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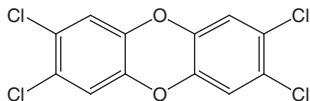


2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD); "Dioxin"

CAS No. 1746-01-6

Known to be a human carcinogen

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



Carcinogenicity

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or TCDD) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans involving a combination of epidemiological and mechanistic information that indicates a causal relationship between exposure to TCDD and human cancer. TCDD was first listed in the *Second Annual Report on Carcinogens* as *reasonably anticipated to be a human carcinogen*. Subsequent to the 1981 listing, a number of studies were published that examined cancers in human populations exposed to TCDD occupationally or through industrial accidents. There also was a concerted research effort to examine 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*.

Epidemiological studies of four high-exposure industrial cohorts in Germany (two separate studies), the Netherlands, and the United States reported an increase in overall cancer mortality. A dose-response relation was observed in the largest and most heavily exposed German cohort. The International Agency for Research on Cancer evaluated data from the highest exposed subcohorts in studies published through 1996 (IARC 1997). A significant increased combined risk was found for all cancers combined, lung cancer, and non-Hodgkin's lymphoma. Increased risk for certain cancers also was reported in an updated examination of the population exposed to TCDD during the 1976 industrial accident in Seveso, Italy.

The evidence that TCDD is a human carcinogen also is supported by experimental animal studies demonstrating that TCDD causes benign and malignant tumors at multiple tissue sites in multiple species. In addition, a compelling body of evidence indicates that the biochemical and toxicological responses to TCDD in both experimental animals and humans have a similar mechanism of action (see the following section). Since 1977, many independent animal studies of TCDD have all found TCDD to be carcinogenic. Tumors have been produced in rats, mice, and hamsters, in both sexes, in various strains, in multiple organs and tissues, and from multiple routes of dosing, including gastrointestinal (gastric instillation or dietary), dermal, and intraperitoneal. TCDD exposure leads to an increased frequency of cancers in a dose-dependent fashion. TCDD is also a potent promoter of cancer in liver and skin in two-stage initiation-promotion models for carcinogenesis. Increased incidences of cancers in laboratory animals following TCDD exposure include the following organs or systems: liver, thyroid, lymphatic, respiratory, adrenal cortex, hard palate, nasal turbinates, tongue, and skin (Huff *et al.* 1994).

Additional Information Relevant to Carcinogenicity

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. TCDD has the

highest affinity of the chlorinated dioxins and furans for both rodent and human forms of the Ah receptor. The Ah receptor is a ubiquitous intracellular protein, found in cells of vertebrates, including rodents and humans, that acts as a signal transducer and activator for gene transcription. Through activation of the Ah receptor, TCDD induces 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 both humans and rodents at similar body burdens or tissue concentrations of TCDD (DeVito *et al.* 1995). There is scientific consensus that binding to the Ah receptor is a necessary, but not sufficient, step in the elicitation of these TCDD-induced responses, including cancer.

One major difference between humans and rodents has been noted in relation to biological half-life; 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 when compared to most experimental animals following chronic low-dose exposure. This increased accumulation suggests that TCDD-induced responses would be expected to occur in humans following prolonged exposures to lower daily doses than would be required to elicit similar responses in experimental animals.

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

Properties

TCDD is a member of the chlorinated dibenzo-*p*-dioxins (CDDs), a class of related chlorinated hydrocarbons that are structurally similar. TCDD has a molecular weight of 322 and occurs as a colorless to white crystalline solid. It has melting point of 305°C to 306°C, a boiling point of 446.5°C, and a log octanol-water partition coefficient of 6.8. It is insoluble in water, slightly soluble in *n*-octanol and methanol, and soluble in other organic solvents (e.g., dichlorobenzene, chlorobenzene, benzene, chloroform, and acetone). **TCDD is very persistent in the environment, but it can be slowly degraded by sunlight (ATSDR 1998, HSDB 2003).**

Use

TCDD has no known commercial applications, but it is used as a research chemical. It was tested, but never used commercially, as a flame-proofing agent and as a pesticide against insects and wood-destroying fungi (ATSDR 1998, HSDB 2003). 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 Sections below).

Production

Currently, TCDD is not produced commercially in the United States, but it is synthesized on a laboratory scale. It is not imported into the United States (ATSDR 1998). There were at least five chemical suppliers for TCDD in the United States in 2003 (ChemSources 2003).

