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Obesogenic and diabetogenic impact of high organochlorine levels (HCB, p,p'-DDE, PCBs) on inhabitants in the highly polluted Eastern Slovakia

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Objective. This study was aimed to evaluate possible obesogenic and diabetogenic impact of highly increased serum level of persistent organochlorinated pollutants POPs, such as polychlorinated biphenyls (PCBs), dichlorodiethyl-dichloroethylene (p,p'-DDE), and hexachlorobenzene (HCB), on the level of obesity markers (cholesterol and triglyceride level in serum, and body mass index [BMI]) and diabetes markers (fasting glucose and fasting insulin in serum) in inhabitans of Eastern Slovakia.

Methods. In young (21-40 years) males (n=248) and females (n=330) as well as in old (41-75 years) males (n=586) and females (n=889), the serum levels of 15 polychlorinated biphenyl congeners (Σ15PCBs), p,p'-DDE and HCB, and serum insulin, testosterone, total cholesterol, triglycerides and glucose levels have been estimated by high resolution gas chromatography/mass spectrometry and by the appropriate electrochemiluminiscent immunoassay or chemical methods, respectively.

Results. In both age groups of males and females, the levels of Σ15PCBs, p,p'-DDE, and HCB were very high and their mutual interrelations were highly significant ($p<0.01$). However, it should be noted that no significant changes were found in individual variables related to very high level of Σ15PCBs, except of increased BMI ($p>0.05$) in females.

In all ages and gender groups, defined above general as related to increasing level of individual OCPs in individual age and gender groups, significant increase in cholesterol and triglyceride levels as well as BMI values, supported their obesogenic effect, while significant increase in fasting glucose and insulin in serum, supported their diabetogenic effect. Finally, highly significant decrease in testosterone level, as found in both young and old males, supported the antiandrogenic effect, namely of HCB. However, somewhat less of p,p'-DDE, while PCBs did not show any such effect in spite of their very high level.

Conclusions. Highly increased blood levels of diabetes (fasting glucose and insulin) and obesity markers (cholesterol, triglyceride and BMI) were found in large groups of males and females in highly polluted area of Slovakia. Significant decrease in testosterone level was also observed in males.

Key words: organochlorines, environmental pollution, body mass index, cholesterol, triglycerides, glucose, insulin, testosterone, diabetes, obesity, human population

The prevalence of obesity, the diabetes type 2, and syndrome of insulin resistance, as closely related to cardiovascular diseases, is considerably increasing worldwide, currently affecting nearly 300 million people accounting for about 12% of health expenditures worldwide (Hu 2011, Neel et al. 2011).

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Recently, numerous reports have appeared showing the interrelations of these major human diseases with global pollution by endocrine disruptors (Montgomery et al. 2008; Tanaka et al. 2011; Lee et al. 2011, 2012; Valvi et al. 2012) as extensively reviewed also by Casals-Casas and Desvergne (2011). Recent findings have demonstrated also the participation of bisphenol A (Bodin et al. 2013; Gong et al. 2013) and an increased arsenic level in drinking water in this process (James et al. 2013; Kim et al. 2013). Recently, a considerable number of similar reports on the induction of the type 2 diabetes by diversified groups of chemicals, have been summarized by Zeliger (2013), who attempted to present a unifying explanation on this process and emphasized that all such chemicals belong to "lipophilic species that permeate lipophilic cellular membranes, thereby promoting the absorption of toxic hydrophilic species that would otherwise not penetrate lipophilic membranes". From this follows that "the type 2 diabetes is pandemic, at least in part, due to the sequential exposure to levels of lipophilic and hydrophilic environmental pollutants that are much lower than those currently believed to be toxic. As a consequence of this hypothesis, the allowable levels of exposure to these pollutants should be dramatically lowered".

The increased incidence of obesity in the male partner, as appears based on the study of 1329 couples in which all male partners were long-term certified pesticide applicators, has been also reported (Sallmen et al. 2006). This could result from their low testosterone level as supported by the finding that after adjusting the SHBG levels, low testosterone level appeared to be correlated with insulin resistance and obesity denoting an independent effect of insulin resistance on testosterone production (Tsai et al. 2004).

