Economic Activity and Congenital Anomalies: An Ecologic Study in Argentina

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In this study, we analyze the association between industrial activity and the occurrence of 34 congenital anomalies. We selected 21 counties in Argentina during 1982–1994 and examined a total of 614,796 births in these counties in consecutive series. We used the *International Standard Industrial Classification of All Economic Activities* (United Nations, 1968) as an indicator of exposure to 80 specific industrial activities. Incidence rate ratios for each congenital anomaly were adjusted by the socioeconomic level of the county according to a census index of social deprivation. For a given exposure/anomaly association to be considered as significant and relevant, the exposure had to be a statistically significant risk for the occurrence of the anomaly and an increase in the birth prevalence rate of the congenital anomaly type involved had to be observed in those counties where the putative causal activity was being performed. Significant associations ($p < 0.01$) were identified between textile industry and anencephaly, and between the manufacture of engines and turbines and microcephaly. These observations are consistent with previous reports on occupational exposure, and their further investigation by means of case–control studies is recommended. *Key words*: anencephaly, automotive industry, congenital anomaly, fur-dyeing, industrial activity, pes equinovarus, textile. *Environ Health Perspect 108*:193–197 (2000). [Online 19 January 2000]
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Chronic exposure to environmental pollutants, before or after conception, is suspected to affect reproduction through cellular damage or death, which may lead to infertility, fetal loss, intrauterine growth retardation, and the occurrence of birth defects, both functional and anatomical, in the progeny of the exposed population (*1*). Nevertheless, the number of proven teratogenic pollutants is still quite limited. The most outstanding examples are methylmercury, which causes central nervous system damage (*2*) and ionizing radiation (*3*) and lead (*4*) contamination, which cause microcephaly and mental retardation. The scarcity of proven examples of environmental teratogens could be due to methodologic limitations imposed by a possible exposure to a weak teratogen, which affects the entire population or a very large part of it.

The exiguous information available on this subject, as well as the serious concern of the community about environmental reproductive risks, justifies an exploratory study such as this one, in which we compare birth prevalence rates for specific types of malformation in populations who are either exposed or unexposed to a given industrial activity.

To propose potentially teratogenic environmental pollutants, we base our study approach on two assumptions:

- Because environmental protection is almost completely lacking in the developing world, industrial activities can be taken as a proxy for specific types of pollutants.
- Because most teratogens are effect specific (they produce a given type or pattern of congenital anomalies), a teratogenic pollutant is expected to be associated with a specific type of congenital anomaly instead of with birth defects in general.

We aimed to test the association between industrial activity and congenital anomalies in small areas (counties) of Argentina, as sampled out by the Latin American Collaborative Study of Congenital Malformations (ECLAMC) (*5*).

Subjects and Methods

The data presented here include 614,796 births of a consecutive birth series during 1982–1994 in 36 maternity hospitals participating in the ECLAMC (*5*). The ECLAMC is a hospital-based registry of birth defects. All consecutive live and stillborn infants weighing ≥ 500 g were examined by a trained pediatrician according to definitions given in a ECLAMC procedures manual (*6*). The 36 hospitals were selected for this study because they are located in 21 counties of Argentina where the ECLAMC included at least 20% of all births that occurred during the study period.

For each county, Table 1 specifies name, geographic location, mean socioeconomic level indicator, number of performed industrial activities, number of annual births, and ECLAMC sample characteristics (i.e., number of maternity hospitals, number of births, and the period covered). The large metropolitan area of Buenos Aires, Argentina, was omitted because of residential mobility and highly heterogeneous economical activities. From the ECLAMC database of prospectively registered congenital anomalies, we included only 34 major isolated anomaly types, with a sample size of at least 20 observed cases (Table 2). We excluded multiple malformed infants and chromosome anomalies except Down syndrome.

Each of 80 industrial activities was used as an exposure factor. The activities carried out in each county were obtained from the Argentine National Economic Census of 1985 (*7*) coded according to the *International Standard Industrial Classification of All Economic Activities* (*8*). For each activity in turn, the counties were grouped into those where the activity was carried out and those where it was not; the prevalence of each malformation at birth in the two groups was compared. Because in developing countries some industrial activities are closely related to the socioeconomic level of the community (*9*), we considered this variable to be a potential confounding factor. The mean socioeconomic level in each county was established through the NBI (Necesidades Básicas Insatisfechas), a social deprivation index (*10*) that defines poverty according to unsatisfactory conditions for housing, health, and school attendance (*11*). According to their NBI

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Table 1. Twenty-one counties in Argentina where the ECLAMC sampled > 20% of annual births.

