Economic Activity and Congenital Anomalies: An Ecologic Study in Argentina

Eduardo E. Castilla,1,2 Hebe Campaña,3 Jorge S. López Camelò,3 and the ECLAMC ECOTERAT Group*  

1ECLAMC (Latin-American Collaborative Study of Congenital Malformations, WHO Collaborating Centre for the Prevention of Birth Defects), Instituto Oswaldo Cruz, Rio de Janeiro, Brazil; 2ECLAMC, Centro de Educación Médica e Investigaciones Clínicas, Buenos Aires, Argentina; 3ECLAMC, Instituto Multidisciplinario de Biología Celular, La Plata, Argentina

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 have 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] http://ehpnet1.niehs.nih.gov/docs/2000/108p193-197/castillaabstract.html

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 have 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] http://ehpnet1.niehs.nih.gov/docs/2000/108p193-197/castillaabstract.html

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 small area, 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

Address correspondence to E.E. Castilla, Genética/ Fiocruz, ECLAMC, CP 926, Rio de Janeiro 20001-970 Brazil. Telephone: 55 21 552 8952. Fax: 55 21 260 4282. E-mail: castilla@centrin.com.br

*The ECLAMC ECOTERAT Group includes A. Echeverray, Maternidad Provincial, Córdoba; C. Alarqr, Hospital del Centenario, Gualeguaychú; C. de Rosas, Hospital Italiano, Mendoza; C. Negri, Hospital Ferrugem, San Martín; C. Picón, Hospital Perrando, Resistencia; C. Saleme, Maternidad de Tucumán, Tucumán; C. Rivelis, Hospital San Roque, Paraná; J. C. Mereb, Hospital de Área, El Bolson; L. Salgado, Hospital Melendez, Adrogue; M. M. Martín, Maternidad Martin, Rosario; M. Lerner, Hospital del Centenario, Gualeguaychú; M. Rittger, Maternidad Sardá, Buenos Aires; M. Roubicek, Hospital de la Comunidad, Mar del Plata; R. Lombardelli, Hospital Zonal, Esquel; and S. Morales, Maternidad Martin, Rosario.

This study was supported by the Consejo Nacional de Investigaciones Científicas y Técnicas and the Comisión de Investigaciones Científicas de la provincia de Buenos Aires of Argentina, the Conselho Nacional de Desenvolvimento Científico e Tecnológico of Brazil, and the Programa de Apoio a Pesquisa Estratégica em Saúde da Fiocruz of Brazil. Received 26 May 1999; accepted 14 September 1999.
Table 1. Twenty-one counties in Argentina where the ECLAMC sampled > 20% of annual births.

| County            | Province | Lat S | Long W | NBI<sup>a</sup> | IA/80<sup>b</sup> | Annual births<sup>c</sup> | Hospitals<sup>d</sup> | ECLAMC sample |
|-------------------|----------|-------|--------|------------------|------------------|--------------------------|-------------------|----------------|
| San Vicente       | BA       | 34°38' | 58°26' | 26.8             | 36               | 1,233                     | 1                 | 2,269          |
| Corneal Rosales   | BA       | 38°44' | 62°16' | 6.4              | 19               | 1,323                     | 1                 | 1,827          |
| General Pueyrredón| BA       | 38°00' | 57°34' | 13.2             | 55               | 9,595                     | 2                 | 66,836         |
| Gualeguaychú     | ER       | 33°01' | 58°31' | 13.4             | 39               | 2,374                     | 1                 | 10,684         |
| Paraná            | ER       | 31°44' | 60°32' | 15.0             | 56               | 5,855                     | 1                 | 27,157         |
| Rosario           | SF       | 32°57' | 60°40' | 16.4             | 72               | 19,231                    | 4                 | 72,172         |
| Córdoba Capital   | CO       | 31°25' | 64°12' | 14.1             | 73               | 23,436                    | 4                 | 107,282        |
| Mendoza Capital   | MZ       | 32°54' | 68°50' | 12.0             | 49               | 3,168                     | 5                 | 57,596         |
| San Rafael        | MZ       | 34°37' | 68°21' | 18.3             | 42               | 3,853                     | 4                 | 26,021         |
| San Martín        | MZ       | 33°05' | 68°28' | 15.4             | 30               | 2,330                     | 1                 | 18,193         |
| Posadas Capital   | MI       | 27°22' | 55°53' | 24.2             | 36               | 5,690                     | 1                 | 3,817          |
| San Fernando      | CA       | 27°27' | 59°00' | 22.7             | 44               | 8,229                     | 1                 | 61,484         |
| Cruz Alta         | TU       | 26°50' | 65°13' | 32.8             | 55               | 15,752                    | 1                 | 112,527        |
| Cafayate          | SA       | 28°15' | 65°56' | 37.9             | 10               | 266                       | 1                 | 827            |
| Salta Capital     | SA       | 24°47' | 65°24' | 23.2             | 52               | 9,523                     | 1                 | 80,511         |
| San Pedro         | JU       | 24°14' | 64°52' | 34.8             | 24               | 2,147                     | 1                 | 1,975          |
| Manuel Belgrano   | JU       | 24°12' | 65°19' | 28.6             | 33               | 6,277                     | 2                 | 24,670         |
| Yavi              | JU       | 22°06' | 65°36' | 36.6             | 4                | 482                       | 1                 | 2,205          |
| Bariloche         | RN       | 41°58' | 71°31' | 27.9             | 29               | 150                       | 1                 | 2,955          |
| Futaleufú         | CU       | 42°35' | 71°20' | 23.2             | 18               | 752                       | 1                 | 4,294          |
| Bildema           | CU       | 42°46' | 65°03' | 30.3             | 23               | 679                       | 1                 | 2,207          |