In addition, it should be also emphasized that in the same population, as presented in this study, also the findings on significantly increasing prevalence of prediabetes and diabetes related to increasing serum concentrations of Σ15PCBs, p,p'-DDE, and HCB have been previously published (Ukropec et al. 2010).

Although this particular investigation, performed in 2001-2005, has been focused to Eastern Slovakia, it should be explicitly reminded that due to serious and culpable environmental negligence of the previous regime in this country (1948-1989) and persecuting of courageous environmentalists, the whole territory of Slovakia has been found heavily polluted shortly after the definite fall of the government in early nineties as found by Kocan et al. (1994) and others (Langer et al. 2003; Pavuk et al. 2004; Chovancova et al. 2005; Jursa et al. 2006; Petrik et al. 2006). From this follows that the data published in this report may be with a high probability extrapolated to the whole territory of Slovakia.

Materials and Methods

Subjects. Within the years 2001-2005, 834 males (248 of 20-40 years, median 27 and 586 of 41-75 years, median 50) and 1212 females (330 of 20-40 years, median 28 and 882 of 41-75 years, median 50) were recruited from three East Slovakian districts (covering about 60 km^2) including Svidnik, Stropkov, and Michalovce, the latter being also heavily polluted by (PCBs) due to hazardous disposal of industrial wastes, while all districts were also subjected to heavy pollution by pesticides of the first generation such as HCB and p,p'-DDE, which have been used in this country from 1950 to 1990, without any serious limitations or warnings.

The examined subjects were recruited by 28 a priori selected district physicians who were instructed to call randomly one subject per each centile of alphabetically listed patients being under their care. Moreover, they were also instructed that from those called to the examination about 40% should be aged between 20 and 40 years and about 60% between 41 and 75 years. The ratio of males to females should be kept at the level from 40 to 60%. By this way 60-100 subjects were finally recruited by each physician and after signing the informed consent examined by a research staff consisting of medical doctors and technicians.

PCBs, p,p'-DDE, and HCB in serum. From each subject 20 ml of blood was withdrawn and centrifuged in a refrigerated centrifuge. The aliquots were transported in a portable freezer to the laboratory and kept frozen until analyzed. In serum of all subjects 15 PCBs congeners (IUPAC No. 28, 52, 101, 105, 114, 118, 123, 138^{+163}, 153, 156^{+171}, 157, 167, 170, 180 and 189), HCB and p,p´-DDE were determined by high resolution liquid chromatography and Ni/63 micro/electron capture detector using a 60 m DB/5 capillary column, as described elsewhere (Kocan et al. 2001; Pavuk et al. 2004; Petrik et al. 2006).

Insulin, testosterone, glucose, and total lipids in serum. In all examined subjects, the levels of cholesterol, triglycerides, and insulin in serum and in males also testosterone were estimated by electrochemiluminiscent immunoassay using an automatic system Elecsys Roche. Fasting glucose level was determined using an analyser

Hitachi 901. Total serum lipids were estimated according to Akins et al. (1989).

Statistical evaluation. The interrelations between individual variables in appropriate cohorts of males and females of the same age range were evaluated using Pearson's multiple correlation method.

Results

PCBs, p,p'-DDE, and HCB in serum. The distribution of individual organochlorine levels in terms of increasing percentiles as found in appropriate individual young males and females is shown in Table 1, while those found in old males and females is shown in Table 2. As shown in these tables, the levels of Σ15PCBs, p,p'-DDE, and HCB namely in higher percentiles are very high as compared to numerous data obtained by various authors in several other countries. Thus, among them only the levels of PCBs found in 50th percentile of young males (i.e. 879 ng/g lipid; Table 1) and of young females (i.e. 736 ng/g lipid; Table 1) or in 25th percentile of old males (i.e. 1012 ng/g; Table 2) and old females (i.e. 680 ng/g; Table 2) appeared approximately comparable to the values found in general US population (Hunter et al. 1997; Stellman et al. 2000; Turyk et al. 2006, 2007).

However, the only PCBs levels (in terms of ng/g lipid), which were at least approximately similar to these we found in 100th percentile in young males (9093 ng/g) and young females (9523 ng/g) as shown in Table 1and in old males (77084 ng/g) and old females (101413 ng/g) as shown in Table 2, were found in the population around the former PCBs factory in Italy, such as 95th percentile of 3520 ng/g and 100th percentile of 34377 ng/g (Donato et al. 2006, 2008).

