DIOXINS

MEDITEXT ® - Medical Management

Document Outline

0.0 OVERVIEW

0.1 LIFE SUPPORT

A) This overview assumes that basic life support measures have been instituted.

0.2 CLINICAL EFFECTS

0.2.1 SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

A) Exposure to dioxins can cause a burning sensation in the eyes, nose, and throat. Headache, dizziness, blurred vision, muscle and joint pain, impaired muscle coordination, asthenia, nausea, vomiting, emotional disorders, nervousness, irritability, and intolerance to cold may all occur. Chloracne, an acne-like eruption of the skin, commonly occurs. Symptoms (itching, swelling, redness) may occur weeks or months before the eruptions appear and may last a few months or up to 15 years.
B) Dioxin exposure can cause immune system dysfunction, ulcers, peripheral neuropathy, and abnormalities of the liver, pancreas, and circulatory and respiratory systems.
C) CAVEATS - Dioxins occur as contaminants, and nearly all exposures are to mixtures containing very low levels. In such cases there is always a possibility that other components may contribute to the toxicity.
1) In many studies the relative composition of the mixture may not have been known; these studies have uncertainty with respect to QUALITATIVE exposures. Many studies also have uncertainty with respect to QUANTITATIVE exposure, or dose.
2) Some studies, such as a long-term follow-up study of Operation Ranch Hand Vietnam War Veterans, exposed to high levels of dioxins as contaminants in Agent Orange during spraying operations between 1962 and 1971, were done so long after exposure that it is difficult or impossible to determine an accurate exposure assessment based on either historical or analytical data.
D) There are no known cases of human fatalities from acute exposure to dioxins. Most acute exposures to dioxins (tetrachlorodibenzo-p-dioxin, TCDD) occur during runaway chemical reactions. Acute early signs and symptoms include chemical burns of the skin, irritation of the mucous membranes and eyes, nausea, vomiting and severe muscle pains.

1) After a latent period of several weeks, chloracne, porphyria cutanea tarda, hirsutism and/or hyperpigmentation may occur. Polyneuropathies and liver damage are frequently noted. Increased blood lipids are common and may persist.
E) TCDD is characterized by EPA as a human carcinogen. It has been most strongly linked with soft-tissue sarcomas. More limited evidence indicates associations with several other cancers. A US EPA reassessment put the upper limit for overall cancer risk for the general population as high as 1:100 to 1:1,000.
F) Dioxins may be human teratogens, specifically for ectodermal dysplasia and CNS, cardiac and skeletal defects.

0.2.1.2 CHRONIC EXPOSURE

A) Little is known about potential human health effects (if any) of long-term exposure to low concentrations. The US EPA considers dioxin (TCDD) to be probably carcinogenic to humans (Group B2). IARC classifies TCDD as Group 1 (carcinogenic to humans), but places other dioxins in Group 3 (not classifiable as to their carcinogenicity to humans).

0.2.4 HEENT

0.2.4.1 ACUTE EXPOSURE

A) Conjunctivitis, irritation and burning may be noted.

0.2.5 CARDIOVASCULAR

0.2.5.1 ACUTE EXPOSURE

A) Cardiovascular disorders such as atherosclerosis and myocardial infarction have been suggested but not conclusively shown to be related to TCDD exposure.

0.2.6 RESPIRATORY

0.2.6.1 ACUTE EXPOSURE

A) Dyspnea may be noted.

0.2.7 NEUROLOGIC

0.2.7.1 ACUTE EXPOSURE

A) Peripheral neuropathy, with sensory impairment and lower extremity weakness, central neuropathy, mental status changes, headache and dizziness occur after exposure. Mild exposure may result in asymptomatic EMG alterations.

0.2.8 GASTROINTESTINAL

0.2.8.1 ACUTE EXPOSURE

A) Right-upper-quadrant pain, anorexia, nausea and vomiting may be early symptoms. Pancreatic injury occurred in one case of industrial exposure.

0.2.9 HEPATIC

0.2.9.1 ACUTE EXPOSURE

A) Enzyme induction is prominent with both acute and chronic exposures. Moderate acute exposures may manifest with increased liver function tests, mild fibrosis, fatty liver changes and hepatomegaly.

0.2.10 GENITOURINARY

0.2.10.1 ACUTE EXPOSURE

A) Urinary tract disorders may be a consequence of exposure. Self-limited hemorrhagic cystitis has been reported. Based on current evidence, no link between dioxin exposure and endometriosis could be found.

0.2.13 HEMATOLOGIC

0.2.13.1 ACUTE EXPOSURE

A) Prothrombin time prolongation has been noted rarely, in conjunction with liver damage.

0.2.14 DERMATOLOGIC

0.2.14.1 ACUTE EXPOSURE

A) The initial dermal reaction is extensive inflammation of exposed areas with photosensitivity, followed by development of chloracne.
1) Chloracne is considered a sensitive indicator of dioxin exposure; however, some patients seem to be resistant.
2) Chloracne consists of pale yellow cysts mostly on the skin of the face but spreading to other areas as time progresses. Erythema, edema, hirsutism and photosensitivity may occur.
3) Chloracne clears or persists for several months in mild cases, whereas in severe cases it may persist for 30 years or longer.
B) Porphyria cutanea tarda may occur in moderate or severe exposures. The involvement of TCDD in its development has been disputed.

0.2.15 MUSCULOSKELETAL

0.2.15.1 ACUTE EXPOSURE

A) Myalgia is common in acute occupational exposure.

0.2.16 ENDOCRINE

0.2.16.1 ACUTE EXPOSURE

A) Dioxins affect various hormone systems. Abnormal glucose tolerance tests and diabetes mellitus have been notes after exposure to dioxins.

0.2.16.2 CHRONIC EXPOSURE

A) Changes in glucose tolerance have been seen with chronic occupational TCDD exposure.

0.2.17 METABOLISM

0.2.17.1 ACUTE EXPOSURE

A) TCDD induces cytochrome P450-1A1 and P450-1A2; the degree of toxicity is related to the extent of enzyme induction. The liver is the main site of induction, but other tissues may also be involved.
B) Fat and carbohydrate metabolism are affected by dioxin exposure. Hyperlipidemia and hypercholesterolemia have been described after acute exposure. Porphyria has also been reported, but a direct causal link to dioxin is unlikely.

0.2.18 PSYCHIATRIC

0.2.18.1 ACUTE EXPOSURE

A) Fatigue, emotional disorders, irritability and nervousness have been noted after exposure to dioxins.

0.2.18.2 CHRONIC EXPOSURE

A) Post-traumatic stress disorder was inconclusively associated with Agent Orange exposure in some Vietnam veterans.

0.2.19 IMMUNOLOGIC

0.2.19.1 ACUTE EXPOSURE

A) Dioxins are considered immunotoxic by some sources, although results are conflicting.

0.2.20 REPRODUCTIVE HAZARDS

A) Dioxins have not been proven to produce adverse reproductive effects in humans. However, low birthweights, ectodermal dysplasia, and growth and neurological deficits have been associated with dioxin exposure. Data on spontaneous abortions, decreased sperm quality and feminizing alterations of sex hormones have been mixed. TCDD accumulates in breast milk, and neurological deficits and increases in T4 and TSH have been associated with lactational exposure. TCDD is considered an animal teratogen.
B) The US EPA has been re-evaluating the health effects of dioxins. In its current report version ("Draft Final" of May 2000), it is concluded that TCDD is a likely developmental and reproductive toxin.

0.2.21 CARCINOGENICITY

0.2.21.1 IARC CATEGORY

A) IARC Carcinogenicity Ratings for CAS1746-01-6 (IARC, 2004):
1) IARC Classification
a) Listed as: 2,3,7,8-Tetrachlorodibenzo-para-dioxin
b) Carcinogen Rating: 1
1) The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in

exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

0.2.21.2 HUMAN OVERVIEW

A) Dioxins are probable human carcinogens; TCDD is a known human carcinogen. Results are conflicting regarding increased overall cancer morbidity and mortality, and for an association with soft tissue sarcomas, non-Hodgkin and Hodgkin lymphoma. There is limited evidence of an association with myeloma and pulmonary, prostate, gastric and breast carcinoma. The upper limit for overall risk in the general population may be as high as 1:1,000.

0.2.21.3 ANIMAL OVERVIEW

A) TCDD is the most potent known animal carcinogen and tumor promoter.

0.2.22 GENOTOXICITY

A) TCDD is not directly genotoxic and usually produces negative results in most genotoxicity assays. However, the TCDD-aryl hydrocarbon receptor complex can bind to specific DNA enhancer sequences. This induces a pleiotropic sequence of genetic expression whose products may activate pro-mutagens.

0.2.23 OTHER

0.2.23.1 ACUTE EXPOSURE

A) Cachexia may occur as a result of exposure to TCDD.

0.3 MEDICAL SURVEILLANCE/LABORATORY

A) It is difficult and expensive to measure dioxins in human tissue specimens. The current analytical techniques involve gas chromatography and mass spectrometry.
B) Liver function tests, CBC, prothrombin time (INR - International Normalized Ratio), serum lipids and uroporphyrins should be obtained in acute exposure. Electrodiagnostic studies such as EMG and nerve conduction velocity may be useful in detecting subclinical neuropathy.

0.4 TREATMENT OVERVIEW

0.4.2 ORAL EXPOSURE

A) Most exposures are chronic. Routine gastrointestinal decontamination is not indicated.

0.5 RANGE OF TOXICITY

A) Cumulative oral doses of 100 mcg/kg are estimated to be the minimum toxic dose.
B) Dermal exposure to soil concentrations of greater than 100 ppm are likely to produce chloracne.

1.0 SUBSTANCES INCLUDED/SYNONYMS

1.1 THERAPEUTIC/TOXIC CLASS

A) Dibenzo-p-dioxins

1.2 SPECIFIC SUBSTANCES

A) CONSTITUENTS OF THE GROUP
1. 2,3,7,8-Tetrachlorodibenzo-p-dioxin
2. TCDD
3. TCDBD
4. CAS 1746-01-6

1.2.1 MOLECULAR FORMULA

1. C12-H4-Cl4-O2

1.3 IDENTIFIERS

1.3.1 CAS REGISTRY NUMBER

A) 1746-01-6 (Dioxine)

1.3.2 NIOSH/RTECS NUMBER

A) HP3500000

1.3.5 DESIGNATIONS

A) BEILSTEIN REFERENCE NUMBER: 5-19-02-00041; BRN 0271116

1.3.6 MOLECULAR FORMULA

A) C12-H4-Cl4-O2

1.6 PREVENTION OF CONTAMINATION

A) INDUSTRIAL CHEMICALS
1) TCDD is a confirmed carcinogen and a deadly experimental poison by ingestion and dermal contact. It is toxic by inhalation and is an eye irritant. Exposure should be avoided (Lewis, 2000; NIOSH , 2002).

1.7 USES/FORMS/SOURCES

A) FORMS
1) Dioxins are substituted dioxanes that are extremely toxic by-products of the manufacture of many chemicals (Lewis, 1998). The class of dibenzo-para-dioxins includes 75 isomers (Bingham et al, 2001).
2) In 1983, the EPA canceled registration and prohibited the transfer, distribution, sale, or importation of these compounds. However, stockpiles exist and may be used in limited amounts. 2,4-Dichlorophenol does NOT contain dioxins, although TCDD may be a contaminant of some preparations (Baselt, 1997; NIOSH, 1984).
B) SOURCES
1) Dioxins are widespread in the environment (Bingham et al, 2001). They do not occur naturally; thus, they are present as a result of man-made (industrial) synthesis (Baxter et al, 2000; ILO, 1998; ATSDR, 1998). Environmental levels peaked around 1970 and have been

decreasing since then, mainly because of changes in industrial processes and environmental regulation banning their use (Bingham et al, 2001; EPA, 1994a). Industrial emissions in the year 2002 are expected to be reduced by more than 90 percent from their levels in the 1980's ((EPA, 2000a)).
2) Dioxins are released into the environment through incineration and combustion, chemical manufacturing processes, processes involving chlorine bleaching or municipal sludge, and recirculation of environmental reservoirs (EPA, 1994a; EPA, 1994b; Johnson, 1995). At present, a significant route of exposure is through the atmospheric fallout of particles and gases contaminated with TCDD (Bingham et al, 2001).
3) Dioxins may be formed during the manufacture of hexachlorophene from 2,4,5-trichlorophenol, pentachlorophenol fungicides and wood preservatives, and from burning pentachlorophenol- or 2,4,5-trichlorophenoxyacetic acid-treated wood. Municipal and medical wastes containing phenol and hydrogen chloride, when burned, can generate dioxins (Eklund et al, 1986).
4) 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is the most toxic of the 75 dioxins (Lewis, 2000). It is formed as a by-product during many industrial, thermal, photochemical and biochemical processes, in the production of certain chlorinated benzene compounds and polychlorinated phenols (Baxter et al, 2000; Bingham et al, 2001).
5) It is also a toxic by-product and a contaminant of defoliant herbicides such as the once widely used 2,4,5-trichlorophenoxyacetic acid, contained in Agent Orange (Baxter et al, 2000). Formulations of the defoliant 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D), commonly known as Agent Orange, used in the Vietnam war contained from 0.1 to 30 ppm TCDD (Baselt, 2000).
6) TCDD is also produced during the incineration of hospital and municipal wastes, toxic wastes, with gasoline and other fossil-fuel combustion, in smelters and in paper and pulp bleaching, and it is in wood preservatives (Baxter et al, 2000; Bingham et al, 2001; (EPA, 2000b)). It is considered by some to be the most toxic synthetic compound known (Baxter et al, 2000).
7) Dioxins are also present in cigarette smoke. The total concentration of polychlorinated dibenzo-p-dioxins was approximately 5 mcg/m(3), corresponding to a TEQ of 1.81 ng/m(3). Smoking 20 cigarettes per day would account for an intake of approximately 4.3 pg/kg/day (Muto & Takizawa, 1989).
8) Exposure to TCDD has decreased since the U.S. EPA banned the use of herbicides containing 2,4,5-T in the late 1970s (NTP, 1998).
C) USES
1) Dioxins have no intended commercial use and are not produced intentionally; exposure is through their presence as a by-product or contaminant of certain defoliant herbicides (Baxter et al, 2000; Freeman, 1998) NTP, 1998; (Sittig, 1991). However, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is produced in small quantities for use as a research chemical (Bingham et al, 2001).
2) TCDD has been tested for use in flameproofing polyester materials and against insects and wood-destroying fungi (NTP, 2000). There is no evidence that these purposes were ever exploited commercially (ATSDR, 1998).

1.10 SYNONYM EXPLANATION

A) When discussing dioxins, literature often does not distinguish between dibenzo-p-dioxins as a class of compounds and an individual isomer. When information specific to an isomer was given in the literature, that information is included within this document; however, when the terms dioxin or dioxins are used in this document, the assumption should be made that there was no clarification made in the literature reference or that the data refer to a mixture of isomers.

B) The majority of data available regard the isomer 2,3,7,8-tetrachlorodibenzo-p-dioxin. The abbreviation TCDD is often used to refer to this isomer. When the term TCDD is employed in this document, the information refers to the 2,3,7,8-tetrachlorodibenzo-p-dioxin isomer or a sum of the TCDD isomers.

3.0 CLINICAL EFFECTS

3.1 SUMMARY OF EXPOSURE

3.1.1 ACUTE EXPOSURE

A) Exposure to dioxins can cause a burning sensation in the eyes, nose, and throat. Headache, dizziness, blurred vision, muscle and joint pain, impaired muscle coordination, asthenia, nausea, vomiting, emotional disorders, nervousness, irritability, and intolerance to cold may all occur. Chloracne, an acne-like eruption of the skin, commonly occurs. Symptoms (itching, swelling, redness) may occur weeks or months before the eruptions appear and may last a few months or up to 15 years.
B) Dioxin exposure can cause immune system dysfunction, ulcers, peripheral neuropathy, and abnormalities of the liver, pancreas, and circulatory and respiratory systems.
C) CAVEATS - Dioxins occur as contaminants, and nearly all exposures are to mixtures containing very low levels. In such cases there is always a possibility that other components may contribute to the toxicity.
1) In many studies the relative composition of the mixture may not have been known; these studies have uncertainty with respect to QUALITATIVE exposures. Many studies also have uncertainty with respect to QUANTITATIVE exposure, or dose.
2) Some studies, such as a long-term follow-up study of Operation Ranch Hand Vietnam War Veterans, exposed to high levels of dioxins as contaminants in Agent Orange during spraying operations between 1962 and 1971, were done so long after exposure that it is difficult or impossible to determine an accurate exposure assessment based on either historical or analytical data.
D) There are no known cases of human fatalities from acute exposure to dioxins. Most acute exposures to dioxins (tetrachlorodibenzo-p-dioxin, TCDD) occur during runaway chemical reactions. Acute early signs and symptoms include chemical burns of the skin, irritation of the mucous membranes and eyes, nausea, vomiting and severe muscle pains.
1) After a latent period of several weeks, chloracne, porphyria cutanea tarda, hirsutism and/or hyperpigmentation may occur. Polyneuropathies and liver damage are frequently noted. Increased blood lipids are common and may persist.
E) TCDD is characterized by EPA as a human carcinogen. It has been most strongly linked with soft-tissue sarcomas. More limited evidence indicates associations with several other cancers. A US EPA reassessment put the upper limit for overall cancer risk for the general population as high as 1:100 to 1:1,000.
F) Dioxins may be human teratogens, specifically for ectodermal dysplasia and CNS, cardiac and skeletal defects.

