NTP REPORT ON CARCINOGENS
BACKGROUND DOCUMENT for
2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD)

FINAL
MARCH 1999

Prepared for

the October 30-31, 1997,
Meeting of the Report on Carcinogens Subcommittee
of the NTP Board of Scientific Counselors

with a Supplement
Prepared for

the December 1-2, 1998,
Meeting of the Report on Carcinogens Subcommittee
of the NTP Board of Scientific Counselors

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NTP Report on Carcinogens Listing for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

Carcinogenicity

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or TCDD) is *known to be a human carcinogen* based on evidence from studies in humans and experimental animals and from supporting mechanistic data.

Epidemiological studies of four high-exposure industrial cohorts in Germany, the Netherlands, and the United States found an increase in overall cancer mortality (IARC V.69, 1997). A recent analysis by the IARC Working Group of dioxin-cancer mortality studies published through 1996 among highly exposed sub-cohorts reported a statistically significant increase in relative risk for all cancers combined, lung cancer, and non-Hodgkin's lymphoma. In the highly exposed industrial sub-cohorts, a causal relationship between TCDD exposure and mortality from all cancers combined was noted, but there was less strong evidence for cancers of any particular site. Increased risk for certain cancers was also reported in a new study of the Seveso, Italy, dioxin-exposed population (Bertazzi et al., 1997). These additional findings were not considered in the IARC evaluation and further strengthen the association between dioxin-exposure and human cancer. Overall, IARC stated that the strongest evidence of increased risk is for all cancers combined rather than for cancers of any specific site (IARC V.69, 1997).

Since 1977, many independent animal studies of TCDD have all found TCDD to be carcinogenic. TCDD is carcinogenic 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. It leads to 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 incidence 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).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

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

There is scientific consensus for a common mechanism of action of TCDD and other chlorinated dibenzodioxins, dibenzofurans, and planar PCBs. In humans and rodents, the mechanism involves initial binding 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. TCDD induces a wide spectrum of biological responses including induction of 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 rodents and humans. There is scientific consensus that binding to the Ah receptor is a necessary, but not sufficient, step in the mechanism of elicitation

of these responses (including cancer). The responses were observed in both humans and rodents at similar body burdens or tissue concentrations of TCDD (DeVito et al., 1995).

Several mechanisms of carcinogenesis have been proposed for TCDD including alteration in cell growth and differentiation, endocrine disruption, indirect genotoxicity via the metabolic activation of endogenous estrogens, and altered expression of genes involved in metabolic activation/detoxification of chemical carcinogens.

One major difference between humans and rodents is 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 bioaccumulates in human tissue following chronic low-dose exposure.

Human exposure to TCDD usually occurs as a mixed exposure together with exposure to other chlorinated dibenzodioxins, dibenzofurans, planar biphenyls, and structurally related compounds. The concept of dioxin toxic equivalence has been applied to these compounds in humans in order to make biologically relevant assessments of human exposure to these mixtures (Ahlborg et al., 1992, 1994). This is an estimate of potency of a compound relative to TCDD and requires that a given compound bioaccumulates in human tissue and elicits a similar spectrum of responses via activation of the Ah receptor.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

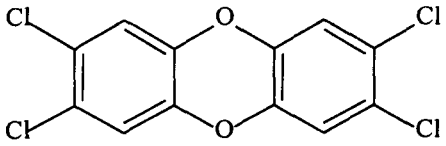
There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL PROPERTIES

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
[1746-01-6]



1.1 Chemical Identification

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin ($C_{12}H_4Cl_4O_2$, mol. wt. = 321.98) will be called TCDD in this report. TCDD is also called:

Dibenzo[*b,e*][1,4]dioxin, 2,3,7,8-tetrachloro- (9CI)
Dibenzo-*p*-dioxin, 2,3,7,8-tetrachloro- (8CI)
Dioxin (herbicide contaminant) (VAN)
Dioxin
Dioxine
D48
NCI-C03714
TCDBD
2,3,7,8-Tetrachlorodibenzo[*b,e*][1,4]dioxan
2,3,7,8-Tetrachlorodibenzo-1,4-dioxin
2,3,7,8-Tetrachlorodibenzo[*b,e*][1,4]dioxin
2,3,7,8-TCDD
2,3,7,8-TetraCDD
Tetrachlorodibenzodioxin
Tetradioxin

1.2 Physical-Chemical Properties

Property	Information	Reference
Color	Colorless to white	HSDB (1997)
Physical State	colorless needles	Lewis (1996)
Melting Point, °C	305-306	HSDB (1997)
Boiling Point, °C	500 (decomposes)	Radian (1991)
Solubility:		
Water at 20 °C	19.3 ng/L	HSDB (1997)
Organic Solvents	1.4 g/L in dichlorobenzene	HSDB (1997)
	0.72 g/L in chlorobenzene	HSDB (1997)
	0.57 g/L in benzene	HSDB (1997)
	0.37 g/L in chloroform	HSDB (1997)
	0.11 g/L in acetone	HSDB (1997)
	0.05 g/L in *n*-octanol	HSDB (1997)

Property	Information	Reference
Organic Solvents	0.04 g/L in lard oil	HSDB (1997)
	0.01 g/L in methanol	HSDB (1997)
Partition Coefficients:		
Log octanol/water	6.8	HSDB (1997)
Vapor pressure at 25 °C	7.4×10^{-11} mm Hg	HSDB (1997)

TCDD can undergo a slow photochemical and bacterial degradation but is normally extremely stable. TCDD, however, is degraded when heated in excess of 500 °C or when exposed to ultraviolet radiation under specific conditions. Photodecomposition does not occur in aqueous solution. TCDD is stable in water, DMSO, 95% ethanol, or acetone (Radian, 1991).

1.3 Packaging and Shipping

TCDD is not commercially produced except as a research chemical.

1.4 Impurity in Commercial Products

TCDD is an inadvertent contaminant in herbicide precursors and, thus, in the herbicides themselves (Schecter et al., 1997b; 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) and was found 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 in the Vietnam War as a defoliant 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 (OHMTADS, 1985).

2.0 HUMAN EXPOSURE

2.1 Use

TCDD is used as a research chemical (NTP, 1994).

2.2 Production

TCDD is currently not produced commercially in the United States, but it is synthesized on a laboratory scale. It is not imported into the United States (OHEA, 1985; cited by NTP, 1998).

Polychlorinated dibenzo-*p*-dioxins (PCDDs) (including TCDD) are also produced by paper and pulp bleaching (Silkworth and Brown, 1996); by incineration of municipal, toxic, and hospital wastes; PCB-filled electrical transformer fires; and smelters (Schecter, 1994). Because it is a by-product of 2,4,5-TCP production, TCDD is also found as a contaminant in some phenoxy herbicides such as 2,4,5-T, in some pesticides such as chlorinated phenols, and in wood preservatives such as pentachlorophenol (Schecter, 1994; IARC, 1997).

2.3 Exposure

PCDDs as well as their structural analogs and usual co-contaminants (the polychlorinated dibenzofurans [PCDFs]) are widespread environmental contaminants. They bioaccumulate throughout the food chain because of their lipophilic character and slow metabolism *in vivo* (De Jongh et al., 1995). The primary source of TCDD exposure to humans is from food. In adults in the United States, average totals of TCDD toxic equivalents are approximately 1 to 6 pg/kg/day (Schecter et al., 1994a, 1994b). This leads to an average blood TCDD equivalent level between 20 and 40 ppt on a lipid basis (Schecter, 1994). More than 90% of the dioxins found in humans in the general population are due to consumption of meat including poultry, dairy products, and fish (Schecter et al., 1994a, 1994b, 1997a).

Historically, chlorinated dibenzo-*p*-dioxins (CDDs), including TCDD, have been deposited onto soil through pesticide applications and disposal of CDD-contaminated industrial wastes, and via land application of paper mill sludges. Currently, however, atmospheric fall-out of CDD-laden particulates and gases appears to be the most predominant source of CDDs to soil. Evidence indicates that TCDD is resistant to natural degradation (ATSDR, 1997).

