— Minireview —

Health Effect of Polychlorinated Biphenyls and Related Compounds

Yoshito Masuda*

Daiichi College of Pharmaceutical Sciences, 22–1 Tamagawa-cho, Minami-ku, Fukuoka 815–8511, Japan

(Received June 2, 2003)

Polychlorinated biphenyls (PCBs) and dioxins have polluted the environment for about 50 years and parts of them have transferred to human being through food chain. Humans are already contaminated with chlorinated compounds at relatively high levels. Yusho PCB poisoning occurred at Northern Kyushu in 1968 and the patients have been suffering from various symptoms for 35 years. High concentrations of toxic PCBs and polychlorinated dibenzofurans in the patients have been very gradually decreased to the levels of only 2 to 6 times higher than those of normal persons. Typical Yusho symptoms of acneiform eruption, dermal pigmentation and increased eye discharge were very gradually recovered with lapse of several years. However, enzyme and/or hormone-mediated signs of high serum triglyceride, high serum thyroxin, immunoglobulin disorder and others are persistently maintained for more than 30 years. Recent tolerable daily intake of dioxins were determined from their hormone-like activities, such as decreased sperm count, immune suppression, increased genital malformation and neurobehavioral effects in the offspring of animals. PCBs are important factors on considering dioxin toxicities to human for the reason that half the dioxin toxicity in normal persons consists of the toxicity of coplanar PCBs. Recent epidemiological studies have reported that higher levels of PCBs and related compounds in the human body associated with various health effects, such as lowering intelligence quotient levels, disorder of thyroid gland, higher rate of endometriosis in women, declining thyroid hormone levels, higher rate of diabetes in pregnant women, lowering age at menarche, and altering play behavior in children at school age.

Key words —— polychlorinated biphenyl, dioxin toxicity, health effect, Yusho polychlorinated biphenyl poisoning, environmental pollution, human pollution

INTRODUCTION

Polychlorinated biphenyls (PCBs) and dioxins have been well known environmental pollutants in animals as well as humans. Health effects of PCBs and dioxins have been observed in not only occupational workers but also common persons. Yusho PCB poisoning occurred in 1968 at Northern Kyushu and the patients have been suffering from various symptoms for 35 years.[1] From the studies on toxic compounds and symptoms in Yusho patients, toxicities and health effects of PCBs and dioxins to humans are evaluated in this review.

*To whom correspondence should be addressed: Daiichi College of Pharmaceutical Sciences, 22–1 Tamagawa-cho, Minami-ku, Fukuoka 815–8511, Japan. Tel.: +81-92-682-0396; Fax: +81-92-661-2574; E-mail: yoshito.masuda@nifty.ne.jp

Environmental Pollution of PCBs and Related Compounds

About sixty thousands tones of PCBs were produced in Japan from 1953 to 1972 and used for electric insulation, heat transfer medium, non-carbon copying paper and others. When Yusho PCB poisoning occurred in 1968, PCBs were not considered to be so toxic compounds, since the annual PCB production increased in the following years of 1969 and 1970. Because PCBs were disclosed to be toxic and accumulative in the environment and human, production and usage of PCBs were all prohibited in Japan in 1972. Discarded PCBs, turning the excellent and chemically stable property in industry into bad and non-destructive in the environment, became persistent pollutants in the global environment.[2] Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) were generated in municipal incinerators or other heating fa-

cilities and polluted the environment together with PCBs. All these chlorinated chemicals are lipophilic and their concentrations increased in the order of seawater, plankton, small fish, bigger fish and fish eating animals by turn. Polar bears, bald eagles in the Great Lakes region and seals in the North Sea, situating at the top of food chain, are known as the most heavily polluted animals with these chlorinated chemicals. Humans and their suckling are also situated at the top of food chain, as humans ingest considerable amounts of fishes and feed babies with polluted mother's breast milk.

