Allergic diseases are on the rise in both prevalence and severity, especially in industrialized countries. The process of allergic sensitization needs an understanding of the role environmental factors play in its development. In addition to traditionally considered air pollutants, various persistent organochlorine pollutants, which accumulate in the human body over a lifetime via food intake, are toxic in humans. Placental contamination by chemicals may act as a biologic marker for the exposure of the mother or for the fetus via transplacental transfer. Placentas were collected from term deliveries in two Slovak regions. The samples were then analyzed for 21 selected organochlorine compounds. Specimens of cord blood from 2,050 neonates were gathered for the determination of levels of total immunoglobulin E (IgE). The regions were chosen according to their environmental characteristics: a city populated with organic chemical industry versus a rural region devoid of industrial sources of pollution. In addition, data regarding the incidence rate of atopic eczema cases in the regions were considered. Comparisons between regions revealed that both the placental contamination with 16 of 21 organochlorine compounds and the cord serum IgE levels were significantly higher in the industrial region. The findings pointed to an association between organochlorine compounds and the higher levels of total IgE in newborns, signaling a higher allergic sensitization in the industrial region. This association was supported by the higher incidence rate of atopic eczema cases in the population registered in the industrial region.

Key words: allergy, atopic eczema, biomarkers, congeners of polychlorinated biphenyls, cord serum immunoglobulin E, human placenta, organochlorine compounds, sensitization. Environ Health Perspect 107:895–899 (1999). [Online 12 October 1999]

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Atopy has a strong genetic component, but environmental and social factors (including lifestyle) appear to have an important relationship with allergic diseases (1,2). The fact that allergic diseases have increased in prevalence, especially in the industrialized countries, has evoked an interest in environmental factors encountered in prenatal and early postnatal life (3). Developing fetuses and young children may be more susceptible to effects of chemical agents in relation to allergic sensitization, especially those fetuses and children with a genetic propensity (4,5).

Environmental factors studied include exposure to tobacco smoke, traditional airborne pollutants (SO2, NO2, ozone, respirable particulates), aeroallergens in home indoor environments, and air from tight and poorly ventilated buildings. (6,7). Tobacco smoke has been suggested to be in a direct relationship with atopic diseases in children, especially with atopic eczema in offspring (8). According to Arshad and Hide (9), environmental factors have a profound effect on the prevalence of asthma in infants. German epidemiologic studies comparing eastern and western German populations have shown differences in the prevalence of respiratory atopic diseases, which were lower in eastern Germany (10), in contrast to the higher incidence of nonatopic respiratory diseases there. Behrendt et al. (11) published the outcome of experimental studies regarding the modulation of allergen release from pollen, as evoked by different effects of SO2 and NO2. Diaz-Sanchez et al. (12) demonstrated that inhalatory exposure to diesel exhaust pollutants led to a significant increase in immunoglobulin (IgE), but not IgG, IgA, or IgM production, and to an increase in IgE-secreting cells.

In general, the fetus is protected against external influences by the placental barrier, but this barrier is selective, especially for maternal IgG antibodies, various antigens, and chemical substances. Contrary to the transplacental IgG transport, only a small amount of IgE antibodies are present in newborns, and it seems that these IgE antibodies are of fetal origin (13). It has been reported that higher IgE levels in cord blood are a good predictive test for atopy (14–16), but others consider this an insensitive indicator for atopy prediction (17–19). According to Martinez et al. (20), serum IgE levels during infancy have a good predictive value for atopy.

There are environmental chemicals and drugs (e.g., xenobiotics) that may enhance the sensitization to allergens of various origins in susceptible persons because of their modulatory effect on T cells. For certain xenobiotics, the risk of immune system impairment or modulation increases if exposure begins in utero or in infancy. Immune reactions to xenobiotics can give rise to allergy and autoimmunity. Therefore, it is of great importance to understand the pathogenic mechanisms (neoantigen formation, metabolism of xenobiotics into reactive–haptenic metabolites, induction of costimulatory enzymes, and sensitization of T cells) involved in the xenobiotics action (21). Prescott et al. (22) recognized the developing patterns of T-cell memory to environmental allergens in the first 2 years of life. According to Lin et al. (23), T-helper (Th) lymphocytes at the maternal–fetal interface synthesize Th2 cytokines. Assuming that the infants undergo antigen/allergen priming in utero, xenobiotics may influence the response to antigen exposure and bring about allergic diseases in early childhood.

