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Maternal Residential Proximity to Waste Sites and Industrial Facilities and Oral Clefts in Offspring

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Learning Objectives

- Recall previously reported studies that examined associations between living near an industrial facility or waste site and the risk of giving birth to an infant having an oral (lip and/or palate) cleft—one of the commonest of birth defects.
- Appraise any correlations between the risk of having a child with an oral cleft and residing within a mile of an industrial plant or contaminated waste site.
- Point out the limitations of this study and the likelihood that they significantly altered the findings.

Objective: *This study examined the association between oral clefts and maternal residential proximity to waste sites or industries.* ***Methods:*** *In a case–control study, maternal residences at birth of 1781 births with oral clefts and 4368 comparison births were related to locations of waste sites and industrial facilities in Texas through geographic information systems.* ***Results:*** *Compared with women who lived farther, women who lived within a mile of these sites or facilities were not more likely to have offspring with oral clefts. Among women ≥35 years, oral clefts in offspring were associated with living within a mile of industrial facilities (odds ratio [OR] = 2.4, 95% confidence interval [CI] = 1.3–4.2), especially smelters (OR = 15.0, 95% CI = 2.8–151).* ***Conclusion:*** *These findings suggest that maternal residential proximity to industries might be associated with oral clefts in births to older mothers.* (J Occup Environ Med. *2006;48: 565–572*)

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Concerns have been raised about the potential effects that environmental hazards might have on reproductive outcomes. In a 1999 telephone survey among U.S. voters, 73% of the respondents thought that environmental factors had an important impact on birth defects.[1] Based on the findings of occupational studies, it is conceivable that low-level environmental exposures to emissions of certain chemicals might be associated with some types of birth defects. Results from several studies indicated elevated odds ratios for oral clefts, one of the more prevalent groups of birth defects, among women who worked with solvents.[2–5] Another study found that fathers who worked as chemical or foundry/smelter workers were more likely to have offspring with oral clefts.[6] Although exposures were far greater than those that would be encountered in the workplace, heavy metals (primarily lead and cadmium) and various industrial solvents have been found to induce cleft palate in animal models such as rats and mice.[7]

Few studies have examined the relation between oral clefts and maternal residential proximity to waste sites or industrial facilities. The results of studies conducted among New York[8] and California[9,10] residents and proximity to hazardous waste sites did not indicate any compelling associations between living within a mile of these sites and oral clefts in offspring. In a European study,[11] however, women who lived within 3 km (1.9 miles) of a hazardous waste site were more likely to deliver offspring with cleft palate than women living further away of

these sites. None of the aforementioned studies considered potential exposures to industrial emissions.

Cordier et al[12] assessed the relation between living in the vicinity of municipal solid waste incinerators (emissions of dioxins and metals) on risk of congenital malformations in France and found an excess of oral clefts among births in exposed communities. Although oral clefts were not specifically examined due to the small numbers of defects available for study, Bhopal et al[13] noted no overall increase of congenital anomalies in offspring among British women who lived in close proximity to steel and petrochemical industries compared with women who lived further away from these facilities. Neither of these studies accounted for maternal or paternal occupations that might have increased the likelihood of living near industrial facilities.

In this study, we investigated whether maternal residential proximity to waste sites or industrial facilities with reported air emissions, particularly solvents and heavy metals, increased risk for oral clefts. We also accounted for the potential confounding effect that maternal or paternal occupations with exposure to solvents or heavy metals might have on the relation between residential proximity to industrial sites with these emissions and oral clefts.

Subjects and Methods

Subjects

We identified 1996–2000 live births and fetal deaths with oral clefts in Texas from the Texas Birth Defects Registry, an active surveillance birth defects monitoring system. This Registry uses the Centers for Disease Control and Prevention modification of the British Pediatric Association (BPA) codes for birth defects, which in turn is a modification of the International Classification of Diseases, 9th Revision (ICD-9) codes. Cases with cleft palate without cleft lip (BPA codes: 749.000–749.090) and cleft lip without (BPA codes: 749.100–749.120) or with cleft palate (BPA codes: 749.200–749.220) were linked to their respective live birth or fetal death certificates that contained information about maternal addresses at birth, maternal demographic characteristics, tobacco use, and usual paternal and maternal occupation. We further classified these two groups of defects into whether they were isolated or not. "Isolated" was operationally defined as an infant or fetus having only one BPA code or having one major BPA code with all remaining defects being minor; the latter were taken from a list in Rasmussen et al.[14]

We obtained comparison births without documented birth defects from a larger project of residential proximity to environmental hazards and selected congenital malformations (neural tube defects, conotruncal heart defects, oral clefts, and chromosomal anomalies). These births were randomly selected from 1996–2000 live birth certificates and frequency-matched to case births by year of birth and public health region of maternal residence (11 regions in Texas).

