*Journal of Exposure Analysis and Environmental Epidemiology* (2002) 12, 409–417


www.nature.com/jea

# Characterization of dioxin exposure in residents of Chapaevsk, Russia

ARSLAN AKHMEDKHANOV,[a] BORIS REVICH,[b] JENNIFER J. ADIBI,[c] VLADIMIR ZEILERT,[d] SCOTT A. MASTEN,[e] DONALD G. PATTERSON, JR.,[f] LARRY L. NEEDHAM[f] AND PAOLO TONIOLO[a]

[a]*New York University School of Medicine, 550 First Avenue, NBV-9E2, New York, New York 10016, USA*
[b]*Center for Demography and Human Ecology of Institute for Forecasting, Russian Academy of Sciences, Nakhimov's Prospect 47, Moscow 117418, Russia*
[c]*Columbia University School of Public Health, 60 Haven Avenue, B-1, New York, New York 10032, USA*
[d]*Chapaevsk Central City Hospital, Meditsinskaya ul. 4, Chapaevsk, Samara Oblast 446100, Russia*
[e]*Environmental Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA*
[f]*National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA*

Since 1967, a chemical plant in the town of Chapaevsk (Samara province, Russia) has produced large amounts of chlorinated compounds and is suspected to be a major source of local environmental dioxin contamination. Dioxins have been detected in the local air, soil, drinking water, vegetables, and cow's milk. Human exposure to dioxins is suspected as a factor in the deteriorating local public health. In an effort to characterize nonoccupational dioxin exposure among local residents, during the summer of 1998, 24 volunteers were recruited to donate blood and to provide information about their residence, employment, demographics, medical history, and dietary habits. Selected polychlorinated dibenzodioxins, dibenzofurans, and coplanar biphenyls were measured in blood serum samples. The mean concentration of total dioxin World Health Organization toxic equivalents (WHO-$TEQ_{98}$) based on polychlorinated dibenzo-*para*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and coplanar polychlorinated biphenyls (PCBs) was 61.2 (range 16.4–168.1) pg/g lipid. Subjects living in close proximity to the plant (less than 5 km) had significantly higher dioxin levels (mean WHO-$TEQ_{98}$, 75.7 pg/g lipid), as compared to subjects living more than 5 km from the plant (mean WHO-$TEQ_{98}$, 44.1 pg/g lipid) ($P<0.04$). Comparisons of the study results with available published data indicate that average blood dioxin levels were substantially higher in Chapaevsk residents than in nonoccupationally exposed populations of other parts of Russia, Europe, and North America. Chronic exposures of such magnitude may have appreciable adverse effects on public health.
*Journal of Exposure Analysis and Environmental Epidemiology* (2002) **12,** 409–417 doi:10.1038/sj.jea.7500243

**Keywords:** *blood level, dibenzofuran, dioxin, nonoccupational exposure, PCB, Russia.*

## Introduction

Exposure to dioxins, which include polychlorinated dibenzo-*para*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and coplanar polychlorinated biphenyls (PCBs), has been associated with adverse health outcomes in humans, including increased cancer incidence and mortality (IARC, 1997; Kogevinas, 2001), as well as effects on cardiovascular system (Bertazzi et al., 1989, 2001), reproductive system (Egeland et al., 1994; Mocarelli et al., 1996, 2000), thyroid function (Pluim et al., 1993; Koopman-Esseboom et al., 1994), neurological development (Huisman et al., 1995; Koopman-Esseboom et al., 1996; Patandin et al., 1999), and immune status (Weisglas-Kuperus et al., 1995, 2000).

1. Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CDC, Centers for Disease Control and Prevention; IARC, International Agency for Research on Cancer; NTP, National Toxicology Program; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*para*-dioxin; PCDF, polychlorinated dibenzofuran; ppt, parts per trillion; SD, standard deviation; TEF, toxic equivalency factor; TEQ, toxic equivalent; WHO, World Health Organization; 2,3,7,8-TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; 1,2,3,7,8-PeCDD, 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin; 1,2,3,4,7,8-HxCDD, 1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin; 1,2,3,6,7,8-HxCDD, 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin; 1,2,3,7,8,9-HxCDD, 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin; 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; 1,2,3,4,6,7,9-HpCDD, 1,2,3,4,6,7,9-heptachlorodibenzo-*p*-dioxin; OCDD, octachloro dibenzo-*p*-dioxin; 2,3,7,8-TCDF, 2,3,7,8-tetrachlorodibenzofuran; 1,2,3,7,8-PeCDF, 1,2,3,7,8-pentachlorodibenzofuran; 2,3,4,7,8-PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; 1,2,3,4,7,8-HxCDF, 1,2,3,4,7,8-hexachlorodibenzofuran; 1,2,3,6,7,8-HxCDF, 1,2,3,6,7,8-hexachlorodibenzofuran; 1,2,3,7,8,9-HxCDF, 1,2,3,7,8,9-hexachlorodibenzofuran; 2,3,4,6,7,8-HxCDF, 2,3,4,6,7,8-hexachlorodibenzofuran; 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,6,7,8-heptachlorodibenzofuran; 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8,9-heptachlorodibenzofuran; OCDF, octachlorodibenzofuran; 3,3′,4,4′-TCB 77, 3,3′,4,4′-tetrachlorinated biphenyl (PCB-77); 3,4,4′,5-TCB 81, 3,4,4′,5-tetrachlorinated biphenyl (PCB-81); 3,3′,4,4′,5-PCB 126, 3,3′,4,4′,5-pentachlorinated biphenyl (PCB-126); 3,3′,4,4′,5,5′-HCB 169, 3,3′,4,4′,5,5′-hexachlorinated biphenyl (PCB-169)

2. Address all correspondence to: Dr. Arslan Akhmedkhanov, Department of Obstetrics and Gynecology, New York University School of Medicine, 550 First Avenue, NBV-9E2, New York, NY 10016, USA. Tel.: +1-212-263-7763. Fax: +1-212-263-8887. E-mail: akhmea01@med.nyu.edu
Received 4 July 2002.

Dioxins are unwanted byproducts produced during the synthesis of certain chlorinated compounds, and as a result of combustion of organic compounds in the presence of chlorine. Beginning in the 1930s, a large network of chemical (Khimprom) factories was created in Russia. One such factory, the Middle Volga chemical plant, was built in the town of Chapaevsk, Samara province. Chapaevsk, with a population of 83,000, is located 43 km southwest of Samara, on the bank of Chapaevka River, a tributary to the Volga. The town occupies 187 $km^2$, 51% of which belongs to industrial plants that account for 86% of the Chapaevsk economy and employ approximately half of the town's population (Revich et al., 1996).

