Science of the Total Environment 409 (2011) 447–451

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Links between environmental geochemistry and rate of birth defects: Shanxi Province, China

Hai-ying Yu [a,b], Ke-li Zhang [a,*]

[a] State Key Laboratory of Earth Surface Processes and Resource Ecology, School of Geography, Beijing Normal University, Beijing 100875, PR China
[b] College of Resources and Environmental Sciences, Sichuan Agricultural University, Ya'an, Sichuan 625014, PR China

ARTICLE INFO

Article history:
Received 16 July 2010
Received in revised form 10 October 2010
Accepted 11 October 2010
Available online 23 November 2010

Keywords:
Birth defect
Geochemical elements
Abnormalities
High birth defect area

ABSTRACT

The rate of birth defects in Shanxi Province is among the highest worldwide. In order to identify the impacts of geochemical and environmental factors on birth defect risk, samples of soil, water and food were collected from an area with an unusually high rate of birth defects (study area) and an area with a low rate of birth defects (control area) in Shanxi Province, China. Element contents were determined by ICP-OES, and the results were analyzed using a non-parametric test and stepwise regression. Differences in the level and distribution of 14 geochemical elements, namely arsenic (As), selenium (Se), molybdenum (Mo), zinc (Zn), strontium (Sr), iron (Fe), tin (Sn), magnesium (Mg), vanadium (V), calcium (Ca), copper (Cu), aluminum (Al), potassium (K) and sulfur (S) were thus compared between the study and control areas. The results reveal that the geochemical element contents in soil, water and food show a significant difference between the study area and control area, and suggest that the study area was characterized by higher S and lower Sr and Al contents. These findings, based on statistical analysis, may be useful in directing further epidemiological investigations identifying the leading causes of birth defects.

1. Introduction

Birth defects (congenital anomalies) are the leading cause of death in babies under 1 year of age (Petrini et al., 2002; Detrait et al., 2005). For the past several decades, epidemiological surveying has been a key approach to identifying the causal factors, and has demonstrated that causes leading to birth defects are very complex. However, all birth defects can be presumed to be caused by a combination or interaction of genetic and environmental factors.

Epidemiologists are interested in whether it is genetic or environmental factors (or both) that distinguish individuals with or without birth defects. In its widest sense, an environmental cause is any nongenetic factor that increases the risk of a birth defect for the exposed individual, generally including nutritional excesses and deficiencies, maternal illness and injection, drug use, chemical exposures in the workplace or home, exposure to radiation, and chemical contaminants in air, food, water and so on.

Although no direct causal connections have been established between the geographic environment and rate of birth defects, the fact that regions with a particularly high rate of birth defects do occur require that studies must be conducted to investigate the causes of birth defects in terms of geographic and environmental factors. The highest rate of birth defects in the world has been reported in China, and of these defects a hospital study has shown that neural tube defects (NTDs) are the most common birth defect. However, the rate of NTDs in China varies greatly between different regions. Data from the Chinese Birth Defects Monitoring Program (CBDMP) indicated that NTD rate at birth in the whole of China is 2.7‰, but is 10.6‰ in Shanxi Province, which ranks highest and has become known as "Everest" due to its high incidence rate (Chen et al., 2009; Xiao et al., 1990; Li et al., 2006). The rate is so high that a logical first step in etiological research is to identify geographic factors associated with risk. Population and family studies indicate a complex etiology in NTDs, involving both environmental and genetic factors. Environmental factors implicated in increasing the risk of birth defects include geography, epidemic trends, socioeconomic class, maternal age, maternal diet, maternal diabetes and obesity.

Early studies of the causes of birth defects were mainly focused on genetic factors. However, by the 1960s, influences of environmental causes on birth defects had been extensively confirmed. Vinceti et al. (2001) monitored birth defects in the area seriously polluted by lead in northern Italy and found that over a period of time, decreasing the environmental lead content reduced the incidence of heart diseases, orificial clefts and bone diseases. Irgens et al. (1998) collected data from all newborn babies between 1970 and 1993 in Norway, and compared data on fetus defects between those from parents who were likely to have been exposed to lead pollution and those from parents with unlikely lead exposure. They concluded that newborns born to mothers exposed to lead pollution had a greater risk of low weight and NTDs. It has further been shown that the occupations of

---

* Corresponding author. Tel.: +86 10 58805163; fax: +86 10 58806955.
E-mail address: keli@bnu.edu.cn (K. Zhang).

