2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Plasma Levels in Seveso 20 Years after the Accident

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In 1976, near Seveso, Italy, an industrial accident caused the release of large quantities of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) into the atmosphere, resulting in the highest levels of the toxicant ever recorded in humans. The contaminated area was divided into three zones (A, B, R) corresponding to decreasing TCDD levels in soil, and a cohort including all residents was enumerated. The population of the surrounding noncontaminated area (non-ABR) was chosen as referent population. Two decades after the accident, plasma TCDD levels were measured in 62 subjects randomly sampled from the highest exposed zones (A and B) and 59 subjects from non-ABR, frequency matched for age, gender, and cigarette smoking status. Subjects living in the exposed areas have persistently elevated plasma TCDD levels (range = 1.2–89.9 ppt; geometric mean = 53.2 and 11.0 ppt for Zone A and Zone B, respectively). Levels significantly decrease by distance from the accident site ($p = 0.0001$), down to general population values (4.9 ppt) in non-ABR, thus validating the original zone classification based on environmental measurements. Women have higher TCDD levels than men in the entire study area ($p = 0.0003$ in Zone B; $p = 0.007$ in non-ABR). This gender difference persists after adjustment for location within the zone, consumption of meat derived from locally raised animals, age, body mass index, and smoking. There is no evidence for a gender difference in exposure, so variation in metabolism or elimination due to body fat or hormone-related factors may explain this finding. Elevated TCDD levels in women may contribute to adverse reproductive, developmental, and cancer outcomes. *Key words*: accident, dioxin, fat, gender, hormones, TCDD. *Environ Health Perspect* 106:273–277 (1998). [Online 31 March 1998]
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The Seveso accident occurred on 10 July 1976 when a reaction vessel in a local factory went exothermically out of control and sent kilogram quantities of 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD) into the atmosphere. The cloud of material was carried southeast in a fan-shaped plume of fallout. Based on soil TCDD measurements, the contaminated area was divided in three zones (A,B,R) with progressively lower but distinct contamination. Over the next few weeks, chloracne developed in almost 200 local residents, and over the next several weeks, the entire population of Zone A (about 730 persons) was evacuated. To investigate the possibility of long-term health effects of TCDD, a cohort, including all the subjects ever living from the time of the accident onward in Zone A (currently around 800), Zone B (around 5,900), and Zone R (around 38,000), was enumerated and periodically updated. Approximately 232,000 subjects from the surrounding noncontaminated area (non-ABR) were followed to serve as a reference population for mortality and cancer incidence studies (*1*).

TCDD is important because of its broad toxicity in experimental animals and humans (*2*), which includes teratogenic (*3*), carcinogenic (*4–7*), hormonal (*8,9*), immunologic (*10*), and possibly sex ratio (*11*) effects. In addition, its persistence in the environment and long half-life in humans [estimated at 7 or more years (*12,13*), and precisely at 8.2 years in the Seveso population (*14*)], create an opportunity for chronic disease in humans and long-term environmental consequences. Seveso offers a unique opportunity to elucidate these effects because the exposure was relatively specific and substantial and occurred over a wide dose range and in a large and stable human population that includes both genders and various age groups.

A 15-year mortality study of the Seveso population showed an increase in gastrointestinal cancer (particularly in females), lymphatic and hematopoietic neoplasms, and possibly soft tissue sarcoma (*15*). A 10-year morbidity study showed similar findings (in particular an increase of hepatobiliary cancer among females) and also showed a slight decrease of breast and uterine cancer incidence (*16*). Several studies have detected a positive association of a variety of cancers in other TCDD-exposed populations (*17–23*), but other studies, generally involving low exposures, have not (*24–28*). However, most studies derive from occupationally exposed groups, which include mostly men, have potential exposure to multiple occupational toxicants, and involve chronic rather than acute exposure. In addition, most of them lack a registry to provide a framework for study. A comprehensive review of these studies can be found in the recent *IARC* (International Agency for Research on Cancer) *Monograph* on polychlorodibenzo-*para*-dioxins and polychlorinated dibenzofurans (*29*) in which TCDD is defined as carcinogenic to humans.

In this paper we present the distribution of TCDD in the Seveso area, almost two decades following the event.

