

POLYCHLORINATED BIPHENYLS AND THE THYROID GLAND - MINIREVIEW

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During last 60-70 years a considerable global environmental pollution developed due to the massive use of several polychlorinated organic compounds, some of which being used as pesticides (DDT, hexachlorobenzene, hexachlorocyclohexane etc.), insecticides (DDT), defoliants (e.g. Agent Orange in Vietnam war), multipurpose industrial chemicals (polychlorinated biphenyls) and some of them originating as byproducts of large scale chemical industrial production (e.g. polychlorinated dibenzodioxins and dibenzofurans).

Perhaps the most widespread global pollutants are polychlorinated biphenyls (PCBs). It should be underlined that the global atmosphere is polluted by those compounds up to the altitude of about 6000 meters. Remarkable amounts of PCBs have been found in all world oceans, in the Arctic and Antarctic and in the middle of all deserts. There are even several areas which are so heavily polluted that they are now called PCB reservoirs, among them the Baltic Sea, Hudson Bay and Great Lakes in North America.

1. General

There are 209 possible PCB congeners having several technically interesting properties and thus wide commercial use. Commercial PCBs and environmental PCB residues contain complex mixtures of congeners and elicit a broad spectrum of biological responses, a majority of them being mediated by Ah-receptor (see below). Actually, two major structural classes of PCB (e.g. the coplanar and monoortho coplanar PCBs) exhibit Ah-receptor agonist activity thus resembling that of most toxic member of planar halogenated substances - 2,3,6,7-tetrachlorodibenzo-p-dioxin (TCDD). Other structural classes of PCB may also elicit simi-

lar responses (including those "non AH-receptor mediated" such as neurotoxicity, estrogenicity, endogenous protein binding activity etc.). In contrast, some PCB mixtures and individual congeners may even inhibit TCDD-induced responses.

Polychlorinated biphenyls, dibenzofurans, dioxins and other groups of above mentioned compounds show several metabolic and toxic activities including mutagenic, immunotoxic and carcinogenic effects (McKINNEY et al. 1994; OKEY et al. 1994). They also mimic several lipophilic natural hormones and thus strongly affect endocrine homeostasis (BIRNBAUM 1994a; WHITLOCK 1994; LI and HANSEN 1997). From such reason they have been called "endocrine disruptors" (KAVLOCK et al. 1996). Although the industrial production of PCBs has been terminated in most countries, the global pollution is still persisting (SAFE 1994). However, the production of most toxic dibenzodioxines and dibenzofurans still continues, since these compounds are still used in chemical industry (e.g. for bleaching paper pulp). In addition, they originate as unwanted byproducts during large scale industrial production, during biochemical processes in sewage and compost or chemical reactions under atmospheric conditions and, finally, are produced during the incineration of communal wastes.

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 there is no evidence for the uptake through roots.

In some cases the dietary exposure may be considerably high (e.g. in Swedish fishermen - SVENSON et al. 1991; Spanish community exposed to airborne PCB - GRIMALT et al. 1993). 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 (BROUWER et al. 1995).

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 et al. (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.

Extensive data from various parts of the world were recently presented by SCHECTER et al. (1994 a,b,c) and PATTERSON et al. (1994). One of the main conclusions was that PCB may contribute more dioxin-like toxicity in human tissues than do dioxins and furans in human tissues 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 fat 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 levels (i.e. 295 $\mu\text{g/g}$) were found in inhabitants around the river Krupa in Slovenia (JAN and TRATNIK 1988). In Navarra (Spain) 2.44 μg total PCBs, 3.37 μg DDE and 3.37 μg HCB per g adipose tissue were found (GOMEZ-CATALAN et al., 1995). In Slovakia, KOČAN et al. (1994) found in 1989-90 an average of 12.3 μg total PCBs per g fat in 14 samples of human adipose tissue from Michalovce and MICHALUS et al. (personal communication) in 1987 found in 62 samples of adipose tissue average value 8.6 $\mu\text{g/g}$ with a maximum value 27.2 $\mu\text{g/g}$.

