PERSISTENT ORGANOCHLORINATED POLLUTANTS (PCB, DDE, HCB, DIOXINS, FURANS) AND THE THYROID – REVIEW 2008

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During the second half of previous century considerable global environmental pollution developed due to massive use of several persistent organohalogenated pollutants (POPs) such as numerous pesticides, insecticides, herbicides and defoliants (hexachlorobenzene - HCB, dichlorodiphenyl-dichloroethylene – DDE, dichlorodiphenyl-trichloroethane – DDT etc.), fire retardants (polybrominated biphenyls - PBB), multipurpose industrial chemicals (polychlorinated biphenyls - PCBs, pentachlorophenol - PCP, plasticizers - octylphenol, bisphenol A) and byproducts of various large scale chemical production (polychlorinated dibenzodioxins - PCDDs and dibenzofurans - PCDFs). Since several of those substances considerably alter normal hormonal regulation, they are called endocrine disruptors (reviewed by MIMURA et al. 2003; TOYOSHIBA et al. 2004; MANDAL 2005; WARING and HARRIS 2005; ARULMOZHIRAJA et al. 2005; VAN DEN BERG et al. 2006; MATTHEWS and GUSTAFSSON 2007).

Actually, large quantities of such substances volatilize in warmer climate, drift into the atmosphere from various sources, precipitate out upon reaching colder climates and thus are deposited in cold polar regions after they arrived from industrialized and developing countries. Considerable role in this atmospheric transport also plays the interhemispheric exchange. In addition, large quantities of POPs containing industrial waste are dumped to the rivers finally flowing to the oceans which are thus serving as a final sink for such atmospherically transported chemicals and as the main transport vectors. Therefore, toxic threat by POPs to marine organisms is a matter of great concern and suspected to be linked to a series of mass mortality cases of marine mammals that occurred during the last decades (UENO et al. 2003).

One of the most widespread global pollutants are polychlorinated biphenyls (PCBs), about 1.5 million metric tons being distributed over the Earth surface by such long range transportation. There are even several areas which are so heavily polluted that they are called PCB reservoirs, among them the Baltic See, Hudson Bay and Great Lakes in North America. In spite of that the manufacturing of most toxic POPs has been recently banned (Stockholm Convention in 2004), the threat from global pollution which developed so far is still persisting. In addition, the production of most toxic polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) still continues, since they are unwanted byproducts of large scale industrial production, originate during biochemical processes in sewage and compost as well as during the incineration of communal waste. POPs are lipophilic and resistant to metabolic degradation. Their estimated half-life in the environment is perhaps equal to decades and centuries. Thus, for instance, thirty four years after Yusho accident in Japan resulting from the consumption of rice oil poisoned by PCBs and PCDFs the level of such substances in blood of exposed subjects was still 11.3 times higher than that in normal controls (TODAKA et al. 2007).

1. Some general aspects

PCBs consist of two chlorinated aromatic hydrocarbon rings. The substitution of chlorine varies from 1-10 atoms at *ortho-, meta-* and *para-* positions and thus there are 10 homolog groups each consisting of several congeners, their total number being 209 with molecular weight from 188 to 498 Da. Because of their useful physicochemical properties and wide industrial and commercial use (hydraulic fluids, heat-transfer fluids, dielectric fluids, lubricants, inks, laminating oils, paints, adhesives, dedusting agents, fire retardants, wax extenders etc.), their production considerably increased between early thirties and late seventies of last centu-

ry. Commercial PCBs and their environmental residues contain complex mixtures of congeners and elicit a broad spectrum of biological responses. The more the high chlorinated congeners the more the compact consistence of such mixtures varying from liquid via vaseline-like to solid one. PCBs with chlorine atoms at *meta*- and *para*- positions are more metabolically resistant and are accumulated in the tissues as "persistent congeners". In contrast, lower chlorinated PCBs, especially these with one or two free *para*-positions, are more rapidly metabolized. Thus, they appear only transiently in animal and human tissues and thus they are called "episodic congeners" (Hansen 1998, 2001; Rose et al. 2001/2002).

POPs in various countries. Animal and human exposure is from secondary sources such as food and water intake, inhalation and skin contact. In general, the species living in water contain higher levels of PCBs than terrestrial ones. The accumulation in plants has been less well studied so far, but it appears that their contamination results from airborne pollution of the leaf surface, while the evidence for the uptake through the roots is not definitely established.

In some cases the dietary exposure may be considerably high such as from sea food, e.g. in Baltic fishermen and Finish population (Kiviranta et al. 2003 and 2005, respectively), Spanish community exposed to airborne PCB (Grimalt et al. 1993), population of Faroe Islands (Fangström et al. 2002; Barr et al. 2003) and Arctic Quebec (Dewailly et al. 2002) or from inland water polluted fish such as in East Slovakia (Langer et al. 2007a). Since PCBs are present in human milk worldwide with considerable concentration namely in industrialized countries (Hong et al. 1994; Johansen et al. 1994; Schäfer et al. 1994; Schecter et al. 1994b), the developing breast fed infants belong to a special risk group.

To simplify the risk assessment and comparisons of data between individual countries, the concept of TCDD toxic equivalency factor (TEF) has been developed, TCDD being arbitrarily weighted with TEF of 1.0. For instance Schecter et al. (1994d) estimated average daily intake TEF in New York for adults between 0.3 and 3.0 pg TEF/kg, while that for a nursing infant was 35-53 pg TEF/kg. Newhook and Meek (1994) estimated the intake of hexachlorobenzene by adults in Canada of 2.8 ng/kg, while that by hunters and fishermen was about 92 ng/kg. However, te TEFs are estimated from a variability of semichronic/chronic or short-term toxicity data, which are not fully available for all congeners. In addition, only those effects mediated via Ah-receptor are included, while other effects are not. Such TEF approach can be used to transform analytical results into toxic equivalents (TEQ) used to calculate the toxic potency of various complex mixtures. Recently human and mammalian TEFs for dioxins and dioxin-like compounds are being reevaluated (Van den Berg et al. 2006).

Extensive data from various parts of the world were presented by Schecter et al. (1994 a,b,c) and Patterson et al. (1994). One of their main conclusions was that PCBs may contribute more dioxin-like toxicity in human tissues than do dioxins and furans in human tis-sues from general population in the United States, and probably for other industrialized countries as well (Schecter et al. 1994b).

Since all polychlorinated pollutants are highly lipophilic, the highest concentrations are found in adipose tissue. Thus, in the population at Baltic sea shore in Poland 1.5±1.3 μg total PCBs/g lipid was found (Falandysz et al. 1994a) and the levels of toxic PCB congeners No. 77+126+169 in Poland were 800-1000 pg/g, while those from UK, Canada and Japan were 300-500 pg/g (Falandysz et al. 1994b). Considerably high le-vels (i.e. 295 μg/g) were found in inhabitants around the river Krupa in Slovenia (Jan and Tratnik 1988). In Navarra (Spain) 2.44 μg/g was found for total PCBs, 3.37 μg/g for DDE and 3.37 μg/g for HCB (Gomez-Catalan et al. 1995). However, in a highly polluted district of Michalovce (Slovakia) Kocan et al. (1994) found the average of 12.3 μg/g in 14 random samples of human adipose tissue from Michalovce and in the same area Michalus et al. (personal communication) found the average of 8.6 μg/g with a maximum value 27.2 μg/g in 62 samples of human adipose tissue.

In serum Schecter et al. (1994b) found the highest percentage of PCB congeners CB-138, CB-153, CB-156 and CB-180 in plasma of patients with so called Yusho disease (i.e. poisoning by contaminated rice oil in Japan) and in human autopsy tissue from the US. In Norway Johansen et al. (1994) found 372 ng/g total PCBs (mainly CB-126) and also considerable levels of DDT (338 ng/g), HCB (41 ng/g) and HCH (36 ng/g). In Germany, Schäfer et al. (1994) found average 860 ng/g total PCBs, 170 ng/g HCB, 510 ng/g total DDT and 3.2 pg/g TCDD. In US women the average of total PCBs (mainly of CB-77, CB-126 and CB-169) was 49 and 55 ng/g (Hong et al., 1994). Schecter et al. (1994b) found 15-23 ng/g in Cambodia, 58-122 ng/g in Vietnam, 118-229 ng/g in former USSR, 760 ng/g in Ger-

many and 146 ng/g in New York State. In all cases about 40-50 % of CB-153 were found, while CB-138 was responsible for about 30-40 % and CB-180 for 10-30 %. Median level of CB-153 and *p,p'*-DDE (respectively) in men as expressed in terms of ng/g lipid in Greenland Inuits was 200 and 560 (n=439), in Sweden 190 and 240 (n=159), in Warsaw (Poland) 17 and 530 (n=257) an in Kharkiv (Ukraine) 44 and 930 (n=287) (Jönsson et al. 2005). In 311 adults from North Italy Apostoli et al. (2005) found a median of 24 PCB congeners level of 705 ng/g.

Among five selected areas of western, central and eastern Slovakia Kocan et al. (1994, 2001) found the average level of 15 PCB congeners sum 2-3 times higher (average of 4150 ng/lipid) than that in four western and central districts (averages from 1260 to 1880 ng/g). Such findings were apparently related to heavy environmental PCBs pollution around Michalovce. However, even the PCBs level found in those control districts were very high. Due to heavy general agricultural pollution, in all districts also considerably high levels of DDE (average of 6060 ng/g) and HCB (average of 5380 ng/g) were found. Detailed data on dioxins, furans and dioxin-like PCBs in heavily polluted eastern Slovakia were recently published by Chovancova et al. (2005) and Jursa et al. (2007), these on PCBs by Petrik et al. (2006) and these on selected OH-PCBs and $MeSO_2$-PCBs by Hovander et al. (2007).