Methods

Sixty-two subjects from the most TCDD-contaminated zones (A and B) and 59 from the noncontaminated area (non-ABR) were studied. Subjects were randomly sampled from the cohort and frequency matched by gender, age, and cigarette smoking status. Residence in the specific zone (A, B, or non-ABR) was established by determining address and verified by establishing actual domicile (i.e., did the subject actually live at the address corresponding to the legal address?) and presence in the specified area at the time of the accident. Subjects with severe medical illness (liver, kidney, cardiac, immune, neoplastic, or major psychiatric disease) were excluded through telephone calls assisted by a physician. Exclusion rates were low and similar across the zones (precisely, five from non-ABR and four from zone B). Informed consent was obtained from participants, and the study was reviewed and approved by the local Institutional Review

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Board. A questionnaire including data on demographics, lifestyle, foods consumed at the time of the accident, residential history, occupation, and reproductive and medical history was administered by trained interviewers. The dioxin assay was performed at the Centers for Disease Control and Prevention (CDC) using a high-resolution gas chromatography/high resolution mass spectrometric analysis performed on human plasma, as described by Patterson et al. (*30*). Specifically, we assayed for TCDD, other dioxins, dibenzofuran congeners, and coplanar polychlorinated biphenyls (PCBs), with results reported in parts per trillion (ppt), lipid adjusted. Of 121 subjects, 11 samples (4 from zone B and 7 from non-ABR) were inadequate for analysis and were excluded. Another 23 samples (9 from zone B and 14 from non-ABR) with valid but nondetectable results had levels estimated by dividing the lipid-adjusted detection limit by the square root of two (*31*). Excluding or assigning zero values for these samples did not substantially change the reported findings. Nonparametric tests (Wilcoxon rank-sum and Kruskal-Wallis) for medians, and *t*- and *F*-tests for geometric means were used in univariate comparisons and in multiple regression analyses. Geometric mean (GM) and standard deviation (SD) values are shown, unless otherwise specified.

Results

Characteristics of the study population are shown in Table 1. There were 7 subjects from Zone A (2 females, 5 males), 55 from Zone B (28 females, 27 males), and 59 from non-ABR (32 females, 27 males).

The current mean TCDD levels in individuals from Zone A, Zone B, and non-ABR were 53.2 ppt, 11.0 ppt, and 4.9 ppt, respectively ($p = 0.0001$) (Table 2). If we assume an 8.2-year half-life (*14*), the extrapolated mean levels at the time of the accident are 230.0 ppt for subjects from Zone A and 47.5 ppt for residents of Zone B (extrapolation is not relevant to the non-ABR area, which was unaffected by the accident). The absolute and extrapolated median levels show a similar difference across zones. All samples in Zone A had detectable TCDD levels; when nine samples from Zone B with nondetectable TCDD levels were excluded, the difference across the zones persisted (extrapolated mean in Zone B became 66 ppt).

Females from Zone B had significantly higher plasma TCDD levels than did males; 26 females had a mean of 17.6 ppt compared to 25 males who had a mean of 6.7 ppt ($p = 0.0003$). In non-ABR, females also exhibited higher TCDD levels than did males (means, 6.1 ppt and 3.7, respectively; $p = 0.007$) (Table 3). The highly significant elevation in females was similarly present when median levels were compared using a ranking statistic (Zone B, $p = 0.0003$; non-ABR, $p = 0.005$). The small numbers of subjects in Zone A precluded a reasonable gender comparison. Besides gender, no other variables were associated with TCDD levels in non-ABR.

Based on analysis of a separate group of Seveso subjects, a longer TCDD half-life has been suggested in females (9.0 years, $n = 15$) than men (7.1 years; $n = 12$) (L. Needham, personal communication). When we extrapolated TCDD levels back to 1976, taking into account the gender-specific half-lives, the gender difference remained significant (females, GM = 66.8 ppt; males, GM = 36.4 ppt; $p = 0.02$, Zone B).

An increase in TCDD levels was found in older subjects in Zone B (*F*-test, GM, $p = 0.03$), most evident in individuals over the age of 60 years. (Fig. 1). With fluctuations due to small numbers, females had higher levels than males in each age class except for subjects over 70 years of age.

