Severe 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Intoxication: Clinical and Laboratory Effects

Alexandra Geusau, Klaus Abraham, Klaus Geissler, Michael O. Sator, Georg Stingl, and Erwin Tschachler

A Department of Dermatology, Division of Immunology, Allergy and Infectious Diseases, University of Vienna Medical School, Vienna, Austria; 2Department of Pediatric Pneumology and Immunology, Charité Children’s Hospital, Humboldt University, Berlin, Germany; 3Department of Medicine, Division of Hematology, and 4Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology and Reproductive Medicine, University of Vienna Medical School, Vienna, Austria

A variety of health effects have been attributed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), but little information is available on the course of a verified high-level TCDD intoxication. In this paper we describe two cases of heavy intoxication with TCDD and present a 2-year follow-up including clinical, biochemical, hematologic, endocrine, and immunologic parameters monitored in two women, 30 and 27 years of age, who suffered from chloracne due to TCDD intoxication of unknown origin. Patient 1, who had the highest TCDD level ever recorded in an individual (144,000 pg/g blood fat), developed severe generalized chloracne, whereas in the second patient, despite heavy intoxication (26,000 pg/g blood fat), only mild facial acne lesions occurred. Both patients initially experienced nonspecific gastrointestinal symptoms. In Patient 1 we observed a moderate elevation of blood lipids, leukocytosis, anemia, and secondary amenorrhoea. The laboratory parameters in Patient 2 were all normal. Despite the high TCDD levels, apart from chloracne, only few clinical and biochemical health effects were observed within the first 2 years after TCDD intoxication. Key words: amenorrhoea, anemia, chloracne, dioxin intoxication, endocrine effects, health effects, TCDD.

Case Summaries

Patient 1. In March 1998, a 30-year-old woman was admitted to the Department of Dermatology of the University of Vienna Medical School with acute centrofacial inflammation and acne, which had begun in late autumn 1997 shortly after she had moved into a new office space at a textile research institute. Clinically, acne fulminans was suspected, and treatment with high-dose methylprednisolone (1 mg/kg body weight/day) was initiated. In the following weeks, acute inflammation subsided, but hundreds of cysts developed not only on the face but also on sites normally not affected in acne patients, such as the auricular areas, the eyelids, the genital region, the limbs, and the trunk. Based on the course and the conspicuous clinical picture, chloracne was suspected and confirmed by the detection of 144,000 pg TCDD/g blood fat, the highest value ever recorded in a human (5); this corresponds to a calculated body burden of 1.6 mg TCDD and a dosage of 25 µg/kg body weight (9). The disease progressed continuously; after 1 year, the patient’s whole face was densely covered with cysts (Figure 1A, B). Until summer 1998 only few lesions were present on the body skin (Figure 1C), but 1 year later the entire skin surface was covered with inflamed, painful cysts (Figure 1D). As a possible new skin manifestation observed in TCDD intoxication, the patient exhibited palmoplantar keratoderma (10).

Besides the skin disease, the patient had experienced gastrointestinal symptoms including nausea, vomiting, epigastric pain, and loss of appetite since late autumn 1997. These symptoms had prompted the patient to follow a medically supervised diet, which resulted in a weight loss of about 10 kg within the 4 months before hospital admission. Of the next year, the patient’s abdominal symptoms subsided.

Moderately elevated levels of blood lipids, a normocytic, normochromic anemia, and leukocytosis were the most prominent pathologic changes of the routine laboratory parameters. The patient was thrombocytopenic in the first 3 months of observation; antiplatelet antibodies were negative. Histology carried out in October 1999 revealed a normocellular bone marrow with prominent myelopoiesis, but there was no morphologic evidence for dysmyelopoiesis and/or an increased blast cell count; no chromosomal abnormality was detectable. Moreover, because immunoglobulin or T-cell receptor rearrangements were not detected, we concluded that these findings were not consistent with a lymphoproliferative disorder.

Address correspondence to A. Geusau, University of Vienna Medical School, Department of Dermatology, Division of Immunology, Allergy and Infectious Diseases, Währinger Gürtel 18-20, A-1090 Vienna, Austria. Telephone: 43-1-40400-7704. Fax: 43-1-40 31 900. E-mail: alexandra.geusau@akhh-wien.ac.at

We thank N. Winker and B. Jäger from the Austrian workers compensation board (AUVA) for their support.

