EPA-540/1-86-044

c.2

Environmental Protection Agency

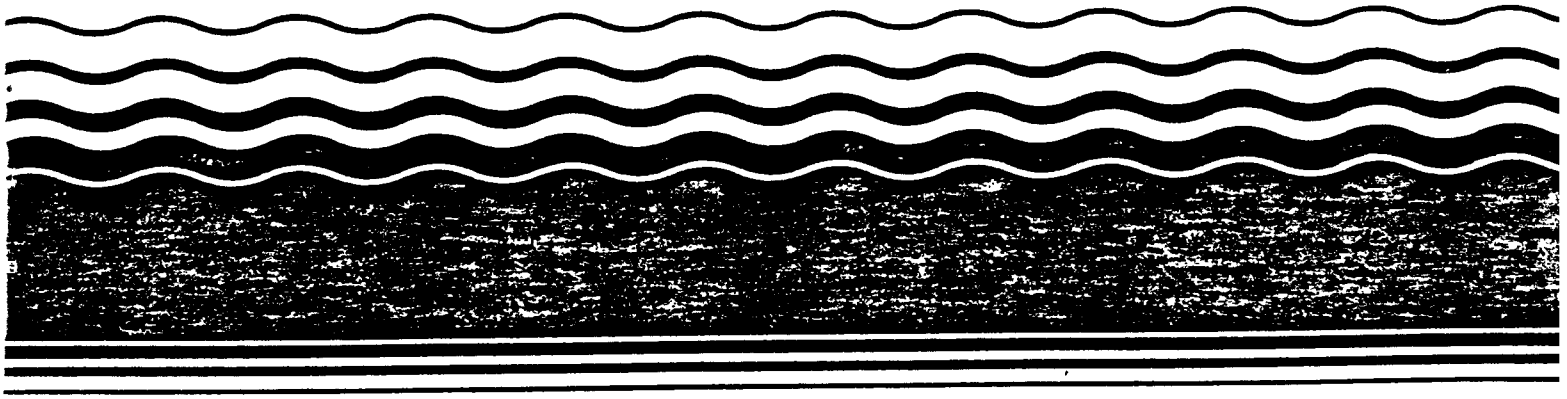
Office of Emergency and Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

Superfund

EPA

HEALTH EFFECTS ASSESSMENT FOR 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN



EPA/540/1-86-044
September 1984

HEALTH EFFECTS ASSESSMENT FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1983b. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of 2,3,7,8-TCDD. Prepared by the Carcinogen Assessment Group, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984a. Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-014A. NITS PB 84-220268.

U.S. EPA. 1984b. Ambient Water Quality Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-072.

U.S. EPA. 1985. Drinking Water Criteria Document on 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. (Final draft)

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is

assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

2,3,7,8-TCDD has been shown to be carcinogenic in many independent rodent bioassays with oral exposure resulting in increases in incidence of a variety of tumor types. Results of *in vitro* mutagenicity tests have been mixed. Human exposure data suggest a link between 2,3,7,8-TCDD exposure and increased cancer incidence, but are inadequate for quantitative risk assessment. Using data for tumor incidence in female rats orally exposed to 2,3,7,8-TCDD, a carcinogenic potency for oral exposure to humans (q_1^*) of 1.56×10^5 $(mg/kg/day)^{-1}$ was estimated.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by:

Bette Zwayer, Pat Daunt, Karen Mann and Jacky Bohanon
Environmental Criteria and Assessment Office
Cincinnati, OH

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

LIST OF TABLES

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
ED_{50}	Effective dose for 50% of recipients
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
PCDD	Polychlorinated dibenzo-p-dioxin
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 2,3,7,8-TCDD (CAS No. 1746-01-6) are given as follows (U.S. EPA, 1984a):

Chemical class:	halogenated dibenzo-p-dioxins
Molecular weight:	321.98
Vapor pressure at 25°C:	1.7×10^{-6} (estimated)
Water solubility (at unspecified temperature):	0.2 µg/ℓ
Octanol/water partition coefficient:	1.4×10^{-6} to 1.9×10^{-7} (estimated)
BCF:	5000
Half-lives in	
Air:	unknown
Water:	1-2 years
Soil:	10-12 years

No estimates of the half-life of 2,3,7,8-TCDD in the atmosphere are available. Based on the available information, photodegradation and wet and dry deposition of particle-bound 2,3,7,8-TCDD are probably the most significant fate-determining processes for atmospheric 2,3,7,8-TCDD (U.S. EPA, 1984a).

Based on the available data (U.S. EPA, 1984a), the possibility of vertical movement of 2,3,7,8-TCDD in soil in negligible under most conditions. Leaching of 2,3,7,8-TCDD from soil is possible under special conditions: for example, from sandy soils, particularly after multiple 2,3,7,8-TCDD application or accidental release of 2,3,7,8-TCDD on soil (U.S. EPA, 1984a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

The GI absorption of 2,3,7,8-TCDD is a function of both the dose administered and the vehicle used. Poiger and Schlatter (1980) reported a linear relationship between the dose of 2,3,7,8-TCDD and rat hepatic tissue levels of 2,3,7,8-TCDD over the range of 0.06-1.4 μg/kg bw. The percentage of the dose absorbed apparently decreased at doses higher than 1.4 μg/kg bw. Rose et al. (1976) estimated that steady-state concentrations would be reached within 13 weeks following gavage administration of 0.1-1.0 μg 2,3,7,8-TCDD/kg bw/day to rats for 5 days/week. Within the dosage range tested, the rate constant defining the approach to steady state was independent of the dosage. Fries and Marrow (1975) found that 2,3,7,8-TCDD at 7 or 20 ppb in the diet fed to rats for 6 weeks was 50-60% absorbed. Single or repeated (5 days/week for 7 weeks) doses given to rats by gavage in acetone:corn oil (2:25 or 1:9) were ~70-86% absorbed (Rose et al., 1976; Piper et al., 1973). A similar extent of absorption was reported in hamsters by Olson et al. (1980) who estimated absorption of a 650 μg/kg bw dose in olive oil at 74%. In guinea pigs, absorption was estimated at 50% [Nolan et al., 1979 (detail of protocol not provided)]. The data for rats suggest that a greater extent of absorption results from gavage rather than from dietary treatment, implying that adsorption to food particles may inhibit absorption. Adsorption on aqueous suspensions of soil has been shown to markedly reduce GI absorption (Poiger and Schlatter, 1980). Replacing soil with activated charcoal nearly eliminated absorption from the GI tract. Van der Berg et al. (1983) found lower hepatic levels of PCDD in rats fed for 19 days with a diet containing PCDD-laden fly ash than in rats fed an extract of fly ash containing PCDDs at comparable levels. The

differences in concentrations of PCDDs in the liver between fly ash and extract-fed rats were greater with the more highly chlorinated PCDDs than with 2,3,7,8-TCDD.

2.2. INHALATION

Pertinent data regarding to the absorption of 2,3,7,8-TCDD from the respiratory tract could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. The subchronic oral toxicity of 2,3,7,8-TCDD is summarized in Table 3-1. Two studies have investigated the effects of very low doses of 2,3,7,8-TCDD. Murray et al. (1979) investigated the teratogenic and reproductive effects of dietary 2,3,7,8-TCDD (0, 0.001, 0.01 or 0.1 µg/kg bw/day) in Sprague-Dawley rats. The F_0 rats were maintained on the treatment diets for 90 days and were then mated twice, producing the F_{1a} and F_{1b} generations. The F_{1b} and F_2 rats were mated at ~130 days of age, producing the F_2 and F_3 litters, respectively. The authors reported a NOAEL of 0.001 µg/kg bw/day for reduced fertility and fetal survival; however, Nisbet and Paxton (1982) reanalyzed the data from this study using different statistical techniques and concluded that a dose of 0.001 µg/kg bw/day resulted in a significantly reduced gestational index, decreased fetal weight, increased liver-to-body-weight ratios and an increased incidence of dilated renal pelvis.

Vos et al. (1973) measured the effect of eight weekly gavage doses of 0.008, 0.04, 0.2 or 1.0 µg/kg bw/week (equivalent to 0.0011, 0.0057, 0.029 or 0.143 µg/kg bw/day) on immune function in groups of 10 female Hartley guinea pigs. Effects on humoral immunity were measured by the response to a subcutaneous injection of tetanus toxoid, and cell-mediated immunity was measured by the delayed-type hypersensitivity to Mycobacterium tuberculosis. The lowest dose that produced a reduction in immune response was 0.0057 µg/kg bw/day, with a no-effect level of 0.0011 µg/kg bw/day.

3.1.2. Inhalation. No data on the subchronic inhalation toxicity of 2,3,7,8-TCDD were located in the available literature.