As expected, the weight, height, and body mass index (BMI) were higher in males, while percentage body fat (PBF) was higher in females (Table 1). Within gender categories, TCDD levels were unrelated to PBF, BMI, height, or weight. Reported weight loss (Table 4) was weakly related to TCDD levels in females only [no weight loss ($n = 21$; TCDD GM = 16.3; SD = 2.1);

Table 1. Characteristics of the study population by zone and gender

Variable	Zone A	Zone B	Non-ABR	Total
Gender (*n*)				
F	2	28	32	62
M	5	27	27	59
Smoking[a] (*n*)				
F	0	6	10	16
M	3	19	18	40
Mean age (years)				
F	48.7	48.8	45.5	47.3[b]
M	57.9	46.1	46.9	
Mean weight (kg)				
F	79.0	58.7	61.0	67.9[b]
M	80.2	77.6	72.9	
Mean height (cm)				
F	161	161	163	167[b]
M	171	172	172	
Mean BMI				
F	30.5	22.7	23.1	24.4[b]
M	27.4	26.3	24.8	
Mean PBF[c]				
F	39.0	28.8	29.5	24.4[b]
M	21.3	20.0	18.0	
Mean years living in the zone				
F	0.07[d]	15.3	16.4	15.8[b]
M	13.3[d]	16.1	16.9	

Abbreviations: Non-ABR, noncontaminated area; BMI, body mass index; PBF, percentage body fat; F, female; M, male.
[a]Ever smoked cigarettes.
[b]M and F combined.
[c]Derived from BMI and normed for gender (*39*).
[d]The Zone A population was evacuated and some people never went back.

Table 2. Current and extrapolated TCDD levels (ppt) by zone

Zone	No.	TCDD levels[a] GM	GSD	Median	Range
A					
Current	7	53.2	2.2	73.3	9.8–89.9
Extrapolated		230.0	2.2	325.9	41.2–399.7
B					
Current	51	11.0	2.7	12.4	1.2–62.6
Extrapolated		47.5	2.7	52.5	5.3-273.0
Non-ABR	52	4.9 ($p = 0.0001$)[b]	1.9	5.5 ($p = 0.0001$)[c]	1.0–18.1

Abbreviations: Non-ABR, noncontaminated area; GM, geometric mean; GSD, geometric standard deviation.
[a]Half-life, 8.2 years (14).
[b]*F*-Test for mean ln(TCDD) difference among zones (current values).
[c]Kruskal-Wallis test for median difference among zones (current values).

Table 3. TCDD Levels (ppt) by zone and gender

Zone	Gender	No.	GM	GSD	Median	Range
A	F	2	60.5	1.5	63.0	45.3–80.7
	M	5	50.5 ($p = 0.81$)[a]	2.5	73.3 ($p = 0.99$)[b]	9.8–89.9
B	F	26	17.6	2.1	16.8	1.3–62.6
	M	25	6.7 ($p = 0.0003$)[a]	2.7	6.5 ($p = 0.0003$)[b]	3.5–44.7
Non-ABR	F	28	6.1	1.7	6.6	1.8–18.1
	M	24	3.7 ($p = 0.007$)[a]	2.0	4.4 ($p = 0.005$)[b]	1.0–13.8

Abbreviations: Non-ABR, noncontaminated area; F, female; M, male; GM, geometric mean; GSD, geometric standard deviation.
[a]*t*-Test for mean ln(TCDD) difference between males and females.
[b]Wilcoxon rank-sum test for median difference between males and females.

weight loss reported (n = 5; TCDD GM = 24.2; SD = 2.5; p = 0.30)]. There was no association between amount of weight loss and TCDD levels, after controlling for other covariates (e.g., distance from the accident, meat consumption, etc.). None of these factors, that is, higher BMI in men, explains away the gender difference when using a multivariate model including gender and other covariates (Table 5).

When other variables were evaluated (Table 4), only consumption of locally raised meat at the time of the accident retained an association with higher TCDD levels, both in females (no meat, n = 15, TCDD GM = 16.4 ppt, SD = 1.7; ate meat, n = 11, GM = 19.3 ppt, SD = 2.8) and in males (no meat, n = 16, GM = 4.8 ppt, SD = 2.3; ate meat, n = 9, GM = 12.1 ppt, SD = 1.0).

