Exposure to Pesticides and Cryptorchidism: Geographical Evidence of a Possible Association

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Synthetic hormone-disrupting chemicals may play a role in the increased frequency of cryptorchidism observed in some studies. We used a spatial ecological design to search for variations in orchidopexy rates in the province of Granada in Spain and to search for relationships between these differences and geographical variations in exposure to pesticides. Orchidopexy rates were estimated for the period from 1980 to 1991 in all municipalities and health care districts served by the University of Granada Hospital. A random sample of males of the same age (1–16 years) admitted for any reason during the same period was used to estimate inpatient control rates. Each municipality was assigned to one of four levels of pesticide use. We used Poisson homogeneity tests to detect significant differences in rates of orchidopexy between districts and between levels of pesticide use. Poisson and logistic regression models were also used to estimate the strength of association between orchidopexy and level of pesticide use. Orchidopexy rates tended to be higher in districts near the Mediterranean coast where intensive farming is widespread. The city of Granada, where the reference hospital is located, also had higher figures both for orchidopexy and inpatient control rates. Regression models showed that the strength of association between orchidopexy and level of pesticide use tended to increase with higher levels of use, with the exception of level 0 (mainly in the city of Granada). Our results are compatible with a hypothetical association between exposure to hormone-disruptive chemicals and the induction of cryptorchidism. Several methodological limitations in the design make it necessary to evaluate the results with caution. *Key words*: cryptorchidism, ecological design, pesticides, hormone-disruptive substances, risk factor. *Environ Health Perspect* 104:1090–1095 (1996)

A number of epidemiological studies published in recent decades have reported a steady increase in the frequency of disorders in male sexual development (cryptorchidism and hypospadias) (*1–5*), in testicular function (*6–11*), and in other potentially related diseases such as testicular cancer (*12–15*). If such an increase is indeed taking place, it may be related to the concurrent rise in the use of chemicals with hormone-disruptive activity, which may affect male sexual maturation *in utero* probably by inhibiting Sertoli cell function (*5,16–18*).

One of the main hormone-disruptive activities recently demonstrated in many compounds has been estrogenic activity (*11,16,19,20*); the number of new substances that may mimic the action of endogenous estrogens is increasing rapidly. These chemicals include pesticides, particularly organochlorine-containing products (*16,21*), large amounts of which have been used during the last 40–60 years (*22*). Some of these compounds (e.g., lindane, endosulfan, and *p,p'*-DDE), which have been shown to damage the endocrine system in several animal species (*11,21,23–26*), are still being used in our setting. The few studies that have investigated their effects in humans point in the same direction. Soto et al. (*27*) showed that some pesticides have estrogenic activity in human cells *in vitro*; and more recently, De Cock et al. (*28*) found a lower fecundity ratio among fruit growers exposed to high levels of pesticides.

If there is indeed an association between exposure to substances with hormone-disruptive activity and certain disorders of sexual maturation, the incidence of such disorders should be greater in areas where exposure to agents with this activity is high. In the province of Granada (southeastern Spain), the use of pesticides varies widely between areas. Along the Mediterranean coast, extensive areas are devoted to intensive farming in plastic greenhouses, where large amounts of pesticides are used. The present study was designed to search for a relationship between differences in the distribution and frequency of cryptorchidism throughout the province and differences in exposure to pesticides.

Methods

Design: Ecological Study.

Population and sample. We recorded the number of males at 1–16 years of age who underwent surgery for orchidopexy between 1980 and 1991 (inclusive) at the University of Granada Hospital (UGH), a reference center for the southern part of the province of Granada. As a control, we selected a random sample, stratified for year of admission, of all males aged 1–16 years admitted to the UGH for any reason during the same period. Appendix 1 lists all diagnoses coded in hospital computer records for these control boys. Census figures for 1980 and 1991 were used to estimate the population of males in each municipality (i.e., within the city limits of each town or city) aged 1–4 years and 5–16 years in each intervening year.

Variables. For each subject, we recorded age, date of admission, and city or town where he habitually resided. Each municipality was classified according to the criteria given below.

