

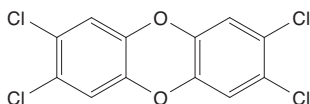
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

CAS No. 1746-01-6

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as dioxin, TCDD, or 2,3,7,8-TCDD



Carcinogenicity

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans, both epidemiological and on the mechanism of carcinogenesis. TCDD was first listed in the *Second Annual Report on Carcinogens* as reasonably anticipated to be a human carcinogen. Subsequently, a number of studies were published that examined cancer in human populations exposed to TCDD occupationally or through industrial accidents. A concerted research effort examined the molecular and cellular events that occur in tissues of humans and animals exposed to TCDD. Based on the new information, the listing was revised to *known to be a human carcinogen* in the January 2001 addendum to the *Ninth Report on Carcinogens*.

Cancer Studies in Humans

Epidemiological studies of four industrial cohorts with high exposure to TCDD, in Germany (two separate studies), the Netherlands, and the United States, found increases in overall mortality from cancer. An exposure-response relationship was observed in the largest and most heavily exposed German cohort. The International Agency for Research on Cancer evaluated data from the most heavily exposed subcohorts in studies published through 1996 and found that the risks of all cancer combined, lung cancer, and non-Hodgkin lymphoma were significantly increased. Increased risks of certain types of cancer also were found in an updated examination of the population exposed to TCDD during a 1976 industrial accident in Seveso, Italy (IARC 1997). After TCDD was listed in the *Ninth Report on Carcinogens*, IARC concluded that there was sufficient evidence of the carcinogenicity of TCDD in humans based on increased risk of all cancer combined (Baan *et al.* 2009).

Studies on Mechanisms of Carcinogenesis

There is scientific consensus for a common mode of action of TCDD and other chlorinated dibenzodioxins, dibenzofurans, and planar polychlorinated biphenyls (PCBs). In humans and rodents, this mode of action involves events that stem from the initial binding of TCDD to the aryl or aromatic hydrocarbon (Ah) receptor. The Ah receptor is a ubiquitous protein in the cells of vertebrates (including rodents and humans), which acts as a signal transducer and activator for gene transcription. Of all the chlorinated dioxins and furans, TCDD has the highest affinity for both rodent and human forms of the Ah receptor. Through activation of the Ah receptor, TCDD causes a wide spectrum of biological responses considered important to the carcinogenic process, including changes in gene expression, altered metabolism, altered cell growth and differentiation, and disruption of steroid-hormone and growth-factor signal-transduction pathways. Similar Ah-receptor-mediated responses have been observed in humans and rodents at similar body burdens or tissue concentrations of TCDD (DeVito *et al.* 1995). The scientific consensus is that bind-

ing to the Ah receptor is a necessary, but not sufficient, step in eliciting these TCDD-induced responses, including cancer.

One major difference between humans and rodents has been noted: TCDD has a half-life of 5.8 to 11.3 years in humans (Olson 1994), compared with generally 10 to 30 days in rodents (IARC 1997). Thus, TCDD accumulates in human tissue at a higher rate than in most experimental animals as a result of chronic low-level exposure. This increased accumulation suggests that TCDD-induced responses would occur in humans following prolonged exposure at lower daily intakes than would be required to elicit similar responses in experimental animals.

TCDD is not believed to be mutagenic. *In vivo* and *in vitro* genotoxicity studies of TCDD in human and animal cells have given inconsistent findings, and findings of chromosomal aberrations in humans exposed *in vivo* to TCDD are equivocal (IARC 1997).

Cancer Studies in Experimental Animals

Since 1977, many independent studies have all found TCDD to be carcinogenic in experimental animals. TCDD caused tumors in various strains of rats, mice, and hamsters, in both sexes, at numerous tissues sites, and by several different routes of exposure, including oral (dietary or by stomach tube), dermal, and intraperitoneal. Tissue sites at which cancer occurred included the liver, thyroid gland, lymphatic system, respiratory tract, adrenal cortex of the kidney, hard palate, nasal turbinates, tongue, and skin (Huff *et al.* 1994). TCDD caused cancer in a dose-dependent fashion and was also a potent promoter of liver and skin cancer in initiation-promotion studies. In addition, a compelling body of evidence indicates that the biochemical and toxicological responses to TCDD in experimental animals and humans have a similar mechanism of action.

Properties

TCDD is member of the class of polychlorinated dibenzo-*p*-dioxins, which vary in their degree of chlorination, resulting in different forms or congeners. TCDD is the index constituent for dioxin-like compounds. It occurs as colorless-to-white needles at room temperature. It is insoluble in water and very slightly soluble in *o*-dichlorobenzene, chlorobenzene, benzene, chloroform, acetone, *n*-octanol, methanol, and lard oil. Physical and chemical properties of TCDD are listed in the following table.

