



Uploaded to the VFC Website

▶▶▶ 2019 ◀◀◀

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

[Veterans-For-Change](#)

If Veterans don't help Veterans, who will?

Note:

VFC is not liable for source information in this document, it is merely provided as a courtesy to our members & subscribers.



CHRONIC TOXICITY SUMMARY

**CHLORINATED DIBENZO-P-DIOXINS AND
CHLORINATED DIBENZOFURANS**
(INCLUDING 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN)

(Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) including 2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) which is the principal congener of concern based on toxicity)

CAS Registry Number: 1746-01-6 (TCDD); 5120-73-19 (TCDF)

I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	0.00004 µg/m³ (40 pg/m³)
<i>Oral reference exposure level</i>	1 x 10⁻⁸ mg/kg/day (10 pg/kg/day)
<i>Critical effect(s)</i>	Increased mortality, decreased weight gain, depression of erythroid parameters, increased urinary excretion of porphyrins and delta-aminolevulinic acid, increased serum activities of alkaline phosphatase, gamma-glutamyl transferase and glutamic-pyruvic transaminase, gross and histopathological changes in the liver, lymphoid tissue, lung and vascular tissues in rats.
<i>Hazard index target(s)</i>	Alimentary system (liver); reproductive system; development; endocrine system; respiratory system; hematopoietic system

II. Physical and Chemical Properties (HSDB, 1995; 1999)

<i>Description</i>	All are white crystalline powders at 25° C.
<i>Molecular Formula</i>	C ₁₂ H ₄ C ₁₄ O ₂ (TCDD)
<i>Molecular Weight</i>	321.97 g/mol (TCDD)
<i>Density</i>	1.827 g/ml (estimated for TCDD)
<i>Boiling Point</i>	412.2°C (estimated for TCDD)
<i>Melting Point</i>	305-306°C (TCDD)
<i>Vapor Pressure</i>	1.52 x 10 ⁻⁹ torr at 25°C (TCDD)
<i>Solubility</i>	In water: 19.3 ng/L at 22°C (TCDD)
<i>Log K_{ow}</i>	6.15-7.28 (6.8 for TCDD)
<i>(octanol/water partition coefficient)</i>	
<i>Log K_{oc}</i>	6.0-7.39
<i>(organic-carbon distribution coefficient)</i>	
<i>Henry's Law Constant</i>	8.1 x 10 ⁻⁵ ATM-m ³ /mol

III. Major Uses and Sources

The chlorinated dioxins and furans are generated as by-products from various combustion and chemical processes. PCDDs are produced during incomplete combustion of chlorine containing wastes like municipal solid waste, sewage sludge, and hospital and hazardous wastes. Various metallurgical processes involving heat, and burning of coal, wood, petroleum products and used tires for energy generation also generate PCDDs. Chemical manufacturing of chlorinated phenols (e.g., pentachlorophenol), polychlorinated biphenyls (PCBs), the phenoxy herbicides (e.g., 2,4,5 T), chlorinated benzenes, chlorinated aliphatic compounds, chlorinated catalysts and halogenated diphenyl ethers are known to generate PCDDs as a by-product under certain conditions. While manufacture of many of these compounds and formulations has been discontinued in the United States, continued manufacture elsewhere in the world combined with use and disposal of products containing PCDD by-products results in the inadvertent release of PCDDs into the environment. Industrial and municipal processes in which naturally occurring phenolic compounds are chlorinated can produce PCDDs; the best example is chlorine bleaching of wood pulp in the manufacture of paper products. Additionally, municipal sewage sludge has been documented to occasionally contain PCDDs and PCDFs. Annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 0.123 pounds of 2,3,7,8-TCDD, 0.244 pounds of 1,2,3,4,7,8-hexachlorodibenzodioxin and lesser amounts of other polychlorinated dibenzodioxins and dibenzofurans (CARB, 1999).

IIIa. 2,3,7,8 Tetrachlorodibenzo-p-dioxin Toxic Equivalents

2,3,7,8-Tetrachlorodibenzo-p-dioxin is considered the most potent congener of the polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) families of compounds. Potency of PCDD and PCDF congeners correlates with the binding affinity to the cytosolic Ah receptor. Structure activity studies have demonstrated that optimal biological activity and Ah-receptor binding requires congeners with a planar conformation and chlorines at the corners of the molecule at the 2,3,7,8 positions (Poland and Knutson, 1982; Safe, 1986). Chlorines at both ortho positions in these molecules (i.e., positions 1 and 9) sterically hinder a planar conformation that lessens the congeners' biological activity. Thus only 15 of 210 different PCDDs and PCDFs congeners possess significant biological activity based on chlorines in the 2,3,7,8 positions and some degree of planar conformation (Safe, 1986; U.S. EPA 1989). These include two tetrachloro-congeners: 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran; three pentachloro congeners: 1,2,3,7,8-pentachlorodibenzo-p-dioxin, 1,2,3,7,8-pentachlorodibenzofuran, and 2,3,4,7,8-pentachlorodibenzofuran; seven hexachloro congeners: 1,2,3,4,7,8 or 1,2,3,6,7,8 or 1,2,3,7,8,9-hexachlorodibenzo-p-dioxins and hexachlorodibenzofurans and 2,3,4,6,7,8-hexachlorodibenzofuran; and three heptachloro congeners: 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachlorodibenzofuran and 1,2,3,4,7,8,9-heptachlorodibenzofuran (U.S. EPA, 1989). The structures of the dibenzo-p-dioxins and dibenzofurans along with their numbering schemes are shown in Figure 1. Toxic equivalents are calculated relative to the most potent congener, 2,3,7,8-tetrachlorodibenzo-p-dioxin, and are determined based on structure activity studies examining relative affinity for the

Ah receptor as well as on relative toxicity of different congeners. Values for the international system of toxic equivalents are provided in Table 1 (U.S. EPA, 1989).