In serum SCHECTER et al. (1994b) found the highest percentage of congeners IUPAC No. 138, 153, 156 and 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 1992 KOČAN et al. (1994) analyzed 50 samples of human serum from 5 areas of Slovakia. In 40 samples from four areas they found total PCBs of 460-4350 ng/g fat. However, the range for 10 samples from the polluted city of Michalovce was 1160-9600 ng/g. The highest levels found in Michalovce were those of IUPAC No.153 (420-2830 ng/g), No.138 (310-2030 ng/g), No.180 (250-1790 ng/g), No.28 (60-1300 ng/g) and No. 118 (96-670 ng/g). In the same city, following concentration ranges were found: HCB (750-13300 ng/g), DDE (1300-34800 ng/g) and DDT (130-790 ng/g). Further analyses in Slovakia were made in 1995, the levels of PCBs in serum being still about twice as high in Michalovce (average of 2890 ng/g) than in the other areas (averages of 969-1770 ng/g).

In human milk MICHALUS et al. (personal communication) found average of 4010 ng/g in Michalovce (the highest value of 19,500 ng/g) and average of 3380 ng/g in Trebisov, while about a half of that amount was found in other 7 districts in East Slovakia (more than 300 samples examined). KOČAN et al. (1995) found the level of PCBs in pooled human milk from Michalovce (10 samples of 100 ml each) 1015.1 ng/g fat. With the exception of similarly polluted area of Uherské Hradiste in Czech Republic (1068.5 ng/g) this was 2 to 500 times higher than in 11 countries participating in the European Study (the average values are ng/g): Spain (461, 451), Belgium (275, 306, 260), Croatia (218,219), Denmark (209,253, 278, 275, 164), Finland (133, 188), Netherlands (253), Russia (102, 196), Ukraine (236, 191), Hungary (45, 61), Albania (42, 63), Pakistan (19).

JOHANSEN et al. (1994) found in Norway 372 ng/g total PCBs (mainly IUPAC No. 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 No. 77m 126 and 169) was 49 and 55 ng/g (HONG et al., 1994). Detailed PCB analyses presented SCHECTER et al. (1994b) who found 15-23 ng/g in Cambodia,

58-122 ng/g in Vietnam, 118-229 ng/g in former USSR, 760 ng/g in Germany and 146 ng/g in New York State. In all cases about 40-50 % of No. 153 were found, while No. 138 was responsible for about 30-40 % and No. 180 for 10-30 %.

2. Metabolism, metabolic and toxic effects

2.1. General view. PCB congeners are biotransformed by cytochrome P-450 isoenzymes. The tissue distribution of lipophilic PCB 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 1994a).

2.2. Ah-receptor. It was originally believed that organochlorines act via the nuclear steroid/thyroid receptors. However, after aromatic hydrocarbon (Ah) receptors have been cloned (BURBACH et al. 1992; DOLWICK et al. 1993), it became clear that this is the appropriate factor mediating the effects of organochlorines. Recent cloning showed that, unlike the steroid/thyroid receptors, Ah-receptor does not contain "zinc-fingers". The ligand-activated Ah-receptor binds to various Ah-Receptor Nuclear Translocator Proteins (ARNT proteins) and thus forms heterodimers which are further bound to specific DNA enhancer sequences known as Ah Responsive Elements (AHRE) (BIRNBAUM 1994b; OKEY et al. 1994, 1995) and function as transcriptional enhancers. It is peculiar that so far no endogenous ligand for Ah-receptor has been definitely demonstrated. Nevertheless, from some data it seems that even some action of PCBs via steroid/thyroid receptors cannot be definitely excluded (OKEY et al.

1995). Ah-receptor is present in most tissues and OKEY et al. (1994) reported that at least 26 genes have been shown to be responsive to Ah-receptor agonists.

2.3. Biochemical effects include: 1. altered metabolism resulting 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, glutathione-transferase etc.) via the induction of CYP1A1 gene responsible for the production of cytochrome P4501A1; 3. NADPH-generating enzymes (malic enzyme, glucose-6-P-dehydrogenase etc.) (BIRNBAUM 1994b; SAFE 1995)).

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 doses), 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. AH-receptor is considered as primary mediator of toxicity, since: 1. the toxicity of individual congeners is correlated with their affinity to AH-receptor; 2. AH-receptor from strains of mice which are "nonresponsive" to toxic effects of PCB binds those compounds with considerably lower affinity than that from "responsive" strains; 3. the antagonists of AH-receptor 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. 1992). 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.