Human Pollution of PCBs and Related Compounds

General persons ingested PCBs and related compounds through foods more than 90% and their intakes by inhalation of air and skin contact of soil, water and other materials were usually very small. Japanese daily intakes of PCBs were estimated to be 40–72 μg per person in 1972. Daily intakes of dioxin toxic equivalents (TEQ) were calculated to be 0.5–3.5 pg/kg/day through mainly foods in 1999. World Health Organization (WHO) examined breast milk of peoples in the world for TEQ levels in 1980, detecting 5–40 pg/g lipid. Higher levels of TEQ were determined in the breast milk of peoples in industrial countries and lower levels in South Asian and East European countries. German blood and breast milk were continuously examined from 1987 to 2001, finding high levels of TEQ decreased to about half values of the original.[3] Total TEQ levels, consisting of PCDDs, PCDFs, non-ortho PCBs and mono-ortho PCBs, in breast milk and blood of Germans were found to be 28.6 and 42.7 pg/g lipid, respectively, in 2001 and one half of the TEQ was from the PCBs. In the blood of Fukuoka residents, average total TEQ level was 28 pg/g lipid in 1999 and 30–55% was from the PCBs.[4] Coplanar PCBs were important factors for evaluating TEQ toxicities.

Second rice oil PCB poisoning called Yucheng occurred in Taiwan in 1979, eleven years after the Yusho PCB poisoning. Blood samples of three Yucheng patients and five Yusho patients were continuously examined for PCB and PCDF congeners. Concentration changes of PCB and PCDF congeners in Yusho patients from 1968 to 1999 were estimated from the data of Yusho and Yucheng patients.[5] Estimated levels of total PCBs (75 μg/g lipid) and TEQ (40 ng/g lipid) in Yusho patients just after the incident decreased to 2.3 μg/g lipid and 0.6 ng/g lipid, respectively, 30 years after the onset with half-lives during first fifteen years, 4.2 and 2.5 years, and during second fifteen years, 9.1 and 7.7 years, respectively. Blood samples of 83 Yusho patients were examined[6] in 1995 for PCBs and TEQ levels, means (ranges) being 0.8 (0.09–5.2) μg/g lipid and 0.16 (0.01–1.02) ng/g lipid, respectively. Blood samples of 152 Fukuoka residents were examined in 1999 for PCBs and TEQ concentrations.[4] Their mean levels and ranges were 0.4, 0.06–1.7 μg/g lipid and 28, 9.2–100 pg/g lipid, respectively. Mean values of PCBs and TEQ in Yusho patients were only 2 and 6 times higher than those in control persons, respectively, in 1999. Concentration ratios of PCBs/TEQ were 5000 in Yusho patients and 14000 in control persons.

Concentrations of total PCBs (130–3400 pg/g whole blood) and dichlorodiphenyl dichloroethene (DDE) (80–3600 pg/g whole blood) in normal persons are comparable or more to normal blood levels of estradiol in female (20–250 pg/ml serum) and male (10–50 pg/ml serum), testosterone in female (100–900 pg/ml serum) and male (3000–10000 pg/ml serum) and free thyroxin (7–20 pg/ml serum). A man of 60 kg body weight usually has 10 kg of lipid which is estimated to contain considerable amounts of total PCBs 0.6–13 mg and TEQ 0.09–1.02 μg.

Health Effects of PCBs and Related Compounds

Tolerable daily intake (TDI) of TEQ, 10 pg/kg/day, was established in 1996 by Ministry of Health and Welfare. The value was estimated from 1/100 of No Observed Adverse Effect Level of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 1 ng/kg/day, on animal experiments. Environmental Agency altered the TDI to 5 pg/kg/day in 1997, investigating the monkey data[7] in detail, that is, TCDD dose of 125 pg/kg/day for 4 years caused endometriosis on 3 out of 7 monkeys. Japanese government changed the TDI to 4 pg/kg/day in 1999, following the WHO's TDI, 1–4 pg/kg/day, in 1998.[8] The lowest body burdens to dams were estimated to be 28–73 ng/kg body weight to cause some symptoms, such as decreased sperm count, immune suppression, increased genital malformation and neurobehavioral effects, in the offspring. These values were converted to human daily intake of 14–37 pg/kg/day. The TDI of WHO was estimated by taking the safety margin of 10 to the converted human daily intake.

