INTRODUCTION

Dioxins are a group of chemically related environmental contaminants, consisting of three major groups: polychlorinated dibenzo-p-dioxins (PCDDs)/furans (PCDFs)/dioxin-like polychlorinated biphenyls (DL-PCBs). PCDDs/PCDFs are unintentionally produced during the process of waste incineration, bleaching of paper pulp, herbicide production, and metal refinery etc. (1), but emissions into the environment have decreased in developed countries in recent years. DL-PCBs were generated as contaminants of PCBs, which were produced for various industrial uses until the 1970’s. Humans are exposed to PCDDs/PCDFs/DL-PCBs through diet, air and soil (1, 2).

Toxicities of dioxins include carcinogenicity and endocrine, immune, reproductive, and neurobehavioral effects (1). As a dietary intake safety standard, the tolerable daily intake (TDI) range of dioxins has been set to 1-4 pg Toxic Equivalents (TEQ)/kg/day by the World Health Organization (WHO) (3). TDI was determined on the basis of the body burden at which the most sensitive adverse health effects, such as reproductive, immune, and developmental effects, were observed in offspring, and by applying an uncertainty factor of 10 (3).

In a review published in 2005 (4), we summarized the blood levels and dietary intake of dioxins in general populations. It was considered that the means or medians of dietary intake of dioxins in various countries were lower than the upper end of the TDI set by the WHO (4 pg/TEQ/kg/day). The associations between background exposure to dioxins and potential health effects, such as diabetes (DM), thyroid function, endometriosis, and neurodevelopment of infants, were also reviewed.

Over the last few decades, countermeasures have been taken against emission of dioxins into the environment in various developed countries. Therefore, it is of interest to review the time-related changes in dioxin exposure among general populations. The association between exposure to dioxins and DM was firstly reported for occupationally exposed U.S. Air Force veterans (4). In recent years, the etiological role of dioxins in the development of not only DM but also its underlying conditions, such as insulin resistance, impaired insulin secretion and metabolic syndrome (MetS) among general populations, has become a matter of concern.

In this paper, the author reviewed recent reports on the dietary intake and blood levels of PCDDs/PCDFs/DL-PCBs among general populations to investigate the trends of dioxin exposure. In addition, the author reviewed recent epidemiologic studies on the association between blood levels of dioxins and DM and related or frequently coexistent metabolic diseases (insulin resistance/impaired β-cell function, MetS, and gout/hyperuricemia).

MATERIALS AND METHODS

Published reports were searched using MEDLINE. The keywords used were “dioxins”, “dietary intake”, and “trend” for temporal changes in dietary intake, and “dioxins”, “blood or serum” and “trend” for changes in blood levels. For the association between
exposure to dioxins and metabolic diseases, the combinations of keywords used were “dioxins” and “diabetes”, “dioxins” and “insulin resistance or β-cell function”, “dioxins” and “metabolic syndrome”, and “dioxins” and “gout or hyperuricemia”.

Publication time was restricted from January 2000 to October 2017. Papers which dealt with only dietary intake of PCDDs/PCDFs or DL-PCBs were excluded. In addition, studies on dietary intake and blood levels of dioxins were limited to those of general populations or populations without heavy exposure. Most studies related to DM and insulin resistance controlled the potential confounding effects by sex, age, and body mass index or waist circumference, using restriction, stratified analysis, or multivariate analysis. In addition, most studies on MetS and gout/hyperuricemia controlled sex, age and alcohol drinking, and studies on gout/hyperuricemia controlled body mass index or obesity.

Meta-analysis was performed for the associations of blood levels of dioxins with MetS and gout/hyperuricemia by the random-effects model, using programming language R.

DECREASING TRENDS OF DIETARY INTAKE

Assessing dietary intake of dioxins is crucial to evaluate the total exposure because respiratory and skin exposures constitute only a minor proportion of overall exposure (2). After 2000, several researchers reported the temporal trends of dioxin intake (Table 1). It should be noted that not all studies used the same survey methods (market basket method or duplicate portion analysis). Toxic Equivalency Factors (TEFs) (WHO 1998 or 2005), methods of calculation (pgTEQ/day or pgTEQ/kg/day), or body weights (50 kg, 70 kg, or weight of each study subject) in addition, one study measured only dioxin intake from fish and shellfish.

