# Estimation of Dioxin Risk in Japanese by Mathematical Models

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**Key Words:** polychlorinated dibenzo-*p*-dioxin, polychlorinated dibenzofuran, body burden, reproductive alteration, female offspring

**Abstract**

Transport processes of seventeen 2,3,7,8-chlorinated congeners of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) from sources to humans are modeled to estimate the time course of the human health risk to Japanese from the past to the future. The modeling approach seems to represent reasonably well the background levels of congeners, except 2,3,7,8-TCDF, in the environment, daily intake, and body burden, from the results of a comparison between estimated and measured values. The margin of exposure (MOE) for the risk of reproductive alteration in female offspring exposed prenatally was calculated based on the estimated maternal body burden. The MOE may not be sufficiently large to guarantee the safety of female offspring of maternal females born in the 1950s. However, the MOE for female offspring born in and after the latter half of the 1990s may be sufficiently large to guarantee safety.

## 1. Introduction

In order to evaluate the risks caused by chemical substances and to establish appropriate countermeasures for the reduction of the risk when necessary, how precisely and rapidly we assess exposure to the substance through several pathways is crucial. We take chemical substances into our body through the inhalation of air, ingestion of foods, and skin contact with materials containing the substances. Mathematical models are applied to estimate concentrations of a substance in environmental media and foodstuff related to the exposure. The models facilitate the estimation of the temporal and/or spatial variation of the concentrations in the environment,

foodstuff, and human body, than the measurement of them. However, the validation of these models is still insufficient, because of the necessity for information regarding the meteorological, environmental, and physiological situations in addition to the concentrations.

Since the latter half of the 1990s, various types of monitoring of dioxins in environmental and biological media have been carried out intensively in Japan, because of the increasing social concern about the risks posed by this chemical group (Environment Agency (EA), 1999a, 1999b, 1999c, 2000; Hori et al., 1999; Iida et al., 1999; Ministry of Health and Welfare (MHW), 1998a, 1999). Furthermore, the Japanese Government has also established several countermeasures such as the reduction of dioxin levels in emissions from incinerators. However, the present daily intake and body burden do not reflect the high dose exposure to large quantities of dioxins released into the environment as impurities in some herbicides and polychlorinated biphenyls in the past (Masunaga, 1999). Indeed, it has been suggested that the intake of dioxins via foods and the body burden of dioxins in Japanese were much higher in the past, based on the results of a recent analysis of breast milk and foods stored in the past (MHW, 1998a, 1999), although there has been less study of the past dioxin levels in the Japanese environment and in the human body.

In the previous workshop, we illustrated the modeling approach to the representation of the transport processes of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) from the main sources to the human body in terms of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxic equivalents (TEQs) (Yoshida et al., 2000a). However, seventeen 2,3,7,8-chlorinated congeners assigned nonzero toxic equivalent factors (TEFs) exhibit clear differences in behaviors in the environment and the human body (Yoshida et al., 2000b; Yoshida, 2000). Thereto, it has been reported that rather different congener patterns of PCDD/Fs are exhibited in exhaust gas from incinerators, herbicide PCP, and herbicide CNP (Hagenmaier et al., 1994; Masunaga and Nakanishi, 1999).

In this study, we modeled the transport processes of seventeen 2,3,7,8-chlorinated congeners of PCDD/Fs from the main sources to the human body and estimated the time course of environmental concentrations, daily intake, and body burdens of the congeners. These estimates were compared with those reported to confirm the predictability of the model, and then the estimated body burden was applied to assessment of the risk of reproductive alteration in female offspring exposed prenatally.

## 2. Description of Modeling Approaches

To estimate the body burden of congeners of PCDD/Fs in the general Japanese population, we considered the sources, environmental transport pathways, and exposure pathways shown in Figure 1.

