REVIEW

Recent decreasing trends of exposure to PCDDs/PCDFs/ dioxin-like PCBs in general populations, and associations with diabetes, metabolic syndrome, and gout/hyperuricemia

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Abstract : The author reviewed recent reports about the blood levels and dietary intake of polychlorinated dibenzo-*p*-dioxins (PCDDs)/furans (PCDFs)/dioxin-like polychlorinated biphenyls (DL-PCBs) to investigate the trends of dioxin exposure, and epidemiologic studies on the associations of blood levels of dioxins with metabolic diseases. In recent years, dietary intake of dioxins has been decreasing, and the means are equal to or less than 1.0 pg Toxic Equivalents (TEQ)/kg/day in the general populations of several countries. The blood levels of dioxins are also decreasing, probably because of reduced dietary intake. Many cross-sectional studies reported positive associations between blood levels of some isomers or TEQ-based concentrations of PCDDs/PCDFs/DL-PCBs and diabetes in general populations. Three cohort studies on populations with heavy exposure and two nested case-control studies on general populations have also been published, but the results are inconsistent. Three large-scale cross-sectional studies and two cohort studies reported an association between blood levels of some isomers or TEQ-based concentrations of PCDDs/PCDFs/DL-PCBs and metabolic syndrome. In addition, three cross-sectional studies reported significant positive associations with gout/hyperuricemia. Further prospective studies and experimental studies are needed to establish cause-effect relationships, and to clarify the biological mechanisms for the association between background exposure to dioxins and potential health effects. J. Med. Invest. 65 : 151-161, August, 2018

Keywords **:** *Dioxins, Diabetes, Insulin resistance, Metabolic syndrome, Gout*

INTRODUCTION

Dioxins are a group of chemically related environmental contaminants, consisting of three major groups : polychlorinated dibenzo-*p*-dioxins (PCDDs) ; furans (PCDFs) ; and 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

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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 TREND 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, Darnerud *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 (8). Perelló *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). Perelló *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 (-77%).

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 TREND 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 26% lower than when WHO 1998 TEF 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 of 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 lipid in 1991 to 20.74 pg/g lipid in 1996 (P=0.01). Ferriby *et al.* (16) compared the mean serum levels of PCDDs/PCDFs between the participants of the National Human

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

Country	Method	No. of subjects	Mean (pgTEQ/day)	Mean (pgTEQ/kg/day)	Year of survey	TEF	Reference	Remarks
Japan	Market basket		109.2	2.18	1999	WHO-TEF 1998	Sasamoto T, *et al.* (2006) [5]	50kg b.w.
			93.3	1.87	2000			
			62.4	1.25	2001			
			80.1	1.60	2002			
			80.0	1.60	2003			
			77.5	1.55	2004			
Sweden	Market basket		255-300		1990	WHO-TEF 1998	Wicklund Glynn A, *et al.* (1996)	
		(123 foods)	96		1999		Darnerud PO, *et al.* (2006) [6]	
Japan	Duplicate portion analysis	75		1.27	2002	WHO-TEF 1998	Arisawa K, *et al.* (2008) [7]	b.w. of each subject
		74		1.32	2003			$P < 0.0001$ by Kruskal-Wallis test
		75		1.02	2004			
		75		1.01	2005			
		75		0.65	2006			
		374	60.36	1.06	2002-2006			
Spain	Market basket		245.5	3.51	2000	WHO-TEF 2005	Perelló G, *et al.* (2012) [9]	70kg b.w.
			78.1	1.12	2006			
			41.7	0.60	2010			
Italy	Market basket			2.28	1994-1996	WHO-TEF 1998	Fattore E, *et al.* (2006) [11]	
	Duplicate diet study			0.27-0.63	2014	WHO-TEF 2005	De Filippis SP, *et al.* (2014) [10]	
China	Market basket			0.68	2007	WHO-TEF 2005	Zhang L, *et al.* (2015) [12]	
				0.59	2011			
Spain	Market basket		111.6		2000	WHO-TEF 2005	Llobet JM, *et al.* (2003)	fish and shellfish only
Spain	Market basket		23.1		2012		Perelló G, *et al.* (2015) [13]	fish and shellfish only
Japan	Duplicate portion	625		0.82	2002-2010	WHO-TEF 2005	Japanese Ministry of the Environment (2017) [8]	b.w. of each subject
	analysis	90		0.49	2011-2016	WHO-TEF 2005	Japanese Ministry of the Environment (2017) [8]	b.w. of each subject
								$P < 0.001$ by t-test