Health care district and municipality where the subject resided. Each health care district (HCD) represents the smallest geographical and administrative unit for which public health care services are provided in Spain. In our study area, each HCD includes several municipalities, with the exception of the cities of Granada and Motril, which were each considered as a single HCD although both comprise more than one HCD. The HCD, rather than the cities and towns themselves, was used as the basic geographical unit for comparing rates of orchidopexy. This was done because of the small numbers of orchidopexies among inhabitants of some of the smallest towns.

Pesticide use. The Agrarian Protection Agency, administered by the Provincial Delegation of the Agricultural Council, Andalusian Regional Government, rated pesticide use along a 4-point scale from 0 (lowest) to 3 (highest) in each municipality

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Table 1. Orchidopexy (OrR) and inpatient control (ICR) rates in each of 15 health care districts (HCD) in the southern part of the province of Granada, Spain, during the period from 1980 to 1991

HCD (Code/Name)	Person-years	Cases	Inpatients	OrR[a]	ICR[a]
1 Granada	162,384	131	243	8.07*	14.96*
2 Bola de Oro	10,824	4	12	3.70	11.09
3 La Zubia	40,133	11	39	2.74	9.72
4 Lecrín	31,517	13	24	4.12	7.61
5 Armilla	28,713	8	33	2.79	11.49
6 Churriana	27,209	3	28	1.10	10.29
7 Vélez	5,506	2	6	3.63	10.90
8 Motril-Este	6,120	3	4	4.90	6.54
9 Salobreña	21,896	16	12	7.31	5.48
10 Almuñécar	33,682	12	20	3.56	5.94
11 Motril	77,909	50	60	6.42*	7.70
12 Orgiva	22,857	6	17	2.63	7.44
13 Cadiar	10,497	4	2	3.81	1.91
14 Ugijar	7,806	0	4	0.00	5.12
15 Albuñol	15,259	7	10	4.59	6.55
Total	502,321	270	514	5.38	10.23
χ^2				54.93*	67.72*

[a]Rates per 10,000 males 1–16 years of age.
*$p < 0.001$

Table 2. Orchidopexy (OrR) and inpatient control (ICR) rates in each of the four groups of municipalities classified according to the level of pesticide use

Level of pesticide[a]	Person-years	Cases	Inpatients	OrR[b]	ICR[b]
0	210,234	150	291	7.13	13.84**
1	114,135	29	100	2.54**	8.76
2	76,850	33	55	4.29*	7.16
3	101,102	58	68	5.74	6.73
χ^2				31.09**	48.43**

[a]0, lowest use; 1, medium-low use; 2, medium-high use; 3, highest use.
[b]Rates per 10,000 males 1–16 years of age.
*$p < 0.05$; **$p < 0.001$.

in the study area, taking into account the total surface area under cultivation and the predominant crops. The technicians who provided this information were unaware of the objectives of the study.

Analyses. Orchidopexy rates (OrRs) and inpatient control rates (ICRs) were calculated for each municipality, HCD, and level of pesticide use, according to the formulas:

$$\text{OrR} = \frac{\text{no. of orchidopexies during 1980–1991}}{\text{Person}_{\text{(males aged 1–16 years)}} - \text{years}_{\text{(from 1980 to 1991)}}} \times 10{,}000 \quad [1]$$

$$\text{ICR} = \frac{\text{no. of inpatients admitted during 1980–1991}}{\text{Person}_{\text{(males aged 1–16 years)}} - \text{years}_{\text{(from 1980 to 1991)}}} \times 10{,}000 \quad [2]$$

The OrRs and ICRs were also calculated for subperiods and for age subgroups (1–4 years and 5–16 years). ICRs were also estimated for selected diagnoses (respiratory, injuries, gastroenteritis, elective and nonelective surgery). The Poisson homogeneity test (*29*) was used to search for significant differences between OrR values and between ICR values in different HCDs and in different levels of pesticide use. Poisson regression models (*30*) were used separately for each group of rates, using OrR per municipality as the dependent variable and level of pesticide use and population of the municipality as terms in the model. These analyses were repeated excluding level 0 of pesticide use.

Although our design was not properly a case–control study, we used the cases of orchidopexy (numerator in Equation 1) and the inpatient controls (numerator in Equation 2), to perform logistic regression analyses (*31*). Case–control status was considered the dependent variable and age, population of the municipality, and level of pesticide use were the independent variables.