Received 23 February 2001; accepted 16 April 2001.
detected in the peripheral blood or bone marrow, it was possible to exclude a systemic clonal lymphoproliferative disease as cause for the anemia. In vitro culture of hematopoietic progenitor cells showed normal growth of myeloid progenitor cells (colony forming unit-granulocyte/macrophage (CFU-GM)) and only a slightly decreased formation of erythroid colonies (burst-forming unit-stromal (BFU-E), 80/100,000 mononuclear cells (MNC), normal value 128–474/100,000 MNC). Lymphocyte subset analysis showed a marginal decrease in the percentage of natural killer (NK) cells. Several other immunologic parameters (Table 1) were within the normal range.

The patient, a mother of two healthy children, had been taking birth control pills; menstruation ceased in late autumn 1997, the presumed time of TCDD intoxication. Secondary amenorrhea was still present in late 2000 after she stopped using hormonal contraceptives in summer 1999. The hormonal status showed slightly decreased estradiol and progesterone levels and, since May 1999, a mild elevation of prolactin, which coincided with the initiation of anti-depressive therapy (paroxetine; Seroxat: SmithKline Beecham, Brunn/Gerbirge, Austria). The measurement of hormone reserve and regulation by dynamic tests (L-arginine test (300 mL 10% L-arginine IV within 30 min: normal increase of growth hormone), thyrotropin-releasing hormone test, gonadotropin-releasing hormone test (Gonadorelin; Relefact LH-RH 0.100 mg; 1 mL as bolus IV; normal increase of follicle-stimulating hormone and luteinizing hormone), adrenocorticotropic hormone (ACTH) test (121 µg corticorelin-trifluoroacetate IV; normal increase of cortisol, testosterone, dehydroepiandrosterone-S, 17α-hydroxyprogesterone, and androstenedione (11)) revealed normal results, which ruled out the possibility of a disturbance of the hypothalamic-pituitary-target system.

Investigations such as ultrasound of the abdomen, chest X ray, pulmonary function tests, and neurologic, psychodynamic, and electrophysiologic investigations were unrevealing. Gastroscopy in February 1998 showed acute helicobacter-negative gastritis, corresponding to the epigastric symptoms reported.

Patient 1 was treated with isotretinoin (0.7 mg/kg body weight/day Roaccutan; Hoffmann-LaRoche, Basel, Switzerland) beginning in April 1998, but this treatment was discontinued in December 1998 because the patient reached cumulative dose of 13 g and with no observed clinical benefit. Recurrent deep inflammation of cysts repeatedly required and still requires surgical interventions and mechanical removal of the comedones, oral administration of methylprednisolone (4–40 mg/day Urbason; Hoechst Marion Rousell, Vienna, Austria), and analgesic drugs and antibiotics. In an attempt to detoxify the patient, we administered olestra, a nonabsorbable, nondigestible fat-substitute, on a trial basis in autumn 1998 (9), and the patient is still receiving this treatment. TCDD blood levels were measured before and during the course of the olestra treatment and are still monitored; the TCDD concentrations have decreased over time (30,300 pg/g blood fat in October 2000).

Patient 2. The patient's colleague, a 27-year-old woman who worked in the same room, consulted us in April 1998. She had developed multiple small cysts on the malar crest (Figure 2A) and the auricular areas, albeit to a much lesser degree than Patient 1. Also, Patient 2 had been suffering from gastrointestinal symptoms from autumn 1997 to early 1998. Her initial TCDD blood level, measured in June 1998, was 26,000 pg/g blood fat, corresponding to a calculated
body burden of 0.4 mg and the dose of 6 µg/kg body weight (9). Apart from marginally elevated values of cholesterol and lipase, an elevated number and percentage of B lymphocytes, and a decreased percentage of NK cells, her routine laboratory and immunologic parameters were within the normal range. Except for elevated levels of thyroid-stimulating hormone and prolactin on single occasions, thyroid and sexual hormones were normal. We treated the patient’s chloracne with topical tretinoin (Retin A Cream; Cilag, Schaffhausen, Switzerland), and within 1 year her skin lesions cleared almost completely (Figure 2B). She also completed a trial with oestra (9).