Prior to 1949, the Chapaevsk plant produced chemical weapons: mustard gas and lewisite. From 1967 to 1987, it produced gamma-hexachlorocyclohexane (lindane) and its derivatives. Currently, it produces crop protection chemicals, liquid chlorine, dichloropropionic acid, methyl chloroform, vinyl chloride, pentachlorophenol, and other chlorinated chemicals (Revich et al., 1996). The total emissions of chlorine-containing compounds by the plant in 1992 were estimated at 120 metric tons/year (Revich et al., 1996). This is a cause of concern because dioxin congeners are extremely stable, both to environmental and biological degradation, leading to their persistence in the environment and accumulation in the food chain. Due to the proximity of the plant to the residential areas of Chapaevsk, dioxin contamination was detected in the town's air (0.116 pg/$m^3$), soil (8.9–298 ng/kg), drinking water (28.4–74.1 pg/l), local vegetables (0.005–0.78 pg/kg), and cow's milk (17.3–61 pg/g fat) (Revich et al., 1996, 1999, 2001). A recent assessment of the town's vital statistics data revealed that Chapaevsk residents experience substantially higher rates of cancer, cardiovascular diseases, spontaneous abortions, preterm deliveries, and congenital malformations, as compared to the average rates for Samara province and Russia (Revich et al., 2001).

These observations suggest that the unfavorable public health situation in Chapaevsk may be related to excessive exposures to dioxin and dioxin-like compounds. The objectives of the present study were: (1) to characterize dioxin exposure in the general population of Chapaevsk residents by measuring the levels of specific dioxin congeners and total dioxin in blood serum; and (2) to compare Chapaevsk data with previously reported dioxin exposure data from other regions of Russia and the rest of the world.

## Methods

### *Study Population*

Participants in the study included a convenience sample of 24 self-selected volunteers (12 women, 12 men) identified from among the residents of Chapaevsk who had never been employed at the Middle Volga chemical plant. Most of the study participants were employees of the local hospital and outpatient facilities. At the time of recruitment during the summer of 1998, the study participants were asked to complete a self-administered questionnaire about their residence, employment, demographics, medical history, current weight and height, and dietary habits.

### *Blood Collection and Dioxin Analyses*

At the time of recruitment, blood samples of nonfasting study participants were collected by local medical staff. Whole blood and serum samples were maintained at $-20^{\circ}C$ or below until analyses. The samples were shipped in dry ice to the US National Center for Environmental Health, Centers for Disease Control and Prevention (CDC; Atlanta, GA) for dioxin analyses. Dioxin and related compounds were measured in the serum samples by high-resolution gas chromatography/high-resolution mass spectrometry using the isotope dilution technique for quantification (Patterson et al., 1987). The laboratory method involves spiking the serum with $^{13}C_{12}$-labeled internal standards and the analytes of interest are isolated using a $C_{18}$ solid phase extraction procedure followed by a multicolumn automated cleanup and enrichment procedure (Turner et al., 1997). The analytes were separated by high-resolution gas chromatography and quantified by isotope dilution high-resolution mass spectrometry using selected ion monitoring at 10,000 resolving power. The concentration of each analyte was calculated using standard linear calibration curves developed for each congener. The results were reported on a lipid-adjusted basis in picograms per gram of lipid (ppt). Serum total lipids were calculated using an enzymatic "summation" method (Akins et al., 1989). The measured analytes included 8 polychlorinated dibenzo-*p*-dioxin congeners (2,3,7,8-TCDD; 1,2,3,7,8-PeCDD; 1,2,3,4,7,8-HxCDD; 1,2,3,6,7,8-HxCDD; 1,2,3,7,8,9-HxCDD; 1,2,3,4,6,7,8-HpCDD; 1,2,3,4,6,7,9-HpCDD; OCDD), 10 PCDFs (2,3,7,8-TCDF; 1,2,3,7,8-PeCDF; 2,3,4,7,8-PeCDF; 1,2,3,4,7,8-HxCDF; 1,2,3,6,7,8-HxCDF; 1,2,3,7,8,9-HxCDF; 2,3,4,6,7,8-HxCDF; 1,2,3,4,6,7,8-HpCDF; 1,2,3,4,7,8,9-HpCDF; OCDF), and 4 dioxin-like coplanar PCBs (3,3′,4,4′-TCB 77; 3,4,4′,5-TCB 81; 3,3′,4,4′,5-PCB 126; 3,3′,4,4′,5,5′-HCB 169). Measured congener levels have been converted to dioxin toxic equivalents (TEQs) using the 1998 World Health Organization (WHO) toxic equivalency factors ($TEF_{98}$) (Van den Berg et al., 1998).

### *Statistical Analyses*

Descriptive statistics (means, ranges, standard deviations, distributions) were calculated for separate groups of dioxin congeners (dibenzodioxins, dibenzofurans, coplanar PCBs), as well as for total dioxin levels. Analysis of variance (ANOVA) and *t*-tests were used to examine the dioxin

**Table 1.** Descriptive characteristics of the study participants in Chapaevsk, Russia, 1998.

| Characteristic | Females *N* (%) | Males *N* (%) | All subjects *N* (%) |
|---|---|---|---|
| *Age (years)* | | | |
| 20–29 | 3 (25.0%) | 3 (25.0%) | 6 (25.0%) |
| 30–39 | 2 (16.7%) | 3 (25.0%) | 5 (20.8%) |
| 40–49 | 3 (25.0%) | 1 (8.3%) | 4 (16.7%) |
| 50–59 | 1 (8.3%) | 2 (16.7%) | 3 (12.5%) |
| ≥60 | 3 (25.0%) | 3 (25.0%) | 6 (25.0%) |
| *BMI ($kg/m^2$)* | | | |
| <25.0 | 4 (33.3%) | 8 (66.7%) | 12 (50.0%) |
| ≥25.0 | 8 (66.7%) | 4 (33.3%) | 12 (50.0%) |
| *Education* | | | |
| Primary school only | 2 (16.7%) | 2 (16.7%) | 4 (16.7%) |
| At least high school | 10 (83.3%) | 10 (83.3%) | 20 (83.3%) |
| *Current smoking*[a] | | | |
| No | 11 (91.7%) | 5 (41.7%) | 16 (66.7%) |
| Yes | 0 (0%) | 7 (58.3%) | 7 (29.2%) |
| *Smoking (cigarettes/day)*[a] | | | |
| 0 | 11 (91.7%) | 5 (41.7%) | 16 (66.7%) |
| 1–9 | 0 (0%) | 4 (33.3%) | 4 (16.7%) |
| ≥10 | 0 (0%) | 3 (25.0%) | 3 (12.5%) |
| *Duration of smoking (years)* | | | |
| <3 | 0 (0%) | 2 (16.7%) | 2 (8.3%) |
| 3–20 | 0 (0%) | 2 (16.7%) | 2 (8.3%) |
| >20 | 0 (0%) | 3 (25.0%) | 3 (12.5%) |
| *Alcohol consumption* | | | |
| Never/rarely | 8 (66.7%) | 5 (41.7%) | 13 (54.2%) |
| Regular[b] | 4 (33.3%) | 7 (58.3%) | 11 (45.8%) |
| *Residence (distance from the plant; km)* | | | |
| <5 | 6 (50.0%) | 7 (58.3%) | 13 (54.2%) |
| ≥5 | 6 (50.0%) | 5 (41.7%) | 11 (45.8%) |

[a]Missing data for one subject.
[b]At least 2–4 times/month.

levels in different exposure groups stratified by gender, age, body mass index (BMI), education, smoking, alcohol use, and residence. To test for differences between various exposure groups, dioxin values were natural log-transformed in order to reduce departures from the normal distribution. All presented *P* values are two-tailed, and *P* values less than 0.05 were considered statistically significant.

