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Risk Assessment Document for Coplanar-PCBs

Executive Summary

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Chapter I Introduction

Polychlorinated biphenyls (PCBs) and dioxins are the class of chemical substances that persist in the environment, become widely distributed geographically, bio-accumulate through food webs, and pose a risk of causing adverse effects to human health and the environment, and have been the subjects of social concerns and issues in Japan and globally. These compounds are within the scope of Stockholm Convention on Persistent Organic Pollutants (POPs) (entered into force in 2004), and their elimination or release reduction has already been agreed upon.

In 1997 (the publication released in 1998), World Health Organization (WHO) and International Programme on Chemical Safety (IPCS) established the toxic equivalency factors (TEFs), indicating relative effect potency to 2,3,7,8-T_4CDD, of twelve compounds of PCBs (IUPAC Numbers 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, and 189) as well as of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) (Van den Berg *et al.*, 1998). There has been increasing focus on these PCBs since then. In Japan, these PCBs have been termed as coplanar-PCBs (Co-PCBs) or dioxin-like PCBs (herein after referred to as Co-PCBs).

Co-PCBs, though being PCBs, have a common mode of toxic action as dioxins, and contribute to more than half of the total toxicity of dioxins under the present exposure conditions in Japan. The evaluation of Co-PCBs, however, has not been sufficient and thorough.

In this risk assessment, with the purpose of providing the basic scientific information and data useful for regulators, industries, and consumers to understand and to make decisions relative to the possible risks of Co-PCBs, comprehensive analyses are conducted based on the existing information and data on Co-PCBs as well as on other PCBs and dioxins. Further, reviewing the data and information including sources and amounts of emissions, environmental concentrations, exposures, pharmacokinetics and body burdens, etc., human health risks of Co-PCBs (and also of the total dioxins including Co-PCBs, PCDDs, and PCDFs) and ecological risks of Co-PCBs in Japan are evaluated with their toxic equivalent (TEQ) values as the toxicity of dioxins calculated with TEFs.

Chapter II Background information

Background information is reviewed and summarized in Chapter II including the types, structures, and physical properties of Co-PCBs and their related compounds; production, use, storage, disposal, and treatment of commercial PCB products; monitoring data on the concentrations of Co-PCBs in the environment, food, and human bodies; and the existing standards and guideline values regarding PCBs and dioxins.

Chapter III Sources and amounts of emissions

(1) Estimation of Co-PCB emissions with a build-up approach of emission source information

Environmental emissions of Co-PCBs are estimated by accumulating the data of emission sources with known contamination and/or releases, such as commercial PCB products, incineration (including thermal processes), and agricultural chemicals.

For commercial PCB products, firstly, information on the mass balance of PCB products (production, use, storage, treatment, disposal, missing/unknown, etc.) is summarized for each usage. Based on the information summarized, the interannual changes in environmental emissions of Co-PCBs are estimated with the interannual changes in consumption of commercial PCB products, amounts of Co-PCBs contained in these products, and emission factors, which are determined with reference to those reported by Breivik *et al.* (2002b).

For incineration, based on the monitoring data in recent years of Co-PCBs, PCDDs, and PCDFs in emission gases (the Japanese dioxin emission inventory by Ministry of the Environment (2006b) and its original data), the interannual changes in environmental emissions of Co-PCBs are estimated using the interannual changes of the amount of waste incinerated, number of incineration facilities, Gross Domestic Production (GDP) in Japan, etc.

For agricultural chemicals, environmental emissions of Co-PCBs are estimated with the detected concentrations of Co-PCBs in individual agricultural chemical products, and their amounts used in Japan.

The estimated interannual changes in environmental emissions of Co-PCBs are presented in Figure 1, and the estimated total cumulative emission of each compound from 1954 to 2005 in Figure 2. It should be noted, however, that these are the rough estimates based on the emission factors with high uncertainties and various assumptions, for no sufficient information is available for accurate estimation, especially on the emissions from the commercial PCB products in recent years.

The results indicate that the emissions from commercial PCB products are higher around 1970, while those from incineration are higher in recent years. Among the total cumulative emissions of the individual Co-PCBs, the emissions of PCB-169 are mainly from incineration, those of PCB-81, 126, 189 are almost equally from both incineration and commercial PCB products, and those of other Co-PCBs are more from commercial PCB products than incineration. The emissions from agricultural chemical products are smaller by several orders for all Co-PCBs. The emissions from PCB products and from incineration contribute almost equally to the total cumulative emission of TEQ for Co-PCBs.

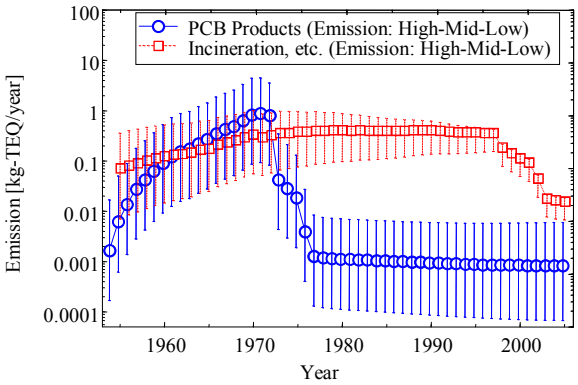


Figure 1 Estimated interannual changes in environmental emissions of Co-PCBs

Note: Plots indicate the estimates with the emissions of mid amounts, lower limits of error bars, of low amounts, and higher limits of error bars, of high amounts. TEQs are calculated with the TEFs of WHO-IPCS determined in 2005 (Van den Berg *et al.*, 2006).

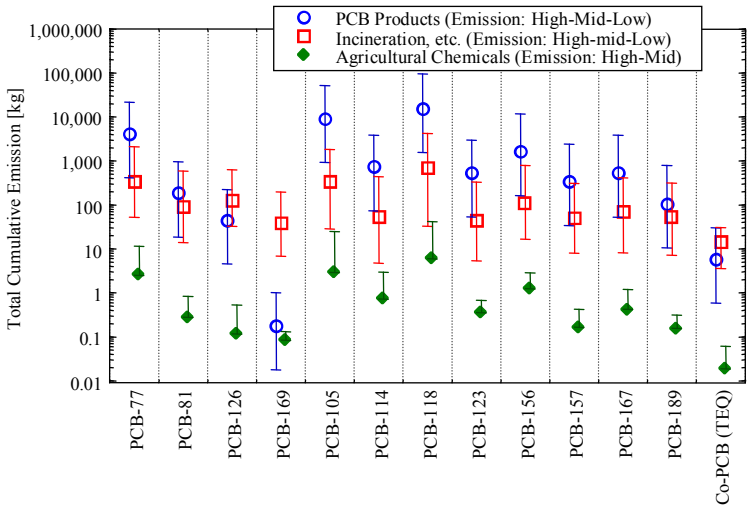


Figure 2 Estimated total cumulative emissions of individual Co-PCBs from 1954 to 2005

Note: Plots indicate the estimates with the emissions of mid amounts, lower limits of error bars, of low amounts, and higher limits of error bars, of high amounts. TEQs are calculated with the TEFs of WHO-IPCS determined in 2005 (Van den Berg *et al.*, 2006).

(2) Estimation of source contributions by analyses of variable factors related to atmospheric concentrations of Co-PCBs

Summarized below are the estimations reported in Ogura *et al.* (2004) and the new analysis additionally conducted after the publication.

Based on the monitoring data in Yokohama City from 1998 to 2000, each contribution is estimated of the emissions from volatilization or incineration to the atmospheric concentrations of Co-PCBs as well as of other PCBs, PCDDs, and PCDFs. The emissions from volatilization include those associated with use, storage, and disposal of commercial PCB products and the contamination in the past.