2. Metabolism and main toxic effects of POPs

2.1. General view. Tissue distribution of lipophilic POPs is controlled by the lipid content of given tissue, the liver and adipose tissue being main sites of their metabolism and storage. Since individual congeners are subjected to selective absorption, distribution and biotransformation, their spectrum found in tissue samples differs from that of corresponding exposure mixtures (Skerfving et al. 1994) which is mainly due to chlorine rearrangements in the molecule. In general, the biological half-life of PCB in humans is unusually high, being up to 7 years for 2,3,7,8-substituted congeners. From toxicological view both the degree of chlorination and stereochemical structure is important. Although several species, including humans, show similar sensitivity to several toxic effects of PCB, there exist some species or strain specific differences (Birnbaum et al. 1994b).

The initial step of PCB biotransformation involves cytochrome P_{450} (CYP) mediated oxidation to arene intermediates which are then rapidly conjugated to either glucuronic acid or glutathione derivatives. Final products are hydroxy- and methylsulfo-PCBs which are more hydrophilic and represent the biologically active form, while the lipohillic precursors are apparently lacking any direct biological role.

2.2. Molecular mechanism of POPs toxicity. Family of toxic chemicals consisting of 7 polychlorinated dibenzo dioxins (PCDDs), 10 polychlorinated dibenzo furans (PCDFs), 4 coplanar polychlorinated biphenyls (cop-PCBs: CB-77, -81, -126, -169) and 8 mono-ortho-PCBs (CB-105, -114, -118, -125, -156, -157, -167, -189) shares a similar chemical structure and common mechanism of toxic action (reviewed by Mimura et al. 2003; Toyoshiba et al. 2004; Mandal 2005; Van den Berg et al. 2006; Matthews and Gustafsson 2007). These chemicals (and also HCB; Hahn et al. 1989) are specific ligands for aryl hydrocarbon receptor (AhR) – a key transcriptional regulatory protein - which, in the absence of ligand, is present in the cytosol with a complex of heat shock protein Hsp90s, small protein p23 and immunophilin-like protein XAP2. Upon dioxin binding, the complex dissociates and AhR translocates into the nucleus to form a heterodimer with its partner molecule ARNT (AhR Nuclear Translocator). Such AhR-ARNT heterodimer further acts as a nuclear transcription factor by specific binding to AHRE (AH Response Element) with core sequence 5'-TGCGGTG-3' in promoter region of dioxin inducible genes. Among such genes perhaps the most important is that of cytochrome P-450 1A1 (CYP 1A1).However, in the nuclei another AhR related factor called AHRR is located (AH Receptor Repressor) which also forms heterodimer with ARNT and recognizes AHRE, but functions as transcriptional repressor by competing with AhR for forming a heterodimer with ARNT.

Among AhR ligand inducible genes are these involved in cell proliferation and cell cycle regulation. For instance, using DNA microarray Frueh at al. (2001) identified 310 genes which were up or down regulated in TCDD-treated HepG2 cells. Although knockout mice demonstrated that this receptor has a role in normal development and physiology, the fundamental biological function of this receptor is still unclear.

Although in mammals only one homologue of AhR has been found, in some fish (e.g. in rainbow trout) two homologues were identified which are derived from independent gene. It is well known that marked species and strain differences exist in sensitivity to TCDD. For instance, hamster appeared about 5000-fold more

sensitive than guinea pig. Such phenomenon apparently results from the polymorphism in AhR loci (Wong et al. 2001) and indicates genetic variations in TCDD-inducible toxicity also in humans. Recently, a novel AHRE-II response element has been characterized in rats which, after binding of AhR-AHRNT element activates a novel gene battery (Pastorelli et al. 2006).

Although AhR knockout mice showed that AhR apparently plays a role in normal physiology, in spite of long-term effort some possible endogenous ligands for AhR still remain to be identified (Hillegass et al. 2006; Nguyen and Bradfield 2007). However, the activation of AhR pathway further activates also the function of nuclear hormone signaling pathways including these of estrogen (Matthews and Gustafsson 2006), thyroid (Gauger et al, 2007) and retinoic acid (Toyoshiba et al. 2004; Murphy et al. 2007) as well as matrix metalloproteinases (MMPs) expression and activity as reviewed by Hillegass et al. (2006).

As concerns the large group of di-*ortho*-PCBs congeners which are considerably prevalent in formerly used commercial mixtures, in a majority of environmental samples and reservoirs as well as in human samples, it was repeatedly supposed that they exhibit their activities by a mechanism independent of AhR. It was found that such PCBs congeners disrupt the Ca^{2+} signaling by the action on the ryanodine receptor-Ca^{2+} channel complex type 1. This results in Ca^{2+} efflux and thus further stimulates several intarcellular events which may be the underlying mechanism for certain non Ah-receptor mediated responses to *ortho*-rich PCBs and that such a mechanism may explain a large part of the cellular toxicity described for such PCB congeners (Pessah et al. 2005)

Finally, it should be admitted that any particular molecular mechanism for toxic activity of several other POPs including such widely used substances as DDT, DDE and others still remains to be elucidated, although a number of their toxic effects is well known.

2.3. Biochemical effects include: 1. altered metabolism re-sulting from changes in enzyme levels; 2. altered homeostasis from changes in hormones and their receptors; 3. altered growth and differentiation resulting from changes in growth factors and their receptors. So far several groups of proteins appear to be responsive to Ah-receptor agonists: 1. growth-regulatory proteins (EGF etc.); 2. drug-metabolizing enzymes (glucuronyltransferase, glutathionetransferase etc.) via the induction of CYP 1A1 gene; 3. NADPH-generating enzymes (malic enzyme, glucose-6-P-dehydrogenase etc.).

PCBs, PCDDs, PCDFs and other groups of POPs also show several metabolic and toxic activities including mutagenic, immunotoxic and carcinogenic effects (McKinney and Waller 1994; Okey et al. 1994). They also mimic several lipophilic natural hormones and thus strongly affect endocrine homeostasis (Whitlock 1994; Birnbaum 1994a).

2.4. Toxic syndrome produced in animals is characterized by severe loss of body mass, lymphoid tissues involution and immunotoxicity (suppression of the primary antibody response, enhanced sensitivity to infections), hepatotoxicity (increase in liver size at low doses, necroses and fatty degeneration at higher do-ses), epidermal changes (chloracne, generalized ectodermal dysplasia, alterations in the teeth and nails), gastric lesions, endocrine dysfunctions (changes in thyroid hormone, androgen and estrogen homeostasis etc.), embryotoxicity (congenital malformations), carcinogenicity etc. AhR-receptor is considered as primary mediator of toxicity, since: 1. the toxicity of individual congeners is correlated with their affinity to AhR; 2. AhR from strains of mice which are "nonresponsive" to toxic effects of PCB binds those com-pounds with considerably lower affinity than that from "responsive" strains; 3. the antagonists of AhR inhibit or reduce the toxic and metabolic effects of PCB.

As mentioned above, the concept of toxic equivalency factor (TEF) has been developed (Ahlborg et al. 1995). However, this is based on those toxicities that are mediated through Ah-receptor, while diverse spectrum of non-Ah-receptor mediated responses (mainly long-term responses such as hypovitaminosis A, hypothyroidism, neurotoxicity, carcinogenicity etc.) is being omitted.

2.5. Markers of susceptibility. Within epidemiological studies it repeatedly appeared that individuals with almost the same organochlorine levels show strikingly different values of individual endpoints evaluated. Recently several studies showed that humans proved to have genetic control over the metabolism of xenobiotics entering the body, so various individuals depending on genetic features could be resistant or, in contrast, to be extremely sensitive to chemical agents. This assumption could be based on the role of Ah-receptor and cytochrome P-450 lAl polymorphism in mediating a variety of species and strain differences in the sensitivity to OCs (Mimura et al. 2003).

For instance, tremendous number of studies reported conflicting results on the risk of breast cancer associated with exposure to PCBs. However, some recent

studies revealed that the risk is elevated four-fold in postmenopausal women carrying M2 variant of CYP1A1 gene which occurs in 7-17 % of Causasian women (ZHANG et al. 2004) and also in African American women (LI Y. et al. 2005). Similarly, HAHN et al. (2004) reported different frequencies of major allele types of AhR gene between dioxin-resistant and dioxin-sensitive populations of Atlantic killifish (*Fundulus heteroclitus*).

Recently we also discussed possible different susceptibility of individuals to the adverse effects of POPs. Such view was based on significantly different thyroid volume measured by ultrasound (RADIKOVA et al. 2007) or on strikingly different level of FT4 and TT3 between large group of males and females with the same range of PCBs level (LANGER et al. 2007c).

3. POPs and the thyroid – experimental studies

Since the chemical structure of several POPs closely resembles that of thyroxine (T4) and triiodothyronine (T3), attention has been repeatedly paid to their possible effects on thyroid homeostasis (BRUCKER-DAVIS 1998; BROUWER et al. 1998, 1999; KIMBROUGH and KROUSKAS 2001; KARMAUS 2001; HAGMAR 2003) and recommendations on screening methods for thyroid hormone disruptors were issued by a workshop of experts (DEVITO et al. 1999).

