

Plasma levels of dioxins, furans, non-ortho-PCBs, and TEQs in the Seveso population 17 years after the accident

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PAROLE CHIAVE

Inquinamento ambientale; diossina; PCDD; PCDF; PCB; TEQ

SUMMARY

Background: *The Seveso accident (Italy) in 1976 caused the contamination of a large population by 2,3,7,8-tetrachlorodibenzo-para-dioxin (2,3,7,8-TCDD). The contaminated territory was divided into three zones: A (very high contamination), B (high contamination), and R (low contamination). We report here the plasma concentrations of seven polychlorinated dibenzo-para-dioxins (PCDDs), 10 polychlorinated dibenzofurans (PCDFs), four non-ortho-polychlorinated biphenyls PCBs (nPCBs), and Toxic Equivalencies (TEQs) in a sample of residents in the most polluted zones A and B and in a reference non-contaminated zone. Methods:* From December 1992 to March 1994, 62 individuals were randomly selected from the population living in zone A (No. =7) and B (No. =55). A sample of 59 subjects living in a surrounding non-contaminated area (non-ABR), frequency-matched by gender, age, and smoking history, was used as reference. All subjects were administered a questionnaire surveying demographic, lifestyle, medical history, and accident-related factors. We assayed plasma PCDD, PCDF, and nPCB concentrations by high-resolution gas chromatography/high resolution mass spectrometric (HRGC/HRMS) analysis, with results reported as pg/g of lipid, or parts per trillion (ppt). We calculated TEQs using the WHO 2005 Toxic Equivalency Factors (TEFs). **Results:** We found elevated median levels of 2,3,7,8-TCDD in plasma samples of subjects living in zone A (73.3 ppt) and zone B (12.4 ppt), compared with residents in the reference zone (5.5 ppt). In analyses adjusted for gender, age, smoking, and body mass index (BMI), none of the other congeners showed levels higher than reference in the contaminated zones. Compared with men, women showed higher levels (113%) of 2,3,7,8-TCDD and a slight elevation (17%) of TEQ for the other congeners. Age was strongly positively associated with most congener levels; TEQs for PCDDs, PCDFs, and nPCBs showed respectively 12%, 24%, and 41% increases for every 10 years of age. Current smokers had lower (from -37% to -67%) TEQ levels than subjects who

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had never smoked. BMI was negatively associated with levels of a few congeners, but with no impact on TEQ values. **Conclusions:** The Seveso accident caused a severe exposure of the population to 2,3,7,8-TCDD only. None of the other congeners analyzed showed variation across zones. Age showed a strong positive association with TEQs for all classes of compounds (PCDDs, PCDFs, and nPCBs).

