Hypospadias and Residential Proximity to Pesticide Applications

WHAT'S KNOWN ON THIS SUBJECT: Some studies suggest a contribution of environmental exposures such as pesticides to risk of hypospadias, whereas others do not. One of the challenges that has limited current knowledge is the lack of detailed exposure data.

WHAT THIS STUDY ADDS: This study examined a more detailed assessment of exposure to pesticides than previous studies. Exposure assignments, whether to groups of chemicals, specific chemicals, or a composite involving a number of chemicals, showed a general lack of association with hypospadias.

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KEY WORDS

hypospadias, pesticides, environment, birth defects, endocrine disruptors

ABBREVIATIONS

BPA—British Pediatric Association
CI—confidence interval
DOC—date of conception
DPR—Department of Pesticide Regulation
DWR—Department of Water Resources
EPA—US Environmental Protection Agency
LMP—last menstrual period
OR—odds ratio
PLSS—public land survey section

Dr Carmichael conceptualized and designed the study and drafted the initial manuscript; Dr Yang carried out the analyses and reviewed and revised the manuscript; Drs Wolff and Roberts conducted the pesticide exposure assessment and reviewed and revised the manuscript; Dr Kegley developed the pesticide exposure matrix and reviewed and revised the manuscript; Drs Guo and English assisted with the pesticide exposure assessment and reviewed and revised the manuscript; Dr Lammer conducted clinical review of cases and reviewed and revised the manuscript; Dr Shaw assisted with the study design and reviewed and revised the manuscript, and all authors approved the final manuscript as submitted.

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abstract

BACKGROUND: Experimental evidence suggests pesticides may be associated with hypospadias.

OBJECTIVE: Examine the association of hypospadias with residential proximity to commercial agricultural pesticide applications.

METHODS: The study population included male infants born from 1991 to 2004 to mothers residing in 8 California counties. Cases ($n = 690$) were ascertained by the California Birth Defects Monitoring Program; controls were selected randomly from the birth population ($n = 2195$). We determined early pregnancy exposure to pesticide applications within a 500-m radius of mother's residential address, using detailed data on applications and land use. Associations with exposures to physicochemical groups of pesticides and specific chemicals were assessed using logistic regression adjusted for maternal race or ethnicity and age and infant birth year.

RESULTS: Forty-one percent of cases and controls were classified as exposed to 57 chemical groups and 292 chemicals. Despite >500 statistical comparisons, there were few elevated odds ratios with confidence intervals that excluded 1 for chemical groups or specific chemicals. Those that did were for monochlorophenoxy acid or ester herbicides; the insecticides aldicarb, dimethoate, phorate, and petroleum oils; and adjuvant polyoxyethylene sorbitol among all cases; 2,6-dinitroaniline herbicides, the herbicide oxyfluorfen, and the fungicide copper sulfate among mild cases; and chloroacetanilide herbicides, polyalkyloxy compounds used as adjuvants, the insecticides aldicarb and acephate, and the adjuvant nonyl-phenoxy-poly(ethylene oxy)ethanol among moderate and severe cases. Odds ratios ranged from 1.9 to 2.9.

CONCLUSIONS: Most pesticides were not associated with elevated hypospadias risk. For the few that were associated, results should be interpreted with caution until replicated in other study populations. *Pediatrics* 2013;132:e1216–e1226

Hypospadias is a congenital malformation in which the urethral opening is on the ventral side of the penis rather than the tip. It affects 4 to 6 male infants per 1000 male births.^{1–3} In most cases the cause is unknown.^{4,5} The public health impact is significant, given that it usually involves surgical correction and may be associated with impaired sexual function and psychosocial difficulties later in life.^{6,7}

Hypospadias can be induced experimentally by exposures that interfere with androgen and estrogen synthesis and signaling pathways during sexual differentiation.^{8–11} Thus, concern exists that endocrine disruptors (ie, exogenous substances that interfere with hormones) may cause hypospadias in humans, although the applicability of animal studies to humans is uncertain. Pesticides, some of which are endocrine disruptors, have received the most attention. A meta-analysis indicated that maternal occupational pesticide exposure was associated with a modest increase in hypospadias risk (odds ratio [OR] 1.4, 95% confidence interval [CI] 1.0–1.8).¹² Three subsequent large maternal occupation–based studies have not suggested elevated risk.^{13–15} Studies examining maternal serum levels of persistent pesticides DDE^{16–20} and chlordane²¹ and 1 study that estimated exposure based on residential proximity to certain crops²² also do not provide evidence for association. These studies are limited by relatively crude measures of exposure, small sample sizes, or investigation of a limited set of specific compounds. Few studies have investigated pesticide exposures in pregnant women's residential environments as possible risks for abnormal fetal development, in particular hypospadias.