3.1. Direct thyroid damage by POPs. COLLINS et al. (1977) observed a hypertrophy and hyperplasia of follicular cells, irregularity in follicle size and colloid content. By electron microscopy the accumulation of numerous large colloid droplets was found as well as irregularly shaped lysosomal bodies in the expanded cytoplasmic area. He postulated altered interaction between numerous colloid droplets with lysosomal bodies that is necessary for enzymatic release of thyroid hormones. Similarly, AKOSO et al (1982), CAPEN and MARTIN (1989), NESS et al. (1993), SAEED and HANSEN (1997), WADE et al. (2002) and NISHIMURA et al (2003) reported increased epithelium height as prominent thyroid lesion in POPs fed rats and also a decrease of colloid area, increased number of intracellular colloid droplets and lysosomes after feeding various organochlorines.

Later COLLINS and CAPEN (1980) reported that ultrastructural thyroid lesions produced either by TSH thyroid stimulation, suppression of pituitary TSH release by exogenous thyroxine or feeding by low iodine diet which stimulates endogenous TSH release, considerably differed from the effect of PCB feeding and thus concluded that the antithyroid effect of PCB is direct and specific.

In rats fed pelleted diet uniformly sprayed by 1, 5, 10 and 50 ppm Arochlor 1254 or PBB (Fire Master BP-6) for 5-7 months, strikingly decreased total T4 and T3 level in dose-response manner was found (BYRNE et al. 1987). There was also significantly diminished response of serum T4 to the injection of bovine TSH and significantly decreased disappearance rate of injected ^{125}IT4. Important enough, there was no difference in body weight and food consumption between groups. It was concluded that such findings result primarily from a direct damage to the thyroid.

3.2. POPs and plasma protein binding. VAN DEN BERG et al. (1991) reported that among 65 compounds from 12 chemical groups as much as 60 percent (including chlorophenols, HCB and DDT) were competitive with T4 binding to purified human transthyretin (TTR; major plasma T4 transporting protein in rats) and also found reduced plasma T4 level in rats. Moreover, HCB metabolite pentachlorophenol was found to be effective competitor for T4-binding sites of TTR, while HCB itself was ineffective (VAN RAAIJ et al. 1991). Competitive potency of all *meta*- and *para*-hydroxylated PCBs as well as of hydroxylated PCDDs and PCDFs was found higher than that of T4 itself, while no competition was found with not hydroxylated substances (LANS et al. (1993). However, such hydroxylated substances could not inhibit T4 binding to purified thyroxine binding globulin (TBG) which is the main T4 transporting protein in human plasma (LANS et al. 1994). In 13 weeks feeding rats with TCDD, PCB-126 and PCB-156 VAN BIRGELEN et al. (1995) found a decrease of T4 and T3 with a simultaneous increase of UDP-glucuronosyltransferase (UGT) and CYP1A1, such increase in UGT after PCB congeners being considerably higher than that after TCDD. The problem of *in vitro* binding was reevaluated by CHAUHAN et al. (2000) who demonstrated also the binding of *ortho*-PCBs to TTR which appeared several times more potent than that of T4, the highest binding affinity being shown by the congeners with di-*meta*-substitution in one of both rings (e.g. 5,5') which most closely resemble the diiodophenolic ring of thyroxine. Among several PCB-OH tested only two bound to TBG with about 100-fold lower affinity than T4 (CHEEK et al. 1999).

3.3. Increased disposal of thyroid hormones by POPs via biliary excretion. Increased glucuronidation of T4 and T3 resulting in increased production of T4-

and T3-glucuronide and their increased disposal via the intestinal route, was reported by VAN RAAIJ et al. (1993) in HCB treated rats, while other UDP-glucuronosyltransferase inducers were described by BARTER and KLAASEN (1994) and LIU et al. (1995). HOOD and KLAASEN (2000a,b) later found that, although all inducers they tested increased the glucuronidation of T4, only phenobarbital (PB) and pregnenolone-16α-carbonitrile (PCN) increased the glucuronidation of T3, while that after 3-methylcholantrene (3MC) or PCB did not change. TSH level increased only after PB and PCN, thus being dependent on the increase of T3 glucuronidation which resulted in a decrease of blood T3.

SEWALL et al. (1995) administered rats biweekly by 7 different TCDD doses between 0.1-125 ng/kg. After 30 weeks of such treatment they found increased induction of genes for UDP-G and CYP1A1, decreased serum T4 and T3, increased serum TSH and follicular cell hyperplasia. SCHUUR et al. (1999) observed a considerable effect of a single dose of 2,3,7,8-TCDD (10 μg/kg) on the decrease of serum T4 level in rats continuously infused by small doses of T4 and T3 by osmotic minipump for 7 days. There was a decrease of serum T4 and T3, no change of TSH, 5-fold or 20 % increase of T4 or T3 glucuronidation (respectively) and increased activity of malic enzyme. Thus, it appeared that decreased hormone levels in blood were predominantly due to increased hepatic enzyme activity. WADE et al. (2002) fed rats for 70 days a mixture of 16 common OCs in doses equivalent to 1x, 10x, 100x and 1000x minimum risk level. Blood T4 level was significantly reduced only after 1000x dose, but T3 was increased in 100x and 1000x dose fed animals, while TSH was significantly increased already after 1x dose and it strikingly increasing until 1000x dose. The height of epithelial cells was increased after 100x and 1000x dose, but the area of follicles increased after 10x, while ti strikingly decreased after 1000x dose. In liver homogenates T4 glucuronidatin highly increased only after 1000x dose, but outer ring deiodination of T4 significantly decreased already after 1x dose and continuously decreased up to 1000x dose.

3.4. Interactions of POPs with thyroid hormone receptors (THR). Considering PCBs as hormonally active structural analogues, MCKINNEY and WALLER (1994) discussed conformational potencies looking for molecular models which would permit to express PCB activity in terms of dioxin, thyroxin or estradiol equivalents. Later, the same authors (MCKINNEY and WALLER 1998) and also PORTERFIELD (2000) speculated that PCBs may affect brain development by directly interfering with thyroid hormone signaling. However, at the same time CHEEK et al. (1999) found only a low affinity of OH-PCBs for THR. Recently structural requirements for the interaction of 91 OH-PCBs with THR were evaluated (ARULMOZHIRAJA et al. 2005) and search for the synthetic THR ligands to be used as thyroid receptor antagonists for treating thyroid hormone excess was reported (MALM et al. 2007).

There is also a cluster of studies based on the hypothesis that, at the cellular level, PCBs might act as a proper thyroid hormone. Among others, such hypothesis seems to be based on the findings that the expression of RC3/neurogranin in the fetal rat brain is controlled not only by thyroid hormone of maternal origin (DOWLING and ZOELLER 2000), but also by technical PCBs mixture Arochlor 1254 (ZOELLER et al. 2000). Such hypothesis has been strongly confirmed by FRITSCHE et al. (2005) who found that the treatment of normal human neural progenitor cells in culture by mono-*ortho*-PCB-118 (2,3',4,4',5-pentachlorobiphenyl) leads to the same dose-dependent oligodendrocyte formation as the treatment by T3 only, while the treatment by coplanar-PCB-126 (3,3',4,4',5-pentachlorobiphenyl) has no effect. In the meantime GAUGER et al. (2006) did not observe any detectable binding either of several PCB congeners or of a number of OH-PCBs or $MeSO_2$- PCBs to THR in isolated hepatic nuclei. They also found that Arochlor 1254 significantly reduced circulating level of T3 and T4 in pregnant rats, but increased the expression of several THR responsive genes in fetal brain cortex thus showing that PCBs may exert a direct effect on THR.

Perhaps the recent step in this field was reported by GAUGER et al. (2007) who evaluated the activity of the mixture consisting of two non-*ortho* (co-planar) PCBs (77 and 126), two mono-*ortho* PCBs (105 and 118) and two di-*ortho* PCBs (138 and 153) which has been added to *in vitro* system of rat somatomammotroph cell line CH3 transfected with luciferase driven thyroid hormone response element (THRE). They suggested that coplanar PCB 126 as AhR activator induces CYP1A1 which then acts on non-coplanar PCB 105 and 118 further producing analogues that activate THRE. Luciferase activity in this system was increased only in case when a mixture contained PCBs -126, -105 and -118. These findings strongly supported the hypothesis that one or more non-coplanar PCB congeners can act as a direct agonist on THR.

In the liver of adult rats administered by the mixture of six PCBs significantly increased mRNA level of

malic enzyme was found, which is a direct target of thyroid hormone action (Gauger et al. 2007) and similar effect. of such dioxin-like compound as HCB on increased transcription of malic enzyme was found by Loaiza-Perez et al. (1999)

Also several other groups studied the interrelations between POPs and THR. Thus, in various cell lines Iwasaki et al. (2002) showed a strong suppression of T3 effect on THR and coactivator complex by PCBs. Similarly, alterations of gene expression in T3-induced metamorphosis of *Xenopus Laevis* by herbicide acetochlor were found by microarray (Crump et al. 2002). Myiazaki et al. (2004) found partial dissociation of thyroid/retinoid X receptor heterodimer complex from thyroid hormone-response element of DNA and suggested this is a novel mechanism of suppressing thyroid hormone receptor-mediated transcription by PCBs. Somewhat different interrelations described Toyoshiba et al. (2004) who used microarray to show tentative findings supporting a hypothesis linking the usual dioxin expression changes to the retinoic acid receptor system. In addition, several PCB and OH-PCB congeners were found to inhibit the binding of T3 to THR, 4-OH being essential for thyroid hormonal estrogenic activity, while 3,5-dichloro substitution favors thyroid hormonal but not estrogenic activity (Kitamura et al. 2005).

