Original Article

Effect of Exposure to Trace Elements in the Soil on the Prevalence of Neural Tube Defects in a High-Risk Area of China*

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Abstract

Objective Our objective is to build a model that explains the association between the exposure to trace elements in the soil and the risk of neural tube defects.

Methods We built a function with different parameters to describe the effects of trace elements on neural tube defects. The association between neural tube defects and trace element levels was transformed into an optimization problem using the maximum likelihood method.

Results Tin, lead, nickel, iron, copper, and aluminum had typical layered effects (dosage effects) on the prevalence of neural tube defects. Arsenic, selenium, zinc, strontium, and vanadium had no effect, and molybdenum had one threshold value that affected the prevalence of birth defects.

Conclusion As an exploratory research work, our model can be used to determine the direction of the effect of the trace element content of cultivated soil on the risk of neural tube defects, which shows the clues by the dosage effect of their toxicological characteristics. Based on our findings, future biogeochemical research should focus on the direct effects of trace elements on human health.

Key words: Trace element; Neural tube defects; Risk factors identification; Poisson model; Maximum likelihood estimation

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INTRODUCTION

The quality of human life and health are affected by the chemical composition of food and the surrounding environment. Advances in analytical chemistry and environmental investigations have substantially added to the knowledge of the biogeochemistry of trace elements. Most chemical elements necessary for life are supplied by the soil overlying the surficial lithosphere. Thus, the soil is not only a part of the ecosystem, but linked to the health and survival of humans through the production of foods. Soil functions as a filtering, buffering, storage, and transformation system that to prevent environment al pollution[1].

The internal biochemistry of the human body is naturally adjusted to the natural contents of the environment. In some regions, however, geochem ical anomalies in the bedrock, soils from agricultural practices and environmental pollution affect the trace element content of food crops and other plants, making them maladjusted to human health. Dietary deficiency or excess of these elements may result in disease and impaired metabolism. The effects of trace elements on human health are complex, and there are few quantifiable standards against which they can be measured[2].

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A birth defect occurs when a fetus is developing with an abnormality in function, structure, or metabolism. Causes of birth defects include both genetic and environmental factors. Genetic factors account for 10% and environmental factors account for 20% of the birth defects. The remainder is mostly caused by interactions between genetic and environmental factors[3]. Environmental factors, such as regional geochemical characteristics like geomagnetism, terrestrial heat, and excessive radioactivity, and air, soil, and water pollution can increase the prevalence of birth defects[4].

The heterogeneity of soil at microscopic level and the susceptibility of individuals to birth defects are challenges to the quantitative analysis of the effects of trace elements in soil on human health. The present study was conducted in the Lvliang region of Shanxi province, which is the area with the highest prevalence of neural tube defects in China[5]. A model was built to analyze the association between the trace element content of cultivated soil and the prevalence of neural tube defects. The object of this model was to determine the normal ranges of trace elements in the soil and their effects on the prevalence of birth defects. Depending on the results, an exploratory analysis of the exposure to environmental risk factors could be carried out.

MATERIALS AND METHODS

Study Area and Data Collection

The study area was the Lvliang region, Shanxi province, China (Figure 1). Birth defect cases included all live births and stillbirths from January 1, 2002 to December 31, 2004. All mothers gave birth either at the hospital or at home and were residents of the study area during the study period. All neural tube defects were verified by doctors in the hospital, regardless of pregnancy outcome. Data collection and quality control were described[6].

At least two patches of the cultivated land in each of the surveyed villages were selected for collection of soil samples. The depth of the soil samples was between 2 cm and 20 cm. All soil samples collected in one village were mixed thoroughly to represent that village[7]. All field sampling works were carried out during a 2 week period in December 2004. We used inductively coupled plasma mass spectroscopy (ICP-MS) to measure the content level of 12 trace elements in the soil samples with standard procedures[8]. Trace elements studied were tin (Sn), arsenic (As), selenium (Se), molybdenum (Mo), zinc (Zn), strontium (Sr), lead (Pb), iron (Fe), nickel (Ni), vanadium (V), copper (Cu), and aluminum (Al).