2.4 Regulations

EPA regulates TCDD under the Clean Water Act (CWA), 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. The maximum contaminant level for the chemical in community water systems and non-transient, non-community water systems is 3×10^{-8} mg/L. FDA regulates TCDD in beverages, specifically 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[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 132—PART 132—WATER QUALITY GUIDANCE FOR THE GREAT LAKES SYSTEM. Promulgated: 60 FR 15387, 03/23/95. U.S. Code: 33 U.S.C. 1251 et seq.	These subparts identify minimum water quality standards, antidegradation policies, and implementation procedures for the Great Lakes System to protect human health, aquatic life, and wildlife, required by section 118(c)(2) of the Clean Water Act.
	40 CFR 132.6—Sec. 132.6 Application of Part 132 Requirements in Great Lakes States and Tribes. States the water quality criteria for the protection of human health and wildlife.	Human Non-Cancer Value (HNV) for drinking and nondrinking water is 6.7×10^{-8} mg/L. The Human Cancer Value (HCV) for drinking and nondrinking water is 8.6×10^{-9} mg/L. The water quality criteria for the protection of wildlife for TCDD is 3.1×10^{-9} mg/L.
	40 CFR 141—PART 141—NATIONAL PRIMARY DRINKING WATER REGULATIONS. Promulgated: 40 FR 59570, 12/24/75. U.S. Code: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, and 300j-9.	This part establishes primary drinking water regulations pursuant to section 1412 of the Public Health Service Act, as amended by the Safe Drinking Water Act (Pub. L. 93-523) and related regulations applicable to public water systems.
	40 CFR 141.60 ff.—Subpart G—National Revised Primary Drinking Water Regulations: Maximum Contaminant Levels.	The maximum contaminant level for TCDD in community water systems and non-transient, non-community water systems is 3×10^{-8} mg/L.
	40 CFR 173—PART 173—PROCEDURES GOVERNING THE RESCISSION OF STATE PRIMARY ENFORCEMENT RESPONSIBILITY FOR PESTICIDE USE VIOLATIONS. Promulgated: 46 FR 26059, 0511/81. U.S. Code: 7 U.S.C. 136w and 136w-2.	These procedures govern any proceeding to rescind a State's primary enforcement responsibility for pesticide use violations conducted under section 27(b) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, 7 U.S.C. 136 et seq.
	40 CFR 173.21 ff.—Subpart B—Preparation of Hazardous Materials for Transportation.	The reportable quantity of the Hazardous Substance TCDD is 1 lb (0.454 kg).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTES. Appendix VII—Basis for Listing Hazardous Waste. Promulgated: 46 FR 4619, 1981 with numerous amendments.	The TCDD equivalent levels for wastewaters must be less than 2 ppb and less than 5 ppt for solid treatment residues. Any residues in excess of this level must be retreated or must be disposed of as acutely hazardous. Appendix VII lists TCDD as a hazardous constituent of industrial waste.
	40 CFR 266—PART 266—STANDARDS FOR THE MANAGEMENT OF SPECIFIC HAZARDOUS WASTES AND SPECIFIC TYPES OF HAZARDOUS WASTE MANAGEMENT FACILITIES. Promulgated: 50 FR 666, 1/4/85. U.S. Code: U.S.C. 6905, 6912(a), 6924, and 6934.	Standards to control emissions of TCDD and other dioxins are promulgated for generators, transporters, and users of materials used in a manner that constitutes disposal.
	40 CFR 266.100 ff.—Subpart H—Hazardous Waste Burned in Boilers and Industrial Furnaces. Promulgated: 56 FR 7208, 2/21/91.	The regulations of this subpart apply to hazardous waste burned or processed in a boiler or industrial furnace. Total dioxin concentration (including TCDD) of wastes or emissions may not exceed 500 ppm by weight.
	40 CFR 266.104—Sec. 266.104 and Appendix V—Risk Specific Doses. Promulgated: 56 FR 7208, 2/21/91; 56 FR 32689, 7/17/91, as amended at 57 FR 38565, 8/25/92; 58 FR 38883, 7/20/93; 60 FR 33914, 6/29/95.	To protect public health, dispersion modeling of carcinogenic hazardous constituents in emissions from hazardous wastes burned in boilers and industrial furnaces should show that average ground level concentrations of TCDD will be below the Risk Specific Dose (RSD) 2.2×10^{-7} μg/m^3.
	40 CFR 268—PART 268—LAND DISPOSAL RESTRICTIONS. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, and 6924.	This part identifies hazardous wastes that are restricted from land disposal and defines those limited circumstances under which an otherwise prohibited waste may continue to be disposed.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 268.30 ff.—Subpart C—Prohibitions on Land Disposal. Promulgated: 53 FR 31216, 08/17/88.	Liquid hazardous wastes containing greater than or equal to 1,000 mg/L HOCs are prohibited from land disposal (effective 7/8/87).
	40 CFR 268.31—Sec. 268.31 Waste specific prohibitions—Dioxin containing wastes. Promulgated: 53 FR 31216, 08/17/88.	Dioxin-containing wastes are prohibited from land disposal (effective 11/8/90) unless it is a response action taken under section 104 or 106 of CERCLA, a corrective action taken under subtitle C of RCRA, or an exemption is given.
	40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Code: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	This part designates under section 102(a) of CERCLA 1980 those substances in the statutes referred to in section 101(14) of CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This part also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.
	40 CFR 302.4—Sec. 302.4 Designation of hazardous substances.	TCDD is listed as a hazardous substance under the CAA and the CWA.
	40 CFR 401—PART 401—GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74, as amended at 47 FR 24537, 06/04/82. U.S. Code: 33 U.S.C. 1251 et seq.	The provisions of this part set forth the legal authority and general definitions which will apply to all regulations issued concerning specific classes and categories of point sources of industrial effluents under parts 402 through 699.
	40 CFR 401.15—Sec. 401.15 Toxic pollutants.	Under the Federal Water Pollution Control Act, TCDD is designated as a toxic pollutant.
	40 CFR 707—PART 707—CHEMICAL IMPORTS AND EXPORTS. Promulgated: 45 FR 82850, 12/16/80. U.S. Code: 15 U.S.C. 2611(b) and 2612.	Requires exporters of TCDD or mixtures containing TCDD to notify EPA. TSCA 12(b).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
EPA	40 CFR 766—PART 766—DIBENZO-PARA-DIOXINS/DIBENZOFURANS. Promulgated: 52 FR 21437, 06/5/87. U.S. Code: 15 U.S.C. 2603 and 2607.	Requires manufacturers and importers of certain organic chemicals to test for the presence of chlorinated and brominated dibenzo-*p*-dioxins and dibenzofurans and to submit process and reaction data.
FDA	21 CFR 165—PART 165—BEVERAGES. Promulgated: 60 FR 57124, 11/13/95; effective 5/13/96. U.S. Code: 21 U.S.C. 321, 341, 343, 343A, 348, 349, 371, and 379e.	The regulations in subparts A and B govern the labeling and effective chemical substance limits for specific standardized beverages.
	21 CFR 165.110 ff.—Subpart B—Requirements for Specific Standardized Beverages—Bottled water.	Allowable concentration of TCDD in bottled water is $3x10^{-8}$ mg/L.
NIOSH	1/84. Recommended reduction of exposure to TCDD to lowest feasible concentration.	Summary of current NIOSH recommendation: exposure limit—Ca, lowest feasible concentration.
	1/23/85. Current Intelligence Bulletin #40—2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCCD, "dioxin").	
OSHA	29 CFR 1910.1200, 1915, 1917, 1918, 1926, 1928. Promulgated: 2/15/89. OSH Act: Hazard Communication.	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program to include labels, material safety data sheets, and worker training. Labels may be subject to FIFRA requirements.
	29 CFR 1910.1450. Promulgated: 1/31/90. OSH Act: Final rule of occupational exposure to hazardous chemicals in laboratories.	As a select carcinogen (IARC Group 2B), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin is included as a chemical hazard in laboratories. Employers are required to provide employee information and training and a Chemical Hygiene Plan.

