HEALTH EFFECTS OF CHRONIC EXPOSURE TO POLYCHLORINATED DIBENZO-P-DIOXINS, DIBENZOFURANS AND COPLANAR PCB IN JAPAN

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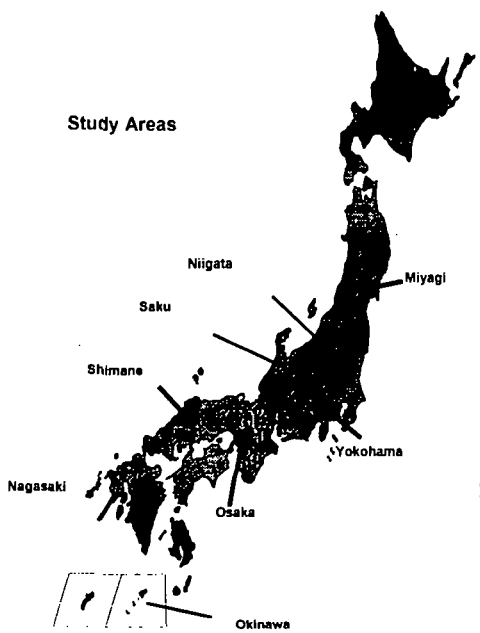
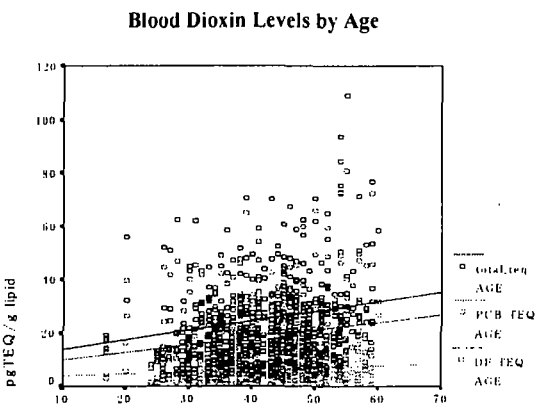
Introduction

A national survey of polychlorinated dibenzo-p-dioxins (PCDD) and dibenzofurans (PCDF) in emission gases from municipal waste incinerators in 1997 revealed that the several factories emitted excess amount of PCDD/PCDF. We reported the results of 92 incinerator workers in DIOXIN'99, in which blood dioxin levels ranged from 13.3 to 805.8 pg TEQ/g lipid. It caused serious social problems among residents around the incinerators, so the Ministry of Health and Welfare started health screening program for the residents in 4 areas around the incinerators and 4 control areas. As the results showed no highly exposed residents in these areas, background exposure level and their health effects of Japanese were requested to be clarified. This report is the summary of blood dioxin levels and their health effects from 15 areas in Japan.

Subjects and Methods

Japanese residents in 15 different areas participated the study on health and dioxin exposure between 1998-2000. Participants were all volunteers aged from 40s' to 60s'. They received detailed explanation of the study and gave us the written informed consent. Areas covered from north to south as shown in Fig. 1.





Life habits and dietary habits were collected by questionnaire and checked by trained dieticians. The questionnaire included dietary habits, smoking and drinking habits, residential and work environment, physical activity, past history of diseases and treatments, reproductive history, etc.

Blood was collected into a 200 ml transfusion bag containing heparin sodium solution (SH-207-Terumo, Japan). About 30 ml of blood was divided to tubes to perform peripheral blood tests, such as RBC, WBC, and platelet counts, and hematocrit, and blood chemistry studies, such as determination of AST(GOT), ALT(GPT), gamma-GTP, LDH, ALP, LAP, CPK, amylase, total cholesterol, HDL-cholesterol, triacylglycerol, total protein, albumin, total bilirubin, blood urea nitrogen, creatinine, uric acid, glucose, creatine phosphokinase, sodium, potassium, calcium, iron, and inorganic phosphate. These tests were performed by the Serum Research Laboratory (Tokyo).

As immunologic markers, T lymphocytes subsets determined by surface antigens, such as CD3, CD4, CD8, and CD4/CD8 ratio, were also measured. NK activity was measured by surface antigen (CD56), and natural killer cell activity was determined against K562 cells. Stimulation by PHA and Con A was also applied. The samples in 2000 were measured for thyroid hormones and some others.

Blood PCDD/PCDF/Co-PCB was measured by a modification of Patterson's method. Lipids were extracted from 70-80 g of whole blood with a solution of 30 ml saturated ammonium sulfate and 80 ml of ethanol:hexane (1:3) solution after the addition of an internal standard of ^{13}C-labeled mixed dioxin congener solution, which contained 30 pg of $^{13}C_{12}$-PCDDs, $^{13}C_{12}$-PCDFs, and $^{13}C_{12}$-Co-PCBs, except OCDD (60 pg)(Wellington Isotope Laboratories, Massachusetts, USA)). All solvents were of dioxin analysis level. Pooled hexane layers were condensed, washed with distilled water, treated with anhydrous sodium sulfate, and evaporated to dryness, and lipid weight was measured.

Clean up was achieved by a multilayer silica column with 44% sulfuric acid and 33% potassium hydroxide, and an activated carbon column. Analysis of PCDD/PCDF/Co-PCB was carried out by gas chromatography-high resolution mass spectrometry (GC-MS). The analytical conditions were as follows: gas chromatography was performed with a Varian-3400 series unit (Hewlett-Packard, Palo Alto, California) equipped with a Finnigan MAT-90 (Finnigan MAT GmbH, Bremen, Germany). PCDDs, PCDFs, and coplanar PCBs were analyzed by the selected ion monitoring method. The column used was a DB-dioxin fused silica capillary column, 0.25 mm i.d., 60 m length, with 0.25 mm film thickness (J&W Scientific, Folsom, California). Further details are described in the previous paper[1].