Out of 30 other employees working at the same institute as these patients, blood

| Laboratory test                  | Reference value | Patient 1 | Patient 2 |
|----------------------------------|-----------------|-----------|-----------|
| Triglycerides                    | 50–172 mg/dL    | 287 (7.4) | 113 (2.9) |
|                                  | (0.56–1.9 mmol/L) | 549 (14.2) | 176 (4.6) |
| Cholesterol                      | 150–200 mg/dL   | 228 (5.9) | 201 (5.2) |
|                                  | (<5.2 mmol/L)   | 338 (8.7) | 284 (6.8) |
| a-Amylase total                  | 28–100 U/L      | 73        | 74        |
| Lipase                           | - 60 U/L        | 39        | 77        |
| CHE                              | 2.8–7.4 U/L     | 4.9       | 5.2       |
| Alkaline phosphatase             | 60–170 U/L      | 140       | 91        |
| GOT (ASAT)                       | - 15 U/L        | 7         | 10        |
| GPT (ALAT)                       | - 19 U/L        | 7         | 8         |
| Gamma-GT                         | 4–18 U/L        | 16        | 11        |
| LDH                              | 120–240 U/L     | 147       | 121       |
| Blood count and differential blood count<sup>b</sup> | 3.5–5.0 10<sup>12</sup>/L | 3.4 | 4.2 |
| Hemoglobin                       | 120–150 G/L     | 101       | 128       |
| Hematocrit                       | 0.33–0.43 L     | 0.30      | 0.36      |
| Platelet count                   | 150–450 10<sup>9</sup>/L | 165 | 179 |
| Leukocytes                       | 3.2–9.8 10<sup>9</sup>/L | 18.4 | 8.1      |
| Reticulocytes                    | 0.7–2.0%        | 1.84      | 1.41      |
| Granulocytes                     | 50–70.0%        | 71.6      | 59.6      |
| Monocytes                        | 0.0–12.0%       | 5.2       | 6.2       |
| Lymphocytes                      | 25.0–40.0%      | 20.5      | 31.6      |
| CRP                              | - 10 mg/L       | 26        | 10 <5     |
| Fibrinogen                       | 1.8–3.9 G/L     | 4.2       | 2.9       |
| Lymphocyte subpopulations<sup>c</sup> |                         |           |           |
| T lymphocytes (CD3<sup>+</sup>)   | 59–85%          | 84        | 73        |
|                                  | 720–2.330/µL    | 3,648     | 1,750     |
|                                  | 6.4–23%         | 12.3      | 23.5      |
| B lymphocytes (CD19<sup>+</sup>) | 100–430/µL      | 537       | 701       |
| T helper cells (CD3<sup>+</sup>CD4<sup>+</sup>) | 31–61% | 45 | 43 |
| T suppressor cells (CD3<sup>+</sup>CD8<sup>+</sup>) | 11–38% | 38 | 25 |
| CD4/CD8 ratio                    | 0.9–3.6         | 1.2       | 1.1       |
| Natural killer cells (CD3<sup>+</sup>CD56<sup>+</sup>CD16<sup>+</sup>) | 5.6–31% | 4.3 | 8.0 |
| CD4<sup>-</sup>CD8<sup>-</sup> ratio | 90–430/µL       | 182       | 121       |
| Hormones<sup>d</sup>             |                 |           |           |
| TSH                              | 0.1–4.0 µU/mL   | 1.5       | 0.7       |
| Thyroxine, free                  | 1.0–1.8 ng/dL   | 1.1 (14)  | 1.1 (14)  |
| Androstenedione                  | 0.5–11.0 ng/dL  | 0.64      | 0.84      |
| DHEAS                            | 0.69–3.98 µg/dL | 0.18      | 0.2       |
| 17-OHP                           | 0.4–1.0 ng/mL   | 0.5       | 0.6       |
| LH                               | 1.5–10 µU/mL    | 1.8       | 2.9       |
| FSH                              | 4–13 IU/L       | 4.3       | 7.3       |
| Prolactin                        | 1.4–24.2 ng/mL  | 26.6      | 21.6      |
| Estradiol                        | F 22–215 pg/mL; L 22–232 pg/mL | 58 | 126 |
| Progesterone                     | F 0.5–1.0 ng/mL | 0.20      | 0.96      |
| Testosterone                     | 0.06–0.86 ng/mL | 0.05 (0.2) | 0.35 (1.2) |
| SBG                              | 19–117 ng/mL    | 102       | 191       |