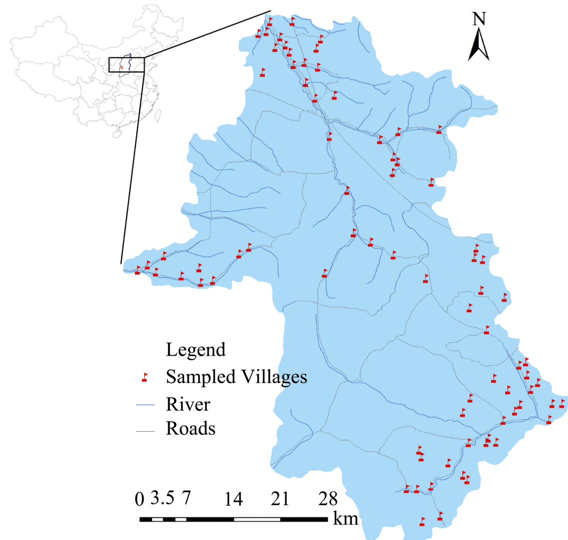


Figure 1. Study area and villages.

All cases of neural tube defects and all soil samples were matched by geo-code of the villages' names and locations. In total, 112 villages had both records of birth defects and data on trace element content of soil samples.

Hypothesis for Model Building

Trace elements can be classified as essential, possibly essential, or non-essential for human health. According to related studies, most elements studied here are essential, such as nickel, arsenic, copper, iron, molybdenum, selenium, vanadium, and zinc. Aluminum, tin, and strontium might be possibly essential while the heavy metal element lead is non-essential and highly toxic to humans[1]. However, these elements play an unclear role in human health. We assumed that there are three possible types of association between trace element content and human health. 1), The trace element content has either a positive or negative relation to health. An increase or decrease in the soil levels would cause a corresponding effect on the health of the population. In terms of the present study this would mean an increase or decrease in the prevalence of birth defects. 2), The relationship between the trace element content level and population health shows a dose effect. That is, higher or lower amounts of the trace element content level would result in a higher or lower prevalence of birth defects. 3), There is no relationship between trace element content and the risk of birth defects, meaning that increasing or decreasing levels of the trace element has no effect on population health, and no effect on the prevalence of the birth defects. Existing studies show that there are different effects of the studied trace elements on population health. The association is not linear; the curve of effects on population health usually shows some one or two critical points (Figure 2).

Model Building

We built a model that could reflect the association between the trace element levels and the occurrence of neural tube defects. The effect of trace elements depends on certain parameters. Different values of these parameters would reveal the effects of various elements on population health, which is the prevalence of neural tube defects here.

Consider the function $f(x, a_1, a_2, b_1, b_2, \varepsilon_1, \varepsilon_2, c)$, where x is the content level of one type of trace element. The parameters $a_1, a_2, b_1, b_2, \varepsilon_1, \varepsilon_2, c$ describe how this element works on population health, in this case the occurrence of neural tube defects. Assuming that $\varepsilon_1 > 0, \varepsilon_2 > 0$, $a_1, a_2, b_1, b_2, c \in R$, the function is expressed as follows:

$$f(x; a_1, a_2, b_1, b_2, \varepsilon_1, \varepsilon_2, c) = b_1 \tanh\left(\frac{x - a_1}{\varepsilon_1}\right) + b_2 \tanh\left(\frac{-x + a_2}{\varepsilon_2}\right) + c$$

where, f means the occurring cases of neural tube defects in village x.

Figure 3 shows the different effects of the trace element content on the prevalence of neural tube defects, given different values for $a_1, a_2, b_1, b_2, \varepsilon_1, \varepsilon_2, c$. The trace element content has different critical points, depending on these parameters. Here are some examples:

1) Case I. There are two critical points, x_1 and x_2. When the element content is less than x_1 or greater than x_2, the risk of neural tube defects is high. Only when the element content is between the two critical thresholds, the risk of birth defects is low. The corresponding parameters $a_1, a_2, b_1, b_2, \varepsilon_1, \varepsilon_2, c$ here might be $a_{11}, a_{21}, \beta_{11}, \beta_{21}$, 0.01, 0.05, and γ_1, respectively. In the reverse situation, the occurring risk of the neural tube defects would be high when the elements content is between the two critical thresholds.