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 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

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

Country	Population	No. of subjects	Samples	Mean	Median	Year of survey	TEF	Reference	Remarks
Germany	General population	95	blood	42.67 (PCDD/Fs)		1991	NATO/CCMS-TEF	Wittsiepe J, *et al.* (2000) [15]	$P = 0.01$ (1991 vs. 1996)
		157		38.12 (PCDD/Fs)		1992			
		17		29.05 (PCDD/Fs)		1993			
		74		29.13 (PCDD/Fs)		1994			
		69		24.06 (PCDD/Fs)		1995			
		95		20.74 (PCDD/Fs)		1996			
U.S.A.	NHATS 1980-1981	57	serum	55 (PCDDs/Fs)		1980-1981	WHO-TEF 1998	Ferriby LL, *et al.* (2007) [16]	
	NHANES 2001-2002	408		12.9 (PCDDs/Fs)		2001-2002			
Japan	General population	259	blood	26.7		2002	WHO-TEF 1998	Uemura H, *et al.* (2008) [17]	$P < 0.001$ by KrusKal-Wallis test
		272		23.6		2003			
		264		23.7		2004			
		288		25.6		2005			
		291		21.0		2006			
Russia	Women living in the vicinity of a chemical plant	8	serum	36		2000	WHO-TEF 2005	Humblet O, *et al.* (2011) [18]	Same subjects
				25		2009			$P = 0.007$ by Paired t-test
Korea	Residents, workers	954	serum	9.29 (PCDD/Fs)		2001-2011	WHO-TEF 2005	Park H, *et al.* (2014) [19]	no decreasing trend
					8.15 (PCDD/Fs)				
	Residents, workers	539		5.39 (DL-PCBs)					no decreasing trend
					4.51 (DL-PCBs)				
Japan	General population	2264	blood	19		2002-2010	WHO-TEF 2005	Japanese Ministry of the Environment (2017) [8]	$P < 0.001$ by t-test
		490		11		2011-2016	WHO-TEF 2005	Japanese Ministry of the Environment (2017) [8]	

TEQ : Toxic Equivalents, TEF : Toxicity equivalency factors, NATO/CCMS : North Atlantic Treaty Organization/Committees on the Challenges of Modern Society, NHATS : National Human Adipose Tissue Survey, NHANES : National Health and Nutrition Examination Survey.

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 TEF-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+Q2). 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 Womens' 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 3. Associations of exposure to dioxins with diabetes, insulin resistance and insulin secretion