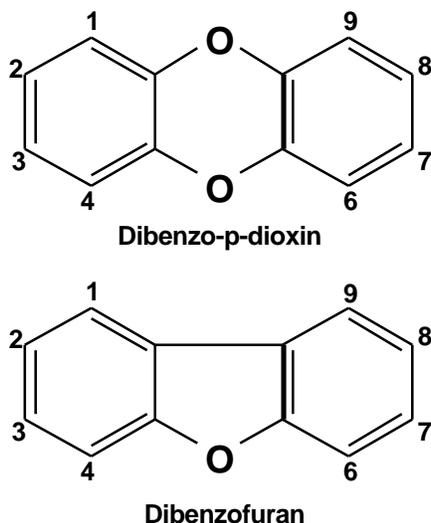
Table 1. International Toxic Equivalency Factors (I-TEFs) for PCDDs and PCDFs Chlorinated in the 2,3,7, and 8 Positions. (U.S. EPA 1989.)

Compound ^{1,2}	I-TEF
Mono-, Di-, and Tri-CDDs and CDFs	0
<u>TetraCDD</u>	
2,3,7,8-substituted	1.0
Others	0
<u>PentaCDD</u>	
2,3,7,8-substituted	0.5
Others	0
<u>HexaCDD</u>	
2,3,7,8-substituted	0.1
Others	0
<u>HeptaCDD</u>	
2,3,7,8-substituted	0.01
Others	0
<u>OctaCDD</u>	
	0.001
<u>TetraCDF</u>	
2,3,7,8	0.1
Others	0
<u>PentaCDF</u>	
1,2,3,7,8-PentaCDF	0.05
2,3,4,7,8-PentaCDF	0.5
others	0
<u>HexaCDF</u>	
2,3,7,8-substituted	0.1
Others	0
<u>HeptaCDF</u>	
2,3,7,8-substituted	0.01
Others	0
<u>OctaCDF</u>	
	0.001

¹ CDD designates chlorinated dibenzo-p-dioxin

² CDF designates chlorinated dibenzofuran

Figure 1. Structures of the Dibenzop-dioxins and Dibenzofurans



IV. Effects of Human Exposure

The information available on possible chronic toxic effects in humans is complicated by the relative insensitivity of epidemiological studies, the limited ability of case studies of exposed individuals to establish cause and effect relationships, the heterogeneous nature of human populations, the broad spectrum of exposures to other toxic agents in the human environment, and the episodic exposure of many of the exposed human populations which have been studied (e.g., Seveso, Italy). As a result, a limited number of effects have been associated with exposure to dioxins in humans. The meaning of these effects in terms of toxicity in most cases remains to be clarified. The majority of information comes from cross-sectional medical studies.

Chloracne is the most widely recognized effect of exposure to 2,3,7,8-TCDD and TCDD-like PCDDs and PCDFs. Chloracne is a persistent condition, which is characterized by comedones, keratin cysts and inflamed papules and is seen after acute and chronic exposure to various chlorinated aromatic compounds (Moses and Prioleau, 1985). Other dermal effects include hyperpigmentation and hirsutism or hypertrichosis (Jirasek *et al.*, 1974; Goldman, 1972; Suskind *et al.*, 1953; Ashe and Suskind, 1950); both appear to resolve themselves more quickly over time than chloracne, making them more of an acute response rather than a chronic response (U.S. EPA, 1994a). Epidemiological data available for 2,3,7,8-TCDD have not allowed a determination of the threshold dose required for production of chloracne (U.S. EPA, 1994b). Case studies suggest that there may be a relationship between 2,3,7,8-TCDD exposure and hepatomegaly (Reggiani, 1980; Jirasek *et al.*, 1974; Suskind *et al.*, 1953; Ashe and Suskind, 1950) and hepatic enzyme changes (Mocarelli *et al.*, 1986; May, 1982; Martin 1984; Moses *et al.*, 1984). Nevertheless, cross sectional epidemiological studies of trichlorophenol (TCP) production workers (Suskind and Hertzberg., 1984; Bond *et al.*, 1983; Moses *et al.*, 1984; Calvert *et al.* 1992), Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988; Roegner *et al.*, 1991) and Missouri residents (Webb *et al.*, 1989; Hoffman *et al.*, 1986)