County	Province	Lat S	Long W	NBI[a]	IA/80[b]	Annual births[c]	ECLAMC sample Hospitals[d]	ECLAMC sample Births	ECLAMC sample Period
San Vicente	BA	34°38′	58°28′	26.8	36	1,233	1	2,269	1982–1984
Coronel Rosales	BA	38°44′	62°16′	6.4	19	1,323	1	1,827	1982–1984
General Pueyrredón	BA	38°00′	57°34′	13.2	55	9,595	2	66,836	1982–1994
Gualeguaychú	ER	33°01′	58°31′	13.4	39	2,374	1	10,064	1982–1994
Paraná	ER	31°44′	60°32′	15.0	56	5,855	1	27,157	1982–1994
Rosario	SF	32°57′	60°40′	16.4	72	19,231	4	72,172	1982–1994
Córdoba Capital	CO	31°25′	64°12′	14.1	73	23,436	4	107,282	1982–1994
Mendoza Capital	MZ	32°54′	68°50′	12.0	49	3,168	5	57,596	1982–1994
San Rafael	MZ	34°37′	68°21′	18.3	42	3,853	4	26,021	1982–1993
San Martín	MZ	33°05′	68°28′	15.4	30	2,330	1	18,190	1982–1994
Posadas Capital	MI	27°22′	55°53′	24.2	36	5,690	1	3,817	1985–1987
San Fernando	CA	27°27′	59°00′	22.7	44	8,229	1	61,484	1982–1994
Cruz Alta	TU	26°50′	65°13′	32.8	55	15,752	1	112,527	1983–1994
Cafayate	SA	26°15′	65°56′	37.9	10	266	1	827	1985–1987
Salta Capital	SA	24°47′	65°24′	23.2	52	9,523	1	8,051	1986–1988
San Pedro	JU	24°14′	64°52′	34.8	24	2,147	1	1,975	1982–1983
Manuel Belgrano	JU	24°12′	65°19′	28.6	33	6,277	2	24,870	1986–1993
Yavi	JU	22°06′	65°36′	36.6	4	482	1	2,205	1989–1993
Bariloche	RN	41°58′	71°31′	27.9	29	150	1	2,955	1987–1994
Futaleufú	CU	42°55′	71°20′	29.2	16	752	1	4,394	1985–1994
Biedma	CU	42°46′	65°03′	20.3	23	679	1	2,207	1990–1994

Abbreviations: BA, Buenos Aires; CA, Chaco; CO, Córdoba; CU, Chubut; ER, Entre Ríos; JU, Jujuy; Lat S, latitude south; Lon W, longitude west; MI, Misiones; MZ, Mendoza; RN, Río Negro; SA, Salta; SF, Santa Fe; TU, Tucumán.
[a]Deprivation index. [b]Number of different industrial activities by county out of 80 analyzed activities. [c]Annual births in the county according to the 1980 census. [d]Number of participating maternity hospitals.

Table 2. Thirty-four types of congenital anomalies with at least 20 cases observed.

Congenital anomaly	No.
Down syndrome	1,054
Cleft lip	597
Postaxial polydactyly	547
Pes equinovarus	450
Anencephaly	384
Spina bifida	370
Hydrocephaly	237
Interventricular septal defect	223
Hypospadias	190
Microtia	183
Preaxial polydactyly	125
Cleft palate	119
Pes talovalgus	109
Anal atresia	104
Cephalocele	100
Longitudinal limb reduction defect	99
Syndactylies	92
Esophageal atresia	90
Diaphragmatic hernia	71
Microcephaly	67
Omphalocele	59
Transverse limb reduction defect	45
Dislocated hip	41
Jejunoileal atresia	40
Gastroschisis	38
Arthrogryposis	36
Polycystic kidney	28
Holoprosencephaly	26
Interauricular septal defect	25
Hydronephrosis	25
Microphthalmia	23
Ambiguous genitalia	22
Duodenal atresia	21
Limb hypoplasia	20

index values, the 21 investigated counties were classified as poorer (NBI of ≥ 22%) or richer (NBI < 22%). This threshold was the median of the NBI distribution of the 21 counties, with 10 counties above the median and 11 below it.

