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Review

Dioxins: An overview

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Abstract

This review article summarizes what is known about human health following exposure to dioxins. It is meant primarily for health professionals but was also written with the general public in mind. The need for such an article became apparent to the authors following media inquiries at the time the then Ukraine presidential candidate Victor Yushchenko was deliberately poisoned with the most toxic dioxin, tetrachlorodibenzodioxin or TCDD.

Keywords: Dioxins; Poisoning; Yushchenko; Agent orange; TCDD

Dioxins have been featured in the news recently following a poisoning incident in Europe (British Broadcasting Corp. (BBC), 2004; Chivers, 2004; Fackelmann, 2004). Because physicians are not usually taught much about dioxins, this article attempts to provide an overview for practicing physicians. Dioxins are unwanted contaminants almost exclusively produced by industrial processes, including incineration (Olie, 1980; Environmental Protection Agency (EPA), 2004), chlorine bleaching of paper and pulp, and the manufacture of some pesticides, herbicides, and fungicides (Gilpin et al., 2003). Small amounts are synthesized for scientific research. Dioxins and dioxin-like chemicals form a large group of compounds which are structurally related, are environmentally and biologically persistent, induce a common spectrum of responses, and have a common mechanism of action (Van den Berg et al., 1998). This group includes polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), biphenyls (PCBs), and related compounds. Dioxins did not exist prior to industrialization except in very small amounts due to natural combustion and geological processes (Czuczwa et al., 1984; Schecter et al., 1988; Ferrario and Byrne, 2000). Today they are found in all humans, with higher levels commonly found in persons living in more industrialized countries (Schecter and Gasiewicz, 2003). These compounds are of concern to both public health workers and clinicians because of the many types of illnesses, both overt and subclinical, they may cause (World Health Organization (WHO), 1997; Centers for Disease Control (CDC), 1998, 2004; Institute of Medicine (IOM), 2001, 2005; Schecter and Gasiewicz, 2003; EPA, 2004).

Dioxins consist of two benzene rings connected by two oxygen atoms and contain four to eight chlorines, for a total of up to 75 compounds or congeners. Fig. 1 shows the chemical structures of a dioxin, a PCDF, and a PCB. The toxic dioxins and PCDFs have chlorines on the 2, 3, 7, and 8 positions. PCDDs, PCDFs, and some PCBs have been assigned dioxin toxic equivalency factors (TEFs) based upon their relative potency compared to the most toxic dioxin, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is assigned a TEF of 1 (Van den Berg et al., 1998). Some of the less potent dioxin-like PCBs have TEF values of only 0.0001; however, they may still be of concern as they are present in much larger amounts than dioxins. Unlike the measured dioxin levels, TEFs may change over

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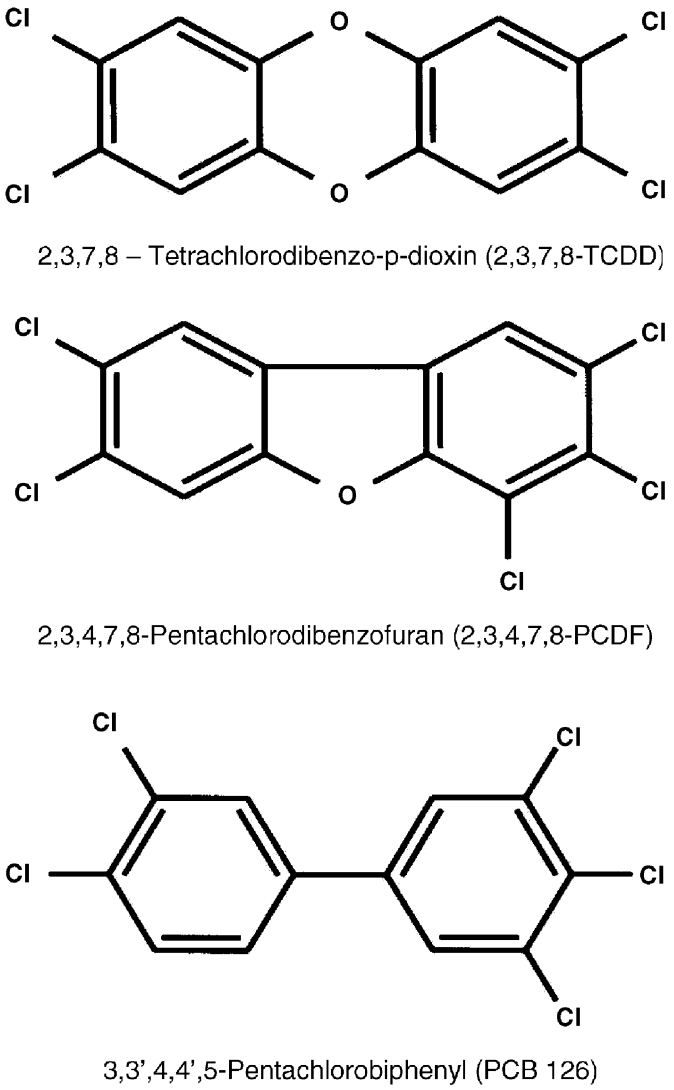

Fig. 1. Chemical structure of a selected dioxin, dibenzofuran, and PCB.