found little evidence for an association between exposure and hepatomegaly suggesting that this is not a chronic response. There is a consistent pattern of increased levels of serum gamma glutamyl transferase in populations exposed to 2,3,7,8-TCDD, which is presumably of hepatic origin (Mocarelli, 1986; Caramaschi *et al.*, 1981, May, 1982; Martin, 1984; Moses *et al.*, 1984; Calvert *et al.*, 1992; Centers For Disease Control Vietnam Experience Study, 1988). Two cross sectional studies have associated diabetes and elevated fasting serum glucose levels with relatively high serum 2,3,7,8-TCDD levels (Sweeney *et al.*, 1992; Roegner *et al.*, 1991). However other studies provided mixed results (Moses *et al.*, 1984; Centers for Disease Control Vietnam Experience Study, 1988; Ott *et al.*, 1993). TCDD has been associated with effects on reproductive hormonal status in males. The likelihood of abnormally low testosterone levels was 2 to 4 times greater in individuals with serum 2,3,7,8-TCDD levels above 20 pg/ml (Egeland *et al.* 1994) and increased serum levels of luteinizing hormone and follicle stimulating hormone have been documented (Egeland *et al.*, 1994). A number of other effects have been reported that were either not seen as chronic effects or effects seen long term in only one population of exposed persons. These include elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase), pulmonary disorders, neurologic disorders, and changes in porphyrin metabolism and kidney disorders (U.S. EPA, 1994c). Areas in which there is presently insufficient information to draw solid conclusions include effects on the circulatory system, reproductive effects, immunological effects, effects on metabolism and handling of lipids, and on thyroid function (U.S. EPA, 1994c). Recent findings in Rhesus monkeys have shown 2,3,7,8-TCDD to cause endometriosis (Reier *et al.*, 1993) and epidemiological studies are currently underway to determine if there is an association between TCDD exposure and endometriosis in human populations exposed by the Seveso accident.

Potential effects of a toxicant on normal fetal development include fetal death, growth retardation, structural malformations and organ system dysfunction. Evidence for all four of these responses has been seen in human populations exposed to dioxin-like compounds. In these poisoning episodes populations were exposed to a complex mixture of halogenated aromatic hydrocarbons contained within PCBs, PCDFs and PCDDs mixtures thus limiting the conclusions that could be drawn from the data. In the Yusho and Yu-Cheng poisoning episodes, human populations consumed rice oil contaminated with PCBs, PCDFs and PCDDs. Yu-Cheng women experienced high perinatal mortality in hyperpigmented infants born to affected mothers (Hsu *et al.* 1985). This occurred in women with overt signs of toxicity (chloracne) (Rogan, 1982) and Rogan notes that, when there is no sign of toxicity in the mother, the likelihood of fetotoxicity appears to lessen considerably in the infants. Signs of toxicity from dioxin like compounds were absent in infants born to mothers apparently not affected in the Seveso, Italy and Times Beach, Missouri, incidents (Reggiani, 1989; Hoffman and Stehr-Green, 1989), which supports Rogan's conclusion. There was an increased incidence of decreased birth weight in infants born to affected mothers in the Yusho and Yu-Cheng incidents suggesting fetal growth retardation (Wong and Huang, 1981; Law *et al.*, 1981; Lan *et al.*, 1989; Rogan *et al.*, 1988). The structural malformation, rocker bottom heel, was observed in Yusho infants (Yamashita and Hayashi, 1985) making this malformation a possible result of exposure to dioxin-like compounds. Nevertheless, it is unknown if these compounds produce malformations in humans. Evidence for possible organ system dysfunction in humans comes from a study of Yu-Cheng children which found that children exposed in utero experienced delays in attaining developmental milestones, and exhibited neurobehavioral abnormalities (Rogan *et al.*, 1988)

suggesting involvement of CNS function. Dysfunction of dermal tissues is noted in exposed infants of the Yusho and Yu-Cheng incidents and is characterized by hyperpigmentation of the skin, fingernails, and toenails, hypersecretion of the meibomian glands, and premature tooth eruption (Taki *et al.*, 1969; Yamaguchi *et al.*, 1971; Funatsu *et al.*, 1971; Wong and Huang, 1981; Hsu *et al.*, 1985; Yamashita and Hayashi, 1985; Rogan *et al.*, 1988; Rogan, 1989; Lan *et al.*, 1989).

V. Effects of Animal Exposure

The toxicity to laboratory animals encompasses a number of areas including changes in energy metabolism manifested as wasting syndrome, hepatotoxicity, effects on tissue of epithelial origin, various endocrine effects, effects on vitamin A storage and use, immune system effects and reproductive and developmental toxicity. The limited number of chronic studies available do not examine all these endpoints. Therefore subchronic exposures are included here in order to provide a more complete coverage of potential chronic toxic effects of these compounds.

