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

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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. *Environ Health Perspect* 109:865–869 (2001). [Online 14 August 2001]
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2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is an environmental pollutant originating from the chemical industry or waste incineration that causes low-level accumulation in the general population via the food chain (*1*,*2*). In the past, TCDD was introduced as a toxic compound to the general public by industrial accidents, most notably in Seveso, Italy, in 1976 (*3*) and at the BASF trichlorphenol unit in Germany in the 1950s (*4*). As in the Seveso incident, where thousands of inhabitants were exposed to TCDD, no significant health effects or pathologic laboratory parameters were reported for humans after 20 years of observation, except for about 200 chloracne cases and minimal laboratory effects in the period of acute exposure (*3*,*5*). Similarly, long-term observations in workers exposed to TCDD revealed that organs other than the skin were only marginally affected or not affected in association with TCDD exposure (*4*,*6*,*7*). Most of the reports on acute TCDD intoxication date from decades ago, before assessment of TCDD levels in blood was possible. Therefore, the severity of TCDD exposure was classified solely on the basis of the chloracne status and history (*8*). In this paper we report on the clinical course and laboratory data in two individuals with the highest TCDD levels ever recorded in adults.

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. Over 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 thrombopenic 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 dyshematopoiesis and/or an increased blast cell count; no chromosomal abnormality was detectable. Moreover, because immunoglobulin or T-cell receptor rearrangements were not

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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 erythrocyte colonies [burst-forming unit-erythroid (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 amenorrhoea 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 antidepressive therapy (paroxetin; 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 androstendion) (*11*)] revealed normal results, which ruled out the possibility of a disturbance of the hypothalamic–pituitary–target system.