Sasamoto et al. (5) estimated dietary intake of PCDDs/PCDFs/DL-PCBs in Tokyo, Japan from 1999 to 2004, using the market basket method. The mean daily intake of total TEQ ranged from 1.25 to 2.18 pg/kg/day (WHO-TEF 1998). A decreasing trend was observed during the first three years. In Sweden, Darnérud et al. (6) estimated dietary intake of dioxins using market basket data in 1999. Intake of total dioxins was 96 pgTEQ/day (WHO-TEQ 1998), which was much lower than that reported in 1990 (255-300 pgTEQ/day). Arisawa et al. (7) reported dietary intake of dioxins, estimated using duplicate portion analysis of consecutive 3-day food samples, among 374 Japanese adults. The mean (2002-2006) was 1.06 pgTEQ/kg/day (WHO-TEQ 1998). In multiple regression analysis, a later survey year was significantly associated with lower dietary intake. When the period of the survey was extended to 2010, the overall mean was 0.82 pgTEQ/kg/day (625 subjects, WHO-TEQ 2005) (8). In a newly designed survey performed between 2011 and 2016, the estimated mean intake of 90 subjects was 0.49 pgTEQ/kg/day (WHO-TEQ 1998). Perello et al. (9) examined the changes in the dietary intake of dioxins in a Spanish population using the market basket method. The estimated daily intake was 3.51 pgTEQ/kg/day in 2000 and 0.60 pgTEQ/kg/day in 2010 (WHO-TEQ 2005). Intake of dioxins from fish and seafood, dairy products, and meat and meat products decreased by 83%, 92%, and 90%, respectively. In Italy, the daily intake of dioxins estimated in the survey in 2014 was 0.27–0.63 pgTEQ/kg/day (duplicate diet study, WHO-TEQ 2005) (10). This was considered to be lower than that estimated from 1994–1996 (2.28 pgTEQ/kg/day, WHO-TEQ 1998, market basket method) (11), although different survey methods and TEFs were used. In China, Zhang et al. (12) estimated the mean daily intake of PCDDs/PCDFs/DL-PCBs among the general population, using the market basket method. The mean intake was 0.59 pgTEQ/kg/day (WHO-TEQ 2005) in 2011, which was approximately 14.8% lower than that in 2007 (0.68 pgTEQ/kg/day). Perello et al. (13) estimated daily intake of PCDDs/PCDFs/DL-PCBs from fish and seafood in a Spanish population using the market basket method. The intake of PCDDs/PCDFs/DL-PCBs was 23.1 pgTEQ/day in 2012, which was much lower than that in 2000 (111.6 pgTEQ/kg/day). When the intake was calculated per kg body weight, daily intake did not exceed 1.0 pgTEQ/kg/day in various sex- and age-categories. The decrease in PCDDs/PCDFs TEQ (-86%) was somewhat larger than that in DL-PCBs TEQ (-78%).

When comparing the dietary intake with TDI, it is important to assess not only the mean, but also the distribution, of the intake. Mato et al. (2) estimated the distribution of the daily dioxin intake using the Monte Carlo simulation method. The 95 percentile of the daily intake in Japan was 2.91 pgTEQ/kg/day (WHO-TEQ 1998), which was lower than the upper end of the TDI set by the WHO (4.0 pgTEQ/kg/day) (3). Arisawa et al. (7) considered the distribution of the long-term intake of dioxins (WHO-TEQ 1998) in Japan by applying random-effects one-way analysis of variance to the repeatedly measured dietary intake of the same people, and excluding day-to-day within person variance. By assuming normal distribution for log (dietary intake), the proportions of subjects whose long-term dietary intake exceeded TDI set by the WHO (4 pgTEQ/kg/day) and European Union (2 pgTEQ/kg/day) were estimated at 0.06% and 2.9%, respectively (7). If the WHO-TEQ 2005 was used, the proportion of the population exceeding the TDI may have been lower, mainly because of the lower TEFs of DL-PCBs, as discussed later.

In summary, it is considered that the mean dietary intake of dioxins has been decreasing in general populations of several countries in Europe and Asia. The most recently reported means are equal to or less than 1.0 pgTEQ/kg/day. This decrease may be mainly because of the reduced emission of dioxins into the environment due to strict regulations in the treatment and disposal of waste. Although data are still limited, only a small percentage of the general populations in Japan may ingest dioxins exceeding the TDI. Some studies reported that the extent of the decrease was larger for dietary intake of PCDDs/PCDFs than DL-PCBs. One explanation may be that improvements in the process of waste incineration that occurred in developed countries were effective to reduce emissions of PCDDs/PCDFs, rather than DL-PCBs, into the environment.

DECREASING TRENDS OF DIOXIN CONCENTRATIONS IN BLOOD AND SERUM

After 2000, several studies examined the trends of dioxin concentrations in human blood and serum (Table 2). It should be noted that different TEFs (North Atlantic Treaty Organization/Committees on the Challenges of Modern Society [NATO/CCMS], WHO 1998 and 2005) were used in these studies, and some studies measured only PCDDs/PCDFs. When the WHO 2005 TEFs are applied, blood levels of dioxins become approximately 20% lower than when WHO 1998 TEFs was used (14). In addition, in some studies, study subjects consisted of not only general populations, but also people living in the vicinity of a waste incinerator or a chemical plant, or workers employed at a municipal waste incinerator. However, exposure to dioxins from routes other than diet (respiratory and skin exposure) may have been small, as suggested by the blood dioxin levels. Unlike dietary intake, no safety standards or reference range for serum or blood levels have been set.