3. Effects on the thyroid

3.1. Effects on the thyroid morphology. Feeding with PCBs and other toxic organochlorines resulted in the changes in thyroid histological picture and ultrastructure. COLLINS et al. (1977) observed a striking hypertrophy and hyperplasia of thyroid follicular cells accompanied by a significant decrease of serum thyroxine level in rats. There was irregularity in follicle size and colloid content, papillary projections of hyperplastic cells, and apical cytoplasmic processes extending into the lumens. The apical portions of the hypertrophic follicular cells stained strongly positive with the acid phosphatase reaction. By electron microscopy the most consistent lesions in follicular cells were the accumulation of numerous large colloid droplets and irregularly shaped lysosomal bodies in the expanded cytoplasmic area. Such lesion presumably contributed to the altered thyroid function consisting of the interference in the interaction between the numerous colloid droplets and lysosomal bodies that is necessary for the enzymatic release of thyroid hormones. Similarly, AKOSO et al. (1982), CAPEN et al. (1989), NESS et al. (1993) and SAEED et al. (1997) reported the decrease of colloid area, increased number of intracellular colloid droplets and lysosomes and increased epithelium height as prominent lesions in the rat thyroid after feeding of polychlorinated- and polybrominated biphenyls.

Additional investigations (COLLINS et al. 1980) permitted the conclusion that the ultrastructural lesions produced by PCB were distinct from; first, short- and long-term stimulation by exogenous thyrotropin; second, pituitary suppression by exogenous thyroxine; and third, stimulation of follicular cells by feeding a low iodine diet. These studies showed evidence of possible direct effect of PCB on the thyroid gland. Although the possibility of such direct effects of PCB on the thyroid was further supported by significantly decreased effect of TSH administration on T_4 and T_3 release from the thyroid in rats pretreated with PCB than in controls (BYRNE et al. 1987), some recent studies support the primary role of UDP-glucuronosyltransferase in the liver followed by increased thyroid hormone conjugation and biliary disposal (see below).

3.2. Effects on the transport of thyroid hormones in plasma and their peripheral metabolism.

One of the best understood effects of organochlorines on the thyroid is the decrease of plasma T_4 level due to the displacement of T_4 from protein binding (VAN DEN BERG et al. 1991; LANS et al. 1993, 1994) and to increased hepatic metabolism of T_4 resulting from the induction of UDP-glucuronosyltransferase (BASTOMSKY 1977; BROUWER 1991; VAN DEN BERG et al. 1991; LANS et al. 1993; MORSE et al. 1993; VAN RAAIJ et al. 1993; BARTER and KLAASEN 1994) which finally contributes to the decrease of blood thyroid hormone level. These findings were recently confirmed by SEWALL et al. (1995) and LIU et al. (1995) who found after TCDD administration to female rats follicular cell hyperplasia in the thyroid, decrease plasma thyroxine and elevated TSH levels, while SCHUUR et al. (1997) did not find any increased TSH level which strongly suggests that the thyroid hormone decreasing effects of organochlorines are predominantly extrathyroidal and mediated by the marked induction of hepatic UDP-glucuronosyltransferase activity.

Several organochlorines inhibit the binding of thyroxine to plasma carrier proteins in man such as transthyretin, TBG (Thyroxine Binding Globulin) and albumin (MCKINNEY et al. 1994). In addition, PCBs were shown to decrease blood total and free T_4 as well as decrease the total but increase the free triiodothyronine level in rats which further resulted in striking increase of pituitary thyrotropin (TSH) level in serum and increase of thyroid weight (ALLEN-ROWLANDS et al. 1982). Such alteration of normal feedback loop between the pituitary and thyroid is considered to be one of the underlying mechanisms of thyroid tumor promotion (BARTER et al. 1994; VAN BIRGELEN et al. 1994). Actually, during 1972 to 1976 40-80 % prevalence of goiter was found by MOCCIA et al. (1977). PCB also produce increased thyroid weight and plasma TSH level in rats (BARTER et al., 1994; SEWALL et al. 1995).