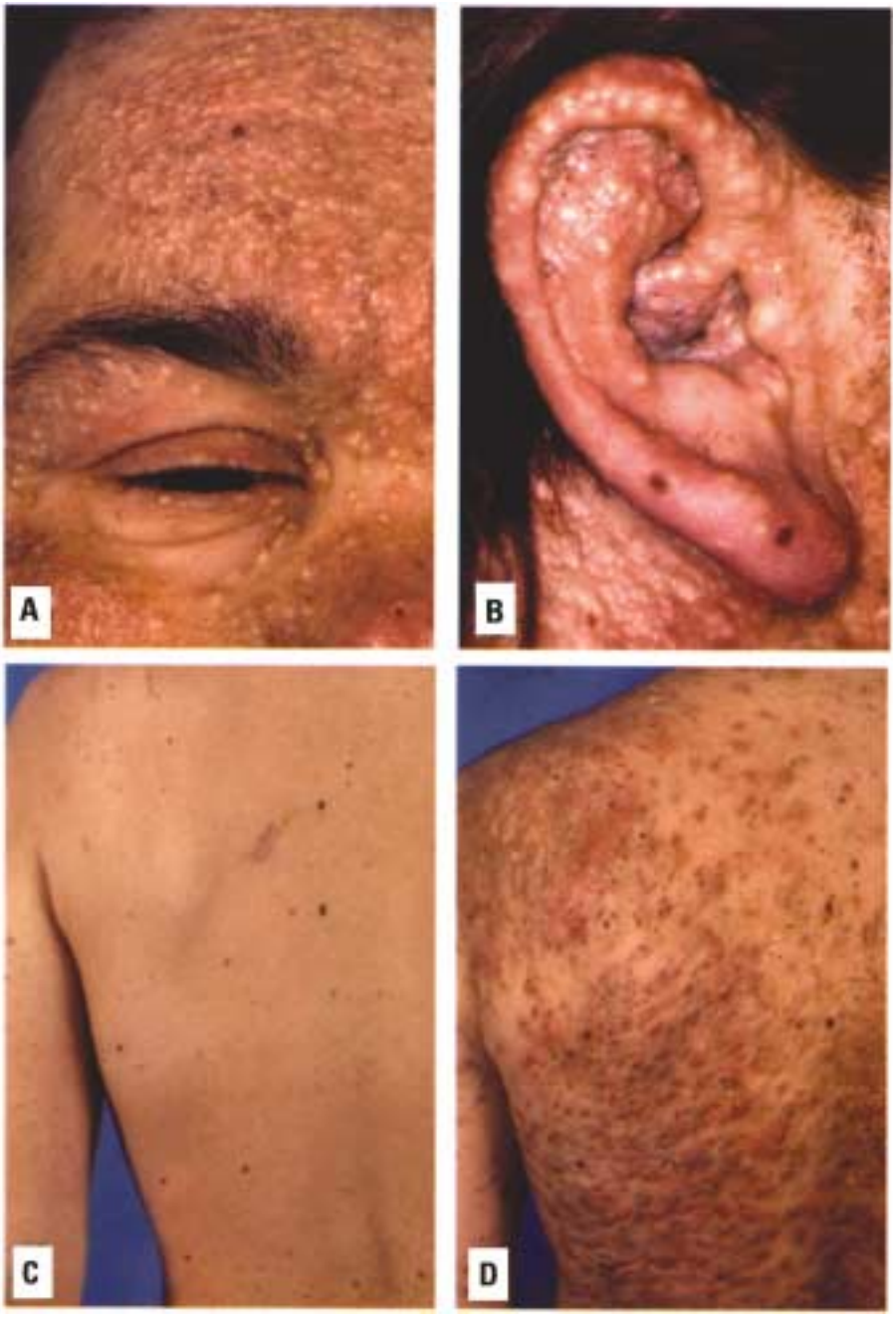

Figure 1. Clinical picture of Patient 1 one year after the diagnosis of chloracne. Multiple cysts were present (*A*) on the face and (*B*) in the auricular areas, which normally are not affected in patients with common acne. Only a few cysts were present on the patient's back in summer 1998 (*C*), whereas 1 year later (*D*) the patient's back was covered with many severely inflamed cysts.

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 adminstration of methylprednisolone (4–40 mg/day Urbason; Hoechst Marion Roussel, 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 crescent (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 olestra (*9*).

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

Table 1. Laboratory results for Patient 1 and Patient 2.

Laboratory test	Reference value	Patient 1			Patient 2		
		Median	Maximum	Minimum	Median	Maximum	Minimum
Triglycerides	50–172 mg/dL (0.56–1.9 mmol/L)	287 (7.4)	549 (14.2)	130 (3.4)	113 (2.9)	176 (4.6)	69 (1.8)
Cholesterol	150–200 mg/dL (< 5.2 mmol/L)	228 (5.9)	338 (8.7)	146 (3.8)	201 (5.2)	248 (6.4)	165 (4.3)
a-Amylase total	28–100 U/L	73	149	44	74	80	69
Lipase	–60 U/L	39	116	0	77	104	47
CHE	2.8–7.4 kU/L	4.9	6.2	3.4	5.2	6.3	4.0
Alkaline phosphatase	60-170 U/L	140	295	80	91	150	72
GOT (ASAT)	–15 U/L	7	11	5	10	12	8
GPT (ALAT)	–19 U/L	7	27	2	8	18	5
Gamma-GT	4–18 U/L	16	51	7	11	22	7
LDH	120–240 U/L	147	215	106	121	170	99
Blood count and differential blood count[a]							
Erythrocytes	3.5–5.0 10^{12}/L	3.4	4.2	2.8	4.2	4.5	3.9
Hemoglobin	120–150 G/L	103	138	84	128	142	118
Hematocrit	0.33–0.43 1	0.30	0.37	0.25	0.36	0.41	0.34
Platelet count	150–450 10^9/L	165	228	74	179	251	141
Leukocytes	3.2–9.8 10^9/L	18.4	30.6	9.9	8.1	12.2	5.7
Reticulocytes	0.7–2.0%	1.84	2.11	1.41	1.4[b]	—	—
Granulocytes	50.0–70.0%	71.6	91	52	59.6	71.4	52.1
Monocytes	0.0–12.0%	5.2	12	1	6.2	7.2	5.5
Lymphocytes	25.0–40.0%	20.5	42	6	31.6	36.8	21.6
CRP	–10 mg/L	26	55	5	5	10	< 5
Fibrinogen	1.8–3.9 G/L	4.2	5.4	3.3	2.6	3.9	1.6
Lymphocyte subpopulations[c]							
T lymphocytes (CD3+)	59–85%	84	88	79	71	73	69
	720–2,330/µL	3,648	5,435	2,537	1,750	2,339	1,520
B-lymphocytes (CD19+)	6.4–23%	12.3	17.0	9.0	23.5	26.0	22.0
	100–430/µL	537	921	336	579	701	463
T-helper cells (CD3+ CD4+)	31–61%	45	49	41	43	48	41
	500–1,760/µL	1,936	2,829	1,289	1,066	1,371	961
T-suppressor cells (CD3+ CD8+)	11–38%	38	41	38	25	26	22
	170–1,050/µL	1,668	2,500	1,197	609	797	513
CD4/CD8 ratio	0.9–3.6	1.2	1.5	1.1	1.7	2.1	1.6
Natural killer cells (CD3-CD56/CD16+)	5.6–31%	4.3	6.0	3.0	5.0	8.0	3.0
	90–430/µL	182	231	92	121	182	73
Hormones[d]							
TSH	0.1–4.0 µU/mL	1.5	2.5	0.7	3.8	10.3	2.1
Thyroxine, free	1.0–1.8 ng/dL (12–23 pmol/L)	1.1 (14)	1.4 (18)	0.8 (10)	1.1 (14)	1.3 (21)	0.8 (10)
Androstenedione	0.3–3.10 ng/mL	0.64	0.84	0.48	2.58	2.79	2.33
DHEAS	0.69–3.98 µg/dL	0.18	0.2	0.17	2.69	3.21	2.19
17-OHP	F 0.4–1.0 ng/mL; L 1.3–4.3 ng/mL	0.5	0.6	0.4	2.3 (L)	2.6 (L)	2.0 (L)
LH	F 1.5–10 mU/mL; L 0.5–13 mU/mL; P 14–72 mU/mL	1.8	2.9	1.3	9.3 (L)	15.0 (L)	5.9 (L)
FSH	F 4–13 IU/L; L 2–13 IU/L; P 5–22 IU/L	4.3	5.4	2.3	7.3 (L)	10.0 (L)	5.5 (L)
Prolactin	1.4–24.2 ng/mL	26.6	46.4	12.3	21.6	32.9	10.2
Estradiol	F 22–215 pg/mL; L 22–232 pg/mL; P 191–572 pg/mL	58	87	11	126 (L)	259 (L)	39 (L)
Progesterone	F 0.5–1.0 ng/mL; L 3.0–18.5 ng/mL; Ov 0.8–2.3 ng/mL	0.20	0.23	0.17	3.96 (L)	11.1 (L)	0.7 (L)
Testosterone	0.06–0.86 ng/mL (0.2–2.9 nmol/L)	0.05 (0.2)	0.06 (0.2)	< 0.05 (<0.2)	0.35 (1.2)	0.42 (1.5)	0.17 (0.6)
SBG	19–117 nmol/L	102	117	84	191	199	185