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.

*Depression index. <sup>a</sup>Number of different industrial activities by county out of 80 analyzed activities. <sup>b</sup>Annual births in the county according to the 1980 census. <sup>c</sup>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 |
| Intervertebral septal defect             | 223 |
| Hypospadias                              | 190 |
| Microtia                                 | 183 |
| Praxial polydactyly                      | 125 |
| Cleft palate                             | 119 |
| Pes talavulosis                          | 109 |
| Anal atresia                             | 104 |
| Cephalocele                              | 100 |
| Longitudinal limb reduction defect       | 99  |
| Syndactyly                               | 92  |
| Esophageal atresia                       | 90  |
| Diaphragmatic hernia                     | 71  |
| Microcephaly                             | 67  |
| Omphalocele                              | 59  |
| Transverse limb reduction defect         | 45  |
| Dilated hip                              | 41  |
| Jejunoileal atresia                      | 40  |
| Gastrochisis                             | 38  |
| Arthrogryposis                           | 36  |
| Polycystic kidney                        | 28  |
| Holoprosencephaly                        | 26  |
| Interauricular septal defect             | 25  |
| Hydroprosphosis                          | 25  |
| Microphalma                              | 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 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 (1,2) and the 99% confidence limits through the method of Miettinen (1,3). Significance levels were subjected to Bonferroni correction (1,4) 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 [t² = 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 talavuloss, 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                      |      |     |              |      |      |      |         |
| Spinally                        | 3211 | 7   | 312          | 6.94 | 1.59 | 1.60 | 1.23–2.08 |
| Spina bifida                    | 3523 | 10  | 323          | 6.59 | 1.78 | 1.84 | 1.29–2.61 |
| Soap, detergents, perfumes, cosmetics | 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 |
| Interverricular–septal defect   |      |     |              |      |      |      |         |
| Knitting mills                  | 3213 | 14  | 210          | 4.20 | 3.70 | 3.20 | 1.70–5.67 |
| Pes equinovirus                 |      |     |              |      |      |      |         |
| Transport equipment NEC         | 3849 | 3   | 228          | 11.55 | 2.21 | 2.21 | 1.74–2.92 |
| Nonferrous metal                | 3720 | 11  | 362          | 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 | 1.92 | 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 | 1.37–2.18 |
| 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 | 3625 | 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 talovalus                    |      |     |              |      |      |      |         |
| 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 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 | Industrial activity | Fisher exact test |
|-----------------------------------------------|---------------------|------------------|
| Anencephaly                                   | Spinning, weaving, and finishing textiles | ISIC 3211 |
| Microcephaly                                  | Textiles NEC        | 3219            |
|                                              | Pulp, paper, and paperboard products NEC | 3419 |
|                                              | Engines and turbines | 3821 |
|                                              | Jewelry and related products | 3901 |
|                                              | Intraventricular septal defect | 3213 |
|                                              | Knitting mills      | 3849 |
|                                              | Pes equinovusus     | Transport equipment NEC |

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’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, the statistical models are highly unreliable for scientific purposes in the developing world.

The extracted textual content includes a table listing industrial activities significantly associated with birth prevalence rates of congenital anomalies. The text discusses the limitations of such studies and suggests that more research is needed to understand the effects of occupational exposures on congenital anomalies.

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.