We examined whether residential proximity to commercial pesticide applications during early pregnancy

was associated with elevated hypospadias risk. Analyses incorporated a large range of pesticides, in the spirit of being as comprehensive as possible with regard to capturing this aspect of the “exposome.” The study population was from the Central Valley of California, one of the highest pesticide use areas in the United States.

METHODS

Study Subjects

The study population included all male infants born from 1991 to 2004 to mothers who were residents of 8 California Central Valley counties (Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, Tulare). California Birth Defects Monitoring Program staff actively ascertained cases by reviewing medical records at hospitals and genetic centers in study counties.²³

Cases were classified by severity based on reported anatomic position of the urethral meatus. Mild cases were those for which the meatus was limited to the coronal or glanular penis (British Pediatric Association [BPA] codes 752.605, 752.625), moderate if it was on the penile shaft, severe if it was at the penoscrotal junction or perineal area (BPA codes 752.606, 752.607, 752.626, 752.627), and not otherwise specified if the location was insufficiently described (BPA codes 752.600, 752.620). Assignment of severity was finalized based on review by a medical geneticist (E.J.L. or Dr Cynthia Curry).²⁴ Mild cases without chordee (ie, no penile curvature, BPA 752.605) were not ascertained during the study period, except for 2004; thus, mild cases in this study are primarily those with chordee. Cases with known single-gene disorders or chromosomal abnormalities were excluded. Cases were linked with birth certificates using personal identifiers. A total of 772 cases were available for study.

The underlying study population included 415 347 nonmalformed (ie, had no major congenital malformations) liveborn male infants. We randomly selected 2460 as male controls, in proportion to the underlying birth population for each year, to give an approximate 3:1 ratio of controls to cases. Information on the following covariates was derived from birth certificates: maternal race or ethnicity, education, age, and parity; plurality; and infant birth weight and gestational age at delivery. Birth certificate accession numbers were used to request access to maternal residential addresses at delivery.

Pesticide Exposure Assessment

We assigned a time window of exposure for each study subject relative to reported date of conception (DOC), derived from reported last menstrual period (LMP) plus 14 days. The time window evaluated was 1 to 14 weeks of embryonic age (ie, 1–98 days after DOC). This window approximately encompasses the time of genital tubercle development (the anlage of the penis) and urethral development and closure,²⁵ as well as several weeks preceding it, given the potential physiologic persistence of some pesticides. LMP was derived primarily from birth certificates, with replacement from medical record data for 35 cases and 45 controls. LMP was considered missing if it resulted in calculated gestational age ≥ 308 days (44 weeks). We imputed LMP for 31 cases and 201 controls as the median among cases or controls with nonmissing LMP (ie, 275 days for cases, 277 for controls). Pesticide data were available starting in 1991. Therefore, deliveries that occurred in 1991 but had a DOC in 1990 were excluded (47 cases, 155 controls).

The California Environmental Health Tracking Program Geocoding Service geocoded subjects' addresses.²⁶ Geocoding was successful for 95.2% of

cases (690/725) and 95.6% of controls (2203/2305).

To estimate pesticide applications, we obtained Pesticide Use Reporting records from the California Department of Pesticide Regulation (DPR) describing agricultural pesticide applications within the study area after January 1, 1991. These data are spatially referenced to public land survey sections (PLSSs). Following the method of Rull and Ritz,²⁷ we spatially refined PLSS polygons through the overlay of matched land use survey field polygons provided by the California Department of Water Resources (DWR); that is, we refined the pesticide application to a specific field polygon, which is smaller than the 1-square-mile area of the PLSS polygon. We matched each DPR record to the land use survey conducted closest in time to the application date (DWR surveys are conducted roughly every 5–7 years in each county). Matching is based on location and crop type, as specified in both the DPR and DWR records. Infrequently rotated crops, such as orchard crops and vineyards, were matched 1-to-1, whereas frequently rotated crops, such as field and truck crops, were grouped together in a single category, and nonagricultural land uses were subtracted from PLSS polygons when no DPR crop types were matched to available DWR polygons. Of the total applications (and active ingredient poundage) recorded by the DPR spanning 1991 to 2004, 86.7% (91.8% by poundage) were successfully linked to DWR land use survey polygons: 31.7% (51.5% by poundage) were matched on individual crop, 52.3% (37.5% by poundage) were under the “frequently rotated” category, and 2.6% (2.7% by poundage) were refined, subtracting nonagricultural land use polygons from PLSS polygons. For the remaining 13.3% of applications (8.2% by poundage), no field polygon in the specified

PLSS grid was identified with an appropriate DWR land use survey or land use polygon, so no spatial refinement was possible; that is, we used the spatial reference of the 1-square-mile PLSS grid for these applications. We determined temporal proximity by comparing dates of applications in the DPR data set (accurate within a few days) with the time window of exposure for each subject.