Using HeLa cells carrying thyroid hormone receptor (TRα) and a reporter gene linked to thyroid hormone response element (TRE), Yamada-Okabe et al. (2004) found that dioxin up-regulated, while pentachloro-PCB-OH down-regulated TR mediated gene expression. Later the same authors (Yamada-Okabe et al. 2005) screened 38 chlorinated substances and found remarkable up-regulation with 4,4'-diiodobiphenyl and widely used fire retardant 1,2,5,6,9,10-hexabromocyclododecane (HBCD). Rushing and Denison (2002) reported the interaction of a nuclear corepressor - silencing mediator of retinoic acid and thyroid hormone receptors (SMRT) – with the mechanism of AhR dependent gene expression Another step of thyroid hormone metabolism which is being influenced by PCBs is the inhibition of thyroid hormone sulfation by hydroxylated metabolites (OH-PCB) which could be a possible mechanism for the developmental neurotoxicity (Schuur et al. 1999). In this respect also the findings of greater effects of PCBs on central nervous system could be of interest, since PCBs suppressed the transcription mediated by thyroid hormone receptor in a series of cells, but particularly in those derived from cerebellum (Iwasaki et al. 2002).

Vezina et al. (2004) used microarray to compare hepatic gene expression profiles for 8,799 genes and found that after 16 weeks exposure of rats to toxicologically equivalent doses of such AhR ligands as TCDD, TCDF, coplanar PCB 126 several genes were expressed which, however, were not expressed after the exposure to *diortho*-PCB 153 which does not interact with to AhR. Interesting enough, among the genes expressed exclusively after PCB-153 were these of proinflammatory cytokines including *IL-1, IL-2* and immune response gene *MX1*, while the expression of apoptotic genes *BCL-2* and *WEE1* was decreased. Selectively enhanced was also the expression of cAMP response element modulator *(CREM)* protein. These findings are considered to provide new targets for studying the toxicity mechanism of PCB-153 and perhaps also of other di-*ortho*-PCBs.

Similarly to POPs, also a non-chlorinated plasticiser - bisphenol A - which closely resembles the structure of T4, was found to antagonize T3 action at the transcriptional level by recruiting the corepressor of T3 action on nuclear THR (Moriyama et al. 2002).

3.5. POPs and pituitary-thyroid interrelations. Since a decrease of blood T4 and T3 level namely in rats exposed to POPs has been repeatedly observed, pituitary TSH response to such serious perturbation of pituitary-thyroid interplay became an attractive chalenge. Wade et al. (2002) observed considerably increased blood TSH level related to simultaneous decrease of T4 in rats fed various doses of OCs mixture which is agreement with the accepted views on pituitary-thyroid interplay.

It is well known that increased rate of intrapituitary T4 to T3 conversion by deiodinase type II results in inhibition of TSH release, while, vice versa, TSH release is stimulated by decreased rate of such conversion. Hood and Klaasen (2000a) found that the increase of serum TSH in rats resulting from the decrease of serum T4 level occurs only after increased T4 glucuronidation by phenobarbital (PB) and pregnenolone-16alpha-carbonitrile (PCN), whereas it is less affected by 3-methylcholanthrene (3-MC) and PCB which, at the same time, do not increase the glucuronidation of T3. The same authors later found that type II deiodinase activity in the pituitary is increased in rats treated by 3-MC and PCB, but the reason why serum TSH is increased in these animals is other than the increase of that activity (Hood and Klaasen 2000b). Khan et al. (2002) tested the effect on nonpersistent *ortho*-PCB congeners 95 and 101 on hypothalamo-pituitary-thy-

roid axis in weanling rats and found a decrease of TT4, decreased hypothalamic dopamine and increase of serum prolactin, while TSH did not change. Later they found a decrease of TSH response to TRH injection in similar weanling rats (KHAN and LARSEN 2003).

3.6. Intracellular effects of organochlorines. Lipophilic organochlorines could accumulate in lipid bilayers of cell membrane and thus disrupt its fluidity (LOPEZ-APARICIO et al. 1997) which could be valid namely for bulky three dimensional structure of the ortho-substituted congeners than for coplanar ones (TAN et al., 2003). From this it could be hypothesized that, in case of thyroid, they possibly facilitate the cross-talk between thyroid antigens and lymphocytes of the modulated immune system and thus contribute to the pathogenesis of autoimmune thyroid disorders.

4. Organochlorines and human thyroid

4.1. Thyroid volume (ThV). In Yusho patients poisoned by rice oil containing PCBs and PCDFs in Japan (MURAI et al. 1987) and later in similar Yucheng patients in Taiwan (GUO et al. 1987) increased prevalence of goitre was found by palpation. Since, due to high consumption of sea food in those countries the iodine intake is high thus counteracting the thyroid growth, the above findings on possible thyroid growth promoting effects of POPs appear of interest. In contrast, however, even slight iodine deficiency in some area could bring false positive findings if ThV increase would be ascribed to POPs effects

In our surveys in the area of eastern Slovakia heavily polluted by a cocktail of PCBs, DDE, HCB and PCP, but also including PCDDs and PCDFs (KOCAN et al., 1994, 2001; CHOVANCOVA et al., 2005; JURSA et al., 2006; PETRIK et al., 2006; HOVANDER et al. 2006; PARK et al. 2007; LINDELHOLM et al. 2007) thyroid ultrasound volumetry has been used to evaluate the effects of POPs on ThV (TAJTAKOVA et al. 1998). By such method ThV was repeatedly found significantly associated with the level of PCBs used as a marker of the cocktail of several OCs (LANGER et al., 1998, 2003, 2007b). Since the level of PCBs as well as of other OCs is also increasing with age, we showed that, in additon to the age, PCBs contributes to the increase of ThV by the component other than age (Langer et al. 2007b) as also shown in Fig. 1.

In fact, the differences in ThV between the subjects with low and high PCB levels as reported in our studies could be found only by ultrasound, while they apparently are virtually undetectable with the aid of palpation. On the other hand, well monitored mandatory consumption of iodized salt in Slovakia already existing for more than 50 years provides a possibility to rule out any possible interfering role of iodine deficiency on the increase of ThV related to POPs which, in addition, gives the unique opportunity to study the effects of factors different from iodine deficiency, e.g. environmental and hereditary ones. Such iodine repletion of Slovak population was confirmed by European study (DELANGE et al., 1997) and also by generally low ThV and normal urinary iodine in several thousand of adults and adolescents as observed in several our studies (TAJTAKOVA et al., 1988, 1998, 2006; LANGER et al., 1995, 1998, 1999, 2003, 2007b).

Possible mechanism of ThV increase by POPs still remains to be explained. It has been demonstrated that human thyroid exhibits the potential for estradiol (E2) synthesis and intracrine or paracrine estrogen responsiveness which may increase during the process of tumorigenesis (VIVACQUA et al. 2006). Estradiol receptors were also evidenced in FRTL-5 rat thyroid cell line that displayed growth stimulatory effects and also down-regulation of sodium-iodide symporter gene upon exposure to E2 (FURLANETTO et al. 1999). Since estrogen receptors were repeatedly found in normal and disordered thyroid (KAWABATA et al. 2003; TAVANGAR et al 2007) and the binding of several POPs (e.g. PCBs and PCB-OHs) to such receptors *in vitro* has been demonstrated (SHIRAISHI et al. 2002; KITAMURA et al. 2005), it may be assumed that the thyroid growth could be also stimulated by estrogen-like effects namely of DDE or some PCB congeners such as CB-52, CB-70 and CB-187 (ARNOLD et al. 1996; WOLFF et al. 1997; HANSEN 1998) and brominated flame retardants (LEGLER and BROUWER 2003). RAJAPAKSE et al. (2002) observed the activation of human estrogen receptor alpha in response to combining effect of suboptimal concentrations of several xenoestrogens. Since estrogens were found to inhibit the intrathyroidal estrogen sulfotransferase (KESTER et al. 2000), such mechanism could also influence estrogen availability in thyroid tissue.

Estrogens and phytestrogens are also enhancing the process of thyroid cell growth and tumorigenesis (MANOLE et al., 2001; KUNG et al., 2002; MADEJ et al. 2002; VIVACQUA et al. 2006). Such effects may be supported by higher incidence of thyroid cancer in women during reproductive age compared to men or postmenopausal women and also by increased risk of thyroid cancer in such women treated by estrogens. Related to

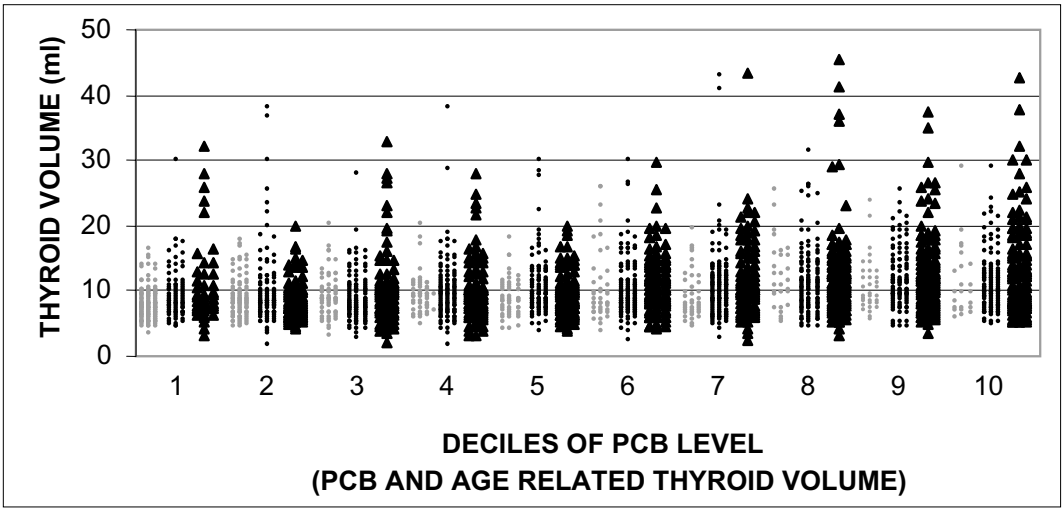

Fig 1 Distribution of thyroid volume (ThV) in a total of 2046 adults (1212 females and 834 males) divided in three age groups (gray points = <35 years of age; black points = 36-50 years of age; black triangles = 51-75 years of age) as stratified in deciles of PCB level. Upper range limits of serum PCB level (ng/g serum lipid) in individual deciles are: 504 – 627 – 767 – 906 – 1,087 – 1,387 – 1,711 – 2,343 – 3,664 – 101,413 (90 % of 10th decile = 15,103).