The analysis of the monitoring data indicates that the changes in atmospheric concentrations of PCB-126, 169, and 189, PCDDs, and PCDFs were similar and almost temperature-independent. In contrast, the atmospheric concentrations of most of the other PCBs (including those other than Co-PCBs) increased with the elevated temperature. Using 2,3,4,7,8-P_5CDF as a reference compound originated from incineration, relative contributions of emissions from volatilization and from incineration to individual Co-PCBs in the

atmosphere are estimated with the assumption that the changes in the concentration ratios of subject compounds (Co-PCBs) to the reference compound associated with temperature changes are the contributions of emissions from volatilization (Figure 3). When evaluated in terms of TEQs for Co-PCBs, the atmospheric concentrations in winter season are estimated to be mostly attributable to incineration, and those in summer season, almost equally to volatilization and incineration.

The estimation above is based on the analysis of monitoring data at a single sampling site in Yokohama City. However, the monitoring data of Co-PCB, PCDDs, and PCDFs in Fiscal Year (FY) 1998 reported by the Environment Agency (1999b) also indicate that of the atmospheric concentrations among one hundred sampling sites in Japan, the concentration ratios in summer versus winter were small for PCB-126, 169 and 189, PCDDs, and PCDFs in many sites, while the concentrations in summer of the other Co-PCBs were higher (Figure 4). For TEQs of Co-PCBs, it is considered that the atmospheric concentrations at many sites are attributable to both of volatilization and incineration judging from the magnitude of their concentration ratios of summer versus winter.

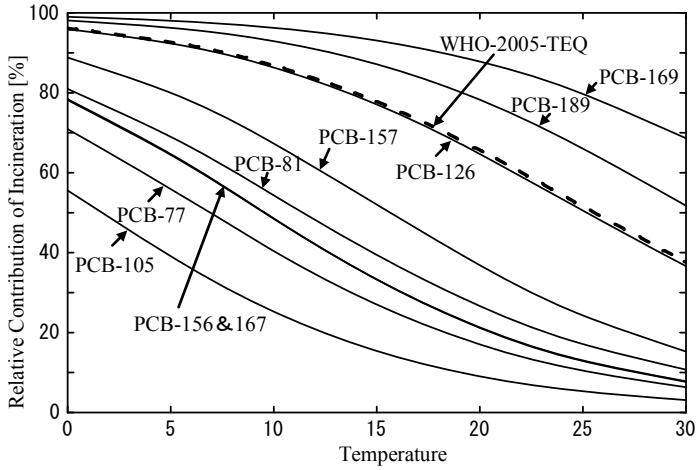


Figure 3 Estimated changes with temperature of relative contributions of emissions from incineration and volatilization to individual Co-PCBs in the atmosphere

Note: TEQs are calculated with the TEFs of WHO-IPCS determined in 2005 (Van den Berg *et al.*, 2006).

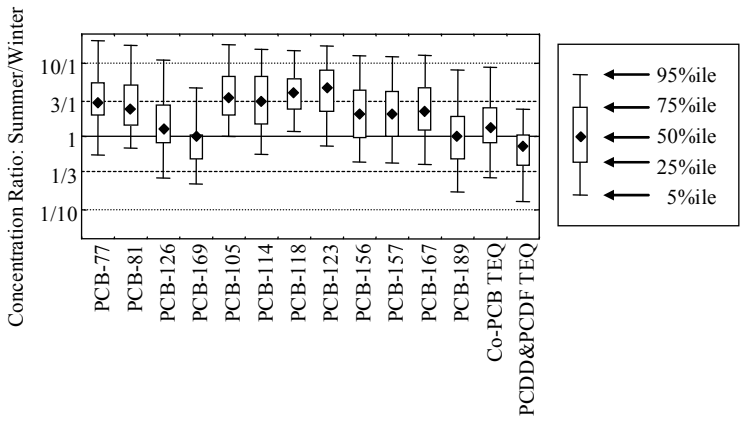


Figure 4 Ratios of atmospheric concentrations in summer to in winter

Note: The concentration ratios of summer versus winter are obtained from the nation-wide atmospheric concentration data in FY 1998 of 100 sampling sites by Environment Agency (1999b). TEQs are calculated with the TEFs of WHO-IPCS determined in 2005 (Van den Berg *et al.*, 2006).

(3) Estimation of source contributions to Co-PCBs in sediment using multivariate analysis techniques

Summarized below are the analysis reported in Ogura *et al.* (2005) and the new analysis additionally conducted after the publication.

For the sediment core samples obtained in Tokyo Bay, Lake Shinji, and Lake Haruna, and the nation-wide surface sediment samples in FY 1999, the sources of Co-PCB are analyzed with a nonnegative constrained factor analysis model (Ozeki *et al.,* 1995; Rachdawong & Christensen, 1997) and a nonnegative constrained chemical mass balance (CMB) model.

As the representative outcomes of the analyses, estimated source contributions to the Co-PCB in the sediment core samples of Tokyo Bay, Lake Shinji, and Lake Haruna by CMB model are shown in Figure 5, and those of the nation-wide surface sediment samples, in Figure 6. With CMB model, commercial PCB products (four kinds of products and volatilized products from them) and incineration are considered as potential sources.

It is estimated that the concentrations of Co-PCBs originated from commercial PCB products started to increase in the 1950s, reached a peak around 1970, and have been decreasing since then. In contrast, those originated from incineration have been increasing since 1950s, and reached a plateau in the 1970s and after. Relative contributions of incineration are the highest with PCB-169, followed by PCB-126, 81, and 189. For the surface sediment samples in FY 1999, it is estimated that the contributions of commercial PCB products and incineration are almost equal, or that of incineration is slightly higher.

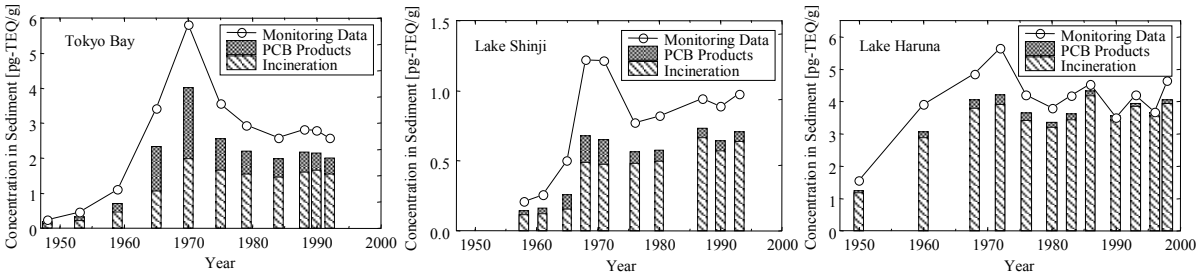


Figure 5 Temporal changes in source contributions to Co-PCBs in sediment core estimated by the CMB model

Note: TEQs are calculated with the TEFs of WHO-IPCS determined in 2005 (Van den Berg *et al.*, 2006).
[Sources of monitoring data: Tokyo Bay (Yao *et al.*, 2002), Lake Shinji (Masunaga *et al.*, 2001b), Lake Haruna (Environment Agency, 2000a)]

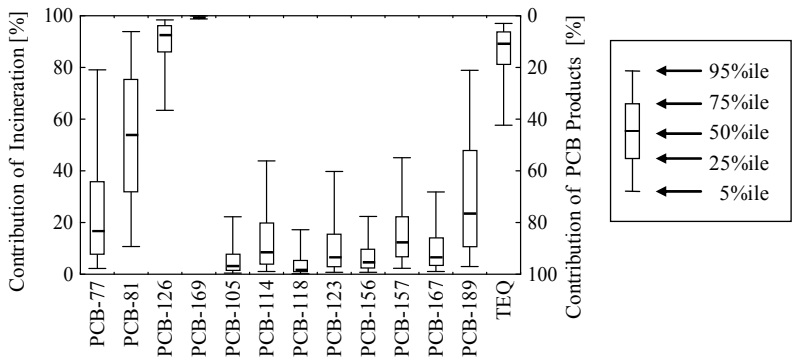


Figure 6 Distribution of source contributions to Co-PCBs in surface sediment estimated by the CMB model

Note. Distribution of each source contributions is estimated with consideration to the variations among the reported profile of each source and those of the profile of sediment concentrations among the 247 sampling sites of nation-wide surface sediments by using Monte Carlo calculation of 10,000 times. TEQs are calculated with the TEFs of WHO-IPCS determined in 2005 (Van den Berg *et al.*, 2006).