TABLE 3-1

Effects of Subchronic Oral Exposure to 2,3,7,8-TCDD[a]

Species	Dose µg/kg/day	Duration of Exposure	Effect Level	Endpoints	Reference
Rat	0.01	13 weeks	NOAEL	Decreased body weight	Kociba et al., 1976
Rat	0.1	13 weeks	LOAEL	Decreased body weight	Kociba et al., 1976
Rat	0.07	13 weeks	NOAEL	Toxic hepatitis	NTP, 1980
Rat	0.14	13 weeks	LOAEL	Toxic hepatitis	NTP, 1980
Rat	1.0	30 days	NOAEL	Decreased body weight	Harris et al., 1973
Rat	0.71	6 weeks	NOAEL	Decreased body weight	Harris et al., 1973
Rat	0.1	30 days	LOAEL	Thrombocytopenia	Zinkl et al., 1973
Rat	0.71	6 weeks	LOAEL	Decreased body weight and thymus weight	Vos et al., 1973
Rat	0.001	3 generations	LOAEL[b]	Decreased body weight, decreased fertility, decreased fetal survival	Murray et al., 1979
Mouse	0.014	13 weeks	LOAEL	Toxic hepatitis	NTP, 1980
Mouse	0.71	4 weeks	NOAEL	Porphyria	Goldstein et al., 1978
Mouse	3.57	4 weeks	LOAEL	Porphyria	Goldstein et al., 1978
Mouse	5.0	4 weeks	LOAEL	Decreased thymus weight and graft-versus-host response	Vos et al., 1973

TABLE 3-1 (cont.)

Species	Dose µg/kg/day	Duration of Exposure	Effect Level	Endpoints	Reference
Mouse	0.14	4 weeks	LOAEL	Decreased resistance to *Salmonella*	Thigpen et al., 1975
Mouse	0.21	4 weeks	LOAEL	Increased endotoxic (*E. coli*) susceptibility	Vos et al., 1978
Mouse	1.3	5 weeks	LOAEL	Decreased tetanus response, antigenic RBC response, sensitization to DNFB, resistance to *Salmonella* infection, resistance to *Listeria* infection	Hinsdill et al., 1980
Guinea pig	0.0011	8 weeks	NOAEL	Decreased body weight, thymus weight and tuberculin hypersensitivity	Vos et al., 1973
Guinea pig	0.0057	8 weeks	LOAEL	Decreased body weight, thymus weight and tuberculin hypersensitivity	Vos et al., 1973

[a]Source: U.S EPA, 1984b

[b]Reported as NOAEL by Murray et al. 1979; considered a LOAEL by Nisbet and Paxton (1982) during a reevaluation of the data.

RBC = red blood cells; DNFB = 2,4-dinitro, 1-fluorobenzene

3.2. CHRONIC

3.2.1. Oral. The chronic oral toxicity of 2,3,7,8-TCDD is summarized in Table 3-2. In rats, NOAELs for liver toxicity were noted at 0.001 (Kociba et al., 1978, 1979), 0.0014 (Goldstein et al., 1982; NTP, 1980) mg/kg/day. These levels resulted in evidence of liver toxicity in mice (NTP, 1980; Toth et al., 1978, 1979). In rats, levels of 2,3,7,8-TCDD in the ranges of 0.007-0.71 mg/kg/day were regarded as LOAELs (Goldstein et al., 1982; King and Roesler, 1974; Kociba et al., 1978, 1979; NTP, 1980; Cantoni et al., 1981).

Toth et al. (1978, 1979) administered weekly doses of 0.0, 0.007, 0.7 or 7.0 µg 2,3,7,8-TCDD/kg bw/week (TWA = 0.0, 0.001, 0.1 or 1.0 µg 2,3,7,8-TCDD/kg bw/day) to male Swiss mice by gavage for 104 weeks. Dermatitis and amyloidosis of the kidney, spleen and liver were observed at all dose levels. This study, therefore, establishes a LOAEL of 0.001 µg/kg bw/day.

3.2.2. Inhalation. No data pertinent to the chronic inhalation toxicity of 2,3,7,8-TCDD to experimental animals could be located in the available literature. The effects of occupational and environmental exposure of humans to 2,3,7,8-TCDD have been reported in a number of clinical case studies and epidemiology studies (U.S. EPA, 1984a,b,c, 1985). The exposures in these cases were probably predominantly by the inhalation and dermal routes. The major effects reported were chloracne, peripheral neuropathy, fatigue, eye irritation, headache, possibly increased incidences of birth defects and possibly tumors. No dose-response information was available from any of these studies.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral.. The teratogenicity of 2,3,7,8-TCDD-contaminated 2,4,5-T has been studied by a number of investigators (Table 3-3). Other investigators have studied the effects of purified 2,3,7,8-TCDD (Table 3-4).

TABLE 3-2

Effects of Chronic Oral Exposure to 2,3,7,8-TCDD*

Species	Dose (µg/kg/day)	Duration of Exposure (weeks)	Effect Level	Endpoints	Reference
Rat	0.0014	16	NOAEL	elevated porphyrin levels	Goldstein et al., 1982
Rat	0.014	16	LOAEL	elevated porphyrin levels	Goldstein et al., 1982
Rat	0.014	28	LOAEL	fatty changes in liver, decreased body weight	King and Roesler, 1974
Rat	0.001	104	NOAEL	degenerative and necrotic changes in the liver	Kociba et al., 1978, 1979
Rat	0.01	104	LOAEL	degenerative and necrotic changes in the liver	Kociba et al., 1978, 1979
Rat	0.0014	104	NOAEL	toxic hepatitis	NTP, 1980
Rat	0.007	104	LOAEL	toxic hepatitis	NTP, 1980
Rat	0.71	45	LOAEL	porphyria	Cantoni et al., 1981
Rat	0.0071	45	LOEL	hepatic enzyme induction	Cantoni et al., 1981
Mouse	0.0014	104	LOAEL	toxic hepatitis	NTP, 1980
Mouse	0.001	104	LOAEL	dermatitis and amyloidosis	Toth et al., 1978, 1979

*Source: U.S. EPA, 1984b

TABLE 3-3

Studies on the Potential Teratogenic Effects of 2,3,7,8-TCDD-Contaminated 2,4,5-T*

Species/ Strain	Route/ Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treat-ment Days	Obser-vation Day	Maternal Response	Fetal Response	Reference
Mice/ NMRI	rape-seed oil	acid	<0.02 ppm (Sample A)	8, 15, 30, 45, 60,90 and 120 mg/kg	6-15	18	No toxic effects; decreased maternal weight at doses of 90 mg/kg and greater	Significant increases in the incidence of cleft palates at doses above 30 mg/kg (see text for additional details). Significantly decreased ($p<0.005$) fetal weight at all dose levels.	Neubert and Dillman, 1972
	rape-seed oil	acid	0.05±0.02 ppm (Sample B)	30, 60 and 90 mg/kg	6-15	18	No toxic effects; decreased maternal weight at 90 mg/kg	Increases in the incidence of cleft palate at 60 and 90 mg/kg; significant ($p<0.005$) at all dose levels.	
	rape-seed oil	acid	NR (Sample C)	90 mg/kg	6-15	18	No toxic effects but decreased maternal weight	Increase in the incidence of cleft palate; significant ($p<0.005$) decrease in fetal weight.	
	rape-seed oil	butyl ester	NR	12 and 17 mg/kg	6-15	18	No toxic effects	Significant decrease in fetal weight but no effect on mortality; increase in the frequency of cleft palate similar to that seen with acid (see text).	
Mice/ NMRI	NR	acid	0.05±0.02 ppm	20, 35, 60, 90 and 130 mg/kg	6-15	NR	Toxic effects observed at 90 and 130 mg/kg	Increases in the percentage of resorptions and/or dead fetuses at 90 and 130 mg/kg; increases in the incidence of cleft palate and retardation of skeletal development at 35 mg/kg and above.	Roll, 1971
Mice/ CD-1	corn oil: acetone (9:1)	acid	<0.05 ppm	115 mg/kg	10-15	18	No significant effect on weight gain or liver-to-body weight ratios	No effect on fetal mortality or fetal weight, but an increase in the incidence of cleft palate.	Courtney, 1977

TABLE 3-3 (cont.)

Species/ Strain	Route/ Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treat-ment Days	Obser-vation Day	Maternal Response	Fetal Response	Reference
Mice/ C57Bl/6	honey:water (1:1)	acid	30 ppm	46.4 and 113 mg/kg	6-14	18	NR	Significant ($p<0.01$) increases in the incidence of cleft palate in the high-dose group and cystic kidney in both dose groups; increased fetal mortality also observed in the high-dose group.	Courtney et. al., 1970a,b
Mice/ AKR	honey:water (1:1)	acid	30 ppm	113 mg/kg	6-15	19	Increase in liver-to-body-weight ratio.	Significant ($p<0.05$) increases in the incidence of cleft palate and fetal mortality	Courtney et. al., 1970a,b
Rats/ Sprague-Dawley (groups of 25 rats)	gavage/ hydroxy-propyl-methyl-cellulose	acid	0.5 ppm	1, 3, 6, 12, or 24 mg/kg/ day	6-15	20	No effect on body weight and no observable signs of toxicity.	A slight but statistically significant ($p<0.05$) decrease in implantations and litter size in lowest dose group only; no frank teratogenic effects based on a detailed examination of the control and 24 mg/ kg dose group; the only effect noted was an increase in the incidence of 5th partially ossified sternebrae.	Emerson et al. 1970, 1971 N.B. This appears to be a full publi-cation of the abstract sum-mary by Thompson et al., 1971
Rats/ Wistar	gavage/ aqueous gelatin or corn oil	acid	<0.5 mg/kg	25, 50, 100, or 150 mg/kg/ day	6-15	22	Some maternal mortality and decreased body weight gain at 150 mg/kg; no signs of toxicity at 100 mg/kg or below.	At 100 or 150 mg/kg, decreased fetal weight, increased fetal mortality and an increase of skel-etal anomalies; no signi-ficant effect at the two lower dose levels.	Khera and McKinley, 1972; Khera et al., 1971
	gavage/ aqueous gelatin or corn oil	butyl ester	<0.5 mg/kg	50 or 150 mg/kg/day	6-15	22	NR	No significant effect on fetal morality, fetal weight, or the incidence of anomalies.	Khera and McKinley, 1972; Khera et al., 1971

TABLE 3-3 (cont.)

