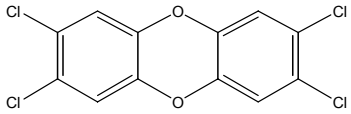
2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD); DIOXIN
CAS No. 1746-01-6

First Listed in the *Second Annual Report on Carcinogens* as *Reasonably Anticipated to be a Human Carcinogen* -- changed to *Known to be a Human Carcinogen* in the January 2001 addendum to the *Ninth Report on Carcinogens*. The revised profile listing TCDD as *Known to be a Human Carcinogen* was published as a result of a ruling by the U.S. Court of Appeals for the District of Columbia circuit dismissing the request for an injunction to prevent the listing of TCDD as a "known human carcinogen" in the Ninth Report.



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 which indicate a causal relationship between exposure to TCDD and human cancer.

Subsequent to the 1981 listing of TCDD as "*reasonably anticipated to be a human carcinogen*" in the Second Edition of the Report on Carcinogens, there have been a number of reports of studies examining cancers in human populations exposed to TCDD occupationally or through industrial accidents. There has also been a concerted research effort examining the molecular and cellular events that occur in tissues of humans and animals exposed to TCDD.

Epidemiological studies of four high-exposure industrial cohorts in Germany, the Netherlands, and the United States reported an increase in overall cancer mortality (IARC 1997). Studies published through 1996 demonstrated statistically significant increases in relative risks for all cancers combined, lung cancer, and non-Hodgkin's lymphoma among highly exposed sub-cohorts. Increased risk for certain cancers was also reported in an updated examination of the population exposed to TCDD during the 1976 industrial accident in Seveso, Italy (Bertazzi *et al.* 1997).

The evidence that TCDD is a human carcinogen is also supported by experimental animal studies that have shown that TCDD induces benign and malignant neoplasms at multiple tissue sites in multiple species. In addition, a compelling body of evidence has been developed that indicates a basic similarity in the mechanism of induction of animal and human tissue biochemical and toxicological responses to TCDD. 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; hepatobiliary, thyroid, lymphatic, respiratory, adrenal cortex, hard palate, nasal turbinates, tongue, and skin (Huff *et al*. 1994).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

There is scientific consensus for a common mode of action of TCDD and other chlorinated dibenzodioxins, dibenzofurans, and planar 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, which 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 compared with generally 10 to 30 days in rodents. 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.

PROPERTIES

TCDD occurs as a colorless to white crystalline solid. It is insoluble in water, slightly soluble in *n*-octanol, methanol, and lard oil, and soluble in organic solvents (dichlorobenzene, chlorobenzene, benzene, chloroform, acetone). TCDD is stable in water, DMSO, 95% ethanol, or acetone. It can undergo a slow photochemical and bacterial degradation, but it is normally extremely stable. TCDD is nonflammable, however, it degrades when heated in excess of 500^{o}C, or when exposed to ultraviolet radiation under specific conditions. Photodecomposition does not occur in aqueous solution (ATSDR 1998, HSDB 2001, NTP 2001).

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, NTP 2001).

PRODUCTION

Currently, TCDD is not produced commercially in the U.S., but it is synthesized on a laboratory scale. It is not imported into the United States (ATSDR 1998). There are five chemical suppliers for TCDD in the U.S. (Chem Sources 2001).

Polychlorinated dibenzo-*p*-dioxins (PCDDs), (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 (Schecter 1994, Schecter *et al.* 1997a, IARC 1997). 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 in the herbicide, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Before 1965, commercial 2,4,5-T contained up to 30 ppm TCDD 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 enforced a maximum of 0.1 ppm TCDD in 2,4,5-T. Agent Orange (a 50:50 mixture of the *N*-butyl esters of 2,4,5-T and 2,4-D that was used as a defoliant in the Vietnam War during 1962-1970) contained 2 to 30 ppm TCDD. It 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, pasture, rice paddies, or rangelands in 1983, and 2,4,5-T use was completely banned in the U.S. (ATSDR 1998).

EXPOSURE

Chlorinated dibenzo-p-dioxins (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 are 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*.

Occupational exposure to CDDs occurs primarily through inhalation and dermal contact. In occupations where CDDs may be present as contaminants (e.g., waste incineration, fire fighting, chemical research, paper bleaching, chlorophenoxy herbicide production and disposal, or production and use of pentachlorophenol and other chlorinated compounds), workers are at an increased risk of exposure; however, the number of workers potentially exposed to CDDs is unknown (ATSDR 1998).

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 U.S. from meat alone was 23 pg/day, or approximately 50% of the total daily intake from food sources. The average daily intakes of TCDD from milk, produce, and fish were 13, 5, and 5 pg/day, respectively; 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 U.S., 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).

REGULATIONS

EPA regulates 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) under the Clean Water Act (CWA), the Safe Drinking Water Act (SDWA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Resource Conservation and Recovery Act (RCRA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Toxic Substances Control Act (TSCA) as a hazardous waste and toxic pollutant. A reportable quantity of 1 lb (0.454 kg) has been established for TCDD under CERCLA. The maximum contaminant level for the chemical in drinking water is 3×10^{-8} mg/L.

FDA regulates TCDD in bottled water; the allowable concentration is also 3×10^{-8} mg/L.

NIOSH has recommended that the exposure limit of TCDD be the lowest feasible concentration. OSHA regulates TCDD under the Hazard Communication Standard and as a hazardous chemical in laboratories. Regulations are summarized in Volume II, Table 168.

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