Country	Population	No. of subjects	Type of study	Outcome	Exposure (pg/g lipid) or pgTEQ/g lipid)	Association	Reference	Remarks
U.S.A.	NHANES 1999 - 2002	2016	Cross - sectional	Diabetes	1,2,3,4,6,7,8HpCDD	OR = 2.7* (highest/lowest), *P* for trend = 0.007	Lee DH, *et al.* (2006) [20]	
					OCDD	OR = 2.1 (highest/lowest, N.S.), *P* for trend = 0.094		
U.S.A.	NHANES 1999 - 2002	1830	Cross - sectional	Diabetes	1,2,3,6,7,8HxCDD	OR = 1.99 (highest/lowset, N.S.)	Everett CJ, *et al.* (2007) [21]	
					PCB126	OR = 3.68* (highest/lowest)		
Denmark	Greenland Inuit	692	Cross - sectional	Diabetes	DL - PCBs (sum of ranks of 3 isomers)	OR = 1.2 (highest/lowest, N.S.), *P* for trend = 0.37	Jørgensen ME, *et al.* (2008) [22]	
				IGT	DL - PCBs (sum of ranks of 3 isomers)	OR = 0.7 (highest/lowest, N.S.), *P* for trend = 0.82		
Taiwan	Yucheng	748	Cohort	Diabetes	(presence of chloracne)	OR = 1.7 (chloracne +/ -, N.S., Men)	Wang SL, *et al.* (2008) [30]	
						OR = 5.5* (chloracne +/ -, Women)		
U.S.A.	Great lakes sport fish consumers	471	Cohort	Diabetes	PCB118	HR = 1.3 (highest/lowest, N.S.), *P* for trend = 0.54	Turyk M, *et al.* (2009) [31]	
Japan	General population	1374	Cross - sectional	Diabetes	PCDDs + PCDFs TEQ (1998)	OR = 2.21* (>= 18 vs. 12<)	Uemura H, *et al.* (2009) [25]	
					DL - PCBs TEQ (1998)	OR = 6.82* (>= 13 vs. 7.6<)		
					Total TEQ (1998)	OR = 3.81* (>= 31 vs. < 20)		
Sweden	General population	725	Nested case - control	Diabetes	PCB105	OR = 8.0 (highest/lowest, N.S.), *P* for trend = 0.30	Lee DH, *et al.* (2011) [28]	
					PCB118	OR = 3.6 (highest/lowest, N.S.), *P* for trend = 0.19		
					PCB156	OR = 2.6 (highest/lowest, N.S.), *P* for trend = 0.14		
					PCB157	OR = 2.9 (highest/lowest, N.S.), *P* for trend = 0.07		
					PCB189	OR = 2.8 (highest/lowest, N.S.), *P* for trend = 0.12		
U.S.A.	NHANES 1999 - 2004	2611	Cross - sectional	Diabetes	1,2,3,6,7,8HxCDD	OR = 2.25* (highest/lowest)	Everett CJ, *et al.* (2012) [26]	
					OCDD	OR = 1.82* (highest/lowest)		
					2,3,4,7,8PeCDF	OR = 2.39* (highest/lowest)		
					PCB169	OR = 2.56* (highest/lowest)		
					PCB118	OR = 3.53* (highest/lowest)		
					PCB156	OR = 2.47* (highest/lowest)		
					Total TEQ (2005)	OR = 3.08* (>= 81.58 vs. 13.82 >)		
Spain	General population	886	Cross - sectional	Diabetes	PCB118	OR = 2.1* (highest/lowest), *P* for trend = 0.048	Gasull M, *et al.* (2012) [23]	
				Pre - diabetes	PCB118	OR = 2.1* (highest/lowest), *P* for trend = 0.007		
Italy	Seveso women	980	Cohort	Diabetes	TCDD	HR = 0.66 (> 135 vs. <= 20, N.S.), *P* for trend = 0.09	Warner M, *et al.* (2013) [32]	
U.S.A.	Nurses' Health Study	1095	Nested case - control	Diabetes	PCB118	OR = 1.41 (highest/lowest, N.S.), *P* for trend = 0.43	Wu H, *et al.* (2013) [29]	
U.S.A.	Native Americans	601	Cross - sectional	Diabetes	DL - PCB TEQ (2005, sum of 6 isomers) (10^{-5} ng/ g wet weight)	OR = 1.82 (highest/lowest, N.S.), *P* for trend = 0.010	Aminov Z, *et al.* (2016) [27]	Adjusted for pesticides
Canada	Arctic Inuit	2595	Cross - sectional	Diabetes	PCB105	*P* < 0.05 (highest/lowest)	Singh K., Chan HM (2017) [24]	
					PCB118	*P* < 0.05 (highest/lowest)		
					DL - PCBs (sum of 3 isomers)	N.S. (highest/lowest)		
Denmark	Greenland Inuit	692	Cross - sectional	HOMA - IR	DL - PCBs (sum of ranks of 3 isomers)	N.S.	Jørgensen ME, *et al.* (2008) [22]	
				HOMA - β		*P* < 0.05 (- 8.5%/quartile)		
Taiwan	Contaminated area	1449	Cross - sectional	HOMA - IR	PCDDs/PCDFs TEQ (1998)	*P* < 0.001	Chang JW, *et al.* (2011) [36]	Mean = 33.2 pgTEQ/g lipid
				HOMA - β	PCDDs/PCDFs TEQ (1998)	*P* = 0.030 (positive correlation)		
Finland	Fishermen	123 (Men)	Cross - sectional	HOMA - IR	Total TEQ	1.74/1.30 (highest/lowest, Men), *P* for trend = 0.09	Turunen AW, *et al.* (2013) [38]	Mean = 98 pgTEQ/g lipid (Men)
		132 (Women)				1.28/1.43 (highest/lowest, Women), *P* for trend = 0.49		Mean = 54 pgTEQ/g lipid (Women)
				HOMA - β	Total TEQ	63.2%/50.2% (highest/lowest, Men), *P* for trend = 0.10		Dietary habit was adjusted
						63.2%/77.1% (highest/lowest, Women), *P* for trend = 0.17		BMI was not adjusted
Korea	General population	83 (T2DM)	Case - control	Diabetes	Ah - R ligand activity (TCDD equivalent)	OR = 2.26 ($\log_2$(Ah-R ligand), *P* = 0.002)	Roh E, *et al.* (2015) [39]	
		130 (IGT)						
		83 (Control)	Cross - sectional	HOMA - IR	Ah - R ligand activity (TCDD equivalent)	Pearson r = 0.289 (*P* < 0.001)		BMI was not adjusted for HOMA - IIR and HOMA - β
				HOMA - β	Ah - R ligand activity (TCDD equivalent)	Pearson r = 0.079 (*P* = 0.334)		
Taiwan	Contaminated area	1466 (Men)	Cross - sectional	HOMA - IR	PCDDs/PCDFs TEQ (1998)	OR = 2.46* (>= 19.35 vs. < 19.35, Men)	Chang JW, *et al.* (2016) [37]	Mean = 25.4 pgTEQ/g lipid
		1410 (Women)			PCDDs/PCDFs TEQ (1998)	OR = 1.11 (>= 23.25 vs.< 23.25, N.S., Women)		Mean = 34.8 pgTEQ/g lipid