3.1.2 CHRONIC EXPOSURE

A) Little is known about potential human health effects (if any) of long-term exposure to low concentrations. The US EPA considers dioxin (TCDD) to be probably carcinogenic to humans (Group B2). IARC classifies TCDD as Group 1 (carcinogenic to humans), but places other dioxins in Group 3 (not classifiable as to their carcinogenicity to humans).

3.4 HEENT

3.4.2 EYES

A) CONJUNCTIVITIS
1) Initial exposure may be accompanied by a burning irritation of the eye and blepharoconjunctivitis (Sittig, 1991; Zenz, 1994).
B) VISION ABNORMAL
1) Exposure may also result in blurred vision (Sittig, 1991).

3.4.4 NOSE

A) IRRITATION
1) Inhalation exposure can cause a burning feeling in the nose and throat (Sittig, 1991).

3.5 CARDIOVASCULAR

3.5.1 ACUTE EFFECTS

A) CORONARY ATHEROSCLEROSIS
1) A 15-year follow-up of the Vietnam veterans involved in Operation Ranch Hand, who were exposed to high levels of dioxins as contaminants in Agent Orange during spraying operations between 1962 and 1971, showed an increased number of deaths from diseases of the circulatory system among personnel exposed to the highest levels of dioxin, mainly from atherosclerotic heart disease (Michalek et al, 1998a).
2) A study of 5,132 US chemical workers, extending an IARC study in 1997, showed a weak increasing trend for heart disease with higher exposure to TCDD (Steenland et al, 1999).
3) Cardiovascular disorders are a consequence of exposure to TCDD (ILO, 1998). Indeed, the heart may be one of the main target organs for TCDD toxicity; decreased beta-adrenergic responsiveness and increased intracellular calcium concentrations were found in guinea pig hearts after exposure (Hayes & Laws, 1991).
4) Advanced progressive atherosclerosis was described in a heavily exposed worker (Pazderova-Vejlupkova et al, 1981). A link between ischemic heart disease and TCDD exposure has been suggested, but not conclusively proven.
5) CASE SERIES - A mortality study of 58 workers showed increased coronary artery disease over the expected US average, but this was not statistically significant (Moses et al, 1984).
B) MYOCARDIAL INFARCTION
1) CASE SERIES - In a 20-year follow-up of 69 workers who developed chloracne due to TCDD exposure, an association between chloracne and death due to myocardial infarction was noted (Dalerupp & Zellenrath, 1983).
2) CASE SERIES - An apparent excess of deaths from myocardial infarction was reported among members of a dioxin-exposed clean-up crew (Moses et al, 1984).

3.6 RESPIRATORY

3.6.1 ACUTE EFFECTS

A) DYSPNEA
1) Respiratory tract disorders are a consequence of exposure to TCDD (ILO, 1998). Dyspnea may be noted.

3.7 NEUROLOGIC

3.7.1 ACUTE EFFECTS

A) NEUROPATHY
1) Peripheral neuropathy, with sensory impairment, as well as central neuropathy, with lassitude, weakness, impotence and loss of libido, result from exposure to dioxin (Baxter et al, 2000; ILO, 1998). Neuritis and polyneuropathy have occurred after dermal exposure to 2,4-dichlorophenol, with incomplete recovery (Baselt, 1997).
2) Polyneuropathy with sensory impairment and lower extremity weakness is a consistent finding in industrial exposure cases. In mild exposure, asymptomatic alteration in EMG and nerve conduction velocity studies may occur. In severe exposures, about one-third of patients have developed neuropathies (Dunagin, 1984).
3) CASE SERIES - Peripheral neuropathy was reported in 43 of 45 workers involved in a spill of a mixture containing a small amount of dioxin (45 to 46 ppb of TCDD) (Klawans, 1987). The contribution of the main components (phenol and chlorophenol) is unclear.
4) CASE SERIES - Dose-dependent subclinical peripheral neuropathy, defined by the presence of at least 2 bilateral signs or 1 abnormal electrophysiological endpoint, was seen in a group of 152 persons, who also had chloracne, 6 years after the Seveso accident, in which the blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area in Seveso, Italy, on 10 July 1976 (Barbieri et al, 1988; Schardein, 2000).
B) DYSTONIA
1) CASE REPORT - Action dystonias of the hands were reported in 24 of 45 workers involved in the spill of a mixture containing a small amount of dioxin (45 to 46 ppb of TCDD) (Klawans, 1987). The involvement of dioxin is unsubstantiated.
C) HEADACHE
1) Acute exposure by inhalation can produce headache and dizziness (Sittig, 1991).
2) Headaches were reported in a chemist acutely exposed to dioxins (Schecter & Ryan, 1992).
D) ABNORMAL MENTAL STATE
1) A reduction of cognitive performance in verbal conceptualization, amnestic organization of verbal and visual stimuli, psychomotor slowing, and subjective complaints such as irritability have been seen on neurologic examination (Peper et al, 1993).

3.7.3 ANIMAL STUDIES

A) ANIMAL STUDIES
1) NEUROPATHY
a) Polyneuropathy was induced in rats by a single IP dose of 2.2 to 6.6 mcg/kg (Grehl et al, 1993).

3.8 GASTROINTESTINAL

3.8.1 ACUTE EFFECTS

A) NAUSEA AND VOMITING
1) Right-upper-quadrant pain, anorexia, nausea and vomiting have occurred after exposure, but a direct causal link has not been proven (Bingham et al, 2001; Sittig, 1991).
2) Nausea and vomiting may be early symptoms of exposure. However, industrial accidents have involved exposure to other chemicals, and it is likely that these symptoms are not related to TCDD (Young AL, Calcagni JA & Thalken CE et al, 1978).
B) DISEASE OF PANCREAS
1) Pancreatic disorders may be a consequence of exposure to TCDD (ILO, 1998).
2) CASE REPORT - A 57-year-old welder was exposed to dioxins while heating a bearing of an autoclave stirrer. Four days later, he developed acute dermatologic and neurologic

symptoms. Within the next 9 months, he was hospitalized twice with enlargement of his liver and pancreas; a large mass of tissue was identified in the right upper quadrant of the abdomen and symptoms of an acute inflammatory process developed. He died approximately 9 months after initial exposure. Pancreatic necrosis, perforation of the stomach and duodenal bulb, liver abscess and chloracne of the trunk were noted on autopsy (Theiss et al, 1982).

3.9 HEPATIC

3.9.1 ACUTE EFFECTS

A) CIRRHOSIS OF LIVER
1) A 15-year followup of the Vietnam veterans involved in Operation Ranch Hand, who were exposed to high levels of dioxins as contaminants in Agent Orange during spraying operations between 1962 and 1971, showed an increased number of deaths from digestive diseases, mainly chronic liver disease and cirrhosis (Michalek et al, 1998a).
B) LIVER DAMAGE
1) An enlarged liver with impaired function is related to TCDD toxicity (ILO, 1998). Indeed, hepatotoxicity is the most consistent finding in acute occupational exposures, and is manifested by increased liver enzyme activities, mild fibrosis, fatty changes, hemofuscin deposition, parenchymal cell degeneration, and hepatomegaly. In severe exposures, about one-third of patients develop liver damage (Dunagin, 1984).
C) LIVER ENZYMES ABNORMAL
1) Increased serum transaminase levels occur with TCDD toxicity (ILO, 1998). Enzyme induction is prominent in acute and chronic exposure.
D) GAMMA-GLUTAMYL TRANSFERASE RAISED
1) Workers exposed to dioxins who also consume alcohol seem to have a significantly increased risk for an increased serum GGT level. The risk increases with dioxin levels (Calvert et al, 1992).
2) Children exposed in the Seveso accident (in which the blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area near Seveso, Italy, on 10 July 1976) had increased GGT as well as increased AST and ALT; adults had increased DGA. Clinical evidence of liver disease, however, was lacking (Baxter et al, 2000; Bingham et al, 2001; Schardein, 2000).

3.10 GENITOURINARY

3.10.1 ACUTE EFFECTS

A) URINARY TRACT FINDING
1) Urinary tract disorders may be a consequence of exposure to TCDD (ILO, 1998).
B) HEMORRHAGIC CYSTITIS
1) CASE REPORT - Hemorrhagic cystitis was reported in a 6-year-old girl chronically exposed to TCDD-containing soil in a horse arena sprayed with contaminated oil. Symptoms resolved within 3 to 4 days (Beale et al, 1977).
C) PORPHYRIA DUE TO TOXIC EFFECT OF SUBSTANCE
1) WITH POISONING/EXPOSURE
a) CASE SERIES - In 11 of 29 patients with dioxin-induced chloracne, urinary uroporphyrins were increased. Concomitant signs and symptoms included 'cola-colored' urine, hyperpigmentation (limited to sun-exposed areas), skin fragility, and hypertrichosis (Bleiberg et al, 1964). After 6 years, none had clinical porphyria and only one had persistent uroporphyrinuria (Poland et al, 1971).

b) The contribution of dioxin was later disputed; hexachlorobenzene was speculated to be the causative agent in some cases (Jones & Chelsky, 1986).
D) LACK OF EFFECT
1) WITH POISONING/EXPOSURE
a) ENDOMETRIOSIS
1) Guo (2004) concluded that based on a critical review of the available literature of both primate and human epidemiologic data, there is no consistent and credible evidence between dioxin exposure and endometriosis. The author suggested further well designed studies with adequate sample size and scientific rigor (Guo, 2004).
2) CASE SERIES - Based on a population-based study in Belgium, 257 subjects (142 women and 115 men) were potentially exposed to environmental dioxins and PCBs. Subjects were obtained from five regions within Belgium, which included living near an iron and steel plant or around a waste dumping site; individuals potentially occupationally exposed to the chemicals were excluded. There was no association between endometriosis and dioxin or PCB exposure as assessed by serum concentrations (Fierens et al, 2003).

3.13 HEMATOLOGIC

3.13.1 ACUTE EFFECTS

A) PROTHROMBIN TIME LOW
1) PROTHROMBIN TIME PROLONGATION has been noted rarely and may be related to liver damage (Zack & Suskind, 1980).

3.14 DERMATOLOGIC

3.14.1 ACUTE EFFECTS

A) CHLORINE ACNE
1) Around 85 to 100 percent of patients with substantial signs of dioxin toxicity also have chloracne; chloracne is considered the most sensitive indicator of dioxin exposure (Dunagin, 1984).
a) However, a small group of people do not manifest chloracne (Pazderova-Vejlupkova et al, 1981). Dioxin toxicity without chloracne has been reported in several instances (Beale et al, 1977; Kimbrough et al, 1977; Oliver, 1975). In a retrospective study, 24 percent of workers classified as heavily exposed did not have a history of chloracne (Moses et al, 1984).
b) Development of chloracne was related to both intensity and cumulative exposure to tetra-, hexa-, and octachlorinated dioxins in an occupational cohort (Bond et al, 1989b).
c) Lesions may occur in relatives of workers through contact with work clothes, tools, or personal contact.
2) The first sign of reaction of exposed skin is extensive inflammation, resembling lupus erythematosis or erythema elevatum diutinum; photosensitivity may be more or less pronounced (Schulz, 1977).
a) Chloracne consists of an eruption of blackheads with small, pale-yellow cysts on the skin of the face, especially the malar crescent of the eyes (ILO, 1998). Hands and feet are usually spared. Subsequently, the upper chest, back and extremities may become involved. The genitalia may be involved, for males (Hayes & Laws, 1991).
b) Chloracne may be considered a refractory follicular dermatosis (Raffle, 1994). The follicular hyperkeratosis of chloracne (with or without cysts and pustules) affects nearly every follicle in involved areas with no intervening normal skin (Hayes & Laws, 1991).
c) Erythema, edema, hirsutism and photosensitivity resulting in eventual hyperpigmentation may occur, although chloracne does occur alone (Hayes & Laws, 1991).

3) Chloracne may appear 2 months after the greatest exposure (Baselt, 2000). However, it usually appears 2 to 4 weeks after initial TCDD contact. A delay in onset of 2 to 3 months post-exposure was reported in some men in an industrial accident involving 79 cases of chloracne (May, 1973).
a) Chloracne is usually slowly reversible, subsiding within 1.5 years; it persists for several months in mild cases; severe cases may persist for 30 years or longer (Baselt, 2000; Hayes & Laws, 1991; Moses et al, 1984). Scarring can complicate healing (Hayes, 1982).
b) CASE SERIES - Children and adolescents exposed during the Seveso accident, in which the blowout of a 2,4,5-trichlorophenol production reactor released TCDD over a large area near Seveso, Italy, on 10 July 1976, did not show acneigenesis 2 years after exposure, but atropic scars remained (Caputo et al, 1988; Schardein, 2000).
c) CASE SERIES - Chloracne had cleared after 7 years in all but 1 of 193 persons exposed in the Seveso accident (Assennato et al, 1989).
4) A grading system for chloracne has been developed by the European Economic Community (EEC), as follows (Moses et al, 1984):
a) Grade 1 - no change
b) Grade 2 - few comedones in specific sites only
c) Grade 3 - more comedones in specific sites, no cysts
d) Grade 4 - numerous comedones in specific sites with cysts
e) Grade 5 - numerous comedones, cysts in specific and other sites
f) Grade 6 - the same as grade 4, with inflammatory changes
B) PORPHYRIA CUTANEA TARDA
1) PORPHYRIA CUTANEA TARDA is associated with exposure to TCDD, but only in genetically predisposed individuals (ILO, 1998; IOM, 1993).
2) CASE SERIES - In 11 of 29 patients with dioxin-induced chloracne, urinary uroporphyrins were increased. Concomitant signs and symptoms included 'cola-colored' urine, hyperpigmentation (limited to sun-exposed areas), skin fragility, and hypertrichosis (Bleiberg et al, 1964). After 6 years, none had clinical porphyria and only one had persistent uroporphyrinuria (Poland et al, 1971).
a) The contribution of dioxin was later disputed; hexachlorobenzene was speculated to be the causative agent in some cases (Jones & Chelsky, 1986).

3.14.2 CHRONIC EFFECTS

A) PORPHYRIA CUTANEA TARDA
1) In a NIOSH survey, there was no increased risk for porphyria cutanea tarda or subclinical uroporphyrinuria and/or coproporphyrinuria among 281 workers exposed to dioxin for more than 15 years (Calvert et al, 1994).

3.15 MUSCULOSKELETAL

3.15.1 ACUTE EFFECTS

A) MUSCLE PAIN
1) Myalgia is a common manifestation in acute occupational exposure (Schecter & Ryan, 1992). Neuromuscular effects include severe joint and muscle pain exacerbated by exertion; this mainly affects the calves and thighs and thorax; fatigue and lower-limb weakness also occur (ILO, 1998; Sittig, 1991).

3.16 ENDOCRINE

3.16.1 ACUTE EFFECTS

A) DISORDER OF ENDOCRINE SYSTEM
1) Dioxin has endocrine activity (Harbison, 1998). TCDD affects various hormone systems, particularly sex steroids, corticosteroids and thyroid hormones. It disrupts normal feedback mechanisms of the pituitary gland (Bingham et al, 2001).
B) ABNORMAL GLUCOSE TOLERANCE TEST
1) Pathological changes in glucose tolerance tests occurred in 40 percent of a group of 80 workers with chronic TCDD exposure (Pazderova-Vejlupkova et al, 1981).
C) DIABETES MELLITUS
1) CASE SERIES - In Vietnam veterans involved in Operation Ranch Hand, who were exposed to high levels of dioxins as contaminants in Agent Orange during spraying operations between 1962 and 1971, the prevalence and severity of diabetes mellitus and the risk of abnormally high glucose increased, and time-to-onset of diabetes decreased, with dioxin exposure (Henriksen et al, 1997).
2) In another study in these veterans, the effect of dioxin body burden on the relation between sex hormone-binding globulin (SHBG) and insulin and fasting glucose was determined. The results suggested a compensatory metabolic relationship between dioxin and insulin regulation (Michalek et al, 1999).
3) However, a study of 5,132 US chemical workers exposed to TCDD, extending an IARC study in 1997, showed a negative exposure-response trend for diabetes (Steenland et al, 1999).
4) CASE SERIES - Based on a population-based study in Belgium, 257 subjects (142 women and 115 men) were potentially exposed to environmental dioxins and PCBs. Subjects were obtained from five regions within Belgium, which included living near an iron and steel plant or around a waste dumping site; individuals potentially occupationally exposed to the chemicals were excluded. The findings indicated that diabetic individuals had higher serum levels of dioxins, coplanar PCBs, and the 12 PCB markers. Also, the results indicated a significant increase in the risk of diabetes was found in the most exposed subjects, suggesting a dose-response effect. All parameters remained statistically significant even after adjustment for possible confounders. The authors suggested that further large scale studies are needed to confirm potential causality (Fierens et al, 2003).
5) CASE SERIES - An excess of diabetes mellitus was reported among dioxin-exposed pulp and paper workers (Axelson et al, 1998).