## Results

The descriptive characteristics of the study subjects are presented in Table 1. There were no significant differences in educational status or age between male (mean 44 years) and female (mean 45 years) participants. The mean BMI [=weight (kg)/height ($m^2$)] was significantly higher among women (29.5 $kg/m^2$), as compared to men (24.6 $kg/m^2$) ($P$=0.01). On the other hand, men were more likely to report current smoking and alcohol consumption (Table 1).

Table 2 presents the mean concentrations of specific dioxin congeners and the mean WHO-$TEQ_{98}$ of total dioxins in the blood of study subjects stratified by gender. Total WHO-$TEQ_{98}$ levels were higher among women (mean 65.4, range 16.4–132.0 pg/g lipid), as compared to men (mean 57.0, range 17.9–168.1 pg/g lipid), but the overall difference was not statistically significant ($P$>0.05). Among all study subjects, the mean WHO-$TEQ_{98}$ of total dioxins was 61.2 pg/g lipid (range 16.4–168.1 pg/g lipid). The predominant dibenzodioxin congeners in the blood of Chapaevsk residents were OCDD; 1,2,3,6,7,8-HxCDD;

**Table 2.** Mean concentrations and mean WHO-$TEQ_{98}$ levels of measured dibenzodioxin, dibenzofuran, and PCB congeners in blood of residents of Chapaevsk, Russia, 1998.

| Congener | WHO $TEF_{98}$ | Females ($N$=12) | | Males ($N$=12) | | All subjects ($N$=24) | |
|---|---|---|---|---|---|---|---|
| | | Concentration mean (range), pg/g lipid | WHO-$TEQ_{98}$ mean (SD), pg TEQ/g lipid | Concentration mean (range), pg/g lipid | WHO-$TEQ_{98}$ mean (SD), pg TEQ/g lipid | Concentration mean (range), pg/g lipid | WHO-$TEQ_{98}$ Mean (SD), pg TEQ/g lipid |
| *PCDDs* | | | | | | | |
| 2,3,7,8-TCDD | 1 | 9.5 (1.7–31.2) | 9.5 (8.4) | 7.1 (2.3–16.1) | 7.1 (4.4) | 8.3 (1.7–31.2) | 8.3 (6.7) |
| 1,2,3,7,8-PeCDD | 1 | 17.8 (3.9–44.4) | 17.8 (13.3) | 14.3 (4.2–47.4) | 14.3 (12.1) | 16.1 (3.9–47.4) | 16.1 (12.5) |
| 1,2,3,4,7,8-HxCDD | 0.1 | 13.5 (1.9–30.7) | 1.4 (0.9) | 10.7 (1.9–40.9) | 1.1 (1.1) | 12.1 (1.9–40.9) | 1.2 (1.0) |
| 1,2,3,6,7,8-HxCDD | 0.1 | 53.2 (9.5–114.0) | 5.3 (3.4) | 50.1 (11.1–196) | 5.0 (5.2) | 51.6 (9.5–196) | 5.2 (4.3) |
| 1,2,3,7,8,9-HxCDD | 0.1 | 9.4 (2.0–21.3) | 0.9 (0.6) | 6.3 (1.4–23.9) | 0.6 (0.6) | 7.9 (1.4–23.9) | 0.8 (0.6) |
| 1,2,3,4,6,7,8-HpCDD | 0.01 | 38.9 (0.0–83.4) | 0.4 (0.3) | 24.5 (0.0–81.4) | 0.2 (0.3) | 31.7 (0.0–83.4) | 0.3 (0.3) |
| 1,2,3,4,6,7,9-HpCDD | 0.0 | 0.0 (0.0–0.0) | 0.0 (0.0) | 0.0 (0.0–0.0) | 0.0 (0.0) | 0.0 (0.0–0.0) | 0.0 (0.0) |
| OCDD | 0.0001 | 241.7 (98.9–519) | 0.02 (0.01) | 258.7 (79.4–428) | 0.03 (0.01) | 250.2 (79.4–519) | 0.03 (0.01) |
| *PCDFs* | | | | | | | |
| 2,3,7,8-TCDF | 0.1 | 1.9 (0.0–4.6) | 0.2 (0.1) | 0.7 (0.0–1.8) | 0.1 (0.1) | 1.3 (0.0–4.6) | 0.1 (0.1) |
| 1,2,3,7,8-PeCDF | 0.05 | 2.0 (0.0–4.9) | 0.1 (0.1) | 0.9 (0.0–2.0) | 0.1 (0.04) | 1.4 (0.0–4.9) | 0.1 (0.1) |
| 2,3,4,7,8-PeCDF | 0.5 | 19.8 (6.0–33.0) | 9.9 (4.5) | 25.9 (6.3–96.2) | 12.9 (13.1) | 22.8 (6.0–96.2) | 11.4 (9.7) |
| 1,2,3,4,7,8-HxCDF | 0.1 | 24.6 (6.1–52.9) | 2.5 (1.4) | 22.3 (4.5–70.7) | 2.2 (2.0) | 23.5 (4.5–70.7) | 2.4 (1.7) |
| 1,2,3,6,7,8-HxCDF | 0.1 | 10.3 (3.0–19.7) | 1.0 (0.5) | 10.6 (2.6–30.9) | 1.1 (0.8) | 10.5 (2.6–30.9) | 1.0 (0.7) |
| 1,2,3,7,8,9-HxCDF | 0.1 | 0.0 (0.0–0.0) | 0.0 (0.0) | 0.0 (0.0–0.0) | 0.0 (0.0) | 0.0 (0.0–0.0) | 0.0 (0.0) |
| 2,3,4,6,7,8-HxCDF | 0.1 | 1.9 (0.0–4.2) | 0.2 (0.1) | 1.7 (0.0–4.5) | 0.2 (0.1) | 1.8 (0.0–4.5) | 0.2 (0.1) |
| 1,2,3,4,6,7,8-HpCDF | 0.01 | 5.9 (0.0–37.5) | 0.1 (0.1) | 4.9 (0.0–17.9) | 0.1 (0.1) | 5.4 (0.0–37.5) | 0.1 (0.1) |
| 1,2,3,4,7,8,9-HpCDF | 0.01 | 0.8 (0.0–2.9) | 0.01 (0.01) | 0.8 (0.0–2.7) | 0.01 (0.01) | 0.8 (0.0–2.9) | 0.01 (0.01) |
| OCDF | 0.0001 | 39.8 (5.7–180) | 0.004 (0.01) | 65.1 (19.3–150) | 0.01 (0.01) | 52.5 (5.7–180) | 0.01 (0.01) |
| *Coplanar PCBs* | | | | | | | |
| 3,3′,4,4′-TCB 77 | 0.0001 | 0.0 (0.0–0.0) | 0.0 (0.0) | 0.0 (0.0–0.0) | 0.0 (0.0) | 0.0 (0.0–0.0) | 0.0 (0.0) |
| 3,4,4′,5-TCB 81 | 0.0001 | 4.3 (0.0–9.2) | 0.0 (0.0) | 2.5 (0.0–7.4) | 0.0 (0.0) | 3.4 (0.0–9.2) | 0.0 (0.0) |
| 3,3′,4,4′,5-PCB 126 | 0.1 | 156.2 (38–328) | 15.6 (8.8) | 112.5 (37.5–263) | 11.3 (6.3) | 134.3 (37.5–328) | 13.4 (7.8) |
| 3,3′,4,4′,5,5′-HCB 169 | 0.01 | 51.6 (21–99.9) | 0.5 (0.2) | 78.3 (21.8–147) | 0.8 (0.4) | 65.0 (21.0–147) | 0.7 (0.4) |
| Total PCDDs | | 384.1 (120–824) | 35.4 (25.8) | 371.7 (102–809) | 28.4 (22.8) | 377.9 (102–824) | 31.9 (24.1) |
| Total PCDFs | | 107.0 (38.6–310) | 13.9 (6.4) | 133.0 (34.9–280) | 16.6 (15.9) | 120.0 (34.9–310) | 15.2 (11.9) |
| Total PCDD/Fs | | 491.1 (159–1133) | 49.3 (31.1) | 504.7 (137–1089) | 45.0 (38.5) | 497.9 (137–1133) | 47.1 (34.3) |
| Coplanar PCBs | | 212.1 (67.6–417) | 16.1 (9.0) | 193.3 (71.8–370) | 12.0 (6.5) | 202.7 (67.6–417) | 14.1 (8.0) |
| Total | | 703.2 (271–1411) | 65.4 (36.2) | 698.0 (209–1402) | 57.0 (42.2) | 700.6 (209–1411) | 61.2 (38.7) |