To enhance the specificity of the association between industrial activity and congenital anomalies, we based our working hypothesis on two premises for a given association to be considered as relevant: *a*) a given industrial activity must represent a statistically significant risk for a given congenital anomaly type; and *b*) there must be an increase in the birth prevalence rate of the congenital anomaly type involved in those counties where the putative causal activity was performed and a decrease in the counties where that activity was not performed.

In a first step, the incidence rate ratios (IRR) for each congenital anomaly type were estimated through the relationship between exposed and unexposed counties. This step involved 2,720 IRRs and their confidence intervals, corresponding to 80 different industrial activities and 34 congenital anomalies. The resulting risks were further adjusted by the NBI index and grouped into two previously defined strata applying the Mantel & Haenszel test (*12*) and the 99% confidence limits through the method of Miettinen (*13*). Significance levels were subjected to Bonferroni correction (*14*) because of the high number of comparisons involved.

In a second step, and for each significant malformation/industrial activity association identified, we compared the proportion of counties with the given activity and a higher than expected prevalence of the given malformation (true positives) with the proportion of counties without the given activity and a lower than expected prevalence of the given malformation (true negatives). We derived expected birth prevalence values for each county from the total sample of this study and we used Fisher's exact test to determine the significance of this comparison.

Results

The mean (± SD) NBI value for the 11 poorer counties (with 225,444 examined births) is 27.6 ± 4.5%, and its range is 22.7–37.9. The mean NBI value of the 10 richer counties (with 389,352 births) is 14.7 + 2.4% and its range is 6.4–20.3. These values are significantly different [$\chi^2 = 903.3$; degrees of freedom (df) = 1; $p < 0.001$].

The first step of the analysis disclosed that for 9 of the 34 congenital anomalies there is a significant risk from exposure to one or more specific industrial activities: anencephaly, spina bifida, cephalocele, microcephaly, microtia, interventricular septal defect, pes equinovarus, pes talovalgus, and postaxial polydactyly (Table 3).

For these 9 congenital anomalies, we identified seven significant associations between exposure and an increase in the birth prevalence rate for the indicated anomaly by county (Fisher exact test, $p < 0.05$). These involved seven industrial activities and four congenital anomaly types. The Fisher exact test was significant at $p < 0.01$ for two of the seven associations: anencephaly was associated

Table 3. Significant adjusted incidence rate ratios (IRR) for 34 different malformation-exposure associations.

Malformation/exposure (industry)	ISIC	Exp	No. of cases	Rate	IRR	AIRR	% 95 CI
Anencephaly							
Spinning, weaving, and finishing textiles	3211	7	312	6.94	1.59	1.60	1.23–2.08
Spina bifida							
Soap, detergents, perfumes, cosmetics	3523	10	323	6.59	1.78	1.84	1.29–2.61
Iron and steel industries	3710	12	329	6.50	1.76	1.84	1.30–2.58
Machinery and equipment except electrical NEC	3829	9	298	6.74	1.63	1.60	1.23–2.17
Photographic and optical goods	3852	5	284	6.82	1.59	1.55	1.22–2.05
Rubber products NEC	3559	7	287	7.07	1.57	1.54	1.21–1.99
Cephalocele							
Fur dressing and dyeing	3232	2	29	3.53	2.78	2.78	1.67–4.60
Microcephaly							
Engines and turbines	3821	3	44	1.79	4.26	4.26	1.74–11.10
Textiles NEC	3219	6	60	1.40	3.73	4.18	1.84–10.05
Pulp, paper, and paperboard products NEC	3419	4	48	1.60	2.63	2.75	1.57–4.85
Jewelry and related products	3901	4	48	1.60	2.65	2.75	1.57–4.85
Electrical appliances and housewares	3833	3	47	1.61	2.60	2.64	1.53–4.62
Microtia							
Cement, lime, and plaster	3692	7	105	4.11	1.90	1.88	1.37–2.69
Interventricular–septal defect							
Knitting mills	3213	14	210	4.20	3.70	3.20	1.70–5.67
Pes equinovarus							
Transport equipment NEC	3849	3	228	11.55	2.21	2.21	1.74–2.82
Nonferrous metal	3720	11	392	8.07	1.79	2.10	1.57–2.81
Fur dressing and dyeing	3232	2	115	14.00	2.02	2.02	1.61–2.55
Miscellaneous products of petroleum and coal	3540	3	207	11.31	2.01	1.93	1.52–2.38
Distilling, rectifying, blending spirits	3131	5	226	10.71	1.93	1.87	1.46–2.30
Aircraft	3845	3	207	11.05	1.94	1.86	1.46–2.25
Prepared animal foods	3122	7	336	8.43	1.60	1.83	1.46–2.27
Grain mill products	3116	9	374	8.13	1.65	1.77	1.37–2.28
Fertilizers and pesticides	3512	4	224	10.35	1.72	1.72	1.35–2.18
Tobacco products	3140	5	184	10.29	1.69	1.71	1.40–2.13
Office, computing, accounting machinery	3825	3	215	10.92	1.68	1.68	1.33–2.13
Synthetic resins, plastic materials, and man-made fibers except glass	3513	8	363	8.03	1.50	1.58	1.24–2.01
Motorcycles and bicycles	3844	4	215	10.03	1.71	1.57	1.24–1.93
Electrical appliances and housewares	3833	3	258	8.84	1.49	1.50	1.25–1.83
Pulp, paper, and paperboard products NEC	3419	4	258	8.60	1.41	1.44	1.20–1.76
Jewelry and related products	3901	4	258	8.60	1.41	1.44	1.20–1.76
Pes talovalgus							
Tobacco products	3140	5	49	2.74	1.99	2.01	1.35–2.97
Wine	3132	6	67	2.47	2.02	1.92	1.33–3.06
Postaxial polydactyly							
Transport equipment NEC	3849	3	227	11.50	1.55	1.55	1.25–1.92
Electrical appliances and housewares	3833	3	301	10.32	1.35	1.36	1.15–1.62