Wasting syndrome is one of the most broadly occurring toxic effects. The wasting syndrome is characterized by loss of adipose tissue and lean muscle mass and is produced in all species and strains tested, but there are difference in sensitivity (U.S. EPA 1994d; Peterson *et al.*, 1984; Max and Silbergeld, 1987). Numerous studies have not yet established the mechanism of wasting syndrome (U.S. EPA, 1994e). Hepatotoxicity is also seen in all species tested, but there is considerable variation in species sensitivity (U.S. EPA, 1994d). TCDD induces hyperplasia and hypertrophy of liver parenchymal cells. Morphological and biochemical changes in the liver include increased SGOT and SGPT, induction of microsomal monooxygenases and proliferation of the smooth endoplasmic reticulum, porphyria, increased regenerative DNA synthesis, hyperlipidemia, hyperbilirubinemia, hypercholesterolemia, hyperproteinemia, degenerative and necrotic changes, mononuclear cell infiltration, multinucleated giant hepatocytes, increased numbers of mitotic figures, and parenchymal cell necrosis (U.S. EPA, 1994d; WHO/IPCS, 1989). Epithelial effects seen include chloracne (rabbit ear and the hairless mouse) (Jones and Krizek, 1962; Schwetz *et al.*, 1973) and hyperplasia and/or metaplasia of gastric mucosa, intestinal mucosa, the urinary tract, the bile duct and the gall bladder (U.S. EPA 1994f). TCDD exposure results in endocrine like effects including epidermal growth factor like effects such as early eye opening and incisor eruption in the mouse neonate (Madhukar *et al.*, 1984), glucocorticoid like effects such as involution of lymphoid tissues (U.S. EPA, 1994g; Sunahara *et al.*, 1989), alteration in thyroid hormone levels and in some cases thyroid hormone like effects (WHO/IPCS, 1989; Rozman *et al.*, 1984), decreases in serum testosterone and dihydrotestosterone (Mittler *et al.*, 1984; Keys *et al.*, 1985; Moore and Peterson, 1985), and changes in arachidonic acid metabolism and prostaglandin synthesis (Quilley and Rifkind, 1986; Rifkind *et al.*, 1990). TCDD is known to decrease hepatic vitamin A storage (Thunberg *et al.*, 1979). TCDD and other dioxin like PCDDs and PCDFs are potent suppressors of both cellular and humoral immune system function, characteristically producing thymic involution at low doses and involution of other lymphoid tissues at higher doses (U.S. EPA 1994h).

In animal studies there is a large body of information available documenting both developmental and reproductive toxicity of 2,3,7,8-TCDD and other PCDDs and PCDFs. These compounds are

acutely toxic to early life stages of fish and birds with fish being most sensitive (LD₅₀ of 0.4 µg/kg for rainbow trout sac fry eggs and LD₅₀ of 34 ng/kg for lake trout eggs); some species of birds are also relatively sensitive (LD₅₀ of 0.25 µg/kg for chicken eggs) (Peterson *et al.*, 1993). 2,3,7,8-TCDD has been documented to increase the incidence of prenatal mortality in a number of species of laboratory animals including the Rhesus monkey, Guinea pig, rabbit, rat, hamster, and mouse (Peterson *et al.*, 1993). Exposure to 2,3,7,8-TCDD during gestation produces a characteristic set of fetotoxic responses in most laboratory animals which includes: thymic hypoplasia, subcutaneous edema, and decreased growth (Peterson *et al.*, 1993). More species specific responses include cleft palate formation in the mouse at doses below maternal toxicity (Moore *et al.*, 1973; Smith *et al.*, 1976; Couture *et al.*, 1990), intestinal hemorrhage in the rat (Sparschu *et al.*, 1971), hydronephrosis in the mouse and hamster (Moore *et al.*, 1973; Smith *et al.*, 1976; Couture *et al.*, 1990; Birnbaum *et al.*, 1989; Olson *et al.*, 1990), and extra ribs in the rabbit (Giavini *et al.*, 1982). Female rats have also been found to be affected by perinatal exposure to 2,3,7,8-TCDD with clefting of the clitoris, incomplete or absent vaginal opening and a smaller vaginal orifice after a dose of 1 µg/kg to the mother on day 15 of gestation (Gray *et al.*, 1993).

A number of effects on adult reproductive function are seen in male animals exposed in utero to 2,3,7,8-TCDD. TCDD reduces plasma androgen levels in the adult male rat and perinatal exposure decreases spermatogenesis, spermatogenic function and reproductive capability, feminizes male sexual behavior, and feminizes male gonadotrophic function (LH secretion) (Mably *et al.*, 1991; Mably *et al.*, 1992a,b,c). Evidence suggests that these effects are the result of impaired sexual differentiation of the CNS, which in male rats is dependent on exposure of the developing brain to testosterone.

There are numerous studies detailing the effects of the PCDDs, PCDFs and other dioxin like compounds, however a large number of these studies were conducted as either acute or subchronic exposures, studies in which it is unlikely that body burdens had reached steady state levels. Detailed below are three chronic studies that were considered in the setting of a chronic toxicity exposure level.

The most definitive study of chronic toxicity in rats is that of Kociba *et al.* (1978). This study involved the administration of 2,3,7,8-TCDD in the diet at doses of 1 ng/kg/day, 10 ng/kg/day, and 100 ng/kg/day to groups of 50 male and 50 female Sprague Dawley rats for two years. A group of 86 male and 86 female rats received diet with solvent vehicle alone and served as controls. The following observations (excluding carcinogenic effects) were seen at the 100 ng/kg/day dose: increased mortality, decreased weight gain, depressed erythroid values, increased urinary excretion of porphyrins and delta-aminolevulinic acid, and increased serum activities of alkaline phosphatase, gamma-glutamyl transferase, and glutamic-pyruvic transaminase. Histopathologic changes were noted in the liver, lymphoid tissue, respiratory and vascular tissues. The primary ultrastructural change in the liver was proliferation of the rough endoplasmic reticulum. At the 10 ng/kg/day dose the severity of toxic symptoms was less than that of the 100 ng/kg/day dose and included increased urinary excretion of porphyrins in females as well as liver and lung lesions. The 1 ng/kg/day dose produced no discernible significant toxic effects. Interpretation of this study by the authors was that the 1 ng/kg/day dose was a NOAEL.