The rationale for performing this second analysis was to determine whether different analyses would yield concordant results. Analyses were also done excluding level 0 of pesticide use. The data were analyzed with the BMDP (programs 2R and LR; BMDP Statistical Software, Inc., Los Angeles, CA) (*32*) and EGRET (Statistics and Epidemiology Research Corporation, Washington, DC) (*33*) statistical software packages.

Results

The highest orchidopexy rates (Table 1) were found in the cities of Granada and Motril (both ($p < 0.001$). The inpatient control rate was highest for the city of Granada ($p < 0.001$). When geographical

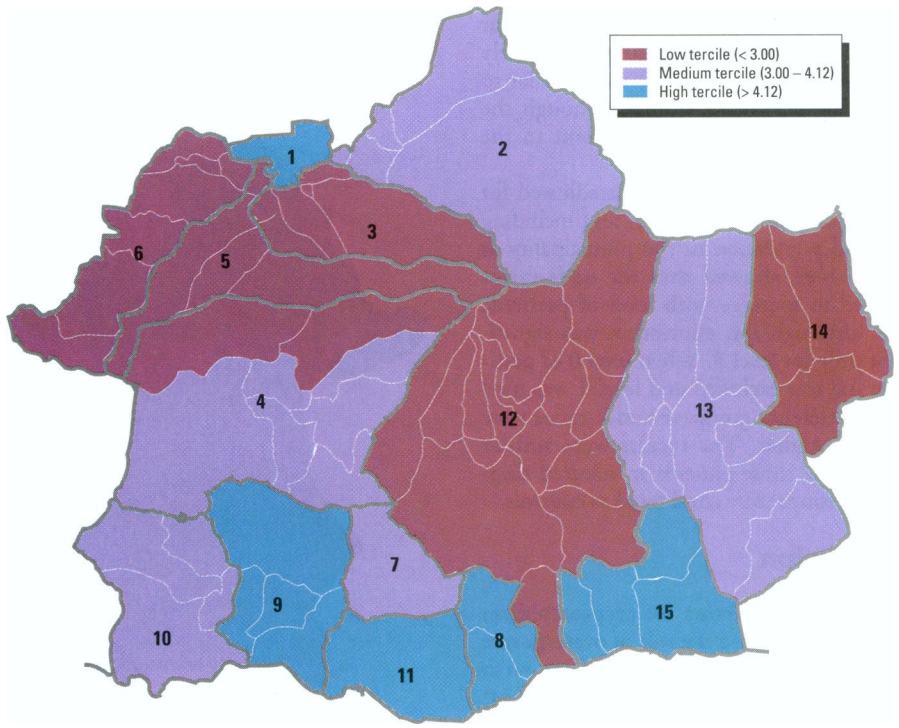

Figure 1. Orchidopexy rates per 10,000 inhabitants in health care districts in the southern part of the province of Granada, Spain. The numbers on the map represent the codes used to designate each district in Table 1.

areas were compared in terms of pesticide use (Table 2), the frequency of orchidopexy increased together with the amount of pesticides applied, except in the level 0 of pesticide use (comprised almost entirely of the city of Granada), which showed the highest rate of orchidopexy. The pattern of ICR was clearly different: these figures tended to decrease as the use of pesticides increased. The results for each subperiod were similar to those for the entire 12-year period.

The pattern of geographical distribution of orchidopexy rates in terciles (Fig. 1) was similar in overall terms to the pattern of pesticide use (Fig. 2), whereas the pattern of ICR was clearly different (Fig. 3). The ICR obtained for selected diagnostic groups did not reveal any substantial differences in comparison with the results obtained for overall ICR.

Table 3 shows the results of the Poisson regression models used to analyze OrR and ICR. The effect of level of pesticide use on both rates was adjusted for population of the municipality. The incidence density ratio (IDR) of orchidopexy rates for each level of pesticide use, using the 0 level as a reference, increased in magnitude as pesticide use increased, although none of the IDR reached significance. When the model was adjusted for control rates, the opposite trend was found: the IDR decreased as pesticide use increased. Models obtained by excluding the 0 level of pesticide use yielded the same pattern, although IDR increased in magnitude. The results for each of the two age subgroups separately (1–4 years and 5–16 years) were similar to those for the entire sample, although the trends were slightly more evident in the older age subgroup.