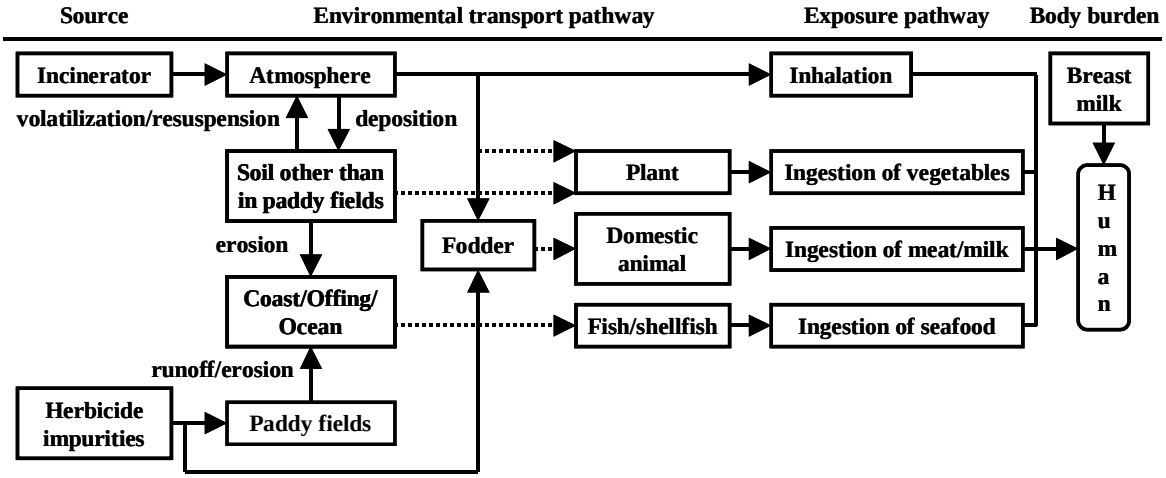


Figure 1 Transport pathways of congeners of PCDD/Fs from sources to human body

**2.1** ***Congeners emitted from incinerators***

The air/soil two-compartment model was applied in order to estimate the environmental concentrations of congeners of PCDD/Fs from incinerators in the air and soil other than that in paddy fields (Yoshida et al., 2000c).

**2.2** ***Congeners released into paddy fields***

The concentrations of the congeners of PCDD/Fs in paddy fields were estimated using the one-compartment model (Yoshida et al., 2000a).

**2.3** ***Congeners in coastal environment***

The concentrations of the congeners in the coastal environment were estimated using the water/sediment two-compartment model (Yoshida et al., 1987).

**2.4** ***Daily intake of congeners***

The daily intake of each congener was individually calculated as products of the inhalation or ingestion rate of air, fish/shellfish, leaf crops, root crops, meat, or dairy products and the concentration of the congener in them, assuming that the ingestion rates of various foods were constant.

The concentration in coastal fish was calculated based on the assumption of equilibrium between the concentrations in water and fish. The concentrations in offshore and oceanic fish were assumed to be half of that in coastal fish (MHW, 1996). The ratio of ingestion rates of coastal fish and other fish was assumed to be 0.4 and 0.3 before and after 1970, respectively.

The concentrations in leaf/root crops, meat, and dairy products were estimated according to the methods described by the U.S. EPA (U.S. EPA, 1994). We assumed that the epidermis of rice plants was contaminated by PCDD/Fs and residual culms and blades after threshing rice were fed to domestic animals as fodder. The concentrations of congeners in the culm and the blade were calculated based on congener-specific concentrations in irrigated water in paddy fields and

the root concentration factors estimated from 1-octanol/water partition coefficients. The utilization ratio of culms and blades as fodder was assumed to decrease from 1.0 in 1958 to 0.1 in 1985 and to be constant thereafter.

### 2.5 *Concentration in breast milk and body burden of congeners*

The concentration in breast milk and the body burden of congeners of PCDD/Fs were estimated using the one-compartment model (Yoshida et al., 2000c). In the calculation, we used congener-specific half-lives in humans (Liem and Theelen, 1997) and age-specific body weights and fat contents (MHW, 1998b; ICRP, 1975).

Although we had to employ the body burden as a measure of exposure as described below, TEFs are based on the administered doses of seventeen 2,3,7,8-chlorinated congeners of PCDD/Fs, not on their tissue doses. We therefore calculated the correction factors for tissue doses of the seventeen congeners, based on the steady-state assumption using congener-specific gastrointestinal absorption and half-lives (Table 1). A rounding-off procedure (nearest 1 or 5) was also employed, because the TEFs are "order of magnitude" estimates of relative toxicity when compared to 2,3,7,8-TCDD (van den Berg et al., 1998).