Two chronic toxicity studies are available in the mouse. The first is a one year study conducted by Toth *et al.* (1979) using male Swiss mice administered weekly oral doses of 7, 700, and 7000 ng/kg/day. In this study 2,3,7,8-TCDD administration resulted in amyloidosis and dermatitis in 0 of 38 control animals, 5 of 44 animals receiving 7 ng/kg/day, 10 of 44 animals receiving 700 ng/kg/day and 17 of 43 animals receiving 7,000 ng/kg/day. The other study was from the NTP 1982 gavage study (NTP, 1982) in B6C3F1 mice. This study employed groups of 50 male and 50 female mice. The males received doses of 0, 10, 50, and 500 ng/kg/week by gavage for two years while female mice received doses of 0, 40, 200, and 2000 ng/kg/week by gavage for two years. No adverse effects were seen at the lowest doses tested in each sex, which correspond to NOAELs of approximately 1.4 and 6 ng/kg/day for males and females, respectively. Neither chronic toxicity study in mice reported data on enzyme activity.

VI. Derivation of Chronic Reference Exposure Level (REL)

<i>Study</i>	Kociba <i>et al.</i> (1978)
<i>Study population</i>	Sprague-Dawley rats of both sexes (50/treatment group/sex)
<i>Exposure method</i>	Continuous dietary exposure starting at seven weeks of age for 2 years
<i>Critical effects</i>	Increased mortality, decreased weight gain, depression of hematologic measures, increased urinary excretion of porphyrins and delta-aminolevulinic acid, increased serum activities of alkaline phosphatase, gamma-glutamyl transferase and glutamic-pyruvic transaminase, gross and histopathological changes in the liver, lymphoid tissue, lung and vascular tissues
<i>Observed LOAEL</i>	210 ppt in diet (0.01 µg/kg/day)
<i>Observed NOAEL</i>	22 ppt in diet (0.001 µg/kg/day)
<i>Exposure continuity</i>	Continuous exposure via the diet
<i>Exposure duration</i>	2 years
<i>Subchronic uncertainty factor</i>	1
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Oral reference exposure level</i>	10 pg/kg/day
<i>Route-to-route extrapolation</i>	3,500 µg/m ³ per mg/kg/day
<i>Inhalation reference exposure level</i>	40 pg/m ³ (0.00004 µg/m ³)

The data available for chronic toxic effects in humans have a number of limitations. Some studies did not determine the body burden of compounds necessary to estimate dose.; The Yusho and Yu-Cheng poisoning episodes have uncertainty because exposure was to complex mixtures of halogenated aromatic hydrocarbons rather than to individual congeners. And epidemiological

studies and case studies have limitations in determining cause and effect relationships. Therefore, an animal study was chosen for determination of a NOAEL/LOAEL. The study chosen for use was that of Kociba *et al.* (1978), based on the duration of the study (2 years), the number of animals employed (50 per treatment group per sex), testing of both sexes, a dose range, which spanned from an apparent NOAEL to severe hepatic effects including carcinogenic effects, a complete histopathological examination of all organ systems, examination of urinary excretion of porphyrins and delta-aminolevulinic acid, and determination of serum activities of alkaline phosphatase, gamma-glutamyl transferase, and glutamic-pyruvic transaminase. The elevation of human serum values for gamma-glutamyl transferase is one of the consistently seen chronic responses in exposed human populations and reflects changes in liver biochemistry. Thus the examination of markers of liver toxicity also altered in animal models of chronic toxicity make the Kociba study an appropriate choice for detecting potential chronic toxic effects of 2,3,7,8-TCDD in humans. The NOAEL in the Kociba *et al.* (1978) study was determined to be 1 ng/kg body weight/day. For the purposes of determining the REL the 1 ng/kg/day dose was considered to be a NOAEL based upon the observations of Kociba *et al.* (1978).

VII. Data Strengths and Limitations for Development of the REL

NOAELs from a number of other studies compare favorably with the 1 ng/kg/day NOAEL. These include the NOAEL from the NTP (1982) study in B6C3F1 mice and the NOEL for enzyme induction in rats and marmosets calculated by Neubert (1991) of 1 ng/kg. Furthermore the 1 ng/kg/day NOAEL is lower than the LOAELs observed by Toth *et al.* (1979) of 7 ng/kg/day in mice and by Schantz *et al.* (1978) of 2.3 ng/kg/day in rhesus monkeys. Current exposure assessments for 2,3,7,8-TCDD and other dioxin-like compounds including the PCBs, PCDDs, and PCDFs estimate that the average daily background dose in the U.S. is 3-6 pg TEQ/kg/day (U.S. EPA 1994i) also placing the REL close to background exposures. The REL of 10 pg/kg/day should be protective of chronic effects on liver function and avoid significant increases in exposure over the background level of human exposure.

The strengths of the inhalation REL include the availability of chronic exposure data from a well-conducted study with histopathological analysis, the observation of a NOAEL, and the demonstration of a dose-response relationship. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic inhalation exposure studies.