3.16.2 CHRONIC EFFECTS

A) ABNORMAL GLUCOSE TOLERANCE TEST
1) Pathological changes in glucose tolerance tests occurred in 40 percent of a group of 80 workers with chronic TCDD exposure (Pazderova-Vejlupkova et al, 1981).

3.16.3 ANIMAL STUDIES

A) ANIMAL STUDIES
1) ALTERED HORMONE LEVEL
a) DECREASE IN ESTRADIOL RECEPTORS - TCDD exerts its toxicity through the aryl hydrocarbon receptor, a mechanism reminiscent of steroid hormones.
1) Acute treatment of guinea pigs, rats, and hamsters with 4, 50, and 1500 mcg/kg TCDD, respectively, decreased 17 beta-estradiol receptors in the liver by 65 and 92 percent in guinea pigs and rats, while no change was seen in hamsters. The density of receptors in uteri is inversely related to the lethal dose of TCDD (Hruska & Olson, 1989).

3.17 METABOLISM

3.17.1 ACUTE EFFECTS

A) ABNORMAL ADRENAL CORTICAL HORMONE
1) INDUCTION OF CYTOCHROME P450 - TCDD induces specific cytochromes, P450-1A1 and P450-1A2, which are involved in the metabolism of certain aromatic compounds, including carcinogens and caffeine.
2) The extent of induction is related to the magnitude of toxicity (McKinney & McConnell, 1982). The highest levels are in the liver, but other tissues, including the gonads, can be involved (Silbergeld & Mattison, 1987).
3) Induction of P-4501A2 was only slightly related to serum TCDD levels in workers with some of the highest known occupational exposures (Halperin et al, 1995).
B) GENERAL METABOLIC FUNCTION
1) Disorders of fat and carbohydrate metabolism are a consequence of exposure to TCDD (ILO, 1998).
C) HYPERLIPIDEMIA
1) CASE SERIES - Hyperlipidemia was described in 3 industrially-exposed men and in none of their nonexposed colleagues (Oliver, 1975). Lipid abnormalities have persisted for 10 years or longer following acute exposure (Martin, 1984); however, it has not been proven conclusively that a cause-effect relationship exists.
D) SERUM CHOLESTEROL RAISED
1) Changes in lipid metabolism, including hypercholesterolemia, have been reported after occupational exposure to TCDD (Baxter et al, 2000; Hayes & Laws, 1991).
E) PORPHYRIA DUE TO TOXIC EFFECT OF SUBSTANCE
1) Deranged porphyrin metabolism may occur after exposure to dioxins (ILO, 1998).
2) CASE SERIES - In 11 of 29 patients with dioxin-induced chloracne, urinary uroporphyrins were increased. Concomitant signs and symptoms included 'cola-colored' urine, hyperpigmentation (limited to sun-exposed areas), skin fragility, and hypertrichosis (Bleiberg et al, 1964). After 6 years, none had clinical porphyria and only one had persistent uroporphyrinuria (Poland et al, 1971).
3) The contribution of dioxin was later disputed; hexachlorobenzene was speculated to be the causative agent in some cases (Jones & Chelsky, 1986).

3.17.3 ANIMAL STUDIES

A) ANIMAL STUDIES
1) HYPERLIPEMIA
a) Rabbits given dioxin intraperitoneally had an increase in serum triglyceride concentrations and a modest increase in serum cholesterol levels. Hepatic low-density lipoprotein binding was significantly depressed (Brewster et al, 1988).
2) METABOLIC DISORDER
a) The cause of death in TCDD-treated rats is progressive inhibition of gluconeogenesis (Rozman, 1989).
3) HYPOVITAMINOSIS
a) Depletion of hepatic stores of vitamin A in rats, guinea pigs and hamsters is one of the most sensitive biological markers for exposure to TCDD (Clayton & Clayton, 1994).

3.18 PSYCHIATRIC

3.18.1 ACUTE EFFECTS

A) FATIGUE
1) Asthenia, with symptoms of headache, fatigue, apathy, sleep disturbance, memory deficits, and severe muscle pain has been described, but may be attributable to other causes (Young AL, Calcagni JA & Thalken CE et al, 1978).
B) NERVOUSNESS

1) Emotional disorders, nervousness and irritability have been found following inhalational exposure to TCDD (Sittig, 1991).

3.18.2 CHRONIC EFFECTS

A) FEELING ANXIOUS
1) POSTTRAUMATIC STRESS DISORDER was associated with exposure to Agent Orange, as determined by the presence of active chloracne, in a small study of Vietnam veterans (6 exposed, 25 unexposed).
a) Because the study design did not identify the majority of exposed veterans, this association is not conclusive evidence for dioxin-induced effect (Levy, 1988).
b) A study of a larger group of exposed veterans also yielded inconclusive information (Albanese RA, 1988).

3.19 IMMUNOLOGIC

3.19.1 ACUTE EFFECTS

A) DISEASE OF IMMUNE SYSTEM
1) Some sources consider dioxins to be immunotoxic (Baxter et al, 2000). Further research has suggested the pathogenesis of immune-related diseases by DDT and tetrachlorodibenzo-p-dioxin (TCDD) exposure may occur through the following molecular mechanisms: modulation of intracellular calcium flux, the expression of NF-kB, and proto-oncogenes, or the levels of cyclin, bel-2, and p53 (Forawi et al, 2004).
2) TCDD was shown to suppress T-helper cell function in workers exposed for 20 years (Goldfrank, 1998).
a) Based on a review of animal data, Sherr (2004) concluded that long term TCDD-induced changes appear evident in the immune system after both primary and secondary exposure to dioxin. Its suggested that these findings may have implications for individuals exposed to TCDD who may be immunocompromised (Sherr, 2004).
b) One report states that epidemiological studies have failed to show immunotoxic effects in individuals having other clinical symptoms (Sharma & Reddy, 1987). Of ten studies assessing immune function, only one found a clear association with immunological impairment (Bingham et al, 2001).
3) CASE SERIES - Increased anergy and abnormal T-cell subsets were reported in a group of 154 persons exposed to dioxins in contaminated sludge waste in Missouri (Hoffman et al, 1986). A follow-up study failed to confirm previously reported anergy (Evans et al, 1988).
B) LACK OF EFFECT
1) A study of the Vietnam veterans involved in Operation Ranch Hand, who were exposed to high levels of dioxins as contaminants in Agent Orange during spraying operations between 1962 and 1971, failed to demonstrate a consistent relationship between the level of exposure to dioxin and immune system alteration (Michalek et al, 1999a).
2) TCDD failed to alter surface marker distribution or suppress human lymphocyte proliferation in vitro (Lang et al, 1994).

3.19.2 CHRONIC EFFECTS

A) CELLULAR IMMUNE DEFECT
1) TCDD was shown to suppress T-helper cell function in workers exposed for 20 years (Goldfrank, 1998).

3.19.3 ANIMAL STUDIES

A) ANIMAL STUDIES
1) IMMUNOGLOBULINS DECREASED
a) SUPPRESSED HUMORAL ANTIBODIES - IgM antibody response to sheep red blood cells was suppressed in mice exposed subchronically to dioxin (Holsapple et al, 1984).
b) Depression of humoral immunity (antibody plaque-forming response to sheep erythrocytes) was a more sensitive endpoint than cellular immunity (cytotoxic T lymphocyte response to P815 mastocytoma cells) in mice given intraperitoneal injections of 1 and 3 mcg/kg/week of TCDD (Hanson & Smialowicz, 1994).
c) TCDD inhibited differentiation of mouse B cells into antibody-secreting cells in vitro. Inhibition in congenic strains correlated with aryl hydrocarbon receptor activity (Tucker et al, 1986).
d) In contrast to results in mice, TCDD enhanced humoral immunity in rats when given in single intraperitoneal injections at 1 to 30 mcg/kg; these doses were sufficient to induce cytochrome P-4501A1 and 1A2 (Smialowicz et al, 1994).
2) ENDOCRINE DISORDER
a) THYMIC ATROPHY has been demonstrated in every mammalian species tested (Anon, 1988).
1) Thymic and splenic atrophy were acute responses in rats fed TCDD at levels up to 1 ppm in the diet for 78 weeks (VanMiller et al, 1977).
3) IMMUNE SYSTEM DISORDER
a) Mice exposed to TCDD pre- and postnatally had bone marrow hypocellularity, depressed macrophage-granulocyte progenitor and stem cell colony formation, depressed lymphoproliferative responses, and increased susceptibility to bacterial or tumor challenge (Luster et al, 1980).

3.20 REPRODUCTIVE HAZARDS

3.20.1 TERATOGENICITY

A) CONGENITAL ANOMALY
1) There is no conclusive evidence that dioxins cause birth defects in humans (Erickson et al, 1984; IOM, 1993; Pearn, 1985). This is because various reports involved mixed exposures, poorly documented exposures, or inconsistent patterns of abnormalities. The controversy continues about whether dioxins are human teratogens; TCDD is considered developmentally toxic by California Proposition 65 (Schardein, 2000).
a) Of the 31 published studies on human reproductive effects of dioxin (combined with 2,4-dichlorophenol and 2,4,5-trichlorophenoxyacetic acid) reviewed by Hayes & Laws (1991), 10 showed positive effects and 21 were negative. Of the studies with negative associations overall, 4 had positive associations in subsets of groups or data.
b) However, TCDD is considered an animal teratogen, producing both developmental and reproductive toxicity (Baxter et al, 2000; Bingham et al, 2001).
c) The US EPA has been re-evaluating the health effects of dioxins. In its report version ("Draft Final" of May 2000), it is concluded that TCDD is a likely developmental and reproductive toxin. The level at which these effects may be experienced remains unclear ((EPA, 2000a)) 2000c).
2) Studies of Vietnam veterans involved in Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam between 1962 and 1971, have provided little support for the theory of a connection between adverse reproductive effects and paternal exposure to Agent Orange and its dioxin contaminants (Michalek et al, 1998b; Wolfe et al, 1995).
a) Increased nervous system defects were seen in children of Vietnam veterans involved in Operation Ranch Hand, but these were based on sparse data (Wolfe et al, 1995). However, increased rates of fetal loss before 20 weeks, and skeletal, CNS and cardiovascular

malformations were seen in a group of 832 Tasmanian Vietnam veterans' families (Field & Kerr, 1988).
b) Other studies have failed to find an association between exposure to dioxins in Vietnam and increased rates of birth defects through paternally mediated effects (Erikson et al, 1984; (Walsh et al, 1983).
3) A study of Canadian saw-mill workers exposed to chlorophenols contaminated with TCDD found an association between male exposure and the occurrence of eye, neural tube and genital malformations (Dimich-Ward et al, 1996).
4) Lower psychomotor scores at 3 months of age were correlated with higher prenatal exposures to TCDD and not to PCB's, determined as maternal levels during the last month of gestation; this difference disappeared by 18 months of age (Koopman-Esseboom et al, 1996).
5) Neurological development of a group of Dutch infants was negatively affected to a slight extent by prenatal, but not by lactational, exposure to dioxins (Huisman et al, 1995).
B) GROWTH RETARDED
1) Lower birthweights have been seen in offspring of women living on the east coast of Sweden, where the diet is rich in fish contaminated with persistent organochlorine compounds from the Baltic Sea (Rylander & Hagmar, 1995).
2) Lower birthweights and lengths were also seen in offspring of 221 teachers exposed to dioxins, dibenzofurans, lindane and pentachlorophenol in indoor air (Karmaus & Wolf, 1995). Because of mixed exposures, these effects could not be attributed specifically to TCDD. They were ascertained not to be due to shorter gestational age, and were therefore possibly due to a direct toxic effect on pregnancy.
3) Two early episodes of 'Yusho' or 'Yucheng' disease ('oil disease') involved contaminated cooking oil in Fukuoka Prefecture, Japan, in 1968 and Yu-Cheng, Taiwan, in 1979 (Hayes & Laws, 1991; Schardein, 2000).
a) The contaminants were dioxins and/or dioxin-like compounds including PCBs, chlorodibenzofurans, and quarterphenyl TCDD, formed from heating of PCBs. The toxic effects were thought to be due mainly to dibenzofurans (Schecter et al, 1994).
b) Offspring had an odd 'cola' skin color and minor skeletal anomalies (Schardein, 2000). Reproductive effects included ectodermal dysplasia, clustered in organs derived from the ectodermal germ layer, including skin, nails, and meibomian glands. Developmental and psychomotor delay and growth retardation were also present, and persisted throughout childhood (Chen et al, 1992; Guo et al, 1994; Hsu et al, 1993; Lai et al, 1993).
4) Studies of Vietnam veterans of Operation Ranch Hand did not demonstrate an increased risk of intrauterine growth retardation associated with paternal exposure to dioxins (Michalek et al, 1998b).
C) LACK OF EFFECT
1) About 2,900 kg organic matter and 1.5 to 2 kg TCDD were released over a 700-acre area of urbanized land near Seveso, Italy, on 10 July 1976, when a runaway exothermic reaction led to a blowout of a 2,4,5-trichlorophenol production reactor (Baxter et al, 2000; Bingham et al, 2001; Schardein, 2000).
a) A study of births after the Seveso accident showed no increased risk of malformations; however, the number of exposed fetuses was too low to detect a small increased teratogenicity risk (Mastroiacovo et al, 1988).
b) One investigator reported an increase in the rate of malformations in the Seveso area, from 0.13 percent before the accident to 0.87 percent when exposed women would have delivered, but there was no consistency as to the types of malformations seen (Reggiani, 1978).
c) A later study of 999 pregnancies in low-exposure areas and 203 in moderate-exposure areas showed a statistically significant increase in cardiovascular, genitourinary and skeletal abnormalities 18 to 30 months after moderate exposure (Schardein, 2000).

d) However, no major malformations were found by a study of the birth registry of the most-contaminated area for births January 1977 to December 1982. It was concluded that the data failed to show an increased risk of birth defects related to dioxin, although controversy over the hazardous effects of this exposure continue (Schardein, 2000).
2) No increases in cleft lip or palate were seen among families living nearby after initiation of waste incineration in Sweden (Jansson & Voog, 1989). In a study of 930 male chlorophenol workers and their wives, no adverse reproductive outcomes were found compared with an unexposed group (Townsend et al, 1982).
D) ANIMAL STUDIES
1) TCDD is an extremely potent teratogen in rodents. Although results have varied, it shows teratogenicity in mice, rabbits, hamsters and ferrets, equivocal results in rats, and negative results in primates (Schardein, 2000; ILO, 1998). Effects on the developing fetus have been demonstrated at doses more than 100 times lower than those producing maternal toxicity (Bingham et al, 2001).
2) TCDD is teratogenic in various strains of mice (Courtney & Moore, 1971). Indeed, the mouse is the most sensitive experimental system for studying the teratogenic effects of TCDD; all mouse studies demonstrate teratogenicity (Couture et al, 1990; Schardein, 2000).
a) In mice, TCDD has reportedly produced developmental abnormalities of the craniofacial, immune, reticuloendothelial, urogenital, endocrine and musculoskeletal systems, as well as fetal death and post-implantation mortality (RTECS , 2001).
b) Decreased developmental rates were noted in mouse embryos after exposure to 1 to 5 ppm TCDD (Tsutsumi, 2000).
c) DBA/2J mice, which are resistant to the induction of cytochrome P-450 by TCDD, were 2- to 3-fold more resistant to induction of hydronephrosis and cleft palate than the C57BL/6J strain (Hassoun & Stohs, 1996).
d) An increased incidence of cleft palate and hydronephrosis was seen in mouse studies with TCDD (Birnbaum et al, 1991). Thymic hypoplasia is also a characteristic finding in mice exposed prenatally to TCDD (Couture et al, 1990).
e) Cleft palate and dilated renal pelvis were seen in fetal mice exposed to 3 mcg/kg/day TCDD by oral gavage on days 6 to 15 of gestation, and cleft palate was noted at a dose of at 1 mcg/kg/day (Smith et al, 1976).
f) No effects on teratogenicity or development were seen in offspring of male mice exposed to 2.4 mcg/kg TCDD in the diet for 8 weeks (mixed with 2,4-dichlorophenol and 2,4,5-trichlorophenoxyacetic acid) and mated with untreated females (Lamb et al, 1981b).
3) In rats, TCDD produced developmental abnormalities of the endocrine, urogenital, and blood and lymphatic systems, and also produced fetal death and stunted fetuses (RTECS , 2001). In rabbits, it produced developmental abnormalities of the musculoskeletal and urogenital systems, and abortions, pre-implantation mortality and fetal death (RTECS , 2001). Cognitive deficits have been reported in monkeys exposed perinatally to dioxins (Schantz & Bowman, 1989).
4) The relative susceptibility of guinea pigs, rats, and hamsters for induction of hydronephrosis was roughly similar, in contrast to their differing sensitivity for acute toxicity of TCDD (Olson & McGarrigle, 1992).
a) This is also true for different strains of rats. Single doses of TCDD in the range of 1 to 10 mcg/kg produced malformations in both Long-Evans and Han/Wistar rats, but the acute LD50s in these two strains differ by 1,000-fold (Huuskonen et al, 1994).
b) The spectrum of effects was different in the two strains of rats. Cleft palate occurred in more than 70 percent of live Long-Evans fetuses exposed to 5 mcg/kg on day 8 or 12 of gestation. Hydronephrosis and gastrointestinal hemorrhaging were produced in the Han/Wistar fetuses (Huuskonen et al, 1994).
5) Other dioxin-like compounds, 2,3,7,8-tetrachlorodibenzofuran and 3,3',4,4'-tetrachloroazoxy benzene, were also teratogenic in mice and produced similar types of

defects seen with TCDD, but with a lower potency, corresponding to their relative affinities for the aryl hydrocarbon receptor (Abdul Malek Hassoun, 1985).
6) Sprague-Dawley rats exposed orally to 1 microgram TCDD/kg body weight on either gestational day (GD) 15, GD 18 and postnatal day (PND) 2 revealed significant decreases in the urogenital complex and ventral prostate weights and urogenital-glans penis length of male offspring of rats exposed on GD 15 only (Ohsako, 2002).
7) Exposure of adult rainbow trout to TCDD at concentrations comparable to current environmental concentrations (females fed 1.8ng TCDD/kg) adversely affected survival of the fry (Giesy, 2002).

