study, 1997-2004. *American Journal of Medical Genetics. Part A, 149A*(6), 1149–1158. doi:https://doi.org/10.1002/ajmg.a.32854

Green, B. B., Karagas, M. R., Punshon, T., Jackson, B. P., Robbins, D. J., Houseman, E. A., & Marsit, C. J. (2016). Epigenome-wide assessment of dna methylation in the placenta and arsenic exposure in the new hampshire birth cohort study (USA). *Environmental Health Perspectives, 124*(8), 1253–1260. doi:https://doi.org/10.1289/ehp.1510437

Han, Z. J., Song, G., Cui, Y., Xia, H. F., & Ma, X. (2011). Oxidative stress is implicated in arsenic-induced neural tube defects in chick embryos. *International Journal of Developmental Neuroscience, 29*(7), 673–680. doi:https://doi.org/10.1016/j.ijdevneu.2011.06.006

Hewett, P., & Ganser, G. H. (2007). A comparison of several methods for analyzing censored data. *The Annals of Occupational Hygiene, 51*(7), 611–632. doi:https://doi.org/10.1093/annhyg/mem045

Hill, D. S., Wlodarczyk, B. J., Palacios, A. M., & Finnell, R. H. (2010). Teratogenic effects of antiepileptic drugs. *Expert Review of Neurotherapeutics, 10*(6), 943–959. doi:https://doi.org/10.1586/ern.10.57

Holson, J. F., Stump, D. G., Ulrich, C. E., & Farr, C. H. (1999). Absence of prenatal developmental toxicity from inhaled arsenic trioxide in rats. *Toxicological Sciences, 51*(1), 87–97.

Hood, R. D., & Bishop, S. L. (1972). Teratogenic effects of sodium arsenate in mice. *Archives of Environmental Health, 24*(1), 62–65.

Hood, R. D., Harrison, W. P., & Vedel, G. C. (1982). Evaluation of arsenic metabolites for prenatal effects in the hamster. *Bulletin of Environmental Contamination and Toxicology, 29*(6), 679–687.

Irgens, A., Kruger, K., Skorve, A. H., & Irgens, L. M. (1998). Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. *American Journal of Industrial Medicine, 34*(5), 431–437.

Jin, X., Tian, X., Liu, Z., Hu, H., Li, X., Deng, Y., … Zhu, J. (2016). Maternal exposure to arsenic and cadmium and the risk of congenital heart defects in offspring. *Reproductive Toxicology, 59*, 109–116. doi:https://doi.org/10.1016/j.reprotox.2015.12.007

Jugessur, A., Farlie, P. G., & Kilpatrick, N. (2009). The genetics of isolated orofacial clefts: from genotypes to subphenotypes. *Oral Diseases, 15*(7), 437–453. doi:https://doi.org/10.1111/j.1601-0825.2009.01577.x

Kummet, C. M., Moreno, L. M., Wilcox, A. J., Romitti, P. A., DeRoo, L. A., Munger, R. G., … Wehby, G. L. (2016). Passive Smoke Exposure as a Risk Factor for Oral Clefts-A Large International Population-Based Study. *American Journal of Epidemiology, 183*(9), 834–841. doi:https://doi.org/10.1093/aje/kwv279

Kwok, R. K., Kaufmann, R. B., & Jakariya, M. (2006). Arsenic in drinking-water and reproductive health outcomes: a study of participants in the Bangladesh Integrated Nutrition Programme. *Journal of Health, Population, and Nutrition, 24*(2), 190–205.

Little, J., Cardy, A., & Munger, R. G. (2004). Tobacco smoking and oral clefts: a meta-analysis. *Bulletin of the World Health Organization, 82*(3), 213–218.

Lorente, C., Cordier, S., Bergeret, A., De Walle, H. E., Goujard, J., Ayme, S., … Bianchi, F. (2000). Maternal occupational risk factors for oral clefts. Occupational Exposure and Congenital Malformation Working Group. *Scandinavian Journal of Work, Environment & Health, 26*(2), 137–145.

MacIntosh, D. L., Williams, P. L., Hunter, D. J., Sampson, L. A., Morris, S. C., Willett, W. C., & Rimm, E. B. (1997). Evaluation of a food frequency questionnaire-food composition approach for estimating dietary intake of inorganic arsenic and methylmercury. *Cancer Epidemiology, Biomarkers & Prevention, 6*(12), 1043–1050.