Property	Information
Molecular weight	322.0
Melting point	305°C to 306°C
Log K_{ow}	6.8
Water solubility	2×10^{-7} g/L at 25°C
Vapor pressure	1.50×10^{-9} mm Hg at 25°C

Source: HSDB 2009.

Use

TCDD has no known commercial applications, but it is used as a research chemical. It was tested, but never used commercially, as a flameproofing agent and as a pesticide against insects and wood-destroying fungi (ATSDR 1998, HSDB 2009). TCDD occurred as a contaminant in chlorophenoxy herbicides, including 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), that were widely used in the 1960s and 1970s to control weeds (including controlling weeds on pastureland and food crops) and as a defoliant during the Vietnam War (see Production and Exposure, below).

Production

TCDD is not currently produced commercially in the United States, but it is synthesized on a laboratory scale. Polychlorinated dibenzo-

p-dioxins (CDDs), including TCDD, are inadvertently produced by paper and pulp bleaching (Silkworth and Brown 1996), by incineration of municipal, toxic, and hospital wastes, in PCB-filled electrical transformer fires, in smelters, and during production of chlorophenoxy herbicides (Schechter 1994, IARC 1997, Schechter *et al.* 1997b). The greatest unintentional production of CDDs occurs from waste incineration, metal production, and fossil-fuel and wood combustion (ATSDR 1998).

Because TCDD is a by-product of the manufacture of polychlorinated phenols, it has been detected in commercial samples of 2,4,5-trichlorophenol (2,4,5-TCP), pentachlorophenol (a wood preservative), and the herbicide 2,4,5-T. Before 1965, commercial 2,4,5-T contained TCDD at concentrations of up to 30 ppm or more. By the mid 1980s, however, commercial 2,4,5-T contained no more than 0.01 ppm TCDD. Since 1971, regulatory agencies in a number of countries worldwide have enforced a maximum TCDD concentration of 0.1 ppm in 2,4,5-T. Millions of gallons of Agent Orange (a 50:50 mixture of the *N*-butyl esters of 2,4,5-T and 2,4-dichlorophenoxyacetic acid [2,4-D]) used as a defoliant in the Vietnam War during 1962 to 1970 contained 2 to 30 ppm TCDD. TCDD has also been detected in the herbicide 2-(2,4,5-trichlorophenoxy)propionic acid (Silvex) and may be present in *o*-chlorophenol, 1,2,4,5-tetrachlorobenzene, Ronnel (fenchlorphos), and 2,4-D. Chlorophenoxy herbicides were banned from use on food crops, pastures, rice paddies, or rangelands in 1983, and the use of 2,4,5-T was completely banned in the United States (ATSDR 1998).

Exposure

Occupational exposure to CDDs, including exposure of military personnel to Agent Orange in Vietnam, has been primarily through inhalation and dermal contact (ATSDR 1998). In occupations where CDDs may be present as contaminants (e.g., waste incineration; fire fighting; chemical research; paper bleaching; chlorophenoxy herbicide production, use, and disposal; or production and use of pentachlorophenol and other chlorinated compounds), workers may be at an increased risk of exposure; however, the number of workers potentially exposed to CDDs is not known.

Many studies of Vietnam veterans exposed to Agent Orange have been conducted (ATSDR 1998). Elevated exposure to TCDD was confirmed in the Air Force unit that was responsible for spraying herbicides in Vietnam (known as Operation Ranch Hand) (Pavuk *et al.* 2003). Operation Ranch Hand veterans were divided into three groups: background, low exposure, and high exposure. The mean serum TCDD concentration in the background group was 5.8 ppt and was not significantly different from that for a matched comparison group (4.6 ppt). Mean serum concentrations in the exposed groups were much higher, at 15.6 ppt (range = 10 to 25.6 ppt) in the low-exposure group and 69.4 ppt (range = 18 to 617.8 ppt) in the high-exposure group. Based on the biological half-life of TCDD, mean serum concentrations were extrapolated back to the end of the last tour of duty in Vietnam and were estimated at 55 ppt for the low-exposure group and 302.5 ppt for the high-exposure group.

CDDs and their structural analogues are highly persistent and widespread environmental contaminants. Exposure to these compounds is typically expressed in terms of TCDD equivalents based on the concentrations and toxicity of the specific CDD and polychlorinated dibenzofuran (CDF) congeners relative to that of TCDD. CDDs and CDFs have been detected in air, water, soil, sediments, and animal and human tissues. They are known to bioaccumulate throughout the food chain because of their lipophilic character and slow metabolism *in vivo*. TCDD is very persistent in the environment and readily bioaccumulates in the food chain, because of its extreme lipophilicity.

Evidence that people in the United States are exposed to TCDD is provided by the 2009–2010 National Health and Nutrition Examination Survey, which detected TCDD in the serum of adults over the age of 40 (CDCC 2018). The lipid-adjusted arithmetic mean serum TCDD levels in adults aged 60 or older (1.34 to 3.54 pg/g of lipid) were about twice the levels seen in adults aged 40 to 59 (0.781 to 1.17 pg/g). Among adolescents and younger adults, the proportion of results below the limit of detection (0.78 pg/g) was too high to allow means to be calculated. The presence of higher levels in older individuals supports a decrease in exposure to TCDD over time, consistent with the major source of exposure being persistence in the environment and bioaccumulation in the food chain.