In a multivariate analysis of subjects in Zone B (subjects from Zone A were excluded because of small numbers), we considered several variables and interaction terms (e.g., gender and BMI, age and BMI). None of these interactions significantly contributed to TCDD variance. The final model, based on factors plausible in our study or reported in other TCDD-exposed groups, included gender, distance from the source within the zone (also taking into account the course of the toxic cloud immediately after the accident), consumption of locally produced meat, age, cigarette smoking, and BMI (as an estimate of PBF). Only the first three variables were significantly associated with measured TCDD levels (Table 5). In a similar model, which also included the gender-specific half-lives, the gender difference remained statistically significant (p<0.01).

Among women in Zone B, oral contraceptive users (n = 13; TCDD GM = 13.2 ppt; SD = 2.4) had lower levels than nonusers (n = 13; GM = 23.4; SD = 1.7; p = 0.05). In a multivariate model that also included distance from the accident site, age, BMI, and meat consumption, oral contraceptive use was significantly inversely associated with TCDD levels (p = 0.04). Adding parity to the model did not substantially change the result. When added to the model, advanced age at menarche exhibited a borderline association with higher TCDD levels (p =0.07). This difference was unrelated to whether women experienced menarche before or after the accident. Other reproductive factors, e.g., age at menopause, were not associated. Parity was not significantly associated with TCDD levels, although the tendency was in accord with expectations (parous, n = 20, GM = 16.7 ppt, SD = 2.3 vs. nulliparous, n = 6, GM = 20.8 ppt, SD = 1.8).

We also measured current levels of some PCBs, polychlorinated dibenzodioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) in the entire study area. None of them varied across the zones, but most of them (PCB126; 1,2,3,7,8-pentaPCDD; 1,2,3,7,8,9-hectaCDD; 1,2,3,4,6,7,8-heptaCDD; octaCDD; 2,3,4,7,8-pentaCDF; 1,2,3,4,7,8-hectaCDF; 1,2,3,6,7,8-hectaCDF; 2,3,4,6,7,8-hectaCDF) had significantly higher levels in women and exhibited an age effect stronger than for TCDD (data not shown).

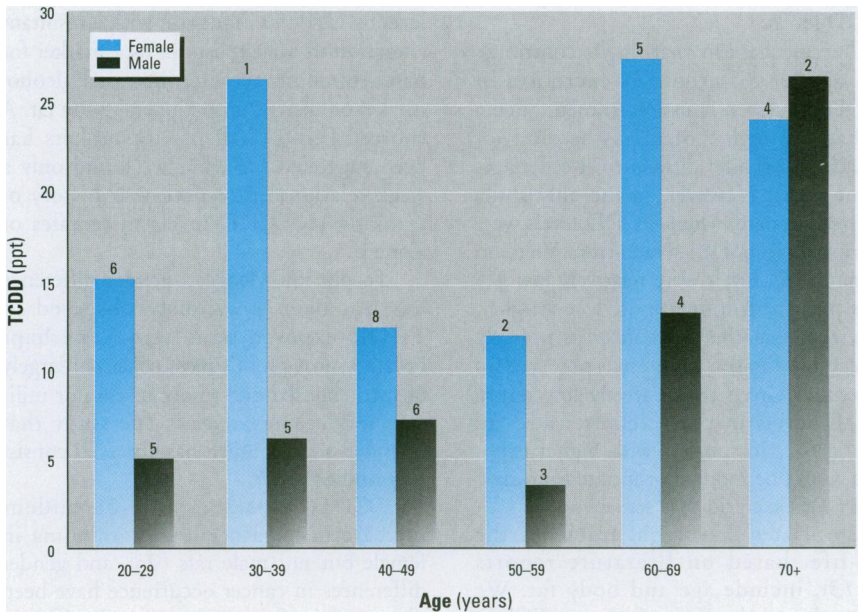

Figure 1. Median TCDD levels (ppt) by gender and age in Zone B.
The numbers over each column indicate the number of subjects in each age and gender category.