VIII. References

- Ashe WF, and Suskind RR. 1950. Reports on chloracne cases, Monsanto Chemical Co., Nitro, West Virginia, October 1949 and April 1950. Cincinnati, OH: Department of Environmental Health, College of Medicine, University of Cincinnati (unpublished).
- Birnbaum LS, Harris MW, Stocking LM, Clark AM, and Morrissey RE. 1989. Retinoic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) selectively enhance teratogenesis in C57BL/6N mice. *Toxicol. Appl. Pharmacol.* 98: 487-500.
- Bond GG, Ott MG, Brenner FE, and Cook RR. 1983. Medical and morbidity surveillance findings among employees potentially exposed to TCDD. *Br. J. Ind. Med* 40: 318-324.
- CARB. 1999. Air toxics emissions data collected in the Air Toxics Hot Spots Program CEIDARS Database as of January 29, 1999.
- Calvert GM, Hornung RW, Sweeney MH, Fingerhut MA, and Halperin WE. 1992. Hepatic and gastrointestinal effects in an occupational cohort exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. *JAMA* 267: 2209-2214.
- Caramaschi F, Del Caino G, Favaretti C, Giambelluca SE, Montesarchio E, and Fara GM. 1981. Chloracne following environmental contamination by TCDD in Seveso, Italy. *Int. J. Epidemiol.* 10: 135-143.
- Centers for Disease Control Vietnam Experience Study. 1988. Health status of Vietnam veterans. II. Physical health. *JAMA* 259: 2708-2714.
- Couture LA, Abbott BD, and Birnbaum LS. 1990a. A critical review of the developmental toxicity and teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin: recent advances toward understanding the mechanism. *Teratology* 42: 619-627.
- Egeland GM, Sweeney MH, Fingerhut MA, Wille KK, Schnorr TM, and Halperin WE. 1994. Total serum testosterone and gonadotropins in workers exposed to dioxin. *Am. J. Epidemiol.* 139: 272-281.
- Funatsu I, Yamashih F, Yosikane T, Funatsu T, Ito Y, and Tsugawa S. 1971. A chlorobiphenyl induced fetopathy. *Fukuoka Acta Med.* 62: 139-149.
- Giavini EM, Prati M, and Vismara C. 1982. Rabbit teratology studies with 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Environ. Res.* 27: 74-78.
- Goldman PJ. 1972. Critically acute chloracne caused by trichlorophenol decomposition products. *Arbeitsmed. Sozialmed. Arbeitshygiene* 7: 12-18.
- Gray LE, Ostby JS, Kelce W, Marshall R, Diliberto JJ, and Birnbaum LS. 1993. Perinatal TCDD exposure alters sex differentiation in both female and male LE Hooded rats. Abstracts: Dioxin '93, 13th International Symposium on Chlorinated Dioxins and Related Compounds, Vienna, pp. 337-339.

HSDB. 1995. Hazardous Substances Data Bank. TOMES®. Vol 20. Denver, CO: Micromedex, Inc.

HSDB. 1999. Hazardous Substances Data Bank. Available online at <http://sis.nlm.nih.gov>

Hoffman RE, and Stehr-Green PA. 1989. Localized contamination with 2,3,7,8-tetrachlorodibenzo-p-dioxin: the Missouri episode. In: Kimbrough R.D, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins, and related products. New York, NY: Elsevier, pp. 471-483.

Hoffman RE, Stehr-Green PA, Wehb KB, Evans RG, Knutsen AP, Schram WF, Staake JL, Gibson BB, and Steinberg KK. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA 255: 2031-2038.

Hsu ST, Ma CI, Hsu SKH, Wu SS, Hsu NHM, Yeh CC, and Wu SB. 1985. Discovery and epidemiology of PCB poisoning in Taiwan: a four-year follow-up. Environ. Health Perspect. 59: 5-10.

Jirasek L, Kalensky K, Kubec K, Pazderova J, and Lukas E. 1974. Chronic poisoning by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Ceskoslov. Dermatol. 49: 145-157.

Jones EL, and Krizek H. 1962. A technique for testing acnegenic potency in rabbits, applied to the potent acnegen, 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Invest. Dermatol. 39: 511-517.

Keys B, Hlavinka M, Mason G, and Safe S. 1985. Modulation of rat hepatic microsomal testosterone hydroxylases by 2,3,7,8-tetrachlorodibenzo-p-dioxin and related toxic isostereomers. Can. J. Pharmacol. 63: 1537-1542.

Kociba RJ, Keyes DG, Beyer JE, Carreon RM, Wade CE, Dittenber DA, Kalnins RP, Frauson LE, and Park CN. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Toxicol. Appl. Pharmacol. 46: 279-303.

Lan S-J, Yen Y-Y, Ko Y-C, and Chin E-R. 1989. Growth and development of permanent teeth germ of transplacental Yu-Cheng babies in Taiwan. Bull. Environ. Contam. Toxicol. 42: 931-934.

Law KL, Hwang BT, and Shaio IS. 1981. PCB poisoning in newborn twins. Clin. Med. (Taipei) 7: 83-91 (in Chinese).

Mably TA, Moore RW, Bjerke DL, and Peterson RE. 1991. The male reproductive system is highly sensitive to in utero and lactational 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure. In: Gallo M A, Scheuplein RJ, van der Heijden CA, eds. Biological basis for risk assessment of dioxins and related compounds, Banbury Report 35. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory; pp. 69-78.

Mably TA, Moore RW, and Peterson RE. 1992a. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 1. Effects on androgenic status. *Toxicol. Appl. Pharmacol.* 114: 97-107.