3.20.2 EFFECTS IN PREGNANCY

A) PLACENTAL BARRIER
1) There is limited transplacental transfer of TCDD to the fetus (Hayes & Laws, 1991). The placental transport of dioxins from mother to fetus that has been shown to occur is probably related to fatty acid transport (Koppe et al, 1992).
B) ABORTION
1) Studies of Vietnam veterans involved in Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam between 1962 and 1971, showed no meaningful increase in the risk for spontaneous abortion or stillbirth associated with paternal exposure to Agent Orange and its dioxin contaminants (Wolfe et al, 1995).
2) In a previous study, a small but statistically significant increase in miscarriage rate was noted in women whose mates were exposed to Agent Orange in Vietnam (Stellman et al, 1988). A study of residents of Times Beach, Missouri, who were exposed to dioxin after roads were sprayed with TCDD-contaminated waste oil for dust control, failed to confirm this (Stockbauer et al, 1988).
3) Apparent clusters of spontaneous abortions related to spraying 2,4,5-trichlorophenoxyacetic acid in forestry operations near Alsea, Oregon were studied by the US EPA. A second EPA study claimed an association between miscarriages and spraying, but it has been strongly criticized because of failure to follow accepted epidemiological methods (discussed in AMA, 1981).
4) Studies of pregnancy outcomes in Seveso showed that abortion rates after the blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area were comparable to the expected rates in other, non-exposed areas (Schardein, 2000).
C) PREGNANCY DISORDER
1) More complications of pregnancy were seen in a group of Tasmanian Vietnam veterans' wives than in a comparison group (Field & Kerr, 1988).
D) STILLBIRTH
1) A study of the Vietnam veterans of Operation Ranch Hand showed an increased risk of preterm death for offspring in both the 'high' and 'background' exposure categories; the authors concluded this risk might not be linked to the paternal dioxin level (Michalek et al, 1998b). Another study found no meaningful increase in the risk of stillbirth (Wolfe et al, 1995)
E) LACK OF EFFECT
1) Studies in Seveso of 623 women pregnant (one-third in the first trimester) at the time of the accident showed that this TCDD exposure produced no unusual incidence of prenatal or postnatal mortality, and the offspring born showed no ill effects (Hayes & Laws, 1991; Schardein, 2000).
F) ANIMAL STUDIES
1) TCDD is lethal to embryos or fetuses of mammals, birds, and fish at doses which are not maternally toxic (EPA, 1994b).
2) Smaller litter sizes, increased neonatal mortality, and reduced growth rates were seen in F2 and F3 generations of rats fed 0.01 mcg/kg/day TCDD (Murray et al, 1977).

3) Increased pre- and post-implantation loss and fetal growth retardation were seen in rats receiving 0.5 to 2 mcg/kg/day by gavage for 2 weeks prior to mating (Giavini et al, 1983).
4) TCDD has been shown to produce cardiovascular toxicity in piscine, avian and mammalian embryos. One study revealed a possible mechanism to be reduction in myocyte proliferation and subsequent thinner ventricle wall (Ivnitski et al, 2001).

3.20.3 EFFECTS DURING BREAST-FEEDING

A) BREAST MILK
1) TCDD is lipophilic, therefore it accumulates in breast milk (Baxter et al, 2000).
a) Nursing infants are a group at highest risk for exposure to dioxins. One survey of 42 US mothers found an average of 16 pg TEQ/g (16 ppt) in the lipid fraction of breast milk, of which only 3.3 ppt was due to TCDD (Schecter et al, 1992). Breast milk from German mothers had even higher levels, averaging 31 ppt (Beck et al, 1991).
b) Levels as high as 1,832 ppt were seen in breast milk fat collected from South Vietnamese women in 1970 (Schecter et al, 1995). Samples of human milk from areas in Vietnam heavily treated with 2,4,5-trichlorophenoxyacetic acid were analyzed in 1974 and found to contain 40 to 50 ppt of TCDD. No TCDD was detected in milk from residents of West Texas where heavy spraying for brush control occurred (Schecter et al, 1995).
c) In one study, dioxin concentrations in the milk fat of breast milk in 14 mothers were found to be 80 to 132 ppt, close to or in the range necessary to induce liver enzymes. The authors suggest the possibility that enzyme induction in these babies may result in vitamin K deficiency, resulting in bleeding (Koppe, 1989).
d) NEUROLOGICAL DEFICITS - Neonatal neurological deficits, determined by the Prechtl neurological examination, were related to concentrations of 17 dioxin congeners and other dioxin-like compounds in breast milk measured 2 weeks post-partum in a group of 209 breast-fed Dutch infants (Huisman et al, 1995).
B) THYROID DISORDER
1) Significant increases in total thyroxine (T4) and thyrotropin (TSH) levels were seen in infants, in relation to dioxin concentrations in the milk fat of their mothers (Pluim et al, 1992; Pluim et al, 1993).
C) ANIMAL STUDIES
1) Adult rats were immunosuppressed after exposure to TCDD through the nursing mothers (Badesha et al, 1995).

3.20.4 FEMALE REPRODUCTIVE HAZARDS

A) ANIMAL STUDIES
1) Decreased female fertility and inability to maintain pregnancy, ovarian dysfunction and alterations in hormone levels have been shown in limited studies in experimental animals (EPA, 1994b). These are among the most sensitive endpoints for reproductive toxicity of TCDD in mammals (Peterson et al, 1993).
2) Rats fed 0.1 mcg/kg/day had severely impaired fertility in the first generation, and a dietary level of 0.01 mcg/kg/day significantly decreased fertility in the F1 and F2 generations. The NOAEL was 0.001 mcg/kg/day (Murray et al, 1977).
3) Endometriosis was induced in Rhesus monkeys by TCDD (Rier et al, 1993).
4) DELAYED SEXUAL DEVELOPMENT - Delayed vaginal opening was seen in female rats exposed to TCDD at doses up to 1,000 ng/kg on day 19 of gestation, followed by 120 or 400 ng/kg/week after birth (Thiel et al, 1994).
5) Female rats fed 1 microgram TCDD/kg on GD 15 were sacrificed on GD 17, 18, 19 and 21, then the fetal reproductive tract was examined. By GD 18, the width of mesenchyme separating the Mulleriand ducts was significantly greater than controls. The zone of unfused Mullarian ducts was significantly increased by GD 19 and 21 (Hurst, 2002).

3.20.5 MALE REPRODUCTIVE HAZARDS

A) HUMANS
1) TESTIS DISORDER
a) DECREASED SPERM QUALITY has been seen in Vietnam veterans by the Centers for Disease Control; this cannot be attributed solely to TCDD because of mixed exposures, but bears further investigation. US military working dogs with similar exposures have had increased risk for testicular dysfunction and testicular seminoma (Hayes et al, 1990).
b) Children exposed in utero during the 'Yusho' incident in Taiwan in 1979 involving contaminated cooking oil subsequently had sperm with increased abnormal morphology, decreased motility and a reduced ability to penetrate hamster oocytes (Guo et al, 2000).
2) ALTERED HORMONE LEVEL
a) Increases in follicle-stimulating hormone or luteinizing hormone and decreases in testosterone, were significantly correlated with current serum dioxin levels in an NIOSH occupational cohort of 248 chemical production workers. These are thought to be the result of subtle gonadal effects and not primary gonadal failure, because low testosterone and high luteinizing hormone were not present in the same individuals (Egeland et al, 1994).
3) IMPOTENCE
a) Impotence and decreased libido have been reported in men occupationally exposed to high acute levels of dioxins (Moses et al, 1984).
4) LACK OF EFFECT
a) Studies of Vietnam veterans involved in Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam between 1962 and 1971, showed no meaningful association between serum dioxin levels and levels of testosterone, follicle-stimulating hormone or luteinizing hormone, or testicular abnormalities, sperm count, sperm abnormalities or testicular volume (Henrickson et al, 1996).
B) ANIMAL STUDIES
1) REDUCED SPERM COUNTS and testicular atrophy, abnormal testicular histopathology, reduced male fertility, decreased testosterone synthesis, altered regulation of pituitary LH secretion, and reduced plasma androgen concentrations have been demonstrated in experimental animals in response to TCDD (EPA, 1994b).
a) Rats exposed perinatally to levels of TCDD up to 1 mcg/kg on day 15 of gestation had dose-related reductions in sperm production and weights of the testis, epididymis, and cauda epididymis for up to 120 days after exposure (Mably et al, 1992c). Descent of testes was delayed (Moore et al, 1990). Fertility, measured at 70 and 120 days of age, was not affected, however (Bjerke et al, 1990).
b) Decreased spermatogenesis is among the most sensitive reproductive endpoints for TCDD in mammals (Peterson et al, 1993).
c) Fifteen percent of male rats given an LD25 dose of TCDD were sterile (Chahoud et al, 1989).
d) A single SC dose of 3 mcg/kg TCDD was sufficient to inhibit spermatogenesis in rats (Chahoud et al, 1992). The aryl hydrocarbon receptor is present in the testes of rats (Johnson et al, 1992).
2) ALTERED SEX HORMONES - Alterations in sexual behavior and LH secretion of male rats occurred in response to oral perinatal doses as low as 0.064 mcg/kg on day 15 of gestation. The TCDD treatment had a demasculinizing and feminizing effect (Mably et al, 1992b).
a) Suppression of serum testosterone occurred pre- and post-natally in male rats born to dams given TCDD up to 1 mcg/kg on day 15 of gestation (Mably et al, 1991; Mably et al, 1992a).
b) TCDD reduced the number and size of Leydig cells in the testes of rats. Leydig cells are the site of testosterone production (Johnson et al, 1994).

3) Paternally mediated reproductive effects were not seen in male rats given TCDD (Chahoud et al, 1991).
4) Male C57BL/6 mice exposed to 2.4 mcg/kg of TCDD in the diet for 8 weeks (mixed with 2,4-dichlorophenol and 2,4,5-trichlorophenoxyacetic acid) did not show significant reduction in fertility or sperm quality (Lamb et al, 1981a).

3.21 CARCINOGENICITY

3.21.1 IARC CATEGORY

A) IARC Carcinogenicity Ratings for CAS1746-01-6 (IARC, 2004):
1) IARC Classification
a) Listed as: 2,3,7,8-Tetrachlorodibenzo-para-dioxin
b) Carcinogen Rating: 1
1) The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

3.21.2 SUMMARY/HUMAN STUDIES

A) Dioxins are probable human carcinogens; TCDD is a known human carcinogen. Results are conflicting regarding increased overall cancer morbidity and mortality, and for an association with soft tissue sarcomas, non-Hodgkin and Hodgkin lymphoma. There is limited evidence of an association with myeloma and pulmonary, prostate, gastric and breast carcinoma. The upper limit for overall risk in the general population may be as high as 1:1,000.

3.21.3 SUMMARY/ANIMAL STUDIES

A) TCDD is the most potent known animal carcinogen and tumor promoter.

3.21.4 HUMAN STUDIES

A) LACK OF INFORMATION
1) There is INADEQUATE/INSUFFICIENT EVIDENCE to determine whether an association exits between dioxin exposure and the following cancers (IOM, 1993):
a) Nasal/nasopharyngeal cancer
b) Neoplasm
c) Bone cancer
d) Cervical cancer and female reproductive cancers
e) Renal cancer
f) Testis neoplasm, malignant
2) There is LIMITED/SUGGESTIVE EVIDENCE OF NO ASSOCIATION of the following cancers and dioxin exposure (IOM, 1993):
a) Skin cancer
b) Bladder cancer
c) Brain tumors

1) Increased deaths from brain cancer were seen 10 years after the Seveso accident, in which the blowout of a 2,4,5-trichlorophenol production reactor released TCDD over a large area near Seveso, Italy, in 1976, but they were not dose-related (Bertazzi et al, 1989).
B) CARCINOMA
1) OVERALL CANCER MORBIDITY AND MORTALITY - TCDD is a known human carcinogen (Bingham et al, 2001; IARC , 1997). The upper limit for overall risk for human cancer among the general population may be as high as 1:1,000 (EPA, 1994b; Johnson, 1995). Evidence is strong for an association with soft tissue sarcomas; Hodgkin disease and non-Hodgkin lymphoma have been linked more with dioxin-contaminated chlorphenoxy herbicides (IOM, 1993).
2) Several studies have shown associations between dioxin exposure and increased risk of cancer morbidity and mortality:
a) IARC reported an increased risk for all cancers combined in a group of cohorts from the US, the Netherlands, Germany and Seveso, Italy, with a higher increase in risk in those suffering the heaviest exposure (IARC , 1997).
b) A study of 5,132 US chemical workers, extending that 1997 IARC study, showed an excess of all cancers combined limited to workers exposed to 100 to 1,000 times the levels of TCDD experienced by the general population (Steenland et al, 1999). Overall cancer mortality was highest in a group of German workers with highest exposure to dioxins (Becher et al, 1996).
c) Dose-dependent increases in risk of mortality from all cancers were seen in a retrospective cohort of 1,189 male chemical workers exposed to TCDD and other higher chlorinated dioxins and furans. The highest relative risk was 3.30 in the highest decile. Quantitative exposures were obtained from analysis of blood and adipose tissue (Fleschjanys et al, 1995).
d) A retrospective cohort study of 1,583 workers potentially exposed to dioxin showed an increased rate of cancer mortality in men with more than 20 years of employment in the chemical plant (Manz et al, 1991).
e) A retrospective cohort study of mortality among 5,172 workers potentially exposed to dioxin showed excess mortality from all cancers combined, cancers of the respiratory tract and soft-tissue sarcoma. The possible contribution of factors such as smoking and occupational exposure to other chemicals cannot be excluded (Fingerhut et al, 1991).
f) Increased deaths from cancers were seen in a group of 74 persons after acute exposure to dioxin in an industrial accident (7 observed versus 4.1 expected) (Thiess et al, 1982).
3) Other studies have found no association between dioxin exposure and cancer mortality:
a) A study of the Vietnam veterans involved in Operation Ranch Hand, who were exposed to high levels of dioxins as contaminants in Agent Orange during spraying operations between 1962 and 1971, showed no statistically significant increase in cancer risk in the group categorized as having the highest dioxin exposure (Ketchum et al, 1999).
b) A 15-year followup of these Operation Ranch Hand veterans also showed no significant increase in the risk of death from cancer at all sites, as well as a nonsignificant increase in the number of deaths from bronchus and lung cancer (Michalek et al, 1998).
c) US Vietnam veterans have a 50-percent increased risk for non-Hodgkin lymphoma, but it is not apparently related to exposure to dioxins. Moreover, they do not seem to be at increased risk for soft tissue or other sarcomas, liver cancer, Hodgkin disease, or nasal or nasopharyngeal cancer (10).
d) A 15-year study of cancer risk in Seveso, after the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area, found no increase in all-cancer mortality or major specific sites (respiratory for males; breast for females) (Bertazzi et al, 1997).
e) No increase in deaths due to all cancers was seen in a cohort study of 2,192 potentially exposed chemical workers (Bond et al, 1989a; Ott et al, 1987).