Table 1
World Health Organization (WHO) dioxin toxic equivalency factors (TEFs)

		WHO TEF
Dioxins	2,3,7,8-Tetra-CDD	1
	1,2,3,7,8-Penta-CDD	1
	1,2,3,4,7,8-Hexa-CDD	0.1
	1,2,3,6,7,8-Hexa-CDD	0.1
	1,2,3,7,8,9-Hexa-CDD	0.1
	1,2,3,4,6,7,8-Hepta-CDD	0.01
	OCDD	0.0001
Dibenzofurans	2,3,7,8-Tetra-CDF	0.1
	1,2,3,7,8-Penta-CDF	0.05
	2,3,4,7,8-Penta-CDF	0.5
	1,2,3,4,7,8-Hexa-CDF	0.1
	1,2,3,6,7,8-Hexa-CDF	0.1
	1,2,3,7,8,9-Hexa-CDF	0.1
	2,3,4,6,7,8-Hexa-CDF	0.1
	1,2,3,4,6,7,8-Hepta-CDF	0.01
	1,2,3,4,7,8,9-Hepta-CDF	0.01
	OCDF	0.0001
Coplanar PCBs	3,3′,4,4′-TCB (77)	0.0001
	3,4,4′,5-TCB (81)	0.0001
	3,3′,4,4′,5-PeCB (126)	0.1
	3,3′,4,4′,5,5′-HxCB (169)	0.01
Mono-*ortho*-PCBs	2,3,3′,4,4′-PeCB (105)	0.0001
	2,3,4,4′,5-PeCB (114)	0.0005
	2,3′,4,4′,5-PeCB (118)	0.0001
	2′,3,4,4′,5-PeCB (123)	0.0001
	2,3,3′,4,4′,5-HxCB (156)	0.0005
	2,3,3′,4,4′,5′-HxCB (157)	0.0005
	2,3′,4,4′,5,5′-HxCB (167)	0.00001
	2,3,3′,4,4′,5,5′-HpCB (189)	0.0001

time as new data become available; they are order-of-magnitude consensus estimates based on all the available data.

The total dioxin toxic equivalency (TEQ) value expresses the toxicity as if the mixture were pure TCDD. The TEQ concept was first developed in New York by the State Health Department in a series of experiments in response to the need for reentry criteria of an office building contaminated by a mixture of PCBs, PCDFs, and dioxins following an electrical transformer fire (Eadon et al., 1986). The TEQ approach and current values (Table 1) have been adopted internationally as the most appropriate way to estimate the potential health risk of mixtures of dioxins (Van den Berg et al., 1998).

The gold standard since the 1980s for diagnosis of dioxin exposure has been congener-specific high-resolution gas chromatography high-resolution mass spectrometry (HRGC-HRMS), a method first used for detection of TCDD in the 1970s for human milk and for fish exposed to dioxin-contaminated Agent Orange in Vietnam (Baughman and Meselson, 1973). Later, in the 1980s, HRGC-HRMS was used to identify dioxin and PCDF congeners in adipose tissue, human milk, and blood; all human and tissues studied to date by this methods have measurable dioxins and PCDFs (Schecter and Tiernan, 1985; Ryan et al., 1987; Schecter and Ryan, 1992). This method is now used by most dioxin laboratories worldwide, including the CDC, the US Air Force, and the WHO for dioxin exposure assessment (Michalek et al., 1990; Fingerhut et al., 1991; WHO, 1996). In addition, bioassays and immunoassays are also sometimes employed as less expensive and relatively rapid screening methods for determination of total TEQ in environmental and biological samples (Ziccardi et al., 2000). However, HRGC-HRMS remains the only way to measure specific dioxin congener levels (Rappe et al., 1979; Schecter and Tiernan, 1985; Schecter et al., 1985). There are a relatively small number of laboratories worldwide which have been certified by the WHO for the analysis of dioxins in blood (WHO, 2000).

The most toxic dioxin, TCDD (Fig. 1), became well known as a contaminant of Agent Orange herbicide used in the Vietnam war (IOM, 2005). Dioxins were found in Times Beach, Missouri (Kimbrough et al., 1977), in Love

Canal (Smith et al., 1983), and in Seveso, Italy, following an industrial explosion in 1976 (Bertazzi and di Domenico, 2003). PCDFs and PCBs were involved in rice oil poisoning incidents in Japan in 1968, known as "Yusho" (Masuda, 2003), an almost identical event in Taiwan in 1979 known as "Yucheng" (Rogan et al., 1988; Guo et al., 2003), as well as in the Binghamton State Office Building fire of 1981 (Schecter and Tiernan, 1985). Dioxins have recently been in the news with the poisoning of President Viktor Yushchenko of Ukraine in 2004 (BBC, 2004; Chivers, 2004; Fackelmann, 2004).