Logistic regression analysis adjusted for cases and controls (Table 4) and including age and population of the municipality as covariables, showed that the odds ratios tended to increase with level of pesticide use, although the association was significant only for level 3. When level 0 of pesticide use was excluded and level 1 was used as the reference group, the odds ratios were slightly higher. The results were similar when only those patients in selected diagnostic groups were considered as controls.

Discussion

Studies of risk factors for cryptorchidism have rarely analyzed the role of overexposure during pregnancy to substances with endocrine disruptive activity. Depue (*34*) found a significant association between the consumption of drugs with estrogenic activity during pregnancy and the risk of cryptorchidism. Interestingly, this study and research by Berkowitz et al. (*35*) reported a significant relationship between risk of cryptorchidism and obesity in the mother (high values in the Quetelet index). According to Depue (*34*), this association may reflect an increase in free estrogen in the maternal circulation. However, no studies published to date have considered the possible overexposure to endocrine-disruptive substances of nonpharmacological origin.

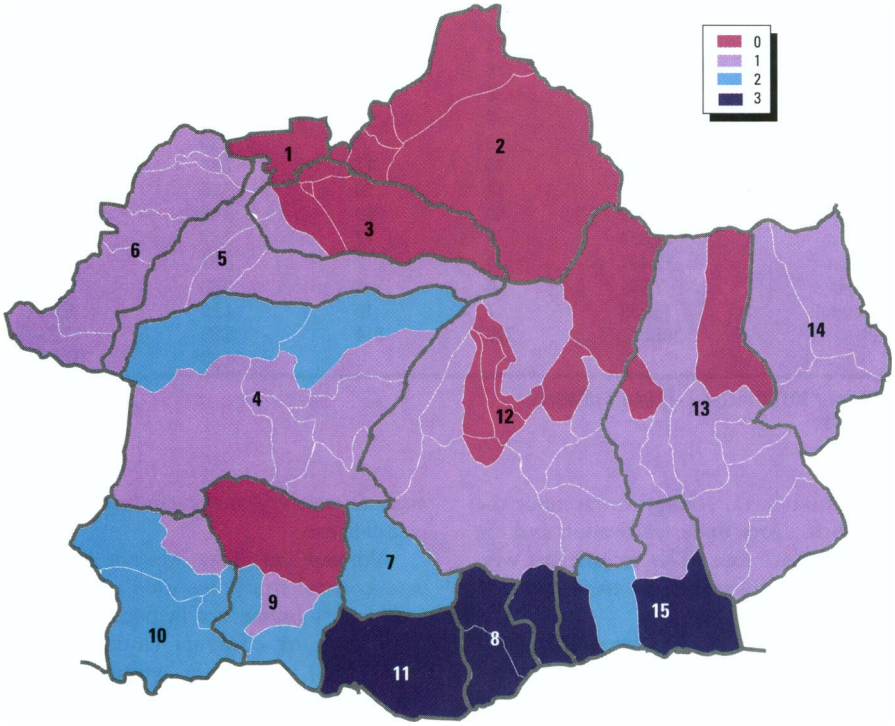

Figure 2. Level of pesticide use in the municipalities in the southern part of the province of Granada, Spain. The numbers on the map represent the codes used to designate each district in Table 1.