RIASSUNTO

«Livelli plasmatici di diossine, furani, non-orto-PCB e TEQ nella popolazione di Seveso 17 anni dopo l'incidente». **Introduzione:** L'incidente Seveso del 1976 causò la contaminazione di una vasta popolazione dell'area con 2,3,7,8-tetraclorodibenzo-para-diossina (2,3,7,8-TCDD). Il territorio inquinato fu suddiviso in tre zone: A (contaminazione molto alta), B (alta contaminazione), R (bassa contaminazione). In questo articolo riportiamo le concentrazioni plasmatiche di 7 dibenzo-para-diossine policlorurate (PCDD), 10 dibenzofurani policlorurati (PCDF), 4 non-orto bifenili policlorurati (nPCB) ed Equivalenze Tossiche (TEQ) in un campione di residenti nelle zone più inquinate A e B e in una zona non inquinata di riferimento. **Metodi:** Fra il dicembre 1992 e il marzo 1994, 62 soggetti furono selezionati casualmente dalla popolazione residente in zona A (N. 7) e B (N. 55). Come riferimento fu usato un campione di 59 soggetti residenti in una zona circostante non inquinata (non-ABR), appaiato per genere, età e abitudini di fumo. Ai soggetti fu somministrato un questionario su caratteristiche demografiche, abitudini di vita, storia medica e fattori legati all'incidente. Tramite high-resolution gas chromatography/high resolution mass spectrometric (HRGC/HRMS) furono misurate le concentrazioni plasmatiche di PCDD, PCDF e nPCB, espresso in pg/g di lipidi, o parti per trilione (ppt). Le TEQ sono state calcolate utilizzando i fattori di equivalenza tossica (TEF) stabiliti dall'OMS nel 2005. **Risultati:** Abbiamo riscontrato elevate livelli mediani di 2,3,7,8-TCDD nei campioni plasmatici dei soggetti di zona A (73,3 ppt) e zona B (12,4 ppt), in confronto ai residenti nella zona di riferimento (5,5 ppt). In analisi aggiustate per genere, età, fumo e indice di massa corporea (BMI), per nessuno degli altri congenere le zone contaminate mostravano livelli più elevati del riferimento. In confronto agli uomini le donne mostravano livelli più elevati (113%) di 2,3,7,8-TCDD e una lieve aumento (17%) della TEQ per gli altri congenere. L'età era fortemente positivamente associata coi livelli della maggior parte dei congenere; le TEQ per PCDD, PCDF, and nPCB mostravano aumenti rispettivamente del 12%, 24% e 41% per ogni decade di età. Gli attuali fumatori avevano livelli più bassi (da -37% a -67%) di TEQ rispetto ai mai fumatori. Il BMI era negativamente associato coi livelli di pochi congenere, ma senza impatto sui valori di TEQ. **Conclusioni:** L'incidente di Seveso causò una severa esposizione della popolazione alla sola 2,3,7,8-TCDD. Nessuno degli altri congenere ha mostrato variazioni tra zone. Per l'età si è evidenziata una forte associazione positiva con le TEQ di tutte le classi di composti (PCDD, PCDF, nPCB).

INTRODUCTION

The term "dioxin(s)" indicates a group of substances which include polychlorinated dibenzo-para-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and a subgroup of polychlorinated biphenyls with dioxin-like properties (dioxin-like PCBs) (11, 26, 27). While PCBs have dielectric properties and were produced for commercial purposes, the other dioxins are unwanted by-products of combustion processes of chlorine containing components. The most toxic compound (congener) of the family is 2,3,7,8-tetrachloro-diben-

zo-para-dioxin (2,3,7,8-TCDD), which has a wide range of effects and has been classified as carcinogen to humans in 1997 (11). Recently, two other congeners (2,3,4,7,8-PeCDF and PCB 126) have been classified as carcinogens for humans (<http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf>). Many of the effects of 2,3,7,8-TCDD are modulated by the Ah receptor (AhR). Several related compounds share the capacity of binding to AhR (hence the term "dioxin-like") and may therefore have similar effects. Currently, they include seven 2,3,7,8-substituted PCDDs, ten 2,3,7,8-substituted PCDFs, four non-

ortho-PCBs (nPCBs), and eight mono-*ortho*-PCBs (mPCBs). The affinity of a specific compound with the Ah receptor determines its toxic potential, measured by the Toxic Equivalency Factor (TEF), which expresses the order of magnitude of toxicity relative to 2,3,7,8-TCDD (TEF=1). They are es-

tablished by an international committee of experts and periodically re-evaluated based on scientific evidence. The most used TEF schemes are reported in table 1 (1, 11, 30, 31). To express the global exposure to dioxin-like compounds a TEF-weighted sum of lipid-adjusted concentrations (in pg/g of

Table 1 - List of main toxic equivalency factors (TEF) in different revisions (references: 1, 11, 30, 31)