To assign exposure, we used the California Environmental Health Tracking Program Pesticide Linkage Tool, a custom-developed Java (Oracle, Redwood Shores, CA) application that incorporates the GeoTools Java GIS Toolkit, version 2.7 (open source, <http://geotools.codehaus.org/>) for geographic information system data management and spatial analysis.²⁸ We calculated the sum of pounds of pesticides used during the relevant time window within a 500-m radius of a geocoded point,²⁹ intersecting DWR land use or PLSS polygons with the buffer and assuming homogeneous distribution of pesticides within each of these polygons.

Selection of Pesticide Compounds

We assessed whether subjects were exposed to 566 individual chemicals and 71 physicochemical groupings of chemicals that had the same chemical classification and proven or putative mechanism of action (eg, organophosphates) and were applied at >100 lb in any county in any study year.³⁰ Low-toxicity chemicals such as biopesticides (eg, microbial pesticides, soaps, essential oils), low-toxicity inorganic compounds (eg, sulfur), and other compounds determined by the US Environmental Protection Agency (EPA) to have low toxicity³¹ were excluded. In addition, compounds were flagged as having reproductive or developmental toxicity based on the California Proposition 65 list³² or as endocrine disruptors,^{33–35} to create

exposure scores. Chemicals with a US EPA–determined reference dose based on a toxicological study with a reproductive or developmental endpoint were also flagged.³¹

Analyses

Risks associated with pesticide exposures were estimated using logistic regression models. Models included maternal race or ethnicity and age and infant birth year as potential confounders. Maternal race or ethnicity and age were included because they were associated with any pesticide exposure among controls (data not shown). Year was included to account for potential changes in the prevalence of hypospadias or use of particular pesticides over time. The models included 690 cases (170 mild; 173 moderate to severe, analyzed together because of sample size considerations; and 347 not otherwise specified) and 2195 controls with complete covariate data. To focus on comparisons likely to have the most precise estimates yet use data fully, we did the following. For pesticides with ≥15 exposed cases, risks were estimated that compared tertiles of exposure versus no exposure, based on distributions among controls. For pesticides with 5 to 14 exposed cases, risks were estimated for any versus no exposure. Risks were not estimated for pesticides with <5 exposed cases. We created overall exposure scores by summing the total number of chemicals or groups, endocrine disruptors, Proposition 65 chemicals, or EPA reproductive and developmental toxicants to which each subject was exposed. We examined the association of hypospadias with these scores specified as continuous and categorical variables (exposed subjects were divided into tertiles based on the control distributions).

RESULTS

Relative to controls, mothers of case infants were more likely to be non-Hispanic white, have a higher education, and be nulliparous, and case infants were more likely to be low birth weight, delivered <37 weeks, and multiple births (Table 1). Eighty-six percent ($n = 590$) of cases were isolated (ie, involved no other major nongenital congenital anomalies).

Subjects were exposed to 57 groups of chemicals and 292 individual chemicals during the first 14 weeks of gestation within 500 m of their residence. A total of 41.4% of cases (286/690) and 41.0% of controls (899/2195) were classified as exposed to any pesticides. The 5 groups

to which controls were most frequently exposed were polyalkyloxy compounds (25%), glyphosate (22%), organophosphorus insecticides (22%), simple alcohols or ethers (19%), and petroleum derivatives (15%). The 5 chemicals to which controls were most frequently exposed were the isopropylamine salt of the herbicide glyphosate (22%), isopropyl alcohol (19%, a simple alcohol used as a solvent), nonyl-phenoxy-poly (ethylene oxy)ethanol (18%, a polyalkyloxy compound used as an adjuvant in pesticide formulations), paraquat dichloride (11%, a bipyridylium herbicide), and oxyfluorfen (11%, a diphenyl ether herbicide).

Table 2 shows the number of chemical groups and chemicals that met sample

size criteria for risk estimation. Tables 3 and 4 show results for associations that had an OR ≤ 0.5 or ≥ 2.0 or for which the CI excluded 1. The only chemical groups with CIs that excluded 1 were: monochlorophenoxy acid or ester herbicides (OR 2.6 for highest tertile versus no exposure) among all cases, 2,6-dinitroaniline herbicides (OR 2.1 for lowest tertile) among mild cases, and chloroacetanilide herbicides (OR 2.8 for any exposure) and polyalkyloxy compounds (OR 1.9 for lowest tertile) among moderate to severe cases.

Specific chemicals with CIs excluding 1 were the insecticides aldicarb (OR 2.7 for lowest tertile exposure), dimethoate (OR 2.5 for lowest tertile exposure), phorate (OR 2.8 for any exposure), and paraffin-based petroleum oil (MCIAL 401) (OR 1.9 for middle tertile exposure) and adjuvant polyoxyethylene sorbitol (OR 3.4 for any exposure) among all cases; oxyfluorfen (OR 2.0 for middle tertile exposure) and copper sulfate (OR 2.9 for any exposure) among mild cases; and aldicarb (OR 2.5 for any exposure), acephate (OR 2.6 for any exposure), and nonyl-phenoxy-poly (ethylene oxy)ethanol (OR 2.0 for lowest tertile) among moderate to severe cases.