Chapter IV Exposure assessment

(1) Co-PCB exposures by routes and food categories

Based on the existing monitoring data from 1998 to 2003, exposures of Co-PCBs by routes and food categories are evaluated. The main routes of human exposure is via food (over 99%), of which the contribution of seafood is the largest (approximately 80%), followed by meats and eggs, and milk and dairy products. Seafood is classified into of inland water/coastal/offshore and of distant-water/imported, and the average Co-PCB concentrations are estimated by types of seafood.

Based on the information including the average concentration of Co-PCBs in each type of seafood, the average consumption among the Japanese population of each type of seafood, and marketing statistics of seafood, the average Co-PCB exposure among the Japanese population is estimated each with a consumption of seafood of inland water/coastal/offshore, and of distant-water/imported. The results indicate that the contribution of each seafood of inland water/coastal/offshore or of distant-water/ imported to the total exposure of Co-PCBs is approximately equal.

Similarly, for each type of livestock products, with consideration to the average concentration of Co-PCBs, the average consumption among the Japanese population, and the self-sufficiency rate, the average Co-PCB exposure among the Japanese population is estimated with the consumption each of domestic production or of imports. To the Co-PCB exposures from meats and eggs, and from milk and dairy products, the contributions from the domestic production are 88% and 74%, respectively. The contribution of imported feed (including raw material) to domestic livestock products, however, cannot be ignored, and thus, origins of Co-PCBs in livestock feed are examined. The results indicate that of Co-PCBs in feed for dairy cows, beef cattle, chicken (meat and egg), and swine, 91%, 62%, 55%, and 55% are of the domestic origin, respectively.

The outcomes of the above analyses are summarized in Figure 7 indicating the each contribution to human exposures via food of the domestic environment (i.e., the total of inland water/coastal/offshore seafood and contribution of domestic feed to domestic livestock products), and the foreign environment (i.e., the total of distant-water/imported seafood, contribution of imported feed to domestic livestock products, and imported livestock products). To the total exposures from seafood, meats and eggs, and milk and dairy products, the contribution of the domestic environment is approximately half. Therefore, the reduction of Co-PCB concentrations within and around Japan through environmental risk reduction measures would directly affect only half of the exposures at most.

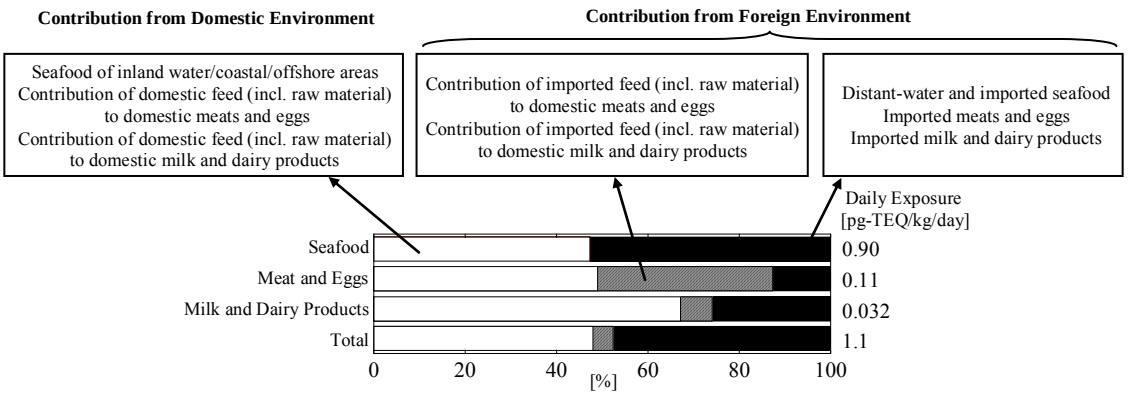


Figure 7 Estimation of contributions from the domestic and foreign environments to Co-PCB exposures via food
Note: The estimation is made based on the existing monitoring data from 1998 to 2003. TEQs are calculated with the TEFs of WHO-IPCS determined in 2005 (Van den Berg *et al.*, 2006).

(2) Regional and individual differences of Co-PCB exposures

In the evaluation of differences of exposures via food by regions or individuals based on the existing monitoring data, it is considered that the differences among individuals (variations in diet) are greater than those among regions. For people who consume a large amount of seafood (95-percentile of the consumption distribution) with the average concentration of Co-PCBs, the exposure is estimated to be approximately three times higher than the average Co-PCB exposure among the Japanese population. For those who consume the average amount of seafood with the high concentration of Co-PCBs (95-percentile of the concentration distribution), the exposure is estimated to be approximately five times higher, and in the worst case of those who consume a large amount of seafood (95-percentile of the consumption distribution) with the high concentration of Co-PCBs (95-percentile of the concentration distribution), the exposure is estimated to be fifteen times higher than the average Co-PCB exposure among the Japanese population. For food categories other than seafood, the exposure levels are estimated not to be significantly different from the average exposure level among the Japanese population even with the assumption of consuming large amounts of food with high concentrations.

Chapter V　Pharmacokinetics and concentrations of Co-PCBs in human body

(1) Pharmacokinetics

The analyses summarized below include those reported in Ogura (2004).

The existing information on pharmacokinetics of Co-PCBs, other PCBs, PCDDs, and PCDFs is reviewed and an estimation model for their pharmacokinetics is developed (Figure 8). The basic structure of the model is constructed with reference to the models by Kreuzer *et al.* (1997) and Van der Molen *et al.* (1996).

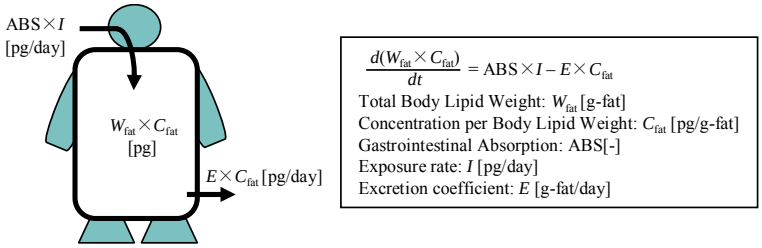


Figure 8　Outline of the estimation model for pharmacokinetics of Co-PCBs, PCDDs, and PCDFs

With this model, the half-life in the body of each compound is estimated for females in Kansai region (Table 1) based on the monitoring data including the temporal changes in exposures via food (Results of total diet studies in Kansai region from 1977 to 2004: Ministry of Health, (Labor) and Welfare, 1998b, 1999a, 2000a, 2001a, 2003, 2004a, 2004b, 2006a) and the interannual concentrations in breast milk (Primigravid women in Osaka Prefecture from 1973 to 2004: Konishi *et al.*, 2006). The estimated half-lives in the adult females with total body lipid weight of 12000 g are mostly between two to ten years with the range of less than one year to over ten years depending on compounds. It is estimated that half-lives are shorter (i.e., higher excretion rate) in children than in adults.

Based on the information on gastrointestinal absorption and the obtained half-lives in the body, accumulation factors (AF) are estimated, which indicate bioaccumulation potential of each compound relative to 2,3,7,8-T_4CDD (Table 1). AF is the ratio of each compound concentration to that of 2,3,7,8-T_4CDD per unit exposure at steady state.