[a]The regulations in this table have been updated through 62 Federal Register 33625, June 20, 1997.

3.0 HUMAN STUDIES

IARC (1997) stated that there is limited evidence from epidemiology studies of humans for the carcinogenicity of TCDD. However, the overall evaluation by IARC (1997) is that TCDD is considered to be carcinogenic to humans based on the following additional evidence: TCDD is a multi-site carcinogen in experimental animals that acts through a mechanism involving the aryl hydrocarbon (Ah) receptor; the receptor is highly conserved and functions the same way in humans as in other mammals; and the tissue concentrations of TCDD were similar in heavily exposed human populations (where an increased cancer risk was observed) and in rats exposed to carcinogenic dosages (DeVito et al., 1995). Boroush and Gough (1994) concluded through meta-analysis of cohort studies that the limited evidence of chronic health effects in humans is based on the relatively low human exposure levels.

A number of cohort studies on the effects of dioxin exposure have been reviewed by IARC (1997). The studies with the highest exposures to TCDD include one cohort of 12 plants in the United States (Fingerhut et al., 1991a; cited by IARC, 1997; Fingerhut et al., 1991b); one cohort in the Netherlands (Hooiveld et al., 1998); and two cohorts in Germany (IARC, 1997). All exposures were found in workers occupationally exposed in chemical plants. A fifth study in Italy examined the epidemiological data collected among a cohort of residents in a contaminated area (Bertazzi et al., 1993, 1996, 1997).

An international cohort assembled by IARC in association with NIEHS (Saracci et al., 1991) included three of the four high-exposure cohorts, and other industrial cohorts not reported in separate publications. An increased, but generally low, risk for all cancers combined was noted in the international cohort.

The IARC Working Group also analyzed results of the IARC international cohort plus those of the industrial sub-cohorts with highest exposure. Their analysis found the highest increase in overall cancer mortality rather than cancer of specific sites. In the largest and most heavily exposed German cohort, a dose-response relationship was noted for overall cancer mortality. The combined highly exposed sub-cohorts had a calculated statistically significant standardized mortality ratio for all cancers combined of 1.4, for lung cancer of 1.4, and for non-Hodgkin's lymphoma of 2.6. In its summary of the epidemiological evidence from the most highly exposed populations, the IARC Working Group identified a causal association between TCDD exposure and all cancers combined, but felt there was less strong evidence for cancers of any particular site (IARC, 1997).

In an analysis of the cohorts overall (not just the highly exposed), IARC concluded that the strongest evidence of increased cancer mortality is for all cancers combined rather than for cancers of any particular sites (IARC, 1997).

A new paper on the Seveso, Italy, exposed population supports and extends the findings previously published from this cohort study (Bertazzi et al., 1993, 1996, 1997).

4.0 EXPERIMENTAL CARCINOGENESIS

Low doses of TCDD (0.001 to 100 μg/kg bw at least once per week for 5 weeks to 2 years) administered via any one of five different routes to rats, mice, and hamsters caused tumors at multiple sites (Huff, 1994; IARC, 1997). Huff (1994) summarized seven published studies, reporting on 18 separate sex-species experiments lasting from 12 months to life span. IARC (1997) stated that "[t]here is sufficient evidence in experimental animals for the carcinogenicity

of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin." In addition, TCDD is a potent promoter of cancer in liver and skin in 2-step models for carcinogenesis (Lucier, 1993b).

4.1 Mice

Male and female mice treated with TCDD by gavage had an increase in hepatocellular carcinomas. In males, an increase was also observed for hepatocellular adenomas as well as a dose-related trend in the increase in lung alveolar/bronchiolar adenomas or carcinomas. In females, an increase in follicular-cell adenomas of the thyroid, lymphomas, and subcutaneous fibrosarcomas was observed. In female mice dermally exposed to TCDD, an increase in fibrosarcomas was observed. In immature male and female mice exposed intraperitoneally (i.p.) to TCDD, an increase in thymic lymphomas and hepatocellular adenomas and carcinomas was observed (Lucier et al., 1993b; IARC, 1997).

4.2 Rats

Male and female rats exposed to TCDD in their diet had an increase in squamous-cell carcinomas of the hard palate and nasal turbinates. In males, an increase in squamous-cell carcinomas of the tongue was observed, whereas in females, an increase in squamous-cell carcinomas of the lung and an increase in hyperplastic nodules and hepatocellular carcinomas of the liver were observed. In an oral gavage study with TCDD, male and female rats had an increase in hepatic neoplastic nodules. In males, a dose-related trend was observed in the increase in follicular-cell adenomas of the thyroid. In female rats, an increase in adenomas or carcinomas in the adrenal cortex was observed, along with an increase in subcutaneous fibrosarcomas (Lucier et al., 1993b; IARC, 1997).

4.3 Hamsters

Hamsters are considered the most resistant species to the acute toxic effects of TCDD. When TCDD was administered subcutaneously or by i.p. route, an increase in squamous-cell carcinomas of the skin occurred (Lucier et al., 1993b; IARC, 1997).

4.4 Fish

TCDD was carcinogenic in the gill, the thyroid, and the swim bladder of medaka (Johnson et al., 1992).

5.0 GENOTOXICITY

Studies of the genotoxic and related effects of TCDD have been reviewed by IARC (1997, draft; see Appendix A, pp. 324-331). In prokaryotic systems, TCDD did not induce gene mutations in *Salmonella typhimurium,* in both the presence and absence of metabolic activation.

In mammalian systems *in vitro,* TCDD produced conflicting results for the induction of gene mutations in mouse lymphoma cells, induced an increase in the frequency of sister chromatid exchanges (SCE) and micronuclei in human lymphocytes, and inhibited gap-junction intracellular communication in mouse hepatoma and rat hepatocytes but not in Chinese hamster or mouse fibroblasts. TCDD did not induce unscheduled DNA synthesis (UDS) in normal human mammary epithelial cells, nor the morphological transformation of mouse embryo C3H 10T1/2 cells.

In vivo, TCDD induced DNA damage (single-strand breaks) in rat liver and peritoneal lavage cells and increased the frequency of SCE in rat lymphocytes. It did not induce DNA adducts in mouse liver.

Although there is some uncertainty, there is scientific consensus that TCDD is not directly genotoxic.

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, Metabolism, and Excretion in Humans

TCDD is retained in all tissue types, although usually in highest concentrations in fat and liver tissue (Van den Berg et al., 1994; cited by IARC, 1997; Ryan et al., 1986). Weber et al. (1991; cited by IARC, 1997) found that penetration values of TCDD into human skin are low (e.g., at a dose of 6.5 ng/cm^2 in acetone, the rate was 5 pg/cm^2/hour). The outer layer of the stratum corneum apparently acts as a reservoir.

Half-lives of TCDD elimination in humans are believed to be between 5.8 and 11.3 years (Poiger and Schlatter, 1986; Pirkle et al., 1989; Wolfe et al., 1994; Schlatter, 1991; all cited by Olson, 1994; Flesch-Janys et al., 1994; Needham et al., 1994; all cited by Institute of Medicine, 1996; Michalek et al., 1995).

Polychlorinated dibenzodioxins and dibenzofurans were detected in human placental tissues from exposed mothers in the United States (Schecter et al., 1996b). An analysis of chlorinated dioxin and dibenzofuran levels in stillborn infants indicated placental transfer of dioxins from mother to child (Schecter et al., 1990). Further, in a two-year study of a mother nursing twins, a decrease in milk and blood dioxin levels were noted. Maternal body burden appears to decrease while the infant dioxin burden increases during nursing (Schecter et al., 1996a).

6.2 Experimental Systems

6.2.1 Absorption

Absorption rates after a single dose of TCDD administered in the diet varied from 50% of the administered dose in the gastrointestinal tract of mice (Koshakji et al., 1984; Curtis et al., 1990; both cited by IARC, 1997) to 70-90% of the administered dose in the gastrointestinal tract of rats, hamsters, and guinea pigs (Piper et al., 1973; Allen et al., 1975; Rose et al., 1976; Olson et al., 1985; all cited by IARC, 1997). Absorption rates in rats were somewhat lower (50-60% absorption) when TCDD was administered in the diet for more than six weeks (Fries and Marrow, 1975; cited by IARC, 1997) compared with the single-dose absorption rate of 70% (Piper et al., 1973; cited by IARC, 1997).