There are direct and indirect interactions among the mother, embryo/fetus, and placenta. The placenta is essentially an allograft; therefore, some protective mechanisms exist for the prevention of placental–fetal rejection (24). A successful pregnancy seems to be a Th2–lymphocyte phenomenon as a result of the defensive immune activity of the fetal–placental unit against the deleterious activity of the maternal immune system (25). To date, there is a lack of knowledge of how xenobiotics deposited in the placental structures interfere with these immune processes.

The placenta can act as an exposure index to xenobiotics either for the mother or for the conceptus via their transfer to the fetus (26). A broad spectrum of substances are classified as xenobiotics. In addition to the known toxic inorganic xenobiotics (mainly heavy metals in the air and in food), many of organochlorine compounds used in various industrial processes and pesticides are toxic to the environment and to humans (27). Because of their occurrence in ambient air, persistence in the food chain, and storage...

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in living organisms (in adipose tissue), xenobiotics are known as semivolatile persistent organochlorine pollutants (POPs). Polycyclic aromatic hydrocarbons are another important group of POPs that are known for their carcinogenic potential. Demonstration of benzo(a)pyrene [B(a)P]–DNA adducts in human placenta and cord blood proved the metabolic capacity of the placenta, the transfer of B(a)P from the mother to the fetus, and the genotoxicity of B(a)P (28).

Organochlorine compounds are accumulated in the body during the lifetime; therefore, the individual body burden increases to levels that are toxic to the organism, and the offspring is exposed in utero by maternal transfer. Organochlorine compounds exert estrogenic effects (endocrine disruption) and a variety of associated effects such as reproductive and immune system dysfunction. Decreased percentages of total T cells and helper T cells but normal percentage of B cells and suppressor T cells were found in polychlorinated biphenyl (PCB)-exposed patients (29). Neonatal exposure to PCBs, especially to congeners 28 and 52, had a persistent neurotoxic effect in adult animals (30). In Slovakia, these PCB congeners were detected in human breast milk as well as in cow’s milk and dairy products (31–33). In addition, water from the Danube River near the city of Bratislava, Slovakia, was contaminated with chlorinated phenols (34). However, there are sparse (if any) data on the relation between organochlorine compounds and atopy development.

Contrary to the data on the role of postnatal environmental exposure in the expression of atopy and asthma, the effects of antenatal chemical exposure remain to be clarified and objective biomarkers of the exposure are needed.

The aims of this study were to compare the contamination of human placentas with organic xenobiotics (21 selected organochlorine compounds) collected at term deliveries in two environmentally different regions, and to investigate the relationship between the placental contamination and the cord blood total IgE level in neonates on the background of incidence rate of atopic eczema cases in selected regions.

Materials and Methods

Study design. This study was based on 2,050 full-term deliveries randomly selected in two Slovak regions (industrial vs. rural) that principally differed from each other in industry-related environmental pollution. The industrial region was represented by a city (Bratislava) polluted mainly by organic chemicals (gasoline, pesticides, and the rubber industry) and by traffic. The rural region was situated in the mountains (Stará Lubovna) and was devoid of any industrial source of environmental pollution, although there was traffic linked to tourism and to a border checkpoint. Data from the Institute of National Health Statistics (Bratislava, Slovakia) regarding the incidence of atopic eczema cases in the total population and in the population ≤14 years of age (registered during 1992–1995) were considered in the choice of regions investigated. The National Environmental Monitoring System collected data on the traditional ambient air pollutants in the study regions (regularly provided by the Slovak Hydrometeorological Institute, Bratislava, Slovakia).

The study was approved by the Research Ethics Committee of the Institute of Preventive and Clinical Medicine in Bratislava, Slovakia. Informed consent was obtained from all subjects. Women were selected according to the following criteria: residence in the investigated areas (at least 3 years before conception), normal-term deliveries (40 ± 2 weeks of gestation), and nonoccupational exposure to organochlorine compounds. The data from the questionnaires focused on mothers (e.g., residence, smoking habits, occupation) were monitored. Other monitored data included external parameters of placentas (longest and transverse diameters and thickness) and of newborns (birth weight and height). The average age of the mothers studied in the industrial region was 24.2 years of age; in the rural region, it was 22.6 years of age. Maternal cigarette consumption in the industrial and rural regions was 26 and 27%, respectively (35).