Table 5 shows ORs for sums of specific types of pesticide exposures. Results did not provide evidence that hypospadias risk increased with exposure to increasing numbers of pesticide groups, endocrine disruptors, reproductive or developmental toxicants, or Proposition 65 listed chemicals.

DISCUSSION

We examined the association of hypospadias with residential proximity to agriculture-related pesticide applications in the Central Valley of California. Exposure assignments, whether to groups of chemicals, specific chemicals, or a composite involving total

TABLE 1 Descriptive Characteristics of Hypospadias Case Infants and Nonmalformed Controls

	Percentage of Cases ^a ($n = 690$)	Percentage of Controls ^a ($n = 2195$)	<i>P</i> Value ^b
Maternal race or ethnicity			
Non-Hispanic white	51.6	34.3	<.01
US-born Hispanic	17.4	23.6	
Foreign-born Hispanic	19.3	27.2	
Other	11.7	14.9	
Maternal education			
<High school	28.8	38.1	<.01
High school	36.4	33.4	
>High school	33.9	27.2	
Missing	0.9	1.3	
Maternal age (years)			
<25	43.5	47.8	.11
25–34	45.5	42.8	
≥35	11.0	9.4	
Parity			
0	44.5	35.7	<.01
1 or more	55.5	64.3	
Infant birth wt (g)			
500–1499	7.3	0.4	<.01
1500–2499	14.8	4.7	
≥2500	77.5	94.9	
Missing	0.4	<0.1	
Gestational age (wk)			
<37	20.0	9.5	<.01
≥37	75.8	82.7	
Missing	4.2	7.8	
Plurality			
Singleton birth	93.6	98.4	<.01
Multiple birth	6.4	1.6	
Year of birth			
1991–1995	46.5	44.0	<.01
1996–2000	36.5	30.3	
2001–2004	17.0	25.7	

^a Percentages may not equal 100 because of rounding.

^b *P* values from χ^2 tests.

TABLE 2 Number of Chemical Groups and Specific Chemicals That Met Case Count Criteria for Risk Estimation

No. of Exposed Cases	No. of Chemical Groups			No. of Specific Chemicals		
	All Cases	Mild Cases	Moderate to Severe Cases	All Cases	Mild Cases	Moderate to Severe Cases
≥15	29	11	11	53	9	6
5–14	18	10	16	69	30	33

The table shows the number of chemical groups and individual chemicals that had 15 or more exposed cases or 5 to 14 exposed cases, out of a total of 57 chemical groups and 292 individual chemicals to which any study subjects were exposed. Risks were only estimated for these chemical groups and specific chemicals.

number of chemicals, showed a general lack of association with hypospadias. The general lack of association agrees with recent studies indicating that hypospadias is not associated with maternal occupations that involve pesticide exposure^{13–15} or serum levels of the persistent pesticides chlordane²¹ and DDE.^{16–20} We are aware of 1 other study that examined residential proximity to agriculture-related pesticide applications.²² It too did not find an association with specific chemical exposures, but its exposures were derived from annual statewide summaries of applications to specific crop types. A few pesticide groups were associated with elevated hypospadias risk, but most were not. Among all cases, monochlorophenoxy acid or ester herbicides were associated with elevated risk. These compounds have short half-lives in humans (<48 hours) and tend to be known reproductive or developmental toxicants,³⁶ but exposure was rare (1.6% of controls). The 2,6-dinitroaniline herbicides (which include benfluralin, trifluralin, ethalfluralin, oryzalin pendimethalin, and prodi-amine) were associated with elevated risk of mild hypospadias. These compounds are moderately volatile, with vapor pressures higher than 10⁵ mm Hg at 25°C (ie, high potential for exposure via volatilization drift), they are lipophilic, their use was frequent (11% of controls were exposed), and trifluralin,^{37–39} prodi-amine,⁴⁰ and

pendimethalin^{40,41} are suspected endocrine disruptors. Chloracetanilide herbicides (metolachlor, acetochlor, and alachlor) and polyalkyloxy compounds used as adjuvants were associated with elevated risk of moderate to severe hypospadias. Many of the chemicals in these groups are suspected endocrine disruptors.^{34,39–42} Results for several specific chemicals also had elevated ORs and CIs that excluded 1. Among all cases, insecticides aldicarb, dimethoate, phorate, and paraffin-based petroleum oil and the adjuvant polyoxyethylene sorbitol were associated with elevated risk. The first 2 chemicals are known endocrine disruptors and reproductive or developmental toxicants.^{34,39} Phorate is an organophosphate, and polyoxyethylene sorbitol is a polyalkyloxy compound; phorate is a reproductive and developmental toxicant. Paraffin-based petroleum oil was part of the petroleum distillates group, one of the highest-use groups in California, with typically 20 to 30 million pounds used annually. Among mild cases, oxyfluorfen and copper sulfate were associated with elevated risk; neither is a known endocrine disruptor or reproductive or developmental toxicant.^{34,39} Among moderate and severe cases, aldicarb, acephate, and nonyl-phenoxy-poly (ethylene oxy)ethanol were associated with elevated risk, and all 3 are known endocrine disruptors.^{34,43,44} Among these chemicals, only 2 had exposure >5% among the controls: 11% were exposed to oxyfluorfen and 18% to