Table 1 Estimated half-lives in the body and accumulation factors of Co-PCBs, PCDDs, and PCDFs

		Gastrointestinal absorption [a] (ABS) [-]	Half-life [b] ($T_{1/2}$) [year]	Accumulation factor [c] (AF) [-]	Toxic equivalency factor [d] (TEF) [-]	TEF/AF [-]
Co-PCBs	PCB-77	0.99	0.33	0.060	0.0001	0.0017
	PCB-81	0.99	0.75	0.14	0.0003	0.0022
	PCB-126	0.98	2.4	0.42	0.1	0.24
	PCB-169	0.94	6.3	1.1	0.03	0.028
	PCB-105	0.98	3.6	0.65	0.00003	0.000047
	PCB-114	0.98	8.0	1.4	0.00003	0.000021
	PCB-118	0.98	3.5	0.64	0.00003	0.000047
	PCB-123	0.98	-	-	0.00003	-
	PCB-156	0.95	9.7	1.7	0.00003	0.000018
	PCB-157	0.97	6.3	1.1	0.00003	0.000027
	PCB-167	0.96	5.4	0.96	0.00003	0.000031
	PCB-189	0.92	5.7	0.96	0.00003	0.000031
PCDDs	2,3,7,8-T_4CDD	0.98	5.6	1	1	1
	1,2,3,7,8-P_5CDD	0.94	7.3	1.3	1	0.80
	1,2,3,4,7,8-H_6CDD	0.87	7.2	1.1	0.1	0.087
	1,2,3,6,7,8-H_6CDD	0.86	25	3.9	0.1	0.026
	1,2,3,7,8,9-H_6CDD	0.85	6.9	1.1	0.1	0.093
	1,2,3,4,6,7,8-H_7CDD	0.71	3.7	0.49	0.01	0.021
	O_8CDD	0.53	7.2	0.70	0.0003	0.00043
PCDFs	2,3,7,8-T_4CDF	0.99	0.73	0.13	0.1	0.76
	1,2,3,7,8-P_5CDF	0.98	1.3	0.23	0.03	0.13
	2,3,4,7,8-P_5CDF	0.97	7.6	1.4	0.3	0.22
	1,2,3,4,7,8-H_6CDF	0.94	5.4	0.93	0.1	0.11
	1,2,3,6,7,8-H_6CDF	0.94	7.6	1.3	0.1	0.076
	1,2,3,7,8,9-H_6CDF	0.91	-	-	0.1	-
	2,3,4,6,7,8-H_6CDF	0.93	3.8	0.64	0.1	0.16
	1,2,3,4,6,7,8-H_7CDF	0.86	4.1	0.64	0.01	0.016
	1,2,3,4,7,8,9-H_7CDF	0.79	-	-	0.01	-
	O_8CDF	0.61	-	-	0.0003	-

[a] Estimated with the empirical formula of relationship between octanol/water partition coefficient and gastrointestinal absorption by Moser & McLachlan (2001).
[b] Estimated half-lives in the body with total body lipid weight of 12000 g.
[c] Based on the information on gastrointestinal absorption and half-lives in the body, accumulation factors are estimated, which indicate bioaccumulation potential of each compound relative to 2,3,7,8- T_4CDD.
[d] TEFs determined by WHO-IPCS in 2005 (Van den Berg *et al.*, 2006).

The TEFs of WHO-IPCS are determined based on the exposures reflecting both the relative bio-reactivity and bioaccumulation potential to 2,3,7,8-T_4CDD of individual compounds. Therefore, it is not appropriate to multiply concentrations in the body with these TEFs. Concentrations in the body, which already reflect relative bioaccumulation potential, multiplied with the TEFs based on the exposure result in the outcomes adjusted twice by the effects of bioaccumulation potential. Consequently, for calculation of TEQs with the concentrations in the body, the values as TEF divided by AF (TEF/AF in Table 1) are used instead of the TEFs based on the exposures.

It is noted that the TEQs of concentrations in the body calculated with the TEF/AF values are equal to those calculated by the following procedure:

1) Convert concentrations in the body of individual compounds to the corresponding exposure levels at steady state using the information on gastrointestinal absorption and half-lives in the body.
2) Multiply the exposure levels with the TEFs of WHO-IPCS to obtain the TEQs of the exposures.
3) Considering the calculated TEQ of the exposures as 2,3,7,8-T_4CDD exposures, convert the 2,3,7,8-T_4CDD exposures to the corresponding concentrations in the body of 2,3,7,8-T_4CDD at

steady state, which are defined as the TEQs of concentrations in the body.

Conversion between exposure levels and concentrations in the body at steady state is the same way used by various agencies/organizations for calculation of tolerable intakes.

(2) Estimation of Co-PCB concentrations in the body

With the information on the temporal changes in exposures of Co-PCBs via food, the temporal changes of concentrations in the body of populations by birth year are estimated using the model (Figure 9). For all generations, the concentrations in the body are estimated to have decreased after 1970s. As the half-lives in the body of Co-PCBs during childhood are shorter than those of adults together with the dilution effects associated with growth, it is estimated that in the generation of people who were children at around early 1970s of the highest pollution levels, the decreases in concentrations in the body thereafter are estimated to be large while those in the generation of people who were already grownup by early 1970s are estimated to be small. Further, it is estimated that in recent years, concentrations are higher in the older generations due to several factors including longer half-lives in the body associated with the increase of total body lipid weight in middle age, larger consumption of seafood among elderly, and decrease in excretion ability with aging, etc.

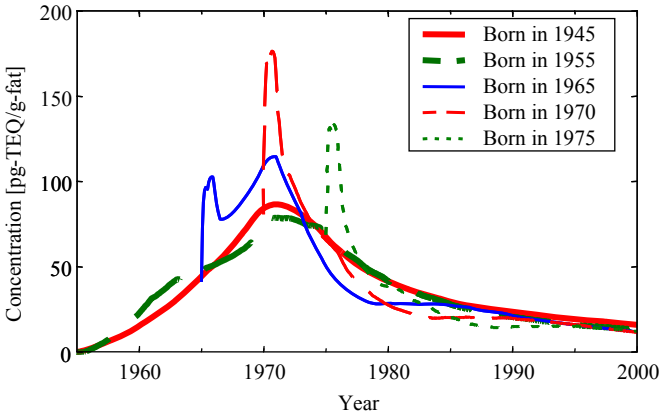


Figure 9 Estimated temporal changes of Co-PCB concentrations in the body by birth year

Note: Estimations are made with the average concentrations in the body of females in Kansai region. TEQs are calculated with the TEF/AF values in Table 1.

Similarly, with the information on the temporal changes in exposures, the nation-wide average Co-PCB concentrations in the body of females at 25 to 34 years old in future are estimated using the model (Figure 10). The estimated Co-PCB concentration when the estimation reaches to the steady state is 5.9 pg/g-fat.

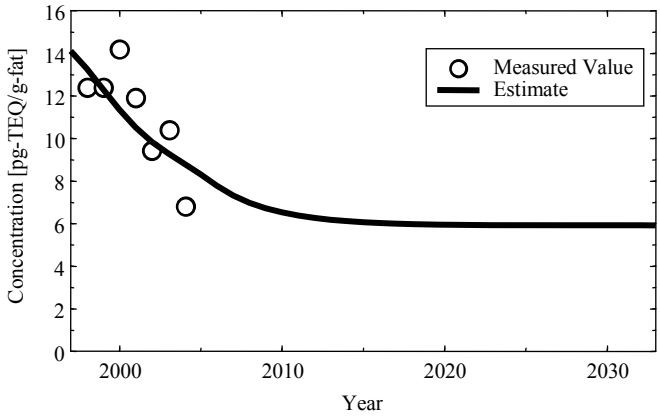


Figure 10 Estimated Co-PCB concentrations in females of 25 to 34 years old in future

Note: Data from the monitoring in the recent years are presented with ○ in the figure as a reference. TEQs are calculated with the TEF/AF values in Table 1 both for the monitoring data and estimations.