Because of a structural similarity to T_4 , PCBs may also interfere with the transport of T_4 into the cell and T_4 to T_3 conversion. They may also mimic thyroid hormone action and even modulate the mechanism of T_3 binding to its nuclear receptor and resulting gene expression (PORTERFIELD 1994; SAFE et al. 1995; RAASMAJA et al. 1996) and, finally, even in-

terfere with the binding of T_3 to its nuclear receptor (PLUIM et al. 1993) which is a transcript of cellular protooncogene c-erb-A. Actually, the expression of c-erb-A in mice treated with PCBs (BOMBICK et al. 1988) and in Chang liver cells after PCBs has been found (HORNHARDT et al. 1994).

Since the biphenyl structure of PCBs more or less resembles that of thyroid hormone, it is not surprising that BROUWER (1991) underlined striking similarities between the toxic endpoints of PCBs and symptoms associated with avitaminosis A and/or hypothyroidism (such as dermal and epithelial lesions and altered energy metabolism). It may be speculated that this hypothesis could be somehow related to the recently elucidated role of retinoic acid in the coactivation of thyroid hormone nuclear receptors.

3.3. Effects on central nervous system maturation during fetal life and neonatal and postnatal neurological development. Actually, it is well known that those children who were exposed to organochlorines by transplacental route and via mother milk, develop irreversible neurological damage (PORTERFIELD 1994). Thus, persistent increase of biogenic amines (SEEGAL 1992) and deiodinase type II activity (MORSE et al. 1993) was found in the brain of rat pups (NESS et al. 1993). In humans, such exposure resulted in hyporeflexia (ROGAN et al. 1986), hypotonia (HUISMAN et al. 1995), poorer short-term memory function and poorer cognitive and behavioral development (CHEN et al. 1994; WINNEKE et al. 1995; PORTERFIELD 1994; BROUWER et al. 1995; SCHANTZ 1996; JACOBSON and JACOBSON 1997).

As recently recognized, transthyretin plays an important role in transporting T_4 through cerebrospinal fluid to fetal brain structures (CHANOINE et al. 1992) and from mother's blood to coelomic fluid (CONTEMPRE et al. 1993), both mechanisms being essential for the developing fetus and its brain maturation. Since, as described above, T_4 is being displaced by PCBs from the binding to protein carriers and such mechanism might contribute to the development of well known neurotoxic effects of organochlorines on neonatal and postnatal brain development in exposed infants.

However, it is not definitely ascertained which fraction of such damage results from the direct neurotoxic effects of organochlorines and which role may

be perhaps played by the impairment of maternal-fetal thyroid function and thyroid hormone metabolism. The participation of the latter mechanism was suggested by PLUIM et al. (1993) who found significantly increased level of TSH and T_4 at the age of 11 weeks in high exposure group of neonates. In PCB exposed pregnant mice, DARNERUD et al. (1996) found increased binding of hydroxylated PCB metabolites to transthyretin resulting in significantly decreased fetal plasma T_4 levels.

In Japan (1968) and Taiwan (1979) two major poisoning incidents in which the rice oil was contaminated by PCBs that were used as heat transfer fluids during the decolorization process, but leaked into the oil. The disease resulting from the ingestion of such oil was called "Yusho disease" in Japan and "Yucheng disease" in Taiwan. This was first characterized by acneform lesions, brown pigmentation, ocular swelling and several neurological disorders (headache, memory loss, numbness, hypoesthesia, neuralgia of the limbs etc.). These changes apparently resulted from direct neurotoxic effect of PCBs. Pregnant women who suffered from Yusho gave birth to babies that were small and had dark brown pigmentation of the skin. Later they developed several neurological abnormalities. Several years after the accident the Yucheng children in Taiwan showed decreased IQ and several prolonged neurological, cognitive, musculoskeletal and behavioral abnormalities (GUO et al. 1997). However, it is important to point out that PCBs in rice oil were thermally degraded and thus contained unusually high concentrations of polychlorinated dibenzodioxines and dibenzofurans.