f) Deaths from all causes, all cancers, or any specific cancer were not significantly increased in 963 Dutch workers who had been occupationally exposed to TCDD, or in a subset of 139 who probably had higher-level acute exposure during a production accident involving 2,4,5-trichlorophenol (de Mesquita & Doornbos, 1993).
g) No excess deaths from cancer were seen in a group of 121 workers thought to be exposed to TCDD in an industrial accident in West Virginia nearly 30 years previously. Exposure was presumed from development of chloracne (Anon, 1980).
4) A review of the EPA's assessment of dioxin as a cause of cancer found that in fact dioxin is a promoter blocker of certain cancers, including those previously considered by the EPA to be promoted by dioxin, a promoter of some cancers not identified by the EPA, and, overall, a net anticarcinogen (Kayajanian, 1997).
5) Dioxin (as TCDD) may have chemoprotective properties; its aryl hydrocarbon receptor turns off proliferation in tumor cells and suppresses their ability to invade normal tissue (Greenlee et al, 2001).
C) SARCOMA
1) There is reportedly sufficient evidence of an association between dioxins and the development of soft-tissue sarcoma, with a two-fold increase reported in a 1997 IARC study of 30,000 dioxin-exposed workers in 12 countries (ILO, 1998; IOM, 1993).
a) A 15-year study of cancer risk in Seveso, after the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area, found an increase in soft-tissue sarcoma only in males in the area of lowest exposure (Bertazzi et al, 1997).
b) A retrospective cohort study of mortality among 5,172 workers potentially exposed to dioxin showed excess mortality from all cancers combined and soft-tissue sarcoma. The possible contribution of factors such as smoking and occupational exposure to other chemicals cannot be excluded (Fingerhut et al, 1991).
c) Nonsignificant increases in deaths from soft-tissue sarcoma (n=4) were seen 10 and 19 years after first occupational exposure in an IARC cohort of 18,910 production workers or sprayers exposed to chlorophenoxy herbicides (Saracci et al, 1991).
d) Eriksson et al (1990) found an increased risk for soft-tissue sarcoma in a population-based case control study.
e) Sarcomas were attributed to TCDD exposure in several small case-control studies in Sweden; however, exposure to other chemicals (chlorophenols and phenoxyherbicides) was evident (Cook, 1981; Hardell, 1979) Hardell & Sandstrom, 1979; (Hardell & Eriksson, 1988; Honchar & Halperin, 1981).
f) An increased risk for soft-tissue sarcoma was seen in relation to exposure to TCDD (OR=5.2) and polychlorinated dibenzodioxins or furans (OR=5.6) in two nested case-control studies. The risk was higher for exposure to any phenoxy herbicide, however (OR=10.3) (Kogevinas et al, 1995).
2) Other studies have shown no association between soft-tissue sarcomas and dioxin exposure:
a) Increased mortality from soft-tissue sarcoma was seen in a group of 754 persons occupationally exposed to 4-aminobiphenyl and TCDD in an industrial accident, but not in those thought to be exposed to TCDD alone (Collins et al, 1993).
b) Two larger case-control studies involving a total of 363 sarcoma patients found no relationship with occupational exposure to phenoxyherbicides, chlorophenols, or exposure to herbicides used in Vietnam (Greenwald et al, 1984; Smith et al, 1984).
3) The latency period for soft-tissue sarcoma in adults is probably long; many years of observation will be necessary before more-conclusive evidence can be obtained (Kogan & Clapp, 1988).
D) LYMPHOMA-LIKE DISORDER
1) There is reportedly sufficient evidence for an association of lymphoma-like disorders with herbicides (IOM, 1993).

2) There was a significant increase in morbidity related to malignant lymphoma in 105 cases exposed to phenoxy acids or chlorophenols (Hardell, 1981).
3) Studies on NON-HODGKIN LYMPHOMA have produced conflicting results:
a) Most studies reported by IARC have shown a nonsignificant increased risk for non-Hodgkin lymphoma (IARC , 1997). The increased rate of non-Hodgkin lymphoma was especially true for workers exposed to TCDD-contaminated herbicides (ILO, 1998).
b) Increased deaths from non-Hodgkin lymphoma were seen in a cohort of 2,479 German workers who were exposed to dioxins and phenoxy herbicides (Becher et al, 1996).
c) The association between phenoxy herbicides (and TCDD specifically) and non-Hodgkin lymphoma was lower than the risk for soft-tissue sarcoma in two nested case-control studies of an international cohort (Kogevinas et al, 1995).
d) Some data show an increased risk for non-Hodgkin lymphoma in persons exposed to dioxins and not to phenoxy herbicides. The relative risk for morbidity from non-Hodgkin lymphoma was 3.5 in the least-exposed persons Seveso, after the 1976 blowout of a 2,4,5-trichlorophenol production reactor that released TCDD over large area. This study did not show a clear dose-response, however (Bertazzi et al, 1993).
e) No significant increases in non-Hodgkin lymphoma were found in large studies on occupationally exposed persons (Fingerhut et al, 1991; Manz et al, 1991; Saracci et al, 1991; Zober et al, 1990).
1) A significant increase in morbidity related to non-Hodgkin lymphoma was found in a study 106 cases exposed to phenoxy acids (Persson et al, 1989). Increased but nonsignificant risks for non-Hodgkin lymphoma were found in studies of farmers and agricultural workers exposed to the herbicide 2,4-dichlorophenoxyacetic acid (Hoar et al, 1986; Zahm et al, 1990).
2) Because these would have been the most heavily TCDD-exposed groups, the evidence suggests that the association with non-Hodgkin lymphoma is due to PHENOXY HERBICIDES, not dioxins (IOM, 1993). Refer to CHLORPHENOXY COMPOUNDS MEDITEXT(R) medical management for further information.
4) For HODGKIN DISEASE, there is reportedly sufficient evidence of an association with HERBICIDES (IOM, 1993). Studies relating Hodgkin disease with dioxin exposure and/or herbicides have had mixed results:
a) A 15-year study of cancer risk in Seveso after the 1976 accident found an increase in hematological neoplasms; one of the highest risks was Hodgkin disease in both men and women, in the area of lower exposure (Bertazzi et al, 1997).
b) A suggestive increase in incidence of Hodgkin disease occurred during the first 10 years after the Seveso accident in the youngest segment of the exposed population (Pesatori et al, 1993).
c) Nearly all of the 13 case-control and occupational studies have shown an association between exposure and Hodgkin disease, but not all results have been statistically significant (IOM, 1993). The occupational groups most heavily exposed to dioxins did NOT show an increase in Hodgkin disease, however (IOM, 1993).
d) In a group of 60 patients, there was a dose-related risk for development of Hodgkin disease in relation to exposure to chlorophenols (which may contain dioxins as contaminants) (Hardell et al, 1981; Hardell & Bengtsson, 1983). A nonsignificant association between exposure to phenoxy acids and Hodgkin disease was seen in a cohort of 54 cases (Persson et al, 1989).
E) MYELOMA
1) There is limited/suggestive evidence of an association of dioxin exposure and myeloma (IOM, 1993). Increased risk for multiple myeloma has been reported after occupational exposure to TCDD (IARC, 1977).
2) A 15-year study of cancer risk in Seveso, after the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area, found an increase in

hematological neoplasms; one of the highest risks was multiple myeloma in women in the area of lower exposure (Bertazzi et al, 1997).
3) The relative risk for morbidity from multiple myeloma among women with intermediate exposure in the Seveso accident was 5.3 after 10 years (Bertazzi et al, 1993).
4) Of 10 studies of forestry and agricultural workers exposed to dioxins in herbicides (and possibly as by-products of burning), all showed an elevated risk for multiple myeloma. The association was statistically significant in seven of these studies (IOM, 1993).
5) Stratification of exposure groups has shown increased risk with herbicide (with dioxin contaminant) exposure (Alavanja et al, 1989; Boffetta et al, 1989; Burmeister et al, 1983; Cantor & Blair, 1984).

F) LEUKEMIA

1) There is inadequate/insufficient evidence to determine whether or not an association exits between dioxin exposure and leukemia (IOM, 1993).
2) A 15-year study of cancer risk in Seveso, after the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area, found an increase in hematological neoplasms; one of the highest risks was leukemia in men in the area of lower exposure (Bertazzi et al, 1997).
3) Increased deaths from leukemias were seen 10 years after the Seveso accident, but they were not dose-related (Bertazzi et al, 1989). The relative risk for morbidity from myeloid leukemia was 3.7 among women living in the zone of intermediate exposure (Bertazzi et al, 1993). The incidence of myeloid leukemia was increased in the youngest population segment 10 years after exposure, but this increase was not statistically significant (RR = 2.7) (Pesatori et al, 1993).

G) PULMONARY CARCINOMA

1) There is limited/suggestive evidence of an association of dioxin exposure and pulmonary carcinoma (IOM, 1993). Workers exposed to TCDD had an increase in cancer mortality from respiratory cancer (Goldfrank, 1998).
2) Increased deaths from cancers of the respiratory tract (SMR = 154) and buccal cavity/pharynx (SMR = 295) were seen in a cohort of 2,479 German workers exposed to dioxins and phenoxy herbicides (Becher et al, 1996).
3) A retrospective cohort study of mortality among 5172 workers potentially exposed to dioxins showed excess mortality from all cancers combined and cancers of the respiratory tract. The possible contribution of factors such as smoking and occupational exposure to other chemicals cannot be excluded (Fingerhut et al, 1991).
4) Other occupational cohorts heavily exposed to TCDD have also shown an increase in respiratory cancers (Manz et al, 1991; Saracci et al, 1991; Zober et al, 1990).
5) Herbicide applicators have also shown an increase in respiratory tract cancers (Axelson & Sundell, 1974; Blair et al, 1983) Green, 1991; (Riihimaki et al, 1982).

H) PROSTATE CARCINOMA

1) There is limited/suggestive evidence of an association of dioxin exposure and prostate cancer (IOM, 1993).
2) Increased risk of prostate cancer in Canadian farmers was associated with herbicide spraying (Morrison et al, 1993).
3) Because prostate cancer is one of the most common cancers and is increasingly prevalent with age, the likelihood of finding a clear-cut association with any exposure is small.

I) HEPATIC CARCINOMA

1) There is reportedly inadequate/insufficient evidence to determine whether or not an association exits between dioxin exposure and liver cancer (IOM, 1993).
2) Increased deaths from biliary cancer were seen in women 10 years after the Seveso accident, in which the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area near Seveso, Italy, but they were not dose-related (Bertazzi et al, 1989; Schardein, 2000). The relative risk for morbidity among persons in the intermediate-exposure group was 2.8 (Bertazzi et al, 1993).

J) GASTRIC CARCINOMA
1) There is reportedly limited/suggestive evidence of no association between dioxin exposure and stomach, pancreatic, colon and rectal cancers (IOM, 1993).
2) However, a 15-year study of cancer risk in Seveso, after the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area near Seveso, Italy, found a moderate increase in mortality from 'digestive' cancer among women in the zone of highest exposure to dioxin, and, in an area of lower exposure, increased mortality from stomach cancer in women and increased mortality from rectal cancer in men (Bertazzi et al, 1997).
3) Workers exposed to TCDD had an increase in cancer mortality from 'digestive cancer' (Goldfrank, 1998). Increased deaths from stomach cancer (3 versus 0.6 expected) occurred in a group of 74 persons exposed to TCDD in an industrial accident (Thiess et al, 1982).
K) BREAST CARCINOMA
1) An increased incidence of breast cancer was seen in a group of Swedish women who consumed a diet high in fatty fish contaminated with persistent organochlorine compounds from the Baltic Sea, in relation to the general Swedish population and a comparison group from the west coast (Rylander & Hagmar, 1995).
L) THYROID CARCINOMA
1) An increased incidence of thyroid cancer (RR = 4.6; n=2 cases) was seen in the youngest population segment 10 years after the Seveso accident, in which the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over a large area near Seveso, Italy (Pesatori et al, 1993; Schardein, 2000).

3.21.5 ANIMAL STUDIES

A) CARCINOMA
1) TCDD is a carcinogen in rats, mice and hamsters (EPA, 1994b). It induced hepatocellular carcinomas in female but not male rats (5).
2) TCDD and the furans PCDF and HCDF are also promoters for inducing skin tumors in hairless mice by the dermal route (Hebert et al, 1990).
a) It is the most potent known animal carcinogen and tumor promoter (Bingham et al, 2001; Xu et al, 1992). It is a potent hepatocarcinogen that initiates and promotes cancer (Baxter et al, 2000).
B) CARCINOGENICITY IN MICE -
1) In mice, TCDD induces tumors of the thyroid gland, lung, liver, lymphatics, skin, and subcutaneous tissue and induces thymic lymphomas (Huff et al, 1991; ILO, 1998; RTECS , 2001).
2) In mice, TCDD induced tumors of the thyroid gland, liver, and subcutaneous tissue, and induced thymic lymphomas (Huff et al, 1991). Thymic lymphomas were induced in both sexes of (C57BL/6J X C3Hf)F1 (B6C3) and (C57/BL/6J X BALB/c)F1 (B6C) hybrid mice when given in six intraperitoneal doses of 60 mcg/kg TCDD. Hepatocellular adenomas were increased in B6C3 but not B6C mice (Della Porta et al, 1987).
3) In a gavage study, TCDD induced hepatocellular carcinomas in both sexes and follicular-cell thyroid adenomas in female mice (11).
4) TCDD induced fibrosarcomas in the integumentary system of female mice when applied dermally in acetone at a dose of 0.005 mcg, 3 days/week for 104 weeks (11).
5) RESULTS WITH RELATED COMPOUNDS: DICHLOROdibenzo-p-dioxin induced leukemias or lymphomas in male but not female mice (NCI, 1979).
C) CARCINOGENICITY IN RATS -
1) In rats, TCDD induced tumors of the liver, lung, oral/nasal cavities, kidneys, adrenal and thyroid glands (Huff et al, 1991; ILO, 1998; RTECS , 2001).
2) TCDD promoted ovarian tumor development in Sprague-Dawley rats after initiation with diethylnitrosamine (Davis et al, 2000).

3) Hepatocellular carcinomas, squamous cell carcinomas of the lung, hard palate, and nasal turbinates developed in rats ingesting 0.1 mcg/kg/day for 2 years. Tumors appeared only in rats manifesting other signs of toxicity, and the NOAEL was 0.001 mcg/kg/day. Hepatocellular carcinomas were sex-specific in female rats only (Kociba et al, 1978).
4) This study was re-evaluated using current criteria for assigning scores to hepatocellular carcinomas in female rats from the original slides. The conclusion was that TCDD is still carcinogenic, but only one-third as potent as previously thought, with a NOAEL of 0.01 mcg/kg/day (Keenan et al, 1991).
5) A 38-percent incidence of neoplasms was seen in male rats fed TCDD at levels of 1 to 1,000 ppb in the diet (VanMiller et al, 1977).
6) In a gavage study, TCDD induced follicular-cell thyroid adenomas in male and neoplastic liver nodules in female Osborne-Mendel rats (11).
7) RESULTS WITH RELATED COMPOUNDS include:
a) A mixture of HEXAchlorodibenzo-p-dioxins induced hepatocellular carcinomas and adenomas in female but not male Osborne-Mendel rats at doses up to 5 mcg/kg/week for 104 weeks by gavage (5).
b) DICHLORObenzo-p-dioxin was not carcinogenic in Osborne-Mendel rats (NCI, 1979).
D) CARCINOGENICITY IN HAMSTERS -
1) Squamous cell carcinomas developed in Syrian golden hamsters given a total dose of 600 mcg/kg TCDD by the subcutaneous or intraperitoneal route. Hamsters are the species most resistant to the acute effects of TCDD (Huff et al, 1991; Rao et al, 1988).
2) PROMOTING ACTIVITY results include:
a) TCDD is the most potent tumor promoter known; it increases cell turnover and fixes DNA defects (Baxter et al, 2000; Xu et al, 1992).
b) The degree of tumor promotion by TCDD in different strains of mice that differed in their aryl hydrocarbon receptor genotype was not directly related to the level of induction of cytochrome P450 1a. This result indicates that other genetic factors are involved in determining the extent of tumor promotion by TCDD (Beebe et al, 1995).
c) TCDD and dioxin-like compounds 2,3,4,7,8-pentachlorodibenzofuran (PCDF), and 1,2,3,4,7,8-hexachlorodibenzofuran (HCDF), were all potent promoters of MNNG-induced squamous cell papillomas in hairless mice via the dermal route (Hebert et al, 1990).
d) 1,2,3,7,8-Pentachlorodibenzo-p-dioxin (PeCDD) was nearly equipotent with TCDD in promoting induction of liver foci in female Sprague-Dawley rats initiated with nitrosamine. 2,3,4,7,8-Pentachlorodibenzofuran (PeCDF) and 3,3',4,4',5-pentachlorobiphenyl (PCB126) were approximately 10 percent as active as the dioxins (Flodstroem & Ahlborg, 1992).