Discussion

This is the first study to confirm that elevated TCDD levels persist in people from the exposed areas almost 20 years after the accident. Furthermore, mean TCDD levels correspond to zone categorization based on soil TCDD measurements determined in 1976 (*1*). Typical population values are present in the surrounding non-ABR area. Exceptionally high levels of TCDD have been previously measured in serum specimens drawn in 1976 from people who were living in Seveso, particularly those with chloracne (*32, 33*). These studies were

Table 4. TCDD levels (ppt) by zone, gender, and selected variables[a]

	Females		Males	
Variables	No.	GM	No.	GM
Pack-years[b]				
Zone B				
0	21	16.9	7	5.9
0.1–9	4	19.9	8	11.2
9.1 +	1	23.0	10	4.9
Non-ABR				
0	19	6.2	8	4.4
0.1–9	6	6.4	7	2.8
9.1 +	3	4.8	9	4.1
Alcohol				
Zone B				
No	18	18.3	5	5.4
Yes	8	15.9	20	7.1
Non-ABR				
No	19	5.8	8	4.1
Yes	9	6.6	16	3.6
Coffee[c]				
Zone B				
0–2	13	15.3	12	5.8
3+	13	20.2	13	7.7
Non-ABR				
0–2	17	7.0	14	4.2
3+	11	4.9	10	3.2
Weight loss				
Zone B				
No	21	16.3	21	7.2
Yes	5	24.2	4	4.7
Non-ABR				
No	23	6.3	19	3.6
Yes	5	5.2	5	4.3
Employed in 1976[d]				
No	20	17.8	12	6.7
Yes	6	19.6	13	11.6
Knowledge of accident[d]				
No	15	19.6	18	5.6
Yes	10	15.2	6	11.3
Consumed locally grown vegetables[d]				
No	6	14.8	11	7.3
Yes	17	18.4	14	6.3
Consumed locally raised animals[d]				
No	15	16.4	16	4.8
Yes	11	19.3	9	12.1

Abbreviations: GM, geometric mean; Non-ABR, noncontaminated area.

[a]Subjects responding "don't know" or "don't remember" were not included when totals fell short of 26 females and 25 males in Zone B and 28 females and 24 males in non-ABR.

[b]Packs of cigarettes per year.

[c]Only two subjects drank no coffee.

[d]Zone B only.

Table 5. Multivariate model[a] considering the relationship of measured TCDD dose[b] (ppt) to predictor variables in Zone B

Independent variables	Specification	No.	*F*-value	GM	*p*-Value
Gender	F	25	16.30	26.70	0.0002
	M	24		8.40	
Distance[c]	1	7	4.59	25.80	0.02
	2	27		10.10	
	3	15		12.80	
Consumed locally raised animals	No	30	3.91	12.00	0.05
	Yes	19		18.50	
BMI	Continuous	49	3.24	1.06[d]	0.08
Smoking[e] (pack-years)	0	27	2.72	12.50	0.08
	0.1–9	12		22.20	
	9+	10		11.90	
Age	Continuous	49	3.11	1.01[d]	0.09

Abbreviations: GM, geometric mean; F, female; M, male; BMI, body mass index.

[a]Each variable was adjusted for the others in the model. Of the 51 subjects of Zone B, 49 are included in the model because information on distance from the accident site within the zone was missing for 2 subjects.

[b]Dependent variable is measured ln(TCDD).

[c]Zone B was divided into three areas according to the distance from the accident site and direction of the toxic cloud; 1 is the closest to the accident.

[d]Values shown are β.

[e]Current/ever/never smoking and smoking in 1976 (the time of the accident) were not associated with TCDD in other models.

focused on the potentially most highly exposed residents. On the contrary, we selected subjects randomly in order to have a more representative sample of the general population of the area. In this study group, subjects with severe medical illness and previous chloracne were excluded.

We observed higher TCDD levels in women in both univariate analysis and after adjustment for other variables potentially associated with TCDD. We consider exposure to be an unlikely source for the gender effect. First, presence in the area at the time of the accident, number of years spent in the zone, occupation, and distance from the accident site within the zone, did not explain the gender difference. Second, if the difference was solely due to some factor that favored women being exposed to TCDD during the accident, the effect should not be present in the non-ABR area, which was unaffected by the accident. We observed a significant gender difference in the unexposed area, suggesting that the effect does not specifically depend upon the Seveso accident. We also found higher levels of most dioxins, furans, and PCBs in women of the entire area, suggesting that the gender effect may be relevant for a wider array of related compounds and exposure settings. Finally, studies performed on a separate group of exposed individuals showed no hint of a gender difference at the time of the accident (*33*).