3.4. Effects of organochlorines on human thyroid. From several recent reviews it appears that less is known about possible effects of chronic, low background level general exposure of human population and further field studies should be undertaken (AHLBORG et al. 1992; BIRNBAUM 1994a; CHEN et al. 1994; SCHECTER et al. 1994 a,b,c; SKERFVING et al. 1994). Actually, more attention has been paid to the effects of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) which is the most toxic member of organochlorine family, but some studies also deal with the effects of PCBs. Thus, among the first reports was that by BAHN et al. (1980) who found 11 percent prevalence of

hypothyroidism in workers from PCBs producing factory and these subjects had also elevated titres of autoantibodies against thyroid microsomes. SARACCI et al. (1991) collected data on 13,482 workers exposed chlorophenoxy herbicides or chlorophenols who were followed for 17 years and found, among others, that 4 of them died from thyroid cancer which was significantly more than no case of thyroid cancer in 4908 workers with unknown exposure or probably exposed. ZOBEL et al. (1994) conducted a retrospective cohort morbidity study of 158 men exposed to TCDD (tetrachloro-dibenzodioxin) in 1953 due to uncontrolled exposition reaction of trichlorophenol unit in BASF factory in Hamburg. The final data were obtained in 1989 and after comparing them with those of 161 control subjects (BASF employees not exposed to TCDD) they found significantly higher percentage of thyroid diseases (7 % vs. 1.2 %) and appendectomies (16.5 % vs. 5.6 %) in the exposed group, the appendectomies being considered as a marker of decreased immune response. In a Spanish village located in a vicinity of organochlorine factory, GRIMALT et al. (1994) found significantly increased incidence of thyroid cancer (out of 5003 inhabitants 3 new cases within 10 years of 1980-89), soft-tissue sarcoma and brain neoplasms and significantly higher mortality for neoplasms of unknown origin. Surprisingly, no attention has been paid to the thyroid in a number of epidemiological studies of industry workers exposed to PCBs and TCDD as reviewed by NICHOLSON and LANDRIGAN (1994) and SWANSON et al. (1994) or recently published (KOGEVINAS et al. 1995; FLESH-JANYS et al. 1995).

In the employees of highly polluted formerly PCB producing factory in East Slovakia and surrounding area we recently found (LANGER et al. 1998) increased thyroid volume (means \pm S.E.) in adults (18.85 \pm 0.60 ml, N=238 in polluted area vs. 13.47 \pm 0.48 ml, N=486 in controls) and in 17 year old adolescents (9.41 \pm 0.15 ml, N=454 in polluted area vs. 8.33 \pm 0.09 ml, N=965 in controls). At the same time the prevalence of thyroid antibodies (anti-thyroid peroxidase, anti-thyroglobulin and anti-TSH receptor) was increased in adults from polluted area.

Related to this topic, the views published by PORTERFIELD (1994) should be presented who suggested that very low levels of these compounds - levels below those generally recognized as toxic - could in-

fluence both maternal and fetal thyroid function and, second, that the combined insult of exposure to the toxin in the presence of pre-existing thyroid disorder could exacerbate the effects of the toxin. KOOPMAN-ESSEBOOM et al. (1994) investigated 105 mother-infant pairs from highly industrialized area of Rotterdam and found that high level of organochlorines (dioxins, furans and PCBs) in human milk correlated significantly with lower maternal plasma levels of thyroxine and triiodothyronine and with higher plasma level of TSH in the infants.

3.5. Hypothesis on possible interrelations between PCBs and autoimmune thyroiditis. Long-term iodine deficiency or intake of goitrogens or both together may result in thyroid hyperplasia or goiter (rev. LANGER and GREER 1977; LANGER 1982; LANGER and MICHAJLOVSKIJ 1992). In a majority of cases this may be classified as **simple goiter** which means hyperplastic and mostly normally functioning enlarged thyroid. Another variety of enlarged thyroid may be the **autoimmune goiter** accompanying either autoimmune thyroiditis (M. Hashimoto) or thyrotoxicosis (M. Graves-Basedow), although both of them may actually develop from originally simple goiter under certain additional circumstances. Autoimmune thyroiditis results from autoimmune and progressive destruction of the thyroid due to the infiltration by the autoantibodies producing lymphocytes. From this follows that such thyroid, though its function may be normal for more or less relatively long period, is losing the ability to synthesize hormones which finally results in hypothyroidism.