Table 1 Correction factors for calculating 2,3,7,8-TCDD toxic equivalent body burden

| Congener | Gastrointestinal absorption | Half-life (year) | WHO-TEF | Equivalent body burden | Correction factor |
|---|---|---|---|---|---|
| 2,3,7,8-TCDD | 0.97 | 6.2 | 1 | 1.00 | 1 |
| 1,2,3,7,8-PeCDD | 0.99 | 8.6 | 1 | 1.42 | 0.5 |
| 1,2,3,4,7,8-HxCDD | 0.98 | 8.4 | 0.1 | 13.7 | 0.05 |
| 1,2,3,6,7,8-HxCDD | 0.97 | 13.1 | 0.1 | 21.1 | 0.05 |
| 1,2,3,7,8,9-HxCDD | 0.96 | 8.5 | 0.1 | 13.6 | 0.05 |
| 1,2,3,4,6,7,8-HpCDD | 0.86 | 6.6 | 0.01 | 94.4 | 0.01 |
| OCDD | 0.76 | 5.6 | 0.0001 | 7080 | 0.0001 |
| 2,3,7,8-TCDF | 0.97 | 0.4 | 0.1 | 0.65 | 1 |
| 1,2,3,7,8-PeCDF | 0.99 | 0.9 | 0.05 | 2.96 | 0.5 |
| 2,3,4,7,8-PeCDF | 0.98 | 9.9 | 0.5 | 3.23 | 0.5 |
| 1,2,3,4,7,8-HxCDF | 0.97 | 5.7 | 0.1 | 9.19 | 0.1 |
| 1,2,3,6,7,8-HxCDF | 0.97 | 6.2 | 0.1 | 10.0 | 0.1 |
| 1,2,3,7,8,9-HxCDF | 0.95 | 1.1 | 0.1 | 1.74 | 0.5 |
| 2,3,4,6,7,8-HxCDF | 0.96 | 2.4 | 0.1 | 3.83 | 0.5 |
| 1,2,3,4,6,7,8-HpCDF | 0.87 | 0.2 | 0.01 | 2.89 | 0.5 |
| 1,2,3,4,7,8,9-HpCDF | 1.00 | 3.2 | 0.01 | 53.2 | 0.01 |
| OCDF | 0.95 | 0.2 | 0.0001 | 316 | 0.005 |

TCDD : tetrachlorodibenzo-*p*-dioxin
PeCDD : pentachlorodibenzo-*p*-dioxin
HxCDD : hexachlorodibenzo-*p*-dioxin
HpCDD : heptachlorodibenzo-*p*-dioxin
OCDD : octachlorodibenzo-*p*-dioxin
TCDF : tetrachlorodibenzofuran
PeCDF : pentachlorodibenzofuran
HxCDF : hexachlorodibenzofuran
HpCDF : heptachlorodibenzofuran
OCDF : octachlorodibenzofuran

### 2.6 *Estimation of risk*

As the endpoint for the assessment of human health risk, we selected morphological reproductive alterations in female offspring as a consequence of in utero exposure (Gray et al.,

1997), because the Japanese tolerable daily intake (TDI) of dioxins has been determined based on this reproductive toxicity (Central Environment Council/Living Environment Council/Food Sanitation Investigation Council, 1999). Based on data by Hurst et al. (Hurst et al., 2000), we calculated a 28.6 ng/kg body burden of 2,3,7,8-TCDD between gestation day 16 and 21 of rats administered 2,3,7,8-TCDD at a dosage level of 50 ng/kg, a dosage level at which there was found to be no significant alteration in Gray et al.'s study. We described the risk of reproductive alteration as the margin of exposure (MOE). The margin was calculated by dividing the body burden for NOAEL by the estimated maternal body burden.

## 3. Results

### 3.1 *Environmental levels of congeners*

The estimated time courses of the congener-specific concentrations in the air and the soil other than that in paddy fields are shown in Figure 2 and Figure 3, respectively. The estimated concentrations were in agreement with those monitored in Japan (Environment Agency, 1999a, 2000).