Compound	I-TEF* (NATO-CCMS)	WHO 1998	WHO 2005
Polychlorinated-dibenzo-<i>para</i>-dioxins (PCDDs)			
2,3,7,8-TCDD	1	1	1
1,2,3,7,8-PeCDD	0.5	1	1
1,2,3,4,7,8-HxCDD	0.1	0.1	0.1
1,2,3,6,7,8-HxCDD	0.1	0.1	0.1
1,2,3,7,8,9-HxCDD	0.1	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01	0.01
OCDD	0.001	0.0001	0.0003
Polychlorinated dibenzofurans (PCDFs)			
2,3,7,8-TCDF	0.1	0.1	0.1
1,2,3,7,8-PeCDF	0.05	0.05	0.03
2,3,4,7,8-PeCDF	0.5	0.5	0.3
1,2,3,4,7,8-HxCDF	0.1	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1	0.1
1,2,3,7,8,9-HxCDF	0.1	0.1	0.1
2,3,4,6,7,8-HxCDF	0.1	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01	0.01
1,2,3,4,7,8,9-HpCDF	0.01	0.01	0.01
OCDF	0.001	0.0001	0.0003
Non-<i>ortho</i>-polychlorinated biphenyls (nPCBs)			
3,3',4,4'-TCB (PCB 77)	0.0005	0.0001	0.0001
3,4,4',5'-TCB (PCB 81)	-	0.0001	0.0003
3,3',4,4',5'-PeCB (PCB 126)	0.1	0.1	0.1
3,3',4,4',5,5'-HxCB (PCB 169)	0.01	0.01	0.03
Mono-<i>ortho</i>-polychlorinated biphenyls (mPCBs)			
2,3,3',4,4'-PeCB (PCB 105)	0.0001	0.0001	0.00003
2,3,4,4',5'-PeCB (PCB 114)	0.0005	0.0005	0.00003
2,3',4,4',5'-PeCB (PCB 118)	0.0001	0.0001	0.00003
2',3,4,4',5'-PeCB (PCB 123)	0.0001	0.0001	0.00003
2,3,3',4,4',5'-HxCB (PCB 156)	0.0005	0.0005	0.00003
2,3,3',4,4',5'-HxCB (PCB 157)	0.0005	0.0005	0.00003
2,3',4,4',5,5'-HxCB (PCB 167)	0.00001	0.00001	0.00003
2,3,3',4,4',5,5'-HpCB (PCB 189)	0.0001	0.0001	0.00003
Di-<i>ortho</i>-polychlorinated biphenyls (dPCBs)			
2,2',3,3',4,4',5'-HpCB (PCB 170)	0.0001	-	-
2,2',3,4,4',5,5'-HpCB (PCB 180)	0.00001	-	-

Values in bold print indicate changes with respect to previous revision

* TEFs for PCBs from Ahlborg 1994 (1)

lipid) is calculated to obtain the Toxic Equivalency (TEQ).

The Seveso, Italy, dioxin episode caused severe 2,3,7,8-TCDD exposure to a population comprising people of both genders and all ages. The accident took place on July 10, 1976, in the trichlorophenol production department of a chemical plant located near the town of Seveso, 25 km north of Milan. A chemical cloud containing several kilograms of 2,3,7,8-TCDD was released into the environment and contaminated a vast and densely populated area (23, 27). The contaminated area was divided into three zones named A (very high contamination, with displacement of the population), B (high), and R (low) (figure 1). To investigate the long-term health effects of the accident, mortality and cancer incidence studies are on-going. The surveyed population included 4000 subjects in the contaminated zones and 180000 subjects living in the surrounding territory (termed non-ABR), used as reference (6, 24).