Because there are currently low concentrations (parts per trillion—ppt; ng/g) of the 7 dioxins, 10 PCDFs, and 12 dioxin-like PCBs of concern in humans, a relatively small additional exposure from work, environment, or food cannot always be detected. However, with heavy exposure to these compounds, as can occur with chemical workers, dioxin elevation can be found in blood or other lipid-containing tissues such as adipose tissue or milk up to 35 years following exposure as seen in Russian (Ryan and Schecter, 2000), US (Steenland and Deddens, 2003), and German workers (Schecter and Ryan, 1988; Flesch–Janys et al., 1995); US Air Force sprayers of Agent Orange; and Vietnamese exposed to Agent Orange (Michalek et al., 1990). Several exposure studies showed that some US Vietnam veterans who were exposed to Agent Orange had serum TCDD levels up to 600 ppt in lipid many years after they left Vietnam, compared to general population levels of approximately 1–2 ppt of TCDD (Kahn et al., 1988; Schecter et al., 1990a, 1992; Michalek et al., 1995). In Vietnam, TCDD levels up to 1,000,000 ppt have been found in soil or sediment from Agent Orange-contaminated areas 3–4 decades after spraying. In addition, elevated levels have been measured in food and wildlife in Vietnam (Olie et al., 1989) as well as in Vietnamese from a contaminated area (Schecter et al., 2001a, 2002, 2003; Dwernychuk et al., 2002).

The patterns of dioxins and dioxin-like chemicals reflect their sources. To a specialist the measured dioxin congener patterns in blood or other tissues can be as informative as an electrocardiogram to a cardiologist. Table 2 shows patterns in patients from different dioxin exposures. The first is an American with massive pentachlorophenol exposure (Ryan et al., 1987). Primarily higher chlorinated (with 5–8 chlorines) dioxins and PCDFs are noted compared to the background level of the general American population (Schecter et al., 1990b). The second shows blood from an Agent Orange-exposed Vietnamese with marked elevation of TCDD, the characteristic dioxin of Agent Orange (Schecter et al., 2001a). The third shows

Table 2
Comparison of human tissue levels and toxic equivalents of dioxins and dibenzofurans from different exposures

Level (pg/g or ppt, lipid)	Fat (USA)		Blood (Vietnam)		Blood (Japan)	
	General population[a]	PCP-exposed person[b]	Pooled Vietnamese blood[c]	Agent Orange-exposed[c]	General population[d]	Incinerator worker[d]
2,3,7,8-Tetra-CDD	3.6	33	2.2	101	2.6	6.4
1,2,3,7,8-Penta-CDD	6.6	70	3.5	6.1	8.6	60
1,2,3,4,7,8-Hexa-CDD	8	698	3.5	6.4	0.4	7.7
1,2,3,6,7,8-Hexa-CDD			7.7	16.5	0.4	14.5
1,2,3,7,8,9-Hexa-CDD	61.2	346	2.4	5.4	0.9	10.6
1,2,3,4,6,7,8-Hepta-CDD	na	15,260	15.4	37	0.4	3.1
OCDD	794	128,913	114	212	0.1	0.1
2,3,7,8-Tetra-CDF	1.3	nd (4.3)	1	0.9	0.6	0.2
1,2,3,7,8-Penta-CDF	na	na	0.5	0.5	0.2	0.7
2,3,4,7,8-Penta-CDF	5.6	50	6.8	3.1	7.3	122
1,2,3,4,7,8-Hexa-CDF	6.4	174	10.1	7.8	1.1	27.8
1,2,3,6,7,8-Hexa-CDF	5		7.8	4	0.8	51
1,2,3,7,8,9-Hexa-CDF	na	na	0.5	0.5	0.1	34.4
2,3,4,6,7,8-Hexa-CDF	1.4	37	2.1	1.5	0.4	5
1,2,3,4,6,7,8-Hepta-CDF	95	6021	8.6	10.4	0.1	15.4
1,2,3,4,7,8,9-Hepta-CDF	na	787	0.8	0.9	0	1.1
OCDF	na	15,348	2.5	2.5	0	0
TEQ (pg/g or ppt, lipid)						
2,3,7,8-TCDD	3.6	33	2.2	101	2.6	6.4
PCDD	14	374	5	7	11	96
PCDF	5.2	202	5.8	3	11	1365
Total TEQ	22.8	609	13	111	24.6	1467

nd, not detected, with detection limit; na, not analyzed; PCP, pentachlorophenol.
[a]Schecter et al. (1990b).
[b]Ryan et al. (1987).
[c]Schecter et al. (2001a).
[d]Schecter et al. (1999a).

blood from a Japanese municipal solid waste incinerator worker and primarily demonstrates elevated PCDFs compared to the general Japanese population (Schecter et al., 1999a). While the congener patterns differ, the total dioxin TEQ is elevated in all three of these cases.