Information about maternal and paternal usual occupation and place of employment was obtained from the computerized records of the live births. Occupational information was missing, however, on fetal death certificates for a total of 66 (3.3%) of the oral cleft cases. The Standard Occupational Classification system (SOC)[15] and the North American Industrial Classification System (NAICS)[16] were used to code parental occupation and industry, respectively. We classified occupations by whether exposures to solvents or heavy metals were likely (yes/no) based on information available in the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles, National Institute for Occupational Safety and Health (NIOSH) criteria documents, and the National Library of Medicine HazMap.[17] The Texas Department of State Health Services (DSHS) and Texas State University Institutional Review Boards for the protection of human subjects approved the study protocol.

Environmental Data

Information about Texas National Priority Listing (NPL) sites (contaminants present) was obtained from the ATSDR online Hazardous Substances Release/Health Effects Database (HazDat)[18] and the Texas Commission on Environmental Quality (TCEQ) online superfund database.[19] HazDat is ATSDR's scientific and administrative database developed to provide information on the release of hazardous substances from NPL hazardous waste sites or from emergency events. The database includes information on site characteristics, contaminants found, affected environmental media, impact on nearby populations, and other pertinent site data. Study investigators abstracted data about site contaminants at state superfund sites from paper and microfilmed records at the TCEQ repository in Austin, Texas. A total of 43 NPL sites and 70 state superfund sites were active during the study period. Site boundaries were digitized from Digital Orthophoto Quarter Quads (DOQQ) images with a 1-meter resolution; images were obtained from the Texas Natural Resources Information System.

We obtained site and air emission information about Texas industrial facilities from the U.S. Environmental Protection Agency (EPA) Toxic Release Inventory (TRI) program.[20] The online TRI databases contain the names of facilities required to report under section 313 of the Emergency Planning and Community Right-to-Know Act and include information about location, year of report, chemicals released, and type of industry. We further classified these industries by whether they were a petroleum refinery (SIC major group 29: Petroleum Refining and Related Industries), primary metals or smelter facility (SIC major group 33: Primary Metals Industries), or a chemical industry (SIC major group 28: Chemicals and Allied Products). Although the online databases included industry-reported lati-

tudes and longitudes, our review of a sample of these geocodes revealed several errors; therefore, we geocoded the addresses in the databases to increase positional accuracy.

We classified site contaminants at NPL and state superfund sites and air releases from TRI industries by whether heavy metals or solvents were present or released. Solvents were further classified by structural categories (eg, aromatic hydrocarbons, alkyl halides). The oral cleft and comparison births and environmental data were combined to create a comprehensive geographic information system (GIS) within the ArcGIS environment. Maternal addresses at birth were related to hazardous waste site boundaries and street addresses of TRI industrial facilities; actual distances within 10 miles of these sites and facilities were linked to the oral cleft case and comparison records.

Data Analysis

We used logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for oral clefts in relation to maternal residential proximity to hazard waste sites and industrial facilities; exact logistic regression was used in analyses with sparse data.[21] A distance of less than 1 mile was used to define residential "proximity" to waste sites or industrial facilities. The referent group in the analyses of proximity to hazardous waste sites included all women who lived 1 mile or more from the boundaries of NPL or state superfund sites. Women who lived 1 mile or more from the street addresses of industrial facilities served as the referent group for all analyses pertaining to residential proximity to these facilities.