SD, standard deviation.

1,2,3,4,6,7,8-HpCDD, and the corresponding furans: OCDF; 1,2,3,4,7,8-HxCDF; and 2,3,4,7,8-PeCDF. However, in terms of TEQs, 2,3,7,8-TCDD; 1,2,3,7,8-PeCDD and 2,3,4,7,8-PeCDF contributed the most to the total. The latest three congeners combined represented 58% of total WHO-$TEQ_{98}$ among all subjects (57% among women, 60% among men). Overall, polychlorinated dibenzodioxin congeners accounted for more than half of total WHO-$TEQ_{98}$ in the blood of Chapaevsk residents (52%), while dibenzofurans and coplanar PCBs contributed less (25% and 23%, respectively). Pentadibenzofurans, especially 2,3,4,7,8-PeCDF, were the predominant dibenzofurans, representing about 76% of total dibenzofurans WHO-$TEQ_{98}$. Among coplanar PCBs, the predominant congener was 3,3′,4,4′,5 (PCB 126) representing 95% of total coplanar PCBs WHO-$TEQ_{98}$.

Table 3 presents the mean dioxin WHO-$TEQ_{98}$ serum levels stratified by subjects' age, BMI, and residence (distance from the plant). The total dioxin blood concentrations increased with age with the highest levels observed in the age group 40–49 years (mean WHO-$TEQ_{98}$, 100.9 pg/g lipid). The dioxin levels were lower in the age group 50–59 years (mean WHO-$TEQ_{98}$, 51.5 pg/g lipid). Subjects aged 60 years and older had substantially elevated dioxin levels (mean WHO-$TEQ_{98}$, 90.3 pg/g lipid). The dioxin congener patterns were similar between different age groups, with the highest relative PCDD/PCDFs contribution to total TEQs (82.1%) in the age group 40–49 (Table 3).

A positive association between dioxin levels and BMI was observed. Subjects with the highest BMI had almost twice as high total dioxin serum concentrations (mean WHO-$TEQ_{98}$, 78.7 pg/g lipid), as compared to subjects with the lowest BMI (mean WHO-$TEQ_{98}$, 43.8 pg/g lipid), even though these values were corrected for serum lipid content, and the difference was statistically significant ($P=0.04$) (Table 3). Dioxin levels were negatively associated with level of education. Subjects who attended primary school only had significantly higher levels of dioxins in serum, as compared to subjects who graduated from high school, college, or university (Table 3). No statistically significant trends were observed between dioxin levels and history of smoking or alcohol use.

Dioxin serum levels were inversely associated with the distance of subjects' residence from the plant (Table 3). Subjects living in close proximity to the plant (less than 5 km) had considerably higher total dioxin levels (mean WHO-$TEQ_{98}$, 75.7 pg/g lipid), as compared to subjects living more than 5 km from the plant (mean WHO-$TEQ_{98}$, 44.1 pg/g lipid), and the difference was statistically significant ($P<0.04$). These results are in agreement with data indicating that dioxin levels in Chapaevsk

**Table 3.** Mean WHO-$TEQ_{98}$ levels in blood by subjects' age, BMI, and residence (distance from the plant), Chapaevsk, Russia, 1998.