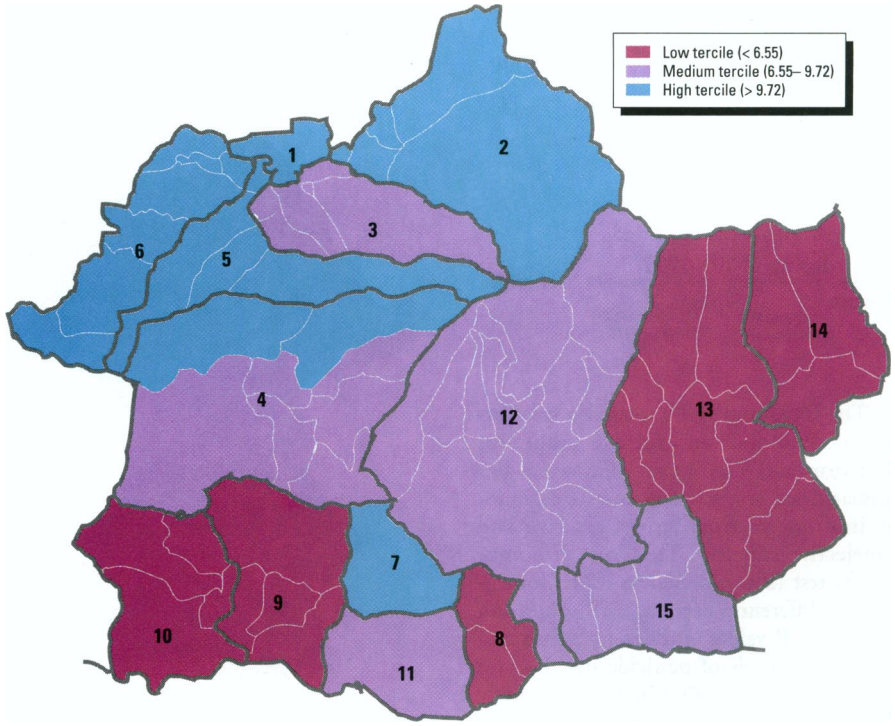

Figure 3. Inpatient control rates per 10,000 inhabitants in health care districts in the southern part of the province of Granada, Spain. The numbers on the map represent the codes used to designate each district in Table 1.

Many products used as pesticides have endocrine disruptive activity. Estrogenic activity has been found in several substances habitually used as inert ingredients in pesticides, including a number of nonylphenol derivatives (*19*). It is worth noting that the U.S. Environmental Protection Agency recently reclassified nonyl-phenol as an inert material with no public health effects (*36*). Pesticides may pose risks not through a single exposure during pregnancy, but through the steady accumulation of endocrine-disrupting substances in adipose tissues during a woman's lifetime (*18*). These liposoluble substances may be absorbed through the skin and respiratory mucosa and can persist in the body for years because of their long half-life. During pregnancy when nutritional demands are increased, fat deposits are mobilized and molecules accumulated in this tissue, including those with hormone-disruptive activity, are released. This mechanism may partially explain the association between maternal obesity and risk of cryptorchidism (*34,35*), although this fact could also be related to increased free estradiol in obese women. Several mechanisms may explain how the *in utero* effects of these compounds increase the risk of orchidopexy. One mechanism may be related to their estrogenic activity. As Sharpe and Skakkebaek (*37*) have hypothesized, circulating estrogens may inhibit Sertoli cell activity and thus inhibit the production of Müllerian-inhibiting substance (MIS), which would then impede regression of the Müllerian ducts (*38*). The persistence of these ducts is usually associated with testicular maldescent (*39*). In a recent study, Sharpe et al. (*40*) showed that exposure during pregnancy to environmental estrogenic chemicals resulted in reduced testicular size and sperm production in adult life in rats.

The geographical distribution of orchidopexy in the province we studied may be explainable, at least in part, by the hypothetical relationship between the use of endocrine-disrupting pesticides and the risk of cryptorchidism. Apart from the city of Granada, the highest rates of orchidopexy were found along the Mediterranean coast, where large amounts of pesticides are used in intensive agriculture. The hypothesis we tested here would also account for the observed trend for OrR to increase together with the level of pesticide use. Exposure to pesticides in the area we studied can be considered from two standpoints: environmental and occupational. With regard to environmental exposure, recent unpublished analyses of pesticide residues in soil, water, and wildlife confirm a considerable degree of contamination by organochlorine compounds, especially in areas devoted to intensive agriculture in greenhouses. In the province of Murcia, east of the province of Granada, high concentrations of pesticides including endosulfan and lindane have been found in the fatty tissues of children. In relation to professional exposure in our setting, farming is often a family occupation involving work carried out by all members, including mothers. Greenhouse farming involves particular dangers with regard to the toxic effects of pesticides (*11,41*). Because plant density per unit surface area is high, workers are in frequent close contact with pesticides and treated crops. In most plastic greenhouses, pesticides cannot easily be dispersed and are concentrated within an enclosed space. Humidity, high temperatures, and high crop densities all favor the appearance of plant pests and diseases, making frequent treatments necessary.

Although the results of the present study support the hypothesis we set out to test, they should be evaluated with caution. Because the study was based on pooled data, the results may have been affected by ecologic bias, i.e., the failure of expected ecologic effect estimates to reflect the biologic effect at the individual level (*42*).