0048-9697/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.scitotenv.2010.10.019

pregnant women have a major affect on the health of children, and also that women's exposure to glycol might lead to birth defects (Cordier et al., 1997). More recent research has suggested that women with long-term occupational exposure to anesthetic gases, and pregnant women living in areas polluted by nuclear radiation, might be at higher risk of giving birth to a child with birth defects (Ratzon et al., 2004). Some researchers have considered that the rate of nongenetic birth defects is proportional to the level of the economic poverty (Vrijheid et al., 2000); in particular, the socioeconomic circumstances during a woman's childhood were shown to have more influence on birth defects than those during pregnancy (Sever and Emanuel, 2008). Although the prevalence rate of birth defects has been attributed to numerous environmental factors, the geographic "gradients" of relatively higher rates compared with other places in the world reveal that the geographic environment has a significant impact on birth defects (Olney and Mulinare, 1999). Even in China, epidemiological surveys have indicated that there is an obvious territorial clustering of high prevalence areas, whereby the incidence in the north of China is higher than that in the south (Cynthia et al., 1998). Also, in general the birth defects rate in rural areas is higher than that in urban areas.

Although many environmental factors associated with increased risk of birth defects have been discussed in the studies mentioned, the contribution of environmental factors to birth defects is still inconclusive. Meanwhile, so-called environment factors have generally been limited to secondary environmental factors, such as pollution in water, air and foods, and unusual workplace environments. Few studies have dealt with causal factors based on comprehensive analysis of raw geographic information in a high prevalence region of birth defects. We therefore believe that the identification of leading causes of birth defects through their link with abnormal environmental conditions is of great importance in areas with high rates of birth defects.

Here, we statistically analyzed and compared geochemical anomalies in areas with high and normal rates of birth defects to elucidate the relationship between incidence rate of birth defects and geochemical anomalies, and to provide a non-medical basis for effective prevention and cure of birth defects.

2. Materials and methods

2.1. Study areas and birth defect surveys

Shanxi Province has the highest rate of birth defects in China. The province is located in northern China, and is surrounded by the Luliang mountains in the west and Taihang mountains in the east. Epidemiological surveys show that the birth defects rate is highest in the Luliang mountains. In this study, Zhongyang County and Jiaokou County in the Luliang region were selected as areas with high rates of birth defects, at 717.64 per 10,000 births and 917.06 per 10,000 births, respectively, according to the survey by the Capital Institute of Pediatrics. Pingyao County, located in the middle of Shanxi Province, was chosen as the control area (Fig. 1).

A population-based retrospective study was conducted in high prevalence areas from Jan. 1, 2002 to Dec. 31, 2004. During these three years, 542 cases of birth defects were diagnosed among 6420 fetuses. Types and incidence rate of birth defects are shown in Table 1.

2.2. Sampling

In the epidemiological survey, 146 surface soil samples (cropland and woodland), 146 drinking water samples (well water and river water) and 170 crop samples (corn) were sampled in the study area and control area from January to May in 2005. Samples were collected from both sides of the river, in an area where the population is relatively dense, while soil samples were collected in areas far away from residential areas and roads to ensure the samples were representative.

2.3. Sample preparation and laboratory analysis

The samples were immediately processed in the laboratory after sampling. Air dried soil samples were sieved with a 100 mesh sieve. 0.1 g of each soil sample was then mixed with 3 ml nitric acid, 1 ml perchloride acid and 1 ml hydrofluoric acid. The samples were placed in an oven for nitration for 5 h, then removed and heated on an