Species/ Strain	Route/ Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Rats/ Holtzman	gavage/ 1:1 solution of honey and water	acid	30 ppm	4.6, 10.0 and 46.4 mg/kg/day	10-15	20	NR	Significant ($p<0.01$) increases in fetal mortality at the 2 higher dose levels; dose-related increases in the percent of abnormal fetuses per litter; a high incidence of cystic kidneys in treated groups.	Courtney et al., 1970a,b
Rats/ CD	gavage/ 15% sucrose solution	acid	0.5 ppm	10.0, 21.5, 46.4 and 80.0 mg/kg/ day	6-15	20	Reduced maternal weight gain at the 2 higher dose levels ($p<0.05$) and increased liver-to-body-weight ratio at the highest dose level ($p<0.05$)	Increase in the incidence of kidney anomalies but no increase in cleft palate.	Courtney and Moore 1971
Rats/ Sprague-Dawley	gavage/ methocellulose	acid	0.5 ppm	50 mg/kg	6-15	NS	No effect on mortality or body weight gain.	No significant effect on fetal mortality or fetal weight; a significant ($p<0.05$) increase in the incidence of delayed ossification.	Sparschu et al., 1971a
	gavage/ methocellulose	acid	0.5 ppm	100 mg/kg	6-10	NS	Increased mortality and decreased body weight gain.	Increase in the incidence of delayed ossification and poorly ossified or malaligned sternebrae ($p<0.05$)	Sparschu et al., 1971a
Syrian hamsters/ Mesocricetus auratus	gavage/ acetone, corn oil, and carboxymethyl cellulose in ratio of 1:5.8:10	acid	<0.1-4.5 ppm	20, 40, 80 and 100 mg/kg	6-10	14	NS	Dose-related increases in fetal mortality, gastrointestinal hemorrhages, and fetal abnormalities	Collins et al., 1971

*Source: U.S. EPA, 1985

NS = Not specified; NR = not reported

TABLE 3-4

Studies on the Potential Teratogenic and Reproductive Effects of 2,3,7,8-TCDD[a]

Species/Strain	Vehicle	Compound	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Mouse/C57Bl/6 Mouse/AKR	DMSO or honey:water (1:1)	2,4,5-T containing 30 ppm TCDD	21.5, 46.4, 113.0 mg/kg	6-14 or 9-17	19[b]	Increased liver-to-body-weight ratio	Fetal death, cleft palate, cystic kidney	Courtney et al., 1970a,b
Mouse/CD-1 Mouse/DBA/2J Mouse/C57Bl/6J	DMSO	2,3,7,8-TCDD	0.5, 1, 3 µg/kg	6-15	17[b] or 18	Increased liver-to-body-weight ratio	Cleft palate, kidney anomalies[c]	Courtney and Moore, 1971
Mouse/C57Bl/6	acetone: corn oil (1:9)	2,3,7,8-TCDD	1, 3 µg/kg	10-13 or 10	18[b]	None reported	Cleft palate, kidney anomalies[c]	Moore et al., 1973
Mouse/CD-1	DMSO or corn oil	2,3,7,8-TCDD	25, 50, 100, 200, 400 µg/kg	7-16	18[d]	Increased liver-to-body-weight ratio	Cleft palate, hydronephrotic kidneys, hydrocephalus, open eyes, edema, petechiae	Courtney, 1976
Mouse/CF-1	corn oil: acetone (98:2)	2,3,7,8-TCDD	0.001, 0.01, 0.1, 1.0, 3.0 µg/kg	6-15	18[b]	None reported	Cleft palate, dilated renal pelvis	Smith et al., 1976
Mouse/NMRI	rape-seed oil	2,3,7,8-TCDD	0.3, 3.0, 4.5, 9.0 µg/kg	6-15	18	No effect observed	Fetocidal at the high dose; cleft palate at doses at or above 4.5 µg/kg	Neubert and Dillman, 1972
Rat/CD	DMSO	2,3,7,8-TCDD	0, 0.5, 2.0 µg/kg	6-15, 9 and 10, or 13 and 14	20[b]	None reported	Kidney malformations at both dose levels	Courtney and Moore, 1971
Rat/Sprague-Dawley	corn oil/ acetone	2,3,7,8-TCDD	0, 0.03, 0.125, 0.5, 2.0, and 8.0 µg/kg	6-15	20[b]	Vaginal hemorrhage at 2.0 and 8.0 µg/kg	Intestinal hemorrhage at 0.125 and 0.5 µg/kg; fetal death at higher doses; subcutaneous edema	Sparschu et al., 1971b

TABLE 3-4 (cont.)

Species/Strain	Vehicle	Compound	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Rat/Wistar	corn oil/ anisole	2,3,7,8-TCDD	0.0, 0.125, 0.25, 1, 2, 4, 8, 16 µg/kg	6-15	22	Maternal toxicity observed at or above 1 µg/kg	Increased fetal death observed at or above 1 µg/kg; subcutaneous edema and hemorrhages in the 0.25 µg/kg groups	Khera and Ruddick, 1973
Rat/Sprague-Dawley	corn oil/ acetone (9:1)	2,3,7,8-TCDD	0.1, 0.5, 2.0 µg/kg	1-3	21	Decrease in body weight gain in the high-dose group	Decreased fetal weight in the 0.5 and 2 µg/kg group; cystic kidneys and dilated renal pelvis occurred in the 2 µg/kg group	Giavini et al., 1982a
Rat/Sprague-Dawley	diet	2,3,7,8-TCDD	0.001, 0.01 and 0.1 µg/kg[e]	throughout gestation	post-parturition	Low fertility at 0.01 and 0.1 µg/kg; decreased body weight at 0.01 and 0.1 µg/kg; dilated renal pelvis	Low survival at 0.01 and 0.1 µg/kg; decreased body weight at 0.01 slight dilated renal pelvis at 0.001 µg/kg	Murray et al., 1979
Rabbit/ New Zealand	corn oil/ acetone (9:1)	2,3,7,8-TCDD	0.0, 0.1, 0.25, 0.5 and 1 µg/kg	6-15	28	Maternal toxicity at doses of 0.25 µg/kg and above	Increases in extra ribs and total soft tissue anomalies	Giavini et al., 1982b
Monkey/rhesus	diet	2,3,7,8-TCDD	8.6 pg/kg/day	7 months prior to and during gestation	at term	6/8 conceived; normal serum estradiol and progesterone	3/8 normal births	Allen et al., 1979
Monkey/rhesus	diet	2,3,7,8-TCDD	55.7 pg/kg/day	7 months prior to and during gestation	at term	3/8 conceived; decreased serum estradiol and progesterone	1/8 normal births	Allen et al., 1979

[a]Source: U.S. EPA, 1985

[b]First day of gestation designated day 0.

[c]Kidney anomalies were not specifically defined.

[d]First day of gestation designated day 1.

[e]The high dose level (0.1 µg/kg/day) was discontinued due to very low fertility in adults.

DMSO = dimethyl sulfoxide

Neubert and Dillmann (1972) reported an ED_{50} of 4.6 μg 2,3,7,8-TCDD/kg bw for the production of cleft palate in mice. Smith et al. (1976) reported a minimum effective oral dose of 1.0 μg 2,3,7,8-TCDD/kg bw/day for the production of teratogenic effects in CF-1 mice. Rats are less sensitive to the teratogenic effects of 2,3,7,8-TCDD; however, significant fetotoxic effects have been observed at doses of 1.0 μg/kg bw/day and higher (Giavini et al., 1982a, 1983; Khera and Ruddick, 1973; Khera et al., 1971; Khera and McKinley, 1972).

The teratogenic and reproductive effects of low doses of 2,3,7,8-TCDD have been investigated in a 3-generation reproduction study using 16 male and 32 female Sprague-Dawley rats/generation (Murray et al., 1979). The authors concluded that doses of 0.01 or 0.1 μg 2,3,7,8-TCDD/kg bw/day resulted in decreased fertility, decreased litter size and decreased fetal survival, and that 0.001 μg 2,3,7,8-TCDD/kg bw/day was a NOEL. Nisbet and Paxton (1982) reanalyzed these data using different statistical methods; they concluded that a dose of 0.001 μg 2,3,7,8-TCDD/kg bw/day significantly reduced the gestational index and fetal weights, and increased the liver-to-body-weight ratios and the incidence of dilated renal pelvis.