6.2.2 Distribution

The liver and adipose tissue are the major storage sites for TCDD in all rodent species. The skin can also act as an important storage site and high concentrations can be found in the adrenals (IARC, 1997). For example, one day after exposure, 25-70% of the administered dose (route not listed) of TCDD was stored in the liver of rats, mice, hamsters, and guinea pigs. In contrast, retention in the liver of monkeys was lower (Van den Berg et al., 1994; cited by IARC, 1997).

The primary cause of long retention in tissues is the steric hindrance towards cytochrome P450 caused by chlorine atoms at positions 2, 3, 7, and 8, which results in limited metabolism (Van den Berg et al., 1994; cited by IARC, 1997).

The hepatic disposition of TCDD is dose-dependent (Abraham et al., 1988; cited by IARC, 1997; Kociba et al., 1978). This is believed to be caused by the presence of inducible protein-binding sites in the liver (Poland et al., 1989a, 1989b; both cited by IARC, 1997), now known to be CYP1A2 (Voorman and Aust, 1987, 1989; Poland et al, 1989a, 1989b; Diliberto et al., 1995; all cited by IARC, 1997). TCDD was not sequestered in the liver of transgenic mice lacking the cytochrome P450 1A2 gene. In age-matched lineage strains of C57B1/6N and 129/Sv mice, TCDD was highly sequestered in the liver (as was to be expected) (Diliberto et al., 1997).

6.2.3 Metabolism

As in humans, chlorine substitution at the 2,3,7, and 8 positions of TCDD strongly inhibits metabolism in animals (IARC, 1997).

6.2.4 Excretion

Whole body half-lives of TCDD ranged from 17 to 31 days in rat studies, and elimination rates from the liver and adipose tissue were similar to that of the whole body (Piper et al., 1973; Allen et al., 1975; Fries and Marrow, 1975; Rose et al., 1976; Abraham et al., 1988, 1989; Pohjanvirta et al., 1990; all cited by IARC, 1997). Half-lives were found to be lower for mice (Gasiewicz et al., 1983; Birnbaum, 1986; both cited by IARC, 1997). However, the half-life in female rhesus monkeys with four years of dietary exposure was much longer (about 391 days) (Bowman et al., 1989a, 1989b; both cited by IARC, 1997). Thus, the half-life of elimination of TCDD in laboratory animals is much shorter than that of humans, which is between 5.8 and 11.3 years (see subsection 6.1).

6.3 Structure-Activity Relationships (SARs)

6.3.1 Hexachlorodibenzo-*p*-dioxins

An increase in liver tumors in both male and female rats and mice was observed after a 2-year exposure to a mixture of 1,2,3,6,7,8-hexaCDD and 1,2,3,7,8,9-hexaCDD (Lucier et al., 1993b).

6.3.2 2,7-Dichlorodibenzo-*p*-dioxin

An increase in lymphomas (or hemangiosarcomas) and neoplasms of the liver was observed in male mice exposed to 2,7-dichlorodibenzo-*p*-dioxin for 110 weeks (Lucier et al., 1993b).

6.4 Body Burden

Since unmetabolized TCDD is considered responsible for the range of adverse effects associated with this compound, the metabolism, disposition, and subsequent elimination of TCDD are factors that regulate the body burden and the relative toxic potency of TCDD.

One study compared the TCDD body burdens that produce effects in experimental animals to body burdens associated with these effects in humans (DeVito et al., 1995). For effects that are clearly associated with dioxins, e.g., chloracne, humans and laboratory animals

respond at similar body burdens. Human body burden estimates were based on assumptions of equal distribution of dioxins in body fat, adult body weight of 70 kg with 22% body fat (lipid), and first-order elimination kinetics with an elimination half-life of 7.1 years. Calculations using the toxic equivalency factor (TEF) method were based on dioxin levels measured in serum, adjusted for lipid content, at last exposure. The average background concentration in the U.S. adult general population was estimated at 58 ng TCDD equivalents per kilogram serum lipid. Populations with known exposure to dioxins and increased incidences of cancer have body burdens of 109 to 7,000 ng TCDD equivalents per kilogram body weight at the time of highest exposure. Cancer induction in animals occurs at body burdens of 944 to 137,000 ng TCDD/kg body weight (DeVito et al., 1995).

Body burdens were estimated for hamsters, rats, and mice following chronic administration of TCDD. Hamsters given 100 μg TCDD/kg 6 times every 4 weeks over a 24-week period developed tumors and were estimated to have a body burden of 137,000 ng/kg after the last treatment. A half-life of 14.9 days was assumed (DeVito et al., 1995).

Rats given 100 ng/kg/day for 2 years had an increased incidence of hepatocellular tumors. The body burden was estimated to be 2,976 ng/kg with an assumption of first-order elimination, a whole body elimination of 23.7 days, and a gastrointestinal tract absorption of 86% (DeVito et al., 1995).

Mice given 71.4 ng/kg/day for 2 years showed a significant increase in the incidence of hepatocellular carcinoma. This chronic dose corresponds to a body burden of 944 ng/kg based on the assumption of an apparent half-life of 11 days and a body weight of 20 g (DeVito et al., 1995).

In summary, humans are as sensitive as laboratory animals for TCDD-induced responses such as chloracne, cytochrome P450 1A1 induction, and cancer, using body burden as the measure of dose.

7.0 MECHANISMS OF CARCINOGENESIS

7.1 General Issues

The following topics relating to carcinogenicity of TCDD were reviewed by IARC (1997): genotoxicity, the aromatic or aryl (Ah) receptor, effects of TCDD on gene expression, oxidative damage, cell transformation, cell proliferation and tumor production, and suppression of immune surveillance. IARC (1997) concluded that TCDD is not likely to be directly genotoxic.

Studies indicate that Ah receptor activation is required for the carcinogenicity of TCDD (Lucier et al., 1993a; Okey et al., 1995; Demby and Lucier, 1996; IARC, 1997). There is scientific consensus for a common mechanism of action of TCDD and other chlorinated dioxins and furans in humans and rodents which involves initial binding to the 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 of gene transcription. TCDD induces a wide spectrum of biological responses, including induction of 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 rodents and humans. There is scientific consensus that binding to the Ah receptor is a necessary step in the mechanism of elicitation of these responses and that this mechanism is conserved in humans and rodents. Similar responses observed in both humans and rodents occur at similar tissue concentrations of TCDD (DeVito et al., 1995).

Several mechanisms of carcinogenesis have been proposed for TCDD, including alteration in cell growth and differentiation, endocrine disruption, indirect genotoxicity via the metabolic activation of endogenous estrogens, and altered expression of genes involved in metabolic activation/detoxification of chemical carcinogens. One major difference between humans and rodents is biological half-life; TCDD has a half-life of 5.8 to 11.3 years in humans compared with 10 to 30 days in rodents. Thus, TCDD bioaccumulates in human tissue following chronic low-dose exposure.

Human exposure to TCDD goes together with exposure to other dioxin-like compounds, including the class of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls. A dioxin-like compound is a compound that binds to the Ah receptor, results in dioxin-like effects, and bioaccumulates. These are the three factors for inclusion of dioxin-like chemicals in the TEF scheme (Ahlborg et al., 1992, 1994). Risk assessment of dioxin-like compounds is based on using these TEFs. TEFs are consensus values which are based on the available data on relative potency values for a specific compound. Relative potency values express the potency of a specific compound in comparison to TCDD, the most potent dioxin-like compound with a relative potency of one. For the estimation of the total dioxin-activity in a certain matrix, the TEF value of a compound is multiplied by the concentration in the specific matrix. This results in a certain amount of toxic equivalents (TEQs) for this compound. The summation of all TEQs in a certain mixture gives the total dioxin-activity of this mixture. In this way the total dioxin-exposure to humans can be estimated.