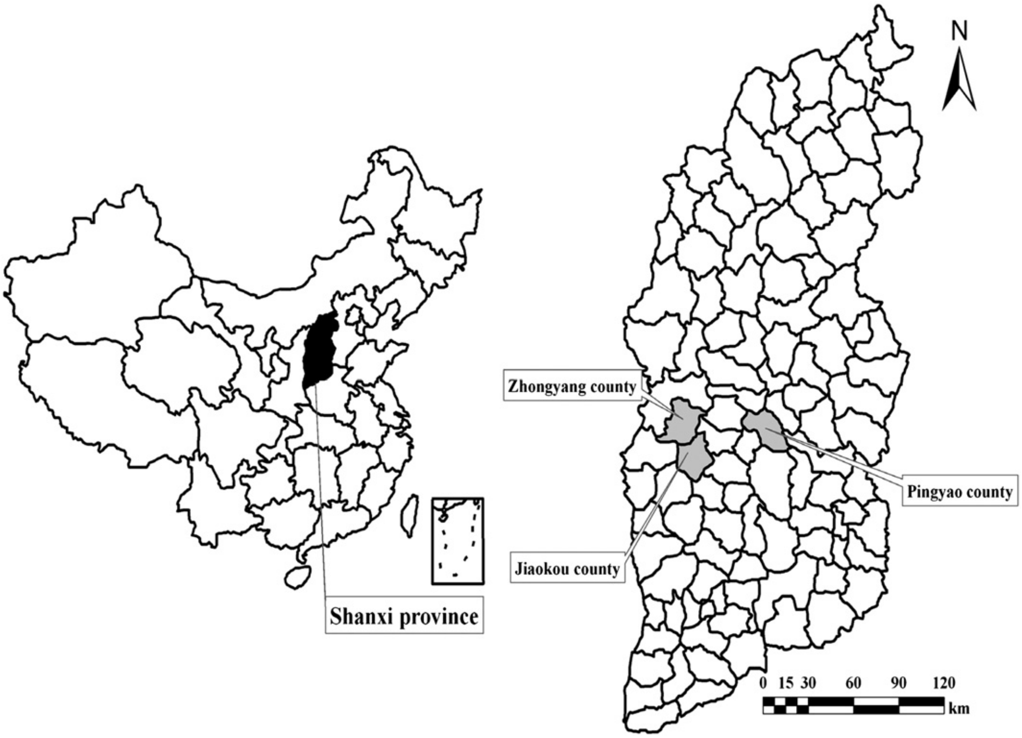

Fig. 1. Location of the study areas.

Table 1
Prevalence of various birth defects in the high birth defects area (2002–2004).

Birth defect	Number of patients	Rate (per 10,000 births)	Birth defect	Number of patients	Rate
Inguinal hernia	117	182.2	Cleft lip	6	9.4
Anencephaly	67	104.4	Acromphalus	6	9.4
Congenital mental retardation	51	79.4	Cheilopalatognathus	4	6.2
Congenital heart diseases	47	73.2	Hypospadia	4	6.2
Spina bifida	41	63.9	Anal atresia	3	4.7
Hydrocephalus	26	40.5	Down's syndrome	3	4.7
Encephalocele	20	31.2	Strephenopodia	2	3.1
Angioma	19	29.6	Microophthalmia	2	3.1
Hydrocele of tunica vaginalis	15	23.4	Congenital cataract	2	3.1
Cryptorchidism	14	21.8	Limb shortening	2	3.1
Hyperdactylia and ectrodactylia	12	18.7	Coeloschisis	2	3.1
Crinosity	12	18.7	Strephexopodia	1	1.6
Deformity of external ear	9	14.0	The others	49	76.3
Cleft palate	6	9.4			

electric heating board for about 1 to 2 h. After the liquid had evaporated to leave beads, pure water was added to the samples to bring the volume to 10 ml, and samples were set aside for analysis.

Food samples were firstly washed, dried and carefully ground. 0.1 g of each sample was mixed with 1 ml nitric acid and 1 ml hydrogen peroxide. The mixture was heated, and once the liquid had evaporated pure water was added to the samples to bring the volume to 10 ml. Contents of 14 elements in the samples (As, Se, Mo, Zn, Sr, Fe, Sn, Mg, V, Cu, Al, K, S and Ca) were determined with ICP-OES.

2.4. Statistical analysis

The measured data were divided into two groups, representing the study area (high birth defect rate) and control area. Firstly, statistical analysis of all elements was carried out to identify elements with little variation in content within samples and eliminate those elements with larger variations. Next, we compared element contents in samples from the high birth defect area with those collected from the control area, and analyzed environmental anomalies in the high birth defect area via a non-parametric test (Mann–Whitney signed-rank test) and stepwise regression analysis. Statistical analysis was carried out with SPSS 10.0.