Wittsiepe et al. (15) reported a decreasing trend in PCDDs/PCDFs levels in blood among a German population between 1991 and 1996. The mean PCDDs/PCDFs TEQ (NATO/CCMS) decreased from 42.67 pg/g līdij in 1991 to 20.74 pg/g līdij in 1996 (P<0.01). Ferréby et al. (16) compared the mean serum levels of PCDDs/PCDFs between the participants of the National Human
Adipose Tissue Survey (1980-1981, 57 subjects) and the National Health and Nutrition Examination Survey (NHANES) (2001-2002, 408 subjects) in the U.S. The means of the two surveys were 55 and 12.9 pgTEQ/g lipid, respectively. Uemura et al. (17) reported blood levels of dioxins in 1,374 Japanese adults who were examined in 2002-2006. The blood levels of PCDDs/PCDFs, DL-PCBs and total dioxins differed significantly according to the survey year \((P < 0.001)\), with mean values being lowest in 2006. When the period of the survey was extended to 2011 and WHO-TEF 2005 was used (2,264 subjects), the overall mean was 19 pgTEQ/g lipid (8). In an newly designed survey performed during 2011 and 2016, the overall mean of 490 subjects was 11 pgTEQ/g lipid (8). Humblet et al. (18) examined the temporal trend of dioxins in sera from 8 Russian women living in the vicinity of a chemical plant. The mean total TEQ was 36 pg/g lipid in 2000, which decreased to 25 pg/g lipid in 2009 \((P = 0.007)\). In Korea, Park et al. (19) examined the temporal trend of serum levels of dioxins from 2001 to 2011 among 954 subjects (workers at a municipal waste incinerator and people living around or away from a waste incinerator). The overall mean was 9.3 pgTEQ/g lipid for PCDDs/PCDFs and 5.4 pgTEQ/g lipid for DL-PCBs. They reported that there was no clear decreasing trend in the serum levels of PCDDs/PCDFs or DL-PCBs, although formal statistical testing was not performed.

In summary, dioxin concentrations in blood and serum have been decreasing in several countries in Europe and Asia, and U.S.A. This decreasing trend may be mainly because of the decreased dietary intake of dioxins.

### Table 1. Trends of mean dietary intake of dioxins in various countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Method</th>
<th>No. of subjects</th>
<th>Mean (pgTEQ/day)</th>
<th>Mean (pgTEQ/kg/day)</th>
<th>Year of survey</th>
<th>TEF</th>
<th>Reference</th>
<th>Remarks</th>
</tr>
</thead>
</table>

TEQ: Toxic Equivalents, TEF: Toxicity equivalency factors.

**Adipose Tissue Survey (1980-1981, 57 subjects) and the National Health and Nutrition Examination Survey (NHANES) (2001-2002, 408 subjects) in the U.S.** The means of the two surveys were 55 and 12.9 pgTEQ/g lipid, respectively. Uemura et al. (17) reported blood levels of dioxins in 1,374 Japanese adults who were examined in 2002-2006. The blood levels of PCDDs/PCDFs, DL-PCBs and total dioxins differed significantly according to the survey year \((P < 0.001)\), with mean values being lowest in 2006. When the period of the survey was extended to 2011 and WHO-TEF 2005 was used (2,264 subjects), the overall mean was 19 pgTEQ/g lipid (8). In a newly designed survey performed during 2011 and 2016, the overall mean of 490 subjects was 11 pgTEQ/g lipid (8). Humblet et al. (18) examined the temporal trend of dioxins in sera from 8 Russian women living in the vicinity of a chemical plant. The mean total TEQ was 36 pg/g lipid in 2000, which decreased to 25 pg/g lipid in 2009 \((P = 0.007)\). In Korea, Park et al. (19) examined the temporal trend of serum levels of dioxins from 2001 to 2011 among 954 subjects (workers at a municipal waste incinerator and people living around or away from a waste incinerator). The overall mean was 9.3 pgTEQ/g lipid for PCDDs/PCDFs and 5.4 pgTEQ/g lipid for DL-PCBs. They reported that there was no clear decreasing trend in the serum levels of PCDDs/PCDFs or DL-PCBs, although formal statistical testing was not performed.

In summary, dioxin concentrations in blood and serum have been decreasing in several countries in Europe and Asia, and U.S.A. This decreasing trend may be mainly because of the decreased dietary intake of dioxins.

### POTENTIAL HEALTH EFFECTS ASSOCIATED WITH ENVIRONMENTAL EXPOSURE TO PCDDs/PCDFs/ DL-PCBs

**Diabetes**

In 2006, Lee et al. (20) reported significant positive trends for the associations of serum levels of six persistent organic pollutants (POPs), including 1,2,3,4,6,7,8-HpCDD, with the prevalence of DM among participants of the 1999-2002 NHANES in the U.S. (Table 3). Everett et al. (21) also examined the associations of serum levels of 1,2,3,6,7,8-HxCDD, PCB126 and p.p'-DDT with DM in the 1999-2002 NHANES. The results showed that PCB126, but not 1,2,3,6,7,8-HxCDD, was significantly associated with the prevalence of DM. Even when the subjects with poor liver or kidney function were excluded, the results were unchanged. Jørgensen
et al. (22) examined the association between the sum of ranks of three DL-PCBs (115, 118 and 156) with DM and glucose metabolism in 692 Greenland Inuit, who were highly exposed to POPs. Sum of ranks of DL-PCBs were not significantly associated with DM or impaired glucose tolerance (IGT). Gasull et al. (23) reported that serum levels of PCB118 and three non-DL-PCBs were associated with an increased odds ratio (OR) of DM and pre-DM (125 mg/dl > plasma glucose levels > 110 mg/dl) in 886 subjects in Catalonia, Spain. In the Adult Inuit Health Study (2,595 subjects) (24), PCB 105 and 118, but not the sum of three DL-PCBs, were significantly associated with self-reported diabetes. In these five studies, concentrations of only 1-3 dioxin isomers were examined as exposure variables, and a TEQ-based approach was not used.