Mably TA, Moore RW, Goy RW, and Peterson RE. 1992b. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood. *Toxicol. Appl. Pharmacol.* 114: 108-117.

Mably TA, Bjerke DL, Moore RW, Gendron-Fitzpatrick A, and Peterson RE. 1992c. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 3. Effects on spermatogenesis and reproductive capability. *Toxicol. Appl. Pharmacol.* 114: 118-126.

Madhukar BV, Browster DW, and Matsumura F. 1984. Effects of in vivo-administered 2,3,7,8-tetrachlorodibenzo-p-dioxin on receptor binding of epidermal growth factor in the hepatic plasma membrane of rat, guinea pig, mouse, and hamster. *Proc. Natl. Acad. Sci. USA* 81: 7407-7411.

Martin JV. 1984. Lipid abnormalities in workers exposed to dioxin. *Br. J. Ind. Med.* 41: 254-256.

Max SR, and Silbergeld EK. 1987. Skeletal muscle glucocorticoid receptor and glutamine synthetase activity in the wasting syndrome in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol. Appl. Pharmacol.* 87: 523-527.

May G. 1982. Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. *Br. J. Ind. Med.* 39: 128-135.

Mittler JC, Ertel NH, Peng RX, Yang CS, and Kiernan T. 1984. Changes in testosterone hydroxylase activity in rat testis following administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Ann. N.Y. Acad. Sci.* 438: 645-648.

Mocarelli P, Marocchi A, Brambilla P, Gerthoux PM, Young DS, and Mantel N. 1986. Clinical laboratory manifestations of exposure to dioxin in children. A six year study of the effects of an environmental disaster near Seveso, Italy. *JAMA* 256: 2687-2695.

Moore JA, Gupta BN, Zinkl JG, and Voss JG. 1973. Postnatal effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Environ. Health Perspect.* 5: 81-85.

Moore RW, and Peterson RE. 1985. Enhanced catabolism and elimination of androgens do not cause the androgenic deficiency in 2,3,7,8-tetrachlorodibenzo-p-dioxin-treated rats. *Fed. Proc.* 44: 518.

Moses M., Lilis R, Crow KD, Thornton J, Fischbein A, Anderson HA, and Selikoff IJ. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid. Comparison of findings with and without chloracne. *Am. J. Ind. Med.* 5: 161-182.

Moses M, and Prioleau PG. 1985. Cutaneous histologic findings in chemical workers with and without chloracne with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J. Am. Acad. Dermatol.* 12:497-506.

NTP 1982. National Toxicology Program. Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Osborne-Mendel rats and B6C3F1 mice (gavage study). NTP Tech. Rept. Ser. 209. DHHS, PHS, NIH, Research Triangle Park, NC.

Neubert D. 1991. Animal data on the toxicity of TCDD and special aspects of risk assessment. Presented at a WHO consultation of tolerable daily intake of PCDDs and PCDFs from food, Bilthoven, The Netherlands, 1990.

Olson JR, McGarrigle BP, Tonucci DA, Schechter A, and Eichelberger H. 1990. Developmental toxicity of 2,3,7,8-TCDD in the rat and hamster. *Chemosphere* 20: 1117-1123.

Ott MG, Zober A, Messerer P, and German C. 1993. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. Presented at: 13th International Symposium on Chlorinated Dioxins and Related Compounds; September 20-24, 1993; Vienna, Austria.

Peterson RE, Seefeld MD, Christian BJ, Potter CL, Kelling K, and Keesey R. 1984. The wasting syndrome in 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity: basic features and their interpretation. In: Banbury report: biological mechanisms of dioxin action, Vol. 18. Poland A, Kimbrough R, eds. Plainview, NY: Cold Spring Harbor Laboratory, pp. 291-308.

Peterson RE, Theobald HM, and Kimmel GL. 1993. Developmental and reproductive toxicity of dioxins and related compounds: cross-species comparisons. *Crit. Rev. Toxicol.* 23(3):283-335.

Poland A, and Knutson JC. 1982. 2,3,7,8-Tetrachlorodibenzo-p-dioxin and related aromatic hydrocarbons: examination of the mechanism of toxicity. *Annu. Rev. Pharmacol. Toxicol.* 22: 517-554.

Quilley CP, and Rifkind AB. 1986. Prostaglandin release by the chick embryo heart is increased by 2,3,7,8-tetrachlorodibenzo-p-dioxin and by other cytochrome P-448 inducers. *Biochem. Biophys. Res. Commun.* 136(2): 582-589.

Reggiani G. 1980. Acute human exposure to TCDD in Seveso, Italy. *J. Toxicol. Environ. Health* 6: 27-43.

Reggiani GM. 1989. The Seveso accident: medical survey of a TCDD exposure. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam: Elsevier Science Publishers; pp. 445-470.

Reier SE, Martin DC, Bowman RE, Dmowski WP, and Becker JL. 1993. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fundam. Appl. Toxicol.* 21:433-441.

Rifkind AB, Gannon M, and Gross SS. 1990. Arachidonic acid metabolism by dioxin-induced cytochrome P450: a new hypothesis on the role of P-450 in dioxin toxicity. *Biochem. Biophys. Res. Commun.* 172(3): 1180-1188.

Roegner RH, Grubbs WD, Lustik MB, Brockman AS, Henderson SC, Williams DE, Wolfe WH, Michalek JE, and Miner JC. 1991. Air Force Health Study: an epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. Serum dioxin analysis of 1987 examination results. NTIS# AD A-237-516 through AD A-237-524.