Typical Yusho symptoms of acneiform eruption, dermal pigmentation, and increased eye discharge were very gradually recovered with lapse of several years, corresponding to the decrease of PCDF and

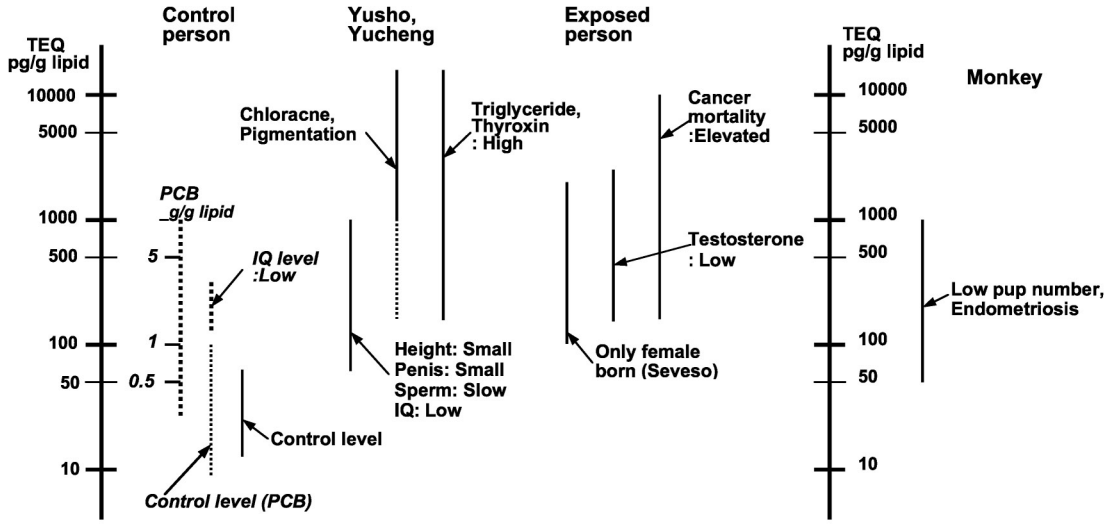

Fig. 1. TEQ and PCB Levels and Affected Symptoms in Human and Monkey

PCB levels in the body. However, enzymatic and/or hormonal affects of high serum triglyceride, high serum thyroxin levels and immunoglobulin disorders, persistently maintained for more than 30 years.[5] Taiwan Yucheng children prenatally exposed to PCBs and PCDFs had poorer cognitive development at age 4–7 years. The body height and penis length of Yucheng children were lower than those of control at age of 11–14 years. These changes might be caused by the estrogenic or antiestrogenic effects of PCBs/PCDFs in Yucheng children, which were 10–30 fold higher than the controls.[9]

Figure 1 arranges the symptoms and disorders in Yusho and Yucheng patients to compare the levels of TEQ in the patients and controls.[5] TEQ levels in exposed persons are also compared in Fig. 1. Among the TCDD exposed persons in Seveso, the parents with blood TCDD level high as 100–2340 pg/g lipid gave birth female babies only. Blood testosterone level was lowered in the workers exposed to high levels of TCDD. In herbicide producing workers in Germany, a significant trend was observed between cancer mortality and estimated TEQ levels. Numbers of offspring decreased in monkeys exposed to the diet containing TCDD up to 25 ppt, and incidence of endometriosis 10 years after the exposure correlated with dioxin exposure levels. Since the difference of TEQ levels between controls and exposed persons with enzymatic and hormonal effects are about one order of the magnitude, the control persons with relatively high levels of TEQ may suffer from subtle effects of enzymatic and/or hormonal disorders. An epidemiological study[10] on 212 children born to women who had eaten Lake Michigan fish proved that prenatal exposure to PCBs was associated with significantly lower intelligence quotient (IQ) scores (Fig. 1).

Human blood has been contaminated with PCBs and related compounds at similar levels of estradiol, testosterone and free thyroxin through life. The PCBs and related compounds in mothers may cause disturbance of hormonal effects in the successive growing of embryo, fetus, neonate and baby through placenta and breast milk. Health effects will be realized after growth. The followings are several epidemiological studies on the health effects. Residents of New York State were statistically surveyed[11] and found that incidences of disorder of the thyroid gland, disorder of female genital tract and endometriosis were significantly high in the females who live in the Niagara River area where had been contaminated with PCBs, dioxin and others. Analytical study of PCBs and thyroid hormone concentrations in plasma of 182 fisherman's wives from the Swedish east coast along the polluted Baltic Sea showed PCB concentration was negatively correlated with total triiodothyronine concentration.[12] A cross-sectional study of 2245 pregnant women, of whom 44 had diabetes showed that the adjusted mean serum level of PCBs among the subjects with diabetes was 30% higher than in the control subjects.[13] Survey on 135 female offspring from 1177 Michigan anglers showed that maternal DDE levels inversely related to age at menarche.[14] Survey on 208 offspring in 101 families showed the sex odds ratio was increased if paternal PCB concentrations exceeded 8.1 μg/l se-