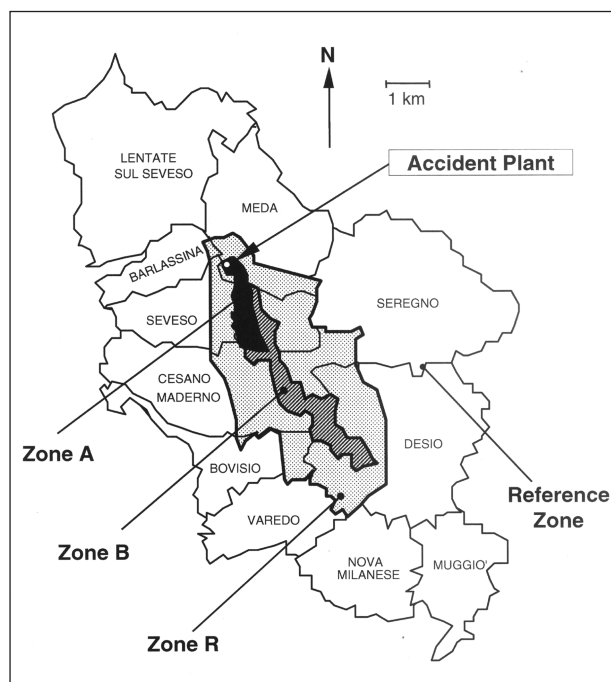


Figure 1 - The Seveso, Italy, area, including the territory of 11 towns. The map indicates the three dioxin-contaminated zones with decreasing mean soil levels (A, B, and R) and the surrounding non-contaminated zone (non-ABR) adopted as the reference

Several measurements of plasma concentrations of 2,3,7,8-TCDD were performed in the weeks or months after the accident (18) and many years later on subgroups of the involved population (14, 15), confirming a strong gradient across contamination zones. However, although it had been verified that levels of other congeners were not associated with zone of residence (14), a detailed report of the whole congener profile has never been published. In this paper we report the plasma concentrations of PCDDs, PCDFs, and nPCBs in a sample of the population living in the accident area. In addition, we calculated partial and total TEQs using the WHO 2005 scheme and investigated the relationships with zone of residence, gender, and age.

METHODS

Detailed information on methods has been previously published (14, 15). Briefly, from December 1992 to March 1994, 62 individuals were enrolled from the population living in the most polluted zones A (No. 7) and B (No. 55). A sample of 59 subjects living in a surrounding non-contaminated area (non-ABR), frequency-matched by gender, age, and smoking history, was used as reference. After signing a written informed consent, all subjects were administered a questionnaire surveying demographics, lifestyle, medical history, and accident-related factors. Blood samples were obtained and refrigerated samples were shipped to the Centers for Disease Control and Prevention (CDC), Atlanta, USA for plasma assay using a high-resolution gas chromatography/high resolution mass spectrometric (HRGC/HRMS) analysis (20). Concentrations were reported in pg/g of lipid, or parts per trillion (ppt). Levels below the detection limits (DL) were assigned a value equal to $DL/\sqrt{2}$ (3). We calculated partial TEQs for PCDDs, PCDFs, nPCBs, and total TEQ (including or not the 2,3,7,8-TCDD contribution) using the WHO 2005 TEFs (31).

Congener and TEQ plasma levels in polluted zones A and B were compared with those found in the reference non-ABR zone using the Mann-Whitney test (2). We then fitted multiple regres-

sion models containing the covariates zone of residence, gender (female versus male), age (years/10), smoking status (never, former, current), and body mass index (BMI, in kg/m²). Since congener and TEQ distributions are right-skewed, they were (natural) log-transformed. We then calculated percent changes (%) relative to the intercept with the formula $[\exp(\text{coefficient}) - 1] \times 100$.

RESULTS

Gender, age, and smoking status distributions were similar across zones as a result of matching, while subjects in zone A had a higher BMI average (table 2). In crude analyses, only the congener 2,3,7,8-TCDD showed a strong gradient across zones (table 3). Of the other compounds, OCDD and PCB 169 levels were lower in zone B compared with the reference. PCB 126 was somewhat higher in Zone A. The values of TEQs were heavily influenced by the 2,3,7,8-TCDD levels. The high PCB 126 in zone A caused a higher level of TEQ of nPCBs.