this could be the increased frequency of thyroid cancer in menopausal women treated by estrogens for a long time, except for low dose estrogen replacement (Persson et al. 1996). Potential of human thyroid for both estrogen synthesis and autocrine or paracrine estrogen responsiveness which is being enhanced together with the process of tumorigenesis was described by Valle et al. (1999). Manole et al. (2001) found E2 a potent mitogen for benign and malignant thyroid tumor cells and attempted to explain such effect by up-regulation of its own receptors. Recently, Araujo et al. (2006) found considerably higher thyroid weight and follicular cell height after treating ovariectomized rats with estrogens (200 μg/kg) and tamoxifen (1 mg/kg) daily for 50 days as compared to untreated ovariectomized controls.

All such findings support the view that estrogens could contribute to the growth of malignant and possibly also normal thyroid which might be potentially valid also for POPs displaying estrogenic activity, such as CB-52, CB-70, CB-101 and CB-157 (Wolff et al. 1997). However, Hansen (1998) underlined the importance to determine a number of different tissue specific estrogenic activities of indivudual congeners and presented a comparison of MCF-7 cells proliferation assays, estrogen receptor binding and uterotropic assay for various PCBs and OH-PCBs, among them CB-18, CB-52, CB-77, CB-95 nad CB-110. Khan et al. (2002) found increase of epithelial cell height in CB-95 and estradiol treated weanling female rats. Finally, close interrelations between female gender and thyroid may be supported by very well known high prevalence of all thyroid disorders which, in each ethnic, is at least about four times higher than that in males.

Among other possibilities of thyroid growth stimulating effect might be the disruption of cellular membranes fluidity by strongly lipophilic OCs (Tan et al. 2003) thus possibly influencing the cross talk between thyroid membrane antigens and circulating lymphocytes. Such mechanism may further facilitate the development of autoimmune thyroiditis at least in hereditary predisposed individuals which also could contribute to the thyroid growth. Nevertheless, any possible other specific effect of POPs on thyroid growth cannot be excluded.

4.2. POPs and thyroid cancer (ThCa). After treatment of thyrocyte culture with TCDD and PCB-126, Pocar et al. (2006) observed a significant down regulation in the expression of NIS (Natrium Iodide Symporter) and cathepsin B (lysosomal protease which mediates partial proteolysis of thyroglobulin preceding its endocytosis). Such decreased expression of NIS may represent an early response during the thyrocyte transformation pathway (Filetti et al. 1999) and possibly results in the formation of follicular thyroid adenoma as observed after oral administration of TCDD in rats (Na-

tional Toxicology Program 1982) or in Beluga whales from Hudson Bay with high PCB level (Mikaelian et al. 2003). Vansell et al. (2004) fed rats a diet containing 100 ppm of commercial PCB mixture Arochlor 1254 for 19 weeks and observed drastic decrease of T4 from week 3 and somewhat less decrease of T3, while TSH increased 3fold by week 2 and returned to initial level by week 19. Four of 22 rats had ThCa at week 19, not associated with the proliferative type of lesion thus indicating that separate mechanism could exist for the production of ThCa in rodents by chemicals which are considered microsomal enzyme inducers.

Grimalt et al. (1994) reported 3 cases of ThCa within 1980-1989 in the community of 5003 inhabitants located in the vicinity of OCs producing factory in Spain. Among 2885 US workers employed between 1944-1977 in capacitator manufacturing plant the age, gender, and calendar year adjusted mortality in 2000 showed, among others, significantly elevated mortality from ThCa in males (Mallin et al. 2004). In contrast, no significant increase in overall cancer deaths was found among 1,939 males working in transformer manufacturing plant in Canada between 1947-1975 (Yassi et al. 1995) and among 7075 workers exposed at least for 90 days between 1946-1977 (Kimbrough et al. 1999). In Swedish Cancer Register 1230 male and 2937 female ThCa cases were reported during 1961-1979, significantly elevated risk being found among pharmacists, drivers, workers in canning and preserving industry as well as petroleum industry and laboratory assistants (Cartensen et al. 1990). Among 20,000 young subjects aged 0-19 years two cases of ThCa appeared (relative risk [RR] 4.6 , CI 0.6-32.7) within 10 years after industrial accident in Seveso (Pesatori et al. 1993). In agricultural region of Minnesota with extensively use of fungicides and chlorophenoxy herbicides and their common aerial applications significantly increased mortality rate from ThCa in men (SRR 2.95, CI 1.35-6.44) was found (Schreinemachers et al. 1999).

When using excellent Norwegian Cancer Register, Frich et al. (1997) found significantly elevated risk of ThCa in 40,849 women (174 cases per 1 210 683 person/years; SIR 1.91, CI 1.65-2.21) whose spouses were employed in fishing, whaling or sealing work. Although the authors did not analyze any further detailed interrelations, it may be speculated that such high prevalence may be well related to increased POPs level in fish from northern Atlantic.

4.3. Effects of OCs on blood thyroid hormone level and pituitary-thyroid feed-back system. In spite of no doubts about repeatedly reported decrease of total T4 (TT4) in plasma of various animal species after the administration of relatively high PCBs doses, the effects of PCBs on thyroid hormone and TSH level in humans still remain to be definitely elucidated.

Several authors (Van den Berg et al. 1991; Van Raaij et al. 1991; Lans et al. 1993; Cheek et al. 1999; Chauhan et al. 2000) found the binding of PCBs and their hydroxylated metabolites to transthyretin (TTR) – one of two major plasma thyroxine carrier proteins in humans and in rodents which was then assumed to play a crucial role in the above mentioned acute decrease of (TT4) level in rats (Byrne et al. 1987; Van Raaij et al. 1993; Seo et al. 1995; Fowles et al. 1997; Kuriyama et al. 2003). However, since the doses of PCBs used in such experiments (e.g. mg/kg body weight) were by an order of magnitude higher than the assumed intake in humans, the question remains whether the displacement itself might influence the thyroid hormone level in humans. Ishihara et al. (2003) found the inhibition of T3 binding *in vitro* to chicken and bullfrog TTR by pentachlorophenol and diethylstilbestrol, while these chemicals had little or no influence on T3 binding to thyroid hormone receptor. However, so far no binding of PCBs was found to TBG (thyroxine binding globulin) which is the major thyroxine binding protein in humans (Lans et al. 1994).

As summarized by Liu J. et al. (1995), the decrease of blood TT4 level in animals was further enhanced by the increase of T4 hepatic conjugation and biliary excretion due to induction of hepatic UDP-glucuronyltransferase after few weeks of high dose PCBs feeding and later Hood and Klaasen (2000) specified such inducers in more detail. Schuur et al. (1999) demonstrated a 5-fold increase in glucuronidation activity in rats after a single high dose of 2,3,7,8-TCDD (10 μg/kg) and concluded that decreased thyroid hormone level in blood was predominantly due to increased activity of that hepatic enzyme. Possible role of such increased glucuronidation in humans is still not clear.

However, several contradictory data were published on the association between serum OCs and thyroid hormone as well as thyrotropin level in human beings. Actually, a great majority of such studies faced the cohorts exposed to the POPs cocktail consisting of the same major substances such as PCBs, DDE and HCB. Among the first studies was that by Triebig et al. (1998) who did not find any difference in TT4,. TT3 and TSH level between low and high PCDDs and PCDFs (the levels were not estimated) exposed metal recycling

workers. No difference in TT4 level was also found between 244 referents and 262 dioxin exposed US workers, but the latter group showed significantly increased free thyroxine index (Calvert et al. 1999). Although Murai et al. (1987) described an increase of TT4 and TT3 in Yusho patients, this was not confirmed 14 years later by Nagayama et al (2001) who, in 16 Yusho patients with median PCDDs plus PCDFs TEQ level of 222.4 pg/g lipid did not see any effect on serum level of TT3, TT4 nd TSH. In 12 schoolchildren from Aral Sea area highly exposed to OCs (mean levels for DDE of 1078, beta-HCH of 1376, HCB 33 and PCB 177 ng/g lipid) Mashitova et al. (1998) found the level of TT4 and TSH within the reference range. We also did not find any difference in TT4 level between 238 highly exposed workers of PCBs producing manufacture and 454 adults from the area of low pollution. However, since in these subjects the level of OCs was not estimated (Langer et al. 1998), our assumption on very high OCs levels in such workers was based on our later examinations of large cohorts from the same areas in which, vice versa, we did not measure TT4, but rather FT4, TT3 and TSH (Langer et al. 2007c; Rádiková et al. 2007).