[Source of the monitoring data: Konishi *et al.* (2006). Concentrations in breast milk of the primigravid women at ages of 25 to 29 in Osaka Prefecture from 1998 to 2004, a composite sample of 13 to 35 subjects for each year.]

Further, the changes in Co-PCB concentrations in the body are estimated for the cases of breast-fed and formula-fed infants using the model (Figure 11). It is estimated that the Co-PCB concentrations per lipid gram in the breast-fed infants are twice to three times higher than those of mothers. After weaning, however, the exposure levels decrease and with the dilution effects associated with growth, the elevated concentrations in the body of the breast-fed infants are estimated to decrease rapidly. The difference between the concentrations in the body of the breast-fed and formula-fed infants is estimated to decrease with growth and diminish by around the age of ten.

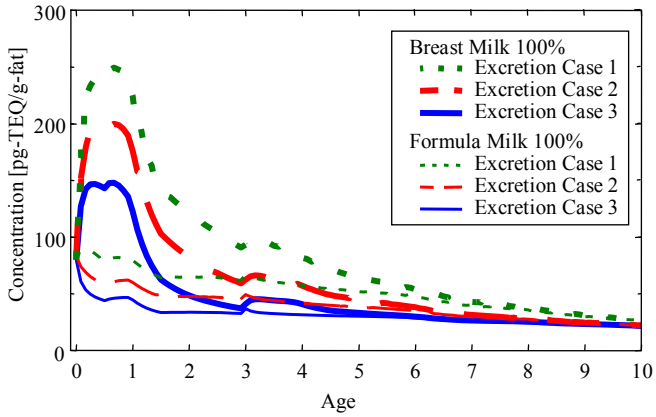


Figure 11 Estimated Co-PCB concentrations in the body of breast-fed and formula-fed infants

Note: Estimated concentrations are in the case of average females born in 1971 in Kansai region. Excretion Case 1 is based on the assumption that changes in the value of excretion coefficient (*E*) associated with growth depend on and are relative to the size of liver. Excretion Case 2 is based on the assumption that changes in the value of *E* associated with growth depend on food consumption. Excretion Case 3 is based on the assumption that the value of *E* is constant independent of age. TEQs are calculated with the TEF/AF values in Table 1.

(3) Regional and individual differences in Co-PCB concentrations in the body

In the evaluation of differences of Co-PCB concentrations in the body by regions or individuals based on

the existing monitoring data, it is estimated that the differences among individuals are greater than those among regions. The monitoring data in recent years revealed that the highest concentration in breast milk of similar age group (about 1,500 samples) is approximately four times higher than the average, the highest concentration in blood of the populations with various age groups (about 1,800 samples), thirteen times higher, and the second highest, seven times higher than the average.

Chapter VI Hazard assessment

(1) Epidemiology studies

The effects observed in epidemiology studies are reviewed and summarized. For the representative endpoints of significant effects reported in epidemiology studies, the ranges of 2,3,7,8-T_4CDD (or TEQ) concentrations in blood per lipid weight in the lowest group with effects are presented in Figure 12 (with carcinogenicity, however, the range is of the average life-time concentrations in the body corresponding to 1% increase of cancer mortality risk).

In epidemiology studies, high correlations of chloracne and carcinogenicity with dioxin exposures have been suggested, however, those of other endpoints are not necessarily clear. It is considered more relevant to apply toxic effects observed with low dose exposures in experimental animals rather than carcinogenicity as the endpoints for human health risk assessment, for a number of reasons including 1) dioxins induce cancers through promotional effects; 2) no clear correlation is identified between carcinogenic effects in specific organs and dioxin exposures; and 3) carcinogenic potential is not very high even in the high exposure populations (approximately 1.4 times).

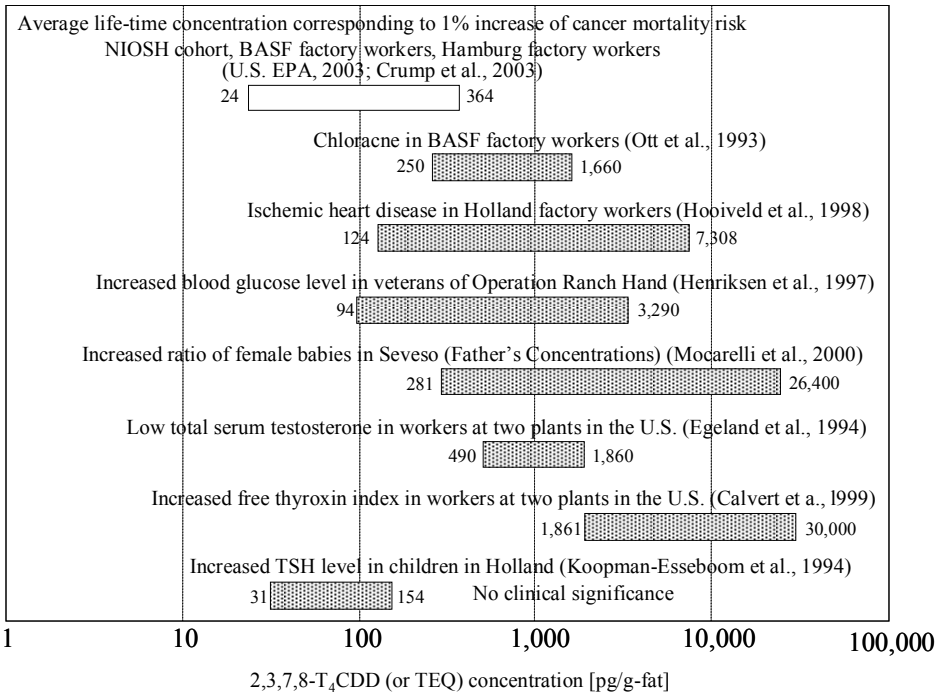


Figure 12 Ranges of 2,3,7,8-T_4CDD (or TEQ) concentrations in blood per lipid weight in the lowest group with effects in epidemiology studies and the average life-time concentrations in the body corresponding to 1% increase of cancer mortality risk

Note: For the representative endpoints of significant effects reported in epidemiology studies, the ranges of 2,3,7,8-T_4CDD (or TEQ) concentrations in blood per lipid weight in the lowest group with effects are presented. With carcinogenicity, however, the range is of the average life-time concentrations in the body corresponding to 1% increase of cancer mortality risk. For Chloracne, 2,3,7,8-T_4CDD concentrations in blood are over 250 pg/g-fat in more than 80% of patients with severe symptoms. Although no consistent results have been obtained with the relationship between 2,3,7,8-T_4CDD concentrations and ischemic heart disease or increased blood glucose (or diabetes), there are a number of reports suggesting such correlations. Increased ratio of females among the babies of the fathers exposed to dioxins has been reported with only one cohort of population including those exposed before and during puberty. Correlations between changes in male reproductive hormones (high luteinizing hormone, high follicle-stimulating hormone, and low testosterone) and 2,3,7,8-T_4CDD concentrations have been reported with a single cohort, however, the magnitudes of changes are not large. Indicated in Figure 12 is the range of 2,3,7,8-T_4CDD concentrations in blood of the group with significantly high odds ratio of low testosterone. While there have been many reports on the effects on thyroid, the reported results are not necessarily consistent. In the studies with adults, the effects were observed with high exposure groups.

(2) Experimental animal studies

For major experimental animal studies, body burden levels (amount per body weight of dioxins in the body) corresponding to the NO(A)ELs (no observed (adverse) effect level) or LO(A)ELs (lowest observed (adverse) effect level) are calculated. The body burden levels corresponding to LO(A)ELs observed with low concentration exposures are presented in Figure 13.