Multiple regression analyses (table 4) confirmed the strong gradient across zones for 2,3,7,8-TCDD (1068% and 130% increase in zones A and B compared with the reference, respectively) and for TEQs. Conversely, the suggestively elevated levels of PCB 126 and nPCBs in Zone A were no longer apparent after adjustment for gender and age. Only

1,2,3,4,7,8,9,-HpCDF was moderately higher (35%) in zone A, while Zone B showed slightly lower levels of OCDD and PCB 169. For some congeners women showed higher levels than men, with a 17% increased TEQ for congeners other than 2,3,7,8-TCDD. For several compounds (five PCDDs, three PCDFs, and two nPCBs) a positive association was found with age; as a result, the TEQs for PCDDs, PCDFs, and nPCBs showed respectively 12%, 24%, and 41% increases for every 10 years of age. Smoking had a negative effect on several congeners. TEQs in former smokers were similar to those in subjects who had never smoked, while current smokers had lower (from -37% to -67%) TEQ levels. BMI was negatively associated with some furans and PCB 169, and positively associated with 1,2,3,4,6,7,8-HpCDD and PCB 126, but no impact on TEQ values was found.

DISCUSSION

We confirmed that the population living in the area of the 1976 Seveso accident was heavily exposed to 2,3,7,8-TCDD only. None of the other congeners showed important variation across zones. In interpreting 2,3,7,8-TCDD levels, we note that blood samples were obtained 15-16 years after the accident (corresponding to about two half-lives of the compound). The concentrations extrapolated back to the time of the accident were

Table 2 - Characteristics of subjects in the Seveso area, by zone of residence, 1993-1995

	Zone A		Zone B		Zone non-ABR (reference)
	N (%)	p*	N (%)	p*	N (%)
Men	5 (71.4%)	0.20	27 (49.1%)	0.72	27 (45.8%)
Women	2 (28.6%)		28 (50.9%)		32 (54.2%)
Age (years) mean (SD)	55.2 (16.4)	0.14	47.5 (16.8)	0.58	46.1 (16.7)
BMI (kg/m ²) mean (SD)	28.2 (2.3)	0.005	24.5 (3.9)	0.31	23.9 (4.1)
Smoking					
Current	4 (57.1)	0.15	30 (54.5)	0.47	31 (52.5)
Former	3 (42.9)		14 (25.4)		11 (18.6)
Never smokers	0 (0.0)		11 (20.0)		17 (28.8)

Abbreviations: BMI, body mass index; N, number of subjects; SD, standard deviation

*p-value from Mann-Whitney test, compared with the reference zone

Table 3 - Plasma concentrations (pg/g lipid) of polychlorinated-dibenzo-*para*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), non-*ortho*-polychlorinated biphenyls (PCBs), and toxic equivalencies (TEQs) in the Seveso area, by residence zone, Dec 1992 - Mar 1994