| Characteristic | *N* | PCDDs mean (SD), pg TEQ/g lipid | PCDFs mean (SD), pg TEQ/g lipid | PCDD/Fs mean (SD), pg TEQ/g lipid | Coplanar PCBs mean (SD), pg TEQ/g lipid | Total mean (SD), pg TEQ/g lipid |
|---|---|---|---|---|---|---|
| *Age (years)* | | | | | | |
| 20–29 | 6 | 14.8 (8.8) | 6.9 (3.6) | 21.7 (12.4) | 7.0 (2.4) | 28.7 (12.1) |
| 30–39 | 5 | 18.3 (6.6) | 10.8 (6.0) | 29.1 (10.0) | 10.4 (3.5) | 39.5 (13.2) |
| 40–49 | 4 | 62.1 (25.4) | 20.7 (4.3) | 82.8 (26.6) | 18.1 (3.7) | 100.9 (29.9) |
| 50–59 | 3 | 23.7 (12.4) | 10.9 (3.2) | 34.6 (15.2) | 16.9 (15.0) | 51.5 (28.6) |
| ≥60 | 6 | 44.2 (25.0) | 25.8 (18.1) | 70.0 (42.6) | 20.3 (6.2) | 90.3 (41.0) |
| *P* value[a] | | <0.002 | 0.002 | 0.001 | <0.006 | 0.0005 |
| *BMI ($kg/m^2$)* | | | | | | |
| <25.0 | 12 | 21.8 (12.2) | 12.9 (9.0) | 34.7 (20.3) | 9.1 (3.7) | 43.8 (22.8) |
| ≥25.0 | 12 | 41.9 (29.1) | 17.6 (14.3) | 59.6 (41.3) | 19.1 (8.0) | 78.7 (44.2) |
| *P* value[b] | | 0.04 | NS | NS | 0.001 | 0.04 |
| *Education* | | | | | | |
| Primary school only | 4 | 52.9 (25.8) | 31.3 (20.4) | 84.2 (45.7) | 22.6 (9.8) | 106.8 (41.3) |
| At least high school | 20 | 27.7 (22.0) | 12.0 (6.5) | 39.7 (27.3) | 12.4 (6.6) | 52.1 (32.0) |
| *P* value[b] | | 0.04 | <0.008 | 0.02 | 0.04 | 0.01 |
| *Residence (distance from the plant; km)* | | | | | | |
| <5 | 13 | 42.1 (27.4) | 19.6 (14.2) | 61.7 (39.0) | 14.0 (5.7) | 75.7 (42.7) |
| ≥5 | 11 | 19.8 (11.7) | 10.2 (5.9) | 30.0 (16.5) | 14.1 (10.3) | 44.1 (25.8) |
| *P* value[b] | | <0.02 | 0.02 | <0.02 | NS | <0.04 |

NS, not significant ($P>0.05$).
[a]ANOVA test using $\log_e$-transformed values.
[b]Student's *t*-test using $\log_e$-transformed values.

soil and in locally grown vegetables are also inversely associated with the distance from the plant (Revich et al., 2001).

## Discussion

Beginning in the 1930s, a network of at least 15 Khimprom chemical plants was built in Russia. Since 1960s, the Khimprom plants have been mainly producing chlorinated pesticides, household chemicals, and detergents. After 1991, most of these plants have reduced production of organochlorine compounds. However, dioxin contamination persists in areas surrounding the Khimprom plants. In Chapaevsk, dioxin contamination affects the areas adjacent to the Middle Volga Chemical Plant, where dioxin was produced during the manufacturing processes and where the unlined, uncapped, chemical wasteholding ponds are suspected to be a secondary source of dioxin pollution.

Although exposure pathways have not been investigated in detail, it is suspected that one of the routes of exposure is the consumption of locally produced dairy products, meat, pork fat for cooking, and fish. Animal products are contaminated through the uptake and bioaccumulation of dioxin-like substances from the local environment. In addition, inhalation and dermal absorption are additional potential pathways of exposure due to the continuous release of dioxin-contaminated particles from reservoir sources (soil, wasteholding ponds, dust from the chemical plant) into the ambient air and subsequent local dispersion and deposition.

In previous investigations, dioxin contamination was detected in the air, soil, drinking water, local vegetables, and cow's milk in Chapaevsk (Revich et al., 1996, 1999, 2001). The predominant congeners in the serum of Chapaevsk residents were polychlorinated dibenzodioxins accounting for more than half of total dioxin WHO-TEQs. Data from this and earlier study (Revich et al., 2001) of Chapaevsk residents suggest that there appears to be a gradient of dioxin exposure, dependent on the distance of residence from the chemical plant. Subjects living close to the plant have significantly higher serum dioxin levels than subjects living further from the plant. These results are in agreement with data indicating that dioxin content in Chapaevsk soil is the highest in areas surrounding the factory (Revich et al., 2001). Chapaevsk residents extensively use these areas as garden plots for food production, which is often sold at the local market.

Table 4 presents the mean dioxin WHO-$TEQ_{98}$ levels in serum of Chapaevsk residents in comparison to reported levels in workers and general population samples from other parts of Russia, North America, Europe, and Asia (Päpke, 1998; Longnecker et al., 2000; Ryan and Schecter, 2000; Amirova and Kruglov, 2001; Amirova et al., 1998; Revich et al., 2001; Schecter et al., 2001, 2002). For comparison purposes, previously published data on dioxin TEQ exposure from Russia and other countries, which used the 1994 I-TEFs (Ahlborg et al., 1994), were recalculated using the 1998 WHO-TEFs (Van den Berg et al., 1998).

The total PCDD/PCDFs WHO-$TEQ_{98}$ for residents of Chapaevsk in 1998 (mean, 47.1 ppt) appears to be very similar to the 1997 levels (median, 46.6 ppt) for residents of Ufa, Russia, where another Khimprom chemical plant is located (Amirova and Kruglov, 2001; Amirova et al., 1998) and to the 1986 German general population levels (mean, 48.5 ppt) (Päpke et al., 1992).

Previously, it has been reported that the occupationally exposed workers at Chapaevsk and Ufa plants have extremely high blood concentrations of PCDD/PCDFs (mean WHO-$TEQ_{98}$, 412.4 and 328.9 ppt, respectively) (Ryan and Schecter, 2000; Revich et al., 2001). The mean levels of PCDD/PCDFs were seven- to ninefold higher among exposed workers compared to nonoccupationally exposed residents in Chapaevsk and Ufa (Table 4).

Further comparison of data on dioxin exposure among the general population revealed that residents of Chapaevsk had higher serum dioxin levels than residents in other parts of Russia, such as Irkutsk and Baikalsk (Schecter et al., 2002). In comparison to other industrialized countries, the dioxin burden in Chapaevsk residents was also substantially higher than general population levels reported for North America (Longnecker et al., 2000; Schecter et al., 2002), Germany (the 1996 data) (Päpke, 1998), and Hanoi, Vietnam (Schecter et al., 2001). On the contrary, mean WHO-$TEQ_{98}$ levels of 2,3,7,8-TCDD in Chapaevsk residents (8.3 ppt) were lower, as compared to populations with known high 2,3,7,8-TCDD exposure, such as South Vietnam residents exposed to Agent Orange (69.7 ppt) (Schecter et al., 2001) and residents of the most contaminated zone in Seveso, Italy (53.2 ppt) (Landi et al., 1997).