Dioxins are extremely persistent and bioaccumulative. The half-life of TCDD in rodents is usually 2–4 weeks (Rose et al., 1976; Olie 1980) but in humans has been estimated to be 7–11 years although with wide individual variation (Pirkle et al., 1989). Recent pharmacokinetic studies have demonstrated that the half-life of dioxin is dose-dependent, elimination being faster at higher concentrations, and also varies with body composition, so that higher amounts of body fat lead to increased persistence (Emond et al., 2005; Aylward et al., 2005). Other dioxins may be eliminated more or less rapidly with as little as a 6-month half-life of elimination estimated for some PCDFs, but 20 years for others (Schecter et al., 1990a; Ryan et al., 1993; Flesch-Janys et al., 1995; Ogura, 2004).

Dioxins exert their effects via high-affinity binding to a specific cellular protein known as the aryl hydrocarbon receptor (AhR). The AhR is an intracellular ligand-activated transcription factor involved in regulation of the expression of a large number of genes. The activated form of the AhR also interacts with other regulatory proteins such as specific cellular kinases, cell cycle control proteins, and other proteins involved in apoptosis (Puga et al., 2005). Recent studies with both cells and transgenic mice with a constitutively active AhR or mice in which the AhR has been knocked out suggest that the AhR is a key regulatory protein in normal development and homeostasis (Andersson et al., 2002, 2003).

Animal studies first characterized the health effects of varying doses and combinations of dioxins (Martinez et al., 2003). In certain laboratory animals and wildlife species, dioxin can cause death following even tiny doses, leading TCDD to be called "the most toxic man-made chemical." The LD_{50} for guinea pigs is ~1 μg/kg body weight, but ~1000 μg/kg for hamsters. The LD_{50} is not known for humans, but from the results of poisoning episodes it is clearly higher than for guinea pigs. Death in laboratory animals is preceded by a wasting syndrome (Gasiewicz et al., 1980), which typically takes from 2 to 4 weeks in rodents and 6–8 weeks in nonhuman primates (Birnbaum and Tuomisto, 2000) and is not based on decreased dietary intake since pair-fed animals with matched reduced diets do not die of decreased food intake (Gasiewicz et al., 1980). While there is a great deal of species variability in the lethal dose of dioxins, other adverse effects, such as developmental toxicity, occur at similar doses in multiple vertebrate species (Birnbaum and Tuomisto, 2000).

In humans and other vertebrates dioxins have been shown to be risk factors for cancer (Fingerhut et al., 1991; Steenland et al., 1999); immune deficiency (Weisglas-Kuperus et al., 2000); reproductive and developmental abnormalities (Guo et al., 2003); central and peripheral nervous system pathology (Guo et al., 2003); endocrine disruption, including diabetes (Longnecker and Michalek, 2000) and thyroid disorders (Pavuk et al., 2003); decreased pulmonary functions and bronchitis (Shigematsu et al., 1978; Nakanishi et al., 1985); altered serum testosterone level (Egeland et al., 1994); eyelid pathology, including meibomian gland hypersecretion and hyperpigmented conjunctivae; gum pigmentation (Masuda, 2003); nausea; vomiting; loss of appetite; skin rashes, including, rarely, chloracne or acne caused by chlorine-containing organic chemicals; hypertrichosis; liver damage; elevated serum cholesterol and triglycerides (Kimbrough et al., 1977); and enamel hypomineralization of permanent first molars in children (Alaluusua et al., 2004). Table 3 summarizes these clinical manifestations. An increased risk of mortality was associated with high levels of occupational exposure to dioxins with acute ischemic cardiovascular events (Flesch-Janys et al., 1995). Transient acute health effects including headache, pruritis, fatigue, irritability, inability to have erections or ejaculations, personality changes, pain in the abdomen or extremities, diarrhea, and insomnia have been reported, especially following industrial exposures (Kimbrough and Jensen, 1989).

Reviews of the human effects are largely from occupational and epidemiological studies (WHO, 1997; CDC, 1998; IOM, 2001, 2005; Schecter and Gasiewicz, 2003; EPA, 2004). Because dioxins are highly toxic, it would not be moral, ethical, or legal to knowingly dose humans with these compounds. Instead, human studies have largely depended upon unfortunate incidents such as exposures of chemical workers (Oliver, 1975; Schecter and Ryan, 1992), contaminated rice oil used for cooking (Masuda, 2003), people living near chemical factory explosions, for example, in Seveso in 1976 (Bertazzi and di Domenico, 2003), and Vietnam veterans who sprayed Agent Orange (Michalek et al., 1990; Pavuk et al., 2003, 2005). In addition, since dioxin contamination is currently ubiquitous, positive epidemiological findings have been observed in children born to women whose TEQ levels are at the high end of the general population (Koopman-Esseboom et al., 1994; Weisglas-Kuperus et al., 2000).