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 negative: 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, CH 50), antinuclear antibodies and subsets, and measures of thyroid function (serum total thyroxine, triiodothyronine, thyroxin-binding globulin, thyroid stimulating test).

[a]Female reference values. [b]Single measurement. [c]Reference values (95th percentile; data sheet of the Becton Dickinson Simultest IMK-Lmphocyte assay; Becton-Dickinson, San Jose, CA). [d]Except for thyroid-stimulating hormone and prolactin, only hormone values measured at least 2 months after cessation of hormonal contraceptives were included.

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-PeCDD; Patient 1, 47.2 pg/g; Patient 2, 14.5 pg/g blood fat), we detected no polyhalogenated compounds above background levels.

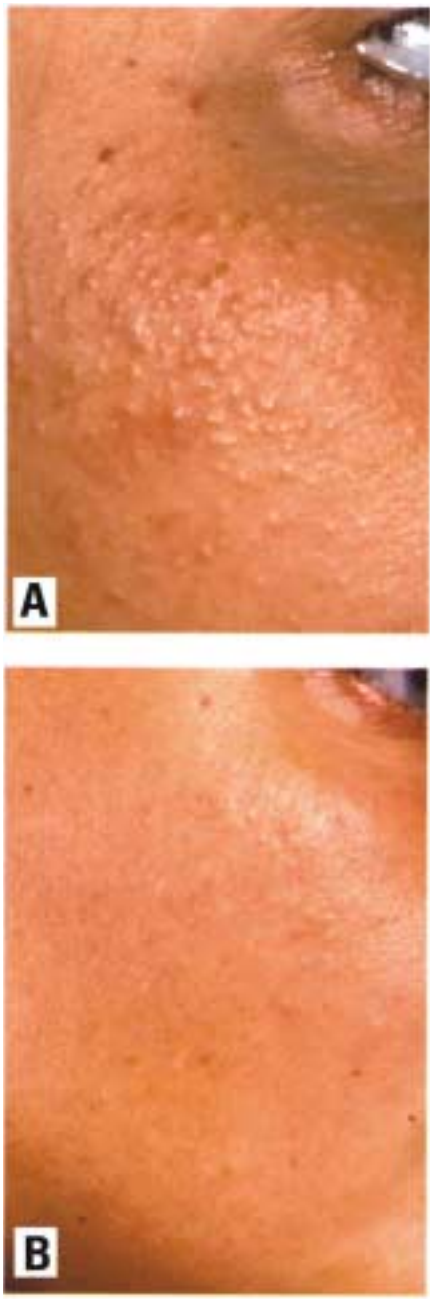

Figure 2. Clinical picture of chloracne in Patient 2. (*A*) Multiple closed and opened comedones were confined to the malar region at the time of chloracne diagnosis. (*B*) After one year of treatment with topical tretinoin (Retin A cream), the acne lesions had almost completely cleared.

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 presumable 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-PeCDD, 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*,*6*), 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 amenorrhoea 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*). Amenorrhoea 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 (LD_{50}) 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 chloracne was present in Patient 2 despite the high TCDD blood level. The varying clinical findings reported here should alert physicians that severe TCDD intoxication may occur in the absence of tangible organ manifestations or laboratory abnormalities and that occasionally, in severely intoxicated patients, only discrete chloracne may be present. Long-term follow-up of these patients is important because the risk of developing cancer cannot be currently assessed (*2*,*7*).

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