Goldman et al. (2000) reported serum PCDD/PCDFs levels for California residents living in close proximity to a wood preservative treatment plant, where there had been a fire involving pentachlorophenol. The mean PCDD/PCDFs ITEQs (using the 1994 I-TEFs) were substantially higher among subjects consuming locally produced eggs and beef (63.7 ppt, $n=5$), as compared to subjects consuming local eggs (26.7 ppt, $n=4$) (Goldman et al., 2000). This corresponds to mean WHO-$TEQ_{98}$ (recalculated using the 1998 WHO-TEFs) of 83.5 and 33.0 ppt, respectively. In Chapaevsk residents, the mean PCDD/PCDFs WHO-$TEQ_{98}$ was 47.1 ppt (range 11.2–149.5 ppt), which overlaps with the range of subjects consuming dioxin-contaminated eggs and beef in the Goldman et al. (2000) study. Although both studies have utilized the same laboratory at CDC, some of the difference may be due to the fact that the Chapaevsk samples were analyzed

**Table 4.** Mean WHO-TEQ$_{98}$ levels in residents of Chapaevsk in comparison with reported data from Russia and other countries.

| Congener | WHO TEF$_{98}$ | Russia | | | | | | USA | | Canada | Germany | | Vietnam | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Chapaevsk residents 1998 | Chapaevsk female workers 1998[a] | Ufa residents 1997[b] | Ufa workers 1992[c] | Irkutsk residents 1998[d] | Baikalsk residents 1989[d] | 1998[d] | 1998[d] | blood donors 1994[e] | 1986[f] | 1996[g] | Hanoi residents 1999[h] | South 1999[h] |
| | | Number of samples | | | | | | | | | | | | |
| | | 24 | 4 | 44 | 34 | 14 | 8 | 100 | 100 | 63 | 102 | 139 | 100 | 20 |
| *PCDDs* | | | | | | | | | | | | | | |
| 2,3,7,8-TCDD | 1 | 8.3 | 80.5 | 17.9 | 230.7 | 3.7 | 3.7 | 1.4 | 3.8 | 1.9 | 3.6 | 2.3 | 2.2 | 69.7 |
| 1,2,3,7,8-PeCDD | 1 | 16.1 | 164.9 | 12.7 | 70.8 | 4.2 | 13.8 | 2.9 | 9.6 | 7.1 | 13.8 | 5.9 | 3.5 | 8.1 |
| 1,2,3,4,7,8-HxCDD | 0.1 | 1.2 | 5.8 | 0.5 | 5.1 | 0.9 | 6.6 | 0.3 | 1.0 | 6.2 | 1.1 | 0.6 | 0.4 | 0.6 |
| 1,2,3,6,7,8-HxCDD | 0.1 | 5.2 | 15.7 | 0.9 | | 0.7 | NA | 1.7 | 4.8 | NA | 5.5 | 2.3 | 0.8 | 2.1 |
| 1,2,3,7,8,9-HxCDD | 0.1 | 0.8 | 5.2 | 0.5 | | 0.5 | 1.1 | 0.4 | 0.6 | 0.8 | 1.1 | 0.4 | 0.2 | 0.5 |
| 1,2,3,4,6,7,8-HpCDD | 0.01 | 0.3 | 1.5 | 0.2 | NA | 0.3 | 0.9 | 0.3 | 0.6 | 1.2 | 0.9 | 0.3 | 0.2 | 0.5 |
| OCDD | 0.0001 | 0.03 | 0.2 | 0.01 | NA | 0.02 | 0.1 | 0.02 | 0.06 | 0.05 | 0.1 | 0.03 | 0.01 | 0.04 |
| *PCDFs* | | | | | | | | | | | | | | |
| 2,3,7,8-TCDF | 0.1 | 0.1 | 3.9 | 0.5 | NA | 1.2 | 0.3 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 |
| 1,2,3,7,8-PeCDF | 0.05 | 0.1 | 1.8 | 0.4 | NA | 0.3 | 0.0 | NA | NA | NA | 0.1 | 0.0 | 0.03 | 0.1 |
| 2,3,4,7,8-PeCDF | 0.5 | 11.4 | 89.0 | 10.2 | 15.6 | 11.3 | 7.5 | 1.5 | 3.1 | 4.3 | 18.5 | 5.5 | 3.4 | 2.7 |
| 1,2,3,4,7,8-HxCDF | 0.1 | 2.4 | 13.6 | 1.3 | 5.1 | 2.8 | 2.0 | 0.4 | 0.8 | 1.1 | 1.5 | 0.6 | 1.0 | 1.7 |
| 1,2,3,6,7,8-HxCDF | 0.1 | 1.0 | 27.8 | 0.6 | | 0.9 | NA | 0.3 | 0.4 | NA | 1.3 | 0.5 | 0.8 | 1.1 |
| 1,2,3,7,8,9-HxCDF | 0.1 | 0.0 | <1.0 | 0.4 | | 0.4 | 0.1 | NA | NA | NA | 0.2 | 0.0 | 0.05 | 0.1 |
| 2,3,4,6,7,8-HxCDF | 0.1 | 0.2 | 1.4 | 0.4 | | 1.0 | 0.2 | 0.1 | 0.2 | 0.3 | 0.4 | 0.2 | 0.2 | 0.2 |
| 1,2,3,4,6,7,8-HpCDF | 0.01 | 0.1 | <0.12 | 0.1 | NA | 0.4 | 0.0 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.2 |
| 1,2,3,4,7,8,9-HpCDF | 0.01 | 0.01 | <0.12 | 0.1 | NA | 0.05 | 0.0 | NA | NA | NA | 0.0 | 0.0 | 0.0 | 0.04 |
| OCDF | 0.0001 | 0.01 | 0.003 | 0.002 | NA | 0.0001 | 0.0 | 0.0 | 0.0 | NA | 0.0 | 0.0 | 0.003 | 0.004 |
| *Coplanar PCBs* | | | | | | | | | | | | | | |
| 3,3′,4,4′-TCB 77 | 0.0001 | 0.0 | NA | NA | NA | 0.0 | NA | NA | NA | 0.002 | NA | NA | NA | NA |
| 3,3′,4,4′,5-PCB 126 | 0.1 | 13.4 | NA | NA | 21.0 | 3.8 | NA | 1.9 | 5.0 | 2.9 | NA | NA | NA | 3.9 |
| 3,3′,4,4′,5,5′-HCB 169 | 0.01 | 0.7 | NA | NA | NA | 0.2 | NA | 0.1 | 0.4 | 0.3 | NA | NA | 0.3 | 0.3 |
| Total PCDDs | | 31.9 | 273.8 | 32.7 | 307.4 | 10.3 | 26.2 | 7.0 | 20.5 | 17.3 | 26.1 | 11.8 | 7.3 | 81.5 |
| Total PCDFs | | 15.2 | 138.6 | 13.9 | 21.5 | 18.4 | 10.1 | 2.4 | 4.6 | 5.9 | 22.4 | 7.0 | 5.7 | 6.3 |
| Total PCDD/Fs | | 47.1 | 412.4 | 46.6 | 328.9 | 28.7 | 36.3 | 9.4 | 25.1 | 23.2 | 48.5 | 18.8 | 13.0 | 87.8 |
| Coplanar PCBs | | 14.1 | NA | NA | 21.0 | 8.1 | NA | 2.0 | 5.4 | 3.2 | NA | NA | 0.3 | 4.2 |
| Total | | 61.2 | NA | NA | 349.9 | 36.8 | NA | 11.4 | 30.5 | 26.4 | NA | NA | 13.3 | 92.0 |

NA, not available.