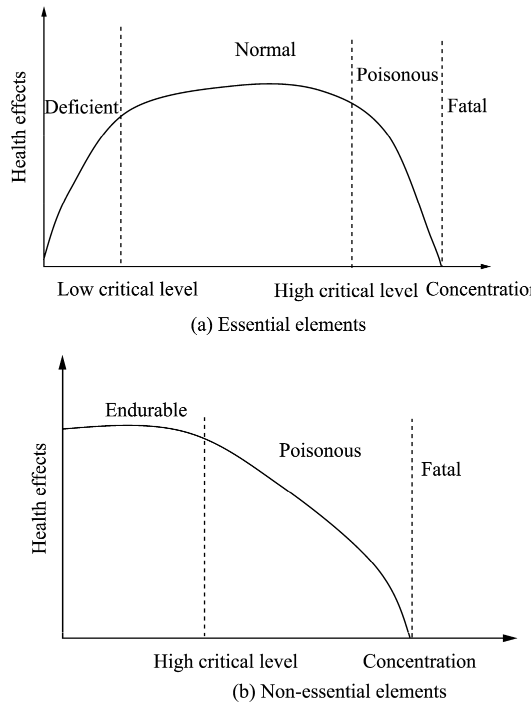


Figure 2. Relationship between trace element content level and human health[9].

2) Cases II and III. There is a critical threshold that abruptly changes the risk of the neural tube defects. When the element content level is higher or lower than that threshold, the risk of defects increases or decreases. In Case II, if the trace element content is greater than the critical threshold x_1, the risk of neural tube defects clearly increases. Case III is the reverse situation: When the content is less than x_1, the risk of the defects is high, but it decreases when the content is greater than x_1.

3) Case IV. The trace elem ent content has no effect on the risk of birth defects. In this case, the curve of the risk of neural tube defects is a horizontal line, expressing that the occurrence of birth defects is independent of the trace element content.

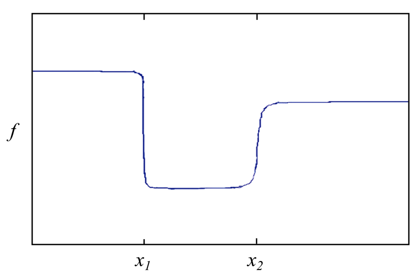
With the object function built, we considered how to quantify the prevalence of neural tube defects, or occurring risk, in a village. Because birth defects are a small probability event, we hypothesized that the number of birth defects would follow a Poisson distribution[10].

The probability of an infant being born with a kind of neural tube defect is P $(0 \leqslant P \leqslant 1)$; the probability that the infant is born without any neural tube defects is $1- P$. The number of infants who have any type of neural tube defects follows a binomial distribution, which means that the probability of k birth defect cases over n births would be $C_n^k P^k (1-P)^{n-k}$. When P is small enough, the limitation of a binomial distribution is the Poisson distribution as n tends to be infinite and $n \times P$ remains constant[11]. In practice, the occurring probability of birth defects must be less than 1.

Given that the village is relatively independent of soil samples and neural tube defects, we assume that the occurrence of defects follows a Poisson distribution with parameter λ, which is the average number of birth cases with any type of neural tube

$a_1=\alpha_{11}$, $a_2=\alpha_{21}$, $b_1=\beta_{11}$, $b_2=\beta_{21}$,

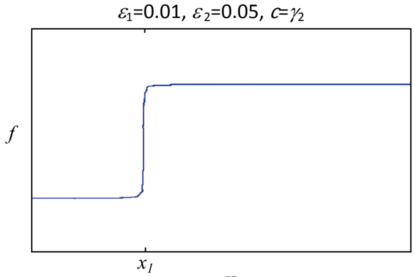
$\varepsilon_1=0.01$, $\varepsilon_2=0.05$, $c=\gamma_1$



I

$a_1=\alpha_{12}$, $a_2=\alpha_{22}$, $b_1=\beta_{12}$, $b_2=\beta_{22}$,

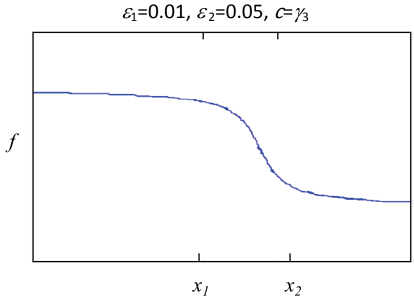
$\varepsilon_1=0.01$, $\varepsilon_2=0.05$, $c=\gamma_2$