nonyl-phenoxy-poly(ethylene oxy)ethanol. These compounds have not previously been reported to be associated with hypospadias. Our study has several strengths, including the large sample size, population-based design, careful case ascertainment, and exposure assessment that was highly detailed, was spatially and temporally specific, and captured a broad spectrum of pesticides. Exposure assessment was not subject to recall bias, because it was derived from addresses. We expect selection bias to be minimal, given that exposure assessment was successful for 95% of subjects. Several limitations also merit discussion. Degree of severity was not available for many cases. Exposure assessment was based on address at delivery rather than conception. Misclassification of exposure could have occurred for women who moved. If moving is unrelated to case status, results would be biased toward the null; if not, the direction is unpredictable. Our assessment of residential proximity to pesticide applications was thorough but does not take into account other factors such as qualities of the pesticides and individuals' metabolism or behaviors that would affect exposures (eg, chemical half-lives and vapor pressure, wind patterns, cumulative exposures over time, an individual's ability to metabolize chemicals, and other exposure sources such as occupation or home use). However, it is also notable that most pesticides are prone to drift and detectable in air samples at locations beyond the application site,^{45,46} and residential proximity to pesticide-treated fields has been associated with household dust and urine levels.^{47–50} For many exposures, analysis of dose was not feasible because of limited sample size. For those for which dose was analyzed, results tended to suggest stronger

TABLE 3 ORs for Pesticide Chemical Groups and Hypospadias

Chemical Group	Application Amount (lb) ^a	No. Cases	No. Controls	Adjusted OR (95% CI) ^b
All cases				
Insect growth regulator	No exposure	684	2187	Reference
	Any exposure	6	8	2.51 (0.85–7.46)
Halogenated organic	No exposure	659	2080	Reference
	<17.11	11	38	0.92 (0.46–1.83)
	17.11–186.02	14	38	1.16 (0.62–2.17)
	≥186.03	6	39	0.48 (0.20–1.15)
Monochlorophenoxy acid or ester	No exposure	674	2160	Reference
	<0.43	2	11	NC
	0.43–2.31	4	13	1.12 (0.36–3.49)
	≥2.32	10	11	2.58 (1.07–6.18)
Organochlorine	No exposure	658	2093	Reference
	<2.04	15	33	1.44 (0.77–2.71)
	2.04–10.37	5	36	0.48 (0.19–1.24)
	≥10.38	12	33	1.13 (0.57–2.23)
Organotin	No exposure	674	2126	Reference
	<0.44	4	23	0.57 (0.19–1.66)
	0.44–3.72	8	23	1.11 (0.49–2.53)
	≥3.73	4	23	0.49 (0.17–1.44)
Phosphine	No exposure	684	2158	Reference
	Any exposure	6	37	0.48 (0.20–1.15)
Thiocarbamate	No exposure	672	2141	Reference
	<3.95	11	18	1.59 (0.74–3.42)
	3.95–21.96	4	19	0.68 (0.23–2.03)
	≥21.97	3	17	0.50 (0.15–1.75)
Mild cases				
2,6-Dinitroaniline	No exposure	148	1943	Reference
	<0.93	11	84	2.09 (1.07–4.08)
	0.93–6.74	6	84	1.08 (0.45–2.54)
	≥6.75	5	84	0.85 (0.34–2.17)
Moderate to severe cases				
Chloroacetanilide	No exposure	167	2165	Reference
	Any exposure	6	30	2.76 (1.12–6.75)
Phosphonoglycine	No exposure	146	1714	Reference
	<1.22	9	159	0.68 (0.34–1.37)
	1.22–6.92	6	162	0.44 (0.19–1.01)
	≥6.93	12	160	0.88 (0.48–1.64)
Organophosphate	No exposure	144	1721	Reference
	<2.25	12	155	0.93 (0.50–1.72)
	2.25–15.72	6	163	0.46 (0.20–1.07)
	≥15.73	11	156	0.90 (0.47–1.70)
Polyalkyloxy compound	No exposure	119	1649	Reference
	<0.51	24	180	1.94 (1.21–3.10)
	0.51–3.12	13	186	1.01 (0.56–1.84)
	≥3.13	17	180	1.38 (0.81–2.37)
Pyrethroid	No exposure	156	1962	Reference
	<0.10	3	76	0.46 (0.14–1.49)
	0.10–0.62	5	80	0.74 (0.29–1.85)
	≥0.63	9	77	1.54 (0.75–3.15)

^a Reflects pounds of pesticides applied within a 500-m radius of the mother's residential address during early pregnancy.