[a]Data from Revich et al. (2001).

[b]Data (median levels) from Amirova and Kruglov (2001) and Amirova et al. (1998).

[c]Data from Ryan and Schecter (2000).

[d]Data from Schecter et al. (2002).

[e]Data (median levels) from Longnecker et al. (2000).

[f]Data from Päpke et al. (1992).

[g]Data from Päpke (1998).

[h]Data from Schecter et al. (2001).

in 1998, whereas the Goldman et al. study samples were analyzed in 1988, when analytical methods may have been less sensitive and several dibenzofuran congeners (including 1,2,3,7,8-PeCDF; 1,2,3,7,8,9-HxCDF; 2,3,4,6,7,8-HxCDF; 1,2,3,4,7,8,9-HpCDF; and OCDF) were not reported.

Covaci et al. (2001) reported total serum dioxin WHO-$TEQ_{98}$ for older women living in two industrial areas of Belgium. The local industrial sources include nonferrous and chemical plants as well as two municipal waste incinerators. Total PCDD/PCDFs WHO-$TEQ_{98}$ were similar between 47 women ages 50–65 years old in two industrial areas of Belgium (mean 48.6, range 45.6–51.8 ppt) and four women of similar age in Chapaevsk (mean 48.4, range 29.0–62.7 ppt), although total coplanar PCBs WHO-$TEQ_{98}$ was higher in Chapaevsk women (mean 24.5, range 16.8–33.6 ppt), as compared to women in Belgium (mean 12.6, range 11.3–14.1 ppt).

It is thought that differences in the relative proportions of dioxin congeners in human tissues could be indicative of the source of exposure. Unlike other parts of Russia (e.g., Irkutsk) where dibenzofurans rather than dioxins contributed more to the total TEQs (Schecter et al., 2002), the proportion of dibenzodioxins was higher among Chapaevsk residents (ranging from 42% to 66%). The dibenzodioxin proportions in Chapaevsk resemble those found in other industrialized countries, such as US, Canada, and Germany (the 1996 levels), although the mean WHO-$TEQ_{98}$ levels were considerably higher in Chapaevsk residents (Table 4).

An elevated dioxin body burden has been associated with adverse health effects in humans. In 1997, after the review of experimental and epidemiological evidence, the International Agency for Research on Cancer (IARC) upgraded 2,3,7,8-TCDD, the most toxicologically potent dioxin, to the status of "carcinogenic to humans" (IARC, 1997). In January 2001, the US National Toxicology Program updated 2,3,7,8-TCDD to "known to be a human carcinogen" status in the addendum to its "Ninth Report on Carcinogens" (NTP, 2001). Moreover, accumulating evidence from animal and human studies suggests that dioxins can cause endocrine, immune, reproductive, developmental, and neurological effects (Kogevinas, 2001).

It has been reported that dioxin levels in Chapaevsk residents have been positively correlated with emotional stress and chromosomal aberration levels (Ingel et al., 2001; Revazova et al., 2001). Prospective epidemiological studies are underway to investigate the effects of dioxin exposure on reproductive health and endocrine function among adolescents in Chapaevsk (Sergeyev et al., 2000).

The results of the present study suggest that the deteriorating public health indicators in Chapaevsk may result in part from local environmental dioxin contamination. Future research in this area should focus on a better characterization of the transport of dioxins through the environment and the local food chain, as well as on examining the long-term effects of dioxin exposure on public health. The reduction of emissions of dioxin-contaminated compounds and an appropriate cleanup of the areas surrounding the Middle Volga chemical plant and other Khimprom hot spots may also be indicated as a long-term solution.

## Acknowledgments

Collection and analysis of human samples were supported through an agreement with the Environmental Toxicology Program of the US National Institute of Environmental Health Sciences and by Public Health Service Grants ES00260 and CA16087. Dioxin analyses were supported by interagency agreement Y1-ES-8062-02 between the National Institute of Environmental Health Sciences and the National Center for Environmental Health. This work was undertaken during the tenure of Dr. Paolo Toniolo from a Senior Visiting Scientist Award from the IARC (Lyon, France). The authors are grateful to the administration of the City of Chapaevsk for logistical support.

## References

Ahlborg U.G., Becking G.C., Birnbaum L.S., Brouwer A., Derks H.J., Feeley M., Golor G., Hanberg A., Larsen J.C., Liem A.K.D., Safe S.H., Schlatter C., Waern F., Younes M., and Yrjanheikki E. Toxic equivalency factors for dioxin-like PCBs; report on a WHO-ECEH and IPCS consultation. *Chemosphere* 1994: 28: 1049–1067.

Akins J.R., Waldrep K., and Bernert J.T. Jr. The estimation of total serum lipids by a completely enzymatic "summation" method. *Clin Chim Acta* 1989: 184: 219–226.

Amirova Z., and Kruglov E. Time history of PCDD/Fs content in blood of the population in the city of Ufa, Bashkortostan. Dioxin '2001 Symposium, Korea. *Organohalogen Compounds* 2001: 52: 269–272.

Amirova Z., Kruglov E., Loshkina E., Chalilov R., and Minin G. Dioxins in Russia. IV. Ufa, Bashkortostan. *Organohalogen Compounds* 1998: 38: 105–108.

Bertazzi P.A., Consonni D., Bachetti S., Rubagotti M., Baccarelli A., Zocchetti C., and Pesatori A.C. Health effects of dioxin exposure: a 20-year mortality study. *Am J Epidemiol* 2001: 153: 1031–1044.

Bertazzi P.A., Zocchetti C., Pesatori A.C., Guercilena S., Sanarico M., and Radice L. Ten-year mortality study of the population involved in the Seveso incident in 1976. *Am J Epidemiol* 1989: 129: 1187–1200.

Covaci A., Koppen G., Cluevenbergen R.V., Schepens P., Winneke G., and Schoeters G. Persistent organochlorine compounds in human serum of 50–65 years old women living in two regions of Flanders, Belgium. Dioxin '2001 Symposium, Korea. *Organohalogen Compounds* 2001: 52: 265–268.

Egeland G.M., Sweeney M.H., Fingerhut M.A., Wille K.K., Schnorr T.M., and Halperin W.E. Total serum testosterone and gonadotropins in workers exposed to dioxin. *Am J Epidemiol* 1994: 139: 272–281.

Goldman L.R., Harnly M., Flattery J., Patterson D.G., Jr., and Needham L.L. Serum polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans among people eating contaminated home-produced eggs and beef. *Environ Health Perspect* 2000: 108: 13–19.