3.3.2. Inhalation.. Pertinent data regarding the teratogenicity or other reproductive effects of inhalation exposure to 2,3,7,8-TCDD in experimental animals could not be located in the available literature. Several investigators have studied the incidence of birth defects in areas where 2,3,7,8-TCDD has been accidentally released or 2,3,7,8-TCDD-contaminated 2,4,5-T had been sprayed (U.S. EPA, 1979; Hanify et al., 1981; Field and Kerr, 1979; Nelson et al., 1979; Thomas, 1980; Department of Health, New Zealand, 1980; McQueen et al., 1977; Aldred, 1978; Townsend et al., 1982; Bonaccorsi et al., 1978; Bisanti et al., 1980; Reggiani, 1980). The individuals in these

studies were probably exposed by a variety of routes (inhalation, dermal, oral). Even in those studies in which a positive correlation between exposure and birth defects or abortions was found, 2,3,7,8-TCDD could not be unequivocally identified as the causative agent.

3.4. TOXICANT INTERACTIONS

2,3,7,8-TCDD is a potent enzyme inducer and, as such, may interact with a wide range of xenobiotics. These interactions can result in either inhibition or potentiation of the biological effects of the compounds that are substrates for these enzymes. Thus, 2,3,7,8-TCDD pretreatment alters the metabolism and reduces the carcinogenic potency of benzo[a]pyrene (Boobis and Nebert, 1976; Berry et al., 1976; Uotila et al., 1978). 2,3,7,8-TCDD pretreatment has also been demonstrated to alter the metabolism of aflatoxin B_1 (Gurtoo, 1980); nitrosamines (Scarpelli et al., 1980), N-2-fluorinylacetamide (DiGiovanni et al., 1979), 3,4-diaminisole (Reddy et al., 1980) and 7,12-dimethylbenz[a]-anthracene (DiGiovanni et al., 1979). Pretreatment with 2,3,7,8-TCDD also significantly alters the effects of the anesthetics zoxazolamine and hexabarbitone in rats (Greig, 1972).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the oral carcinogenicity of 2,3,7,8-TCDD in humans could not be located in the available literature.

4.1.2. Inhalation. Several investigators have reported a possible link between occupational or environmental exposure to 2,3,7,8-TCDD and the development of tumors, mostly soft tissue sarcomas, lymphomas and stomach carcinomas (Holden, 1979; Cook et al., 1980; Moses and Selikoff, 1981; Honchar and Halpern, 1981; Cook, 1981; Thiess and Frentzel-Beyme, 1977; Axelson and Sandell, 1974; Hardell, 1977; Axelson et al., 1979; Hardell and Sandstrom, 1979; Riihimake et al., 1980; Axelson et al., 1980; Eriksson et al., 1981; Hardell.et al., 1981). The routes of exposure were probably mixed, but dermal and inhalation exposure would be expected to be the most common. Although the data are suggestive, the variety of compounds these populations were exposed to (short follow-up periods, self-selection and reliance on patients' recall to determine exposure and personal histories) limit the ability of these studies to link exposure to 2,3,7,8-TCDD unequivocally with induction of tumors in humans.

4.2. BIOASSAYS

4.2.1. Oral. The available data on the carcinogenicity of orally administered 2,3,7,8-TCDD are summarized in Table 4-1. Oral administration of 2,3,7,8-TCDD results in the induction of hepatocellular carcinoma in both sexes of mice and in female rats (Kociba et al., 1978; NTP, 1980; Toth et al., 1979), squamous cell carcinomas of the hard palate in both sexes of rats (Kociba et al., 1978), and follicular-cell adenomas of the thyroid in male rats and female mice (NTP, 1980). The studies of Toth et al. (1979) and Van Miller et al. (1977a,b) are of limited value for risk assessment

TABLE 4-1

Carcinogenicity Bioassays of 2,3,7,8-TCDD Administration by the Oral Route[a]

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Vehicle	Tumor Type	Tumor Incidence	p Value	Reference
Gavage	rats/ Osborne-Mendel	M	0.0 µg/kg/week	104 weeks	105 weeks	corn oil-acetone (9:1)	follicular-cell adenomas of the thyroid, carcinoma of the thyroid	1/69 0/69	=0.006	NTP, 1980
			0.01 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	follicular-cell adenomas of the thyroid, carcinoma of the thyroid	5/48 0/48	=0.042	
			0.05 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	follicular-cell adenomas of the thyroid, carcinoma of the thyroid	6/50 2/50	=0.021	
			0.5 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	follicular-cell adenomas of the thyroid, carcinoma of the thyroid	0/50 1/50	=0.001	
Gavage	rats/ Osborne-Mendel	F	0.0 µg/kg/week	104 weeks	105 weeks	corn oil-acetone (9:1)	neoplastic nodules of the liver, hepatocellular carcinoma of the liver	5/75 0/75	<0.001	NTP, 1980
			0.01 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	neoplastic nodules of the liver, hepatocellular carcinoma of the liver	1/49 0/49	NS	
			0.05 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	neoplastic nodules of the liver, hepatocellular carcinoma of the liver	3/50 0/50	NS	
			0.5 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	neoplastic nodules of the liver, hepatocellular carcinoma of the liver	12/49 3/49	=0.006	

TABLE 4-1 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Vehicle	Tumor Type	Tumor Incidence	p Value	Reference
Gavage	mice/ $B6C3F_1$	M	0.0 µg/kg/week	104 weeks	105 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma	8/73	=0.002	NTP, 1980
			0.01 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma	9/49	NS	
			0.05 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma	8/49	NS	
			0.5 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma	17/50	=0.002	
Gavage	mice/ $B6C3F_1$	F	0.0 µg/kg/week	104 weeks	105 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma, follicular-cell adenomas of the thyroid	1/73 0/69	=0.008 =0.016	NTP, 1980
			0.04 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma, follicular-cell adenomas of the thyroid	2/50 3/50	NS NS	
			0.2 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma, follicular-cell adenomas of the thyroid	2/48 1/47	NS NS	
			2.0 µg/kg/week	104 weeks	107 weeks	corn oil-acetone (9:1)	hepatocellular carcinoma, follicular-cell adenomas of the thyroid	6/47 5/46	=0.014 =0.009	
Oral	rat/ Sprague-Dawley	M	0.0 ppb	78 weeks	95 weeks	in diet	all tumors[b]	0/10	NR	Van Miller et al., 1977a,b
			0.001 ppb	78 weeks	95 weeks	in diet	all tumors[b]	0/10	NR	

TABLE 4-1 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Vehicle	Tumor Type	Tumor Incidence	p Value	Reference
Oral (cont.)			0.005 ppb	78 weeks	95 weeks	in diet	all tumors[b]	5/10	NR	Van Miller et al., 1977a,b
			0.05 ppb	78 weeks	95 weeks	in diet	all tumors[b]	3/10	NR	
			0.5 ppb	78 weeks	95 weeks	in diet	all tumors[b]	4/10	NR	
			1.0 ppb	78 weeks	95 weeks	in diet	all tumors[b]	4/10	NR	
			5.0 ppb	78 weeks	95 weeks	in diet	all tumors[b]	7/10	NR	
Oral	rat/ Sprague-Dawley	M	0.0 µg/kg/day	105 weeks	105 weeks	in diet	squamous cell carcinoma of the hard palate,	0/85	NS	Kociba et al., 1978
							squamous cell carcinoma of the tongue,	0/85	NS	
							adenoma of the adrenal cortex	0/85	NS	
			0.001 µg/kg/day	105 weeks	105 weeks	in diet	squamous cell carcinoma of the hard palate,	0/50	NS	
							squamous cell carcinoma of the tongue,	1/50	NS	
							adenoma of the adrenal cortex	0/50	NS	
		M	0.01 µg/kg/day	105 weeks	105 weeks	in diet	squamous cell carcinoma of the hard palate,	0/50	NS	
							squamous cell carcinoma of the tongue,	1/50	NS	
							adenoma of the adrenal cortex	2/50	NS	
			0.1 µg/kg/day	105 weeks	105 weeks	in diet	squamous cell carcinoma of the hard palate,	4/50	<0.05	
							squamous cell carcinoma of the tongue,	3/50	<0.05	
							adenoma of the adrenal cortex	5/50	<0.05	

TABLE 4-1 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Vehicle	Tumor Type	Tumor Incidence	p Value	Reference
Oral	rat/ Sprague-Dawley	F	0.0 µg/kg/day	105 weeks	105 weeks	in diet	hepatocellular carcinoma,	0/86	NS	Kociba et al., 1978
							squamous cell carcinoma of the tongue,	0/86	NS	
							squamous cell carcinoma of the lung	0/86	NS	
			0.001 µg/kg/day	105 weeks	105 weeks	in diet	hepatocellular carcinoma,	0/50	NS	
							squamous cell carcinoma of the tongue,	0/50	NS	
							squamous cell carcinoma of the lung	0/50	NS	
			0.01 µg/kg/day	105 weeks	105 weeks	in diet	hepatocellular carcinoma,	2/50	NS	
							squamous cell carcinoma of the tongue,	1/50	NS	
							squamous cell carcinoma of the lung	0/50	NS	
		F	0.1 µg/kg/day	105 weeks	105 weeks	in diet	hepatocellular carcinoma,	11/49	<0.05	
							squamous cell carcinoma of the tongue,	4/49	<0.05	
							squamous cell carcinoma of the lung	7/49	<0.05	
Gavage	mice/ Swiss/H/ Riop	M	0.0 µg/kg/week	365 days	588 days	sunflower oil	liver tumors[c]	7/38	NS	Toth et al., 1979
			0.007 µg/kg/week	365 days	649 days	sunflower oil	liver tumors[c]	13/44	NS	
			0.7 µg/kg/week	365 days	633 days	sunflower oil	liver tumors[c]	21/44	<0.01	
			7.0 µg/kg/week	365 days	424 days	sunflower oil	liver tumors[c]	13/43	NS	

TABLE 4-1 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Vehicle	Tumor Type	Tumor Incidence	p Value	Reference
Oral	mice/ Peromyscus polionotus	M and F	0.0012 µg/kg/day	NA	NA	contaminated soil	liver	0/15	NS	Cockerham et al., 1980
			0.0 µg/kg/day	NA	NA	contaminated soil	liver	0/15	NS	

[a]Source: U.S. EPA, 1985

[b]No single target organ for cancer was outstanding.