	Zone A			Zone B			Zone non-ABR (reference)				
	N	Median	p25-p75	p*	N	Median	p25-p75	p*	N	Median	p25-p75
PCDDs											
2,3,7,8-TCDD	7	73.3	45.3-80.7	<0.0001	51	12.4	6.3-24.6	<0.0001	52	5.5	3.2-7.9
1,2,3,7,8-PeCDD	7	7.6	7.0-9.1	0.62	51	6.8	4.9-9.9	0.17	50	7.8	5.8-10.0
1,2,3,4,7,8-HxCDD	1	2.1	2.1-2.1	0.52	25	2.5	2.2-3.5	0.65	23	3.0	2.0-4.2
1,2,3,6,7,8-HxCDD	**										
1,2,3,7,8,9-HxCDD	7	3.9	2.6-8.3	0.83	52	4.0	2.8-6.2	0.56	50	4.1	2.9-6.8
1,2,3,4,6,7,8-HpCDD	7	60.1	44.6-89.8	0.42	52	51.4	33.6-69.6	0.81	52	49.9	36.1-80.7
OCDD	7	389	228-686	0.96	50	268	215-430	0.01	52	412	276-585
PCDFs											
2,3,7,8-TCDF	7	1.6	1.4-2.2	0.69	50	1.6	1.3-2.0	0.57	52	1.7	1.4-2.0
1,2,3,7,8-PeCDF	7	1.6	1.3-1.8	0.63	53	1.7	1.3-2.1	0.90	55	1.8	1.3-2.1
2,3,4,7,8-PeCDF	7	25.5	18.5-31.4	0.98	52	21.5	15.5-29.4	0.29	52	24.3	18.6-30.3
1,2,3,4,7,8-HxCDF	7	7.7	6.7-9.3	0.75	51	6.9	5.1-10.6	0.70	51	7.2	5.4-10.4
1,2,3,6,7,8-HxCDF	7	7.7	6.1-9.7	0.94	50	7.5	5.3-9.8	0.76	52	7.5	5.3-10.9
1,2,3,7,8,9-HxCDF	7	2.4	1.6-3.0	0.60	52	2.1	1.7-2.8	0.87	57	2.4	1.6-2.8
2,3,4,6,7,8-HxCDF	7	3.3	2.1-5.6	0.35	51	2.6	1.8-3.7	0.47	52	2.5	1.7-3.5
1,2,3,4,6,7,8-HpCDF	7	10.3	6.7-15.7	0.94	50	9.6	8.3-12.4	0.94	52	10.2	7.5-13.3
1,2,3,4,7,8,9-HpCDF	7	2.0	1.5-4.7	0.60	53	1.8	1.6-2.3	0.61	57	1.9	1.6-2.5
OCDF	5	2.4	1.9-7.8	0.03	51	9.3	4.0-12.4	0.78	52	9.8	3.0-13.0
Non-ortho PCBs											
33'44'-TCB (77)	4	97.6	69.6-317	0.48	52	78.1	63.5-94.0	0.38	53	82.0	62.2-105
344'5'-TCB (81)	6	8.9	5.9-12.4	0.59	52	7.5	5.7-9.0	0.54	53	7.8	5.7-11.7
33'44'5'-PeCB (126)	7	143	68.0-137	0.10	51	93.2	55.1-159	0.56	51	81.3	64.5-121
33'44'5'5'-HxCB (169)	6	89.0	70.5-125	0.88	51	82.0	54.6-106	0.05	51	101.0	72.8-122
TEQs											
PCDDs	7	78.0	53.7-90.2	0.0001	52	21.5	12.9-25.2	0.003	52	15.1	10.7-18.8
PCDDs/no 2378-TCDD	7	9.2	8.4-10.1	1.00	51	7.9	5.7-11.2	0.27	52	9.3	6.5-11.3
PCDFs	7	15.6	11.4-18.9	0.57	54	12.5	9.4-17.4	0.60	57	14.3	10.6-17.9
Non-ortho PCBs	7	15.0	6.8-20.8	0.08	54	9.4	5.7-15.8	0.47	57	8.9	6.5-12.4
Total	7	94.0	84.3-118	<0.0001	52	43.7	32.5-67.4	0.11	52	38.8	30.7-50.8
Total/no 2378-TCDD	7	39.0	26.7-50.8	0.47	51	31.8	20.6-43.7	0.55	52	32.3	25.9-44.0

Abbreviations: p25-p75: 25th and 75th percentiles.

p-value from Mann-Whitney test, compared with the reference zone. **Undetectable in all plasma samples.