Intentional dioxin poisoning has been described on only two occasions (Geusau et al., 2001a; BBC, 2004; Chivers, 2004). In a deliberate poisoning at a textile institute in Vienna in 1997, three workers with measured levels of TCDD up to 1000 ppt lipid in blood had few if any clinical symptoms (Geusau et al., 2001a). [*Note:* The level of TCDD in the US and European general populations today is approximately 1–2 ppt lipid, while the total TEQ is about 20–30 ppt lipid (Schecter and Päpke, 1998). These levels have been declining in the past 2 decades (Schecter et al., 1989; EPA, 2004).] There were two more highly poisoned individuals, one with the highest TCDD value ever measured in blood lipid, 144,000 ppt, and another with 27,000 ppt lipid. The most highly exposed woman felt very ill, developed chloracne with pruritis, experienced fatigue and pain in the extremities, and was sick for 2 years (Geusau et al., 2001a). The other intentional poisoning

Table 3
Clinical manifestation and chemicals

Clinical manifestation	Chemicals	References
Cancer	2,3,7,8-TCDD	Fingerhut et al. (1991), Steenland et al. (1999)
Cancer mortality	PCDD/F	Flesch-Janys et al. (1995)
Immune deficiency	PCB congeners (118, 138, 153, 180)	Weisglas-Kuperus et al. (2000)
	PCDD/F	
Reproductive abnormalities	PCBs, PCDFs	Guo et al. (2003)
Developmental abnormalities	TCDD	Guo et al. (2003)
CNS and PNS pathology	PCBs, PCDFs	Guo et al. (2003)
Endocrine pathology		
Diabetes	2,3,7,8-TCDD	Longnecker and Michalek (2000)
Thyroid	2,3,7,8-TCDD	Pavuk et al. (2003)
Decreased pulmonary function and bronchitis	PCBs	Shigematsu et al. (1978)
	PCBs, PCDFs	Nakanishi et al. (1985)
Elevated serum cholesterol and triglycerides	2,3,7,8-TCDD	Kimbrough et al. (1977)
Death from cardiovascular disease	PCDD/F 2,3,7,8-TCDD	Flesch-Janys et al. (1995)
Death from ischemic heart disease	PCDD/F 2,3,7,8-TCDD	Flesch-Janys et al. (1995)
Liver damage	2,3,7,8-TCDD	Kimbrough et al. (1977)
Skin rashes	2,3,7,8-TCDD	Kimbrough et al. (1977)
Chloracne		Herxheimer (1899)
Pruritis	PCBs, PCDFs	Guo et al. (2003)
Hypertrichosis	2,3,7,8-TCDD	Kimbrough et al. (1977)
Enamel hypomineralization of permanent first molars in children	2,3,7,8-TCDD	Alaluusua et al. (2004)
Gum pigmentation	2,3,7,8-TCDD	Kimbrough et al. (1977)
Eyelid pathology	2,3,7,8-TCDD	Kimbrough et al. (1977)
Meibomian gland hypersecretion	PCBs	Masuda (2003)
Hyperpigmented conjunctivae	PCBs	Masuda (2003)
Nausea	2,3,7,8-TCDD	Kimbrough et al. (1977)
Vomiting	2,3,7,8-TCDD	Kimbrough et al. (1977)
Loss of appetite	2,3,7,8-TCDD	Kimbrough et al. (1977)
Headache	PCBs, PCDFs	Guo et al. (2003)
Fatigue/general malaise	PCBs, PCDFs	Guo et al. (2003)
Change in serum testosterone	2,3,7,8-TCDD	Egeland et al. (1994)

recently documented was that of the current Ukrainian president, Victor Yushchenko (BBC, 2004; Chivers, 2004; Fackelmann, 2004).