Similarly, the levels of p,p'-DDE (in terms of ng/g lipid) we also found in 50th and 100th percentiles in young and old males and females (Tables 1 and 2) much higher than those reported in several other countries. Thus, in Great Lakes fish consumers a mean level of p,p'-DDE level such as 4600 ng/l (approx. 670 ng/g) has been found in males and that of 3300 ng/l (approx. 657 ng/g) in females by Persky et al. (2001), while similar relatively low levels (in terms of ng/g lipid) have been also found in the US by Turyk et al. (2006, 2007, 2008), Bloom et al. (2009), and Meeker et al. (2007). However, considerably higher levels of p,p'-DDE (e.g 50th and 95th percentile of 828 and 3252 ng/g, respectively) have been found in Baltic fishermen by Hagmar et al. (2001), in Swedish males (range of 110-2140 ng/g) by Rylander et al. (2005) and in adults in southern Spain (maximum of 2330 ng /g) by Arrebola et al. (2013), while the highest p,p'-DDE level possibly have been reported from the countries outside of Slovakia (such as 8700 ng/g) in several pregnant women in Spain (Lopez-Espinosa et al. 2009) as a possibly due to some heavy local pollution.

Finally, regarding the HCB levels, only those of 5000-6000 ng/g lipid, as found in workers and population around HCB factory in Spain by Sala et al. (2001), were at least comparable with the highest values we found in young males or females (i.e. 4117 and 2954 ng/g, resp., Table 1). However, they were much lower than those we found in old males and females (i.e. 17928 and 12915 ng/g, resp. Table 2) and which are, according to our best knowledge, the highest reported so far.

As expected, considerably higher values of all organochlorines were found in old subjects (Tables 4 and 6) as compared to young ones (Tables 3 and 5), as apparently results from much longer period of exposure of old subjects to these highly lipophilic substances which are well known to be retained permanently in the hu-

Table 1

Individual values of organochlorines (ng/g lipids) in young males and females (19-40 years old)

	Males			Females		
Percentile	PCB	DDE	HCB	PCB	DDE	HCB
1	211	160	22	149	54	47
25	580	592	90	482	563	159
50	879	872	134	736	926	263
75	1374	1594	209	1194	1194	472
90	2627	1783	417	2079	2569	735
95	3687	2666	606	2793	3485	1277
100	9093	8254	4417	9523	6308	2954

Table 2

Individual values of organochlorines (ng/g lipids) in old males and females (41-75 years old)

	Males			Females		
Percentile	PCB	DDE	HCB	PCB	DDE	HCB
1	346	177	26	193	68	42
25	1012	1359	390	680	1307	657
50	1509	2340	697	1049	2173	1052
75	2768	3881	1129	1900	3687	1665
90	5423	4991	1374	3494	5596	2514
95	9603	7664	1634	4523	7369	3284
100	77084	22382	17928	101413	20160	12915

Table 3

Males aged less than 40 years

	PCB	DDE	HCB	CHOL	TG	BMI	GLU-0	INS-0	TEST
PCB		>0.01	>0.01	NS	NS	NS	NS	NS	NS
DDE	>0.01		NS	NS	NS	NS	>0.01	NS	NS
HCB	>0.01	>0.01		>0.01	NS	>0.01	NS	NS	-0.01
CHOL	NS	NS	>0.01		>0.01	>0.01	>0.01	>0.05	-0.01
TG	NS	NS	NS	>0.01		>0.01	>0.01	>0.01	-0.01
BMI	NS	NS	>0.01	>0.01	>0.01		>0.01	>0.01	-0.01
GLU-0	NS	>0.01	NS	>0.01	>0.01	>0.01		>0.01	-0.01
INS-0	NS	NS	NS	>0.05	>0.01	>0.01	>0.01		-0.01
TEST	NS	NS	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	

PCB – polychloinated biphenyls (Σ15PCBs); DDE – p,p‘-DDE (dichlorodiethyl-dichloroethylene), HCB – hexachlorobenzene; CHOL – cholesterol; TG – triglycerides; BMI – body mass index; GLU-0 – fasting glycemia (glycemia at fast), INS-0 – fasting insulinemia (insulinemia at fast), TEST – testosterone