Meat, fish, and dairy products are the major source (> 90%) of human exposure to CDDs (Schechter *et al.* 1997a). The average daily intake of TCDD for a U.S. adult from meat alone was estimated at 23 pg, or approximately 50% of the total daily intake from food sources. The average daily intake of TCDD was 13 pg from milk, 5 pg from produce, and 5 pg from fish; however, for certain subpopulations (recreational and subsistence fishers), fish consumption may be the most important source of exposure. The maximum daily intake of TCDD for residents of the Great Lakes region who regularly consumed fish was estimated to range from 390 to 8,400 pg. The developing fetus may be exposed to CDDs transferred across the placenta, and breastfed infants may be exposed to CDDs in their mother's milk. In the United States, breastfed infants might have been exposed to TCDD equivalents at 35 to 53 pg/kg of body weight per day through their mother's milk during their first year of life (ATSDR 1998).

Other pathways of exposure for the general population include inhalation of TCDD from municipal, medical, and industrial waste incinerators or other combustion processes (about 2% of daily intake) and ingestion of TCDD in drinking water (< 0.01% of daily intake). Fires involving capacitors or transformers containing chlorobenzene and PCBs are potential sources of CDDs. TCDD has been found in plastic packaging, clothes-dryer lint, vacuum-cleaner dust, room and car air filters, furnace-filter dust, and bleached paper products (ATSDR 1998). In a survey of 116 chemicals in blood and urine from 2,500 people across the United States in 1999 and 2000, the average concentration of TCDD was below the limit of detection for people of all ages (CEN 2003). U.S. weighted arithmetic mean lipid-adjusted serum TCDD levels from the 2009–2010 National Health and Nutrition Examination Survey by age group and race or ethnicity group are shown in the following table.

The U.S. Environmental Protection Agency's National Dioxin Study, conducted in the mid 1980s, detected TCDD at about 8% of urban sites and less than 1% of rural sites that were not expected to be contaminated with dioxins (i.e., background sites). The maximum concentration reported for these background sites was 11.2 ppt. However, soil concentrations in areas with past sources of TCDD contamination (i.e., hazardous-waste sites or sites where 2,4,5-TCP was produced and stored) typically were in the parts-per-billion range, with a maximum of about 2,000 ppm (ATSDR 1998). The data from the National Dioxin Study were consistent with concentrations of TCDD reported from previous studies of contaminated sites at Love Canal, in Niagara Falls, New York, and at various sites in Missouri that were sprayed for dust control in the early 1970s with dioxin-contaminated waste oil (Tiernan *et al.* 1985). TCDD concentrations in storm-sewer sediments collected at Love Canal in the late 1970s and early 1980s ranged from below detection (typically 10 to 100 ppt) to about 670 ppm. Concentrations of TCDD reported in the mid 1970s to early 1980s in soil from contaminated sites throughout Missouri, including the town of Times Beach, ranged from 4.4 to 1,750 ppb.

Both Love Canal and Times Beach were evacuated after the contamination was discovered. Love Canal was contaminated with many different organic and inorganic chemicals, but dioxins were the only chemicals of concern at Times Beach. Dioxin contamination at Times Beach was confirmed in November 1982; all residents (about 2,000 people) and businesses were permanently relocated, and all structures were torn down (EPA 2001). TCDD concentrations in some soil samples exceeded 100 ppb, with a maximum concentration of 317 ppb (Tiernan *et al.* 1985). More than 37,000 tons of dioxin-contaminated soil and other materials was removed from Times Beach and incinerated (EPA 2001). The ash residue from the incinerator was disposed of on site (on land), and all areas with residual dioxin concentrations between 1 and 20 ppb were covered with clean soil and revegetated (EPA 1988).

Regulations

Department of Transportation (DOT)

TCDD is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Dioxin and furans are listed as a mobile-source air toxic for which regulations are to be developed.

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Regulations to limit dioxin emissions from various types of waste combustion and incineration units have been developed.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 5×10^{-9} µg/L; based on fish or shellfish consumption only = 5.1×10^{-9} µg/L.

Dioxin-containing wastes are prohibited from underground injection.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of TCDD = F020, F022, F023, F026, F027, F028, F032, K174.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 3×10^{-8} mg/L.

Toxic Substances Control Act

Manufacturers, importers, or processors of chemical substances specified under 40 CFR 766.25 must test for halogenated dibenzodioxins/dibenzofurans.

Food and Drug Administration (FDA, an HHS agency)

Maximum permissible level in bottled water = 3×10^{-8} mg/L.

Guidelines

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Listed as a potential occupational carcinogen.

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