A red skin rash or erythema sometimes followed by an acneform eruption over the face and body was first noted in groups of exposed chemical workers in the late 1800s and early 1900s. This acne eruption became known as chloracne, or acne caused by chlorinated synthetic organic chemicals such as polychlorinated napthalenes, dioxins, PCDFs, PCBs, and hexachlorobenzenes (Herxheimer, 1899; Kimmig and Schulz, 1957). Chloracne, in the past referred to as the hallmark of dioxin exposure, is shown in Figs. 2–6. Fig. 2 shows Ukraine President Viktor Yushchenko before and after he developed chloracne from a deliberate poisoning with TCDD. Fig. 3 shows the face of a child from Seveso, Italy, exposed to TCDD in whom chloracne and increased reddish facial pigmentation can be observed. Fig. 4 shows the back of a woman with chloracne and brownish hyperpigmentation who was exposed decades earlier to PCDFs and PCBs in the Yusho rice oil incident. Fig. 5 shows the dark "cola-colored" hyperpigmentation characteristically seen in some Yusho babies. Fig. 6 shows chloracne and hyperpigmentation on the face of a Japanese incinerator worker who was exposed predominantly to PCDFs. His blood congener analysis is shown in Table 2. Chloracne is a relatively insensitive and rare pathology following high-dose dioxin contamination, usually requiring blood lipid concentrations greater than 8000–10,000 ppt (Mocarelli et al., 1991; Needham et al., 1997; Landi et al., 1998; Bertazzi and di Domenico, 2003). Most persons with exposures up to 8000 ppt lipid and even some with higher levels did not develop chloracne in the Seveso incident. It was predominantly children who developed chloracne. While chloracne sometimes lasts for years, even decades in some cohorts, the cases usually resolved within 1 year in the Seveso children. In another population, Coenraads et al. (1999) found that chloracne occurred in all seven Chinese chemical workers who had TEQ blood lipid levels greater than 1000 ppt after producing the biocides pentachlorophenol and hexachlorocyclohexane (Coenraads et al., 1999).

Treatment for chloracne does not differ from treatment of common acne. Various approaches to lowering dioxin body burden, including dietary intake of mineral oil

Fig. 2. President Viktor Yushchenko of Ukraine before and after dioxin poisoning with 2,3,7,8-TCDD (courtesy of the Associated Press).

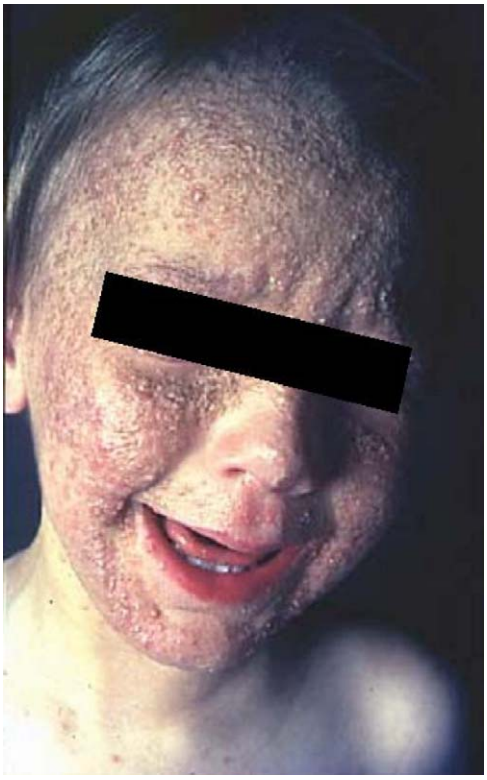

Fig. 3. Chloracne and hyperpigmentation in a child from Seveso, Italy, exposed to 2,3,7,8-TCDD (courtesy of Professor Paolo Mocarelli).

(Moser and McLachlan, 1999), activated charcoal (Araki, 1974), rice bran oil (Ilda, 1995), or the fat substitute Olestra (Geusau et al., 1999, 2002), as well as cutaneous elimination by the application of petrolatum have been tried to reduce dioxin body burden in dioxin-exposed persons with little or no clinical success (Geusau et al., 2001b). Since dioxins are lipid soluble, lactation can reduce the level in the nursing woman (Schecter et al., 1996). Unfortunately, this leads to increased exposure of the nursing infant.

Although the original sources of dioxins are largely industrial, the general population's route of exposure is almost exclusively through consumption of animal foods including meat, fish, and dairy products (Startin and Rose, 2003; EPA, 2004). Because dioxins are fat soluble, lowering fat content in food can reduce the amount of dioxin intake. Skim milk will have no dioxins, whereas milk with fat will contain higher levels. Low-fat yogurt will typically contain far less dioxins than ice cream (Schecter et al., 2001b). Broiling meat or fish and allowing the fat to drip from the food will markedly decrease the remaining amount of dioxins present (Schecter et al., 1998). Vegetables and fruit are typically very low in dioxins; therefore, long-term vegans may have much lower body burden of dioxins than people consuming animal-based products (Schecter and Päpke, 1998). The average US adult currently has a daily TEQ intake of approximately 1 pg/kg, lower than a decade ago, whereas a nursing infant has an average TEQ intake of 35–53 pg/kg/day (Schecter et al., 1994; EPA, 2004). Fortunately, because of the rapid growth of the infant and more rapid elimination, the body burden of the infant usually does not exceed that of the adult by more than about threefold (Lorber and Phillips, 2002).