Uemura et al. (25) examined the relationships of 7 PCDDS, 9 PCDFs, and 12 DL-PCBs isomers in blood with the prevalence of DM in 1,374 Japanese adults using a TEQ-based approach. PCDDs/PCDFs TEQ, DL-PCBs TEQ, and total TEQ were all significantly associated with the prevalence of DM. The association was strongest for DL-PCBs, with an OR of 6.82 (95% confidence interval [CI] 2.59-20.1, quartile [Q]4 vs. Q1-2). In a study by Everett et al. (26), total TEQ, as well as individual dioxin isomers such as 1,2,3,6,7,8-HxCDD, OCDD, 2,3,4,7,8-PeCDF, PCB169, 118, and 156, were significantly associated with increased OR of DM, among participants of the 1999-2004 NHANES. Aminov et al. (27) reported that the linear trend for the association between DL-PCBs TEQ (sum of 6 isomers) and prevalent diabetes was significant (P = 0.010) among 601 native Americans, after adjustment for the concentrations of three organochlorine (OC) pesticides.

The results from prospective observations are different. Two nested case-control studies examined the association between serum levels of DL-PCBs with type 2 DM in general populations, but neither study produced significant results (28, 29). Three cohort studies have been reported regarding the association between high exposure to dioxins and DM. In the Yucheng cohort, the presence of chloracne, a sign of acute heavy exposure, was significantly associated with an increased risk of DM in women (OR = 5.5, 95% CI 2.3-13.4), but not in men (OR = 1.7, 95% CI 0.7-4.6) (30). In Great Lakes sport fish eaters in the U.S., there was no significant trend for the multivariate-adjusted association between serum levels of PCB118 and incidence rate of DM (P = 0.54) (31). In 980 women enrolled in the Seveso Women’s Health Study, serum levels of TCDD were not associated with development of DM (hazard ratio [HR] = 0.66, 95% CI 0.24-1.85, > 135 ppt/ vs. ≤ 20 ppt) (32).

In summary, several cross-sectional studies on general populations showed significant associations between serum/blood levels of PCDDs/PCDFs/DL-PCBs and DM. One problem that should be considered when evaluating the effect of dioxin exposure on DM is whether or not the TEQ-based approach is appropriate. If the mechanisms mediated by the aryl hydrocarbon receptor (Ah-R) play some roles in the development of DM, as suggested by an experimental study using Ah-R null mice (33), an analysis using the TEQ-based approach (25, 26) may be justified. However, the fact that not only DL-PCBs, but also non-DL-PCBs, often show significant relationships with DM (28, 34) suggests that involvement of mechanisms not mediated by Ah-R should also be considered in the pathogenesis of DM. Another problem when interpreting the previous studies on DM is the inconsistency between cross-sectional studies on general populations (20, 21, 25, 26) and prospective studies on populations with heavy exposure (31, 32) or general populations (28, 29). Heterogeneities in the results with respect to study design and exposure levels have been pointed

### Table 2. Trends of mean or median concentrations of dioxins in blood and serum (pgTEQ/g lipid) in general populations of various countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>No. of subjects</th>
<th>Samples</th>
<th>Mean</th>
<th>Median</th>
<th>Year of survey</th>
<th>TEF</th>
<th>Reference</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>17</td>
<td></td>
<td>29.05 (PCDD/Fs)</td>
<td>1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>74</td>
<td></td>
<td>29.13 (PCDD/Fs)</td>
<td>1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>69</td>
<td></td>
<td>24.06 (PCDD/Fs)</td>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>95</td>
<td></td>
<td>20.74 (PCDD/Fs)</td>
<td>1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHATS 2001-2002</td>
<td>408</td>
<td>serum</td>
<td>12.9 (PCDDs/Fs)</td>
<td>2001-2002</td>
<td>WHO-TEF1998</td>
<td>154</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>272</td>
<td></td>
<td>23.6</td>
<td>2003</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>264</td>
<td></td>
<td>23.7</td>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>288</td>
<td></td>
<td>25.6</td>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>291</td>
<td></td>
<td>21.0</td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>Women living in the vicinity of a chemical plant</td>
<td>8</td>
<td>serum</td>
<td>36</td>
<td>2000</td>
<td>WHO-TEF2005</td>
<td>154</td>
<td>Humblet O et al. (2011)</td>
<td>Same subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>2009</td>
<td></td>
<td></td>
<td></td>
<td>P = 0.001 by Paired t-test</td>
</tr>
<tr>
<td>Korea</td>
<td>Residents, workers</td>
<td>954</td>
<td>serum</td>
<td>9.29 (PCDD/Fs)</td>
<td>2001-2011</td>
<td>WHO-TEF2005</td>
<td>154</td>
<td>Park H et al. (2014)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>539</td>
<td>serum</td>
<td>5.39 (DL-PCBs)</td>
<td>2011-2016</td>
<td>Japanese Ministry of the Environment (2017)</td>
<td>154</td>
<td>Samesubjects</td>
<td>0.001</td>
</tr>
<tr>
<td>Japan</td>
<td>General population</td>
<td>284</td>
<td>blood</td>
<td>19</td>
<td>2002-2010</td>
<td>WHO-TEF2005</td>
<td>154</td>
<td>Japanese Ministry of the Environment (2017)</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td></td>
<td>490</td>
<td></td>
<td>11</td>
<td>2011-2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Associations of exposure to dioxins with diabetes, insulin resistance and insulin secretion