II

$a_1=\alpha_{13}$, $a_2=\alpha_{23}$, $b_1=\beta_{13}$, $b_2=\beta_{23}$,

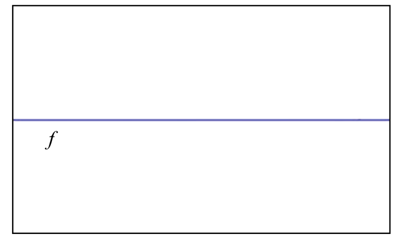
$\varepsilon_1=0.01$, $\varepsilon_2=0.05$, $c=\gamma_3$



Ⅲ

$a_1=\alpha_{14}$, $a_2=\alpha_{24}$, $b_1=\beta_{14}$, $b_2=\beta_{24}$,

$\varepsilon_1=0.01$, $\varepsilon_2=0.05$, $c=\gamma_4$



IV

Figure 3. Different functions obtained using different parameters.

defect. With the Poisson model, the probability of a village having Y birth cases with neural tube defects is:

$$P(Y;\lambda) = \lambda^Y e^{-\lambda} / Y!.$$

Here, the Poisson parameter λ is determined by the function f. To ensure that λ is positive, we use a simple transformation of f to get λ: $\lambda = (f + \sqrt{f^2 + \varepsilon})/2$, where ε <<1, and λ is:

$$0 \; for \; f < 0, \; or \gg f \; for \; f > 0.$$

Assuming that in village i the content level of one trace element in the soil is x_i, the number of births with a neural tube defect is y_i, and the Poisson parameter is λ_i, the probability of y_i birth cases with a neural tube defect is:

$$P(Y = y_i; \lambda_i) = \lambda_i^{Y_i} e^{-\lambda_i} / Y_i!.$$

As the risks of neural tube defects in different villages are independent random variables, the probability of y_i cases with a neural tube defects in village i ($1 \leqslant i \leqslant n$, where n is the number of total births in the village) is:

$$P(Y_1 = y_1, Y_2 = y_2, \ldots, Y_n = y_n; \lambda_1, \lambda_2, \ldots, \lambda_n) = \prod_{i=1}^{n} P(Y_i = y_i; \lambda_i)$$

$$= \prod_{i=1}^{n} \frac{\lambda_i^{Y_i}}{Y_i!} e^{-\lambda_i}$$

With a three-year investigation, we can assume that the surveyed data in this area accurately reflects the risk of neural tube defects in those villages[6]. The association between the trace element content of the soil and the occurring risk of neural tube defects of those villages is relative stable. Thus, we can convert the probability of content levels of trace elements in the soil and the occurring risk in each village into a maximum likelihood problem as below[12]:

$$\max_{\substack{a1,a2,b1,b2,\\ \varepsilon 1,\varepsilon 2,c}} \prod_{i=1}^{n} \frac{\lambda_i^{Y_i}}{Y_i!} e^{-\lambda_i}$$

Where

$$\lambda_i = (f(x_i) + \sqrt{f(x_i)^2 + \varepsilon}) / 2 ,$$

$$f(x_i) = b_1 \tanh\left(\frac{x_i - a_1}{\varepsilon_1}\right) + b_2 \tanh\left(\frac{-x_i + a_2}{\varepsilon_2}\right) + c$$

We used the optimization toolbox in MATLAB to solve this problem[13].

RESULTS

There are many differences in the levels of trace elements in the soil between our study data and background values in Shanxi province. This may partly explain why our study area has the highest prevalence of neural tube defects in China. With the optimization model solved with the optimization toolbox software package of MATLAB, we examined 12 trace elements. The results show that tin, lead, nickel, iron, copper, and aluminum had typical layered level effects on the occurring risk of birth defects. The association between the levels of trace elements and the occurring risk of birth defects followed various patterns. This is similar to the dosage effects of toxicological characteristics of trace elements. Arsenic, selenium, zinc, strontium, and vanadium had no direct effect on the occurring risk of neural tube defects. This might be because these elements really have no effects on human health, or there may be antagonistic interactions with other elements, as these elements are typically more easily combined with others. Furthermore, there are no significant differences in content levels of those elements among the villages as is shown by the variance of content levels. Detailed results are shown in Table 1.