The older occupational medicine literature is most useful with respect to describing acute reactions to high doses of dioxins and related chlorinated organics. A number of scientific texts provide good summaries of the dioxin literature (Kimbrough and Jensen, 1989; Schecter and Gasiewicz, 2003). A number of government and other documents also provide relatively up-to-date and comprehensive reviews. The EPA has a very large draft review of dioxins currently available only electronically (EPA, 2004). The IARC published an excellent review several years ago, but focused on cancer more than other adverse health outcomes (WHO, 1997). The WHO reviewed the risk of individual dioxins in 1998, publishing background information and conclusions regarding TEFs (Van den Berg et al., 2000). The Institute of Medicine of the National Academy of Sciences on contract from the Office of Veterans' Affairs publishes a review and evaluation of the literature every 2 years, focusing on possible health effects of dioxin or herbicides to which US veterans of the Vietnam war might have been exposed (IOM, 2005). Some of the references which exist are relatively comprehensive but they are generally not clinically oriented (Kimbrough and Jensen, 1989; Schecter and Gasiewicz, 2003). The Agency for Toxic Substances and Disease Registry of the CDC publishes periodic updates in their *Toxicological Profiles* which include dioxins, PCDFs, and PCBs; these are also available online (CDC, 1998). The Department of Health and Human Services recently concluded that 2,3,7,8-TCDD is carcinogenic to humans (National Toxicology Program, 2004). This is in agreement with both the IARC and the draft US EPA position.

Occupational medicine and preventive medicine texts do not usually devote much attention to dioxins (Zenz et al., 1994; Wallace et al., 1998). Internal medicine texts usually

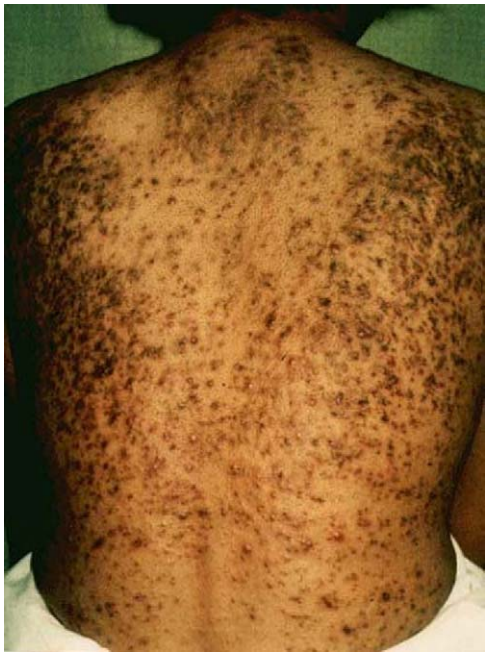

Fig. 4. Chloracne on the back of a Yusho patient (courtesy of Professor Yoshito Masuda).

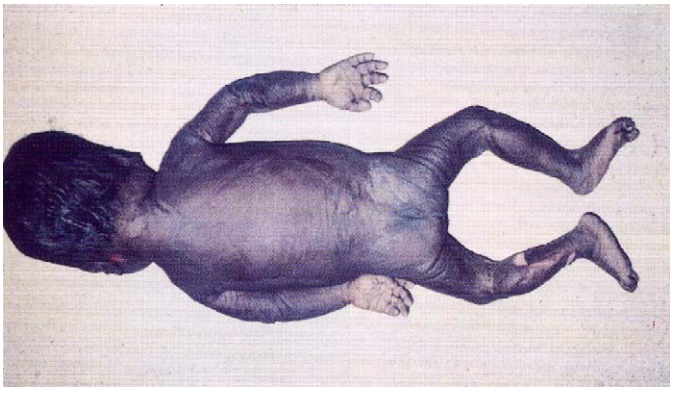

Fig. 5. A "cola-colored" Yusho baby with the hyperpigmentation characteristically seen (courtesy of Professor Yoshito Masuda).

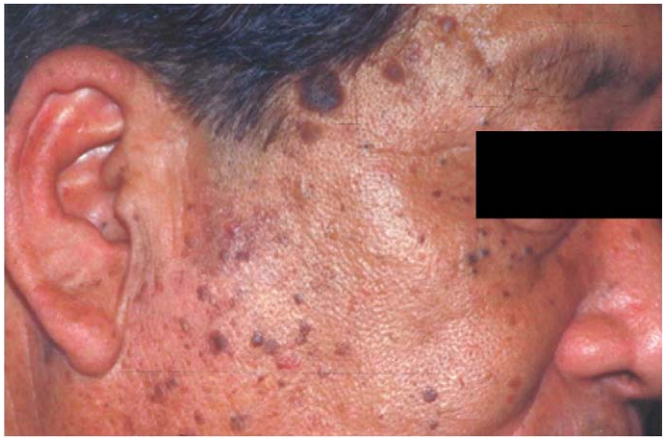

Fig. 6. Chlorance and hyperpigmentation on the face of a Japanese incinerator worker (courtesy of Goro Nakamura).

present little on this subject and are usually written by authors not very familiar with clinical aspects of these compounds (Kasper et al., 2004). Clinicians may recognize high-dose responses to dioxins, especially with the presence of chloracne as seen in the relatively rapid identification of dioxin poisoning of Ukrainian President Viktor Yushchenko. Low-dose exposure will not be as noticeable clinically, but can be clinically diagnosed with certainty only following laboratory measurements documenting levels increased above background.