Selection bias may have been introduced by including only patients who underwent surgery at the only public hospital covering the entire area studied. We were not able to obtain data on the number of children with cryptorchidism who may have undergone surgery at other hospitals (private centers or hospitals associated with the public health system). Although the number of such cases was probably very small (orchidopexy does not require referral to a tertiary center, and most pediatric surgeons who perform this operation are employed within the public health system), the proportion of cases missed in each municipality may not have been homogeneous.

Another possible source of bias may have been the classification of municipalities according to level of pesticide use. The agricultural authorities we approached were unfortunately unable to provide data on the exact volume of different pesticides used in each municipality or for each type of crop. This precluded a quantitative estimate of pesticide use in each area. The classification of pesticide use on a 4-point semiquantitative scale thus represents only an approximate estimate. Nonetheless, the classification was produced by technicians of the regional government's Council of Agriculture who were unaware of our reasons for requesting the information, and this probably tended to limit differential classification bias. Our findings would have undoubtedly been enhanced if we had been able to obtain access to valid information about the major types of pesticides used in each region. Unfortunately, we were informed that no reliable records exist for the areas we studied; we concluded that the data supplied by regional government agrarian authorities did not accurately reflect real usage because usage guides were probably not strictly followed in the field. As stated above, there is evidence indicating that the use of organochlorine compounds is high and, although the classification we use lumped all pesticides together, we have no reason to believe that the distribution of pesticides with hormone-disruptive activity (mainly organochlorine-containing products) was significantly different from the overall geographical pattern of total pesticide use.

The effect variable in our design is not a diagnosis of cryptorchidism, but the surgical procedure termed orchidopexy. This criterion is easily reproducible, can be determined accurately from hospital records, and excludes cases of neonatal cryptorchidism that resolve spontaneously

Table 3. Poisson regression analyses of incidence density ratios for orchidopexy (OrR) and inpatient control rates (ICR) for levels of pesticide use, adjusted by population of the municipality

Level of pesticide use	Including 0 level		Excluding 0 level	
	IDR	95% C.I.	IDR	95% C.I.
OrR				
0[a]	1	NA		
1[b]	0.63	0.35–1.13	1	NA
2	1.16	0.63–2.11	1.70	0.99–2.84
3	1.61	0.86–3.00	2.35	1.39–3.99
ICR				
0[a]	1	NA		
1[b]	0.87	0.61-1.23	1	NA
2	0.60	0.39–0.91	0.69	0.49–0.98
3	0.56	0.36–0.89	0.61	0.42–0.88

[a]Reference group when 0 level of pesticide use is included.
[b]Reference group when 0 level of pesticide use is excluded.
IDR, incidence density ratio; NA, not applicable.

Table 4. Logistic regression analysis of odds ratio for case status according to pesticide exposure, adjusted by age and population of the municipality

Level of pesticide use	OR	95% C.I.	OR	95% C.I.
0[a]	1	NA		
1[b]	0.93	0.43–2.01	1	NA
2	1.56	0.72–3.38	1.68	0.82–3.46
3	2.32*	1.26–4.29	2.53	0.88–7.31

[a]Reference group when 0 level is included.
[b]Reference group when 0 level is excluded.
OR, odds ratio; NA, not applicable.
*$p < 0.05$.

and are unlikely to be related with physiological and pathological alterations in the fetus. However, this definition also means that our figures do not include cases of cryptorchidism that were not treated surgically. According to the prevalence of cryptorchisdism published in other studies (*43,44*), more than 50% of all diagnosed cases may have been excluded from our data. Most of these patients were among those who responded to hormonal treatment, although some may have been lost to follow-up after the diagnosis was made.

The geographical distribution of orchidopexy rates may have been affected by the greater likelihood of cryptorchidism being diagnosed (and appropriately treated by hormones or surgery) in urban areas, e.g., the cities of Granada and Motril, than in rural areas. However, when the regression model included population of the municipality, the geographical pattern in the distribution of OrR remained unchanged.