Mazumdar, M., Valeri, L., Rodrigues, E. G., Ibne Hasan, M. O., Hamid, R., Paul, L., … Christiani, D. C. (2015). Polymorphisms in maternal folate pathway genes interact with arsenic in drinking water to influence risk of myelomeningocele. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 103*(9), 754–762. doi:https://doi.org/10.1002/bdra.23399

McCoy, C. R., Stadelman, B. S., Brumaghim, J. L., Liu, J. T., & Bain, L. J. (2015). Arsenic and its methylated metabolites inhibit the differentiation of

neural plate border specifier cells. *Chemical Research in Toxicology, 28*(7), 1409–1421. doi:https://doi.org/10.1021/acs.chemrestox.5b00036

Morrissey, R. E., & Mottet, N. K. (1983). Arsenic-induced exencephaly in the mouse and associated lesions occurring during neurulation. *Teratology, 28*(3), 399–411. doi:https://doi.org/10.1002/tera.1420280311

Mossey, P. A., Little, J., Munger, R. G., Dixon, M. J., & Shaw, W. C. (2009). Cleft lip and palate. *Lancet, 374*(9703), 1773–1785. doi:https://doi.org/10.1016/s0140-6736(09)60695-4

Nemec, M. D., Holson, J. F., Farr, C. H., & Hood, R. D. (1998). Developmental toxicity assessment of arsenic acid in mice and rabbits. *Reproductive Toxicology, 12*(6), 647–658.

Nordstrom, S., Beckman, L., & Nordenson, I. (1979). Occupational and environmental risks in and around a smelter in northern Sweden. VI. Congenital malformations.*Hereditas, 90*(2), 297–302.

Quansah, R., Armah, F. A., Essumang, D. K., Luginaah, I., Clarke, E., Marfoh, K., … Dzodzomenyo, M. (2015). Association of arsenic with adverse pregnancy outcomes/infant mortality: A systematic review and meta-analysis. *Environmental Health Perspectives, 123*(5), 412–421. doi:https://doi.org/10.1289/ehp.1307894

Rappazzo, K. M., Warren, J. L., Meyer, R. E., Herring, A. H., Sanders, A. P., Brownstein, N. C., & Luben, T. J. (2016). Maternal residential exposure to agricultural pesticides and birth defects in a 2003 to 2005 North Carolina birth cohort. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 106*(4), 240–249. doi:https://doi.org/10.1002/bdra.23479

Rasmussen, S. A., Olney, R. S., Holmes, L. B., Lin, A. E., Keppler-Noreuil, K. M., Moore, C. A., & National Birth Defects Prevention Study. (2003). Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 67*(3), 193–201. doi:https://doi.org/10.1002/bdra.10012

Reefhuis, J., Gilboa, S. M., Anderka, M., Browne, M. L., Feldkamp, M. L., Hobbs, C. A., … National Birth Defects Prevention Study. (2015). The National Birth Defects Prevention Study: A review of the methods. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 103*(8), 656–669. doi:https://doi.org/10.1002/bdra.23384

Rocheleau, C. M., Bertke, S. J., Lawson, C. C., Romitti, P. A., Desrosiers, T. A., Agopian, A. J., … National Birth Defects Prevention Study. (2017). Factors associated with employment status before and during pregnancy: Implications for studies of pregnancy outcomes. *American Journal of Industrial Medicine, 60*(4), 329–341. doi:https://doi.org/10.1002/ajim.22700

Rogers, E. H., Chernoff, N., & Kavlock, R. J. (1981). The teratogenic potential of cacodylic acid in the rat and mouse. *Drugs and Chemical Toxicology, 4*(1), 49–61. doi:https://doi.org/10.3109/01480548109066371

Romitti, P. A., Herring, A. M., Dennis, L. K., & Wong-Gibbons, D. L. (2007). Meta-analysis: pesticides and orofacial clefts. *The Cleft Palate-Craniofacial Journal, 44*(4), 358–365. doi:https://doi.org/10.1597/06-100.1

Rudnai, T., Sandor, J., Kadar, M., Borsanyi, M., Beres, J., Metneki, J., … Rudnai, P. (2014). Arsenic in drinking water and congenital heart anomalies in Hungary. *International Journal of Hygiene and Environmental Health, 217*(8), 813–818. doi:https://doi.org/10.1016/j.ijheh.2014.05.002

Rybicki, B. A., Johnson, C. C., Peterson, E. L., Kortsha, G. X., & Gorell, J. M. (1997). Comparability of different methods of retrospective exposure assessment of metals in manufacturing industries. *American Journal of Industrial Medicine, 31*(1), 36–43.

Sanders, A. P., Desrosiers, T. A., Warren, J. L., Herring, A. H., Enright, D., Olshan, A. F., … Fry, R. C. (2014). Association between arsenic, cadmium, manganese, and lead levels in private wells and birth defects prevalence in North Carolina: a semi-ecologic study. *BMC Public Health, 14*, 955. doi:https://doi.org/10.1186/1471-2458-14-955

SAS Institute Inc. (2013). *SAS 9.4 (Version 9.4)*. Cary, NC: SAS Institute Inc.