[c]Includes hepatomas and hepatocellular carcinomas.

NR = Not reported; NS = not significant

purposes because of the relatively short exposure times and small group sizes or both. The study in beach mice (Peromyscus polionotus) by Cockerham et al. (1980) was reported in insufficient detail (duration of treatment and observation periods were not reported). Treatment was in soil as a vehicle, a single low level was given, and negative results were obtained. The studies by Kociba et al. (1978) and NTP (1980) involved sufficiently long dosing schedules and large enough groups to be used for quantitative risk assessment.

Kociba et al. (1978) fed diets resulting in doses of 0.0, 0.001, 0.01 or 0.1 µg 2,3,7,8-TCDD/kg bw/day to groups of 50 male and 50 female Sprague-Dawley rats for 2 years. The control group consisted of 86 males and 86 females. Tumor incidences were significantly increased in both sexes in the high-dose group ($p<0.05$). The tumors observed were located in the hard palate, tongue and adrenal cortex of males and in the liver, tongue and lungs of females. The most common finding was hepatocellular carcinoma in the females, with incidences of 0/86, 0/50, 2/50 and 11/49 in the control, low-, mid- and high-dose groups, respectively.

The NTP, (1980) tested 2,3,7,8-TCDD for carcinogenicity in B6C3F$_1$ mice and Osborne-Mendel rats. Groups of 50 male and 50 female animals received 2,3,7,8-TCDD by gavage in corn oil:acetone (9:1), 2 days/week for 104 weeks. Male mice and male and female rats received 0, 0.01, 0.05 or 0.5 µg 2,3,7,8-TCDD/kg bw/week, and female mice received 0, 0.04, 0.2 or 2.0 µg 2,3,7,8-TCDD/kg bw/week. Control groups consisted of 75 vehicle treated and 75 untreated animals. In mice, statistically significant increases in hepatocellular carcinomas and neoplastic nodules were noted in the high dose-males, and increased incidences of hepatocellular carcinomas and adenomas, fibrosarcoma, histiocytic lymphoma, thyroid follicular-cell

adenoma and cortical adenoma or carcinoma were observed in high-dose females. A statistically significant increase in the incidence of follicular cell adenomas occurred in all treated groups of male rats, but the incidence did not occur in a dose-related fashion. Among female rats, significantly increased incidences of tumors occurred only in the high-dose group. These tumor incidences include subcutaneous tissue fibromas, adrenal cortical adenomas, and hepatocellular carcinomas and neoplastic nodules.

4.2.2. Inhalation. Pertinent data regarding the inhalation carcinogenicity of 2,3,7,8-TCDD could not be located in the available literature.

4.3. OTHER RELEVANT DATA

With few exceptions, 2,3,7,8-TCDD has not proven mutagenic in Salmonella typhimurium, either with or without metabolic activation (Table 4-2). The two positive tests with Salmonella were with TA1532, which is particularly sensitive to frame shift mutations. Positive results have been obtained in yeast in both in vitro assays using a metabolic activating system and host-mediated assays (Bronzetti et al., 1983). 2,3,7,8-TCDD has been shown to increase the frequency of reverse mutations in E. coli: Sd^{-4} (Hussain et al., 1972). Hay (1982) reported positive results for transformation of baby hamster kidney cells as did Rogers et al. (1982) for mouse lymphoma cells. Khera and Ruddick (1973) reported negative results in the dominant lethal assay using Wistar rats. Conflicting results have been obtained from in vivo, in vitro and epidemiological investigations of chromosomal aberrations (IARC, 1977, 1982; Czeizel and Kiraly, 1976; Hay, 1978; Tenchini et al., 1979; Mottura et al., 1981; Green et al., 1977; Green and Moreland, 1975).

4.4. WEIGHT OF EVIDENCE

IARC (1982) considered the evidence for carcinogenicity to humans to be "inadequate," the evidence for carcinogenicity to animals to be "sufficient"

TABLE 4-2

The Results of Mutagenicity Assays in Salmonella typhimurium[a]

Type of Assay	Strains of Salmonella Typhimurium													References
	S-9	TA98	TA1530	TA1535	TA1537	TA1538	TA1532	TA1950	TA1975	TA1978	G46	TA100	TA1531	TA1534	
Spot test	+/-	NT	NT	0	0	0	0	NT	NT	NT	NT	NT	NT	NT	McCann, 1978
Plate incorporation	+/-	NT	NT	0	0	0	0	NT	NT	NT	NT	NT	NT	NT	McCann, 1978
Plate incorporation	NR	NT	NT	0	NT	0	NT	NT	NT	NT	NT	NT	NT	NT	Nebert et al., 1976
Plate incorporation[b]	+/-	0	0	0	0	0	0	0	0	0	0	0	NT	NT	Gilbert et al., 1980
Fluctuation	+/-	0	0	0	0	0	0	0	0	0	0	0	NT	NT	Gilbert et al., 1980
Spot test	-	NT	0	NT	NT	NT	+	NT	NT	NT	0	NT	QR	QR	Seiler, 1973
Plate incorporation	+	0	NT	0	0	0	NT	NT	NT	NT	NT	0	NT	NT	Geiger and Neal, 1981
Plate incorporation	-	NT	NT	NT	0	NT	NT	NT	NT	NT	NT	NT	NT	NT	Geiger and Neal, 1981
Suspension assay	-	NT	0	NT	NT	NT	+	NT	NT	NT	NT	NT	NT	NT	Hussain et al., 1972

[a]Source: U.S. EPA, 1984a

[b]The assay was performed under both aerobic and anaerobic conditions.

NT = Not tested; NR = not reported; QR = questionable response; + = positive result; 0 = negative result

and the evidence for activity in short-term tests to be "inadequate." Applying the criteria for evaluating the overall weight of evidence for carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), 2,3,7,8-TCDD is most appropriately classified a Group B2 - Probable Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

Canada established a limit of 20 ppt 2,3,7,8-TCDD (20 ng/kg fish) in the Lake Ontario commerical fish exported to the United States. This limit was chosen to comply with an FDA determination that 2,3,7,8-TCDD levels <25 ppt (25 ng/kg fish) in fish pose no serious health concern (Food Drug Cosmetic Law Reports, 1981).

The National Academy of Sciences Committee on Drinking Water and Health (NAS, 1977) proposed an ADI of 10^{-4} µg 2,3,7,8-TCDD/kg bw/day, based on a 13-week rat feeding study (Kociba et al., 1976). This ADI was proposed before convincing evidence for the carcinogenicity of 2,3,7,8-TCDD had been obtained. The U.S. EPA is considering criteria of 1.3×10^{-7}, 1.3×10^{-8} or 1.3×10^{-9} µg 2,3,7,8-TCDD/ℓ (corresponding to excess cancer risks of 10^{-5}, 10^{-6} or 10^{-7}) in ambient waters, based on an assumed daily consumption of 6.5 g of contaminated fish and shellfish and 2 ℓ of drinking water (U.S. EPA, 1984b).

Kimbrough et al. (1983) recommended unofficially that contamination in soil limited to 1 ppb in residential areas would result in intake of 2,3,7,8-TCDD <126 pg/day, considered to be tolerable for a 70 kg human.

The New York State Dept. of Health has unofficially proposed 10 ppt in fish as a ceiling level for safe human consumption (DEC, 1985).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

2,3,7,8-TCDD has been demonstrated to be carcinogenic in laboratory animals and data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to derive an AIS for this chemical.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

2,3,7,8-TCDD has been demonstrated to be carcinogenic in laboratory animals and data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to derive an AIC for this chemical.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. A number of bioassays have clearly demonstrated the carcinogenicity of 2,3,7,8-TCDD in experimental animals (see Table 4-1). These studies have recently been reviewed by the U.S. EPA (1984b). Human carcinogenic potency factors (q_1^*) were estimated from the study of Kociba et al. (1978) and the NCI bioassay (NTP, 1980). The highest q_1^* obtained [1.56×10^5 $(mg/kg\ bw/day)^{-1}$] was based on a review of the Kociba et al. (1978) study (U.S. EPA, 1984b). This q_1^* was derived from the dose-response data for tumors of the liver, lung, hard palate and/or nasal turbinates in female rats. The data used in the derivation of this q_1^* are presented in Appendix B.