Abbreviations: CHE, cholinesterase; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone; F, follicular phase; FSH, follicle-stimulating hormone; gamma-GT, gamma-glutamyl transferase; GOT (ASAT), glutamicoxaloacetic-transaminase; GPT (ALAT), glutamic pyruvate transaminase; L, luteal phase; LDH, lactate dehydrogenase; LH, luteinizing hormone; 17-OHP, 17α-hydroxyprogesterone; P, peak; SBG, sex hormone-binding globulin; TSH, thyroid stimulating hormone. Tests were performed from April 1998 to October 2000 for Patient 1 and from June 1998 to October 2000 for Patient 2, with 3–20 measures/parameter. Routine laboratory tests, T-cell receptor tests, and immunoglobulin rearrangement were performed by the Clinical Laboratory of the General Hospital, Vienna, Austria; lymphocyte subset analysis was performed at the laboratory of the Division of Immunology and Infectious Diseases, Department of Dermatology, University of Vienna; bone marrow analysis was performed at the Department of Clinical Pathology and the Department of Internal Medicine, Division of Hematology, University of Vienna; and karyotype analysis of the blood and stem cells was carried out at the Institute of Medical Biology, University of Vienna. The results of the following additional laboratory tests were within the normal range and/or very low: bilirubin, high density lipoprotein, low density lipoprotein, very low density lipoproteins, fasting glucose and oral glucose tolerance test, renal function tests (electrolytes, blood urea nitrogen, creatinine, uric acid), total serum protein and albumin, blood coagulation measures, urinary analysis, urinary porphyrins, immunoglobulins (IgA, IgG, IgM) including IgG subsets, complement analysis (C3, C4, CH50), antinuclear antibodies and subsets, and measures of thyroid function (serum total thyroxine, triiodothyronine, thyroid-binding globulin, thyroid stimulating hormone).

<sup>a</sup>Except for thyroid-stimulating hormone and prolactin, only hormone values measured at least 2 months after cessation of hormonal contraceptives were included.

<sup>b</sup>Single measurement.

<sup>c</sup>Reference values (95th percentile; data sheet of the Becton Dickinson Simultest IMK-Lymphocyte assay; Becton-Dickinson, San Jose, CA).

<sup>d</sup>Female reference values. Reference values (95th percentile; data sheet of the Becton Dickinson Simultest IMK-Lymphocyte assay; Becton-Dickinson, San Jose, CA).
analysis for TCDD showed that two men and one woman had elevated blood levels (856, 149, and 93 pg/g blood lipids). These three individuals were asymptomatic.

To analyze TCDD in blood samples, we used published methods employing isotope-labeled internal standards and high resolution gas chromatography coupled to high resolution mass spectrometry (ERGO Forschungsgesellschaft, Hamburg, Germany) (12,13). These methods were externally validated in international intercalibration exercises.

We analyzed initial blood samples for all 2,3,7,8-substituted polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs). Other than a slight elevation of 1,2,3,7,8-pentachlorodibenzo-p-dioxin (1,2,3,7,8-PCDD; Patient 1, 47.2 pg/g; Patient 2, 14.5 pg/g blood fat), we detected no polyhalogenated compounds above background levels.

Discussion

At present, despite thorough environmental and police investigations, the cause of this unfortunate incident has not been fully explained. One important reason for this was the long interval between the presumed time of intoxication (October 1997) and the beginning of examinations in spring 1998, after the diagnosis had been established. The possibility of a criminal act could not be excluded, but the respective investigations of our state attorney were terminated without success. It is possible that the patients were exposed to TCDD that was produced, for example, from 2,4,5-trichlorophenol (TCP), in the chemical laboratory at the institute where the patients (who themselves only performed secretarial work) were employed. In one of the laboratories there was a high concentration of TCDD detected in a water basin and inside the drain. The concurrence of low-level 1,2,3,7,8-PCDD, as observed in our two patients, is a typical pattern in cases in which TCDD derives from 2,4,5-TCP (14).

Although the route of application could not be clarified, because of the high TCDD blood levels, oral ingestion appears to be the most likely mode of intoxication. Exposures by other routes of intoxication (through the skin or by inhalation) are not likely to cause such high blood levels in two individuals without strongly contaminating the whole environment.

Although this has still not been explained, it has allowed us the opportunity to follow the immediate clinical and laboratory course in patients with high TCDD intoxication. In humans, the highest reported TCDD levels so far, 10,400 pg/g blood fat in an adult and 56,000 pg/g blood fat in a child, were measured in individuals exposed to TCDD in the Seveso incident (5).