We considered the following variables as covariates: year of birth (1996–2000); public health region of maternal residence (11 regions in Texas); maternal age (<20, 20–24, 25–29, 30–34, 35+ years); maternal race/ethnicity (non-Hispanic white, Hispanic white, black, other); maternal education (0–8, 9–11, 12, 13–15, 16 or more years); and maternal tobacco use (yes/no). Analyses of maternal residential proximity to industrial facilities with solvent or heavy metals releases included adjustment for parental occupations with potential exposures to these substances (yes/no). Adjustment for year of birth, maternal age, and public health region of maternal residence had minimal or no effects on risk estimates and were not included as main effects in the final analyses. However, we examined the effect of various maternal age groups on the risk estimates of oral clefts associated with maternal residential proximity to waste sites and industrial facilities.

Misclassification of maternal proximity to waste sites and industrial facilities could have been introduced by using maternal address at delivery instead of address during the periconceptional period (3 months before to 3 months after conception). We assessed the impact of potential misclassification on risk estimates by comparing the odds ratios obtained from using maternal address at delivery with odds ratios obtained from the Texas portion of the National Birth Defects Prevention Study (NBDPS) in which information regarding maternal residence during the periconceptional period is available. The methodology of the NBDPS has been described in detail elsewhere.[22] In the NBDPS, women are questioned about where they lived 3 months before conception until birth of the index pregnancy. We restricted these analyses to the years 1998–2000 and the western and southern regions of Texas so that study years and populations were similar between the two analyses. Although the comparison groups were different, considerable overlap of oral cleft cases would be expected between these studies.

Results

A total of 2013 births were identified with oral clefts and linked to their birth or fetal death certificates, including 1289 births with cleft lip with or without cleft palate and 724 births with cleft palate alone. Of these, 883 of the cleft lip and 362 of the cleft palate defects were isolated.

Table 1 shows the demographic, behavioral, and occupational characteristics of case and comparison mothers. Compared with control mothers, mothers of cleft lip cases were somewhat more likely to be Hispanic or less educated. Mothers of cleft palate cases were more likely to be non-Hispanic white or smokers. The three groups were similar with respect to parental occupational exposures to solvents or heavy metals. Approximately 89% ($N = 1136$) of cleft lip maternal addresses, 88% ($N = 645$) of cleft palate maternal addresses, and 88% ($N = 4368$) of comparison birth maternal addresses were successfully geocoded and available for study.

Approximately 2.6% of mothers of births with cleft lip, 1.7% of mothers of births with cleft palate, and 2.7% of mothers of comparison births lived within 1 mile of an NPL or state superfund waste site. Table 2 summarizes the relation between maternal residential proximity to waste sites and oral clefts by waste site characteristics. With adjustment for maternal race/ethnicity, education, and tobacco use, odds ratios were consistent with unity for the associations between these defects and maternal residential proximity to NPL sites, state superfund sites, and sites contaminated with solvents or heavy metals. Although numbers of exposed cases were too few to examine these relations specifically for isolated cleft lip or palate, we analyzed the relation between maternal proximity to waste sites and isolated oral clefts as a single group. Results of these analyses were consistent with those found with all cleft lip and cleft palate cases; women who lived within 1 mile of one or more hazardous waste sites were not more likely to deliver offspring with isolated oral clefts (adjusted OR = 0.84, 95% CI = 0.54–1.3).

Women in the study were more likely to live within 1 mile of industrial facilities than waste sites includ-

TABLE 1
Characteristics of Oral Cleft Case and Comparison Births, Texas, 1996–2000