^b If at least 15 cases were exposed, tertiles of exposure were examined; if 5 to 14 cases were exposed, any versus no exposure was examined. ORs were adjusted for maternal race or ethnicity (non-Hispanic white, US-born Hispanic, foreign-born Hispanic, other) and age (continuous, in years) and infant birth year (continuous).

associations at lower rather than higher exposure levels; the explanation for this finding is uncertain. However, it is known that endocrine disruptors may exert

more potent effects at lower rather than higher doses and have nontraditional dose–response curves.⁵¹ The breadth of chemicals we examined was a strength

in that we captured as much of the pesticide “exposome” as possible but also a limitation (from a multiple-comparison perspective). Our risk score approach was an attempt to capture cumulative effects of exposure to multiple chemicals, but it was somewhat limited by its simplicity (ie, scores were sums of exposures, not weighted by other properties such as dose or toxicity).

As noted earlier, few previous studies have carefully studied the association of hypospadias with pesticide exposure. Results have been mixed. Our study had some statistically significant findings, but they have not been reported previously and need confirmation. In addition, studies with more direct measurement of pesticide exposure would be helpful, but we acknowledge that they are difficult to conduct.

We consider this study to be hypothesis-generating, given that we evaluated exposures to all reported pesticide applications in the study area rather than limiting evaluation to those for which we had prior knowledge about potential effects on urogenital development. Such effects have not been evaluated previously for most of the studied pesticides. Because of the hypothesis-generating approach, we conducted >500 statistical comparisons. The number of statistically precise findings we highlight is within the number of false positive results one would expect to observe under typical type I error considerations. We tried to maximize power of our comparisons and reduce their number by imposing sample size criteria. Because of the novel nature of our study and because we limited the number of risk estimates based on sample size criteria, we did not correct our results for multiple comparisons or restrict our presentation of results to strict criteria of statistical significance. That said, our “positive” results should be

TABLE 4 ORs for Specific Pesticide Chemicals and Hypospadias

Chemical Group ^a	Chemical Name	Application Amount (lb) ^b	No. Cases	No. Controls	Adjusted OR (95% CI) ^c
All cases					
n.a.	Chloropicrin	No exposure	669	2113	Reference
		<0.98	12	26	1.46 (0.73–2.94)
		0.98–14.21	4	29	0.46 (0.16–1.32)
		≥14.22	5	27	0.56 (0.21–1.48)
n.a.	Chlorothalonil	No exposure	671	2115	Reference
		<1.70	6	27	0.68 (0.28–1.68)
		1.70–12.58	10	27	1.19 (0.57–2.50)
		≥12.59	3	26	0.40 (0.12–1.34)
n.a.	Triforine	No exposure	685	2163	Reference
		Any exposure	5	32	0.45 (0.17–1.16)
Azole	Myclobutanil	No exposure	661	2070	Reference
		<0.15	14	41	1.04 (0.56–1.94)
		0.15–0.87	5	42	0.42 (0.16–1.06)
		≥0.88	10	42	0.75 (0.37–1.52)
Dithiocarbamate	Ziram	No exposure	674	2131	Reference
		<7.62	8	21	1.19 (0.52–2.73)
		7.62–37.41	3	21	0.43 (0.13–1.47)
		≥37.42	5	22	0.65 (0.24–1.74)
Monochlorophenoxy acid or ester	MCPA, dimethylamine salt	No exposure	674	2163	Reference
		<0.54	2	10	NC
		0.54–2.73	6	11	1.83 (0.66–5.07)
		≥2.74	8	11	2.12 (0.84–5.37)
N-Methyl carbamate	Carbofuran	No exposure	682	2185	Reference
		Any exposure	8	10	2.17 (0.84–5.61)
	Formetanate hydrochloride	No exposure	682	2135	Reference
		Any exposure	8	60	0.48 (0.23–1.03)
	Methomyl	No exposure	660	2080	Reference
		<0.45	13	37	1.22 (0.64–2.32)
		0.45–4.30	14	41	1.06 (0.57–1.98)
		≥4.31	3	37	0.27 (0.08–0.87)
	Aldicarb	No exposure	673	2163	Reference
		<3.48	8	10	2.69 (1.04–6.96)
		3.48–8.67	2	11	NC
		≥8.68	7	11	1.89 (0.72–4.99)
	Endosulfan	No exposure	683	2148	Reference
		Any exposure	7	47	0.48 (0.21–1.07)
Organophosphate	Diazinon	No exposure	641	2050	Reference
		<0.97	20	48	1.34 (0.78–2.30)
		0.97–5.29	8	49	0.49 (0.23–1.05)
		≥5.30	21	48	1.41 (0.83–2.40)
	Dimethoate	No exposure	652	2105	Reference
		<1.34	20	30	2.45 (1.36–4.39)
		1.34–5.44	9	29	0.85 (0.40–1.84)
		≥5.45	9	31	0.96 (0.45–2.04)
	Phosmet	No exposure	672	2111	Reference
		<1.21	3	28	0.32 (0.10–1.06)
		1.21–8.79	9	28	1.08 (0.50–2.34)
		≥8.80	6	28	0.69 (0.28–1.70)
	Methyl parathion	No exposure	685	2161	Reference
		Any exposure	5	34	0.46 (0.18–1.19)
	Phorate	No exposure	680	2182	Reference
		Any exposure	10	13	2.76 (1.19–6.44)
	Methidathion	Zero applications	668	2121	Reference
		<0.92	4	25	0.49 (0.17–1.43)
		0.92–5.74	9	25	1.05 (0.48–2.28)
		≥5.75	9	24	1.24 (0.57–2.71)
	Methyl parathion, other related	No exposure	685	2161	Reference
		Any exposure	5	34	0.46 (0.18–1.19)