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>No. of subjects</th>
<th>Type of study</th>
<th>Outcome</th>
<th>Exposure (pg/g lipid) or (pg TEQ/g lipid)</th>
<th>Association</th>
<th>Reference</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.A. NHANES 1999-2002</td>
<td>2914</td>
<td>Cross-sectional</td>
<td>Diabetics</td>
<td>L,2,3,4,6,7,8PCDD (20DE)</td>
<td>OR = 2.1 (highest/lowest), P for trend = 0.007</td>
<td></td>
<td>Lee DL, et al. (2006) [20]</td>
<td></td>
</tr>
<tr>
<td>Denmark Greenland Inuit</td>
<td>692</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>DL-PCBs (sum of rank of 3 isomers)</td>
<td>OR = 1.2 (highest/lowest), N.S.</td>
<td></td>
<td>Jepsson ME, et al. (2008) [22]</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>General population</td>
<td>83 (T2DM)</td>
<td>Cross-sectional</td>
<td>HOMA-IR</td>
<td>Ah-R ligand activity (TCDD equivalent)</td>
<td>Pearson r = 0.289</td>
<td>Chang JW, et al. (2006) [27]</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>General population</td>
<td>886</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>PCB118</td>
<td>OR = 2.1 (highest/lowest), P for trend = 0.007</td>
<td></td>
<td>Gauld M, et al. (2012) [23]</td>
</tr>
<tr>
<td>Italy</td>
<td>Sessos-women</td>
<td>980</td>
<td>Cohort</td>
<td>Diabetes</td>
<td>TCDD</td>
<td>OR = 2.5 (highest/lowest), N.S.</td>
<td></td>
<td>Winter M, et al. (2013) [32]</td>
</tr>
<tr>
<td>U.S.A. Nurses Health Study</td>
<td>1850</td>
<td>Nested-case control</td>
<td>Diabetes</td>
<td>PCB118</td>
<td>OR = 2.1 (highest/lowest), N.S.</td>
<td></td>
<td>Wu H, et al. (2012) [29]</td>
<td></td>
</tr>
<tr>
<td>U.S.A. Native Americans</td>
<td>681</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>DL-PCB (2005), sum of 6 isomers (8ng/g lipid)</td>
<td>OR = 1.08 (highest/lowest), N.S.</td>
<td></td>
<td>Aminov Z, et al. (2014) [27]</td>
<td>Adjusted for pesticides</td>
</tr>
<tr>
<td>Canada</td>
<td>Arctic Inuit</td>
<td>205</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>PCB118</td>
<td>OR = 0.05 (highest/lowest), N.S.</td>
<td></td>
<td>Song K, Chan IH (2017) [24]</td>
</tr>
<tr>
<td>Denmark Greenland Inuit</td>
<td>692</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>DL-PCBs (sum of rank of 3 isomers)</td>
<td>N.S.</td>
<td></td>
<td>Jepsson ME, et al. (2008) [22]</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>Contaminated area</td>
<td>1448</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>PCB118</td>
<td>P = 0.002 (positive correlation)</td>
<td></td>
<td>Chang JW, et al. (2011) [30]</td>
</tr>
<tr>
<td>Faisalid Fishermen</td>
<td>127 (Men) 122 (Women)</td>
<td>Cross-sectional</td>
<td>Total TEQ</td>
<td>Total TEQ</td>
<td>1741.20 (highest/lowest, Men), P for trend = 0.08 1269.10 (highest/lowest, Women), P for trend = 0.48</td>
<td></td>
<td>Turyk M, et al. (2006) [20]</td>
<td>Mean = 9 pgTEQ/g lipid (Men) Mean = 5 pgTEQ/g lipid (Women) Dietary habit was adjusted BMI was not adjusted</td>
</tr>
<tr>
<td>Korea</td>
<td>General population</td>
<td>30 (T2DM) 10 (BGT) 40 (Control)</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>Ah-R ligand activity (TCDD equivalent)</td>
<td>Pearson r = 0.289</td>
<td>Bobbi E, et al. (2013) [29]</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>Contaminated area</td>
<td>1484</td>
<td>Cross-sectional</td>
<td>Diabetes</td>
<td>PCB118</td>
<td>OR = 2.5 (highest/lowest), N.S.</td>
<td></td>
<td>Chang JW, et al. (2005) [37]</td>
</tr>
</tbody>
</table>

out in a meta-analysis on dioxin exposure and DM (35).