Characteristic	Control Births (*N* = 4,965)		Cases With Cleft Lip With or Without Cleft Palate (*N* = 1,289)			Cases With Cleft Palate Alone (*N* = 724)		
	N	Percent	N	Percent	Odds Ratio	N	Percent	Odds Ratio
Maternal race/ethnicity								
White, non-Hispanic	1,921	38.7	466	36.2†	Referent	333	46.0†	Referent
Black	502	10.1	92	7.1	0.76	54	7.5	0.62
Hispanic	2,393	48.2	679	52.7	1.2	313	43.2	0.75
Other	146	2.9	52	4.0	1.5	24	3.3	0.95
Maternal age (yr)								
<20	834	16.8	193	15.0†	0.81	123	17.0	1.2
20–24	1,406	28.3	400	31.0	Referent	172	23.8	Referent
25–29	1,313	26.4	341	26.5	0.91	201	27.8	1.3
30–34	916	18.4	208	16.1	0.80	140	19.4	1.3
35–39	413	8.3	121	9.4	1.0	76	10.5	1.5
>39	83	1.7	26	2.0	1.1	11	1.5	1.1
Maternal education (yr)								
0–8	547	11.2	169	13.4‡	1.3	71	10.0	0.93
9–11	1,147	23.4	298	23.7	1.1	163	23.0	1.0
12	1,532	31.3	408	32.5	1.2	225	31.7	1.1
13–15	815	16.6	185	14.7	0.99	131	18.5	1.2
16+	856	17.5	197	15.7	Referent	119	16.8	Referent
Maternal smoking								
Yes	335	6.8	103	8.1	1.2	72	10.0†	1.5
No	4,589	93.2	1,174	91.9	Referent	646	90.0	Referent
Potential occupational exposures*								
Maternal—solvents	92	1.9	18	1.5	0.79	7	1.0	0.52
Maternal—metals	95	1.9	24	2.0	1.0	12	1.7	0.88
Paternal—solvents	919	22.6	235	24.1	1.1	117	20.3	0.87
Paternal—metals	1,276	31.4	320	32.8	1.1	167	29.0	0.89
Maternal addresses geocoded								
Yes	4,368	88.0	1,136	88.1	—	645	89.1	—
No	597	12.0	153	11.9	—	79	10.9	—

*Information about occupation missing for 461 oral cleft case fathers, 903 comparison birth fathers, 100 oral cleft case mothers, and 76 comparison birth mothers. Referent categories are case or control fathers and mothers who had job titles that were not likely to have the respective exposures of interest. Metal exposures are to those classified as heavy metals.

†$P < 0.05$ for differences in group proportions between case and control mothers.

‡$P = 0.058$.

ing 14% of mothers of births with cleft lip, 15% of mothers of births with cleft palate, and 14% of mothers of comparison births. Overall, minimal association was found between oral clefts in offspring and living within 1 mile of industrial facilities, including chemical industries, smelters, petroleum refineries, or facilities with air releases of heavy metals or solvents (Table 3); all 95% confidence intervals of the odds ratios included 1.0. Furthermore, isolated oral clefts were not associated with maternal residential proximity to these facilities (OR = 1.0, 95% CI = 0.85–1.3).

Maternal age modified the risk estimates of oral clefts associated with maternal residential proximity to industrial facilities but had no effect on risk estimates associated with proximity to hazardous waste sites. Although maternal age did not modify risk estimates in the younger age groups, women who were 35 years or older were more likely to give birth to offspring with cleft lip, cleft palate, or an isolated oral cleft if they lived within 1 mile of any industrial facility with reported air emissions (range of ORs = 2.0–2.4), within 1 mile of a metals or smelter facility (range of ORs = 8.3–15.0), or within 1 mile of a facility with air emissions of heavy metals (range of ORs = 2.7–4.2) (Table 4). Some association was also seen between these defects and maternal proximity to industrial facilities with air emissions of solvents (range of ORs = 1.4–2.2), although the 95% confidence limits around all these odds ratios were consistent with unity.

In the Texas portion of the NBDPS, 140 cases with oral clefts and 267 controls with estimated delivery dates during 1998–2000 were available to assess the effects of potential misclassification of maternal residence on risk estimates. Approxi-

TABLE 2
Relation Between Maternal Residential Proximity to Hazardous Waste Sites and Oral Clefts in Offspring, Texas, 1996–2000