TEQ : Toxic Equivalents, NHANES : National Health and Nutrition Examination Survey, OR : odds ratio, IGT : impaired glucose tolerance, HR : hazard ratio, HOMA - IR : Homeostasis Model Assessment - Insulin Resistance, HOMA - β : Homeostasis Model Assessment - β, T2DM : type 2 diabetes, Ah - R : aryl hydrocarbon receptor.
* *P* < 0.05, N.S. : not significant.

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.

HOMA-IR = insulin (μU/ml) × fasting blood glucose (mg/dl) /405

HOMA-β (%) = (360 × insulin [μU/ml])/(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 lipid (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 pgTEQ/g lipid for men and 54 pgTEQ/g lipid 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. Roh *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 $\log_2$(Ah-R ligand activity) and HOMA-IR ($r = 0.29$, $P < 0.001$), but not between $\log_2$(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 PCDF, 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 (31.2 pgTEQ/g lipid) was higher than that of general populations in Japan (Median = 20 pgTEQ/g lipid [WHO TEF 1998]) (17) and Korea (Mean = 9.12 pgTEQ/g lipid [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 glycaemia, 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 Seveso women (median serum TCDD = 55.9 ppt) (32). Serum levels of $\log_{10}$ (TCDD) 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 (wet-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 (*IL1B*), interleukin 8 (*IL8*), interleukin receptor antagonist (*IL1ra*), and prostaglandin-endoperoxide 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