Chloracne was the most severe health effect, which led to the diagnosis in Patient 1. Due to this progressive, disfiguring disease, which is often associated with an unpleasant odor, her social and marital life has been significantly affected. Despite exceedingly high TCDD levels, Patient 2 had only mild acne; the diagnosis might not have been established at all if her colleague had not been diagnosed with chloracne. The mild manifestation in Patient 2 is also surprising in light of recent studies which show that chloracne may appear at dioxin blood levels of approximately 1,000 pg/g blood fat (7,15,16). Apart from interindividual variation, a possible explanation for the discrepancy could be that the preceding data are derived from investigations in people with predominantly external exposure. TCDD concentrations in the skin of these patients presumably exceeded those observed in patients with internal intoxication. Because skin exposure was unlikely in these two patients, our data might reflect that, in the absence of direct skin contamination, higher systemic threshold levels are necessary for chloracne to develop.

Apart from initial lymphocytosis in the Seveso victims (3,5) and exposure-response associations of the platelet count in the BASF workers (4,8), hematologic abnormalities have not been described in other cohorts with TCDD exposure (7). In the more severely affected patient (Patient 1), we observed persistent leukocytosis. This might be caused by both the extensive inflammatory skin condition and the intermittently given corticosteroids, rather than being a direct effect of TCDD. However, we cannot formally rule out the latter possibility. Similarly, persistent anemia in this patient was most likely due to the inflammatory skin condition, although we cannot exclude a toxic effect on the erythropoiesis by TCDD. A toxic effect might also explain the initial thrombopenia in Patient 1.

Because the immune system has been shown to be a sensitive target of TCDD toxicity in animal studies (17), we investigated immunologic parameters and lymphocyte subpopulations in our patients. The notable results included a leukocytosis in Patient 1 and a decreased percentage of NK cells in both patients. Quantitative and functional analysis of both the humoral and cellular arms of the immune system have been unrevealing so far. A controlled study on the immune function is currently under way.

Slightly elevated blood lipids were still present after the discontinuation of the retinoid treatment in Patient 1, indicating that this could be an effect of TCDD; however, the steroid intake may also have played a role in this increase.

The cause of the amenorrhea is something that can only be speculated. TCDD may have an inhibitory effect on ovulation, either by a direct effect on ovarian function [i.e., inhibition of estradiol synthesis (18,19)] or by induction of cytochrome P450-mediated metabolism of estradiol (20). Amenorrhea may also be caused by hyperprolactinemia, which in turn coincided in our patient with the initiation of Patient 1's...
antidepressive therapy with serotonin antagonists, which are known to increase prolactin levels (21,22).

Apart from chloracne and gastrointestinal symptoms, few clinical symptoms were observed in these patients in the acute phase of intoxication. This indicates that compared to other species, humans are not particularly sensitive in regard to lethal doses of TCDD; that is, the applied doses in our patients highly exceed the median lethal dose (LD50) of 0.6–2.0 μg/kg body weight in the guinea pig, the most sensitive species tested (23).

Conclusion

In conclusion and in accordance with the literature (3–7,13,24,25), we found that our patients’ chloracne and gastrointestinal symptoms were associated with TCDD intoxication, but, even in case of severe poisoning, this was not indicated by our routine laboratory investigation. In Patient 1, the disfiguring course of chloracne, which was unresponsive to isotretinoin, was most impressive, whereas only a mild expression of intoxication. This indicates that compared to these patients in the acute phase of intoxication. This indicates that compared to other species, humans are not particularly sensitive in regard to lethal doses of TCDD; that is, the applied doses in our patients highly exceed the median lethal dose (LD50) of 0.6–2.0 μg/kg body weight in the guinea pig, the most sensitive species tested (23).