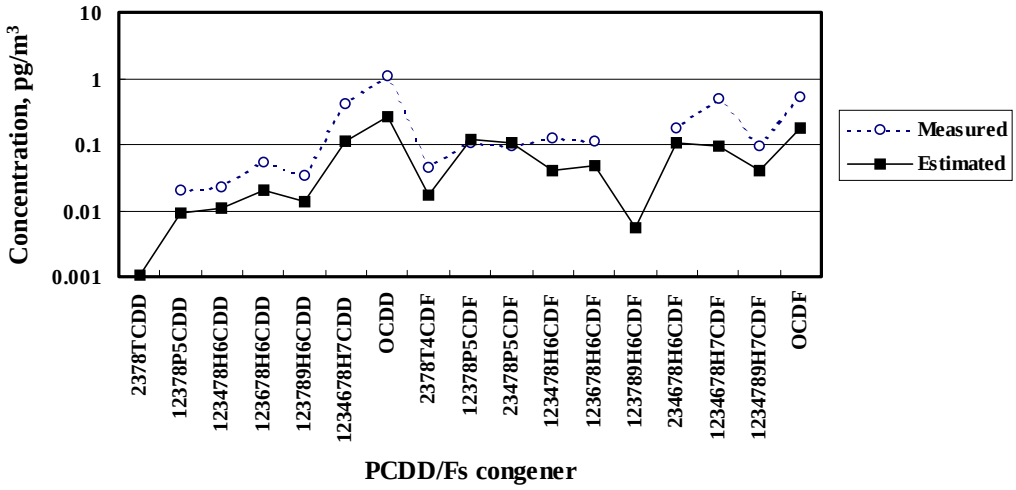


Figure 2 Comparison of measured and estimated congener-specific concentrations in the air

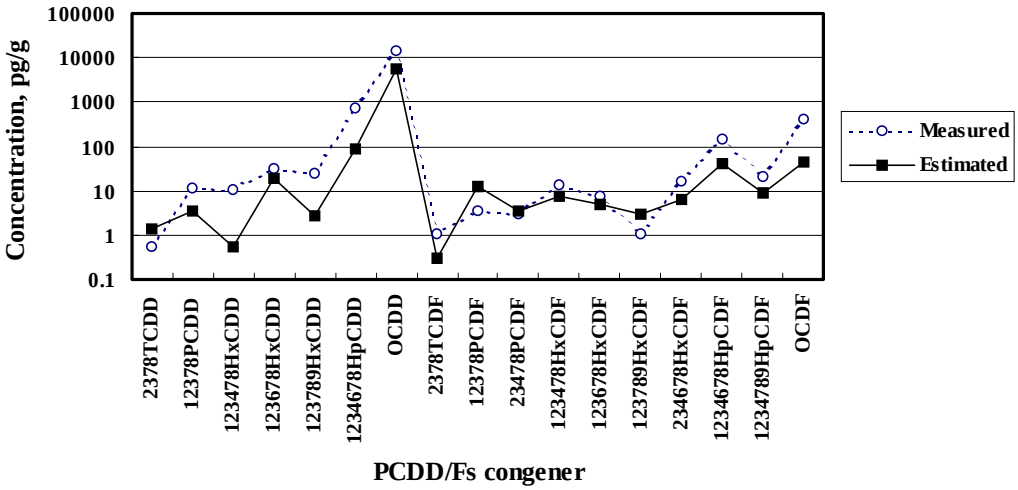


Figure 3 Comparison of measured and estimated congener-specific concentrations in soil of paddy fields

### 3.2 *Daily intake of congeners*

Estimated daily intakes of seventeen congeners via food ingestion were compared with those reported (MHW, 1999). As shown in Figure 4, the estimated total daily intakes via food ingestion are in good agreement with those measured, except in 1988. Furthermore, the daily intakes of the major congeners, 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 2,3,4,7,8-PeCDF, are also in good agreement with those measured. However, the estimated daily intakes of 2,3,7,8-TCDF are one or two orders of magnitude lower than those measured.