CYP1A1 and CYP1A2 induction after TCDD binding to the Ah receptor has been a useful measurement for determining effects of TCDD exposure (IARC, 1997). However, it is unlikely that induction of these cytochromes contributes directly to the carcinogenic effects of TCDD (Sewall and Lucier, 1995). TCDD-induced CYP1A1 and CYP1A2 were similar in human and rodent liver slices (Drahushuk et al., 1997). Induction of CYP1A1 occurs at similar body burdens for humans and rodents (DeVito et al., 1995).

In rats and mice, single treatment with high doses of TCDD have caused increased superoxide anion production, lipid peroxidation, and DNA single-strand breaks, but the biological significance of these responses are unknown (Stohs et al., 1990; Alsharif et al., 1994; both cited by IARC, 1997). In low non-cytotoxic doses, production of oxidative damage by TCDD was consistent in several different experimental systems, both *in vivo* and *in vitro* (IARC, 1997). Rats require ovarian hormones in the mechanism of liver tumor promotion by TCDD (Lucier et al., 1991). Tritscher et al. (1996; cited by IARC, 1997) suggested that the requirement for ovarian hormones in rats is associated with a 2- to 3-fold higher level of 8-OH-dG DNA adduct formation in intact compared with ovariectomized rats. Further, this increase in 8-OH-dG DNA adducts may be a result of a production of genotoxic metabolites through redox cycling of catechol estrogens.

In regard to cell proliferation and tumor promotion, TCDD may be either promoting the development of tumors and/or causing mutations through an indirect mechanism (Andersen et al., 1994; IARC, 1997). A rat tumor initiation-promotion experiment found that the labeling index (BrdU incorporation) for hepatic cell proliferation decreased compared to controls at low

doses of TCDD (0.11 nmol/kg/ day). At higher doses of TCDD (0.388 nmol/kg/ day), there was a 3-fold increase in the labeling index. Both responses occurred after 30 weeks of TCDD treatment. Additionally, significant variation occurred among individual animals. Half of the animals had significantly higher labeling index than other animals treated with the same dose of TCDD over the same length of time (Maronpot et al., 1993). In another study, hepatocyte proliferation was not increased; but apoptosis in foci was found to be reduced, and TCDD only marginally affected DNA synthesis in GSTP-positive liver foci following treatment with 0.311 nmol TCDD per day for 115 days (Stinchcombe et al., 1995).

Suppression of immune surveillance from TCDD exposure is of significant importance since it could aid in the progression and development of malignancy by allowing altered cells to escape immune response. Although much information is available on the suppression of immune surveillance by TCDD for animals, evidence for immune system compromise in humans is not well characterized (IARC, 1997).

7.2 Tissue-Specific Mechanisms

7.2.1 Liver

The mechanisms of carcinogenicity of TCDD specific to liver tissue were reviewed by IARC (1997) with regard to sex differences in carcinogenicity, the possible role of ovarian hormones in tumorigenesis, the effects on epidermal growth factor, cellular localization, alterations in gap-junction communication by TCDD, and cytotoxicity as a mechanism for hepatic lesions.

In regard to hepatocarcinogenic effects, female rats were found to be more sensitive than male rats, although the same was not true for mice (IARC, 1997). Ovarian hormones may be involved in the mechanism of this sex difference in rats. In a chronic two-stage initiation-promotion model, TCDD exposure-related increases in cell proliferation and altered hepatic foci formation were observed in the livers of intact animals but not in ovariectomized female rats. One hypothesis is that TCDD may be acting via an indirect genotoxic mechanism. TCDD induces cytochrome P450 CYP1A2, which is hypothesized to metabolize estradiol to form catechol estrogens. Further metabolism of the catechol estrogen forms semiquinone and quinone metabolites which are able to undergo redox cycling, resulting in the production of reactive oxygen species. This may lead to oxidative stress and damage to cellular macromolecules including DNA, protein, and lipids. This is supported by the observation of 3- to 6-fold higher levels of 8-OH-dG DNA adducts in the livers of TCDD-treated intact rats compared to ovariectomized rats (Tritscher et al., 1996; cited by IARC, 1997). A second hypothesis is that TCDD alters the signal transduction pathway for estrogen. Hepatic estrogen receptor complex level and binding are down-regulated in rats after *in vivo* exposure to TCDD (Romkes et al., 1987; Romkes and Safe, 1988; Harris et al., 1990; Zacharewski et al., 1991, 1992, 1994; all cited by IARC, 1997; Clark et al., 1991).

Multiple studies have found that TCDD decreases the amount of detectable plasma membrane epidermal growth factor (EGF) receptor in liver *in vivo* and in keratinocytes *in vitro* (Madhukar et al., 1984; Hudson et al., 1985; Astroff et al., 1990; Choi et al., 1991; Lin et al., 1991; Sewall et al., 1993, 1995; all cited by IARC, 1997). However, down regulation of the EGF receptor was not observed in the livers of ovariectomized rats treated chronically with TCDD, paralleling the absence of TCDD-induced changes in cell proliferation and altered hepatic foci

formation in these animals (Sewall et al., 1993; cited by IARC, 1997; Clark et al., 1991; Lucier et al., 1991).

Several studies imply that the hepatocytes in different regions of the liver differ in their sensitivity to the effects of TCDD. Tritscher et al. (1996; cited by IARC, 1997) observed an acinar-dependent pattern of expression of CYP1A1 and CYP1A2 following chronic exposure to TCDD. The dose-dependent induction of CYP1A1 and CYP1A2 was observed as an increase in the number of hepatocytes induced in acinar zones 2 and 3. Even at high doses there were hepatocytes in acinar zone 1 that were not induced. By contrast, changes in cell proliferation following TCDD exposure do not show an acinar-dependent pattern (Maronpot et al., 1993) and in one study occurred in hepatocytes in acinar zone 1, where induction of CYP1A1 and CYP1A2 was absent (Fox et al., 1993).

Inhibition of gap-junction intercellular communication (GJIC) has been observed in mechanistic studies on carcinogenesis. Changes in gap junction protein expression and reductions in GJIC have been observed following TCDD exposure (Baker et al., 1995; cited by IARC, 1997). It has not been determined whether its role is causal or a response occurring due to other events (IARC, 1997).

7.2.2 Other Target Tissues

Extrahepatic target tissues for TCDD-induced carcinogenesis include lung, nasal ethmoturbinates, hard palate, adrenal cortex, thyroid, lymphoid tissues, skin, and tongue tissues. Since Ah receptor expression and receptor-dependent responses have been observed in many of these tissues, they presumably play a role in TCDD carcinogenesis. An indirect mechanism involving enhanced metabolism of thyroid hormones in the liver is proposed for thyroid carcinogenesis. This enhanced metabolism is Ah receptor dependent (IARC, 1997).

The enhanced metabolism of thyroid hormones in the liver is supposedly regulated through T4 uridine glucuronyl transferase (T4UGT) (Barter and Klaassen, 1992). T4UGT is a mixture of at least UGT1A1 and UGT1A2 (Visser et al., 1993a, 1993b). UGT1A1 has been reported to be regulated through the Ah receptor (Bock, 1991).

7.2.3 Mechanisms for Reduced Cancer Incidence Following TCDD Exposure

A reduction of the cancer incidence of tumors in specific tissues following exposure to TCDD might be explained as a result of exposure-related reductions in body weight gain (Tannenbaum, 1940 [cited by IARC, 1997, p. 335]; Kociba et al., 1978). It can also be due to a disruption in the endocrine homeostasis by TCDD, reducing the incidence of hormone-dependent cancers (e.g., mammary and uterine cancers) (IARC, 1997).