Abbreviations: AIRR, adjusted incidence rate ratio; Exp, number of counties where the activity is carried out; IRR, unadjusted incidence rate ratio; ISIC, International Standard Industrial Classification of All Economic Activities (*7*); NEC, not elsewhere classified.

with spinning, weaving, and finishing of textiles ($p = 0.003$); microcephaly was associated with the manufacture of engines and turbines ($p = 0.007$) (Table 4).

Textiles were manufactured in 7 of the 21 counties; the birth prevalence rate of anencephaly was lower than the expected prevalence rate in 1 county and higher in 6. Furthermore, the birth prevalence rate of anencephaly was higher than expected in only 2 of the 14 counties where textiles were not manufactured.

Engines and turbines were manufactured in 3 of the 21 counties, and the birth prevalence rate of microcephaly was higher than expected in all of them. In the 18 counties without this industrial activity, the birth prevalence rate of microcephaly was lower than expected in 16 counties and higher than expected in 2.

In other words, the association between textile manufacturing and anencephaly shows that textiles are manufactured in 85% of the counties with a high prevalence of anencephaly, whereas it is not performed in 86% of the counties with a low prevalence. The association between the manufacture of engines and turbines and microcephaly shows that this activity is performed in all counties with a high prevalence of microcephaly, but it is not performed in 89% of the counties where the prevalence of microcephaly is low.

Discussion

The approach. Although in developing countries environmental pollution often leads to extreme situations (*15*), these countries usually lack reliable data on environmental monitoring. Therefore, an indirect indicator, such as industrial activity, may provide a low-cost, readily accessible substitute. Our results from 21 counties in Argentina constitute the first application of this approach to representative birth samples (20–100%) from small areas.

Among the South American countries covered by the ECLAMC project (*5*), we selected Argentina because of its rather stable developmental conditions during the 1982–1994 study period. Its stagnant economy, demographic stability, and ethnic and socioeconomic homogeneity make it more suitable for this study than other South American countries.

Table 4. Industrial activities significantly associated with the birth prevalence rate of a given congenital anomaly shown as the number of counties where a given industrial activity is or is not carried out.

Frequency of malformation/ exposure association	ISIC	Industrial activity Yes Low	Yes High	No Low	No High	Fisher exact test
Anencephaly						
Spinning,weaving, and finishing textiles	3211	1	6	12	2	0.003
Microcephaly						
Textiles NEC	3219	2	4	14	1	0.011
Pulp, paper, and paperboard products NEC	3419	1	3	15	2	0.027
Engines and turbines	3821	0	3	16	2	0.007
Jewelry and related products	3901	1	3	15	2	0.027
Intraventricular septal defect						
Knitting mills	3213	5	9	6	1	0.042
Pes equinovarus						
Transport equipment NEC	3849	0	3	14	4	0.026

Abbreviations: ISIC, International Standard Industrial Classification of all Economic Activities (*8*); NEC, not elsewhere classified. High frequency indicates that the observed birth prevalence rate is higher than expected; low frequency indicates that the observed birth prevalence rate is lower than expected.