Sample collection. In the maternity clinics of the selected regions, samples of cord blood of newborns (n = 2,050) were collected, and sera prepared by centrifugation were kept frozen at -20°C until their laboratory analysis. Simultaneously, randomly selected samples (n = 120) of full-term placentas (approximately 30 g full-thickness tissue) were uniformly excised in a triangle shape from the periumblical zone through the intermediate zone to the marginal zone, and were kept at -20°C until their processing in a laboratory.

Determination of IgE level in cord sera. The Pharmacia CAP System RAST FEIA technique based on ImmunoCAP technology (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) was used for the in vitro determination of total IgE concentrations in cord sera specimens. Enzyme-labeled antibodies against IgE were added to form a complex. After incubation, unbound enzyme-anti-IgE was washed away and the bound complex was then incubated with a developing agent. After stopping the reaction, the fluorescence of the eluate was measured in FluoroCount 96 (Kabi Pharmacia Diagnostics AB). The fluorescence values (FU) of measured specimens were compared with FU for standard. In our laboratory, an IgE value of 0.35 kU/L in the sample was the detection limit, and the IgE level of 0.7 kU/L was assessed as a positive sample.

Organochlorine compound determination in placental samples. Residues of 21 organochlorine compounds in placental samples were analyzed:

- Chlorinated benzenes: 1,4 + 1,3-dichlorobenzene (1,4 + 1,3-DCB); 1,2-dichlorobenzene (1,2-DCB); 1,3,5-trichlorobenzene (1,3,5-TCB); 1,2,4-trichlorobenzene (1,2,4-TCB); 1,2,3-trichlorobenzene (1,2,3-TCB); Σ(1,2,3,5 + 1,2,4,5)tetrachlorobenzene (TeCB); pentachlorobenzene (pentaCB); hexachlorobenzene (HCB)
- Organochlorine insecticides: α-hexachlorocyclohexane (α-HCH); β-hexachlorocyclohexane (β-HCH); γ-hexachlorocyclohexane (γ-HCH); δ-hexachlorocyclohexane (δ-HCH); 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (p,p'-DDT); 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE)
- Polychlorinated biphenyls (indicated congeners): 2,4,4'-trichlorobiphenyl (PCB 28); 2,2',5,5'-tetrachlorobiphenyl (PCB 52); 2,2',4,5,5'-pentachlorobiphenyl (PCB 101); 2,3,3',4,4',5-pentachlorobiphenyl (PCB 118); 2,2',3,4,4',5'-hexachlorobiphenyl (PCB 138); 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153); 2,2',3,4,4',5,5'-heptachlorobiphenyl (PCB 180).

The three steps for sample preparation were sample homogenization, Soxhlet extraction, and clean-up procedure. For analytical identification and determination of the compounds, we used capillary gas chromatography with 63Ni electron capture detection.

Chemicals. Acetone, n-hexane, n-heptane, and dichloromethane were purchased from Merck (Bratislava, Slovakia). All solvents were pesticide grade. The standards of PCB indicator congeners (International Union of Pure and Applied Chemistry numbers 28, 52, 101, 138, 153, and 180) were purchased from the Slovak Institute for Metrology, Bratislava, Slovakia. The standard mixtures of organochlorine insecticides and chlorinated benzenes were purchased from Supelco SA (Gland, Switzerland) and Aldrich (Steinheim, Germany). Florisil (60/100 mesh) was washed with bidistilled water, acetone, and n-hexane. Anhydrous sodium sulfate was Soxhlet-extracted with n-hexane to avoid possible interference.

Sample preparation and extraction. A sample of approximately 10 g placental tissue was homogenized with sodium sulfate in a grinder to a pulverized consistency. The sample was then quantitatively replaced in a Soxhlet apparatus and underwent 5 hr of Soxhlet extraction with 250 cm³ n-hexane. The extract was evaporated on a vacuum rotary evaporator to the volume of 5 cm³.
Sample clean-up and gas chromatography. The clean-up and gas chromatography procedures used in this study were based on previously published methods (32,33).

Statistical analyses. Statistical analyses were carried out using Statgraphics 5.0 (STSC, Inc., Rockville, MD) and SPSS for Windows (SPSS, Inc., Chicago, IL). The nonparametric Wilcoxon’s test corrected for ties for placental organochlorine compounds, and the unpaired Student’s t-test was used for cord serum IgE levels. A result of \( p < 0.05 \) was considered statistically significant. The interindividual correlations between the concentrations of organochlorine compounds and cord serum IgE levels were evaluated using nonparametric Spearman correlations.