As explained above, the administration of PCBs finally results in an increase of TSH level which further results in thyroid growth. Another effect of PCBs as lipophilic substances might be presumably concerned with influencing the fluidity or fine structure of cell membrane. It is well known that the presentation of cellular antigens to hereditary impaired immune system in some genetically predisposed individuals may result from the action of infections, high doses of iodine, exogenous cytokines and also of some environmental factors (rev. WEETMAN 1992). Actually, the prevalence of such susceptible population in different countries is not fully known in advance (WHO STATEMENT 1994), but namely from the effects of iodine or infections it is known that such

factors accelerate the incidence of thyroiditis (SUNDICK et al. 1992).

Thus, it may be assumed that the environmental toxins would have similar effect. Actually, increased prevalence of goiter has been found in several localities in Colombia and Kentucky which were supplied with drinking water originating from organic-rich sedimentary rocks and containing phenols, dihydroxyphenols (resorcinol), substituted dihydroxybenzenes, thiocyanate, disulfides, phthalic acids, pyridines and halogenated aromatic hydrocarbons which showed the goitrogenic activity in rats (GAITAN et al. 1993). The same authors (GAITAN et al. 1991) found increased prevalence of goiter, high TSH level and antiperoxidase antibodies (7-13 %) in several contaminated localities in Kentucky which showed the development of autoimmune thyroiditis confirmed by thin needle biopsy in 4 % of children. These findings are consistent with those observed by other authors in the same area 30 years ago (HOLLINGSWORTH et al. 1967).

WEETMAN (1991) showed that anthracene derivatives are potent inducers of autoimmune thyroiditis in genetically susceptible strains of rats. On the other hand, increased intake of iodide results in increased formation of oxygen radicals in the thyroid due to increased iodide oxidation rate by thyroid peroxidase (rev. by SUNDICK et al. 1992). Since PELTOLA et al. (1994) found increased measures of free radical toxicity in rat testis after PCBs, it may be hypothesized that PCBs might participate in the acceleration of autoimmune thyroiditis development in susceptible individuals and thus increase the incidence of such disorder in exposed population.

In addition, LOPEZ-APARICIO et al. (1997) showed the damaged fluidity of testicular cell membranes resulting from the accumulation of PCBs which may be also the case for the thyroid.

Another considerable circumstance contributing to the impairment of the thyroid may be the lipophilic nature of PCBs. It cannot be excluded that these substances accumulate in the lipophilic cellular membrane and thus deteriorate its fine structure which might facilitate the communication between thyroid autoantigens and circulating immunocompetent cells able to clonally proliferate in response to autoantigens and to promote recruitment of additional thyroid infiltrating B and T lymphocytes. This process

might be stimulated by iodine which may result in the overexpression of thyroid peroxidase and thus stimulate the iodination of some thyroid membrane proteins such as tubulin (SANTISTEBAN et al. 1985) and also the peroxidation of membrane lipids and lysis of cell membrane. In some genetically predisposed individuals this facilitates the contact of thyroid autoantigens with the impaired immune system and by such a mechanism autoimmune thyroiditis may develop.

Although no much attention has been paid to this problem so far, this view might be supported by the above mentioned paper by BAHN et al. (1980) who found increased prevalence of hypothyroidism and antithyroid autoantibodies in workers exposed to PCBs. In Slovakia, PODOBA JR. (1992) found 6.3 % prevalence of autoimmune thyroiditis (confirmed by a thin needle biopsy) among 360 adolescent girls (14-18 years of age) in the city of Bratislava. Recently we found (HANZEN, LANGER et al., unpublished) 49 cases (17.6 %) of positive anti-peroxidase antibodies among 278 women over 40 years of age (TSH IRMA level >4.5 mU/l being found in 18 subjects = 6.5 %) in one village in northern Slovakia which belongs to the highest figures ever reported (cf. ROBUSCHI et al. 1987; PRENTICE et al. 1990; ROTI et al. 1993).

Recently we found significantly increased prevalence of anti-thyroid peroxidase, anti-thyroglobulin and anti-TSH receptor antibodies in the employees of heavily contaminated formerly PCB producing factory (LANGER et al. 1998) and we suggested that the role of organochlorines in the etiology of increased level of anti-peroxidase antibodies in genetically predisposed individuals cannot be excluded. The participation of organochlorines in the development of autoimmune disease may be further supported by the findings of increased prevalence of autoimmune diabetes mellitus and hyperinsulinemia in Vietnam veteran Agent Orange sprayers (HENRIKSEN et al. 1997).

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