Table 4 – Results of multiple regression models* on plasma concentrations (pg/g lipid) of polychlorinated-dibenzo-*para*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), non-*ortho*-polychlorinated biphenyls (PCBs), and toxic equivalencies (TEQs) in the Seveso area, by residence zone, Dec 1992 – Mar 1994. Indicated are the relative changes (%) and their 95% confidence intervals (95% CIs)

Congener	N	Zone A		Zone B		Women		Age (10 yrs)		Former smokers		Current smokers		BMI (kg/m ³)	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
PCDDs															
2,3,7,8-TCDD	110	1068	524, 2087	130	71, 210	113	52, 198	13	3, 24	11	-24, 63	6	-28, 58	46	-49, 316
1,2,3,7,8-PeCDD	108	-14	-43, 28	-8	-24, 11	24	0, 54	16	10, 23	-18	-36, 5	-5	-27, 3	-1	-3, 2
1,2,3,4,7,8-HxCDD	49	-26	-79, 159	-15	-39, 20	6	-28, 55	14	0, 30	11	-27, 70	23	-20, 89	-3	-8, 2
1,2,3,6,7,8-HxCDD	**														
1,2,3,7,8,9-HxCDD	109	-2	-39, 57	-1	-21, 23	16	-10, 50	8	0, 15	-32	-49, -9	-8	-32, 24	1	-2, 4
1,2,3,4,6,7,8-HpCDD	111	-10	-38, 33	-9	-24, 9	20	-2, 47	3	-3, 9	-28	-43, -9	-56	-65, -44	3	0, 5
OCDD	109	-9	-42, 42	-26	-40, -8	22	-4, 56	7	0, 15	-27	-45, -4	-41	-56, -22	0	-2, 3
PCDFs															
2,3,7,8-TCDF	109	23	-13, 76	1	-15, 19	-7	-23, 13	-4	-9, 1	2	-18, 27	6	-15, 31	-2	-4, 1
1,2,3,7,8-PeCDF	115	8	-25, 55	5	-11, 25	-14	-29, 4	-4	-9, 1	-6	-25, 17	7	-13, 33	-1	-3, 2
2,3,4,7,8-PeCDF	111	-6	-28, 22	-8	-19, 4	12	-3, 29	16	12, 21	-10	-24, 5	-23	-34, -9	-1	-3, 0
1,2,3,4,7,8-HxCDF	109	-6	-31, 29	-5	-18, 10	14	-4, 35	13	8, 18	-12	-27, 7	-25	-38, -8	0	-2, 2
1,2,3,6,7,8-HxCDF	109	-2	-30, 37	-2	-16, 14	20	0, 43	11	6, 17	-5	-23, 16	-29	-42, -12	-1	-3, 1
1,2,3,7,8,9-HxCDF	116	26	-8, 73	4	-10, 21	-2	-17, 15	0	-5, 4	2	-16, 24	4	-14, 25	-2	-4, 0
2,3,4,6,7,8-HxCDF	110	35	-13, 110	10	-11, 36	19	-7, 51	1	-5, 8	-21	-40, 4	-25	-43, -2	0	-3, 2
1,2,3,4,6,7,8-HpCDF	109	-7	-38, 40	-8	-24, 12	-12	-29, 10	-4	-10, 1	5	-19, 35	-17	-36, 8	-1	-3, 2
1,2,3,4,7,8,9-HpCDF	117	35	0, 82	0	-12, 15	-4	-18, 12	-2	-6, 2	-3	-19, 16	9	-9, 29	-2	-4, 0
OCDF	108	-43	-72, 18	-4	-28, 29	-10	-36, 25	-12	-20, -4	9	-25, 61	-3	-34, 42	0	-4, 4
Non-ortho PCBs															
33'44'-TCB (77)	109	63	-6, 183	-15	-30, 4	0	-20, 26	-5	-11, 1	5	-19, 38	7	-18, 39	-1	-4, 2
34'45'-TCB (81)	111	25	-27, 115	-11	-30, 13	0	-24, 31	-7	-14, 0	-2	-28, 35	28	-6, 74	-2	-5, 1
33'44'5'-PeCB (126)	109	10	-23, 58	4	-12, 23	18	-2, 43	17	11, 23	-20	-36, -1	-41	-53, -26	2	0, 4
33'44'55'-HxCB (169)	108	-11	-33, 19	-15	-25, -4	-15	-26, -1	21	16, 26	-12	-26, 3	-13	-26, 3	-4	-5, -2
TEQs															
PCDDs	111	398	214, 687	54	24, 91	59	24, 103	12	5, 20	-1	-25, 31	-13	-35, 16	0	-3, 3
PCDDs/no 2378-TCDD	110	-7	-44, 52	-4	-24, 21	21	-7, 58	12	4, 20	-18	-39, 11	-37	-54, -14	-2	-5, 1
PCDFs	118	6	-46, 109	8	-20, 48	13	-20, 61	24	13, 37	2	-32, 53	-36	-57, -6	0	-5, 4
Non-ortho PCBs	118	66	-62, 622	30	-34, 154	22	-43, 163	41	14, 73	-11	-63, 115	-67	-86, -21	-1	-10, 8
Total	111	149	84, 237	20	4, 38	34	14, 58	14	9, 19	-7	-22, 12	-20	-34, -4	-1	-3, 1
Total/no 2378-TCDD	110	0	-25, 33	-4	-16, 10	17	0, 36	15	10, 20	-16	-29, 1	-31	-42, -17	-1	-3, 1