Results

Organochlorine compounds in human placental samples. The minimum, median, and maximum concentrations of 21 organochlorine compounds (e.g., selected chlorinated benzenes, organochlorine insecticides, and PCB congeners) as well as the percentage of the negative samples (e.g., the concentrations of organochlorine compounds below detection limits) in the human placentals samples collected from the industrial and the rural region are presented in Table 1. The statistical analyses comparing two regions (at the confidence level \( \alpha = 0.05 \)) revealed that the concentrations of 16 of 21 organochlorine compounds analyzed were significantly higher in the industrial region. Furthermore, the percentage of noncontaminated placental samples was significantly higher in the rural region as compared to the industrial region. Four compounds of chlorinated benzenes (1,4 + 1,3-DCB, 1,2,4-TCB, 1,2,3-TCB, and pentaCB) in the placental samples were found at similar levels in both regions, and the concentration of one compound (1,2-DCB) was higher in the rural region. The contents of the PCB congeners (mainly PCB congeners 101 and 153) and organochlorine insecticides analyzed in the placental samples were higher in the industrial region.

Total IgE levels in cord sera. Data on the total IgE in the cord sera samples of neonates collected from two regions is given in Figure 1. The neonates were divided into three groups according to their cord serum IgE concentrations: < 0.7 (e.g., negative newborns), 0.7–3.5, and > 3.5 kU/L. A higher number of IgE-positive newborns in the second and third group (expressed in percent) were found in the industrial region as compared to the rural region (\( p < 0.001 \)). The differences were fewer IgE-negative newborns in the industrial region (68.7%) as compared to the rural region (82.4%).

Additionally, in 120 individuals, correlations between each organochlorine compound concentration in the placental tissue and cord serum total IgE level using Spearman correlations were performed. The positive correlations for \( p,p'-\text{DDE} \) \( (r = 0.329, p = 0.01) \) and for PCB 118 \( (r = 0.3482, p = 0.006) \) were found.

External parameters of placentals and newborns. External parameters of human term placentas and birth parameters of neonates between the rural and the industrial region are compared in Table 2. In spite of nondiffering average weights of placentas in both regions, other parameters (e.g., longest diameter, transverse diameter, and thickness) were significantly higher in the rural region. Comparison of birth parameters (weight and height) revealed that there was no significant difference between the investigated regions.

Discussion

Research on environmental exposure during fetal development and early childhood indicates that biologic markers can provide dosimeters of environmental exposures and tools for evaluating interindividual variability in response and age-related susceptibilities (36). According to official data for 1995 (Institute of National Health Statistics, Slovakia) on the population ≤ 14 years of age, the incidence of atopic eczema cases per 10,000 children was 30.82 at Bratislava city and 12.78 in the Stará Lubovna region. The incidence rate has been growing since 1992 (37) in both regions, but the difference between the regions has been maintained. Unfortunately, data regarding other allergic diseases are not available.

Studies demonstrate associations between road traffic pollutants and respiratory diseases in children. Exposures that have profound health effects on an individual (e.g., road traffic pollutants) may occur at periods of time, such as an exposure to a mother before the conception of her child. Fetal organs are undergoing development and differentiation and may be affected by environmental pollutants including lead. Both prenatal and postnatal exposure to lead may result in growth retardation, changes in cognitive capabilities, decreased intelligence quotient, diminished respiratory volume, and deleterious effects on...
with resulting tissue damage. In C57BL/6J and DBA/2J pregnant mice, after oral administration of pesticides (lindane and endrin) on day 12 of gestation, production of superoxide anion and lipid peroxidation and DNA single-strand breaks were found (47). Other experiments have pointed to possible growth retardation or fetal death in mink. Additionally, morphologic changes in fetal and placental tissue have been observed, as demonstrated by degenerative changes and extensive placental infarction. Lectin staining has revealed the effects of PCB toxicity, which are shown by increased injury to maternal endothelium and severe trophoblastic damage (48). Walsh and Wang (49) pointed to a secretion of lipid peroxides in normal human placenta that can circulate in pregnant women. The mother's environmental exposure to organochlorine compounds might evoke the enhancement of lipid peroxide secretion in human placenta. Lipid peroxides are responsible for endothelial cell impairment and vasoconstriction, leading to preeclampsia and high-risk pregnancy. According to Klaunig et al. (50), oxidative stress might be evoked by drugs, hormones, and various environmental chemicals such as organochlorine pesticides. These findings are of interest if related to the data on the increased inflammatory cytokine production in the human placenta under hypoxic conditions (51).