Huisman M., Koopman-Esseboom C., Lanting C.I., van der Paauw C.G., Tuinstra L.G., Fidler V., Weisglas-Kuperus N., Sauer P.J., Boersma E.R., and Touwen B.C. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. *Early Hum Dev* 1995: 43: 165–176.

IARC. Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. *IARC Monogr Eval Carcinog Risk Hum* 1997: 69: 219–343.

Ingel F., Platonova V., and Katosova L. Human emotional stress, dioxin blood content and genetic damage in Chapaevsk town. *Chemosphere* 2001: 43: 989–998.

Kogevinas M. Human health effects of dioxins: cancer, reproductive and endocrine system effects. *Hum Reprod Updat* 2001: 7: 331–339.

Koopman-Esseboom C., Morse D.C., Weisglas-Kuperus N., Lutkeschipholt I.J., Van der Paauw C.G., Tuinstra L.G., Brouwer A., and Sauer P.J. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatr Res* 1994: 36: 468–473.

Koopman-Esseboom C., Weisglas-Kuperus N., de Ridder M.A., Van der Paauw C.G., Tuinstra L.G., and Sauer P.J. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. *Pediatrics* 1996: 97: 700–706.

Landi M.T., Needham L.L., Lucier G., Mocarelli P., Bertazzi P.A., and Caporaso N. Concentrations of dioxin 20 years after Seveso. *Lancet* 1997: 349: 1811.

Longnecker M.P., Ryan J.J., Gladen B.C., and Schecter A.J. Correlations among human plasma levels of dioxin-like compounds and polychlorinated biphenyls (PCBs) and implications for epidemiologic studies. *Arch Environ Health* 2000: 55: 195–200.

Mocarelli P., Brambilla P., Gerthoux P.M., Patterson D.G., Jr., and Needham L.L. Change in sex ratio with exposure to dioxin. *Lancet* 1996: 348: 409.

Mocarelli P., Gerthoux P.M., Ferrari E., Patterson D.G., Kieszak S.M., Brambilla P., Vincoli N., Signorini S., Tramacere P., Carreri V., Sampson E.J., Turner W.E., and Needham L.L. Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* 2000: 355: 1858–1863.

NTP. *2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD); Dioxin (CAS No. 1746-01-6). Addendum to the Ninth Report on Carcinogens*, National Toxicology Program, Bethesda, MD, 2001.

Päpke O. PCDD/PCDF: human background data for Germany, a 10-year experience. *Environ Health Perspect* 1998: 106(suppl 2): 723–731.

Päpke O., Ball M., and Lis A. Various PCDD/PCDF patterns in human blood resulting from different occupational exposures. *Chemosphere* 1992: 25: 1101–1108.

Patandin S., Lanting C.I., Mulder P.G., Boersma E.R., Sauer P.J., and Weisglas-Kuperus N. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *J Pediatr* 1999: 134: 33–41.

Patterson D.G. Jr., Hampton L., Lapeza C.R. Jr., Belser W.T., Green V., Alexander L., and Needham L.L. High-resolution gas chromatographic/high-resolution mass spectrometric analysis of human serum on a whole-weight and lipid basis for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Anal Chem* 1987: 59: 2000–2005.

Pluim H.J., Wever J., Koppe J.G., Vandenslikke J.W., and Olie K. Intake and fecal excretion of chlorinated dioxins and dibenzofurans in breast-fed infants at different ages. *Chemosphere* 1993: 26: 1947–1952.

Revazova J., Yurchenko V., Katosova L., Platonova V., Sycheva L., Khripach L., Ingel F., Tsutsman T., and Zhurkov V. Cytogenetic investigation of women exposed to different levels of dioxins in Chapaevsk town. *Chemosphere* 2001: 43: 999–1004.

Revich B., Aksel E., Dvoirin V., Kolbeneva L., and Pervunina R. Dioxin in the environment of Chapaevsk (Russia), health of its population. Dioxin '96 Symposium, Amsterdam. *Organohalogen Compounds* 1996: 30: 350–353.

Revich B., Brodsky E., and Sotskov Y. Dioxin in environmental, blood, breast milk, cow milk in Chapaevsk town. Dioxin '99 Symposium, Italy. *Organohalogen Compounds* 1999: 44: 229–232.

Revich B., Aksel E., Ushakova T., Ivanova I., Zhuchenko N., Klyuev N., Brodsky B., and Sotskov Y. Dioxin exposure and public health in Chapaevsk, Russia. *Chemosphere* 2001: 43: 951–966.

Ryan J.J., and Schecter A. Exposure of Russian phenoxy herbicide producers to dioxins. *J Occup Environ Med* 2000: 42: 861–870.

Schecter A., Dai L.C., Päpke O., Prange J., Constable J.D., Matsuda M., Thao V.D., and Piskac A.L. Recent dioxin contamination from Agent Orange in residents of a southern Vietnam city. *J Occup Environ Med* 2001: 43: 435–443.

Schecter A., Pavuk M., Amirova D.A., Grosheva E.I., Päpke O., Ryan J.J., Adibi J., and Piskac A.L. Characterization of dioxin exposure in firefighters, residents, and chemical workers in the Irkutsk region of Russian Siberia. *Chemosphere* 2002: 47: 147–156.

Sergeyev O., Zeilert V., Revich B., Ushakova T., Williams P., Korrick S., Lee M.M., Altshul M., Adibi J., and Hauser R. Sexual and physical maturation of male adolescents in a dioxin contaminated region: Chapaevsk, Russia. Dioxin '2000 Symposium, USA. *Organohalogen Compounds* 2000: 48: 211–214.

Turner W., DiPietro E., Lapeza C., Green V., Gill J. and Patterson D.G., Jr. A fast universal automated cleanup system for the isotope-dilution high-resolution mass spectrometric analysis of PCDDs, PCDFs, coplanar PCBs, PCB congeners, and persistent pesticides from the same serum sample. *Organohalog Compd* 1997: 31: 26–31.

Van den Berg M., Birnbaum L., Bosveld A.T., Brunstrom B., Cook P., Feeley M., Giesy J.P., Hanberg A., Hasegawa R., Kennedy S.W., Kubiak T., Larsen J.C., van Leeuwen F.X., Liem A.K., Nolt C., Peterson R.E., Poellinger L., Safe S., Schrenk D., Tillitt D., Tysklind M., Younes M., Waern F., and Zacharewski T. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ Health Perspect* 1998: 106: 775–792.

Weisglas-Kuperus N., Patandin S., Berbers G.A., Sas T.C., Mulder P.G., Sauer P.J., and Hooijkaas H. Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. *Environ Health Perspect* 2000: 108: 1203–1207.

Weisglas-Kuperus N., Sas T.C., Koopman-Esseboom C., van der Zwan C.W., De Ridder M.A., Beishuizen A., Hooijkaas H., and Sauer P.J. Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. *Pediatr Res* 1995: 38: 404–410.