Country	Population	No. of subjects	Design	Outcome	Exposure (pg/g lipid or pgTEQ/g lipid)	Association	Reference	Remarks
U.S.A.	NHANES (1999-2002)	721	Cross-sectional	Metabolic syndrome	3 PCDDs (sum of ranks) 4 PCDFs (sum of ranks) 1,2,3,4,7,8-HxCDF 4 DL-PCBs (sum of ranks) PCB 74, 118, 126 (4 organochlorine pesticides, sum of ranks)	OR = 1.3 (highest/lowest, N.S.), *P* for trend = 0.35 OR = 1.6 (highest/lowest, N.S.), *P* for trend = 0.11 OR = 2.0* (highest/lowest), *P* for trend < 0.01 OR = 2.1* (highest/lowest), *P* for trend = 0.01 *P* for trend < 0.01 OR = 5.3* (highest/lowest), *P* for trend < 0.01	Lee DH, *et al.* (2007) [45]	
Japan	General population	1374	Cross-sectional	Metabolic syndrome	PCDDs TEQ (1998) DL-PCBs TEQ (1998) Total TEQ (1998) 11 isomers	OR = 3.4* (> = 11 vs. < 4.49), *P* for trend < 0.01 OR = 7.3* (> = 12.87 vs. < 4.28), *P* for trend < 0.01 OR = 5.1* (> = 30 vs. < 12), *P* for trend < 0.01 *P* for trend < 0.05	Uemura H, *et al.* (2009) [46]	Subjects with diabetes were excluded
Taiwan	Polluted area	1490	Cross-sectional	Metabolic syndrome	PCDDs/PCDFs TEQ (1998) PCDDs PCDFs 14 isomers	OR = 2.3* (highest/lowest), *P* for trend < 0.001 OR = 1.7* (highest/lowest), *P* for trend < 0.001 OR = 1.7* (highest/lowest), *P* for trend < 0.001 *P* for trend < 0.01	Chang JW, *et al.* (2010) [47]	Mean = 31.2 pgTEQ/g lipid
Korea	General population	Diabetes 23 IFG 23 Control 50	Case-control	Metabolic syndrome DM	Ah-R ligand activity	*P* < 0.05 *P* < 0.05	Park WH, *et al.* (2013) [48]	
Italy	Seveso women	806	Cohort	Metabolic syndrome	TCDD	OR = 2.03* ($\log_{10}$(TCDD)) (age < = 12 y at explosion) OR = 0.96 ($\log_{10}$(TCDD), N.S.) (age > 12 y at explosion) *P* interaction (age) = 0.01	Warner M, *et al.* (2013) [32]	Median of TCDD = 55.9 ppt
Canada	General population	MAO 40 MHO 36	Case-control	Metabolicaly abnormal obese	5 DL-PCBs + 9 nonDL-PCBs (pg/mL) (Trans nonachlor , pg/mL)	OR = 4.7* (> = Median/< Median) OR = 6.1* (> = Median/< Median)	Gauthier MS, *et al.* (2014) [49]	Alcohol drinking was not adjusted
Sweden	General population	452	Cohort	Metabolic syndrome	PCB126 (pg/mL) PCB118 (pg/mL) OCDD (pg/mL)	OR = 1.73* (highest/lowest) OR = 1.36* (highest/lowest) N.S.	Lind L, *et al.* (2017) [50]	
Japan	General population	1051 men	Cross-sectional	Gout	PCDDs/PCDFs TEQ (2005) DL-PCBsTEQ (2005) Total TEQ (2005)	OR = 8.7* (> = 15.05 vs. < 6.075), *P* for trend = 0.02 OR = 3.3 (> = 10 vs. < 3.2, N.S.), *P* for trend = 0.04 OR = 6.2* (> = 25 vs. < 9.7), *P* for trend = 0.007	Nakamoto M, *et al.* (2013) [54]	
U.S.A.	NHANES (2003-2004)	1118	Cross-sectional	Hyperuricemia	3 PCDDs (sum of ranks) 2 PCDFs (sum of ranks) 8 DL-PCBs (sum of ranks)	OR = 2.5* (highest/lowest), *P* for trend = 0.01 OR = 1.9* (highest/lowest), *P* for trend = 0.11 OR = 2.4* (highest/lowest), *P* for trend = 0.04	Lee, YM *et al.* (2013) [55]	
U.S.A.	Polluted area	715 men	Cross-sectional	Hyperuricemia	PCDDs/PCDFs TEQ (2005)	OR = 3.0* (> = 17.7 vs. < 7.4)	Chang, JW, *et al.* (2013) [56]	Geometric mean = 12.4 pgTEQ/g lipid

TEQ : Toxic Equivalents, NHANES : National Health and Nutrition Examination Survey, IFG : Impaired fasting Glycaemia, OR : odds ratio, MAO : Metabolically abnormal obese, MHO : Metabolically healthy obese.
* *P* < 0.05, N.S. : not significant.