Because we assumed that the county of a child's birth is the same county where the mother resided during pregnancy, a high residential mobility could weaken the associations between exposures and congenital anomalies (*16*). For this reason, we did not include the large area of metropolitan Buenos Aires, with high residential mobility, in the present study.

Unlike acute or limited exposures, such as those caused by accidents or certain types of occupations, respectively, chronic and widespread environmental exposures constitute risks for diseases, which may be of little importance at the individual level but are important for the population as a whole (*17,18*). Therefore, the cohort or case–control approaches, usually applied to the study of occupational exposures, are not readily appropriate for environmental pollutants. An available alternative is the cohort or case–control study in small exposed and unexposed geographic areas for which exposure rates are obtained from census data. Unfortunately, statutory statistics are highly unreliable for scientific purposes in the developing world.

The associations. Although the aim of this study was to suggest rather than to prove exposure–effect associations, the large number of comparisons recommends that only the highly significant and relevant associations should be considered. We found two specific associations between industrial activity and congenital anomalies that had statistically significant IRRs and an increased birth prevalence rate of the congenital anomaly in the counties where the given industrial activity was performed.

The textile industry was involved in one of these highly significant associations—the association between textile manufacturing and anencephaly. Furthermore, we identified seven associations involving seven different industrial activities and four congenital anomaly types. Two of the four anomalies are related to the central nervous system (anencephaly and microcephaly), and both of them were associated with activities of the "textile, wearing apparel, and leather industries," corresponding to code 32 at the two-digit level (*8*). The textile industry includes three consecutive steps (preparing, dyeing, and finishing) and uses diverse chemicals, including pesticides carried in the sheep's wool, formic and sulfuric acids, and organic solvents (*19*). In occupational exposure studies, organic solvents have been reported to have adverse reproductive effects in humans (*20–24*).

In a study on paternal occupation (vehicle manufacturers) and birth defects, Schnitzer et al. (*21*) reported higher risks for central nervous system defects and cleft lip; in the present study, the same type of industrial activity was associated with microcephaly.

Profits and pitfalls. In spite of several strengths shown by the present approach, our results should be interpreted cautiously. Positive conditions include the following:

- The study group is large enough (600,000 births) to estimate valid expected and observed birth prevalence rates for most congenital anomalies, and the sample is representative (> 20%) of the total population of the small areas (counties) analyzed.
- The exposure indicator is objective, based on an international coding system, making this approach suitable for other countries, and our observations are comparable with those of other studies.
- Data were collected without knowledge of the working hypothesis, which was applied to material stored in the ECLAMC project data bank.
- Diagnosis and description of specific malformations are of good quality, inasmuch as ECLAMC is an ongoing clinical and epidemiologic research project of birth defects.

Nevertheless, the following limitations should be considered when evaluating the proposed method and the present results:

- The employed approach suffers from the so-called "ecological fallacy" (*25*), which results by inferring individual risks from populational studies.
- Exposure data are of poor quality in the sense that the exposure indicator is unspecific as to the involved teratogen (one single industrial activity can release many different chemicals).
- The exposure indicator denotes the presence of a given industry, which probably pollutes the environment of a small area, but at the same time increases the probability of specific maternal occupational exposures. Therefore, environmental and occupational exposures cannot be disentangled by this approach.
- When analyzing the exposure risk for a given activity, the remaining 79 activities that make up the nonexposed group decrease the sensitivity of the test to detect teratogenic activities. However, this is a common drawback for most studies on environmental exposures.
- Most congenital anomalies are of a complex nature as to their multifactorial causation; the effect of a given teratogen depends on the embryologic stage of exposure, the threshold dose to produce the defect, and many other concurring variables.
- Our study adjusted the estimated risks by means of a socioeconomic index based on the census. This, however, does not control for all lifestyle-related confounders, such as the use of alcohol and smoking of cigarettes.

Conclusions

The aim of this study was to determine associations between potentially teratogenic industrial pollutants and congenital anomalies. In spite of the technical limitations of our approach, we identified significant associations between the textile industry and anencephaly, and between the manufacture of engines and turbines and microcephaly.

Although the two observations are consistent with previous reports on occupational exposure, further investigations, such as case–control studies in small areas, would be worthwhile. There is no clear pattern of risk for environmental teratogens in general, not even through studying hazardous-waste landfill sites (*9,26*).

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