The ICR values show some tendency to be lower in municipalities located farther from the reference hospital. The most likely explanation for this effect is that the use of hospital services is favored by geographical proximity. This may therefore also account for the high rates of orchidopexy in the city of Granada (where the hospital is located and accessibility is greatest) and coincidentally in the level 0 of pesticide use (comprised almost entirely of the city itself), although exposure to hormone-disruptive substances in urban settings cannot be ruled out. The influence of geographical proximity to the hospital may partially mask the association between orchidopexy rates and level of pesticide use: Having taken level 0 of pesticide use as a reference, it is unsurprising that no significant differences were found between the IDR for orchidopexy rates for the other three levels of pesticide use. When level 0 is excluded, the orchidopexy rate for level 3 increases significatively in comparison with level 1. However, this effect would tend to overestimate odds ratios for different levels of pesticide use in logistic regression analysis, as in fact was the case.

Coincidentally, there was an almost perfect direct correlation between distance from the reference center and level of pesticide use, making it all but impossible to separate the effects of these two factors. In the city of Granada, pesticide use was the lowest of all HCDs, whereas the highest levels of pesticide use were found in coastal areas located farthest from the hospital. This effect also explains the tendency for the control IDR to decrease with increasing pesticide use, generally in areas where hospital care was less accessible.

Appendix 1: Distribution of the control sample by reason for admission

Diagnosis	*n*	(%)	Diagnosis	*n*	(%)
Tuberculosis	5	0.97	Twisted hydatid duct	4	0.78
Septicemia	3	0.58	Cryptorchidism	13	2.53
Measles	2	0.39	Other urogenital/renal disease	3	0.58
Hepatitis	3	0.58			
Other infectious disease	1	0.19	Urticaria	5	0.97
			Polymorphous erythema	5	0.97
Diabetes/ketoacidosis	2	0.39	Pyogenic arthritis	3	0.58
Nutritional deficiency	2	0.39			
Other metabolic/nutritional alterations	2	0.39	Congenital malformation	3	0.58
Ferropenic anemia	2	0.39			
Other hematologic alterations	7	1.36	Epistaxis	2	0.39
			Jaundice	2	0.39
Encephalitis/encephalopathies	6	1.17	Fever of unknown origin	2	0.39
Meningitis	8	1.56	Meningism	4	0.78
Epilepsy	6	1.17			
Other CNS disease	2	0.39	Head injury	16	3.11
Eye disease	11	2.14	Upper/lower limb fracture	22	4.28
Hearing alterations	5	0.97	Multiple injury	10	1.94
			Abdominal injury	2	0.39
Upper respiratory tract infection	16	3.11	Acute intoxication	18	3.50
Acute pharyngitis	19	3.70	Ingestion of foreign body	3	0.58
Acute laryngitis	5	0.97	Burn	8	1.56
Pharyngotonsillitis	10	1.94	Anaphylactic reaction	2	0.39
Bronchitis/bronchial obstruction	25	4.86	Other accident/injury	3	0.58
Pneumonia/pneumopathies	26	5.06			
Asthma	4	0.78	Tosillectomy/adenoidectomy	74	14.40
			Herniorrhaphy	9	1.75
Acute gastroenteritis	54	10.50	Dermatological surgery	5	0.97
Acute appendicitis	22	4.28	Eye surgery	8	1.56
Malabsorptive syndrome	4	0.78	Ear surgery	5	0.97
Other digestive disease	3	0.58	Other surgery	4	0.78
Hydrocele	3	0.58	Unknown	18	3.50
Balanitis/phimosis	3	0.58			

n, number; CNS, central nervous system.

If an association between pesticide use and orchidopexy rates does indeed exist, as our data suggest, the public health consequences would be very great. Cryptorchidism is far from being the most severe disorder that can be related to exposure to hormone-disruptive agents; other potential effects include testicular and breast cancer, malformations of the urogenital tract, and sterility-related problems. Moreover, the volume of pesticides that are released into the environment is enormous: in 1990, more than 2 million kilograms of agrochemicals alone were used in the province of Granada. Approximately 4.65% of the entire area devoted to farming in Spain is used to grow fruit and vegetable crops; this area alone was treated with 51% of all the pesticides used in the country. In 1992, Spain ranked fifth in Europe after France, Italy, Germany, and the United Kingdom in pesticide consumption (*45*).

In conclusion, the results of this study are compatible with an association between exposure to xenobiotics with hormone-disruptive activity and increased risk of cryptorchidism. The relationship between these substances in the environment and human disease requires further research.

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