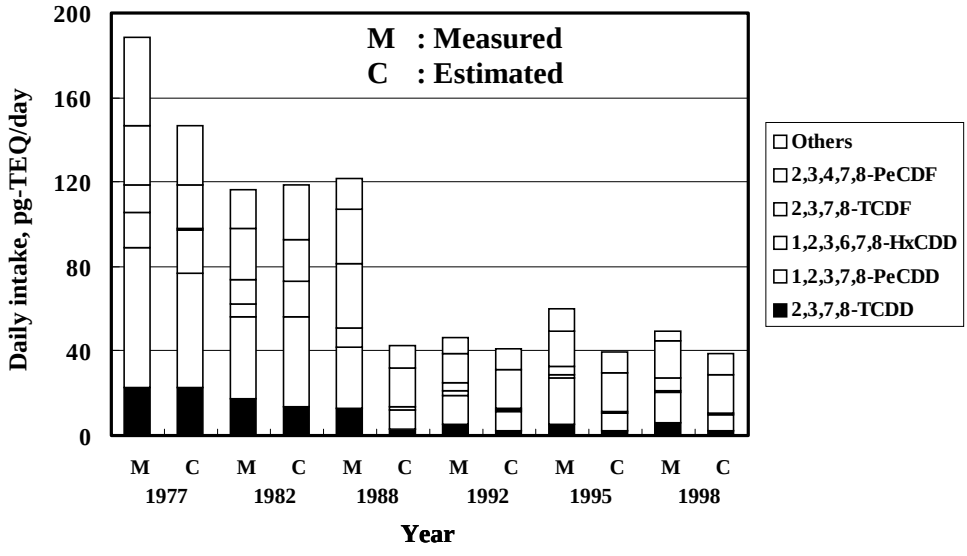


Figure 4 Comparison between measured and estimated congener-specific daily intakes

### 3.3 *Concentration in breast milk and body burden of congeners*

Figure 5 shows estimated concentrations of 2,3,7,8-TCDD in the fat of 27-year-old females

(Yoshida and Nakanishi, 2000), together with those measured in the breast milk of 25 - 29-year-old females (Hori et al., 1999). As shown in this figure, the tendencies of measured and estimated concentrations toward lower levels of this congener in fat are in good agreement. Furthermore, the estimated concentrations of other congeners, except 2,3,7,8-TCDF, are also in reasonable agreement with those measured. The estimated concentration of 2,3,7,8-TCD/F is two orders of magnitude lower than the measured one.

Figure 6 shows the time courses of the body burdens of 2,3,7,8-TCDD, OCDD, and 2,3,4,7,8-PeCDF in males and females born in 1960. As shown in this figure, the body burden of 2,3,4,7,8-PeCDF was estimated to be almost unchanged during their lifetime. On the other hand, the body burdens of OCDD and 2,3,7,8-TCDD mainly released as impurities in herbicides were estimated to reach the maximum levels at 11 and 20 years of age, respectively, and then to decrease gradually.

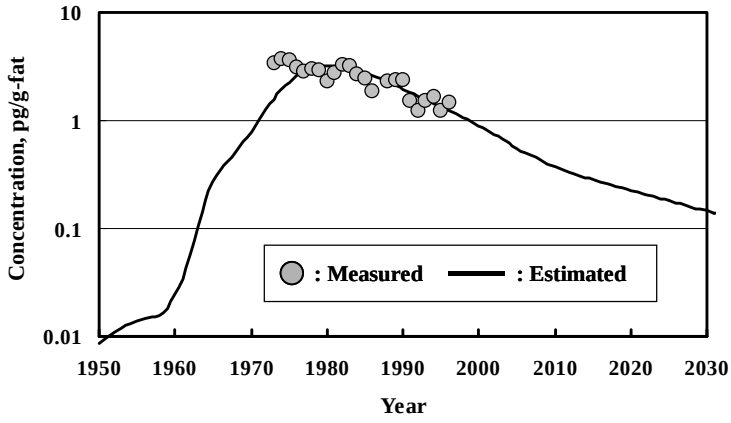


Figure 5 Estimated concentrations of 2,3,7,8-TCDD in the breast milk of 27-year-old females