Table 4

Males aged 41-70 years

	PCB	DDE	HCB	CHOL	TG	BMI	GLU-0	INS-0	TEST
PCB		>0.01	>0.01	NS	NS	NS	NS	NS	NS
DDE	>0.01		>0.01	NS	>0.01	>0.01	>0.01	>0.01	-0.05
HCB	>0.01	>0.01		NS	NS	>0.01	>0.01	>0.01	-0.01
CHOL	NS	NS	NS		>0.01	NS	NS	NS	NS
TG	NS	>0.01	NS	>0.01		>0.01	>0.01	>0.01	-0.01
BMI	NS	>0.01	>0.01	NS	>0.01		>0.01	>0.01	-0.01
GLU-0	NS	>0.01	>0.01	NS	>0.01	>0.01		>0.01	-0.01
INS-0	NS	>0.01	>0.01	NS	>0.01	>0.01	>0.01		-0.01
TEST	NS	-0.05	-0.01	NS	-0.01	-0.01	-0.01	-0.01	

PCB – polychloinated biphenyls (Σ15PCBs); DDE – p,p‘-DDE (dichlorodiethyl-dichloroethylene), HCB – hexachlorobenzene; CHOL – cholesterol; TG – triglycerides; BMI – body mass index; GLU-0 – fasting glycemia (glycemia at fast), INS-0 – fasting insulinemia (insulinemia at fast), TEST – testosterone

man organism without any possibility to be excreted, with the exception of lipid fraction of maternal milk in females or of negligible fraction of lipids as excreted by stool in males.

Organochlorines and obesity. Several positive and highly significant interrelations between the level of p,p’-DDE and HCB and signs of obesity such as the serum level of cholesterol and triglycerides as well as the BMI value, were found in both males and females. Thus, in young males (Table 3) only a significant increase in cholesterol level ($p<0.01$) and BMI value ($p<0.01$) with HCB was found. In old males (Table 4) the level of triglycerides ($p<0.01$) and BMI value ($p<0.01$) was found significantly increased with p,p’-DDE and that of BMI value ($p<0.01$) with HCB only. In both young females (Table 5) and old females (Table 6) significant increase of BMI with p,p’-DDE ($p<0.05$) and with HCB ($p<0.01$) was found and, in addition, in young females also a significant increase of triglycerides with HCB ($p<0.05$) appeared, while in old females also the increase of triglycerides with p,p’-DDE and HCB ($p>0.01$) and that of cholesterol with p,p’-DDE ($p>0.05$) appeared.

Organochlorine and diabetes. Moreover, several positive and highly significant interrelations were also found in both males and females between the level and appropriate signs of diabetes such as serum level of fasting glucose and fasting insulin. Thus, in young males (Table 3) only the level of fasting glucose in-

Table 5

Females aged less than 40 years

	PCB	DDE	HCB	CHOL	TG	BMI	GLU-0	INS-0
PCB		>0.01	NS	NS	NS	-0.05	NS	NS
DDE	>0.01		>0.01	NS	NS	>0.05	>0.01	NS
HCB	NS	>0.01		NS	>0.05	>0.01	>0.01	>0.05
CHOL	NS	NS	NS		>0.01	>0.01	NS	NS
TG	NS	NS	NS	>0.01		>0.01	>0.05	>0.01
BMI	>0.05	>0.05	>0.01	>0.01	>0.01		>0.01	>0.01
GLU-0	NS	>0.01	>0.01	NS	>0.01	>0.01		>0.01
INS-0	NS	NS	>0.05	NS	>0.01	>0.01	>0.01	

PCB – polychloinated biphenyls (Σ15PCBs); DDE – p,p‘-DDE (dichlorodiethyl-dichloroethylene), HCB – hexachlorobenzene; CHOL – cholesterol; TG – triglycerides; BMI – body mass index; GLU-0 – fasting glycemia (glycemia at fast), INS-0 – fasting insulinemia (insulinemia at fast), TEST – testosterone