In children living nearby the toxic waste incineration plant Osius et al. (1999) reported positive association of CB-118 and TSH, negative association of CB-153, CB-180, CB-183 and CB-187 with FT3 and no association of PCB congeners with FT4. However, the examined adolescents showed considerably low PCBs level, that of 7 PCB congeners (5 % – 95 %) being 180-1600 and median of 470 ng/per liter of whole blood. Since red blood cells represent about 50 % of blood volume and their PCB level has not yet been estimated, it should be assumed that the median of 470 ng corresponds to about 500 ml serum which further means that the PCB level could be about 90-120 ng/g lipid assuming about 4-5 g lipid per 500 ml serum. In 16 Yusho patients with median TEQ level of PCDDs plus PCDFs of 222.4 pg/g lipid Nagayama et al. (2001) did not see any effect on serum level of TT3, TT4 nd TSH. In New York anglers with median TT4 level of 214 ng/g lipid Bloom et al. (2003) did not find any considerable changes in TT4 level. Significant decrease of T3 with simultaneously increasing levels of OCs after weight loss in obese subjects was described by Pelletier et al. (2002), but the true levels of T3 found in these subjects were not presented. Julander et al. (2005) did not find any relevant changes in thyroid hormone levels related to polybrominated diphenyl ethers (PBDE) exposure in workers at an electronic recycling facility. Sala et al. (2001b) found significant decrease of TT4 in cohort of about 600 adults of both sexes with increased levels of hexachlorobenzene (e.g. about 2500 ng/g serum lipid) and PCBs (e.g. about 500 ng/g). In Great Lakes fish consumers negative association of TT4 with PCBs was found (Persky et al. 2001), while Turyk et al. (2006) found similar negative association for TT3, TT4 and TSH. In the later report the mean level of 89 PCB congeners was 806 ng/g lipid, that of DDE was 602 ng/g and TEQ of dioxin-like OCs was 46 pg/g, while Humphrey et al. (2000) found the mean serum PCB level of 14,260 ng/l (about 1400-1700 ng/g lipid assuming 8-10 g lipid per liter of plasma) in 101 fish consumers from that area. In NHANES 1999-2002 study participants Turyk et al. (2007) later found negative association of TT4 with PCBs and PCDDs, positive association of TSH with these two OCS in older women, but negative association in older men. However, in the latter study relatively very low mean level of PCBs (139.8 ng/g lipid) and DDE (1.82 ng/g lipid) was found. In Akwesasne Mohawk youth with mean PCBs level of 150-190 ng/g and DDE level of 35-45 ng/g lipid (Schell et al. 2003) negative association of PCBs with FT4 and TT3 and positive association with TSH was found (Schell et al. 2004). Takser et al. (2005) did not see any significant relationship between OCs and human cord serum thyroid hormones, but significant negative correlation was found of maternal serum TT3 versus three PCBs (CB-138, CB-153 and CB-180) and three pesticides (*p,p'*–DDE, HCB and cis-nanochlor). Also in this study the median level of 7 PCB congeners in individual trimesters was relatively low (e.g. about 0.33 to 0.39 μg/l which means 330-390 ng/l or about 30-50 ng/g lipid assuming the lipid level of 8-10 g/l). In 341 adult men Meeker et al. (2007) found positive association between DDE and both FT4 and TT3, while that between PCB-153 and TT3 was negative when potential confounding variables were considered. Median OCs level (ng/g lipid) was also low, being 211 for PCBs, 204 for DDE and 0.074 for HCB.

In summary, several human studies were possibly influenced by the findings of decreased TT4 level in rats administered by OCs and by the assumption that the level of TT4 as the main thyroid hormone perhaps should be used as a marker of OCs effect on the thyroid. However, a majority of observations showed either no association or negative association of OCs with TT4. Such mostly negative findings could be also influenced by well known fact that TT4 level depends on

the level of plasma binding proteins rather than on the thyroid function itself. From such reason TT4 estimation is neither recommended for thyroid diagnostics by American Thyroid Association (ATA 2003) nor for the screening of POPs effects on the thyroid by US Environmental Protection Agency (De Vito et al., 1999). Hagmar (2003) reviewed 13 studies (among them 6 in neonates) and concluded that any effect of PCBs exposure on thyroid hormone homeostasis in humans cannot be convincingly shown. However, in the meantime it appeared that negative association either not convincing or conflicting data were obtained in cohorts exposed to relatively low level of OCs, while highly significant changes were found in cohorts exposed to high POPs levels (Langer et al.. 2007c; Rádiková et al. 2007).

As concerns FT4 and TT3, several authors observed either no associations or negative associations between OCs and these hormones (Osius et al. 1999; Sala et al. 2001; Hagmar et al. 2001a,b; Pelletier et al., 2002; Schell et al., 2004; Takser et al., 2005; Rylander et al., 2006), while only Meeker et al. (2007) found positive association between DDE and both FT4 and TT3, though that between PCB-153 and TT3 was also negative. We recently found different association between categorical levels of PCBs on one side and FT4 and TT3 on the other (Langer et al. 2007c). Thus, in the whole cohort of 2046 subjects it appeared that within the category of PCBs level <530 ng/g lipid (n=232) the correlation between PCBs and FT4 ($p<0.09$) as well as TT3 ($p<0.03$) was negative, while within the category of PCBs level of 531-1000 ng/g (n=691) such correlation fluctuated about zero. In contrast, in the category of 531-2000 ng/g (n=1307) positive association appeared between PCBs and FT4 ($p<0.001$) as well as TT3 ($p<0.05$). Highly significant correlation of PCBs with FT4 ($p<0.001$) was further found in the PCBs level categoiries of 1001-101414 ng/g (n=1307) and 2001-101414 (n=1123), while significant correlation with TT3 was observed only in the category of 531-2000 ng/g. Such findings suggest possible threshold level in positive effect of PCBs on FT4 and TT3 in serum which. seems to be individual and located somewhere around the PCBs level of 1000-1500 ng/g, while in cohorts consisting predominantly of individuals with OCs level <1000 ng/g both positive or negative correlation should be expected which was possibly the reason of controversial data obtained in several studies. Such controversial findings, as obtained in 743 men and women aged 41-50 years, are also shown in Fig. 2 from which follows that the associations found by various authors in cohorts with a majority of PCBs levels <1000 ng/g lipid may be, at least to some extent, simply misleading and thus may simply result from the effects other than organochlorines.

Reported associations between POPs and TSH level in adolescents and adults were mostly positive. Thus, positive association of TSH with mono-ortho PCB-118 was found by Osius et al. (1999) in schoolchildren, that with PCBs, but not with DDE and HCB by Schell et al. (2004) in young Akwesasne Mohawks and that with DDE, but not with PCB-153 by Rylander et al. (2006) in Baltic fishermen, while inconsistent interrelations for those OCs with TSH were observed in Great Lakes fish consumers (Persky et al., 2001). Recently, negative association between DDE and TSH was reported by Meeker et al. (2007). In adults exposed to very large range of PCBs level including a cluster of subjects with strikingly high levels of PCBs, DDE and HCB cocktail we found only very slight and not significant negative association of TSH with PCB (Radikova et al. 2007).

However, it should be noted that relatively very low PCBs levels (e.g. either in terms of the mean or median between about 50–300 ng/g lipid or in terms of 95th percentile or maximum between about cca 200-900 ng/g) were reported by some authors (Osius et al. 1999; Bloom et al. 2001; Hagmar et al. 2001b; Schell et al. 2004; Takser et al. 2005). Taken together, a majority of their cases apparently had PCBs level <1000 ng/g. However, in one of our studies (Langer et al. 2007c) we found negative correlation between PCBs level <530 ng/g (n=232) and both the FT4 ($p<0.09$; not significant) and TT3 ($p<0.03$) in a group of subjects with PCBs level <530 ng/g (n=232), while either negative or no correlation with these hormones was found in a group with PCBs level of 531-1000 ng/g (n=691). Since these data approximately resembled those reported by the above authors, there still remains a question whether namely a certain effect of PCBs is involved in such cases or not. In contrast, in the category with PCBs level of 531-2000 ng/g (n=1307) we found a positive correlation between PCBs and FT4 ($p<0.001$) as well as TT3 ($p<0.05$). If the whole range of PCBs level has been taken in account, the significant positive correlation was obtained with FT4 ($p<0.001$) and TT3 ($p<0.05$). Such findings suggest possible threshold level in positive effect of PCBs on FT4 and TT3 level which seems to be somewhere around the PCBs level of 1000 ng/g.