Tissue microstructural changes accompanied by decreased activity of oxidative enzymes in human placenta collected from heavily polluted regions in Poland have been reported (52). In our studies, a higher percentage of microstructural lesions was diagnosed in human placentas from the industrial region (Bratislava city) as compared to the rural region (Stará Lubovna) (53). These microstructural lesions may be responsible for the different external parameters of human placentas (e.g., higher longest diameter, transverse diameter, and thickness) found in the industrial region (Table 2). Our findings concerning the deviations in placental parameters were consistent with the Polish study by Zadroga (54). Thus, the higher frequency in placental microstructural lesions may be associated with the higher placental contamination found in the industrial region (Table 1).

Ferguson et al. (55) found a link between asthma risk and large head circumference at birth in New Zealand children. In spite of the unknown mechanism for this link, the findings supported data on the fetal programming of immune function and respiratory diseases by prenatal dietary experience (56).

A comparison of the biomarkers of the mother's chemical exposure in our cohorts (e.g., different placental metal and organochlorine contents in the placental samples) to cord sera IgE levels between two environmentally different regions has led to a hypothesis of the possible fetal allergic sensitization evoked by organochlorine compounds in the placenta. Data on the higher rate of atopic eczema cases recorded in the population residing in the industrially polluted region, and the presumption of the human exposure to organochlorine compounds via food (demonstrated by the contamination of breast milk, cow's milk, and dairy products) support this hypothesis. Furthermore, feeding infants with breast milk that contains organochlorine compounds may contribute to the sensitization in the early postnatal period. Further research focused on the mechanism of heavy metals and organochlorine compounds and their interaction in the antenatal and postnatal sensitization is needed.

### Table 2. External parameters of human term placentas and birth parameters as compared between industrial and rural regions.

| Parameter        | Industrial | Rural          | Diff | p  |
|------------------|------------|----------------|------|----|
|                  | Mean ± SD  | Mean ± SD      |      |    |
| Placental weight (g) | 598.9 ± 135.7 | 572.5 ± 107.3 | NS   |    |
| Longest diameter (cm) | 18.9 ± 2.8   | 16.3 ± 2.9     | *    |    |
| Thickness (cm)     | 2.3 ± 0.6   | 1.8 ± 0.7      | *    |    |
| Birth weight (g)   | 3,287.9 ± 595.7 | 3,347.2 ± 462.0 | NS   |    |
| Birth height (cm)  | 49.9 ± 2.5  | 49.6 ± 2.1     |      |    |

**Abbreviations:** Diff, difference; NS, not significant; SD, standard deviation.

*p = 0.001.

the immune system (38). The body burden of lead stored in maternal bones may be mobilized and released during pregnancy into the blood circulation and therefore contribute to fetal lead exposure (39). The underlying molecular mechanisms for Pb's complex effects could be explained through activation of the transcription factor nuclear factor-KB, which is critical for T lymphocyte function (40). Pb enhances B-cell differentiation and modulate antigen presentation to Th1 versus Th2 cell clones in favor of Th2 cells (41).

We have published results regarding biomarkers of exposure, impairment of tracheal mucosa, and immunotoxic effects related to heavy metals contained in the ambient air particulates using the animal model (42–45).

In contrast to the significantly higher concentrations of organochlorine compounds found in placental samples collected from the industrial region (Bratislava city) and shown in Table 1, the content of lead on average was higher in the samples gathered from the rural region (Stará Lubovna), as we reported in our previous work (35). The lead accumulation in the placental samples from the rural region was presumably derived from traffic (via leaded gasoline) linked to tourism and to a border checkpoint. Additionally, analyses of placental lead contents in other regions of Slovakia implicated traffic-related environmental lead pollution rather than industrial sources (35). Furthermore, the predominant site of metal particle accumulation in placental tissue has been demonstrated in the syncytiotrophoblast, which is capable of phagocytosis, and represents a site for the exchange between fetus and mother (46).

Exposure to organochlorine compounds can be determined in samples from various tissues and encountered fetal and placental tissues. Experimental findings revealed that organochlorine compounds may induce oxidative stress in fetal and placental tissue.

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