**Insulin resistance and β cell function**

Several cross-sectional studies have examined the association between environmental exposure to dioxins and insulin resistance/β cell function (Table 3). In epidemiologic studies, Homeostasis Model Assessment (HOMA) - Insulin Resistance (IR) and HOMA-β are defined using the following equations, and are often used as an index of insulin resistance and β cell function, respectively.

\[
\text{HOMA-IR} = \frac{\text{insulin (µU/ml)} \times \text{fasting blood glucose (mg/dl)}/405}{\text{HOMA-β (}) = (360 \times \text{insulin (µU/ml)})/(\text{glucose [mg/dl]} - 63)
\]

Jørgensen et al. (22) examined the association between serum levels of DL-PCBs and glucose homeostasis among 692 Greenland Inuit. There was a significant inverse association with HOMA-β (8.5% /quartile), but no association with HOMA-IR. Chang et al. (36) examined the correlations of serum levels of PCDDs/PCDFs TEQ with HOMA-IR among 1,449 subjects living near a deserted pentachlorophenol factory in Taiwan from 2005 to 2007. The mean PCDDs/PCDFs TEQ was 33.2 pg/g lip (WHO 1998 TEF), suggesting somewhat high exposure. In multiple regression analysis, PCDDs/PCDFs TEQ in serum was significantly associated with HOMA-IR (P < 0.001). HOMA-IR increased as serum levels of PCDDs/PCDFs and blood levels of mercury increased. The same research team performed a cross-sectional study on 1,466 men and 1,410 women living in the same study area from 2005 to 2010 (37). High serum levels of PCDDs/PCDFs TEQ were significantly associated with insulin resistance, defined as HOMA-IR > 75 percentile, in men (OR = 2.46, 95% CI 1.63-3.70), but not in women (OR = 1.11, 95% CI 0.58-2.12), when abdominal obesity was absent. Turunen et al. (38) examined the association between total TEQ in blood and glucose homeostasis among fishermen (123 males and 132 females) in Finland. The mean blood level of total dioxins was 98 pg/TEQ/g lip for men and 54 pg/TEQ/g lip for women, indicating high exposure. The P for trend for the association of total TEQ with HOMA-IR was 0.09 for men and 0.49 for women. The P for trend of total TEQ with HOMA-β was 0.10 for men and 0.17 for women. Rob et al. (39) performed a case-control study on the association between blood levels of dioxins (estimated by Ah-R ligand activity) and DM (83 patients with DM, 130 patients with IGT, and 83 controls). When the subjects with IGT and controls were combined, there was a significant positive correlation between log(Ah-R ligand activity) and HOMA-IR (r = 0.29, P < 0.001), but not between log(Ah-R ligand activity) and HOMA-β (r = 0.08, P > 0.33).

In summary, significant positive correlations of serum levels of dioxins with insulin resistance and a significant inverse correlation with β-cell function have been reported in some studies, but the results are inconsistent. The results may not depend on the characteristics of each population (general or highly exposed) or chemical substances (PCDDs/PCDFs, DL-PCBs), or use or no use of a TEQ-based approach.