8. REFERENCES

Aldred, J.E. 1978. Report of the Consultative Council on Congenital Abnormalities in the Yarrom District. Minister of Health, Melbourne, Victoria, Aust. (Cited in U.S. EPA, 1985)

Allen, J.R., D.A Barsotti, L.K. Lambrecht and J.P. Van Miller. 1979. Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Ann. NY Acad. Sci. 320: 419-425. (Cited in U.S. EPA, 1985)

Axelson, O. and L. Sundell. 1974. Herbicide exposure, mortality, and tumor incidence. An epidemiological investigation on Swedish railroad workers. Work Environ. Health. 11: 21-28. (Cited in U.S. EPA, 1985)

Axelson, O., C. Edling, H. Kling, K. Anderson, C. Hogstedt and L. Sundell. 1979. Updating of the mortality among pesticide exposed railroad workers. Lakartigningen. 76: 3505-3506. (Cited in U.S. EPA.1985)

Axelson, O., L. Sundell, K. Anderson, C. Edling, C. Hogstedt and H. Kling. 1980. Herbicide exposure and tumor mortality: An updated epidemiologic investigation on Swedish railroad workers. Scand. J. Work Environ. Health. 6: 73-79. (Cited in U.S. EPA, 1985)

Berry, D.L., P.K. Zachariah, M.J. Namkung and M.R. Juchau. 1976. Trans-placental induction of carcinogen-hydroxylating systems with 2,3,7,8-tetra-chlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 36(3): 569-584. (Cited in U.S. EPA, 1985)

Bisanti, L., F. Bonetti and F. Caramaschi, et al. 1980. Experiences from the accident of Seveso. Acta. Morphol. Acad. Sci. Hung. 28(1-2): 139-157. (Cited in U.S. EPA, 1985)

Bonaccorsi, A., R. Fanelli and G. Tognoni. 1978. In the Wake of Seveso. Ambio. 7(5): 234-239. (Cited in U.S. EPA, 1985)

Boobis, A.R. and D.W. Nebert. 1976. Induction and inhibition of the formation of benzo(a)pyrene metabolites that covalently bind to DNA by inbred mice. J. Pharmacol. 18(2): 210. (Abstr.) (Cited in U.S. EPA, 1985)

Bronzetti, G., E. Zeiger, I. Lee, K. Suzuki and H.V. Malling. 1983. Mutagenicity study of TCDD and ashes from urban incinerator "in vitro" and "in vivo" using yeast D7 strain. Chemosphere. 12: 549-553. (Cited in U.S. EPA, 1985)

Cantoni, L., M. Rizzardini, G. Belvedere, R. Cantoni, R. Fanelli and M. Salmona. 1981. Induction of mixed-function oxidase by chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin in female rats. Toxicology. 21(2): 159-167. (Cited in U.S. EPA, 1985)

Cockerham, L.G., A.L. Young and C.E. Thalken. 1980. Histopathological and ultrastructural studies of liver tissue from TCDD-exposed beach mice (Peromyscus polionotus). J. AD-A083 323/6 PC A04/MF A01. p. 61. (Cited in U.S. EPA, 1985)

Collins, T.F.S., C.H. Williams and G.C. Gray. 1971. Teratogenic studies with 2,4,5-T and 2,4-D in the hamster. Bull. Environ. Contam. Toxicol. 6(6): 559-567. (Cited in U.S. EPA, 1985)

Cook, R.R. 1981. Dioxin, chloracne and soft tissue sarcoma. Lancet. 618-619. (Cited in U.S. EPA, 1985)

Cook, R.R., J.C. Townsend, M.G. Ott and L.G. Silverstein. 1980. Mortality experience of employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J. Occup. Med. 22: 530-532. (Cited in U.S. EPA, 1985)

Courtney, K.D. 1976. Mouse teratology studies with chlorodibenzo-p-dioxins. Bull. Environ. Contam. Toxicol. 16(6): P674-681. (Cited in U.S. EPA, 1985)

Courtney, K.D. 1977. Prenatal effects of herbicides: Evaluation by the prenatal development index. Arch. Environ. Contam. Toxicol. 6(1): 33-46. (Cited in U.S. EPA, 1985)

Courtney, K.D. and J.A. Moore. 1971. Teratology studies with 2,4,5-T and 2,3,7,8-TCDD. Toxicol. Appl. Pharmacol. 20: 396-403. (Cited in U.S. EPA, 1985)

Courtney, K.D., D.W. Gaylor, M.D. Hogan and H.L. Falk. 1970a. Teratogenic evaluation of pesticides: Large-scale screening study. Teratology. 3: 199. (Cited in U.S. EPA, 1985)

Courtney, K.D., D.W. Gaylor, M.D. Hogan, M.L. Falk, R.R. Bates and I. Mitchell. 1970b. Teratogenic evaluation of 2,4,5-T. Science. 168: 864-866. (Cited in U.S. EPA, 1985)

Czeizel, E. and J. Kiraly. 1976. Chromosome examinations in workers producing Klorinol and Bvinol (Hung.) In: The Development of a Pesticide as a Complex Scientific Task, L. Banki, Ed. Budapest, Medicina. p. 239-598. (Cited in IARC, 1982.)

DEC (Department of Environmental Conservation, New York State). 1985. Draft environmental impact statement for proposed policy on contaminants in fish. Prepared by Department of Environmental Conservation. Division of Fish and Wildlife, Bureau of Environmental Protection. Albany, New York.

Department of Health, New Zealand. 1980. Report to the Minister of Health of an investigation into allegations of an association between human congenital defects and 2,4,5-T spraying in and around teKuiti. New Zealand Med. J. p. 324-315. (Cited in U.S. EPA, 1985)

DiGiovanni, J., D.L. Berry, T.J. Slaga, A.H. Jones and M.R. Juchau. 1979. Effects of pretreatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin on the capacity of hepatic and extrahepatic mouse tissues to convert procarcinogens to mutagens for Salmonella typhimurium auxotrophs. Toxicol. Appl. Pharmacol. 50(2): 229-239. (Cited in U.S. EPA, 1985)

Emerson, J.L., D.J. Thompson, C.G. Gerbig and V.B. Robinson. 1970. Teratogenic study of 2,4,5-trichlorophenoxyacetic acid in the rat. Toxicol. Appl. Pharmacol. 17: 317. (Cited in U.S. EPA, 1985)

Emerson, J.L., D.J. Thompson, R.J. Strebing, C.G. Gerbig and B. Robinson. 1971. Teratogenic studies of 2,4,5-T in the rat and rabbit. Food Cosmet. Toxicol. 9: 395-404. (Cited in U.S. EPA, 1985)

Eriksson, M., L. Hardell, N. O'Berg, T. Moller and O. Axelson. 1981. Soft-tissue sarcomas and exposure to chemical substances: A case-referent study. Br. J. Ind. Med. 38: 27-33. (Cited in U.S. EPA, 1985)

Field, B. and C. Kerr. 1979. Herbicide use and incidence of neural-tube defects. Lancet. 1(8130): 1341-1342. (Cited in U.S. EPA, 1985)

Federal Register. 1984. Environmental Protection Agency. Proposed guidelines for carcinogenic risk assessment. Federal Register 49: 46294-46299.

Food Drug Cosmetic Law Reports. 1981. FDA Advises Great Lake States to Monitor Dioxin-Contaminated Fish. FDA Talk Paper, dated August 28, 1981. Para. 41321.

Fries, G.F. and G.S. Marrow. 1975. Retention and excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin by rats. J. Agric. Food Chem. 23(2): 265-269. (Cited in U.S. EPA, 1985)

Geiger, L.E. and R.A. Neal. 1981. Mutagenicity testing of 2,3,7,8-tetrachloro-dibenzo-p-dioxin in histidine auxotrophs of Salmonella typhimurium. Toxicol. Appl. Pharmacol. 59(1): 125-129. (Cited in U.S. EPA, 1984a)

Giavini, E., M. Prati and C. Vismara. 1982a. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin administered to pregnant rats during the preimplantation period. Environ. Res. 27(1): 74-78.