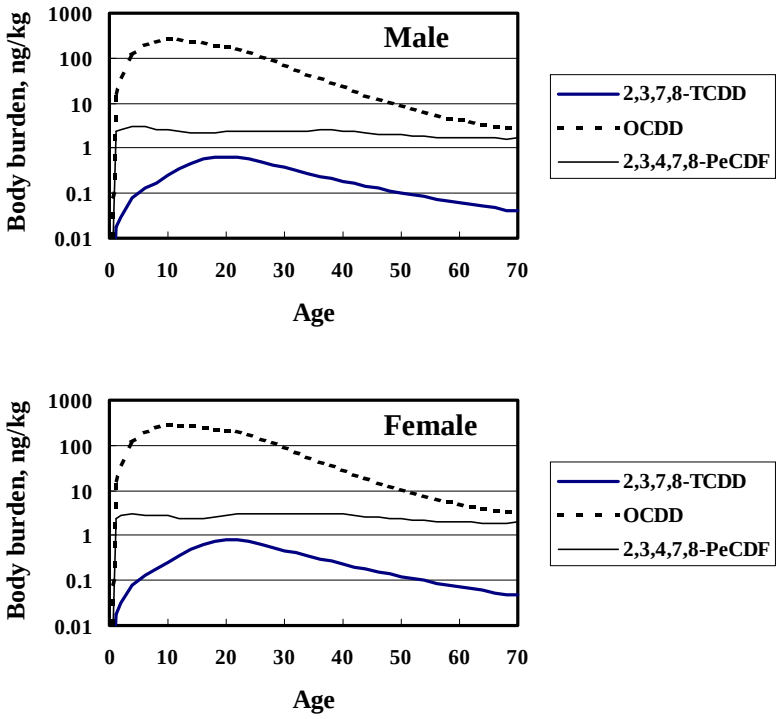


Figure 6 Estimated time course of body burdens of 3 congeners in the population born in 1960

### 3.4 *Estimated risk*

Table 2 lists the body burden of the PCDD/Fs in 25 - 30-year-old females who were born in 1950, 1960, 1970, and 1980 and the MOE for the risk of reproductive alteration in their female offspring. As shown in this table, the MOE for the offspring of females born in 1950 and 1960 were two- or threefold smaller than the MOE for the offspring of females born in 1980, as a consequence of the higher body burden of PCDD/Fs in the mothers of the former.

Table 2 2,3,7,8-TCDD equivalent body burden and MOE

| Maternal female | | Female offspring |
|---|---|---|
| Year of birth | 2,3,7,8-TCDD equivalent body burden, ng/kg | MOE |
| 1950 | 4.9 - 5.5 | 5 |
| 1960 | 4.1 - 5.2 | 5 - 6 |
| 1970 | 2.7 - 3.1 | 8 - 9 |
| 1980 | 1.7 - 2.0 | 12 - 14 |

## 4. Discussion

In this study, we estimated the congener-specific body burden of PCDD/Fs taking account of the transport from sources to humans. The results of the modeling approaches seem to give reasonably estimates of the current and past background levels of congeners of PCDD/Fs in the environment, daily intake, and body burden, except for 2,3,7,8-TCDF. Although the estimated concentrations of 2,3,7,8-TCDF in the air and soil in paddy fields are slightly lower than those

measured, they are in the same order of magnitude. However, the estimated daily intakes of this congener via the ingestion of leaf and root crops, fish and shellfish, meat, and dairy products are one or two orders of magnitude lower than those measured. These underestimates are propagated to the body burden estimates. 2,3,7,8-TCDF is a characteristic congener in effluent and sludge from paper manufacturing (Wakimoto, 1991). However, estimated release rates from the bleaching process and the incineration of sludge in paper manufacturing are low (about 6 g-TEQ/year) (Hiraoka and Okajima, 1998). The discrepancy between estimated and measured daily intake and body burden cannot be explained by PCDD/Fs from this source. Because we have already validated the parameters describing the transport from an incinerator to the soil through the air, we would like to clarify the reason for this discrepancy, with the inclusion of a reassessment of the parameters describing the transport from the soil to the human body.

The smallest MOE value was estimated to be 5 for the female offspring of maternal females born in 1950 and 1960. The margin for the risk of reproductive alteration might not be sufficiently large to guarantee their safety, when we consider that a safety factor of 3 – 10 is applied to extrapolate from the general population to the sensitive subpopulation (Dieter and Konietzka, 1995) and also that the body burden of 2,3,7,8-TCDF was underestimated in our simulation. However, the MOE for female offspring born in and after the latter half of the 1990s may be sufficient to guarantee safety.

In conclusion, although the modeling approaches have been successfully applied in the screening-level risk assessment of organic chemical substances, we must continue to improve the mathematical models in order to achieve reliable prediction of exposure to many kinds of chemical substances in the environment. We therefor must establish procedures to monitor chemical concentrations in the long term together with sufficient meteorological, environmental, and physiological situations to validate the predictability of the models and also procedures to compensate the lack of these data.

## 5. Acknowledgments

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