References and Notes

1. Hemminki K, Salonen I, Luoma K, Salonen T, Partanen T, Vainio K. Transplacental carcinogens and mutagens: childhood cancer, malformations and abortions as risk indicators. J Toxicol Environ Health 6:1115–1125 (1980).
2. Harada M. Congenital Minamata disease: intrauterine methylmercury poisoning. Teratology 18:325–336 (1978).
3. Schull WJ, Nortin S, Jenhs RP. Ionizing radiation and the developing brain. Neurotoxicol Teratol 12:249–256 (1990).
4. Beattie AD, Moore MR, Goldberg A. Role of chronic low level lead exposure in the aetiology of mental retardation. Lancet 1:589–592 (1975).
5. Castilla EE, Lopez-Camelo JS. The surveillance of birth defects in South-America: I. The search for time clusters: epidemics. Adv Mutagen Res 2:191–210 (1990).
6. ECLAMC. ECLAMC Manual Operacional. Rio de Janeiro:ECLAMC (Latin-American Collaborative Study of Congenital Malformations), 1982
7. INDEC. Censo Nacional Económico 1985. Industria Manufacturera. Resultados definitivos. Total del país y jurisdicciones. Buenos Aires:República Argentina Presidencia de la Nación. Instituto Nacional de Estadística y Censos, 1989.
8. ISIC. International Standard Industrial Classification of All Economic Activities. Statistical Papers, Series M No. 4, Revision 2. New York:United Nations, 1968.
9. Dolk H, Vrijheid M, Armstrong B, Abramsky L, Bianchi F, Garne E, Nielen V, Robert E, Scott JE, Stone D, Tenconi R. Risk of congenital anomalies near hazardous waste landfill sites in Europe: the EUHORAZON study. Lancet 352:423–427 (1998).
10. Carstairs V. Deprivation indices: their interpretation and use in relation to health. J Epidemiol Community Health 49(suppl 2):S3–S8 (1995).
11. CEPA. Comite Ejecutivo para el estudio de la Pobreza en la Argentina. Doc # 4, INDEC. Buenos Aires:Ministerio de Economia de la Nación Argentina, 1994.

12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 32:719–748 (1959).
13. Miettinen OS. Simple interval estimation of risk ratio. Am J Epidemiol 100:515–516 (1974).
14. Armitage P, Berry G, eds. Multiple Measurements. In: Statistical Methods in Medical Research, 3rd ed. London:Blackwell Scientific Publications, 1994:312–335.
15. Monteleone-Neto R, Castilla EE. Apparently normal frequency of congenital anomalies in the highly polluted town of Cubatão, Brazil. Am J Med Genet 52:319–323 (1994).
16. Khoury MJ, Stewart W, Weinstein A, Pannya S, Lindsay P, Eisenberg M. Residential mobility during pregnancy: implications for environmental teratogenesis. J Clin Epidemiol 41:15–20 (1988).
17. Ericson A, Eriksson M, Källén B, Zetterström R. Maternal occupation and delivery outcome: a study using central registry data. Acta Pediatr Scand 76:512–518 (1987).
18. Källén B, Landgren MS. Delivery outcome in pregnancies when either parent worked in the chemical industry. A study with central registries. J Occup Med 36:563–568 (1994).
19. International Agency for Research on Cancer. Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry. IARC Monogr Eval Carcinog Risk Chem Hum 48: (1990).
20. Brender JD, Suarez L. Paternal occupation and anencephaly. Am J Epidemiol 131:517–521 (1990).
21. Schnitzer PG, Olshan AF, Erickson JD. Paternal occupation and risk of birth defects in offspring. Epidemiology 6:577–583 (1995).
22. Marshall EG, Gensburg LJ, Dieren DA, Geary NS, Cayo MR. Maternal residential exposure to hazardous wastes and risk of central nervous system and musculoskeletal birth defects. Arch Environ Health 52:416–425 (1997).
23. Correa A, Gray RH, Cohen R, Rothman N, Shahi F, Sescat H, Corin M. Ethylene glycol ethers and risks of spontaneous abortion and subfertility. Am J Epidemiol 143:707–717 (1996).
24. Lindbohm ML, Hemminki K, Bonhomme MC, Antilla A, Rantala K, Heikila P, Rosenberg MJ. Effects of paternal occupational exposure on spontaneous abortions. Am J Public Health 81:1029–1033 (1991).
25. Morgenstern H. Uses of ecological analysis in epidemiologic research. Am J Public Health 72:1236–1244 (1982).
26. Cronen LA, Shaw GM, Sanbonmatsu L, Selvin S, Buffler PA. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. Epidemiology 8:347–354 (1997).