Rogan WJ. 1982. PCBs and cola-colored babies: Japan 1968 and Taiwan 1979. *Teratology* 26: 259-261.

Rogan WJ, Gladen BC, Hung K-L, *et al.* 1988. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. *Science* 241: 334-336.

Rogan W. 1989. Yu-Cheng. In: Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Kimbrough RD, Jensen AA, eds. New York: Elsevier, pp. 401-415.

Rozman K, Rozman T, and Greim H. 1984. Effect of thyroidectomy and thyroxine on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induced toxicity. *Toxicol. Appl. Pharmacol.* 72: 372-376.

Safe SH. 1986. Comparative toxicology and mechanism of action of polychlorinated dibenzo-p-dioxins and dibenzofurans. *Annu. Rev. Pharmacol. Toxicol.* 26: 371-398.

Schwetz BA, Norris JM, Sparschu GL, Rowe VK, Gehring PJ, Emerson JL, and Gehring CG. 1973. Toxicology of chlorinated dibenzo-p-dioxins. *Environ. Health Perspect.* 5: 87-99.

Schantz SL, Barsotti DA, and Allen JR. 1978. Toxicological effects produced in nonhuman primates chronically exposed to fifty parts per trillion 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Toxicol. Appl. Pharmacol.* 48(1): A180.

Smith FA, Schwetz BA, and Nitschke KD. 1976. Teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in CF-1 mice. *Toxicol. Appl. Pharmacol.* 38: 517-523.

Sparschu GL, Dunn FL, and Rowe VK. 1971. Study of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. *Food Cosmet. Toxicol.* 9: 405-412.

Sunahara GI, Lucier G, McCoy Z, Bresnick EH, Sanchez ER, and Nelson KG. 1989. Characterization of 2,3,7,8-tetrachlorodibenzo-p-dioxin-mediated decreases in dexamethasone binding to rat hepatic cytosolic glucocorticoid receptor. *Mol. Pharmacol.* 36: 239-247.

Suskind R, Cholak J, Schater LJ, and Yeager D. 1953. Reports on clinical and environmental surveys at Monsanto Chemical Co., Nitro, West Virginia, 1953. Cincinnati, OH: Department of Environmental Health, University of Cincinnati (unpublished).

Suskind RR, and Hertzberg VS. 1984. Human health effects of 2,4,5-T and its toxic contaminants. *JAMA* 251:2372-2380.

Sweeney MH, Hornung RW, Wall DK, Fingerhut MA, and Halperin WE. 1992. Prevalence of diabetes and increased fasting serum glucose in workers with long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Presented at: 12th International Symposium on Dioxins and Related Compounds; August 24-28; Tampere, Finland.

Taki I, Hisanaga S, and Amagase Y. 1969. Report on Yusho (chlorobiphenyls poisoning) pregnant women and their fetuses. *Fukuoka Acta Med.* 60: 471-474 (Japan).

Thunberg T, Ahlborg UG, and Johnsson H. 1979. Vitamin A (retinol) status in the rat after a single oral dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Arch. Toxicol.* 42: 265-274.

Toth K, Somfai-Relle S, Sugar J, and Bence J. 1979. Carcinogenicity testing of herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. *Nature* 278: 548-549.

U.S. EPA. 1989. Interim procedures for estimating risks associated with exposures to mixtures of chlorinated dibenzo-p-dioxins and dibenzofurans (CDDs and CDFs) and 1989 update. Washington, DC: Risk Assessment Forum.

U.S. EPA. 1994. Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. Office of Health and Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Washington, D.C. Vol 3:9-8 to 9-12.

U.S. EPA. 1994a. *ibid.* Vol 2:7-107.

U.S. EPA. 1994b. *ibid.* Vol 2:7-101.

U.S. EPA. 1994c. *ibid.* Vol 2:7-238.

U.S. EPA. 1994d. *ibid.* Vol 1:3-17.

U.S. EPA. 1994e. *ibid.* Vol 1:3-14.

U.S. EPA. 1994f. *ibid.* Vol 1:3-6.

U.S. EPA. 1994g. *ibid.* Vol 1:3-25.

U.S. EPA. 1994h. *ibid.* Vol 1:3-4-1.

U.S. EPA. 1994i. *ibid.* Vol 3:9-86.

Webb KB, Evans RG, Knudsen DP, and Roodman S. 1989. Medical evaluation of subjects with known body levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J. Toxicol. Environ. Health* 28: 183-193.

WHO/IPCS. 1989. World Health Organization/International Programme on Chemical Safety. Polychlorinated dibenzo-p-dioxins and dibenzofurans. Environmental Health Criteria 88.

Wong KC, and Hwang MY. 1981. Children born to PCB poisoning mothers. Clin. Med. (Taipei) 7: 83-87 (in Chinese).

Yamaguchi A, Yoshimura T, and Kuratsune M. 1971. A survey on pregnant women having consumed rice oil contaminated with chlorobiphenyls and their babies. Fukuoka Acta Med. 62: 117-121 (in Japanese).

Yamashita F, and Hayashi M. 1985. Fetal PCB syndrome: clinical features, intrauterine growth retardation and possible alteration in calcium metabolism. Environ. Health Perspect. 59: 41-45.