To evaluate our Poisson statistical model, we defined the fitness value as

$$V_i = \frac{P_{\lambda_i}(m = Y_i)}{\max_m P_{\lambda_i}(m)} ,$$

when the parameter λ_i and the experimental data y_i are known. As the event with the highest probability appears most likely, we have the highest fitness value V_i =1 when the observable y_i exactly corresponds to the event with the highest probability in the Poisson model with parameter λ_i; otherwise it will be less than 1, and we take it as a quantitative assessment of the model. The results obtained for the current data set are shown in the 4th column in Table 1, which gives reasonable fitness values around 0.80 with the estimated parameters.

The element of molybdenum had a threshold value for the effect on neural tube defects. When the molybdenum content level is below the threshold (8.51 ug/mg), and when content level of it is more than that threshold, the association would become positively related, reducing and increasing content level of it would both increase the risk of neural tube defects.

Table 1. Effects of trace elements on prevalence levels of neural tube defects

Element (μg/g)	Average Level#	Mean	V_i	Std. (var.)	Layer Level	Prevalence Low	Prevalence Medium	Prevalence High
Sn	0.9	3.71	0.7839	1.09 (1.18)	3	<2.5 or >3.2	2.5–3.2	\
Pb	14.7	56.14	0.7980	11.43 (130.58)	2	<45	>55	\
Ni	29.9	41.38	0.8110	6.39 (40.77)	3	30–34	>34	<30
Fe*	2.95	3.28	0.7858	0.58	3	<3.1	>3.35	3.1–3.35
Cu	22.9	23.42	0.7906	3.65 (13.34)	3	<20	>22	20–22
Al*	6.35	3.47	0.8150	0.95	2	<3.8	>3.8	\
As	9.1	20.48	0.8098	14.38 (0.7)	0	\	\	\
Se	0.16	\	\	\	\	\	\	\
Zn	63.5	110.88	0.8075	45.73 (0.41)	0	\	\	\
Sr	207	258.88	0.8098	75.47 (0.29)	0	\	\	\
V	63.4	86.41	0.8222	10.44 (0.12)	0	\	\	\
Mo	0.50	12.25	0.8128	3.09 (9.53)	1		8.51	

Note. *Fe and Al are in mg/g. #average content levels in soil from Shi[14].

DISCUSSION

Trace Elements That Have Dose Effects on the Occurring Risk of Neural Tube Defects

The results show that the lower the content level of lead and aluminum in the soil, the lower occurring risk of neural tube defects, and vice versa. This is in accordance with existing studies, as lead is a non-essential and highly poisonous element for humans[2]. The element of aluminum also has bio-poisonous effects, especially on the neural system[15].

Lead can enter the human body through the respiratory system and alimentary tract along with food or dust particles. After being absorbed by the body, it is distributed to the liver, kidney, brain, and major arteries[16]. Generally, lead poisons the central neural system and blood, harming the digestive system and compromising kidney function. It also has strong effects on child development[17]. Some studies show that lead in herbal medicine might cause the risk of neutral tube defects[18].

Aluminum is another non-essential element that might affect brain function. People with high aluminum content in the brain show reduced memory, low intelligence, and decreased physical functioning[19]. In addition, aluminum directly affects bone cell activity by preventing the composition of bone basis and calcium absorption. Increased aluminum content in the body can ultimately lead to anemia and kidney disease[20]. Because of this, the World Health Organization and the Food and Agriculture Organization of the United Nations declared in 1989 that aluminum content in food must be controlled, recommending standard daily intakes of less than 7 mg/kg body weight[21].

These results show that there are associations between lead and aluminum levels in the soil and the occurring risk of neural tube defects. This means that women should avoid lead and aluminum exposure when pregnant or trying to become pregnant.

Copper is a major component of enzymes, and is also an essential element for the liver, brain, kidney, heart, lung, spleen, muscles, and bones in humans. However, both deficiencies and excessive amounts of copper cause pathological changes in the brain. Deficiencies can cause brain shrinkage, decreased neural units, stagnancy of spirit, tiredness, and limited physical functioning. Excessive amounts of copper lead to brain and neural system cell disorders. Excessive copper stores in the liver can be released into the blood and cause hemolysis and jaundice[22]. Moreover, hepatocirrhosis and bile silt in children are related to excessive copper levels. Copper enters the human body through the food chain. In the environment, copper is less threatening to population health because humans do require a certain amount. Excessive amounts of copper usually have a negative effect on human health[23]. However, some studies show that copper deficiency may not be related to the risk of neural tube defects[24].