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APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 69 (Polychlorinated Dibenzo-*para*-Dioxins and Polychlorinated Dibenzofurans) 2,3,7,8-TCDD pp. 3-343, 525-630, 1997

APPENDIX B

EIGHTH REPORT ON CARCINOGENS LISTING FOR 2,3,7,8-TCDD (MAY 1998)

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

First Listed in the *Second Annual Report on Carcinogens*

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in experimental animals (IARC V.5, 1977; NTP 201, 1982; NTP 209, 1982; IARC S.4, 1982; IARC S.7, 1987). When administered by gavage, TCDD increased the incidences of thyroid follicular cell adenomas in male rats and neoplastic nodules of the liver in female rats. When administered by the same route, TCDD increased the incidences of hepatocellular carcinomas in mice of both sexes and thyroid follicular cell adenomas in female mice. When administered in the diet, the compound induced hepatocellular carcinomas and squamous cell carcinomas of the lung and hard palate nasal turbinates in female rats. It also induced squamous cell carcinomas of the tongue and hard palate nasal turbinates in male rats (Kociba et al., 1978a; idem., 1978b). When administered topically, TCDD induced fibrosarcomas of the integumentary system of female mice. When administered by intraperitoneal injection, TCDD induced thymic lymphomas and liver tumors in infant mice. In a two-stage skin carcinogenesis study, TCDD was a weak tumor initiator in mice when applied topically before application of 12-*O*-tetradecanoylphorbol-13-acetate. TCDD was also effective as a promoter, increasing the incidences of hepatocellular carcinomas in rats treated subcutaneously with TCDD and intragastrically with *N*-nitrosodiethylamine.

An IARC Working Group reported that there are no adequate data to evaluate the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in humans (IARC S.7, 1987). There are no reports of human exposure to TCDD alone. However, there are numerous case-control studies associating soft tissue sarcoma and lymphoma with exposure to phenoxyacetic acids or chlorophenols, probably contaminated with TCDD. A number of cohort studies revealed an increased incidence of deaths from cancer including lymphoma and soft tissue sarcoma when exposed to TCDD during the manufacture or use of 2,4,5-trichlorophenol and/or 2,4,5-trichlorophenoxy acids. Several epidemiology studies of humans exposed to herbicides contaminated with TCDD indicate an association between exposure and stomach cancer, lymphoma, and soft tissue sarcoma (IARC S.4, 1982; ATSDR, 1989f).

PROPERTIES

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is a colorless solid with no distinguishable odor. It is soluble in *o*-dichlorobenzene, chlorobenzene, benzene, and chloroform. TCDD is slightly soluble in acetone and methanol and is practically insoluble in water. TCDD is susceptible to photodegradation in the presence of ultraviolet light.

USE

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is used only as a research chemical (HSDB, 1987).

PRODUCTION

Chem Sources identified two suppliers of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in 1990 (Chem Sources, 1991). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is not currently produced commercially in the United States but is synthesized on a laboratory scale. TCDD is not imported into the United States (OHEA, 1985b). TCDD is produced as an undesired by-product during the manufacture of 2,4,5-

trichlorophenol, an intermediate for the manufacture of several agricultural products (Kirk-Othmer V.5, 1979).

EXPOSURE

The primary routes of potential human exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin have changed since EPA banned the use of herbicides containing 2,4,5-T in the late 1970s (ATSDR, 1989f). Both occupational and consumer exposure to TCDD due to herbicide manufacture and use no longer exist. Current sources of exposure are municipal incinerators, dump sites, and contaminated soil. Primary exposure is from ingestion of food from TCDD-contaminated sites. Consumer exposure could possibly occur through skin contact with soil, vegetation, or paper products contaminated with TCDD; consumption of root vegetables, fish, meats, and milk contaminated with TCDD; and inhalation of TCDD-polluted air from hazardous waste sites, industrial and municipal incinerators, combustion of leaded gasoline, diesel fuel, and wood; cigarette smoke; fields sprayed with certain pesticides, herbicides, germicides, or defoliants; plant accidents, and transformer/capacitor fires involving PCBs and chlorobenzenes. Workers at certain municipal and industrial incinerators and hazardous waste sites possibly could be exposed to TCDD. TCDD has been detected following fire accidents involving transformers containing polychlorinated biphenyls (PCBs), as well as in effluents from commercial incineration units (ATSDR, 1989f). Potential exposure to TCDD could occur for workers involved in the clean-up of PCB-capacitor/transformer fires.

The phenoxy herbicide, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), produced prior to 1960 contained up to 100 μg TCDD/g. In recent years, this has been reduced to < 0.1 μg/g. Agent Orange, a 1:1 mixture of butyl esters of 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) produced before 1970, contained 0.02-54 μg TCDD/g. Some 0.2 to 0.5 ng TCDD/g has been found in some batches of hexachlorophene, a germicide manufactured from trichlorophenol. TCDD was detected at a concentration of < 1 ng/g in sodium pentachlorophenate, 2,3,4,5-tetrachlorophenol, and hexachlorophene. 2,4,5-Trichlorophenol contains up to 6.2 μg/g TCDD. Approximately 2 million acres in the United States have been treated for weed control on one or more occasions with approximately 15 million lb of TCDD-contaminated 2,4,5-T, 2,4-D, or combinations of the two. Breast-fed babies nursed by mothers residing near improperly controlled municipal incinerators or other sources of possible TCDD exposure are potentially exposed to TCDD in the milk. Potential occupational exposure to TCDD may have occurred during the production, formulation, or use of trichlorophenol and its derivative products, hexachlorophene, Silvex, 2,4,5-T, and other herbicides containing 2,4,5-T, with the heaviest exposure during purification of 2,4,5-T from its contaminants, since these products contain much higher concentrations of TCDD than the purified products (ATSDR, 1989f). However, production of 2,4,5-T and 2,4,5-trichlorophenol has been discontinued in the United States (SRIa, 1987).

The total estimated release of TCDD into the environment is approximately 80 lb per year. A 1982 EPA study estimated average air concentrations of chlorinated dioxins and dibenzofurans in the United States to be 1,100 ppt (Chem. Eng. News, 1986). Municipal incinerators are one of the major sources of atmospheric TCDD. Accidents involving transformers/capacitors containing PCBs are another major source of TCDD in the air. TCDD has not been detected in drinking water, but it has been detected in aqueous industrial effluents, sediments, and leachates from hazardous waste sites. TCDD has also been detected in soil from industrial sites, waste disposal sites, and sites involved in accidental releases of chemicals containing TCDD. The accidental or improper disposal of still-bottom residue from the manufacture of 2,4,5-trichlorophenol may be the largest source of

TCDD in soils. There is some evidence that TCDD is resistant to natural degradation and has the potential to bioaccumulate (ATSDR, 1989f).

REGULATIONS

TCDD is regulated by EPA under the Clean Water Act (CWA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Resource Conservation and Recovery Act (RCRA), the Superfund Amendments and Reauthorization Act (SARA), and the Toxic Substances Control Act (TSCA). CWA establishes TCDD as a priority pollutant and requires the publication of ambient water quality criteria for the compound. A reportable quantity (RQ) of 1 lb has been established for TCDD under CERCLA. Under FIFRA, EPA banned detectable TCDD in 2,4,5-T and Silvex. RCRA designates TCDD as a hazardous constituent of waste, which subjects waste containing the chemical to special handling and report/recordkeeping requirements. EPA has included TCDD on the list of CERCLA hazardous substances which subjects it to reporting requirements under SARA. TCDD-contaminated wastes are subject to conditions of disposal, including notification of EPA, under TSCA. TSCA also requires notification of EPA for export of TCDD or mixtures containing TCDD. EPA is conducting an agency-wide review of the technical basis of its regulatory approach. FDA has proposed detection techniques for TCDD in food-producing animals. NIOSH has recommended that exposure to TCDD be reduced to the lowest feasible level, based on its carcinogenic and chloracne effects. OSHA regulates TCDD under the Hazard Communication Standard and as a chemical hazard in laboratories.

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
E P A	1/85. OAQPS Communication. CAA: Assessment of sources and exposures completed 3/83. 40 CFR 401.15, 401.16. Published 2/1/74. CWA 307: Establishes TCDD as a priority pollutant and requires publication of ambient water quality criteria. 45 FR 9549. Proposed 2/12/80. CWA 301, 304, 316: Establishes ocean discharge criteria. 45 FR 79318. Published 11/28/80. CWA 304(a): Ambient water quality criteria for TCDD published in final form.	OAQPS is participating in the dioxins strategy development workgroup.