3.22 GENOTOXICITY

3.22.1 SUMMARY

A) TCDD is not directly genotoxic and usually produces negative results in most genotoxicity assays. However, the TCDD-aryl hydrocarbon receptor complex can bind to specific DNA enhancer sequences. This induces a pleiotropic sequence of genetic expression whose products may activate pro-mutagens.

3.22.2 DNA DAMAGE/REPAIR

A) TCDD is not directly genotoxic and usually produces negative results in most genotoxicity assays, such as the Ames test (IARC , 1997; Schiestl et al, 1997). TCDD produces unscheduled DNA synthesis and DNA inhibition in humans, rats and mice (RTECS , 2001). TCDD induced DNA deletions in vivo in mouse embryo through intrachromosomal recombination (Schiestl et al, 1997).

B) Neither TCDD nor 1,2,3,7,8-pentachlorodibenzo-p-dioxin (PeCDD) was covalently bound to DNA in liver and kidney DNA of rats administered 1 mcg/kg/week in corn oil by gavage for periods up to 6 months (Randerath et al, 1988).
C) A 7.5-fold increase in single-strand DNA breaks was reported in hepatocellular DNA from rats given a single dose of 100 mcg/kg TCDD (Wahba et al, 1988).
D) TCDD is not directly genotoxic, but it binds to the aryl hydrocarbon receptor.
1) The TCDD-aryl hydrocarbon receptor complex can bind to DNA at specific DNA enhancer sequences (Hannah et al, 1986). This induces a pleiotropic sequence of genetic expression leading to activation of pro-mutagens and oncogenes (Puga et al, 1992; Matsumura, 1992; Tullis et al, 1992) Whitlock et al, 1982).
2) The various gene products induced by TCDD may produce secondary effects, such as changes in hormone levels, which in turn lead to other physiological changes (EPA, 1994b).

3.22.3 MUTAGENICITY

A) Studies show TCDD has little if any potential for mutagenic activity (Hayes & Laws, 1991). TCDD was reported to be mutagenic in mouse lymphoma cells, but was inactive in bacterial mutagenicity assays and in rodents in vivo (Huff et al, 1991).
B) TCDD was positive for mutations in Escherichiae coli and Salmonella typhimurium and Saccharomyces cerevisiae, as well as in mouse lymphocytes (RTECS , 2001). However, early reports of mutagenicity in S. typhimurium were not reproducible (Hayes & Laws, 1991).

3.22.4 CHROMOSOME ABERRATIONS

A) TCDD has been inactive for inducing sister chromatid exchanges in several test systems.
1) Neither sister chromatid exchanges nor chromosome aberrations were increased in peripheral lymphocytes of Rhesus monkeys fed 25 ppt TCDD in the diet for 4 years (Lim et al, 1987).
2) Sister chromatid exchanges were not increased in liver cells of male Han/Wistar rats after exposure to TCDD for 2 weeks (Mustonen et al, 1989).
3) No increases in sister chromatid exchanges were seen in male C57Bl/6 mice given up to 2.4 mcg/kg TCDD in the diet for 8 weeks (Lamb et al, 1981a).
4) No increases in sister chromatid exchanges occurred in either C57Bl/6J (high-affinity aryl hydrocarbon receptor) or DBA/2J (low-affinity receptor) mice after receiving a single intraperitoneal injection of TCDD at doses as high as 150 mcg/kg (Meyne et al, 1985).
B) TCDD has been inactive for inducing chromosome aberrations in several test systems.
1) No evidence of chromosome aberrations was seen in liver cells of C57Bl/6 mice given intraperitoneal doses of TCDD up to 150 mcg/kg (Brooks et al, 1988).
2) Neither C57Bl/6J (high-affinity aryl hydrocarbon receptor) nor DBA/2J (low-affinity receptor) mice showed increases in bone marrow chromosome aberrations or micronuclei after receiving a single intraperitoneal injection of TCDD at doses as high as 150 mcg/kg (Meyne et al, 1985).
C) TCDD has not induced micronuclei in rodents in vivo (Huff et al, 1991).

3.22.5 OTHER

A) GENOTOXIC EFFECTS
1) Both TCDD and its bromo analog TBrDD were active in transforming peritoneal macrophages in NMR1 mice. TCDD was 7 times more active than TBrDD (Massa et al, 1992).
2) TCDD was active in transforming C3H/10T 1/2 mouse cells in culture at a concentration of 40 pM. On a molar basis, it was 10,000 times more potent than 12-O-

tetradecanoylphorbol-13-acetate (a model promoter). The primary mode of action of TCDD was promotion rather than initiation of the transformation process (Abernethy et al, 1985). The in vitro promoting activity of TCDD was inhibited by the antioxidants ascorbic acid plus alpha-tocopherol (Wolfle & Marquardt, 1996).

3.23 OTHER

3.23.1 ACUTE EFFECTS

A) CACHEXIA
1) One effect of exposure to TCDD is cachexia. It may suppress the formation of hunger signals, possibly through serotonergic mechanism. Diminished food intake and progressive weight loss are consequences of this (Bingham et al, 2001). Death may occur after a period of wasting (Baxter et al, 2000).

3.23.3 ANIMAL STUDIES

A) ANIMAL STUDIES
1) CACHEXIA
a) TCDD produces a wasting syndrome, which is the ultimate cause of death in several species of animals (Zenz, 1994). The basis of the wasting syndrome is unknown.
b) Rats given 3 or 10 mcg/kg/day TCDD for 91 days developed wasting syndrome (Ivens et al, 1993). Death from acute exposure to TCDD is delayed by 2 to 6 weeks in experimental animals (Zenz, 1994).

4.0 MEDICAL SURVEILLANCE/LABORATORY

4.1 MONITORING PARAMETERS/LEVELS

4.1.1 SUMMARY

A) It is difficult and expensive to measure dioxins in human tissue specimens. The current analytical techniques involve gas chromatography and mass spectrometry.
B) Liver function tests, CBC, prothrombin time (INR - International Normalized Ratio), serum lipids and uroporphyrins should be obtained in acute exposure. Electrodiagnostic studies such as EMG and nerve conduction velocity may be useful in detecting subclinical neuropathy.

4.1.2 SERUM/BLOOD

A) BLOOD/SERUM CHEMISTRY
1) Monitor liver function tests and serum lipids (Hayes, 1982).
2) Serum dioxin concentrations measured in 1987 were similar in veterans with and without Vietnam duty in 1967 to 1968 (4.1 and 4.2 ng/L, respectively) (Baselt, 2000).
3) However, plasma TCDD levels measured in Seveso in 1992-1993, following the 1976 blowout of a 2,4,5-trichlorophenol production reactor released TCDD over large area, showed that those with the highest exposure had the highest levels (mean, 53.2 ppt), and levels decreased with decreasing exposure, with means of 11.0 ppt down to 4.9 ppt for unexposed (Landi et al, 1998).
4) Serum TCDD levels of the highest known occupationally exposed group ranged from <20 pg/g to >148 pg/g (ppt) (Halperin et al, 1995).

5) Serum TCDD levels were as high as 56,000 ppt in persons acutely exposed in the Seveso accident who did not develop chloracne. These are the highest serum levels ever measured, but there were no apparent adverse clinical effects in this group (Mocarelli et al, 1991).
6) Average blood levels of dioxins and dioxin-like substances were similar in Europe and North America; total TEQ (TCDD equivalents) was 42 pg/g (42 ppt) in German subjects and 41 pg TEQ/g in US subjects (Schecter, 1991).
7) Blood levels of 2,3,7,8-TCDD correlated with adipose tissue levels in fasted Vietnam veterans. Although blood analysis was less invasive than a fat biopsy, 300 to 400 mL of blood were needed for the analysis (Kahn et al, 1988).
8) Serum TCDD levels are an accurate 'surrogate' for steady-state levels in human adipose tissue from low-level exposures (Patterson et al, 1988). Serum levels may not be predictive of the severity of clinical effects, however (Mocarelli et al, 1991).
9) PERSISTENT BLOOD LEVELS - Significant serum dioxin levels were measured in a chemist 35 years after exposure. In this single case, the serum level was 18 ppt, compared with a mean level of 5 ppt in the general population (Schecter & Ryan, 1992).
B) HEMATOLOGIC
1) Monitor CBC.
C) COAGULATION STUDIES
1) Monitor prothrombin time (International Normalized Ratio).

4.1.3 URINE

A) URINARY LEVELS
1) 2,4-dichlorophenoxyacetic acid (2,4-D) can be detected in urine (Baselt, 1997). Dioxin is a contaminant of some preparations of 2,4,-D.
2) Monitoring urinary uroporhyrins may be of value after substantial exposure. Uroporphyrin output reached 2.23 mg/24 hours in workers exposed to TCDD who then developed porphyria; excretion of delta aminolevulinic acid increased (Hayes, 1982).
3) Ratios of urinary caffeine metabolites are a measure of induction of cytochrome P-4501A2, a genetically determined response to TCDD exposure (Halperin et al, 1995).
4) An increase in urinary uroporphyrins and coproporphyrins is an early sign of porphyria cutanea tarda (Bleiberg et al, 1964).

4.1.4 BIOLOGICAL MONITORING

A) ACGIH BEI Values for CAS1746-01-6 (ACGIH, 2004):
1) Not Listed

4.1.5 OTHER

A) OTHER
1) ADIPOSE LEVELS
a) TCDD accumulates in fat stores, and is detectable in adipose tissue (Harbison, 1998). However, fat biopsies are not routinely useful. Analysis of Vietnam veterans showed levels from 0 to 13 ppt, which were not different from unexposed controls. Adipose tissue samples from Canada showed random levels of 4 to 130 ppt.
b) Average body burdens in humans from background environmental exposure are 40 to 60 pg TEQ (TCDD equivalents) per gram lipid, including all dioxins, furans, and polychlorinated biphenyls. This is equivalent to approximately 40 to 60 ppt, or 9 ng/kg, from an average daily intake of 3 to 6 pg TEQ/kg/day. Body burdens of dioxins and chlorobenzodifurans increase with age (EPA, 1994b).

c) In a 10-year follow-up of veterans of Operation Ranch Hand, the half-life of TCDD was estimated to be 8.7 years; the half-life was directly related to the amount of body fat, but not with age or relative changes in percent of body fat (Michalek et al, 1996).
d) Median half-life for elimination of TCDD in occupationally exposed persons was estimated to be 7.2 years in a one-compartment, first-order kinetic model (Fleschjanys et al, 1996).
e) Body burdens of dioxins and dioxin-like substances associated with onset of various clinical effects in humans are (EPA, 1994b):

Estimated Body Burden (ng/kg)	Effect
9	" Background " level
14	Decreased testis size
14 to 110	Altered glucose tolerance
45 to 3,000	Chloracne
83	Decreased testosterone
109 to 7,000	Cancer

f) The highest occupational exposures to TCDD measured so far were in nine chemical production workers, who had an average concentration in adipose tissue of 246 ppt, compared with 8.7 ppt in unexposed employees at the same plant (Patterson et al, 1989).
g) Levels of TCDD found in 27 residents of South Vietnam measured in 1989 ranged from 0.3 to 49.6 ppt in adipose tissue. This would have been approximately 20 years after peak exposure to TCDD in Agent Orange. Levels of other dioxin and furan isomers paralleled TCDD in this population (Verger et al, 1994).
h) Cumulative exposure over time is given by the area under the time-concentration curve for dioxin in fat (Bois & Eskenazi, 1994).
2) ELECTROPHYSIOLOGICAL TESTING
a) Electrodiagnostic studies such as EMG and nerve conduction velocity may be useful in detecting subclinical neuropathy.

4.3 METHODS

A) OTHER
1) It is difficult and expensive to detect dioxin in human tissue specimens. The average cost is between $1,500 and $2,500 per sample (Schecter et al, 1994).
B) MULTIPLE ANALYTICAL METHODS
1) Because levels are very low, a very sensitive and specific method is required. 2,4-dichlorophenol can be detected in plasma and urine using flame-ionization chromatography with on-color methylation (Baselt, 1997).
2) The current analytical techniques involve gas chromatography and mass spectrometry (Raisonen et al, 1981). High resolution gas chromatography with mass spectrometry has a lower detection limit of 0.6 ppt on a lipid-weight basis (Johnson et al, 1992).
3) Cloud-point extraction of serum using Triton X-100 shows promise as a cleaner and easier way to analyze polycyclic aromatic hydrocarbons and polychlorinated dibenzo-p-dioxins (Sirimanne et al, 1996).
4) There is a large margin of error in measuring levels of dioxin less than 100 ppt; error may range from 20 to 50 percent (Verger et al, 1994). This concentration range would include almost all biological samples except those from patients with very high acute exposures.
5) An enzyme-linked immunosorbent assay for TCDD using monoclonal antibodies has a lower detection limit of 0.5 ng (Stanker et al, 1987).

5.0 CASE REPORTS

A) CHRONIC EFFECTS
1) ADULT

a) Three men involved in the synthesis of TCDD developed chloracne, hyperpigmentation, and hypercholesterolemia despite observing appropriate precautions. Two developed hirsutism, anorexia, headaches, and fatigue 2 years after the episode (Oliver, 1975). These are the only known cases of significant exposure to pure TCDD.
2) PEDIATRIC
a) A 6-year-old girl playing in a Missouri horse arena sprayed with TCDD-contaminated motor oil developed self-limited epistaxis, severe hemorrhagic cystitis, and GI complaints. Samples taken from the arena soil contained 31.8 to 33 ppm of TCDD (Beale et al, 1977).

6.0 TREATMENT

6.1 LIFE SUPPORT

A) Support respiratory and cardiovascular function.

6.4 MONITORING

A) It is difficult and expensive to measure dioxins in human tissue specimens. The current analytical techniques involve gas chromatography and mass spectrometry.
B) Liver function tests, CBC, prothrombin time (INR - International Normalized Ratio), serum lipids and uroporphyrins should be obtained in acute exposure. Electrodiagnostic studies such as EMG and nerve conduction velocity may be useful in detecting subclinical neuropathy.

6.5 INHALATION EXPOSURE

6.5.1 DECONTAMINATION

A) DECONTAMINATION: Move patient from the toxic environment to fresh air. Monitor for respiratory distress. If cough or difficulty in breathing develops, evaluate for hypoxia, respiratory tract irritation, bronchitis, or pneumonitis.
B) OBSERVATION: Carefully observe patients with inhalation exposure for the development of any systemic signs or symptoms and administer symptomatic treatment as necessary.
C) INITIAL TREATMENT: Administer 100% humidified supplemental oxygen, perform endotracheal intubation and provide assisted ventilation as required. Administer inhaled beta adrenergic agonists if bronchospasm develops. Exposed skin and eyes should be flushed with copious amounts of water.

6.6 DERMAL EXPOSURE

6.6.1 DECONTAMINATION

A) DERMAL DECONTAMINATION
1) Remove contaminated clothing and wash exposed area extremely thoroughly with soap and water. A physician may need to examine the area if irritation or pain persists after washing.
B) PERSONNEL PROTECTION
1) Personnel involved in washing patients should wear gloves and avoid contact with contaminated clothing.

6.6.2 TREATMENT

A) CHLORINE ACNE
1) Chloracne is generally resistant to modes of therapy used for acne vulgaris. Tetracyclines, topically or orally, have proven useful in some cases. Acne surgery and dermabrasion have been beneficial in severe cases. Topical retinoic acid 0.05 to 0.3% for up to 10 months may be useful (Plewig, 1971).
B) Treatment should include recommendations listed in the ORAL EXPOSURE section when appropriate.

6.7 EYE EXPOSURE

6.7.1 DECONTAMINATION

A) Remove contact lenses and irrigate exposed eyes with copious amounts of room temperature 0.9% saline or water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist after 15 minutes of irrigation, an ophthalmologic examination should be performed.

6.8 ORAL/PARENTERAL EXPOSURE

6.8.1 PREVENTION OF ABSORPTION/PREHOSPITAL

A) SUMMARY
1) Most exposures are chronic. Routine gastrointestinal decontamination is not indicated.