**Metabolic syndrome (MetS)**

Metabolic syndrome is characterized by the clustering of visceral obesity, high blood pressure, high serum triglyceride levels, low serum HDL-cholesterol levels, and high fasting blood glucose, often accompanied by a pro-inflammatory state and pro-thrombotic state (40). People with MetS are at an increased risk for developing type 2 DM and cardiovascular diseases (41-43). Lifestyle factors, such as excessive energy intake, a western dietary pattern, and low physical activity levels, are known as risk factors for the development of MetS (40, 44). Recently, environmental exposure to POPs, including dioxins, has attracted attention as a potential etiological factor for MetS. Lee et al. (45) explored the association between serum levels of various POPs and the prevalence of MetS in 721 U.S. adults who participated in the 1999-2002 NHANES survey (Table 4). There were significant positive dose-response relationships between DL-PCBs (sum of ranks of 4 isomers, PCB74, 118, 126, 169, 1,2,3,4,7,8-HxCDF and OC pesticides (sum of ranks of 4 substances), and MetS. The strongest association was found for OC pesticides. On the other hand, there was no association between serum levels of PCDDs (sum of ranks of 3 isomers) or PCDFs (sum of ranks of 3 isomers) and MetS. Uemura et al. (46) examined the associations of 29 PCDDs/PCDFs/DL-PCBs isomers in blood with the prevalence of MetS in 1,374 Japanese subjects. Significant positive trends were observed for TEQs of PCDDs and DL-PCBs, total TEQ, and concentrations of 4 PCDDs, 1 PDCF, and 6 DL-PCBs. The results were essentially unchanged regardless of whether or not the subjects with diabetes were excluded from the analysis. In Taiwan, Chang et al. (47) examined the association between serum levels of 17 PCDDs/PCDFs isomers and the prevalence of MetS in 1,490 subjects living near a highly contaminated area. The mean TCDDs/PCDFs TEQ (WHO 1998) in serum (312 pg/TEQ/g lip) was higher than that of general populations in Japan (Median = 20 pg/TEQ/g lip [WHO TEF 1998]) (17) and Korea (Mean = 9.12 pg/TEQ/g lip [WHO TEF 2005]) (19), suggesting the presence of excessive exposure. The P for trend was significant for TEQ of PCDDs/PCDFs and concentrations of 14 PCDDs/PCDFs isomers. In a case-control study conducted in Korea (23 patients with DM, 23 patients with impaired fasting glycemia, and 50 controls), serum levels of Ah-R ligand activity were significantly associated with the presence of DM and MetS (48). In Canada, Gauthier et al. (49) performed a case-control study on obesity-associated metabolic abnormality and serum levels of various POPs. Cases consisted of obese people with insulin resistance and metabolic abnormalities, while controls were those who were obese, but had no insulin resistance. The sum of concentrations of 5 DL-PCBs and 9 non-DL-PCBs (> = median) was significantly associated with case/control status, with an OR of 4.7 (95% CI 1.8-12.5). However, ORs were not separately estimated for DL-PCBs and non-DL-PCBs.

Warner et al. prospectively examined the association between exposure to TCDD and MetS in Sevoso women (median serum TCDD = 55.9 ppt) (32). Serum levels of log(Ah-R ligand activity) were significantly associated with the presence of MetS among those who were equal to or less than 12 years of age at the time of exposure (OR = 2.03, 95% CI 1.25-3.30), but not among the remainder of the cohort (OR = 0.96, 95% CI 0.68-1.35). In a cohort study of the Swedish general population, PCB 126 and 118, but not OCDD in plasma (weight based concentration), were associated with significantly increased OR of MetS (50).

When the random effects model was applied to three large scale cross-sectional studies (45-47), summary ORs for the highest category relative to the lowest category of PCDDs, PCDFs, and DL-PCBs were estimated at 1.9 (95% CI 1.2-3.0, P for heterogeneity = 0.16, Fig. 1a), 1.9 (95% CI 1.3-3.0, P for heterogeneity = 0.25, Fig. 1b), and 3.8 (95% CI 1.1-13, P for heterogeneity = 0.04, Fig. 1c), respectively. All summary ORs were significantly higher than 1.0. These results suggest that serum/blood levels of PCDDs/PCDFs and DL-PCBs were significantly associated with MetS, despite some differences in the study design (use of concentrations, sum of ranks, TEQs, or Ah-R ligand activity) and inconsistencies in chemical substances that showed significant associations with MetS. Possible biological mechanisms include obesogenic effects of dioxins observed in experimental animals (51) and humans (52), and Ah-R mediated effects on expression of genes involved in inflammatory pathways, such as interleukin 1β (IL1β), interleukin 8 (IL8), interleukin receptor antagonist (IL1ra), and prostaglandin-endoperoxidase synthase 2 (PTGS2) (53). Further experimental and prospective studies are needed to draw a firm conclusion.
Table 4. Association between exposure to dioxins and metabolic syndrome and gout/hyperuricemia

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>No. of subjects</th>
<th>Design</th>
<th>Outcome</th>
<th>Exposure (pg/g lipid or pgTEQ/g lipid)</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.A.</td>
<td>NHANES (1999–2002)</td>
<td>721</td>
<td>Cross-sectional</td>
<td>Metabolic syndrome</td>
<td>1PCDDs (sum of isomer)</td>
<td>OR = 1.5 (highest/lowest, N.S.); P for trend = 0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2PCDFs (sum of isomer)</td>
<td>OR = 1.6 (highest/lowest, N.S.); P for trend = 0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4DL-PCBs (sum of isomer)</td>
<td>OR = 2.5 (highest/lowest, N.S); P for trend = 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PCB 74, 99, 124</td>
<td>OR = 2.1 (highest/lowest, N.S); P for trend = 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 organochlorine pesticides, sum of isomer</td>
<td>OR = 3.3 (highest/lowest, N.S); P for trend = 0.01</td>
</tr>
</tbody>
</table>

Japan General population 1374 Cross-sectional Metabolic syndrome 1PCDDs (TEQ) (2003) DL-PCDFs (TEQ) (2003) Total TEQ (2003) 13 smokers OR = 1.41 (highest/lowest, N.S.; P for trend = 0.01) OR = 1.75 (highest/lowest, N.S.; P for trend = 0.01) OR = 1.13 (highest/lowest, N.S.; P for trend = 0.01) P for trend = 0.15