REFERENCES AND NOTES

1. van den Berg M, de Jongh J, Poiger H, Olson JR. The toxicokinetics and metabolism of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) and their relevance for toxicity. Crit Rev Toxicol 24:1–74 (1994).
2. Kaiser J, J ust how bad is dioxin. Science 288:1941–1944 (2000).
3. Mocarelli P, Gerthoux PM, Brambilla P, Marocchi A, Beretta C, Bertona M, Cazzaniga M, Colombo L, Crespi C, Ferrari E, et al. Dioxin health effects on humans twenty years after Seveso: a summary. In: Chemistry, Man, and Environment: The Seveso Accident 20 Years On: Monitoring, Epidemiology, and Remediation (Ballarin-Denti A, Bertazzi PA, Facchetti S, Mocarelli P, eds). New York: Elsevier, 1999:41–51.
4. Zober A, Ott MG, Messerer P. Morbidity follow up study of BASF employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1953 chemical reactor incident. Occup Environ Med 51:470–486 (1994).
5. Bertazzi PA, Beretta C, Brambilla G, Consonni D, Pesatori AC. The Seveso studies on early and long-term effects of dioxin exposure: a review. Environ Health Perspect 106(suppl 2):625–633 (1998).
6. Ott MG, Zober A, Germann C. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. Chemosphere 29:2423–2437 (1994).
7. Sweeney MH, Calvert GM, Egeland GA, Fingerhut MA, Halperin WE, Piacitelli LA. Review and update of the results of the NIOSH medical study of workers exposed to chemicals contaminated with 2,3,7,8-tetrachlorodibenzofurans in a States. Environ Health Perspect 127:241–247 (1997–98).
8. Suoksid RR, Chloracne, the hallmark of dioxin intoxication. Scand J Work Environ Health 21:165–173 (1985).
9. Geusau A, Tschachler E, Meixner M, Sandermann S, Päpke O, Wolf C, Valic E, Stingl G, Mclachlan M. Diestra increases faecal excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Lancet 354:1266–1267 (1999).
10. Geusau A, J urecka W, Nahavandi H, Schmidt J, Stingsl G, Tschachler E. Punctate keratoderma-like lesions on the palms and soles in a patient with chloracne: a new clinical manifestation of dioxin intoxication? Br J Dermatol 143:1067–1071 (2000).
11. Griffin J. Dynamic tests of endocrine function. In: Williams Textbook of Endocrinology, 8th ed (Wilson JD, Foster DW, eds). Philadelphia: Saunders, 1992:1663–1670.
12. Päpke O, Ball M, Iis A, Scheunert K. PCDD/PCDFs in whole blood samples of unexposed persons. Chemosphere 19:941–948 (1989).
13. Päpke O. PCDDs/PCFs in human blood, a fast and sensitive method. Organohalogen Compounds 31:212–214 (1997).
14. Ott M, Messerer P, Zober A. Assessment of past occupational exposure to 2,3,7,8-TCDD using blood lipid analysis. Int Arch Occup Environ Health 65:1–8 (1993).
15. Coenraads PJ, Dier K, Tang N. Blood lipid concentration of dioxins and dibenzofurans causing chloracne. Br J Dermatol 141:694–697 (1999).
16. Needham LL, Gerthoux PM, Patterson DG, Brambilla P, Turner WE, Beretta C, Pilkis J, Colombo L, Sampson EJ, Tramacere PL, et al. Serum dioxin levels in Seveso, Italy, population in 1976. Teratog Carcinog Mutagen 17:225–240 (1997–98).
17. Holzapple MP, Snyder RK, Wood SC, Morris DL. A review of 2,3,7,8-tetrachlorodibenzodioxin-induced changes in immunocompetence: 1991 update. Toxicology 69:19–255 (1991).
18. Gao X, Petroff BK, Rozman KK, Terranova PF. Gonadotropin-releasing hormone (GnRH) partially reverses the inhibitory effect of 2,3,7,8-tetrachlorodibenzodioxin on ovulation in the immature gonadotropin-treated rat. Toxicology 147:15–22 (2000).
19. Moran FM, Conley AJ, Corbin CJ, Enan E, VandeVoort C, Overstreet JS, Lasley BL. 2,3,7,8-Tetrachlorodibenzodioxin decreased estradiol production without altering the enzyme activity of cytochrome P450 aromatase of human luteinized granulosa cells in vitro. Biol Reprod 63:1102–1118 (2000).
20. Spink DC, Lincol DW II, Dickerman HW, Gierthy JF. 2,3,7,8-Tetrachlorodibenzodioxin causes an extensive alteration of 17β-estradiol metabolism in MCF-7 breast tumor cells. Proc Natl Acad Sci 87:6917–6921 (1990).
21. Mauri MC, Bravin S, Bidetto A, Rizzarelli E, Invernizzi G. A risk-benefit assessment of sulpiride in the treatment of schizophrenia. Drug Saf 14:288–298 (1996).
22. Konig MP, Kopp P. Hyperprolactinemia. Schweiz Med Wochenschr 116:265–270 (1986).
23. Schwartz BA, Norns J, Rapoports GL, Rowe K, Gehring PJ, Emerson JL, Gerbig CG. Toxicology of chlorinated dioxin-p-dioxins. Environ Health Perspect 5:87–99 (1991).
24. Mocarelli P, Marocchi A, Brambilla P, Gerthoux PM, Young DS, Mantel N. Clinical laboratory manifestations of exposure to dioxin in children. JAMA 256:2687–2695 (1986).
25. Neubert D. Reflections on the assessment of the toxicity of “dioxins” for humans, using data from experimental and epidemiological studies. Teratog Carcinog Mutagen 17:257–265 (1997–98).