rum. Paternal exposure was therefore linked to a higher proportion of male offspring.[15] Effects of prenatal exposure to PCBs and dioxins were examined on play behavior in Dutch children at school age.[16] In boy, higher prenatal PCB levels were related with less masculinaized play, whereas in girls higher PCB levels were associated with more masculinaized play.

REFERENCES

1) Masuda, Y. (1996) Causal agents of Yusho. In *Yusho: A human disaster caused by PCBs and related compounds* (Kuratsune, M., Yoshimura, Y., Hori, Y., Okumura, M. and Masuda, Y., Eds), Kyushu University Press, Fukuoka, pp. 47–80.
2) Masuda, Y. (1985) PCB pollution, special review. In *Synthetic Hygiene and Public Health* (Fujiwara, M., Watanabe, G. and Takakuwa, E., Eds), Nankodo, Tokyo, pp. 471–478.
3) Fürst, P. and Päpke, O. (2002) PCDDs, PCDFs and dioxin-like PCBs in human milk and blood from Germany. *Organohalogen Compounds*, **55**, 251–254.
4) Masuda, Y., Haraguchi, K., Kono, S., Tsuji, H. and Päpke, O. (2002) Concentrations of dioxins and related compounds and their effects to biochemicals in Fukuoka residents. *Organohalogen Compounds*, **55**, 257–270.
5) Masuda, Y. (2001) Fate of PCDF/PCB congeners and change of clinical symptoms in patients with Yusho PCB poisoning for 30 years. *Chemosphere*, **43**, 925–930.
6) Iida, T., Hirakawa, H., Matsueda, T. and Nakagawa, R. (1997) Concentrations of PCDDs, PCDFs and coplanar PCBs in the blood of 83 patients with Yusho. *Fukuoka Acta Med*., **88**, 169–176.
7) Rier, S. E., Martin, D. C., Bowman, R. E., Dmowski, W. P. and Becker, J. L. (1993) Endometriosis in rhesus monkey (Macaca mulatto) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fundam. Appl. Toxicol*., **21**, 433–441.
8) WHO European Centre for Environmental and Health, Brussels (1998) *Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI)*.
9) Masuda, Y. (1999) Risk evaluation of dioxin environmental pollution. *Energy and resources*, **20**, 37–43.
10) Jacobson, J. L. and Jacobson, S. W. (1996) Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *N. Engl. J. Med*., **335**, 783–789.
11) Carpenter, D. O., Shen, Y., Nguyen, T., Le, L. and Linger, L. L. (2001) Incidence of endocrine disease among residents of Yew York areas of concern. *Environ. Health Perspect*., **109** (Suppl. 6), 845–851.
12) Hagmar, L., Rylander, L., Dyremark, E., Klasson-Wehler, E. and Erfurth, E. M. (2001) Plasma concentrations of persisted organochlorines in relation to thyrotropin and thyroid hormone levels in women. *Int. Arch Occup. Environ. Health*, **74**, 184–188.
13) Longnecker, M. P. and Daniels, J. (2001) Environmental contaminants as etiologic factor for diabetes. *Environ. Health Perspect*., **109** (Suppl. 6), 871–876.
14) Karmaus, W., Vasiliu, O., Muttinneni, J. and Hungerink, A. (2002) Age at menarche in women exposed to polychlorinated biphenyls and dichlorodiphenyl dichloroethene in utero. In *The second PCB workshop* (Holoubek, I., Ed), Brno, p. 114.
15) Karmaus, W., Huang, S. and Cameron, L. (2002) Parental concentration of dichlorodiphenyl dichloroethene and polychlorinated biphenyls in Michigan fish eaters and sex ratio on offspring. *J. Occup. Environ. Med*., **44**, 8–13.
16) Vreugdenhil, H. J. I., Slijper, F. M. E., Mulder, P. G. H. and Weisglas-Kuperus, N. (2002) Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. *Environ. Health Perspect*., **110**, A593–A598.