Giavini, E., M. Prati and C. Vismara. 1982b. Rabbit teratology study with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ. Res. 27(1): 74-78. (U.S. EPA, 1985)

Giavini, E., M. Prati and C. Vismara. 1983. Embryotoxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin administered to female rats before mating. Environ. Res. 31: 105-110. (Cited in U.S. EPA, 1985)

Gilbert, P., G. Saint-Ruf, F. Poncelet and M. Mercier. 1980. Genetic effects of chlorinated anilines and azobenzenes on Salmonella typhimurium. Arch. Environ. Contam. Toxicol. 9(5): 533-541. (Cited in U.S. EPA, 1984a)

Goldstein, J.A., M. Friesen, T.M. Scotti, P. Hickman, J.R. Hass and H. Bergman. 1978. Assessment of the contribution of chlorinated dibenzo-p-dioxins and dibenzofurans to hexachlorobenzene-induced toxicity, porphyria, changes in mixed function oxygenases, and histopathological changes. Toxicol. Appl. Pharmacol. 46(3): 633-649. (Cited in U.S. EPA, 1984a)

Goldstein, J.A., P. Linko and H. Bergman. 1982. Induction of porphyria in the rat by chronic versus acute exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Biochem. Pharmacol. 31(8): 1607-1613. (Cited in U.S. EPA, 1985)

Green, S. and F.S. Moreland. 1975. Cytogenetic evaluation of several dioxins in the rat. Toxicol. Appl. Pharmacol. 33: 161. (Abstr.) (Cited in U.S. EPA, 1985)

Green, S., F. Moreland and C. Sheu. 1977. Cytogenic effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on rat bone marrow cells. U.S. FDA, Washington, DC. FDA By-Lines. 6: 292-194. (Cited in IARC, 1982.)

Greig, J.B. 1972. Effect of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin on drug metabolism in the rat. Biochem. Pharmacol. 21(23): 3196-3198. (Cited in U.S. EPA, 1984a)

Gurtoo, H.L. 1980. Genetic expression of aflatoxin B1 metabolism: Effects of 3-methylcholanthrene and 2,3,7,8-tetrachlorodibenzo-p-dioxin on the metabolism of aflatoxin B1 and aflatoxin B2 by various inbred strains of mice. Mol. Pharmacol. 18(2): 296-303. (Cited in U.S. EPA, 1985)

Hanify, J.A., P. Metcalf, C.L. Nobbs and R.J. Worsley. 1981. Aerial spraying of 2,4,5-T and human birth malformations: An epidemiological investigation. Science. 212: 349-351. (Cited in U.S. EPA, 1985)

Hardell, L. 1977. Soft-tissue sarcomas and exposure to phenoxy acids: A clinical observation. Lakartidningen. 74(33): 2753-5754. (Cited in U.S. EPA, 1985)

Hardell, L. and A. Sandström. 1979. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br. J. Cancer. 39: 711-717. (Cited in U.S. EPA, 1985)

Hardell, L., M. Eriksson, P. Lenner and E. Lundgren. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. Br. J. Cancer. 43: 169-176. (Cited in U.S. EPA, 1985)

Harris, H.W., J.A. Moore, J.G. Vos and B.N. Gupta. 1973. General biological effects of TCDD in laboratory animals. Environ. Health. Perspect. 5: 101-109. (Cited in U.S. EPA, 1985)

Hay, A. 1978. Vietnam's dioxin problem. Nature. 271: 597-598. (Cited in IARC, 1982.)

Hay, A. 1982. Toxicology of dioxins. In: The Chemical Scythe Lessons of 2,4,5-T and Dioxin. Plenum Press, NY. p. 41-47.

Hinsdill, R.D., D.L. Couch and R.S. Speirs. 1980. Immunosuppression in mice induced by dioxin (TCDD) in feed. J. Environ. Pathol. Toxicol. 4(2-3): 401-425. (Cited in U.S. EPA, 1985)

Holden, C. 1979. Agent Orange furor continues to build. Science. 205: 770-772. (Cited in U.S. EPA, 1985)

Honchar, P.A. and W.E. Halpern. 1981. 2,4,5-T, trichlorophenol and soft tissue sarcoma. Lancet. 268-269. (Cited in U.S. EPA, 1985)

Hussain, S., L. Ehrenberg, G. Löfroth and T. Gejvall. 1972. Mutagenic effects of TCDD on bacterial systems. Ambio 1: 32-33. (Cited in U.S. EPA, 1985)

IARC (International Agency for Research on Cancer). 1977. Monographs. 15: 41-102. (Cited in IARC, 1982.)

IARC (International Agency for Research on Cancer). 1982. Tetrachlorodibenzo-para-dioxin (TCDD). In: Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Supplement 4: p. 238-243.

Khera, K.S. and W.P. McKinley. 1972. Pre- and postnatal studies on 2,4,5-T and 2,4-D and their derivatives in rats. Toxicol. Appl. Pharmacol. 22: 14-28.

Khera, K.S. and J.A. Ruddick. 1973. Polychlorodibenzo-p-dioxins: Perinatal effects and the dominant lethal test in Wistar rats. Adv. Chem. Ser. 12C: 70-84. (Cited in U.S. EPA, 1985)

Khera, K.S., B.L. Huston and W.P. McKinley. 1971. Pre- and postnatal studies on 2,4,5-T, 2,4-D, and derivatives in Wistar rats. Toxicol. Appl. Pharmacol. 19: 369-370. (Cited in U.S. EPA, 1985)

Kimbrough, R.D., H. Falk, P. Stehr, C. Portier and G. Fries. 1983. Risk assessment document on 2,3,7,8-tetrachlorodibenzodioxin (TCDD) levels in soil. Center for Environmental Health, Centers for Disease Control, National Institute of Environmental Health Sciences, USDA, Beltsville, MD.

King, M.E. and A.R. Roesler. 1974. Subacute intubation study on rats with the compound 2,3,7,8-tetrachlorodioxin. U.S. Department of Commerce. Washington, DC. NTIS PB-257 677. (Cited in U.S. EPA, 1985)

Kociba, R.J., P.A. Keeler, C.N. Park and P.J. Gehring. 1976. 2,3,7,8-Tetrachlorodibenzo-p-dioxin results of a 13-week oral toxicity study in rats. Toxicol. Appl. Pharmacol. 35: 553-574. (Cited in U.S. EPA, 1985)

Kociba, R.J., D.G. Keyes, J.E. Beyer, et al. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol. Appl. Pharmacol. 46(2): 279-303. (Cited in U.S. EPA, 1985)

Kociba, R.J., D.G. Keyes, J.E. Beyer, R.M. Carreon and P.J. Gehring. 1979. Long-term toxicologic studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in laboratory animals. Ann. NY Acad. Sci. 320: 397-404. (Cited in U.S. EPA, 1985)

McCann. 1978. Unpublished study. (Cited in U.S. EPA, 1985)

McQueen, E.G., A.M.O. Veale, W.S. Alexander and M.N. Bates. 1977. 2,4,5-T and human birth defects. Report of the Division of Public Health, New Zealand Dept. of Health. (Cited in U.S. EPA, 1985)

Moore, J.A., B.N. Gupta, J.G. Zinkl and J.G. Vos. 1973. Postnatal effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Environ. Health Perspect. 5: 81-85. (Cited in U.S. EPA, 1985)

Moses, M. and I.J. Selikoff. 1981. Soft tissue sarcomas, phenoxy herbicides, and chlorinated phenols. Lancet. 1(8234): 1370. (Cited in U.S. EPA, 1984a)

Mottura, A., G. Zei, F. Nuzzo, et al. 1981. Evaluation of results of chromosome analyses on lymphocytes of TCDD exposed subjects after the Seveso accident (Abstract). Mutat. Res. 80: 238-239. (Cited in IARC, 1982)

Murray, F.J., F.A. Smith, K.D. Nitschke, C.G. Humiston, R.J. Kociba and B.A. Schwetz. 1979. Three-generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the diet. Toxicol. Appl. Pharmacol. 50: 241-251. (Cited in U.S. EPA, 1985)

NAS (National Academy of Sciences). 1977. Drinking Water and Health: Part II. NAS, Washington, DC. (Cited in U.S. EPA, 1985)

Nebert, D., S. Thorgiersson and J. Felton. 1976. Genetic differences in mutagenesis, carcinogenesis, and drug toxicity. In: In vitro metabolic activation in mutagenesis testing. F. de Serros, J. Folets, J. Bend and R. Philpot, Ed. Elsevier/North Holland Biomedical Press, Amsterdam. p. 105-124. (Cited in U.S. EPA, 1984a)

Nelson, C.J., J.F. Holson, H.G. Green and D.W. Gaylor. 1979. Retrospective study of the relationship between agricultural use of 2,4,5-T and cleft palate occurrence in Arkansas. Teratology. 19: 377-384.