	Cleft Lip With or Without Cleft Palate			Cleft Palate Alone		
Residential Characteristic	Ca/Co	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	Ca/Co	Unadjusted Odds Ratio (95% CI)	Adjusted odds Ratio* (95% CI)
One or more miles from waste site	1,106/4,251	1.0 (Referent)	1.0 (Referent)	634/4251	1.0 (Referent)	1.0 (Referent)
Within 1 mile of any waste site	30/117	0.99 (0.66–1.5)	0.91 (0.60–1.4)	11/117	0.63 (0.34–1.2)	0.60 (0.31–1.2)
Within 1 mile of National Priority List site	8/47	0.65 (0.31–1.4)	0.58 (0.26–1.3)	3/47	0.43 (0.13–1.4)	0.47 (0.14–1.5)
Within 1 mile of state superfund site	22/78	1.1 (0.67–1.7)	1.0 (0.64–1.7)	8/78	0.69 (0.33–1.4)	0.64 (0.29–1.4)
Within 1 mile of site with heavy metals	30/102	1.1 (0.75–1.7)	0.95 (0.63–1.5)	9/102	0.59 (0.30–1.2)	0.55 (0.27–1.1)
Within 1 mile of site with solvents	18/60	1.2 (0.68–2.0)	1.1 (0.63–1.9)	6/60	0.67 (0.29–1.6)	0.60 (0.24–1.5)
Alkyl halide solvents	15/53	1.1 (0.61–1.9)	1.0 (0.56–1.8)	5/53	0.63 (0.25–1.6)	0.69 (0.27–1.7)
Aromatic hydrocarbons	17/51	1.3 (0.74–2.2)	1.2 (0.68–2.1)	5/51	0.66 (0.26–1.7)	0.71 (0.28–1.8)

*Odds ratio adjusted for maternal race/ethnicity, education, and tobacco use.
Ca indicates number of cases; Co, number of controls; CI, confidence interval.

TABLE 3
Relation Between Maternal Residential Proximity to Toxic Release Inventory (TRI) Facilities and Oral Clefts in Offspring, Texas, 1996–2000

	Cleft Lip With or Without Cleft Palate			Cleft Palate Alone		
Residential Characteristic	Ca/Co	Unadjusted Odds Ratio (95% CI)	Adjusted odds Ratio* (95% CI)	Ca/Co	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
One or more miles from TRI industrial facility with air emissions	977/3,760	1.0 (Referent)	1.0 (Referent)	551/3,760	1.0 (Referent)	1.0 (Referent)
Within 1 mile of facility with reported air emissions	159/608	1.0 (0.83–1.2)	0.96 (0.79–1.2)	94/608	1.1 (0.83–1.3)	1.1 (0.87–1.4)
Within 1 mile of a chemical facility	49/162	1.2 (0.84–1.6)	1.1 (0.80–1.6)	25/162	1.1 (0.69–1.6)	1.1 (0.74–1.8)
Within 1 mile of a petroleum refinery	10/28	1.4 (0.67–2.8)	1.3 (0.64–2.8)	2/28	0.49 (0.12–2.1)	0.52 (0.12–2.2)
Within 1 mile of a metals/ smelter facility	15/66	0.88 (0.50–1.5)	0.93 (0.52–1.6)	15/66	1.6 (0.88–2.7)	1.7 (0.97–3.1)
Within 1 mile of facility with heavy metals emissions	70/277	0.97 (0.74–1.3)	0.78† (0.55–1.1)	42/277	1.0 (0.74–1.4)	1.3† (0.92–1.9)
Within 1 mile of facility with solvent air emissions	99/375	1.0 (0.81–1.3)	0.84‡ (0.63–1.1)	54/375	0.98 (0.73–1.3)	1.3‡ (0.76–2.3)
Alkyl halide solvents	23/93	0.95 (0.60–1.5)	0.76‡ (0.41–1.4)	10/93	0.73 (0.38–1.4)	0.91‡ (0.43–1.9)
Aromatic hydrocarbons	61/249	0.94 (0.71–1.3)	0.85‡ (0.59–1.2)	36/249	0.99 (0.69–1.4)	1.2‡ (0.77–1.8)

*Odds ratio adjusted for maternal race/ethnicity, education, and tobacco use.
†Odds ratio also adjusted for parental occupations with potential exposures to heavy metals.
‡Odds ratio also adjusted for parental occupations with potential exposures to solvents.
Ca indicates number of cases; Co, number of controls; CI, confidence interval.

mately 3.6% of the case women and 3.4% of the control women lived within 1 mile of a hazardous waste site during the periconceptional period (OR = 1.1, 95% CI = 0.35–3.2). During the same period, a higher proportion of these women lived within 1 mile of industrial facilities, including 8.6% of the case women and 10.5% of the control women (OR = 0.80, 95% CI = 0.39–1.6). The percentages of women who lived within 1 mile of hazardous waste sites did not change when analyses were restricted to res-