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
E P A	46 FR 9404. Published 1/28/81. CWA 204, 208, 301, 304, 307: General pretreatment regulations for existing and new sources of pollution.	Comment solicited by 3/28/80, and public hearing was held 3/21/80.
	48 FR 23552. Proposed 5/25/83. CERCLA 101(14): Designates and establishes statutory RQ of 1 lb.	Criteria document identifies effects of TCDD on public health, welfare, aquatic life, and recreation. Excess cancer risk of 10^{-4} to 10^{-7} from exposure to 1.3 x 10^{-12} mg/l TCDD.
	40 CFR 302. Promulgated 8/14/89. CERCLA 101(14). Final rule establishes RQ of 1 lb.	Effective 3/13/81.
	43 FR 17118, 41268, 48456. Published 4/21/78, 9/15/78, 10/18/78. FIFRA: RPAR issued for 2,4,5-T, 2,4,5-trichlorophenol, and Silvex.	If promulgated, would provide control over releases of TCDD into the environment. Pesticide/herbicides contaminated with TCDD.
	44 FR 15874. Published 3/15/79. FIFRA: Emergency suspension of pesticide registration. Cancellation/suspension notices for 2,4,5-T and its esters and Silvex.	Litigation seeking temporary injunction against emergency suspension order dismissed. Cancellation hearings started 3/14/80.
	45 FR 2899. Published 1/15/80. FIFRA: Application for registration of pesticide/herbicide products contaminated with TCDD denied.	
	45 FR 60483. Published 9/12/80. FIFRA/RCRA: Establishes a disposal plan for pesticide products contaminated with TCDD.	

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 261.11. Promulgated 5/19/80. RCRA 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1,000 kg to handling and report/recordkeeping requirements. Also designates TCDD as a hazardous constituent of waste and subjects wastes known to contain it to the same requirements.	Based on toxic effects other than acute. EPA Carcinogen Assessment Group has included TCDD on its list of potential carcinogens. As a result of this listing, TCDD is regulated under the hazardous waste disposal rule of RCRA.
	52 FR 12866. Published 4/17/87. SARA 110: Establishes priority list of CERCLA hazardous substances subject to reporting requirements.	Amends CERCLA 104(i). Establishes requirements for preparation of a list of hazardous substances found at National Priority List sites, toxicological profiles of those substances, and a research program to fill data gaps associated with these substances.
	40 CFR 775. Promulgated 5/19/80. TSCA 6: Prohibits disposal of TCDD, 2,4-D, 2,4,5-T, Silvex, 2,4,5-TCP, and herbicide orange.	Restricted removal of wastes except with EPA approval in compliance with RCRA requirements. Revoked when RCRA regulation became effective on 7/15/87.
	40 CFR 707. Promulgated 12/16/80. TSCA 12(b): Requires exporters of TCDD or mixtures containing TCDD to notify EPA.	
	40 CFR 766. Published 6/5/87. TSCA: Requires manufacturers and importers of certain organic chemicals to test for the presence of chlorinated and brominated dibenzo-*p*-dioxins and dibenzofurans. Also requires submission of process and reaction data.	
F D A	44 FR 17077. Proposed 3/20/79. FD&CA: Detection techniques for TCDD in food-producing animals.	

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
NIOSH	1/84. Recommended reduction of exposure to TCDD to lowest feasible concentration.	Based on potential for cancer and chloracne in humans and carcinogenicity in animals.
	1/23/84. Current Intelligence Bulletin #40, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD, "dioxin").	Summary of current NIOSH recommendation: exposure limit - Ca, lowest feasible concentration.
OSHA	29 CFR 1910.1200, 1915, 1917, 1918, 1926, 1928. Promulgated 2/15/89. OSH Act: Hazard Communication	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program to include labels, material safety data sheets, and worker training. Labels may be subject to FIFRA requirements.
	29 CFR 1910.1450. Promulgated 1/31/90. OSH Act: Final rule for occupational exposure to hazardous chemicals in laboratories.	As a select carcinogen (IARC Group 2B), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin is included as a chemical hazard in laboratories. Employers required to provide employee information and training and to provide Chemical Hygiene Plan.

APPENDIX C

DESCRIPTION OF ONLINE SEARCHES FOR TCDD

DESCRIPTION OF ONLINE SEARCHES FOR TCDD

Searches were limited from 1992 to September 1997 for environmental pollution information. Few searches were performed for carcinogenicity data due to the recent publication of the IARC monograph (IARC V.69, 1997).

Online searches for TCDD [CASRN 174-01-6] were performed in databases on the systems of STN International, DIALOG, NLM's TOXNET, and the Chemical Information System from 1992 to date. Toxicology information was sought in the EMIC, EMICBACK, RTECS, and TOXLINE (using MESH terms for all neoplasms). The Chemical Abstracts file was searched by appropriate section codes (59, air pollution and industrial hygiene; 60, waste treatment and disposal; 61, water) for reviews on environmental pollution. The Chemical Abstracts Service Registry file, SANSS, the NTP Chemical Repository Database, and OHM/TADS (the Oil and Hazardous Materials Technical Assistance Data System) provided chemical identification information.

Regulatory information was obtained from CHEMLIST, the in-house FEDA CD-ROM containing the latest *Code of Federal Regulations* and the *Federal Register* pertaining to CFR titles 21 (FNDA), 29 (OSHA), and 40 (EPA).

Review of 1200 life sciences journals for current awareness was done using Current Contents on Diskette®.

APPENDIX D

SUPPLEMENT to the 1997 NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT For 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD)

Prepared for

the December 1-2, 1998,
Meeting of the Report on Carcinogens Subcommittee
of the NTP Board of Scientific Counselors

TABLE OF CONTENTS

1.0 INTRODUCTION

The carcinogenesis, epidemiology, and mechanisms of carcinogenesis literature reviewed in the September 30, 1997, Report on Carcinogens Draft Background Document for TCDD relied primarily on the IARC monograph on TCDD published in vol. 69 in early 1997. TOXLINE and Current Contents on Diskette® searches in 1997 provided a few additional references on these topics, all of which were included in the Draft Background Document.

An updated search was performed in mid-October 1998 in the databases BIOSIS, CANCERLIT, CA PLUS, EMIC, MEDLINE, NIOSHTIC, and TOXLINE for relevant reports published in 1997 and 1998. The MESH heading for all neoplasms was used in the NLM databases CANCERLIT, MEDLINE, and TOXLINE. A Current Contents search through October 19, 1998, found a few additional citations.

Readily available 1997 and 1998 epidemiology reports were obtained and the most relevant ones are briefly outlined in Section 2 - Epidemiology Updates. Section 3 provides the Epidemiology References Cited. Copies of these references are included with this supplement.

Section 4 lists Additional Publications for 1997-1998 which were identified by the search and are broken into three groups: Epidemiology (4.1), Animal Studies *In Vivo* (4.2), and Other Publications Relevant to Mechanisms of Carcinogenesis (4.3). Section 4.2 is subdivided into Carcinogenesis, Genetic Toxicity, and Mechanisms of Carcinogenesis.

2.0 EPIDEMIOLOGY UPDATES (Selected Publications 1997 – 1998)

This section provides a brief outline of selected epidemiological reports relevant to carcinogenicity of TCDD published after the NTP TCDD September 30, 1997, Draft Background Document:

The September 30, 1997, Background Document for TCDD referred to an "in press" publication by Bertazzi et al. This paper has now been published and contains the most recent mortality update of the Seveso accident (Bertazzi et al., 1997); these data are also reviewed in Bertazzi et al. (1998). These publications report follow-up covering the 15 years since the accident and estimates relative risks of various cancers in males and females in three exposure Zones.

An updated mortality report of an international cohort of 21,683 phenoxy herbicide production workers and applicators that was assembled by IARC was published recently (Kogevinas et al., 1997). Individual publications reporting mortality experience in subcohorts of the IARC international cohort have also appeared recently (Hooiveld et al., 1998; Lynge, 1998). One of these, an update of a previously studied cohort of Dutch workers, reports mortality from various causes from 1955 through 1991 in 1,167 herbicide production workers (Hooiveld et al., 1998). This chemical factory cohort was exposed to various herbicides and contaminants and an accident occurred which exposed some workers to higher levels of contaminants including TCDD. Serum levels of 2,3,7,8-TCDD and other contaminants were measured in a sub-set of the workers and correlated with work histories in order to predict exposures to the whole cohort.