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% CI 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 (5). 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 three 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

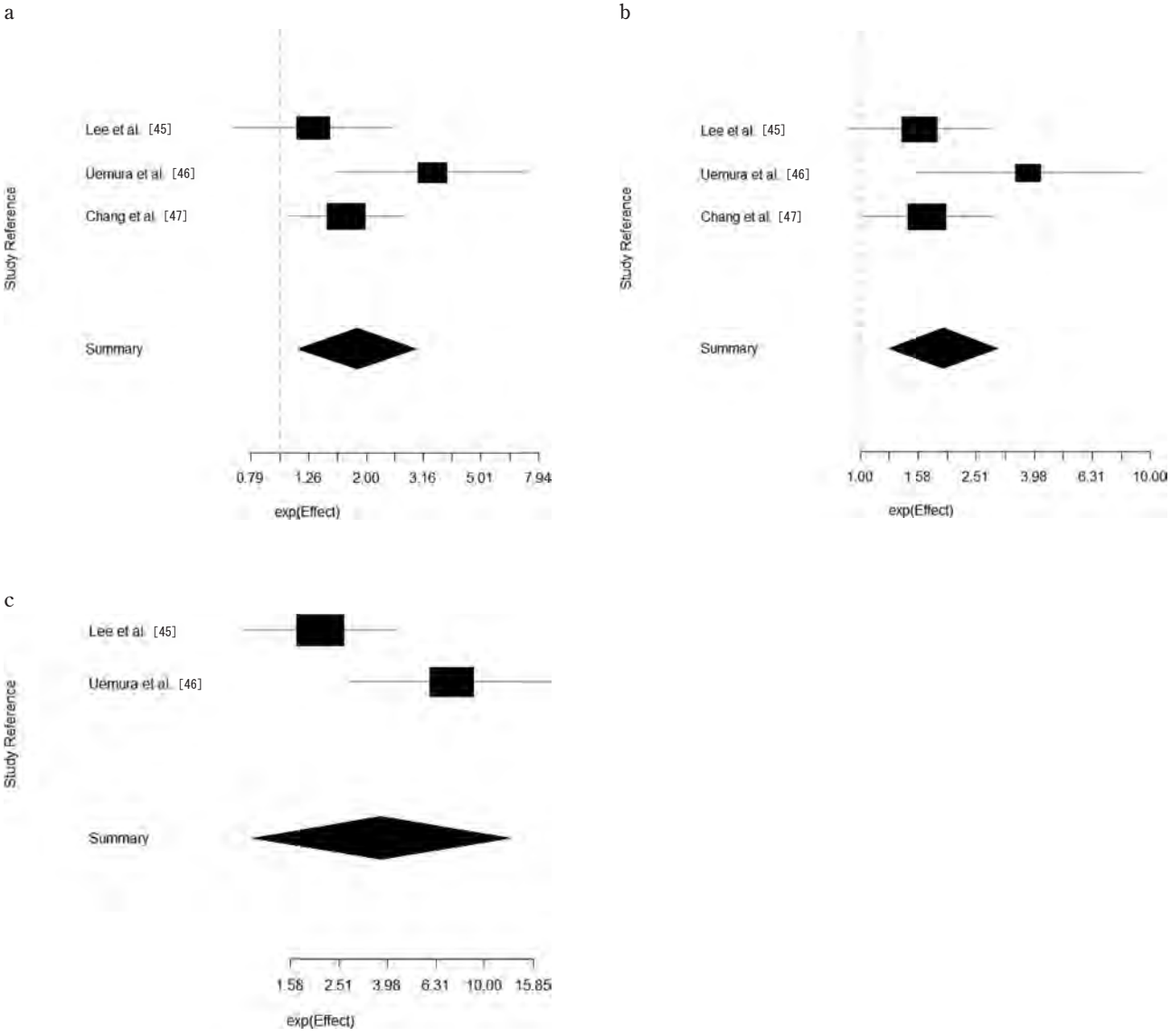

Figure 1.
Meta-analysis for the association between blood levels of PCDDs (1a), PCDFs (1b) and DL-PCBs (1c), and the prevalence of metabolic syndrome using a random effects model. Summary ORs for the highest category relative to the lowest category of PCDDs, PCDFs, and DL-PCBs were estimated at 1.9 (95% CI 1.2-3.0, *P* for heterogeneity = 0.16), 1.9 (95% CI 1.3-3.0, *P* for heterogeneity = 0.25), and 3.8 (95% CI 1.1-13, *P* for heterogeneity = 0.04), respectively. All ORs were significantly higher than 1.0.

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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