Schoof, R. A., Yost, L. J., Eickhoff, J., Crecelius, E. A., Cragin, D. W., Meacher, D. M., & Menzel, D. B. (1999). A market basket survey of inorganic arsenic in food. *Food and Chemical Toxicology, 37*(8), 839–846.

Shimokura, G. H., Savitz, D. A., & Symanski, E. (1998). Assessment of water use for estimating exposure to tap water contaminants. *Environmental Health Perspectives, 106*(2), 55–59.

Spilson, S. V., Kim, H. J., & Chung, K. C. (2001). Association between maternal diabetes mellitus and newborn oral cleft. *Annals of Plastic Surgery, 47*(5), 477–481.

Stump, D. G., Holson, J. F., Fleeman, T. L., Nemec, M. D., & Farr, C. H. (1999). Comparative effects of single intraperitoneal or oral doses of sodium arsenate or arsenic trioxide during in utero development. *Teratology, 60*(5), 283–291. doi:https://doi.org/10.1002/(SICI)1096-9926(199911)60:5<283::AID-TERA9>3.0.CO;2-7

Suhl, J., Romitti, P. A., Cao, Y., Rocheleau, C. M., Burns, T. L., Conway, K., … National Birth Defects Prevention Study. (2018). Maternal occupational cadmium exposure and nonsyndromic orofacial clefts. *Birth Defects Research* doi:https://doi.org/10.1002/bdr2.1202

Tchounwou, P. B., Yedjou, C. G., Patlolla, A. K., & Sutton, D. J. (2012). Heavy metal toxicity and the environment. *EXS, 101*, 133–164. doi:https://doi.org/10.1007/978-3-7643-8340-4_6

United States Department of Agriculture. (2016). *USDA National Nutrient Database for Standard Reference*. Beltsville, MD.

United States Environmental Protection Agency. (2001). *Drinking water standard for arsenic fact sheet*. Retrieved from https://nepis.epa.gov/Exe/ZyPdf.cgi?Dockey=20001XXC.txt.

United States Food and Drug Administration. (2007). *Total Diet Study Statistics on Element Results*. College Park, MD.

United States Food and Drug Administration. (2017). *Total Diet Study Elements Results Summary Statistics – Market Baskets 2006 through 2013* College Park, MD.

United States Food and Drug Administration. (2018). *Analytical Methods Used in the Total Diet Study*. College Park, MD Retrieved from https://www.fda.gov/downloads/Food/FoodScienceResearch/TotalDietStudy/UCM458735.pdf .

Vahter, M. (1986). Environmental and occupational exposure to inorganic arsenic. *Acta Pharmacol Toxicol (Copenh), 59* Suppl 7, 31-34.

Wehby, G. L., & Murray, J. C. (2010). Folic acid and orofacial clefts: a review of the evidence. *Oral Diseases, 16*(1), 11–19. doi:https://doi.org/10.1111/j.1601-0825.2009.01587.x

Willett, W. C., Reynolds, R. D., Cottrell-Hoehner, S., Sampson, L., & Browne, M. L. (1987). Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. *Journal of the American Dietetic Association, 87*(1), 43–47.

Wlodarczyk, B., Spiegelstein, O., Gelineau-van Waes, J., Vorce, R. L., Lu, X., Le, C. X., & Finnell, R. H. (2001). Arsenic-induced congenital malformations in genetically susceptible folate binding protein-2 knockout mice. *Toxicology and Applied Pharmacology, 177*(3), 238–246. doi:https://doi.org/10.1006/taap.2001.9303

Wlodarczyk, B. J., Bennett, G. D., Calvin, J. A., & Finnell, R. H. (1996). Arsenic-induced neural tube defects in mice: Alterations in cell cycle gene expression. *Reproductive Toxicology, 10*(6), 447–454.

Xue, J., Zartarian, V., Wang, S. W., Liu, S. V., & Georgopoulos, P. (2010). Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003-2004 nhanes data. *Environmental Health Perspectives, 118*(3), 345–350. doi:https://doi.org/10.1289/ehp.0901205

Yang, W., Carmichael, S. L., Roberts, E. M., Kegley, S. E., Padula, A. M., English, P. B., & Shaw, G. M. (2014). Residential agricultural pesticide exposures and risk of neural tube defects and orofacial clefts among offspring in the San Joaquin Valley of California. *American Journal of Epidemiology, 179*(6), 740–748. doi:https://doi.org/10.1093/aje/kwt324

Yoon, P. W., Rasmussen, S. A., Lynberg, M. C., Moore, C. A., Anderka, M., Carmichael, S. L., … Edmonds, L. D. (2001). The national birth defects prevention study. *Public Health Reports, 116* Suppl 1, 32–40.

Zierler, S., Theodore, M., Cohen, A., & Rothman, K. J. (1988). Chemical quality of maternal drinking water and congenital heart disease. *International Journal of Epidemiology, 17*(3), 589–594.

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