A gender difference in TCDD metabolism has been shown in rats (*34*), but the mechanism underlining this difference is not clear.

There is evidence that TCDD influences both male (*8*) and female (*9*) hormones, but we are unaware of a hormonal mechanism that can explain TCDD gender differences. Evaluation of hormone-related differences in TCDD metabolism is very difficult because of the slow rate of metabolism. Oral contraceptive use was associated with lower TCDD levels. Oral contraceptive use is known to reduce activity of CYP1A2 (*35*), an enzyme that is involved in estrogen metabolism (*36*) and is also induced by TCDD. Neither of these established effects of CYP1A2 provides a clear mechanistic rationale for the oral contraceptive/TCDD relationship.

Lactation is one of the few known means of eliminating the highly lipophilic dioxin from the body (*37*). Using parity as a surrogate of lactation (the great majority of women in the local region nurse their children), we only observed a weak negative association of childbearing with TCDD levels.

One mechanism that might contribute to a gender difference is excretion of TCDD via semen emission in men. Such a mechanism might potentially account for the lack of a gender difference at older ages in our study. However, in the only study reported, to date, where TCDD levels were determined in pooled semen from Vietnam veterans (*38*), levels were relatively low [<5 parts per quadrillion (ppq), wet-weight], suggesting that this mechanism is unlikely to account for the difference observed in this study. Given the relatively low serum TCDD levels in the veterans study, an investigation in subjects with higher exposures would be more appropriate for assessing TCDD excretion via semen.

Covariates that might influence the half-life, based on literature reports (*12,13*), include age and body fat. We observed a weak effect of age on TCDD levels, possibly due to declining steroid hormones, TCDD excretion via semen, or changes in body fat distribution or amount. The reduction in the age effect between the univariate ($p = 0.03$) and multivariate ($p = 0.08$) models suggests that other factors are likely to contribute to the association of age with TCDD. Body fat is a plausible determinant of the gender effect because higher TCDD levels in women might be due to enhanced retention of the lipid-soluble compound due to a greater proportion of body weight as fat in women. Women had higher PBF than men; however, within each gender, PBF was unrelated to TCDD levels. It was not possible to include PBF and gender in the same multivariate model because PBF is gender normed (*39*). Including BMI alone in the model does not influence the gender effect. Ott and Zober (*40*) observed a relationship of PBF to half-life, with estimates of 5.1 years in those with 20% body fat and 8.9 years for 30% body fat. The failure to observe a strong relationship between PBF and TCDD levels in our study may derive from the fact that in contrast to Ott, we considered body fat at the time of the study (i.e., 1993–1995) rather than at the time of the original exposure (1976), even though we controlled for weight loss.

Diet is likely to be a major route for dioxin exposure in the general population (*41*). Authorities prohibited consumption of animals and vegetables from the contaminated area shortly after the accident, but some residents may have been unaware of or ignored these restrictions. In fact, we found an association with meat consumption, but it did not account for the gender difference.

Smoking might influence the TCDD level by CYP450 induction with a resultant alteration in metabolism or as a marker for hand-to-mouth activity, increased alcohol intake, or changes in peripheral body fat. A shorter TCDD half-life in smokers has been suggested (*13*), but we found only a weak relationship of pack-year history of smoking to TCDD levels in females of Zone B.

To our knowledge, a gender difference has not been previously observed in TCDD-exposed populations, perhaps because most groups have consisted largely of men exposed due to occupation or military service, but at least one study that included a few women has observed consistent findings (*42*).

TCDD causes a dose-dependent increase in hepatocellular carcinoma in female but not male rats (*43*), and gender differences in cancer occurrence have been observed in Seveso (e.g., a significant increase in hepatobiliary cancer in women in Zone B) (*16*).

The observed gender difference in TCDD levels must be considered not only in light of possible adverse effects in women but also for developmental effects in the offspring (*44*) exposed *in utero* as well as via breast feeding. Given the myriad biological effects of this environmental contaminant, further research is needed to determine whether a gender effect is present in other groups exposed to TCDD or related xenobiotics and to better understand its basis.

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