The Mann–Whitney signed-rank test was developed by H. B. Mann and D. R. Whitney in 1947 to compare the median values of two sample sets. The null hypothesis of the test is that there is no difference in population median between the two sample sets. To carry out the test, the combined data set (both sets of samples) is ranked in order, with the minimum value given the rank 1 and any tied values given the mean of the respective tied ranks. Next, two sums, W_1, W_2 are calculated, corresponding to the sum of ranks in each of the two sample sets. The Mann–Whitney U value is then calculated from

$$U = n_1 n_2 + n_1(n_1 + 1) / 2 - W_1 \text{ if } W_1 > W_2 \tag{1}$$

or

$$U = n_1 n_2 + n_2(n_2 + 1) / 2 - W_2 \text{ if } W_1 < W_2 \tag{2}$$

where n_1, n_2 are the number of samples in the respective sample sets. The test statistic z is then calculated as

$$z = \frac{U - \mu_U}{\sigma_U} \tag{3}$$

where

$$\mu_U = \frac{n_1 n_2}{2}, \sigma_u = \sqrt{\frac{n_1 n_2 (n_1 + n_2 + 1)}{12}}$$

If $|Z| > 1.96$, the difference between population medians is significant at the 5% level, while if $|Z| > 2.58$, the difference is significant at the 1% level.

3. Results and discussion

Geochemical anomalies can generally be thought of as the excess or deficiency of a chemical element in soil, water or plants, and the subsequent development or transport of this anomaly within the geosphere, hydrosphere, biosphere and human beings. In the present study, we only focus on the comparison of earth element contents in soil, water and plants between high and low birth defect rate areas, and identify differences between these areas in terms of their environment. Sets of elements that show significant differences between areas of high and low rates of birth defects can be assumed to be the major environmental factors of controlling the rate of birth defects.

3.1. Sample analysis and element selection

Samples collected from the high birth defect rate area and the normal area were split into two independent groups. In order to enable comparison between the two sample groups and to determine the environmental causes, we firstly identified sets of elements that could be used to represent the main features of each group. These selected elements were identified by their low within-group variance and high between-group variance. If the content of an element varied greatly across the high birth defect rate area, it was regarded as having no close relation to birth defects and was removed from the database. Other elements were also excluded if their contents were less than the detection limits of the apparatus. The variation of a sample was represented by the variation coefficient.

Table 2 shows the statistical characteristics of element contents in soil, water and crop samples from the two areas. In the areas of high birth defect rate, the element contents in the soil were comparatively stable, with small changes between sampling sites, while the element contents in the water and crop samples displayed greater variability. Elements with the greatest variability included As, Mo, Sn and Cu in surface water, As, Mo, Zn, Sn and Cu in deep water and Mo and Sn in crops. If the epidemiological survey can identify elements affecting the risk of birth defects, these elements should be the subject of further study. Since As, Mo, Sn and Cu showed high variability, they were eliminated from the database prior to further analysis.

Table 2
Coefficient of variation of elements content in different environmental media in the high birth defects area.

	Index	As	Se	Mo	Zn	Sr	Fe	Sn	Mg	V	Ca	Cu	Al	K	S
Soil	Woodland	0.15	−1.58	0.28	0.18	0.28	0.51	0.18	0.39	0.15	0.45	0.18	0.29	0.18	0.57
	Cropland	0.24	6.88	0.24	0.56	0.23	0.34	0.17	0.36	0.12	0.34	0.31	0.25	0.09	0.3
Water	River water	−2.83	1.15	−1.45	1.85	0.64	−0.3	4.52	0.61	−0.55	0.49	7.61	0.52	0.69	0.87
	Well water	−7.07	1.1	4.3	1.8	0.59	−0.46	3.57	0.64	−0.65	0.8	5.84	1.2	0.38	1.1
Food	Corn	−1.11	−3.95	−44.8	0.43	0.98	2.65	−42.2	0.36	7.92	1.23	0.92	1.03	0.91	0.38

3.2. Identification of anomalous elements

Following the selection or elimination of each element, the remaining elements (with stable contents) were used to compare samples collected from the group in the area of high birth defects rate with samples collected in the normal area, to analyze differences in geochemical features. Distinctive features between the groups were revealed using the non-parametric test (Mann–Whitney signed-rank test) and stepwise regression analysis.