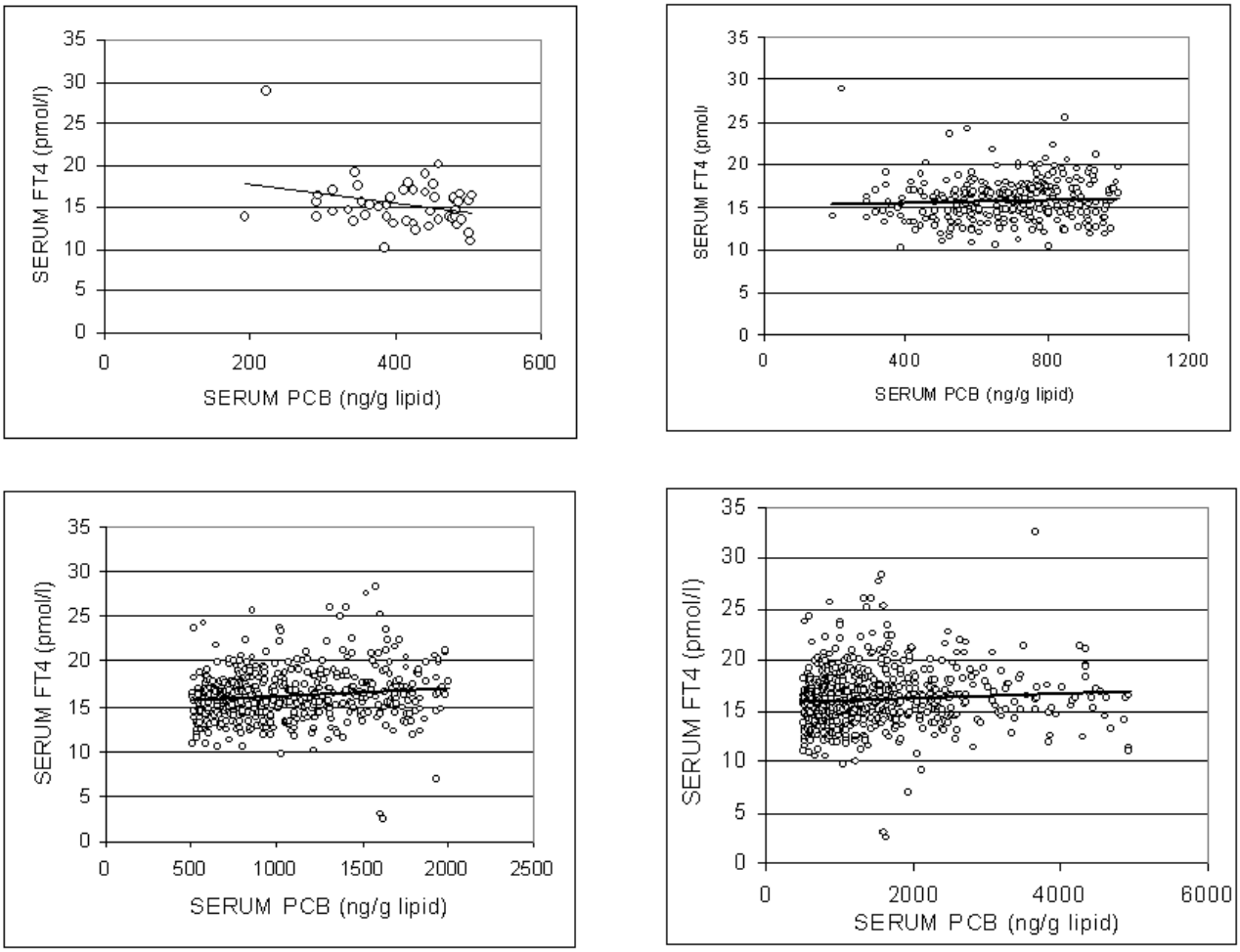

Fig 2 Associaations between categorical ranges of PCBs level and FT4 in pooled males and females aged 41-50 years (n= 743): Left upper panel: negative association between PCB levels <500 ng/g lipid and FT4 (n = 46; r = –0.279; p<0.05); Right upper panel: no association between PCB levels <1000 ng/g lipid and FT4 (n = 298; r = 0.080; not significant); Left lower panel: positive association between PCB levels of 500 - 2000 ng/g lipid (n = 503; r = 0.131; p<0.01); Right upper panel: positive association between PCB levels of 500 – 5000 ng/g lipid (n = 649; r = 0.069; p<0.05)

Such view is in agreement with positive correlation between DDE and FT4 reported by MEEKER et al. (2007), while HAGMAR et al. (2001a) and RYLANDER et al. did not find any positive correlation between PCB or DDE versus FT4 in spite of considerably high level of these OCs in their exposed subjects.

Recently ABDELOUAHAB et al. (2008) examined TT3, TTS and TSH levels in 124 male and 87 female fish consumers in Canada with considerably high PCB levels (e.g. 75th percentile of 16 PCB congeners 2550 ng/g in males and 1990 ng/g in females). For women, serum TT3 were negatively related to serum level of PCB 138, PCB-153 and several other OCs, while no relations were found between TT4 and any of the chemicals measured, while TSH was negatively related to blood lead. For men, TT4 was inversely related the sum of 16 PCB, while TSH was positively related to that PCB sum as well as to several other OCs, but no associations were found with TT3.

However, although we did not find any negative association between PCBs and TSH in our total cohort, among the population from polluted area we detected a group of 13 subjects (4 males and 9 females aged 44-60 years) with very high level of PCBs (median of 7438 ng/g lipid) and, at the same time, with hormonal levels that showed hyperthyroid status. Thus, their mean FT4

level of 23.3 pmol/l (upper limit of reference range 22.0 pmol/l) was increased and, vice versa, their TSH level was decreased, being <0.21 mU/l in eleven among those 13 subjects (lower limit of reference range = 0.27 mU/l). Their average body mass index (BMI) of 26.2 was slightly above the normal value of 25.0 which shows that such hyperthyroid status was subclinical in reality (Manji et al., 2006). Thus, we classified such cases as "high PCB related subclinical hyperthyroidism" which apparently corresponds to the definition recently published by Monaco (2003) as "subclinical hyperthyroidism is an asymptomatic status, in which circulating levels of FT4 and TT3 are increased, but supersensitive TSH is decreased. It is not any disease entity, but a mild stage of thyroid hyperfunction."

Finally, observations on possible interference of organochlorines with hypothalamic-pituitary-thyroid-peripheral feed back loops should be mentioned, among them recent findings on the inhibitory effect of PCB on thyrotropin release from the pituitary after the administration of exogenous hypothalamic hormone TRH (thyrotropin releasing hormone) by Khan and Larsen (2003). Since there are still several doubts and contradictory data about these mechanisms, they should be considered plausible, but not yet definitely accepted.

It is well known that increased rate of intrapituitary T4 to T3 conversion by deiodinase type-2 results in inhibition of TSH release, while, vice versa, TSH release is stimulated by decreased conversion rate. Hood and Klaasen (2000a) found that serum TSH was most increased after the treatment with phenobarbital or pregnenolone-16α-carbonitrile, whereas it was increased after treatment with 3-methylcholantherene (3-MC) and PCB. The same authors later found that type-2 deiodinase activity in the pituitary is increased in rats treated by 3-MC and PCB, but the reason why serum TSH is increased in these animals is other than the increase of that activity (Hood and Klaasen 2000b). Khan et al. (2002) tested the effect on nonpersistent ortho-PCB congeners 95 and 101 on hypothalamo-pituitary-thyroid axis in weanling rats and found a decrease of TT4, decreased hypothalamic dopamine and increase of serum prolactin, while TSH did not change.

4.4. Fetal exposure to POPs, fundamental effects and postnatal thyroid development. During past 2-3 decades considerable knowledge accumulated about the effects of POPs on human fetuses and newborns during the prenatal and early postnatal period. Thus, transplacental transfer of PCBs (DeKoning and Karmaus 2000; Sala et al 2001b; Covaci et al. 2002; Sandau et al. 2002; Ayotte et al. 2003; Mazdai et al. 2003; Guvenius et al. 2003; Soechitram et al. 2004; Fukata et al. 2005) as well as OH-PCBs (Park J-S et al. 2007, 2008) and $MeSO_2$-PCBs and -DDE metabolites (Linderholm et al. 2007) was repeatedly observed in various countries. In addition, some reports described the interrelations between POPs and thyroid hormone levels in newborns such as that by Longnecker et al. (2000) who suggested that, in the US, PCB exposure *in utero* is only slightly related to thyroid hormone and TSH concentration. However, Pluim (1993) and Koopman-Eseboom et al.(1994) observed transient increase of TSH in newborns of mothers highly exposed to dioxin. However, in US newborns Wang et al. (2005a) found negative association of PCDDs and dioxin-like PCBs with TSH and positive correlation of PCDFs with total T3. In Thailand, Asawasinsopon et al. (2006) found negative association of DDE in cord serum with total T4. Chevrier et al. (2007) recently examined the relationship between neonatal TSH levels and prenatal exposure to PCB congeners grouped according to their structure and potential mechanism of action. They found no association either between the sum of 34 PCB congeners or their toxic equivalents and TSH level, but observed a positive association between the sum of congeners inducing the enzyme uridinediphosphate glucuronosyntransferase which included PCBs 52, 99, 101, 118, 153, 156, 157, 167, 180, 183, 187, 189, 176 and 199.

In rats the gestational and lactational exposure to a single dose of 200 and 800 ng TCDD resulted in more than 2 fold increase of TSH and thyroid hyperplasia in male offsprings at 21 and 49 postnatal days (Nishimura et al. 2000).

Because of their low body mass the fetuses, newborns and babies are considered the most exposed human population to adverse effects of OCs such as neuropsychlogical disorders (reviewed by Schantz et al. 2003 and Tusscher and Koppe 2004), immune and thyroid function (reviewed by Kimbrough and Krouskas 2001), decrease of IgA, IgM as well as of total, cytotoxic and suppressor T cells count (Chang et al. 1981), increased frequency of pulmonary diseases (Rogan et al. 1988) and middle ear infections, mums and measless (Chao et al. 1997; Dewailly et al. 2004; Weisglas-Kuperus et al. 2000, 2004). From recent reviews (Holladay 1999; Tusscher and Koppe 2004) it appears that a fundamental step in such immunotoxic effects could be frequently observed thymic atrophy, while Michielson et al. (1999) pointed out also the role of thymus-independent immunopathology.

Such prenatal and postnatal exposure results in several adverse developmental effects such as lower birth weight and slower growth rate (Rogan et al. 1986; Jacobson et al. 1990a; Patandin et al. 1998), decreased newborn behavioral functions such as reflexes, tonicity and activity levels and adverse neurologic effects lasting up to 18 months of age (Fein et al. 1984; Huisman et al. 1995; Stewart et al. 2000), poorer visual recognition memory during infancy (Jacobson et al. 1985, 1990b, 1992; Darwill et al. 2000) and deficit in psychomotor development lasting up to 24 months (Gladen et al. 1988; Rogan et al. 1991).