The toxic effect observed at low doses of 2,3,7,8-T_4CDD in experimental animals, which is considered as a critical endpoint, is the developmental toxicity in offspring exposed throughout pregnancy and/or lactation. The available data on developmental neurotoxicity and immunotoxicity of dioxins are considered insufficient to be applied to risk assessment. The decrease in anogenital distance among male offspring is considered not reliable as a maker of toxicity. Also, the effects observed in sperm and sperm production widely vary among studies with possible effects of strain or individual differences of experimental animals, and experimental conditions. Thus, it is considered inappropriate to evaluate developmental/reproductive

toxicity with results obtained in the lowest dose of a single study.

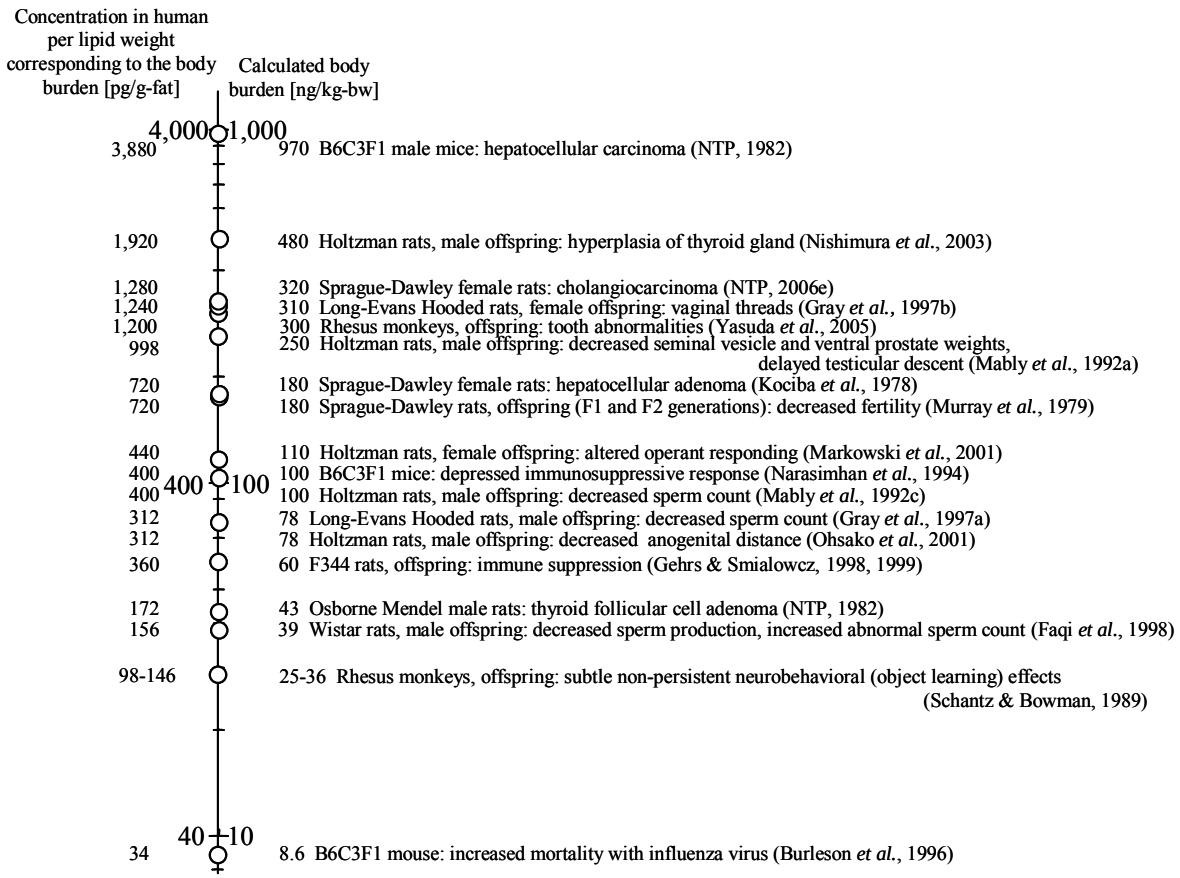


Figure 13 Body burden levels corresponding to LO(A)EL of the major toxic effects observed with low concentration exposures in experimental animal studies

Note: Except the increased mortality with influenza virus (Burleson *et al.*, 1996), the depressed immunosuppressive response (Narasimhan *et al.*, 1994), and tumorigenesis and carcinogenesis, all the effects are those on offspring exposed to 2,3,7,8-T_4CDD throughout pregnancy and/or lactation. With the assumption that dioxins exist in lipid in human body, the concentrations in human per lipid weight corresponding to the body burden levels are calculated with the human body fat percentage of 25%, and presented on the left side of vertical axis.

(3) Determination of the reference value for human health risk assessment

Different procedures have been applied in estimating body burden of dioxins for establishment of tolerable daily intake (TDI) in Japan (Environment Agency & Ministry of Health and Welfare, 1999) and in this assessment including absorption rates, correction for high burden in fetuses with single exposure, etc. The judgment made at the occasion of establishing TDI, however, is considered also applicable to the outcome of the review in this assessment, that the effects are observed with the body burden (the body burden in maternal animals in case of developmental toxicity in offspring) level of approximately 86 ng/kg or above. Therefore, it is decided to apply the same value as the body burden level corresponding to the LO(A)EL of dioxins. With this LO(A)EL and applying the uncertainty factor of 3, the body burden level corresponding to NO(A)EL is established as 30 (≈ 86/3) ng/kg. Based on the assumption that most of the dioxins in the body accumulate in lipid, the body burden of 30 ng/kg is converted to the concentration per

lipid weight of 120 pg/g-fat with the human body fat percentage of 25%. Applying this calculated level of 120 pg/g-fat as the reference value of maternal body concentration, human health risks of Co-PCBs (and also of the total dioxins including Co-PCBs, PCDDs, and PCDFs) are assessed in Chapter VII.

Referring to the uncertainty factors used for establishing tolerable intakes at various agencies/organizations (SCF, 2001; JECFA, 2001; UK COT, 2001), the uncertainty factors in this assessment are considered as follows:

- Interindividual variation in toxicokinetics: As the risk assessment in Chapter VII is conducted with concentrations in body not with exposure levels, the uncertainty factor is one.
- Interspecies differences in toxicokinetics: As the body burden approach allows for toxicokinetics differences, the uncertainty factor is one.
- Interindividual variation and interspecies differences in toxicodynamics: Based on the assumption that the most susceptible humans might be as sensitive to 2,3,7,8-T_4CDD as rats, though humans in general are less sensitive than rats, it is judged that the uncertainty factor is one.

Based on the above, it is determined that no specific uncertainty factor is necessary to be applied in this assessment (i.e., uncertainty factor = 1).

Chapter VII Human health risk assessment

Human health risks with the dioxin-like toxicity of Co-PCBs are evaluated. Also, human health risks are assessed with the total exposures of dioxins including Co-PCBs, PCDDs, and PCDFs because these compounds have a common mode of toxic action.

Risks in the past and recent years are estimated by comparing the concentrations in breast milk from the monitoring surveys, which is a good indicator of concentrations in the maternal body, with the reference value determined in Chapter VI. Interannual changes in the concentrations in breast milk of Co-PCBs and the total dioxins (Co-PCBs, PCDDs, and PCDFs) monitored in Osaka Prefecture (Konishi *et al.*, 2006), and the distribution of the concentrations in breast milk monitored nation-wide in FY 1998 (Tada *et al.*, 1999) are presented in Figure 14. TEQs of the concentrations in breast milk are calculated with the TEF/AF values in Table 1. Assuming that the ratio of the 99-percentile value of the breast milk concentrations from the nation-wide monitoring in FY 1998 to the breast milk concentration from the monitoring in Osaka Prefecture in 1998 is constant over years, the interannual changes of the nation-wide 99-percentile values of breast milk concentrations are estimated and presented in Figure 14. The reference value of 120 pg/g-fat is indicated in the figure.