3.2.1. Non-parametric test

The Mann–Whitney signed-rank test can be used to test whether there is a significant difference in the medians of two populations. Results from the non-parametric tests after elements As, Mo, Sn and Cu were eliminated are shown in Table 3, and demonstrate that the two groups of data from the high and low birth defect rate areas showed a significant difference with respect to some (but not all) the remaining elements. Elements with statistical significance better than 0.05 were classified as anomalous elements and included Fe, S and Zn in soil, Sr, Fe, Mg, A1 and K in water and Sr, Ca and K in food. Combining these three contents from soil, food and water reveals that Sr has the strongest link with birth defect rate.

3.2.2. Stepwise regression analysis

Although a set of elements that contribute to environmental causes has been identified with the non-parametric test, we have not yet determined the nature of their contributions to birth defects. Therefore, regression analysis was employed to further analyze the contribution of each element to the birth defect ratio and to determine which element was the most important when distinguishing birth defects. In stepwise linear regression, the contents of the 14 elements are independent variables that can be analyzed step by step. Elements included in the analysis were those that showed a significant influence on birth defect rate (Table 4), namely Zn, Sr, K and S in cropland soil, S in woodland soil, Mo, Sr, Sn, Ca and Al in surface water, Mo, Sr, Sn, Al, K and S in deep water, and K in crops. If the resulting regression parameter is positive, higher contents of that element are associated with higher birth defect rates. Conversely, if the regression parameter is negative, higher contents of that element are associated with lower birth defect rates. Results show a significant positive relationship between the S content and the birth defect rate, however, Se, Mg, Mo, Zn and Sr showed significant negative correlation with birth defect rate. Finally, the regression equation may be able to predict birth defect rates in an area, using environmental data.

3.2.3. Distinctive Environmental Features

In the analysis mentioned, the non-parametric test revealed that the contents of some elements in the high birth defect rate area were markedly higher or lower than those in the normal area. Stepwise regression analysis highlighted elements with a high contribution to the environmental anomaly in the area of high birth defect rate. Combinations of elements identified in the analysis mentioned and tests may reflect the nature of the geochemical anomaly in the area with a high birth defect rate. Table 5 shows that although the contents of elements in the area with a high rate of birth defects were not the same between different environmental factors, there was a clear trend in which S was higher and Sr, Al were lower in the study area. Consequently, we can conclude that excess S and a deficiency of Sr and Al are the distinctive environmental features associated with the high rate of birth defects.

4. Conclusions

Although all birth defects can be presumed to be caused by a combination or interaction of genetic and environmental factors, the effects of the local environment on birth defects are still unknown.

Table 3
Mean rank of elements by location and media of the non-parametric test.

Index		Se		Zn		Sr		Fe		Mg	
Location and media		n	y	n	y	n	y	n	y	n	y
Soil	Woodland	8.2	9.3	5.2	10.58*	9.6	8.8	7.8	9.5	9.6	8.8
	Cropland	23.3	20.8	23.7	17.6	22.9	24.2	24.5	11.4*	23.4	20.2
Water	River water	21.3	14.0	18.5	14.4	27.5	13.0**	26	13.2**	26.5	13.2**
	Well water	13.5	9.1	14.5	8.8	17.5	8.0**	17.3	8.1**	17.5	8.0**
Food	Corn	20.4	14.0	16.9	15.1	23.1	13.2**	18.6	14.6	18.6	14.6

Index		V		Ca		Al		K		S	
Location and media		n	y	n	y	n	y	n	y	n	y
Soil	Woodland	6.4	10.1	6.6	10.0	10.2	8.5	6.2	10.2	3.0	11.5**
	Cropland	23.6	18.4	24.2	13.4	23.5	23.0	24.2	13.7	24.4	11.6*
Water	River water	16.5	14.8	17.0	14.7	26.5	13.2**	22.75	13.8*	14.3	19.5
	Well water	13.0	9.2	12.0	9.5	17.5	8.0**	15.75	8.5*	9.2	13.0
Food	Corn	19.0	14.4	21.4	13.7*	17.3	13.6	22.3	13.4*	14.1	20.1

Note: n represents the control area while y represents the area with a high rate of birth defects.

* $P<0.05$.

** $P<0.0$ l.

Table 4
Descriptive statistics of stepwise regression analysis.

Element	Const.	Se	Mo	Zn	Sr	Sn	Mg	Ca	Al	K	S
Woodland	−0.327										0.002
Cropland	−1.228			−0.0019	−0.0066					0.00015	0.0017
Surface water	1.073		−51.667		−0.344	2.959		0.0032	−2.951		
Deep water	1.066		−51.667		−0.152	−2.814			−6.942	0.0765	0.0042
Food	1.068									−0.00009	

Table 5
Combination of descriptive statistics from regression analysis and the non-parametric test.