6.8.2 PREVENTION OF ABSORPTION

A) SUMMARY
1) Most exposures are chronic. Routine gastrointestinal decontamination is not indicated. In the unlikely event of acute ingestion administer activated charcoal.
B) ACTIVATED CHARCOAL
1) CHARCOAL ADMINISTRATION
a) Consider administration of activated charcoal after a potentially toxic ingestion (Chyka & Seger, 1997). Administer charcoal as an aqueous slurry; most effective when administered within one hour of ingestion.
2) CHARCOAL DOSE
a) Use a minimum of 240 milliliters of water per 30 grams charcoal (FDA, 1985). Optimum dose not established; usual dose is 25 to 100 grams in adults and adolescents; 25 to 50 grams in children aged 1 to 12 years (or 0.5 to 1 gram/kilogram body weight) ; and 1 gram/kilogram in infants up to 1 year old (USP DI, 2002; Chyka & Seger, 1997).
1) Routine use of a cathartic with activated charcoal is NOT recommended as there is no evidence that cathartics reduce drug absorption and cathartics are known to cause adverse effects such as nausea, vomiting, abdominal cramps, electrolyte imbalances and occasionally hypotension (Barceloux et al, 1997).
b) ADVERSE EFFECTS/CONTRAINDICATIONS
1) Complications: emesis, aspiration (Chyka & Seger, 1997). Aspiration may be complicated by acute respiratory failure, ARDS or bronchiolitis obliterans (Pollack et al, 1981; Harris & Filandrinos, 1993; (Elliot et al, 1989) Harsh, 1986; (Rau et al, 1988; Golej et al, 2001; Graff et al, 2002). Refer to the ACTIVATED CHARCOAL/TREATMENT management for further information.
2) Contraindications: unprotected airway, gastrointestinal tract not anatomically intact, therapy may increase the risk or severity of aspiration; ingestion of most hydrocarbons (Chyka & Seger, 1997).

6.8.3 TREATMENT

A) SUPPORTIVE CARE
1) Treatment is symptomatic and supportive following acute exposure.
B) MONITORING OF PATIENT
1) Monitor liver function tests serially in confirmed exposures.
C) CHLORINE ACNE
1) Chloracne is generally resistant to modes of therapy used for acne vulgaris. Acne surgery and dermabrasion have been the most beneficial in severe cases. Topical retinoic acid 0.05 to 0.3% for up to 10 months may be useful (Plewig, 1971). Tetracyclines may be used to treat secondary pustular follicles.
D) CORTICOSTEROID
1) In acute exposures, it may be beneficial to administer dexamethasone, as this appears to inhibit dioxin-mediated toxicity in animal studies (Taylor et al, 1992).
E) INJURY DUE TO CHEMICAL EXPOSURE
1) VIETNAM REGISTRY - An Agent Orange registry has been established for any Vietnam veteran expressing a concern of exposure to herbicides. Registry includes a thorough history, physical exam, follow-up over several years. Call toll-free 800-424-5402.

7.0 RANGE OF TOXICITY

7.1 SUMMARY

A) Cumulative oral doses of 100 mcg/kg are estimated to be the minimum toxic dose.
B) Dermal exposure to soil concentrations of greater than 100 ppm are likely to produce chloracne.

7.3 MINIMUM LETHAL EXPOSURE

A) ACUTE
1) One review article by Reggiani (1978) reports a minimum lethal dose of 1 mcg/kg (Schardein, 2000).
2) It is estimated that human lethal doses are greater than 100 mcg/kg (Neal, 1983).

7.4 MAXIMUM TOLERATED EXPOSURE

A) The maximum tolerated human exposure to this agent has not been delineated.
B) A cumulative dose of 100 mcg/kg is estimated as the minimum toxic dose, based on extrapolation of data from TCDF-contaminated cooking oil in Japan (Stevens, 1981).
C) ROUTE OF EXPOSURE
1) DERMAL -
a) Assuming daily exposure, it appears that 10 to 30 ppm in oil and 100 to 3,000 ppm in soil-water mixtures are necessary to produce objective effects. Soil concentrations likely to produce chloracne with daily contact probably exceed 100 ppm (Dunagin, 1984).
b) The lowest published toxic dose for a human (dermal route) is 107 mcg/kg (Lewis, 2000; RTECS , 2002).
2) INHALATION -
a) Dioxin has a low vapor pressure (1.7 x 10(-6) mmHg). Inhalation of 70 ng/human/day is the FDA-suggested "no effect" level. If the level in dirt/dust is 1 ppb, the amount inhaled has been calculated as 1.4 pg/day.
3) AIRBORNE -

a) SEVESO, ITALY INCIDENT - A plant producing trichlorophenol in Seveso, Italy, inadvertently overheated, creating a cloud of dioxin (TCDD) containing 650 to 1700 grams (35,000 ppt) (Reggiani, 1978).
1) Children and adults directly exposed to airborne dust complained of nausea, skin redness, and swelling. Others developed chloracne, which rapidly and spontaneously healed, subclinical peripheral neurological impairment, and liver enzyme abnormalities.
2) The highest average soil levels were 584 ppb.
4) ORAL -
a) Cumulative oral doses of 100 mcg/kg are estimated as the minimum toxic dose. The World Health Organization recommended in 1998 that the tolerable daily intake of TCDD not exceed 4 picograms/kg (Birnbaum & Slezak, 1999).
5) SOIL LEVELS -
a) Soil levels of 1 ppb are estimated to increase the risk of developing cancer by 1 in 1 million (MMWR, 1984).
b) Soil concentrations likely to produce chloracne with daily contact probably exceed 100 ppm (Dunagin, 1984).
c) A 6-year-old girl playing in a Missouri horse arena sprayed with dioxin (TCDD)-contaminated motor oil developed self-limited epistaxis, severe hemorrhagic cystitis, and gastrointestinal complaints. Samples taken from the soil contained 31.8 to 33 ppm of dioxin (TCDD) (Beale et al, 1977).
D) ANIMAL DATA
1) Hen pheasants injected with graded single doses of dioxin (TCDD) (6.25, 25 or 100 mcg/kg) had delayed-onset body weight loss and mortality, classic signs of the wasting syndrome (Nosek et al, 1992).
a) The lowest single dose of dioxin (TCDD) to produce this effect was 25 mcg/kg.
b) When hen pheasants were treated weekly with lower doses of dioxin (TCDD) (0.01 to 1.0 mcg/kg/wk) for 10 weeks, signs of the wasting syndrome and mortality were also produced.
c) The lowest cumulative dioxin (TCDD) dose required to produce the wasting syndrome, using a weekly dosing regimen, was 10 mcg/kg. At this dosing regimen, egg production by hens treated with a cumulative dioxin (TCDD) dose of 10 mcg/kg was reduced, as was egg hatchability.
2) RATS - The maximum tolerated dose of TCDD in rats in a 91-day subchronic gavage study was 0.1 pg/kg/day (Ivens et al, 1993).
3) RATS - The maximum tolerated dose of TCDD in rats was 0.01 mcg/kg/day when given 5 days/week for 13 weeks (Kociba et al, 1976).
4) TCDD and two dioxin-like compounds, 2,3,4,7,8-pentachlorodibenzofuran (PCDF), and 1,2,3,4,7,8-hexachlorodibenzofuran (HCDF), were evaluated for relative dermal toxicity in 20-week subchronic skin painting studies in hairless mice (Hebert et al, 1990).
a) Based on dermatotoxic effects and changes in body and organ weights, the last two compounds were relatively more toxic than their acute Toxicity Equivalency Factor (TEF) values would indicate.
b) TEF values may underestimate the risk from repeated low-dose exposures, at least for these compounds.
E) OTHER
1) Where TCDD has been assigned a Toxicity Equivalency Factor (TEF) of 1.0 (on a scale of 0 to 1.0, with 1.0 being the most toxic), the other chlorinated dibenzodioxins and chlorinated dibenzofurans have TEFs ranging from 0 to 0.5 (Freeman, 1998).
2) TCDD is the most toxic of all the known dioxins. Of the 210 possible positional congeners, only 7 chlorinated dibenzodioxins and 10 chlorinated dibenzofurans are believed to have TCDD-like activity. These all have chlorine in the 2,3,7 and 8 positions (EPA, 1994a; EPA, 1994b; Freeman, 1998).
3) The EPA's Exposure Estimation for Dioxin-Like Compounds mainly deals with chlorinated dibenzodioxins and, by extension, chlorinated dibenzofurans and other dioxin-

like compounds. Analogous brominated dioxins and furans, and certain polychlorinated biphenyls, are known to have dioxin-like toxicity but have not yet been assigned TEFs (EPA, 1994a).
4) Only 11 of the 209 possible polychlorinated biphenyl congeners are thought to have dioxin-like activity. These have at least four chlorine substituents (EPA, 1994a).

7.5 TOXIC SERUM/PLASMA/BLOOD CONCENTRATIONS

A) TOXIC CONCENTRATION LEVELS
1) OCCUPATIONAL
a) Heavily exposed Vietnam veterans had blood levels of 2,3,7,8-TCDD exceeding 15 pg/g 15 to 20 years after exposure (Kahn et al, 1988).
b) Median TCDD levels of 8 pg/g plasma lipid (range, 2 to 13) were detected among 11 Swedish men who ate fish almost daily (Svensson et al, 1991). Lower levels were reported among moderate-intake and nonconsumer groups. Clinical correlations were not studied.

7.6 TOXICITY INFORMATION

7.6.1 TOXICITY VALUES

A) References: Bingham et al, 2001 HSDB, 2002 Lewis, 2000 NTP, 2001;) Pohjanvirta et al, 1993 RTECS, 2002 Verschueren, 2001
1) LD50 - (ORAL) DOG:
a) 1 mcg/kg
b) 100-200 mcg/kg (HSDB, 2002)
2) LD50 - (ORAL) GUINEA_PIG:
a) 500 ng/kg
b) 0.6 mcg/kg (HSDB, 2002)
3) LD50 - (INTRAPERITONEAL) HAMSTER:
a) >3 mg/kg -- changes in thymus weight and serum composition, weight loss
4) LD50 - (ORAL) HAMSTER:
a) 1157 mcg/kg -- gastrointestinal changes, weight loss, changes in serum composition
b) 1157-5051 mcg/kg (HSDB, 2002)
5) LD50 - (INTRAPERITONEAL) MOUSE:
a) 120 mcg/kg
6) LD50 - (ORAL) MOUSE:
a) 114 mcg/kg -- convulsions, cardiac changes, mydriasis
7) LD50 - (ORAL) PRIMATE:
a) 2 mcg/kg
b) Female, <70.0 mcg/kg (HSDB, 2002)
8) LD50 - (INTRAPERITONEAL) RABBIT:
a) 252 mcg/kg
9) LD50 - (ORAL) RABBIT:
a) 115 mcg/kg
b) 10 mcg/kg (HSDB, 2002)
10) LD50 - (SKIN) RABBIT:
a) 275 mcg/kg
11) LD50 - (INTRAPERITONEAL) RAT:
a) 24,600 ng/kg
12) LD50 - (ORAL) RAT:
a) 20 mcg/kg
b) Male, 22.0 mcg/kg (HSDB, 2002)
c) Sprague-Dawley, 43 mcg/kg (Bingham et al, 2001)

d) Female, 45.0 mcg/kg (HSDB, 2002)
e) >7200 mcg/kg -- H/W strain (Pohjanvirta et al, 1993)
f) Female, 9.8 mcg/kg -- L-E strain (Pohjanvirta et al, 1993)
g) Male, 17.7 mcg/kg -- L-E strain (Pohjanvirta et al, 1993)
13) LDLo - (INTRAPERITONEAL) CHICKEN:
a) 25 mcg/kg -- weight loss, changes in food intake behavior and metabolism
14) LDLo - (ORAL) CHICKEN:
a) 25 mcg/kg -- dyspnea, weight loss
15) LDLo - (SKIN) MOUSE:
a) 80 mcg/kg -- changes in gastrointestinal system
16) TD - (ORAL) MOUSE:
a) 1 mcg/kg for 2Y-Intermittent -- equivocal tumorigenic agent by RTECS criteria, tumors of the liver and thyroid
b) 36 mcg/kg for 52W-Intermittent -- neoplastic, tumors of the lung, thorax, liver
17) TD - (SKIN) MOUSE:
a) 80 mcg/kg -- equivocal tumorigenic agent by RTECS criteria, tumors of the skin and appendages, tumors at site of application
18) TD - (ORAL) RAT:
a) 1 mcg/kg for 2Y-Intermittent -- equivocal tumorigenic agent by RTECS criteria, tumors of the liver and thyroid
b) 27 mcg/kg for 65W-Continuous-- equivocal tumorigenic agent by RTECS criteria, tumors of the liver and thyroid
c) 73 mcg/kg for 2Y-Continuous -- carcinogenic by RTECS criteria, tumors of the liver
d) 190 mcg/kg for 95W-Continuous -- equivocal tumorigenic agent by RTECS criteria, tumors of the liver and kidney
e) 137 mcg/kg for 65W-Continuous -- equivocal tumorigenic agent by RTECS criteria, tumors of the liver and kidney
f) 328 mcg/kg for 78W-Continuous -- equivocal tumorigenic agent by RTECS criteria, tumors of the lung, thorax
19) TDLo - (ORAL) GUINEA_PIG:
a) 5 mcg/kg for 5W- Intermittent -- changes in the bladder, kidney, ureter and endocrine system, death
b) 1600 ng/kg for 8W- Intermittent -- changes in thymus weight, weight loss
c) 441 ng/kg for 90D- Continuous -- changes in liver and thymus weights, weight loss
20) TDLo - (ORAL) HAMSTER:
a) Female, 2 mcg/kg at 11D of pregnancy -- reduced weight gain in offspring
b) Female, 18 mcg/kg at 9D of pregnancy -- fetal death
c) 600 mcg/kg for 3D- Intermittent -- changes in the liver, oxidoreductases and transferases
21) TDLo - (SKIN) HUMAN:
a) 107 mcg/kg -- allergic dermatitis
22) TDLo - (INTRAPERITONEAL) MOUSE:
a) Female, 20 mcg/kg at 11D of pregnancy -- craniofacial developmental abnormalities
b) Female, 25 mcg/kg at 7-11D of pregnancy -- fetotoxicity, craniofacial developmental abnormalities
c) 120 mcg/kg for 12W-Intermittent -- changes in liver and thymus weight, changes in cell count (unspecified)
d) 180 mcg/kg for 6W-Intermittent -- changes in liver weight and serum composition, transaminases
23) TDLo - (ORAL) MOUSE:
a) 9260 ng/kg for 4W-Intermittent -- changes in liver and thymus weight, changes in erythrocyte count
b) Female, 1 mcg/kg at 10D of pregnancy -- developmental abnormalities of the urogenital system

c) Female, 9 mcg/kg at 12D of pregnancy -- craniofacial (including mouth and tongue) developmental abnormalities
d) Female, 12 mcg/kg at 10-13D of pregnancy -- post-implantation mortality, fetal death
e) Female, 20 mcg/kg at 14D of pregnancy and 3D after birth -- reduced weight gain in offspring
f) 52 mcg/kg for 2Y-Intermittent -- carcinogenic by RTECS criteria, tumors of the liver, thyroid
g) Female, 235 mcg/kg at 28D prior to mating and 21D after birth -- immune and reticuloendothelial system developmental abnormalities
h) Female, 13,500 mg/kg at 6-14D of pregnancy -- developmental abnormalities of the endocrine system
i) 20 mcg/kg for 4W-Intermittent -- changes in thymus weight and endocrine system, decrease in cellular immune response
j) 336 mcg/kg for 8W-Continuous -- changes in leukocyte count, decrease in humoral immune response
k) 520 mcg/kg for 13W-Intermittent -- changes in the liver, death
l) 150 mcg/kg for 6W-Intermittent -- fatty liver degeneration, changes in thymus weight and serum composition
m) 588 mcg/kg for 14D-Intermittent -- changes in the weights of the liver, spleen and thymus
24) TDLo - (SKIN) MOUSE:
a) 97 mcg/kg for 13W-Intermittent -- hepatitis, changes in spleen, death
b) 62 mcg/kg for 2Y-Intermittent -- carcinogenic by RTECS criteria, tumors of the skin and appendages
25) TDLo - (SUBCUTANEOUS) MOUSE:
a) Female, 30 mcg/kg at 10D of pregnancy -- craniofacial (including mouth and tongue) developmental abnormalities
b) Female, 100 mcg/kg at 2D of pregnancy -- post-implantation mortality
c) Female, 100 mcg/kg at 10D of pregnancy -- craniofacial (including mouth and tongue) developmental abnormalities
d) Female, 250 mcg/kg at 7-16D of pregnancy -- fetal death, reduced litter size
e) Female, 250 mcg/kg at 7-16D of pregnancy -- craniofacial (including mouth and tongue), musculoskeletal, and urogenital developmental abnormalities
26) TDLo - (ORAL) PRIMATE:
a) Female, 2 mcg/mg at 12D of pregnancy -- abortion
b) Male, 107 mg/kg at 4Y prior to mating -- behavioral effects in offspring
c) Female, 163 ng/kg at 3.5Y prior to mating -- behavioral effects on offspring
d) Female, 92 ng/kg at 46W prior to mating and 17W after birth -- behavioral effects on offspring
e) Female, 123 ng/kg at 30W prior to mating and 17W after birth -- behavioral effects in offspring
f) 10 mcg/kg for 12D-Continuous -- ulceration or bleeding from the stomach, nutritional and metabolic changes, death
27) TDLo - (ORAL) RABBIT:
a) Female, 1 mcg/kg at 6-15D of pregnancy -- developmental abnormalities of the musculoskeletal system
b) Female, 10 mcg/kg at 6-15D of pregnancy -- pre-implantation mortality, abortion
c) Female, 2500 ng/kg at 6-15D of pregnancy -- post-implantation mortality, developmental abnormalities of the urogenital system
d) 80 mcg/kg for 8W-Intermittent -- decrease in cellular and humoral immune responses, death
28) TDLo - (INTRAPERITONEAL) RAT:
a) Female, 6 mcg/kg at 17D of pregnancy -- biochemical and metabolic effects on offspring