TABLE 4 Continued

Chemical Group ^a	Chemical Name	Application Amount (lb) ^b	No. Cases	No. Controls	Adjusted OR (95% CI) ^c
Organoarsenic ^d	Cacodylic acid	No exposure	685	2165	Reference
		Any exposure	5	30	0.47 (0.18–1.24)
	Sodium cacodylate	No exposure	685	2165	Reference
Organotin	Fenbutatin-oxide	Any exposure	5	30	0.47 (0.18–1.24)
		No exposure	674	2126	Reference
		<0.44	4	23	0.57 (0.19–1.66)
		0.44–3.72	8	23	1.11 (0.49–2.53)
Phosphine	Aluminum phosphide	≥3.73	4	23	0.49 (0.17–1.44)
		No exposure	684	2158	Reference
		Any exposure	6	37	0.48 (0.20–1.15)
Petroleum derivative	Petroleum distillates, aromatic	No exposure	683	2186	Reference
		Any exposure	7	9	2.31 (0.84–6.36)
	Paraffin-based petroleum oil (MCIAL code 401)	No exposure	656	2105	Reference
		<0.51	5	30	0.51 (0.19–1.32)
		0.51–2.99	16	30	1.94 (1.04–3.62)
Polyalkyloxy compound	Polyoxyethylene sorbitol, mixed ethyl ester	≥3.00	13	30	1.35 (0.69–2.63)
		No exposure	683	2188	Reference
		Any exposure	7	7	3.40 (1.17–9.90)
	α-(p-Nonylphenyl)-omega-hydroxypoly (oxyethylene) with an average of 4.2 mol of ethylene oxide	No exposure	674	2136	Reference
		<0.05	5	20	0.79 (0.29–2.15)
		0.05–0.28	8	19	1.31 (0.56–3.05)
		≥0.29	3	20	0.48 (0.14–1.64)
Pyrethroid	Cyhalothrin, λ	No exposure	683	2183	Reference
		Any exposure	7	12	2.17 (0.84–5.64)
	Bifenthrin	No exposure	674	2161	Reference
		<0.13	7	11	2.30 (0.88–6.04)
		0.13–0.80	4	12	1.15 (0.36–3.62)
		≥0.81	5	11	1.33 (0.45–3.91)
Streptomycin	Streptomycin	No exposure	685	2188	Reference
		Any exposure	5	7	2.40 (0.74–7.76)
Mild cases					
n.a.	Benomyl	No exposure	164	2141	Reference
		Any exposure	6	54	2.18 (0.90–5.29)
n.a.	Oxyfluorfen	No exposure	144	1948	Reference
		<0.29	9	81	1.48 (0.72–3.05)
		0.29–1.53	13	84	2.03 (1.09–3.77)
		≥1.54	4	82	0.66 (0.24–1.86)
Dichlorophenoxy acid or ester ^d	2,4-D	No exposure	165	2154	Reference
		Any exposure	5	41	2.11 (0.80–5.56)
	2,4-D, triethylamine salt	No exposure	165	2154	Reference
		Any exposure	5	41	2.11 (0.80–5.56)
		Copper-containing compound	Copper hydroxide	No exposure	155
Copper-containing compound	Copper hydroxide	<5.82	7	67	1.34 (0.60–3.00)
		5.82–33.46	3	71	0.50 (0.16–1.63)
		≥33.47	5	68	1.01 (0.39–2.59)
		No exposure	162	2152	Reference
Copper-containing compound	Copper sulfate (basic)	Any exposure	8	43	2.88 (1.29–6.40)
		Moderate to severe cases			
N-Methyl carbamate	Aldicarb	No exposure	167	2163	Reference
		Any exposure	6	32	2.52 (1.03–6.18)
Organophosphate	Acephate	No exposure	166	2160	Reference
		Any exposure	7	35	2.58 (1.12–5.96)

TABLE 4 Continued

Chemical Group ^a	Chemical Name	Application Amount (lb) ^b	No. Cases	No. Controls	Adjusted OR (95% CI) ^c
Polyalkyloxy compound	Nonyl phenoxy poly (ethylene oxy) ethanol	No exposure	134	1792	Reference
		<0.33	19	132	2.00 (1.19–3.36)
		0.33–1.76	8	137	0.80 (0.38–1.67)
		≥1.77	12	134	1.26 (0.68–2.35)

^a n.a. (not applicable) indicates that the chemical was not part of a larger group.