Samples	Non-parametric test		Stepwise regression	
	Higher content	Lower content	Negative correlation	Positive correlation
Woodland	Zn, S			S
Plough land	Fe, S		Zn, Sr	S
Surface water		Sr,Fe, Mg, Al,K	Sr, Al	
Deep water		Sr, Fe, Mg, Al, K	Sr, Al	
Food		Sr, Ca, K	K	

This study is the first explorative investigation of the association between chemical elements (in soil, water and food) and the rate of birth defects. Chemical element contents showed significant differences between the study area and control area. Anomalous chemical elements were not all the same between the three sample sources (soil, water food), but the results suggest it likely that an excess of S and deficiency of Sr and Al are the distinctive environmental features associated with the high rate of birth defects in the Shanxi Province of China. Our findings in this study are based on samples collected from soil, water and food in the study area and control areas, so we cannot rule out the influences of geomorphology and elevation. Thus, the findings must be interpreted cautiously before epidemiological policies are established. Further, it is unknown whether the chemical elements that were excluded from the databases in this study genuinely have no relation to birth defects. Further research should focus on the transfer of chemical elements among the lithosphere, pedosphere, hydrosphere and biosphere.

Acknowledgements

This work was supported by the National “973” Project on Population and Health (no.2001CB5103), The authors are grateful for Prof. Wang Jinfeng at Insitute of Geography and Natural Resource Research, CAS, and Prof. Zheng Xiaoying at the Beijing University, who supported to the soil sampling. Thanks also to the anonymous reviewers on our manuscript.

References

Chen G, Pei LJ, Huang J, Song XM, Lin LM, Gu X, et al. Unusual patterns of neural tube defects in a high risk region of northern China. Biomed Environ Sci 2009;22:340–4.

Cordier S, Bergeret A, Goujard J, Ha MC, Aymé S, Bianchi F, et al. Congenital malformations and maternal occupational exposure to glycol ethers. Epidemiology 1997;8:355–63.

Cynthia AM, Li S, Li Z, Hong SX, Gu HQ, Berry RJ, et al. Elevated rates of severe neural tube defects in a high-prevalence area in northern China. Am J Med Genet 1998;73:13-118.

Detrait ER, George TM, Etchevers HC, Gilbert JR, Vekemans M, Speer MC. Human neural tube defects: developmental biology, epidemiology, and genetics. Neurotoxicol Teratol 2005;27:515–24.

Irgens Å, Krüger K, Skorve AH, Irgens LM. Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. Am J Ind Med 1998;34:431–7.

Li ZW, Ren A, Zhang L, Ye RW, Li S, Zheng JC, et al. Extremely high prevalence of neural tube defects in a 4-county area in Shanxi province, China. Birth Defects Res 2006;76(4):237–40.

Olney R, Mulinare J. Epidemiology of neural tube defects. Ment Retard Dev D R 1999;4:241–6.

Petrini J, Damus K, Russell R, Poschman K, Davidoff MJ, Mattison D. Contribution of birth defects to infant mortality in the United States. Teratology 2002;66:S3–6.

Ratzon NZ, Ornoy A, Pardo A, Rachel M, Hatch M. Developmental evaluation of children born to mothers occupationally exposed to waste anesthetic gases. Birth Defects Res A 2004;70:476–82.

Sever LE, Emanuel I. Intergenerational factors in the etiology of anencephalus and spina bifida. Dev Med Child Neurol 2008;23:151–4.

Vinceti M, Rovesti S, Bergomi M, Calzolari E, Candela S, Campagna A, et al. Risk of birth defects in a population exposed to environmental lead pollution. Sci Total Environ 2001;278:23–30.

Vrijheid M, Dolk H, Stone D, Abramsky L, Alberman E, Scott JES. Socioecnomic inequalities in risk of congenital anomaly. Arch Dis Child 2000;82:349–52.

Xiao KZ, Zhang ZY, Su YM, Yu Hai-ying, Zhang Ke-li. Central nervous system congenital malformations, especially neural tube defects in 29 provinces, metropolitan cities and autonomous regions of China: Chinese Birth Defects Monitoring Program. Int J Epidemiol 1990;19:978–82.