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.* 1997a). The greatest unintentional production of CDDs

occurs from waste incineration, metal production, and fossil fuel and wood combustion (ATSDR 1998).

Since 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 up to 30 ppm or more of TCDD. 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 enforced a maximum of 0.1 ppm TCDD 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 1962-1970 contained 2 to 30 ppm TCDD. It also has 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 2,4,5-T use was completely banned in the United States (ATSDR 1998).

Exposure

CDDs as well as their structural analogs and usual co-contaminants (the polychlorinated dibenzofurans [CDFs]) are highly persistent and widespread environmental contaminants. Exposure to these compounds is typically expressed in terms of TCDD equivalents based on the concentrations and relative toxicity of the specific CDD and CDF congeners compared to TCDD. CDDs and CDFs have been detected in air, water, soil, sediments, animals, and human tissues, and are known to bioaccumulate throughout the food chain because of their lipophilic character and slow metabolism *in vivo*.

According to EPA's National Dioxin Study conducted in the mid 1980's, TCDD was detected in about 8% of urban sites and less than 1% of rural sites that were not expected to be contaminated with dioxins (background sites). The maximum concentration reported for these background sites was 11.2 parts per trillion (ppt). However, soil concentrations in areas with past sources of TCDD contamination (e.g., hazardous waste sites or sites where 2,4,5-TCP was produced and stored) typically were in the parts per billion (ppb) 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 various 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 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, MO. Dioxin contamination at Times Beach was confirmed in November 1982, and subsequently all residents (approximately 2,000 people) and businesses of the town 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 were removed from Times Beach and incinerated (EPA 2001). The ash residue from the incinerator was land-disposed on site and all areas with residual dioxin concentrations between 1 and 20 ppb were covered with clean soil and revegetated (EPA 1988).

The general population may be exposed to CDDs by inhalation, ingestion, and dermal contact. Foods are an important source of exposure (Schecter *et al.* 1997b). Meat, fish, and dairy products are the major source (> 90%) of human exposure to CDDs. The average daily intake of TCDD for an adult in the United States from meat alone was 23 pg/day, or approximately 50% of the total daily intake from food sources. The average daily intake of TCDD from milk was 13 pg/day, from produce 5 pg/day, and from fish 5 pg/day, 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 consume fish was estimated to range from 390 to 8,400 pg/day. The developing fetus may be exposed to CDDs transferred across the placenta, and breast-fed babies may be exposed to CDDs in their mother's milk. In the United States, breast-fed infants may be exposed to 35 to 53 pg/kg body weight per day of TCDD equivalents 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 (approximately 2% of the daily intake); and drinking water (< 0.01% of the 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). The Centers for Disease Control and Prevention surveyed 116 chemicals in blood and urine from 2,500 people across the United States in 1999-2000. The average level of TCDD was below the limit of detection for all ages (CEN 2003).

Occupational exposure to CDDs, including military personnel exposed to Agent Orange in Vietnam, occurs 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). 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). Serum concentrations in the low exposure group (mean 15.6 ppt, range 10 to 25.6 ppt) and the high exposure group (mean 69.4 ppt, range 18 to 617.8 ppt) were much higher. 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 for the high exposure group.

Regulations

EPA

Clean Air Act

Mobile Source Air Toxics: Dioxin/Furans listed as a Mobile Source Air Toxic for which regulations are to be developed

NESHAP: Listed as a Hazardous Air Pollutant (HAP)

Urban Air Toxics Strategy: Identified as one of 33 HAPs 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/shellfish and water consumption = 5×10^{-9} µg/L; based on fish/shellfish consumption only = 5.1×10^{-9} µg/L

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 in which listing is based wholly or partly on tetrachlorodibenzo-*p*-dioxin - F020, F022, F023, F026, F027, F028, F032
 Listed as a Hazardous Constituent of Waste
Safe Drinking Water Act
 Maximum Contaminant Level (MCL) = 3×10^{-8} mg/L
Toxic Substances Control Act
 Specified manufacturers, importers, or processors of chemical substances must test for halogenated dibenzodioxins/dibenzofurans

FDA

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

Guidelines

NIOSH

Listed as a potential occupational carcinogen

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