Abbreviations: BMI, body mass index; 95% CI, 95% confidence interval.

*Dependent variables were log_e-transformed. Relative change (%) was calculated with the formula: [exp(coefficient)-1]×100. Models contained the following covariates: zone of residence (reference: non-ABR); gender (reference: male); age (years/10); smoking (reference: never smokers); BMI (kg/m²). Each variable is adjusted for the others. **Undetectable in all plasma samples.

about four times higher (14). These results are in agreement with findings from other surveys which documented heavy soil contamination (27) and population exposure (18).

One of the most important recognized determinants of congener and TEQ levels is age, reflecting continuous accumulation in the body not balanced by a corresponding elimination (7, 16, 19, 21, 22, 28). In our study age was strongly related with TEQs for all classes of compounds (PCDDs, PCDFs, and nPCBs). It was also positively associated with several single compounds, including those (2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and PCB 126) classified as human carcinogens by IARC.

Except for 2,3,7,8-TCDD (a 113% increase), women in our study showed a modest increase (17%) of TEQ for congeners other than 2,3,7,8-TCDD. The effect of gender is usually considered to be low. In particular, using the 1998 or 2005 TEFs, males and females in a survey of a large sample of the USA population (2001-2002) had nearly the same distribution of TEQ sub-fractions (21). Coherently, the main TEQ reference ranges for the USA population in the following survey (2003-2004) were presented for both genders combined (22).

Among current smokers we found lower levels of several congeners excluding 2,3,7,8-TCDD and of TEQs which did not include 2,3,7,8-TCDD contribution. Tobacco smoke may be a source of PCDDs (17). On the other hand, it has been shown that smoking increases PCDD/PCDF elimination (10). Our results are in agreement with other studies showing somewhat lower PCDD and/or PCDF blood levels in smokers (4, 8). A similar association has been suggested in a large representative sample of the US population (2001-2002), but only limited to certain age classes (9).

In our study BMI had little or no impact on congeners and was not associated with TEQ values. Percent body fat has been found to be associated with increasing half-life for most of the PCDD/PCDF congeners (10). The role of BMI has been investigated in several studies, but with controversial results (5, 12, 13, 25, 29, 32).

In conclusion, the population living in the Seveso area was highly exposed to 2,3,7,8-TCDD

only. This exposure pattern might be relevant to the interpretation of at least some of the discrepancies noted between this population, which exhibited an increased incidence of and mortality from cancers of the lymphatic and haematopoietic tissues (6, 24), and other, mainly occupational, cohorts exposed to a variety of dioxins and dioxin-like compounds, in which the main finding was a moderate increase in all-cancer mortality (11, 27). Age showed a strong positive association with all the classes of compounds (PCDDs, PCDFs, and nPCBs).

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED

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