Table 6

Females aged 41-70 years

	PCB	DDE	HCB	CHOL	TG	BMI	GLU-0	INS-0
PCB		>0.01	>0.01	NS	>0.01	>0.05	NS	NS
DDE	>0.01		>0.01	>0.05	>0.01	>0.05	>0.01	NS
HCB	NS	>0.01		NS	>0.01	>0.01	>0.01	>0.05
CHOL	NS	>0.05	NS		>0.01	>0.01	NS	NS
TG	>0.01	NS	>0.01	>0.01		>0.01	>0.05	>0.01
BMI	NS	>0.05	>0.01	>0.01	>0.01		>0.01	>0.01
GLU-0	NS	>0.01	>0.01	NS	>0.01	>0.01		>0.01
INS-0	NS	NS	>0.01	NS	>0.01	>0.01	>0.01	

PCB – polychloinated biphenyls (Σ15PCBs); DDE – p,p‘-DDE (dichlorodiethyl-dichloroethylene), HCB – hexachlorobenzene; CHOL – cholesterol; TG – triglycerides; BMI – body mass index; GLU-0 – fasting glycemia (glycemia at fast), INS-0 – fasting insulinemia (insulinemia at fast), TEST – testosterone

creased significantly ($p<0.01$) with p,p’-DDE. However, in old males (Table 4) both glucose and insulin levels significantly increased ($p<0.01$) with both p,p’-DDE and HCB. In both young (Table 5) and old females (Table 6), entirely the same interrelations appeared such as a significant increase of fasting glucose ($p<0.01$) with both p,p’-DDE and HCB, but that of fasting insulin only with HCB ($p<0.05$).

In summary, it may be concluded that several positive interrelations of organochlorine levels (namely these of HCB) with blood levels of obesity signs (the level of cholesterol and triglyceride), but also with BMI value supported the role of organochlorines in the etiology of obesity. Moreover, similar positive interrelations between organochlorine levels and signs of diabetes (fasting glucose and fasting insulin) supported also their possible role in the etiology of diabetes.

Organochlorines and serum testosterone in males. Highly significant decrease of testosterone level ($p>0.01$) was found in both young and old males as related to p,p’-DDE and HCB which is in agreement with our previous report (Langer et al. 2012).

Discussion

As it has been recently reviewed and underlined by Hu (2011), increasing prevalence of the type 2 diabetes seriously influences the economy of all nations, particularly of developing countries. At the same time, Casals-Casas and Desvergne (2011) have extensively reviewed

the role of endocrine disruptors (EDs) simultaneously acting as metabolic disruptors. Positive interrelations between increased prevalence of diabetes and obesity on the one hand and increased blood levels of various EDs on the other hand, were repeatedly observed in numerous countries such as the U.S.A. (Alexander et al. 2003; Lee et al. 2006, 2011, 2012), Japan (Uemura et al. 2009; Tanaka et al. 2011), Spain (Valvi et al. 2012; Arrebola et al. 2013), and Catalonia (Gassul et al. 2012).

As it was shown above, Slovakia undoubtedly belongs to most polluted countries with highly increased EDs blood levels significantly related to considerable disorders in lipid and glucose metabolisms.

In several excellent reviews (Hu 2011; Neel et al. 2011), the authors attempted to explain the diabetes worldwide epidemy by tracing the sequence of pathogenic steps leading to a widening gap between increasing caloric intake and decreasing caloric expenditure. This further resulted in obesity and adiposity, which has been closely related to metabolic stress thus opening the door for the diabetes type 2.

Nevertheless, the magnitude and rapidity by which the obesity rates are increasing raises concern about some other pathogenic factors (Neel et al. 2011). Thus, as one of them, a link between the post World War II increase in synthetic chemical production and the obesity epidemic has been suggested (Baillie-Hamilton 2002). According to Neel et al. (2011), several experimental findings, demonstrating that certain environmental pollutants induce adipogenesis and weight gain in experimental models, led to the environmental obesogen hypothesis that posits a causative role for synthetic chemicals in the pathogenesis of obesity. This hypothesis is also strongly supported by our data obtained from the inhabitans from highly polluted area, as it is reported in this study.

However, Neel et al. (2011) have underlined that "it is important to recognize that obesity per se may not lead to abnormalities in glucose homeostasis ... and the onset of frank diabetes necessitates a deficit in beta-cell insulin production ... therefore, the search for pollution-induced diabetes should include a specific focus on compounds with the capacity to induce insulin resistance and/or impair beta-cell function", as at the same time reviewed also by Hectors et al. (2011).

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