Another recent publication (Flesch-Janys et al., 1998) is an extended analysis of the cancer mortality experience of 1,189 males employed at a German pesticide plant after 1952 and followed through the end of 1992. The study employed new methods to estimate dose rates of TCDD and related chemicals in various departments of the plant and to estimate cumulative exposure to TCDD. Mortality ratios for various cancers are presented in relation to quartiles of cumulative TCDD or TEQ dose. An accompanying report (Becher et al., 1998) presents further analysis of mortality in this with respect to dose-response trends and confounding factors.

The most recent mortality follow-up of 1,261 Air Force Ranch Hands who are part of an on-going cohort study that began in 1982 is reported by Michalek et al. (1998). Ranch Handers were involved in fixed wing aircraft spraying of Agent Orange contaminated with 2,3,7,8-TCDD. Many of them, in certain job categories, have been found to have elevated serum TCDD levels consistent with Agent Orange exposure.

One study (Hay and Tarrel, 1997) reports the results of a cohort mortality follow-up study of 225 person who were exposed to phenoxy herbicides and PCBs while working for a utility company in New Brunswick, Canada, between June 1950 and June 1966. The only attempt to estimate exposures to 2,4,5-T and dioxins was based on soil samples, but the authors conclude that the utility of this approach for estimating human exposure is unreliable.

3.0 EPIDEMIOLOGY REFERENCES CITED

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Bertazzi, P.A., C. Zocchetti, S. Guercilena, D. Consonni, A. Tironi, M.T. Landi, and A.G. Pesatori. 1997. Dioxin exposure and cancer risk: A 15-year mortality study after the "Seveso accident." Epidemiology 8(6):646-652.

Bertazzi, P.A., I. Bernucci, G. Brambilla, D. Consonni, and A.C. Pesatori. 1998. The Seveso studies on early and long-term effects of dioxin exposure: A review. Environ. Health Perspect. 106(Suppl. 2):625-633.

Flesch-Janys, D., K. Steindorf, P. Gurn, and H. Becher. 1998. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. Environ. Health Perspect. 106(Suppl. 2):655-662.

Hay, A., and J. Tarrel. 1997. Mortality of power workers exposed to phenoxy herbicides and polychlorinated biphenyls in waste transformer oil. Ann. N.Y. Acad. Sci. 837(Preventive strategies for living in a chemical world: A symposium in honor of Irving J. Selikoff; International Symposium; November 2-5, 1995):138-159.

Hooiveld, M., D.J. Heederik, M. Kogevinas, P. Boffetta, L.L. Needham, D.G. Patterson, Jr., and H.B. Bueno-de-Mesquita. 1998. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. Am. J. Epidemiol. 147(9):891-901.

Lynge, E. 1998. Cancer incidence in Danish phenoxy herbicide workers, 1947-1993. Environ. Health Perspect. 106(Suppl. 2):683-688.

Michalek, J.E., N.S. Ketchum, and F.Z. Akhtar. 1998. Post-service mortality of U.S. Air Force veterans occupationally exposed to herbicides in Vietnam: 15-year-follow up. Am. J. Epidemiol. 148:786-792.

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4.1. Epidemiology

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Becher, H., and D. Flesch-Janys. 1998. Dioxins and furans: Epidemiologic assessment of cancer risks and other human health effects. Environ. Health Perspect. 106(Suppl. 2):623-624.

Bertazzi, P.A., A.C. Pesatori, D. Turrini, and D. Consonni. 1997. Dioxin exposure and human leukemias and lymphomas lessons from the Seveso accident and studies on industrial workers. Presented at: XIX symposium of the International Association for Comparative Research on Leukemia and Related Diseases; July; Heidelberg, Germany. J. Mol. Med. (Berlin) 75(7):B168. Abstract.

Boffetta, P., M. Hooiveld, and M. Kogevinas. 1998. Cancer risk among workers exposed to chlorophenoxy herbicides, chlorophenols, and dioxins. Presented at: 89th annual meeting of the American Association for Cancer Research; March-April; New Orleans, LA. Proc. Am. Assoc. Cancer Res. Annu. Meet. 39:367. Abstract.

Flesch-Janys, D. 1997-1998. Analyses of exposure to polychlorinated dibenzo-*p*-dioxins, furans, and hexachlorocyclohexane and different health outcomes in a cohort of former herbicide-producing workers in Hamburg, Germany. Teratogen. Carcinogen. Mutagen. 17(4-5): 257-264. German.

Grassman, J.A., X.P. Yang, S.A. Masten, G.C. Clark, C.R. Miller, D.L. Spencer, N.J. Walker, L. Needham, M.T. Landi, D. Jung, and G.W. Lucier. 1997. Assessment of interindividual variability in dioxin responsiveness in populations having different patterns of exposure. Presented at: 88th annual meeting of the American Association for Cancer Research; April; San Diego, CA. Proc. Am. Assoc. Cancer Res. Annu. Meet. 38:618-619. Abstract.

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Yang, X.P., S.A. Masten, G.C. Clark, A.M. Tritscher, C. Miller, J.A. Grassman, N.J. Walker, D.L. Spencer, R. Morris, L. Needham, D. Jung, L. Edler, and G. W. Lucier. 1997. Markers of exposure and susceptibility to dioxin in German chemical plant workers. Proc. Annu. Meet. Am. Assoc. Cancer Res. 38:A2362. Abstract.

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4.2 Animal Studies *In Vivo*

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Hassoun, E.A., S.C. Wilt, M.J. DeVito, A. Van Birgelen, N.Z. Alsharif, L.S. Birnbaum, and S.J. Stohs. 1998. Induction of oxidative stress in brain tissues of mice after subchronic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Toxicol. Sci. 42(1):23-27.

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APPENDIX E

Report on Carcinogens (RoC), 9th Edition
Review Summary

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Review Summary

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

NOMINATION
Review for possible upgrading of current listing from *reasonably anticipated to be a human carcinogen* to a *known to be human carcinogen* based on recent IARC reclassification of TCDD as a known human carcinogens (IARC Vol. 69, 1997).

DISCUSSION
TCDD is a contaminant formed during incineration of municipal, toxic, and hospital wastes, and has been found as a contaminant of some herbicides and pesticides. Several human studies show an association between dioxin exposure and all cancers combined, lung cancer, and non-Hodgkin's lymphoma. TCDD is carcinogenic in multiple species of laboratory animals, in multiple tissues, by multiple routes, and there is similarity in Ah receptor function and responses to TCDD in humans and animals. Similar responses occur in humans and animals at comparable dioxin body burdens. There are low relative risks for cancer mortality in the human studies of TCDD-exposed populations. Confounding of cancer associations by other chemical exposures is difficult to rule out. The mechanism of carcinogenicity for TCDD has not been completely elucidated in animals or humans. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	upgrade and list as known human carcinogen	10 yes/0 no
NTP EC Working Group (RG2)	upgrade and list as known human carcinogen	8 yes/0 no
NTP Board RoC Subcommittee	continue to list as reasonably anticipated to be a human carcinogen	5 yes/7 no/1a

*Subcommittee initially reviewed TCDD at October, 1997 meeting and voted 4 yes/3 no/1 abstention to upgrade listing to a *known to be human carcinogen.* Reviewed a second time, at Dr. Olden's request, at the December, 1998 meeting where the Subcommittee voted against motion to upgrade listing by vote of 5 yes/7 no/1 abstention. Therefore, subcommittee recommendation was to continue to list as *reasonably anticipated to be a human carcinogen.* (a-abstentions)

Public Comments Received
A total of 20 public comments were received:

- 2 in favor of upgrading the listing to known to be human carcinogen
- 13 against upgrading the current listing of reasonably anticipated to be a human carcinogen
- 5 providing comments on the content of the background document prepared for the review of this nomination