Our results show that higher levels of iron cause an increase in the prevalence of neural tube defects. Iron is a key element in blood and is often used as an index of the nutritional level of humans. It is also known to affect pregnancy outcomes[25]. However, excessive iron levels (i.e., several times the normal values) increase the risk of cancer[26]. Therefore, excessive exposure to iron should also be avoided.

Nickel has different compounds and physical shapes. These have different levels of toxicity to humans. Our results also show different associations between exposure to nickel compounds and human health. The genetic toxicity of nickel is a controversial issue[27]. Our results show that both deficiencies in and excessive amounts of nickel cause an increased risk of neural tube defects. Some studies show that low levels of nickel cause changes in metabolism, and excessive amounts can be poisonous (as indicated by the whitening of hair). In environments high in nickel there is a higher prevalence of tumors of the respiratory system and skin disease. Nickel usually enters the human body through the respiratory system[28].

Our study shows that when the cultivated soil content of tin is about 2.5-3.2 ug/mg, the prevalence of neural tube defects increases. Tin naturally exists in plants and soil, but its relationship with human health is not clear. The levels of tin change with the environment[29]. According some studies[30], tin might be a key environmental factor in the association between trace elements exposure and the risk of birth defects in the Lvliang region, given the soil content of tin in this region,

Trace Elements That Have no Clear Effects on the Prevalence of Birth Defects

Our results show that arsenic, selenium, zinc, strontium, and vanadium have no clear effect on the prevalence of birth defects. We first checked the levels of these elements and their differences by village[31]. For example, selenium is a key element for human health. Selenium deficiency can cause Keshan disease, big bone disease etc. However, the soil in our study region shows low selenium content and our model did not show an effect on the risk of birth defects. Arsenic, zinc, strontium, and vanadium also have no clear association with the risk of birth defects. This may be contributed to the fact that the levels of these elements in the soil were similar among the villages. Further study is necessary to develop more accurate models on the effects of these elements on the risk of birth defects.

Molybdenum

The element of molybdenum is a key element for oxygenation[32]. Excessive amounts of molybdenum can cause decreased sexuality, reduction of cartilage, anemia, and diarrhea[33]. Our model shows that its effect on the prevalence of birth defects has a threshold value.

CONCLUSION

In summary, this is an exploratory study, which focused on the association between trace element contents of cultivated soil and the regional risk of neural tube defects. Based on the samples and survey data, the model we have built could determine the direction of the effects of the trace elements' on the risk of neural tube defects, as well as their thresholds levels. Our results show that qualitative conclusions about the association between the trace element content in the soil and the risk of neural tube defects were proven. Further study is required to focus on the mechanisms behind these associations. For example, biogeochemical research should be carried out considering the direct effects of trace elements on human health[34]. Also, longitudinal collection of birth defect data is necessary to ensure more stable data. We chose to study neural tube defects because they are easily identified in clinic, and have complex causes. The region we studied has the highest prevalence of neural tube defects in the world. Cases examined here through a 3 year survey could represent the maximum likelihood of the real prevalence of neural tube defects with more than 6000 birth counts[6]. Furthermore, the routes by which trace elements enter the human body (i.e., through respiration, drinking water, or the food chain) might affect human health differently. Among these, the food chain is the main route for the transfer of trace elements to the human body. The different routes should be a key point in the analysis of the mechanisms of toxicology of trace elements[1].

The model developed in our study must be explained and quantified by judging the meaning of data derived from environmental analysis on biological samples. As bio-indication and bioaccumulation of trace elements is a common chemical phenomenon, the toxicity of these elements might be distorted with different situations in the soil[35-36]. Limited by the measurement of the trace element content, we could not classify the details of physical chemistry among the soil samples. The present results are in accordance with the qualitative knowledge of the toxicity of those trace elements to human health. The model described could be used for the analysis of the toxicological characteristics of trace elements, and for prevention of the risk of exposure to pregnant women.

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