Several links were also observed between prenatal PCB exposure and adverse effects detected during later periods such as poorer intellectual functions at 4 and 11 years (Jacobson et al. 1990a, 1996) and at 42 months (Patandin 1998). In one of recent studies, prenatal exposure to PCB was negatively related to mental/motor development at 30 and 42 months and also to intelligence tests performed at 42 months. Associations were found with breast milk levels rather than with these found in a cord blood (Walkowiak 2001). Recently, increased prevalence of well defined learning disability and attention deficit disorder was found in 278 adolescents aged 12-15 years with detectable POPs levels participating in NHANES 1999-2000 survey (Lee D-H et al. 2008).

Recently two controversial issues were raised. First, uncertainty has emerged regarding the most appropriate index of prenatal exposure to PCBs, since associations with adverse effects have been found with PCB levels in some biologic fluids (e.g. breast milk) but not in others (e.g. serum). Second, developmental deficits were found to be most consistently linked to prenatal rather than to postnatal exposure (Rubas-Fito 2001; Jacobson 2001). However, such contradiction appears to be solved by Ayotte et al. (2003) who showed strong interrelations between PCB levels in maternal plasma, cord plasma and breast milk in Inuit children cohort thus indicating that PCB level in any of these biologic fluids is a good indicator of prenatal exposure. Extensive review of possibly all large longitudinal surveys in mother-newborn pair and long term postnatal development of neurobehavioral functions in children conducted in various parts of the world (e.g. so called Dutch, Oswego, German, Michigan, North Carolina, Faroe Islands, Duesseldorf, Inuit, New Bedford, Yusho and Yu-cheng cohorts) has been recently published by Schantz et al. (2003).

One of important and recently emphasised cause of such profound effects on irreversible neurological damage could be thyroid disorders during critical periods of fetal and perinatal development, the most serious being endemic cretinism resulting from severe maternal dietary iodine deficiency. As thyroid hormones are essential for normal neurological development, it is possible that certain toxins can alter neurological functions by their effects on thyroid hormone action (Porterfield 1994; Zoeller 2003; Brown 2003).

Several immunotoxic and immunomodulatory effects of POPs were repeatedly described and there is an urgent need for epidemiologic studies of the prevalence of autoantibodies which could shad light on the pathways by which environmental exposures trigger abnormal immune response (Hood 2003). In children, increased frequency of childhood infections (e.g. otitis media) and decreased vaccine response after exposure to EDCs in Arctic Quebeck and Faroe Islands was found (Heilmann et al. 2003; Dewailly et al. 2004)

In Dutch cohort with maternal plasma PCB level of 2-293 ng/g lipid and OH-PCB level <0.62 ng/g fresh weight the levels in cord plasma were approximately 50 and 30 % of those in maternal plasma, respectively (Soechitram et al. 2004). In highly exposed population living around Hudson Bay in North Quebec the concentrations of total PCBs was 2710 (range 525-7720) pg/g and that of total OH-PCBs was 553 (range 238-1750) pg/g wet weight of umbilical cord plasma. Since the concentration of free T4 was negatively correlated with that of organochlorines, it is suggested that thyroid status in newborns could be possibly altered (Sandau et al. 2002). However, Ribas-Fito et al. (2003) did not find any changes of TSH levels in newborns whose mothers had extremely high levels of HCB.

4.5. POPs and thyroid autoimmune disorders. Great majority of thyroid diseases is of autoimmune origin. Thus, hypothyroidism results from progressing destruction of thyroid hormone producing tissue by cytotoxic anti-thyroperoxidase and anti-thyroglobulin autoantibodies, while hyperthyroidism (or Graves disease) results from the production of toxic amounts of thyroid hormone due to specific autoantibodies stimulating the thyrotropin receptor. Since several POPs possess immunotoxic effects, it may be suggested that they could either initiate or aggravate the development of such thyroid autoimmune disorders namely in hereditary predisposed individuals.

Numerous reports on a variety of general immunotoxic effects of organochlorines were recently published. Thus, Jung et al. (1998) observed impaired leu-

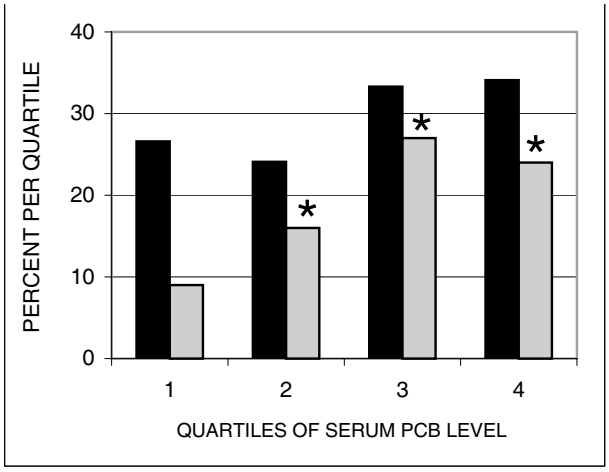

Fig. 3 Prevalence of positive thyroperoxidase antibodies in individual quartiles of PCBs level in pooled males and female aged 41-50 years. Statistical significance: * = p < 0.001 vs. the first quartile.

cocyte function in workers formerly exposed to dioxins, Dewailly et al. (2002) found increased frequency of otitis media in Inuit infants prenatally exposed to organochlorines (DDE, HCB and PCB) and, similarly, Heilmann et al. (2003) found decreased antidiphtheria vaccine response in children from Faroe Islands related to PCB level in maternal milk. Twenty years after dioxin accident in Seveso (Italy) Baccarelli et al. (2002) found decreased IgG level in serum of population from mostly exposed zones and Cooper et al. (2004) reported similar finding in American farmers with increased levels of DDE. In addition, Bernhoft et al. (2000) also reported IgG decrease in plasma of polar bears in Norwegian Arctic. Michielson et al. (1999) showed participation of multiple lesions of immune system after accidental human poisoning by hexachlorobenzene in Turkey. Decreased level of interferon-gamma, interleukin-4 and DR+ cell count in subjects occupationally exposed to PCBs and other organochlorines was found by Daniel et al. (2001). In subjects living near a pesticide dump site Vine et al. (2000) found decreased lymphoproliferative activity. In Flamish adolescents exposed to PCBs and dioxin-like compounds increased IgA was found, while IgG and certain specific IgEs (e.g. against cat dander, house dust and grass pollen) were decreased (van den Heuvel et al. 2002).

As related to thyroid, Bahn et al. (1980) were the first who found increased frequency of antimicrosomal antibodies which are now identical with anti-thyroperoxidase antibodies (TPOab) in workers of PBB factory. Within our first survey in PCB polluted area in eastern Slovakia (Langer et al. 1998) we found increased frequency of TPOab in 190 females from a former PCB factory compared to 482 referent females (28.4 % vs. 20.5 %; $p<0.05$) and also that of thyroglobulin antibodies (TGab) in 36/169 vs. 50/342 respective females ($p<0.05$). In addition, increased frequency of TSH receptor stimulating antibodies (TRab) was found in 238 age and sex matched subjects from respective areas (10.5 % vs. 2.5 % – $p<0.001$). In the employees of PCB factory we also found increased frequency of anti glutamic acid decarboxylase antibodies considered a marker of diabetes mellitus type 1 (Langer et al. 2002), but this was not confirmed in the later survey (unpublished}.

Within the second survey in eastern Slovakia no difference was found in the frequency of positive TPOab between females from PCB polluted and control area of background pollution, but highly significant increase of positive TPOab was found in males from polluted vs. control area (12/59 vs. 4/181; $p<0.001$) (Langer et al. 2003). Within the third survey (PCBRISK study in which 1038 adults from PCB polluted area and 1008 adults from the area of background pollution were rexamined), significantly higher frequency of positive TPOab was found in the 2nd, 3rd and 4th quartile ($p<0.001$) of PCB level vs. the 1st quartile ($p<0.001$) in males, while that in females the difference between the 3rd and 4th quintile vs. the 1st and 2nd quartile was slightly below the significance limit (Fig. 3).However, in all adults irrespectively of age (Rádiková et al. 2007) highly significant increase in the frequency of TPOab was found between 5th and 1st quintile of PCB levels in females (67/184 = 36.4 % vs. 73/308 = 23.7 %; $p<0.01$) and namely in males (49/223 = 21/9 % vs. 10/101 = 9.9 % ; $p<0.01$).

Whereas positive TPOab level in serum is the humoral sign of autoimmune process, simultaneously developing autoimmune thyroiditis results in hypoechogenicity of thyroid ultrasound image. Actually, within PCBRISK survey we found significantly increased frequency of positive TPOab and hypoechogenicity coincidence between 5th and 1st quintile of serum PCB level in males (16/223 = 7.2 % vs. 1/101 = 1.0 %; $p<0.025$), while that in females was not significant (29/184 = 15.7 % vs. 35/308 = 11.3 %), although in terms of absolute numbers it was higher than that in males (Langer et al. 2007b). This further

supported the interrelations between PCB level and frequency of autoimmunity signs. Recently a decrease of thymus size at birth in neonates in the same area of Eastern Slovakia has been found which may be closely related to the above described increase of thyroid autoimmune disorders prevalence in adolescenets and adults (Park H-Y et al. 2008). Such findings together with advancing knowledge on genetic background of autoimmune thyroid disease, as recently reviewed by Zeitlin et al. (2008), belong to milestones in understanding the effects of organochlorines on thyroid autoimmunity.

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