TABLE 4
Relation Between Maternal Residential Proximity to Toxic Release Inventory (TRI) Industrial Facilities and Oral Clefts in Offspring Among Women 35 Yr or Older

	Cleft Lip With/Without Cleft Palate (*N* = 135)		Cleft Palate Alone (*N* = 80)		Isolated Oral Clefts* (*N* = 113)		Controls (*N* = 452)
Residential Characteristic	**No.**	**OR† (95% CI)**	**No.**	**OR† (95% CI)**	**No.**	**OR† (95% CI)**	**No.**
One or more miles from any TRI industrial facility with air emissions	111	1.0 (Referent)	64	1.0 (Referent)	90	1.0 (Referent)	405
Within 1 mile of facility with reported air emissions	24	2.0 (1.1–3.5)	16	2.2 (1.1–4.3)	23	2.4 (1.3–4.2)	47
Within 1 mile of a metals/ smelter facility	5	9.7 (1.5–105)	3	8.3 (0.93–100)	7	15.0 (2.8–151)	3
Within 1 mile of facility with heavy metals air emissions	10	2.7 (1.0–6.9)	8	3.8 (1.3–10.5)	12	4.2 (1.7–10.4)	14
Within 1 mile of facility with solvent air emissions	10	1.4 (0.59–3.3)	10	2.2 (0.85–5.2)	8	1.5 (0.63–3.4)	28

*Isolated cleft lip with or without cleft palate or isolated cleft palate.
†Odds ratios are adjusted for maternal race/ethnicity, education, and tobacco use.
OR indicates odds ratio; CI, confidence interval.

idences during the first trimester, but slightly fewer control women (10.2%) lived within 1 mile of an industrial facility during the first trimester than during the entire periconceptional period (OR = 0.84, 95% CI = 0.39–1.8). Restricting analyses of the vital records study data to the same regional areas and years of study as the Texas NBDPS, the odds ratios for oral clefts associated with maternal residence at delivery within 1 mile of a waste site or industrial facility were, respectively, 0.68 (95% CI = 0.33–1.4) and 0.81 (95% CI = 0.51–1.3).

Although the numbers of "exposed" case and control women aged 35 years or older were sparse in the Texas portion of the NBDPS study, case women in this age group were 3.8 times (95% CI = 0.32–47) more likely than control women to live within 1 mile of an industrial facility. This odds ratio, although consistent with unity, is higher than that obtained for maternal address at delivery in the vital records study for the corresponding regions (OR = 1.7, 95% CI = 0.35–8.1) or for the entire study population for 1996–2000 (OR = 2.4, 95% CI = 1.3–4.2).

Discussion

In this study, women who lived within 1 mile of a hazardous waste site undergoing assessment and/or remediation were not more likely to have offspring with oral clefts. This finding is consistent with the lack of association found between living near waste sites and oral clefts in studies conducted in New York[8] and California.[9,10] Among women in New York State, Geschwind et al[8] noted an odds ratio of 1.2 (95% CI = 0.87–1.5) for oral clefts associated with a maternal address at delivery within 1 mile of a hazardous waste site. Croen et al[9] examined the relation between a periconceptional address in close proximity to waste sites and selected congenital malformations, including oral clefts. Odds ratios for oral clefts associated with residential proximity to these sites ranged from 0.5 to 1.4, depending on the distance (1/4 or 1 mile) or site (type of waste site or contaminants present). Neither of these studies reported odds ratios specifically for cleft palate or cleft lip with or without cleft palate. In a European study,[11] women who lived within 3 km (1.9 miles) of a landfill site were 1.6 times (95% CI = 0.77–3.4) more likely to have offspring with cleft palate. In contrast, women in the present study who lived within 3 km of any hazardous waste sites were not more likely to have offspring with cleft palate (OR = 0.86, 95% CI = 0.61–1.2).