Effects may be occurring but difficult to detect in the more highly exposed members of the general population (Birnbaum and Fenton, 2003). The animal data suggest that there is only a very small margin of exposure, that is, the ratio between the dose at which effects occur in animals and the current levels in the upper end of our background human population (Birnbaum and Farland, 2003; Martinez et al., 2003). Developmental and reproductive toxicity, immunotoxicity, and neurotoxicity have been detected in rats, mice, and nonhuman primates at levels in the animals which are less than 10 times higher than in the more highly exposed members of the general population. Many of these same endpoints have been observed in children whose mothers are at the high end of the general population in terms of levels of dioxin and related chemicals (Koopman-Esseboom et al., 1994; Jacobson and Jacobson, 1996, 2002; Alaluusua et al., 2004; Weisglas-Kuperus et al., 2004). The developmental effects are most likely subclinical on an individual basis, including respiratory infections, behavioral or cognitive difficulties, and altered breast or penile development at puberty (Den Hond et al., 2002). However, as we have learned from decades of research with lead, subtle effects on the individual have major implications for a population. In addition, epidemiological studies suggest that the exposures which have been associated with an increase in cancer occur at dioxin levels in people similar to those that have been reported from the animal studies (Steenland et al., 2004). However, a maximum increased risk of 1/1000 of cancer would not be detected at current human background levels, given that cancer is such a common disease and a leading cause of death.

Although effects of small exposures to dioxins are unlikely to be detected by clinicians, the growing body of toxicological and epidemiological literature demonstrates that dioxins have had adverse impacts on our population. Levels of dioxins in the United States and Europe are decreasing, both in the environment and in the population (Schecter et al., 1989, 2005; EPA, 2004). This is almost certainly a result of stricter regulations of industrial processes throughout the developed world.

The practicing physician faces a major challenge in diagnosing and treating potentially dioxin-contaminated patients, especially in the absence of an exposure history. Dioxin exposure frequently is a public health/epidemiology issue, not usually a clinical one. There is no pathognomonic lesion as is the case from asbestos. Frequently patients have heard of dioxins in the news media and are

convinced their symptoms are due to dioxins. Chemical workers, incinerator workers, and others with long exposures to high amounts of dioxins are most likely to be contaminated. Chloracne is helpful but very rare, since its presence means that there has been exposure to dioxins, but its absence does not mean there has not. In worker populations, or in the Asian rice oil poisonings, large numbers of patients with similar symptoms can alert the physician to the correct diagnosis. Communication between the treating physician and a company physician, nurse, or environmental safety officer is frequently useful. Environmental samples, soot, ash, or the chemical residues at a factory may be found to have elevated dioxins in a pattern characteristic of the chemical process in question. Because an experienced dioxin laboratory usually charges about $1200 for a congener-specific dioxin blood analysis, and because this is usually not covered by health insurance, this gold standard test cannot be ordered routinely. Biological screening tests exist, but in our experience, these are not definitive, nor much less costly after cleanup than analytical methods (Schecter et al., 1999b; Windal et al., 2005). Even if elevated dioxins are found in the patient's blood, the physician still needs to keep in mind other causes of medical abnormalities for conditions such as elevated liver enzymes, skin rashes, fatigue, headaches, or insomnia. Other serious medical conditions may also be present and need diagnosis and treatment. If there is definite evidence of dioxin contamination based on exposure history and an elevated blood dioxin level, the physician can only treat the disorders regardless of the cause as there is no good way to reduce body burden of dioxins. It is not clear whether there might be any clinical utility in reducing body burden of dioxins through breastfeeding or any other means. Damage may have occurred prior to establishing a diagnosis. An occupational medicine specialist in dioxins can be invaluable to assist in pointing out what to expect over time. Since "the dose makes the poison" it is customary to initially measure and then monitor the blood dioxin levels over time until the levels approach background. Serial dioxin blood tests can also alert the physicians to ongoing dioxin contamination should their levels fail to decline. At this time we have no methods to measure sensitivity to the effects of dioxin, only to its exposure. There continues to be considerable current research on the dioxins and in the next few years we may increase our understanding and especially gain a more precise knowledge of their clinical effects and treatments, as well as the population effects, of these potent and persistent chemicals.

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