The estimated nation-wide 99-percentile values of Co-PCB concentrations in breast milk in the 1970s are higher than the reference value. In the recent years, however, the nation-wide 99-percentile values are lower than the reference value. These tendencies are the same with the concentrations of the total dioxins.

Thus, the risks with Co-PCBs and dioxins have been decreasing since 1970s. In the recent years, the

concentrations in the body of majority of the Japanese population are estimated to be lower than the reference value. With the current exposure levels, it is considered that the human health risks with the dioxin-like toxicity of Co-PCBs, PCDDs, and PCDFs are not in the level to pose concerns.

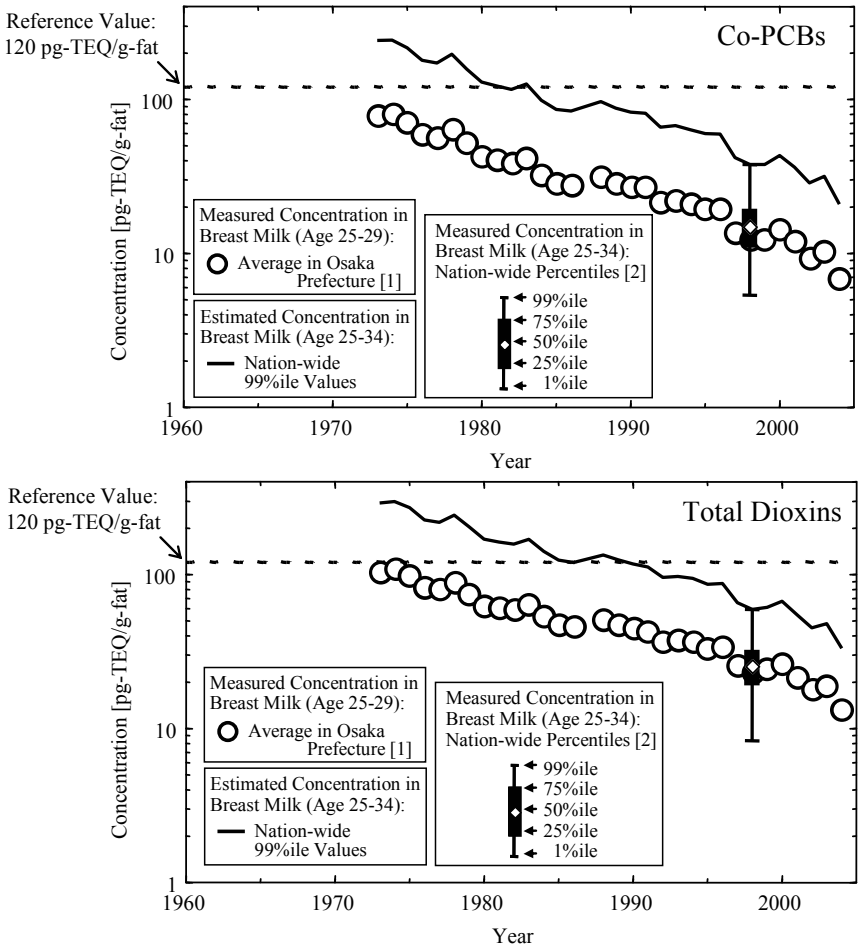


Figure 14 Comparison between concentrations in breast milk and the reference value

Note: The 99-percentile value for the total dioxins is the sum of the 99-percentile value of Co-PCBs and that of PCDDs and PCDFs.
TEQs are calculated with the TEF/AF values in Table 1 for both monitoring data and estimated values.

[Source of the monitoring data: [1] Konishi *et al*., (2006). Concentrations in breast milk of the primigravid women at ages of 25 to 29 in Osaka Prefecture from 1973 to 2004, a composite sample of 13 to 39 subjects for each year; [2] Tada *et al*., (1999). Concentrations in breast milk of the primigravid women at ages of 25 to 34 in 20 areas in Japan in FY 1998, 415 samples]

Further, risks are assessed for the possible high exposure populations at present. With the nation-wide average of the estimated concentrations in the body of females at ages of 25 to 34 (Figure 10) as the base, the concentrations in the body of the high exposure populations are estimated using the results of analysis made in Chapter IV of the possible ratios of high exposure levels against the average exposure (Figure 15).

It is estimated that the concentrations in the body are lower than the reference value in the population with a high consumption of seafood with the average concentration (three times higher exposure than the average) and in the population with the average consumption of seafood with the high concentration (five times higher exposure than the average). In the population with a high consumption of seafood with the high concentration (the worst case; fifteen times higher exposure than the average), however, it is estimated that the concentration in the body of Co-PCBs is about the same level as the reference value, and that of the total dioxins, higher than the reference value. It should be noted that the concentration in the body of such a high exposure population is even higher than the nation-wide 99-percentile value, and considered as an extreme case judging from the maximum concentrations in the body detected in the monitoring surveys (see Chapter V (3)). Although it is not likely that any significant effect is observed with the dioxin exposures slightly exceeding the reference value, it is considered necessary to take some measures to reduce such high exposures.

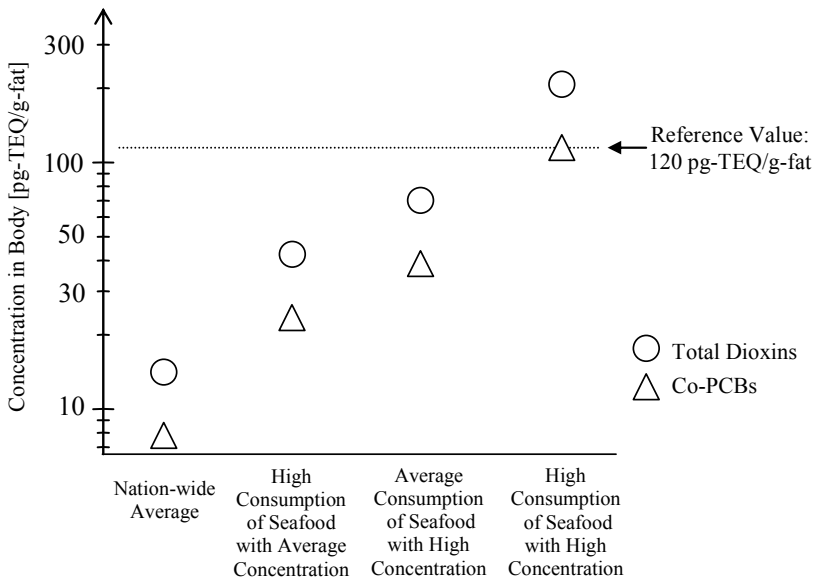


Figure 15 Comparison between the estimated concentrations in the body of females at ages of 25 to 34 in the high exposure populations in 2006 and the reference value

Note: TEQs are calculated with the TEF/AF values in Table 1.

Chapter VIII　Ecological risk assessment

The content of Chapter VIII is the assessment previously published by Naito & Murata (2007), supplemented by the further analysis with the additional information.

The contamination levels of Co-PCBs, PCDDs, and PCDFs in wildlife are summarized. It is found that fish-eating birds accumulate high levels of Co-PCBs. With the representative fish-eating birds in Japan, great cormorant, gray heron, osprey, and kingfisher, risks are evaluated with the dioxin-like toxicity of Co-PCBs at the contamination levels around 2000 in Tokyo Bay and its vicinity, applying egg mortality as the index of toxicity. Tiered approaches are used to quantify ecological risks using different metrics from individual- to population-level endpoints.