29) TDLo - (ORAL) RAT:
a) Female, 1 mcg/kg at 15D of pregnancy -- developmental abnormalities of endocrine system in offspring
b) Female, 1 mcg/kg at 15D of pregnancy -- physical effects in offspring
c) Female, 1 mcg/kg at 15D of pregnancy -- developmental abnormalities of urogenital system, fetal death
d) Female, 12 mcg/kg at 10D of pregnancy -- cytological changes to embryo, developmental abnormalities of urogenital system
e) Female, 20 mcg/kg at 1D prior to pregnancy -- affected uterus, cervix, vagina
f) 52 mcg/kg for 2Y-Intermittent -- carcinogenic by RTECS criteria, tumors of the liver, thyroid
g) Female, 1250 ng/kg at 6-15D of pregnancy -- fetal death, developmental abnormalities
h) Female, 1270 ng/kg -- decreased fertility, developmental abnormalities of blood and lymphatic system
i) Female, 1500 ng/kg at 1-3D of pregnancy -- fetotoxicity, developmental abnormalities of urogenital system
j) 16 mcg/kg for 16W-Intermittent -- changes of the liver and urine composition, porphyrin including bile pigments
k) 30 mcg/kg for 30D-Intermittent -- changes in serum composition and platelet count, multiple enzyme effects
l) 120 mcg/kg for 3D-Intermittent -- changes of the liver and iron metabolism, hepatic microsomal mixed oxidase
m) 140 mcg/kg for 14D-Intermittent -- changes in clotting factors, erythrocyte count and platelet count
n) 450 ng/kg for 45W-Intermittent -- changes in urine composition
o) 6500 ng/kg for 13W-Intermittent -- changes in liver and thymus weights, pigmented or nucleated red blood cells
p) 7300 mg/kg for 2Y-Continuous -- hepatitis, changes in liver weight and urine composition
q) 164 mcg/kg for 78W-Continuous -- carcinogenic by RTECS criteria, tumors of the liver, lung and thorax
30) TDLo - (SUBCUTANEOUS) RAT:
a) Female, 5 mg/kg at 6-15D of pregnancy -- urogenital system abnormalities
b) Female, 2200 ng/kg at 19D of pregnancy and 21D after birth -- reduced weight gain in offspring

7.7 CALCULATIONS

A) AMBIENT CONVERSIONS
1) 1 mg/m(3) = 0.0759 ppm; 1 ppm = 13.17 mg/m(3) (in air at 25 degrees C and 760 mmHg) (ATSDR, 1998)

7.8 OTHER

A) OTHER
1) GENERAL
a) Risk estimates of cancer to humans exposed for their entire lifetime to soil contaminated with dioxin (and dibenzofurans) range from 1x10(-8) to 3x10(-7) (Eschenroeder et al, 1986). Calculations based on the Seveso incident indicate that the lifetime cancer risk does not appear to exceed 10(-5) (DiDomenico & Zapponi, 1986). In its final draft of May 2000, US EPA estimates the cancer risk as being as high as 1:100 to 1:1,000 from dioxin exposure; however, it also states that the actual risk may be lower ((EPA, 2000a); (EPA, 2001a)).

8.0 KINETICS

8.1 ABSORPTION

A) SUMMARY
1) The pharmacokinetics of dioxins are poorly understood, particularly in humans (Hatch & Stein, 1986). The pharmacokinetics also vary by species (Bingham et al, 2001).
2) Bioavailability is generally unknown; it is difficult to determine absorbed doses from environmental sources (Hatch & Stein, 1986).
B) ORAL
1) Gastrointestinal absorption varies with the vehicle used. Dioxins are less well absorbed from aqueous soil suspensions than from oil or solvent mixtures.
2) There seems to be little interspecies difference in gastrointestinal absorption of dioxins, but absorption varies from one congener to another. The more stable congeners are absorbed to a greater extent (EPA, 1994b).
3) Preliminary data indicated a high level of gastrointestinal absorption from a corn oil vehicle (87 percent), based on data from one volunteer (Poiger & Schlatter, 1986).
C) DERMAL
1) At high concentrations (26 ppm), 5 percent was absorbed through rat skin; at 1 ppm, less than 1 percent was absorbed (Poiger & Schlatter, 1980).
2) Of TCDD and several chlorodibenzofurans tested for dermal absorption in rats, 2,3,7,8-tetrachlorodibenzofuran (TCDF) was absorbed to the greatest extent in experimental animals given 0.1 mcmol/kg (Brewster et al, 1989).

8.2 DISTRIBUTION

8.2.1 DISTRIBUTION SITES

A) TISSUE/FLUID SITES
1) Dioxin is lipophilic and lipid-soluble, so it is found mainly in adipose tissue, skin, liver, pancreas and breast milk (Baselt, 2000; Baxter et al, 2000; Bingham et al, 2001). It is preferentially stored in adipose tissue and may be released systematically when an individual loses weight (Flowers et al, 1981).
2) TCDD is absorbed by the lymphatic system and is transported by chylomicrons and lipoproteins (Hayes & Laws, 1991).
3) TCDD and several chlorodibenzofurans were distributed mainly to the liver, adipose tissue, skin and muscle tissue in rats (Brewster et al, 1989).

8.3 METABOLISM

8.3.1 METABOLISM SITES AND KINETICS

A) GENERAL
1) Dioxin is not known to be metabolized in man (Baselt, 2000). It may be metabolized by a detoxification process, possibly by cytochrome P450-associated mixed-function oxidases (Hayes & Laws, 1991).

8.3.2 METABOLITES

A) GENERAL
1) Evidence indicates that TCDD may be slowly metabolized in man to more polar metabolites (Wendling & Orth, 1990).

2) Hydroxylated metabolites of TCDD include 2-hydroxy-3,7,8-trichlorodibenzo-p-dioxin, 2-hydroxy-1,3,7,8-tetrachlorodibenzo-p-dioxin, 1-hydroxy-2,3,7,8-tetrachlorodibenzo-p-dioxin, other hydroxylated chlorinated dibenzo-p-dioxins and diphenyl ethers, and 4,5-dichlorocatechol (Hayes & Laws, 1991).

8.4 EXCRETION

8.4.2 FECES

A) Excretion occurs mainly through the feces, probably by direct intestinal elimination; this varies widely by species (Baselt, 2000; Hayes & Laws, 1991). Up to 78 percent was shown to be eliminated via feces in the adult monkey (Hayes & Laws, 1991).
1) Such fecal excretion (80 to 100 percent) occurs in most animal species, with only minor amounts of metabolites found in the urine. This has been shown in guinea pigs (Olson, 1986).

8.5 ELIMINATION HALF-LIFE

8.5.1 PARENT COMPOUND

A) GENERAL
1) The serum elimination half-life was calculated to be about 7.1 years (Baselt, 2000). Other estimates of the half-life in humans include approximately 7 years, 5 to 8 years or 5.98 to 11.3 years (Baxter et al, 2000; Bingham et al, 2001; MMWR, 1988; Pirkle et al, 1989). The half-life based on experimental data from one human volunteer was 5.8 years (Poiger & Schlatter, 1986).
2) The half-life in rats is 10 to 40 days (Reggiani, 1979). Another estimate was 30 days (Baselt, 2000). In monkeys, the half-life in adipose tissue was about 1 year (Bingham et al, 2001).

9.0 PHARMACOLOGY/TOXICOLOGY

9.2 TOXICOLOGIC MECHANISM

A) The mechanism(s) of action is (are) not clear (Hatch & Stein, 1986). Tetrachlorodibenzo-p-dioxin (TCDD) is the most potent isomer, followed by dibenzofurans, hexachlorobiphenyls, and tetrabromonaphthalenes.
1) Toxic dioxins and dioxin-like compounds consist of two or more aromatic rings in a planar configuration, with four lateral halogen atoms arranged in a 3- x 10-Angstrom rectangular box. Additional chlorine atoms may be present, and tend to decrease toxicity, presumably by increasing molecular thickness and interfering with binding to the receptor.
B) TCDD binds to the aryl hydrocarbon receptor, releasing heatshock protein 90 (Baxter et al, 2000). The TCDD-receptor complex in conjunction with the aryl hydrocarbon nuclear translocator protein then enters the nucleus and interacts with dioxin response elements (Baxter et al, 2000; Hannah et al, 1986).
1) This results in the induction of pleiotropic expression of specific genes, including several cytochrome P450 genes, notably the CYP1A1 gene for cytochrome P-4501A1 (Baxter et al, 2000; EPA, 1994b). This ultimately affects intracellular calcium levels, cytokine expression and estrogen expression; these secondary effects, in turn, lead to other physiological changes (Baxter et al, 2000; EPA, 1994b).
2) Cytochrome P-4501A2 is also induced in rats, but to a lesser extent (Tritscher et al, 1992). In experimental animals, toxicity is related to the induction of cytochromes P-448 and P-450 (McKinney & McConnell, 1982).

C) The aryl hydrocarbon receptor exists in polymorphic forms (multiple genetic alleles). This indicates that different individuals may have different genetically-determined susceptibilities to TCDD and, by inference, other dioxins. This hypothesis has been borne out in studies on different mouse strains, whose susceptibility to TCDD parallels the differing aryl hydrocarbon receptor affinities for TCDD (EPA, 1994b).
1) For example, the mouse strain C56BL/6J is more sensitive to the acute lethal effects of TCDD, and to the induction of cytochrome P-450, than strain DBA/2J (Chapman & Schiller, 1985; Poland & Glover, 1975).
D) Cytochromes induced by TCDD are involved in the metabolism and activation of some genotoxins and carcinogens. Inducibility of cytochrome P-4501A1 is genetically controlled and polymorphic, and individuals who are high inducers are at increased risk for lung cancer (Rannug et al, 1995).
E) TCDD can also induce expression of various oncogenes, both in vivo and in vitro in rats and mice (Matsumura, 1992; Puga et al, 1992; Tullis et al, 1992). Oncogene expression may be independent of induction of cytochromes and could be directly responsible for the carcinogenic effects of TCDD.
F) Dioxin may produce chloracne and associated skin pathology by inducing hyperkeratinization through enhancement of terminal differentiation of epidermal basal cells, a process regulated at least in part by the aryl hydrocarbon receptor (Osborne & Greenlee, 1985).
G) Oxidative stress may be important in the manifestation of TCDD toxicity.
1) TCDD can induce superoxide formation in mouse peritoneal lavage cells (mainly macrophages). This induction is at least partially dependent on the aryl hydrocarbon receptor-TCDD complex (Alsharif et al, 1994).
2) Dioxin appears to inhibit hepatic selenium-dependent, but not selenium-independent, glutathione peroxidase in rats. Optimum dietary selenium seems to provide partial protection from the toxic effects of dioxin in rats (Hassan et al, 1985).
H) Dioxin-mediated changes in tumor necrosis factor pathways may be an important mechanism for acute toxicity (Taylor et al, 1992).
I) The aryl hydrocarbon receptor is also involved in mediating immunotoxicity in mice (Harper et al, 1993).

10.0 STANDARDS/LABELS

10.1 STANDARDS

10.1.1 WORKPLACE STANDARDS

A) ACGIH TLV Values for CAS1746-01-6 (ACGIH, 2004):
1) Not Listed
B) OSHA PEL Values for CAS1746-01-6 (29 CFR 1910.1000, 2005):
1) Not Listed
C) NIOSH REL and IDLH Values for CAS1746-01-6 (NIOSH, 2003):
1) Listed as: 2,3,7,8-Tetrachloro-dibenzo-p-dioxin
2) REL:
a) TWA: Not Listed
b) STEL: Not Listed
c) Ceiling: Not Listed
d) Carcinogen Listing: (Ca) NIOSH considers this substance to be a potential occupational carcinogen (See Appendix A in the NIOSH Pocket Guide to Chemical Hazards).
e) Skin Designation: Not Listed
f) Note(s): See Appendix A
3) IDLH: Not Listed

D) Carcinogenicity Ratings for CAS1746-01-6 :
1) ACGIH (ACGIH, 2004): Not Listed
2) EPA (IRIS, 2004): Not Listed
3) IARC (IARC, 2004): 1 ; Listed as: 2,3,7,8-Tetrachlorodibenzo-para-dioxin
a) 1 : The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.
4) NIOSH (NIOSH, 2003): Ca ; Listed as: 2,3,7,8-Tetrachloro-dibenzo-p-dioxin
a) Ca : NIOSH considers this substance to be a potential occupational carcinogen (See Appendix A in the NIOSH Pocket Guide to Chemical Hazards).
5) MAK (DFG, 2002): Category 4 ; Listed as: 2,3,7,8-Tetrachlorodibenzo-p-dioxin
a) Category 4 : Substances with carcinogenic potential for which genotoxicity plays no or at most a minor part. No significant contribution to human cancer risk is expected provided the MAK value is observed. The classification is supported especially by evidence that increases in cellular proliferation or changes in cellular differentiation are important in the mode of action. To characterize the cancer risk, the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationships are taken into consideration.
6) NTP (NTP, 2005): K ; Listed as: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), Dioxin
a) K : KNOWN = Known to be a human carcinogen

11.0 PHYSICOCHEMICAL

11.1 PHYSICAL PARAMETERS

11.1.1 PHYSICAL CHARACTERISTICS

A) Dioxin exists as colorless to white needles or crystals (Budavari, 2000; Lewis, 2000; NIOSH , 2002). It has no odor or warning characteristics (Bingham et al, 2001).

11.1.2 MOLECULAR WEIGHT

A) 321.97

11.1.4 DENSITY

11.1.4.4 TEMPERATURE AND/OR PRESSURE NOT LISTED

A) 1.827 g/mL (at 25 degrees C) (ATSDR, 1998)

11.2 CHEMICAL PARAMETERS

11.2.2 REACTIVITY

A) TCDD is considered relatively stable toward heat, acids, and alkalies (HSDB , 2002).
B) Combustion of TCP-contaminated 2,4,5-T can result in conversion to small amounts of TCDD (Tvers & Anderson, 1986).
C) Toxic chloride fumes are emitted when dioxin (TCDD) is heated to decomposition (Lewis, 2000).

11.2.3 SOLUBILITY

A) IN WATER
1) Dioxin (TCDD) is only sparingly soluble in water at room temperature (Freeman, 1989):
a) 2x10(-7) g/L (Freeman, 1989; IARC, 1977)
b) 19.3 ng/L (at 20 degrees C) (Bingham et al, 2001)
c) 0.2 ppb (Harbison, 1998; Hayes & Laws, 1991; NIOSH , 2002)
d) 1.9x10(-5) mg/L (ATSDR, 1998)
e) 1.93x10(-5) mg/L (at 25 degrees C) (Bingham et al, 2001; (EPA, 2000c))
f) 7.9x10(-6) to 3.2x10(-4) mg/L (ATSDR, 1998)
B) IN ORGANIC SOLVENTS
1) Solubility of dioxin (TCDD) in solvents (Freeman, 1989; HSDB , 2002):
1. Acetone: 0.11 g/L
2. Benzene: 0.57 g/L
3. Chlorobenzene: 0.72 g/L
4. Chloroform: 0.37 g/L
5. o-Dichlorobenzene: 1.4 g/L
6. Methanol: 0.01 g/L
7. n-Octanol: 0.05 g/L
C) OTHER
1) Solubility of dioxin (TCDD) in lard oil: 0.04 g/L (Freeman, 1989; HSDB , 2002)

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