Overall, the results of this study did not indicate increased risks for oral clefts with a maternal residence at delivery within 1 mile of an industrial facility with reported air emissions. However, we observed a twofold increased risk for these defects (cleft lip with or without cleft palate, cleft palate, and isolated oral clefts) among women 35 years or older who lived within 1 mile of one or more of these facilities. Moreover, a maternal residence within 1 mile of a smelter or a facility with air emissions of heavy metals was even more strongly associated with oral clefts in offspring. In the southeast region of France, women were somewhat more likely to have offspring with oral clefts (OR = 1.3, 95% CI = 1.1–1.6) if they lived in the vicinity of municipal solid waste incinerators with emissions of dioxins and metals (eg, cadmium, lead, and mercury).[12] The investigators did not specifically examine the effect of maternal age on this association.

In the present study, we used maternal address at birth to determine residential proximity to waste sites and industrial facilities. However, maternal residence during the first trimester would correspond to the relevant period of the morphogenesis

of oral clefts. The period shortly before conception would be the relevant period to study the impact of potential paternal exposures. Previous studies have indicated that 20% to 25% of women move one or more times between conception and delivery.[23,24] On the other hand, older women (35 years or older) were less likely to move than younger women in these studies. Therefore, although some misclassification of maternal residence probably occurred in the present study, the addresses of older women during the periconceptional period would be less likely misclassified than the addresses of younger women by using maternal address at delivery.

We were able to assess the potential impact of this misclassification on risk estimates in the western and south central regions of Texas that are part of the National Birth Defects Prevention Study. Although the risk estimates of oral clefts associated with maternal proximity to waste sites were somewhat different between the two studies, the overall conclusions of the two studies were similar in that maternal residential proximity to waste sites or industrial facilities was not associated with oral clefts in offspring. Among women 35 years or older, however, the association between maternal residence near industrial facilities during the periconceptional period and oral clefts was stronger than that of maternal address at delivery near these facilities and oral clefts. The numbers of exposed older women in both substudies were sparse, however, and therefore these risk estimates should be interpreted with caution.

We used the distance between maternal residences and waste and industrial sites as a proxy for potential exposure. Such an approach probably introduced more misclassification of exposure to contaminants at waste sites than to reported air emissions of chemicals from industrial sites. Overlap of exposures also occurred in some instances, eg, facilities occasionally reported releases of both solvents and heavy metals and some women lived within 1 mile of both an industrial facility and a hazardous waste site. However, numbers of women who lived within 1 mile of both types of sites were relatively small. Of women who lived within 1 mile of an industrial facility, 4 (4.3%) mothers of cleft palate cases, 8 (5.3%) mothers of cleft lip cases, and 40 (6.6%) mothers of comparison births also lived within 1 mile of a hazardous waste site.

Because information about folic acid and vitamin intake was not available on vital records, we were unable to adjust risk estimates for these variables. In the Texas portion of the NBDPS, control women who denied using folic acid within 1 month before or after conception were more likely to live near hazardous waste sites or industrial facilities than women who reported taking these supplements.[25] We were able to partly account for this potentially confounding factor when analyzing the vital record data with adjustment for maternal race/ethnicity and education, maternal characteristics that are correlated with folic acid use.[26,27]

In conclusion, although overall maternal proximity to hazardous waste sites or industrial facilities was not associated with oral clefts in offspring, older mothers who lived near industrial facilities, particularly smelters and/or facilities with heavy metals emissions, were more likely to have offspring with oral clefts than women who lived further away from these facilities. Previous studies of the relation between maternal residential proximity to waste sites or industrial facilities and oral clefts have not reported risk estimates by maternal age. Recently, advanced maternal age has been discovered to modify the risk of other adverse reproductive outcomes associated with chemical exposures. In a study of trichloroethylene-emitting sites and congenital heart defects in Milwaukee, Wisconsin, Yauck et al[28] observed over a threefold risk of these defects among the offspring of older women (≥38 years) who lived within 1.32 miles of at least one of these sites compared with offspring of older, unexposed mothers. At a U.S. Marine Corps base in North Carolina,[29] infants of older women (≥35 years) who were exposed to tetrachloroethylene in drinking water had lower mean birth weights and were more likely to be small for gestational age than infants among unexposed women in the same age group. In their discussion of the study findings, Sonneland et al[29] suggested that some fetuses may be more susceptible than others to chemical insults such as those of older mothers. Additional studies of sufficient size and power will be needed to either support or refute the hypothesis that advanced maternal age increases the chances of chemically induced adverse reproductive outcomes.

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