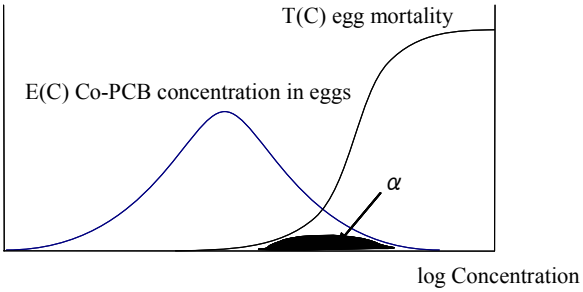
For the assessment at the tier I of hazard quotient evaluation (i.e., risk assessment at individual level), monitoring data or estimated values of Co-PCB concentrations in eggs are compared with the toxicity reference values (TRVs: a concentration considered to exert no toxic effects) of similar species derived from the published hazard data (Table 2). The ratios of the geometric means of Co-PCB concentrations in eggs of all the individual species to TRVs (i.e., hazard quotient) are smaller than one, indicating a low possibility of hazardous effects at the contamination levels observed around 2000 in general. However, of the 95-percentile values of Co-PCB concentrations in eggs of the individual species, the hazard quotients for gray heron, osprey, and kingfisher are larger than one, which suggests that the individuals with high exposures may have been affected by Co-PCBs.

Table 2　Risk characterization at the tier I

Target species	Co-PCB concentration in egg [ng-TEQ/g-egg]				Toxicity reference value (TRV) [ng-TEQ/g-egg]			Hazard quotient	
	Data	Reference	Geometric mean ($C_{egg\text{-}GM}$)	95-percentile ($C_{egg\text{-}95}$)	Species	Reference	TRV	$C_{egg\text{-}GM}$/TRV	$C_{egg\text{-}95}$/TRV
Great cormorant	Measured (n=90)[a]	Ministry of the Environment (2001b)	0.13	0.28	Double-crested cormorant	Powell *et al.* (1997)	1.0 [d]	0.13	0.28
Accipitral birds (Wild)	Measured (n=10)[b]	Ministry of the Environment (2002d)	0.056	0.23	Bald eagle	US EPA (2000b)	0.21 [e]	0.27	1.1
Accipitral birds (Zoo)	Measured (n=9)[c]	Ministry of the Environment (2002d)	0.0043	0.029	Bald eagle	US EPA (2000b)	0.21 [e]	0.020	0.14
Gray heron	Estimation	Naito & Murata (2007)	0.098	0.35	Great blue heron	US EPA (2000b)	0.3 [e]	0.33	1.2
Osprey	Estimation	Murata (2003)	0.15	0.37	Bald eagle	US EPA (2000b)	0.21 [e]	0.71	1.8
Kingfisher	Estimation	Murata (2003)	0.038	0.068	Belted kingfisher	US EPA (2000b)	0.061 [e]	0.62	1.1

[a] Including eggs used in artificial breeding, wild eggs of unsuccessful breeding, and wild eggs.
[b] Hawk eagle (6), falcon (3), owl (1). Number in the parenthesis is the number of samples.
[c] White-headed eagle (1), white-tailed sea eagle (1), golden eagle (5), kestrel (1), great horned owl (1). Number in the parenthesis is the number of samples.
[d] NOAEL of the study with double-crested cormorant (Powell *et al.*, 1997).
[e] Field-based NOAEL from the risk assessment of PCBs in the Hudson River in the U.S.A. (US EPA, 2000b). TRV of belted kingfisher was established based on the data from Forester's tern (Harris *et al.*, 1993) and the uncertainty factor of ten for species difference.
Note: TEQs are calculated with TEFs for birds by WHO-IPCS in 1998 (Van den Berg *et al.*, 1998).

For the assessment at the tier II, the magnitude of risks at individual level are indicated with egg mortality, using the distribution of Co-PCB concentrations in eggs and the dose–response relationships of toxicity (i.e., tolerance distributions) (Figure 16, Table 3). The egg mortality for great cormorant, gray heron, osprey, and kingfisher are estimated to be 6.8, 5.8, 12, and 0.07%, respectively.



$$\textbf{Egg Mortality Risk} = \alpha = \int_0^{\infty} E(C)T(C)dc$$

Figure 16 Conceptual scheme of egg mortality risk assessment

Note: E(C) is the lognormal distribution of Co-PCB concentrations in eggs.
T(C) is cumulative lognormal distribution of egg mortality corresponding to Co-PCB concentrations in eggs.

Table 3 Risk characterization at the tier II

Target species	Co-PCB concentration in egg				Dose–response relationship of egg mortality				Egg mortality [%]
	Data	Reference	GM [ng-TEQ/g-egg]	GSD	Test species	Reference	LD_{50} [ng-TEQ/g-egg]	GSD	
Great cormorant	Measured (*n*=90)	Ministry of the Environment (2001b)	0.13	1.57	Double-crested cormorant	Powell *et al.* (1998)	3.7	8.78	6.8
Gray heron	Estimation	Naito & Murata (2007)	0.098	2.18	Double-crested cormorant	Powell *et al.* (1998)	3.7	8.78	5.8
Osprey	Estimation	Murata (2003)	0.15	1.75	Common kestrel	Nosek *et al.* (1993)	6.1	22.4	12
Kingfisher	Estimation	Murata (2003)	0.038	1.43	Chicken	Brunström & Andersson (1988)	0.32	1.75	0.07

Note: TEQs are calculated with TEFs for birds by WHO-IPCS in 1998 (Van den Berg *et al.*, 1998). GM = geometric mean. GSD = geometric standard deviation. LD_{50} = 50% lethal dose.

At the tier III of population-level risk assessment, the correlation between Co-PCB concentrations in eggs and population growth rate (λ) is estimated incorporating the results of assessment at the tier II and considering life-history parameters of the subjected species (e.g., survival and fecundity rate at each age). Compared with the concentrations at which λ becomes one (i.e., population size remains constant), the margins of exposure for the contamination levels observed around 2000 are approximately 230, 10, 7, and 5 for great cormorant, gray heron, osprey, and kingfisher, respectively. (Note that the estimated risk for kingfisher is considered to be greater than the actual risk for the toxicity data with chicken, which is highly sensitive to dioxins, are used to supplement the lack of toxicity data in similar species with a conservative approach.)

The results obtained indicate that at the contamination levels of Co-PCBs in Tokyo Bay and its vicinity

observed around 2000 the risks for the fish-eating birds are not in the level to pose concerns on the population persistence of these species, though there are some possible hazardous effects with Co-PCB exposures on a small portion of individuals in some species. In this assessment, risks are calculated with the concentrations of Co-PCBs only. Since the contributions of Co-PCBs to TEQs in fish-eating birds of the total dioxins (Co-PCBs, PCDDs, and PCDFs) are dominant, no substantial changes are expected when risks are assessed with the concentrations of the total dioxins. Considering that Tokyo Bay and its vicinity are the areas with relatively high levels of dioxin contaminations in Japan, and that the environmental levels of Co-PCBs, PCDDs, and PCDFs have been decreasing in the recent years, the possibility is estimated to be extremely low that Co-PCBs, PCDDs, or PCDFs greatly affect the population persistence of fish-eating birds in Japan.

Chapter IX　Conclusion

In the both human health risk and ecological risk (risk in fish-eating birds) assessments of Co-PCBs, PCDDs, and PCDFs with the dioxin-like toxicity, it is concluded that the risks at the current exposure levels are not in the levels to pose any concern. Compared to the contamination levels in the past, there is substantial improvement in the current contamination levels and the risks have been decreased.

Only limited effects are to be achieved with risk reduction measures in the domestic environment to further decrease human dioxin exposures, for the significant contributions of the imported food.

It is suggested that the measures with focus to the high exposure populations, or monitoring and regulations of imported food would be effective in future.

The future challenges include the following:

- Evaluation of individual compounds and development of database for individual compounds
- Studies on effects of multiple compounds and validity of TEF values and TEF scheme
- Consideration to the contributions of other chemical compounds with a similar mode of toxic action as Co-PCBs, PCDDs, and PCDFs
- Consideration to non-dioxin type toxicity of Co-PCBs and other PCBs
- Accumulation and evaluation of epidemiology data

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