Neubert, D. and I. Dillmann. 1972. Embryotoxic effects in mice treated with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Pharmacol. 272(3): 243-264. (Cited in U.S. EPA, 1985)

Nisbet, I.C.T. and M.B. Paxton. 1982. Statistical aspects of three-generation studies of the reproductive toxicity of TCDD and 2,4,5-T. Am. Stat. 36(3): 290-298. (Cited in U.S. EPA, 1984a)

Nolan, R.J., F.A. Smith and J.G. Hefner. 1979. Elimination and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in female guinea pigs following a single oral dose. Toxicol. Appl. Pharmacol. 48: A162. (Cited in U.S. EPA, 1984a)

NTP (National Toxicology Program). 1980. Bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin for possible carcinogenicity (Gavage study). DHHS Publication No. (NIH) 82-1765. Carcinogenesis Testing Program, NCI, NIH, Bethesda, MD. and National Toxicology Program, Research Triangle Park, NC. (Cited in U.S. EPA, 1985)

Olson, J.R., T.A. Gasiewicz and R.A. Neal. 1980. Tissue distribution, execretion and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the Golden Syrian hamster. Toxicol. Appl. Pharmacol. 56: 78-85. (Cited in U.S. EPA, 1984a)

Piper, W.N., R.Q. Rose and P.J. Gehring. 1973. Excretion and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Environ. Health Perspect. 5:241-244. (Cited in U.S. EPA, 1985)

Poiger, H. and C. Schlatter. 1980. Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD. Food Cosmet. Toxicol. 18(5): 477-481. (Cited in U.S. EPA, 1985)

Reddy, T.V., T. Benjamin, P.H. Grantham, E.K. Weisburger and S.S. Thorgeirsson. 1980. Mutagenicity of urine from rats after administration of 2,4-diamino-anisole: the effect of microsomal enzyme inducers. Mutat. Res. 79(4): 307-317. (Cited in U.S. EPA, 1985)

Reggiani, G. 1980. Acute human exposure to TCDD in Seveso, Italy. J. Toxicol. Environ. Health. 6(1): 27-43. (Cited in U.S. EPA, 1985)

Riihimake, V., S. Asp, A.M. Seppalainen and S. Herberg. 1980. Symptomatology, Morbidity and Mortality Experience of Chlorinated Phenoxy Acid Herbicide (2,4-D and 2,4,5-T) Sprayers in Finland: A Clinical and Epidemiological Study. Institute of Occupational Health, Helsinki, Finland. (Cited in U.S. EPA, 1985)

Rogers, A.M., M.E. Anderson and K.C. Back. 1982. Mutagenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin and perfluoro-n-decanoic acid in L5178Y mouse lymphoma cells. Mutat. Res. 105: 445-449

Roll, R. 1971. Studies of the teratogenic effect of 2,4,5-T in mice. Food Cosmet. Toxicol. 9(5): 671-676. (Cited in U.S. EPA, 1985)

Rose, J.Q., J.C. Ramsey, T.H. Wentzler, R.A. Hummel and P.J. Gehring. 1976. The fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin following single and repeated oral doses to the rat. Toxicol. Appl. Pharmacol. 36(2): 209-226. (Cited in U.S. EPA, 1985)

Scarpelli, D.G., M.S. Rao, V. Subbarao, M. Beversluis, D.P. Gurka and P.F. Hollenberg. 1980. Activation of nitrosamines to mutagens by postmitochondrial fraction of hamster pancreas. Cancer Res. 40(1): 67-74. (Cited in U.S. EPA, 1985)

Seiler, J.P. 1973. A survey on the mutagenicity of various pesticides. Experientia. 29: 622-623. (Cited in U.S. EPA, 1984a)

Smith, F.A., B.A. Schwetz and K.D. Nitschke. 1976. Teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in CF-1 mice. Toxicol. Appl. Pharmacol. 38(3): 517-523. (Cited in U.S. EPA, 1985)

Sparschu, G.L., Jr., F.L. Dunn, Jr., V.K. Rowe, Jr. 1971a. Study of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Food Cosmet. Toxicol. 9: 405-412. (Cited in U.S. EPA, 1985)

Sparschu, G.L., F.L. Dunn, R.W. Lisowe and V.K. Rowe. 1971b. Effects of high levels of 2,4,5-trichlorophenoxyacetic acid on fetal development in the rat. Food Cosmet. Toxicol. 9(4): 527-530. (Cited in U.S. EPA, 1985)

Tenchini, M.L., C. Crimaudo, G. Simoni, L. DeCarli, R. Giorgi and F. Nuzzo. 1979. Approaches to the evaluation of genetic damage after a major hazard in chemical industry: Preliminary cytogenetic findings on TCDD-exposed subjects after the Seveso accident. In: Genetic Damage in Man Caused by Environmental Agents, K. Berg, Ed. Academic Press, NY. p. 301-316. (Cited in IARC, 1982)

Thiess, A.M. and R. Frentzel-Beyme. 1977. Mortality Study of Persons Exposed to Dioxin Following on Accident Which Occurred in the BASF on 13 November 1953. Proceedings of MEDICHEM Congress V, San Francisco, Sept. 5, 1977. (Cited in U.S. EPA, 1984a)

Thigpen, J.E., R.E. Faith, E.E. McConnell and J.A. Moore. 1975. Increased susceptibility to bacterial infection as a sequela of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin on the immune response of young mice. Drug Chem. Toxicol. 2(1,2): 77-98. (Cited in U.S. EPA, 1985)

Thomas, R.F. 1980. Internal memo to P. Cohn, Office of Toxic substances, U.S. EPA, Washington, DC. (Cited in U.S. EPA, 1985)

Thompson, D.J., J.L. Emerson and G.L. Sparschu. 1971. Study of the effects of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) on rat and rabbit fetal development. Teratology. 4: 243. (Abstr.) (Cited in U.S. EPA, 1985)

Toth, K., J. Sugar, S. Somfai-Relle and J. Bence. 1978. Carcinogenic bioassay of the herbicide, 2,4,5-trichlorophenoxyethanol (TCPE) with different 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) content in Swiss mice. Prog. Biochem. Pharmacol. 14: 82-93. (Cited in U.S. EPA, 1985)

Toth, K., S. Somfai-Relle, J. Sugar and J. Bence. 1979. Carcinogenicity testing of herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. Nature (Lond). 278(5704): 548-549. (Cited in U.S. EPA, 1985)

Townsend, J.C., K.M. Bodner, P.F. Van Peenen, R.D. Olsen and R.R. Cook. 1982. Survey of reproductive events of wives of employees exposed to chlorinated dioxins. Am. J. Epidemiol. 115(5): 695-713. (Cited in U.S. EPA, 1985)

Uotila, P., Parkki, M.G. and A. Aitio. 1978. Quantitative and qualitative changes in the metabolism of benzo(a)pyrene in rat tissues after intragastric administration of TCDD. Toxicol. Appl. Pharmacol. 46(3): 671-683. (Cited in U.S. EPA, 1985)

U.S. EPA. 1979. Report of Assessment of a Field Investigation of Six-year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practice. OTS/EPA. (Cited in U.S. EPA, 1985)

U.S. EPA. 1980. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45:79347-79357.

U.S. EPA. 1983. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984a. Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-014A. NTIS PB 84-220268.

U.S. EPA. 1984b. Ambient Water Quality Criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-84-007. (Cited in U.S. EPA, 1985)

U.S. EPA. 1985. Drinking Water Criteria Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. (Final draft)

Van der Berg, M., K. Olie and O. Hutzinger. 1983. Uptake and selective retention in rats of orally administered chlorinated dioxins and dibenzofurans from fly ash and fly ash extract. Chemosphere. 12(4/5): 537-544 (Cited in U.S. EPA, 1984a)

Van Miller, J.P., J.J. Lalich and J.R. Allen. 1977a. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere. 6(10): 625-632. (Cited in U.S. EPA, 1985)

Van Miller, J.P., J.J. Lalich and J.R. Allen. 1977b. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere. 6(9): 537-544. (Cited in U.S. EPA, 1985)

Vos, J.G., J.A. Moore and J.G. Zinkl. 1973. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the immune system of laboratory animals. Environ. Health Perspect. 5: 149-162. (Cited in U.S. EPA, 1985)

Vos, J.G., J.G. Kreeftenberg and L. Kater. 1978. Immune Suppression by TCDD. In: Dioxin: Toxicological and Chemical Aspects. SD Medical and Scientific Books, NY. p. 163-175. (Cited in U.S. EPA, 1985)

Zinkl, J.G., J.G. Vos, J.A. Moore and B.N. Gupta. 1973. Hematologic and clinical chemistry effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ. Health Perspect. 5: 111-118. (Cited in U.S. EPA, 1985)

APPENDIX A

Summary Table for 2,3,7,8-TCDD

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	Unit Risk or q_1^*	Reference
Inhalation				ND	
Oral	rat	$1x10^{-6}$-$1x10^{-4}$ mg/kg bw/day	tumors of the liver, lung, hard palate, and/or nasal turbinates	$1.56x10^{5}$ $(mg/kg/day)^{-1}$	Kociba et al., 1978; U.S.EPA, 1983b

ND = Not derived

APPENDIX B

Data Used as a Basis for the q_1^*[a]

Species, strain, sex =	Rats, Sprague-Dawley, female
Body weight (measured) =	0.370 kg
Length of exposure =	720 days
Length of experiment =	720 days
Lifespan =	720 days
Tumor site/type (one or more) =	squamous cell carcinomas of the lung, nasal turbinate and hard palate; neoplastic nodules and hepatocellular carcinomas of the liver

Dose (mg/kg/day)	Incidence (No. responders/No. tested)
0.0	16/86
0.001×10^{-3}	8/50
0.1×10^{-3}	27/50
0.1×10^{-3}	34/47[b]

[a]Source: A reanalysis of the Kociba et al. (1978) study by Dr. Robert Squire of Johns Hopkins University (U.S. EPA, 1984a).

[b]This dose-response point was dropped because of a poor fit to the linearized multistage model.