Taiwan Polluted area 1490 Cross-sectional Metabolic syndrome 1PCDDs (TEQ) (1998) 2PCDFs (TEQ) (1998) 4DL-PCBs (sum of isomer) OR = 2.0 (highest/lowest, N.S.) OR = 1.75 (highest/lowest, N.S.) OR = 1.13 (highest/lowest, N.S.) P for trend = 0.15

Korea General population Diabetes 21 Case-control Metabolic syndrome DM Al-E Glucan activity P < 0.01 P < 0.01

Italy Seniors women 866 Cohort Metabolic syndrome TCDD OR = 2.01 (log TEQ) (age < 12y at explosion) OR = 0.76 (log TEQ, N.S) (age > 12 y at explosion) OR = 0.01 (log TEQhammer age) P for trend = 0.35

Canada General population MHO 40 MHO 36 Case-control Metabolically abnormal obese 1,2,3,4,7,8-HxCDF OR = 1.41 (highest/lowest) OR = 0.41 (highest/lowest) Park WH et al. (2012) [48] Median of TCDD = 15.5 ppt

Sweden General population 412 Cohort Metabolic syndrome PCB56 (pg/ml) PCB126 (pg/ml) PCB153 (pg/ml) OR = 1.17 (highest/lowest) OR = 0.39 (highest/lowest) N.S. Park WH et al. (2012) [48] Median of TCDD = 15.5 ppt

Japan General population 1118 men Cross-sectional Gout PCB56/PCDFs/PCDDs (TEQ) (2003) DL-PCDFs/PCDDs (TEQ) (2003) Total TEQ (2003) OR = 0.81 (highest/lowest, N.S.; P for trend = 0.01) OR = 0.7 (highest/lowest, N.S.; P for trend = 0.01) OR = 0.7 (highest/lowest, N.S.; P for trend = 0.01) Lee DL et al. (2011) [47]

U.S.A. NHANES (2003–2004) 1118 Cross-sectional Hyperuricemia 1PCDDs (sum of isomer) 2PCDFs (sum of isomer) 4DL-PCBs (sum of isomer) OR = 2.45 (highest/lowest, N.S.) OR = 1.5 (highest/lowest, N.S.) OR = 2.0 (highest/lowest, N.S.) Lee, YM et al. (2011) [55]


Gout and hyperuricemia

Nakamoto et al. (54) first reported that there were significant positive trends between TEQs of PCDDs/PCDFs, DL-PCBs and total TEQ in blood, and a history of gout in 1,051 Japanese men (Table 4). Lee et al. (55) also examined the association of serum levels of 3 PCDDs, 2 PCDFs and 8 DL-PCBs (sum of rank of each isomer) with hyperuricemia among 1,118 U.S. adults (NHANES 2003–2004 sample). Significant positive trends were observed for PCDDs and DL-PCBs. Chang et al. (56) reported a positive trend between PCDDs/PCDFs’ TEQ and hyperuricemia in 715 U.S. men who were residing near a pentachlorophenol factory (Geometric mean PCDDs/PCDFs’ TEQ in serum = 12.4 pgTEQ/g lipid). When the random effects model was applied to two studies that used PCDDs/PCDFs’ TEQ as an exposure variable (54, 56), the summary OR of Q4 relative to Q1 was estimated at 3.8 (95% Cl 1.6-8.9, P for heterogeneity = 0.24, figure not shown).

These consistent results suggest that exposure to dioxins is a risk factor for gout/hyperuricemia. However, another possible explanation is that risk factors for gout/hyperuricemia and high exposure to dioxins overlap each other. Blood levels of dioxins (15-17) and the prevalence of gout (57) generally increase with age. Purine-rich foods, such as meat and seafood, are risk factors for gout (57) and major dietary sources of dioxins. Alcohol drinking, an established risk factor for gout, was associated with high blood levels of dioxins, independent of fish intake (58). In addition, obesity is often accompanied by high blood levels of dioxins and hyperuricemia. Age, body mass index and alcohol drinking, but not intake of purine, were adjusted in those studies on gout/hyperuricemia (54-56). Therefore, confounding by intake of purine should be controlled in future epidemiologic studies.

CONCLUSION

In this paper, the author reviewed the recent studies on the
temporal changes in blood levels and dietary intake of dioxins among general populations, and epidemiologic studies on the associations of blood levels of dioxins with metabolic diseases. In recent years, dietary intake and blood levels of dioxins has been decreasing in general populations in various countries. Many cross-sectional studies reported positive associations between blood levels of PCDDs/PCDFs/DL-PCBs and diabetes in general populations. However, the results from prospective studies on populations with heavy exposure and general populations are inconsistent. Four cross-sectional or case-control studies and two cohort studies (Seveso Women’s Study and one study on a general population) consistently reported a significant positive association between blood levels of dioxins and metabolic syndrome. Meta-analysis performed in this study showed significantly increased ORs of metabolic syndrome associated with higher blood levels of PCDDs/PCDFs/DL-PCBs. In addition, three cross-sectional studies reported significant positive associations with gout/hyperuricemia. Further prospective studies and experimental studies are necessary to establish cause-effect relationships, and to clarify the biological mechanisms.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interests.

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