^b Reflects pounds of pesticides applied within a 500-m radius of the mother's residential address during early pregnancy.

^c ORs are presented for chemical groups for which the OR was ≤0.5 or ≥2.0 or for which a CI excluded 1. OR was not calculated (NC) for cell count <3 in cases or controls. ORs were adjusted for maternal race or ethnicity and age and infant birth year.

^d All exposures to 2,4-D and 2,4-D, triethylamine salt were simultaneous (ie, derived from the same product and application).

interpreted with caution and need replication in other populations. It should also be reiterated that results did not suggest an association of hypospadias with most of the studied pesticides. Among the few that were associated, exposure tended to be infrequent in our

study area, which is known for high pesticide usage.

CONCLUSIONS

This study of residential proximity to agriculture-related pesticide applications,

which encompassed a broad range of specific chemicals, showed a general lack of association with hypospadias.

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TABLE 5 ORs for Sums of Specific Types of Pesticide Exposures and Hypospadias

	No. Controls (n = 2195)	No. Cases (n = 690)	Adjusted OR (95% CI) for All Cases ^a	No. Mild Cases (n = 170)	Adjusted OR (95% CI) for Mild Cases ^a	No. Moderate to Severe Cases (n = 173)	Adjusted OR (95% CI) for Moderate to Severe Cases ^a
No. of chemical groups with any exposure							
0	1307	407	Reference	108	Reference	99	Reference
1–3	295	91	0.99 (0.76–1.29)	12	0.50 (0.27–0.92)	23	1.04 (0.65–1.66)
4–8	295	108	1.18 (0.91–1.51)	29	1.28 (0.83–1.98)	32	1.48 (0.97–2.26)
9–27	298	84	0.92 (0.70–1.20)	21	0.94 (0.57–1.55)	19	0.88 (0.53–1.47)
Continuous	2195	690	1.00 (0.98–1.02), <i>P</i> = .93	170	1.01 (0.97–1.04), <i>P</i> = .77	173	1.00 (0.97–1.04), <i>P</i> = .97
No. of endocrine disruptors with any exposure ^b							
0	1439	439	Reference	114	Reference	105	Reference
1–2	306	112	1.23 (0.96–1.57)	18	0.85 (0.50–1.42)	33	1.60 (1.05–2.41)
3–5	256	84	1.06 (0.81–1.39)	26	1.35 (0.86–2.14)	22	1.20 (0.74–1.95)
6–20	194	55	0.95 (0.69–1.32)	12	0.93 (0.50–1.74)	13	1.00 (0.55–1.83)
Continuous	2195	690	1.00 (0.96–1.03), <i>P</i> = .92	170	1.01 (0.95–1.08), <i>P</i> = .78	173	1.01 (0.95–1.07), <i>P</i> = .80
No. of Proposition 65 reproductive toxicants with any exposure ^b							
0	1695	543	Reference	138	Reference	139	Reference
1	255	79	0.95 (0.72–1.25)	15	0.72 (0.41–1.25)	22	1.05 (0.65–1.67)
2	138	42	0.97 (0.67–1.39)	11	1.12 (0.59–2.15)	9	0.83 (0.41–1.67)
3–10	107	26	0.74 (0.47–1.15)	6	0.87 (0.37–2.04)	3	0.37 (0.12–1.19)
Continuous	2195	690	0.93 (0.84–1.02), <i>P</i> = .12	170	0.95 (0.78–1.15), <i>P</i> = .58	173	0.83 (0.67–1.03), <i>P</i> = .09
No. of reproductive or developmental toxicants with any exposure ^b							
0	1342	415	Reference	108	Reference	104	Reference
1–2	269	94	1.14 (0.88–1.48)	17	0.80 (0.47–1.37)	24	1.17 (0.73–1.86)
3–6	296	96	1.05 (0.81–1.35)	22	1.00 (0.62–1.62)	27	1.22 (0.79–1.91)
7–37	288	85	0.96 (0.73–1.26)	23	1.07 (0.66–1.74)	18	0.83 (0.49–1.40)
Continuous	2195	690	0.99 (0.97–1.01), <i>P</i> = .39	170	1.00 (0.96–1.04), <i>P</i> = .96	173	0.98 (0.94–1.03), <i>P</i> = .43

^a ORs were adjusted for maternal race or ethnicity and age and infant birth year.

^b See *Methods* for definitions.

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