The toxicity of the dioxins was calculated by the WHO TEF method (1997) and is expressed as TEQ/g lipid. Statistical analysis. SPSS version 10 was used for the statistical analyses. Correlation analysis was performed between PCDD/PCDF/Co-PCB and various variables. Linear regression analysis and logistic analysis were used for evaluating the effects of dioxins, if a significant correlation ($p<0.05$) was obtained, and Odds Ratio was calculated if necessary.

Results

Dioxin levels of so far 470 out of 619 participants were measured..Blood dioxin level of PCDDs and PCDFs was 19.0+/-12.4 (median 15.5) pgTEQ/g lipid, that of PCBs was 6.5+/-5.7 (median 4.9) pgTEQ/g lipid, and the total was 25.5+/-14.5 (median 21.7) pgTEQ/g lipid. Maximum concentrations were 84.3, 42.4, and 109.1 pg TEQ/g lipid, respectively (Table 1).

Table 1. Congener Distribution of Dioxins among Japanese Residents

	mean	s.d	median	max
2,3,7,8-TCDD	1.3	1.4	0.8	11.8
1,2,3,7,8-PeCDD	5.4	4.8	4.2	33.3
1,2,3,4,7,8-HxCDD	4.2	7.8	2.4	63.7
1,2,3,6,7,8-HxCDD	28.4	23.3	21.8	180.0
1,2,3,7,8,9-HxCDD	6.4	8.3	3.9	54.1
1,2,3,4,6,7,8-HpCDD	22.3	14.7	19.0	104.9
OCDD	363.0	441.5	216.7	3981.0
2,3,7,8-TCDF	2.4	3.5	1.0	23.6
1,2,3,7,8-PeCDF	2.1	3.8	0.9	28.6
2,3,4,7,8-PeCDF	10.5	7.8	9.4	51.0
1,2,3,4,7,8-HxCDF	6.2	5.6	4.5	38.3
1,2,3,6,7,8-HxCDF	6.9	6.2	4.7	38.6
1,2,3,7,8,9-HxCDF	2.3	3.9	0.8	28.3
2,3,4,6,7,8-HxCDF	5.2	8.3	2.5	68.4
1,2,3,4,6,7,8-HpCDF	6.8	7.9	4.3	71.5
1,2,3,4,7,8,9-HpCDF	1.6	2.5	0.5	15.7
OCDF	6.1	8.6	5.0	105.0
PCB 77	79.1	101.7	28.8	604.6
PCB 126	51.6	51.9	32.1	390.1
PCB 169	72.3	108.1	48.3	938.0
D_TEQ	10.1	7.4	8.0	54.9
F_TEQ	7.1	5.3	6.0	40.8
DF_TEQ	19.0	12.4	15.5	84.3
PCB_TEQ	6.5	5.7	4.9	42.4
total_teq	25.5	14.5	21.7	109.1

Dioxin and PCB levels were significantly correlated with age. Systolic blood pressure, total cholesterol, triacylglycerol, total bilirubin, total protein, CPK, BUN and uric acid were positively correlated with blood dioxin levels. On the contrary, platelets, CD56 (NK cell marker) and NK activity showed reverse correlation with dioxins.

Congener distribution of residents in 15 areas showed relatively similar pattern (Table 1). Except for one area, OCDD was the most popular congener in blood, and PCDDs were always dominant components. The blood concentration of farmers showed higher blood level of dioxins, so these were considered to be derived from the remnant of herbicides for cultivating rice. Simultaneously performed questionnaires about working history, dietary habits, drinking and smoking habits, family history and past history, history of gestation and number of children, etc.

were analyzed in relation to the blood dioxin levels (results are not shown here).

Past history or hypertension, diabetes mellitus and hyperlipidemia showed significantly increased risk by blood dioxin levels (Table 2).

Table 2. Number of Past History by Quartile of Blood Dioxin Levels

Blood dioxin levels	<15.2pgTEQ	15.2-21.7pgTEQ	21.7-31.3pgTEQ	31.3pgTEQ<	Total	p
n	116	118	116	117	467	
None	33	49	57	57	196	
Past History	83	69	59	60	271	
Hypertension	**5**	7	**12**	**11**	**35**	0.04
Diabetes Mellitus		**2**	**1**	**8**	**11**	0.001
Hyperlipidemia	**5**	**9**	**16**	7	**37**	0.04
Allergy	14	12	18	10	54	
Peptic ulcer	8	11	13	10	42	
Thyroid disease	0	0	1	2	3	

Discussion

In Japan, 90% of the daily intake of PCDDs, PCDFs, and other dioxin-like compounds is estimated to come from food. However, congener pattern of fish and other foods were different from those accumulated in the body. The effect of herbicide remnant is considered to be still present. Dioxin accumulation in the body showed significant increase by age due to very long half-life of dioxins. The low dose chronic accumulation should give adverse health effects.

A history of hypertension and hyperlipidemia had significantly increased odds ratios. Although the history was self-reported, it was well correlated with laboratory data. Diabetes mellitus showed marginal association. Lipid soluble dioxins may present in the lipid membrane, which could modify cellular function through impaired surface receptor functions.

Prediction of future health effects in the subjects with low-level exposure is difficult. Very long half-life of dioxins inside the body, however, may cause various effects at the lipid membrane of lipoprotein and cells. Follow-up of the chronically exposed people should be important.

References

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